Review Article

Gastro-esophageal reflux disease in primary care practice: a narrative review

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Background and Objective: This article is aimed to describe the current state of the gastroesophageal reflux disease (GERD) and its significance in the primary care practice. GERD is currently one of the most common gastrointestinal (GI) diagnoses with substantial impact on patients' quality of life and high healthcare resource utilization. Its diagnosis is convoluted and management is complex. Primary care physicians (PCP) are frequently faced with challenges of choosing appropriate care strategies, especially when initial interventions fail.

Methods: Literature search was conducted of the PubMed database for publications with relevant search terms for each section of the presented article. Generally, articles written in English and published after 2000 were considered and reviewed. Manual review of references from retrieved literature was conducted to supplement search results. Older sources were included if considered a landmark paper or lacked a newer publications on the subject. Thorough review of relevant guidelines and authoritative sources were also conducted to produce this review.

Key Content and Findings: Presented comprehensive narrative review elucidated on the significance of the GERD in the practice of primary care physicians. It demonstrated rising prevalence of the disease, details of its pathophysiology, risk of complication, initial presentation and management, including that of medical therapy. It demonstrated central role of PPI in the management of GERD, side effects and complications of chronic PPI use and strategies for de-escalation of therapy. It finally provided overview of the subsequent steps in cases of initial therapy failures.

Conclusions: GERD is one of the most prevalent pathologies in the primary care practice and physicians need to be aware of the modern approaches to the diagnosis and management of this condition.

Keywords: Gastroesophageal reflux disease (GERD); heartburn; esophagitis; medical management; quality of life; primary care

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Introduction

Gastroesophageal reflux disease (GERD) is currently one of the most common gastrointestinal (GI) diagnoses in patients, presenting to primary care physicians (PCP). This condition has a substantial impact on patients' quality of life and is associated with high healthcare resource utilization. Diagnosis of GERD is convoluted and management is complex, especially in cases where initial interventions fail. PCP are frequently faced with challenges of choosing appropriate care strategies.

We aimed to review the current state and significance of GERD for PCP, including prevalence, pathophysiology, complications, initial presentation and diagnosis,

Table 1 The search strategy summary

Items	Specification
Date of Search	May – August 2021
Databases and other sources searched	PubMed/Manual search of references from selected publications
Search terms used	Search terms corresponded to the subtitles of the sections of the current publication: ❖ GERD & History ❖ GERD & Definition ❖ GERD & Pathophysiology ❖ GERD & Epidemiology ❖ GERD & Presentation & Symptoms ❖ GERD & Complications ❖ GERD & Management ❖ GERD & Medical & Therapy ❖ PPI & Side Effects & Complications ❖ PPI & De-escalation ❖ GERD & Escalation & Care ❖ GERD & Surgery & Endoscopic Therapy
Timeframe	Publications after 2000 were included. Older sources were included if considered a landmark paper or lacked a newer publication on the subject. In the history section original publications on the topic were selected
Inclusion criteria	Trials/Observational studies/Cohort studies/Epidemiological studies/Reviews
Selection process	Literature review and sources selection was conducted by the first author. The results were presented to all coauthors and the consensus was reached regarding inclusion or exclusion of the selected sources

treatment strategies and subsequent steps in cases of failure of initial management. We present the following article in accordance with the Narrative Review reporting checklist (available at https://aoe.amegroups.com/article/view/10.21037/aoe-21-62/rc).

Methods

Literature search was conducted of the PubMed database of publications with relevant search terms for each section of the presented article. Generally, articles written in English language and published after 2000 were considered and reviewed (*Table 1*). Manual review of references from retrieved literature was conducted to supplement the search results. Older sources were included if considered a landmark paper or lacked a newer publication on the subject. Thorough review of relevant guidelines and authoritative sources were also conducted to produce this review.

History of gastro-esophageal reflux disease

GERD is one of the most common chronic conditions of the GI tract, affecting nearly 60 million Americans and over a billion people worldwide (1). It is the second most common GI-related diagnosis, preceded only by abdominal pain and accounts for over 5.25 million office and 325 thousand emergency room (ER) visits annually (2). The expenditures on the prescribed acid suppression medication have grown substantially from $7.9 billion dollars in 2001 to $12.4 billion in 2015 in the US alone (2). Currently two of the top five selling drugs in the United States are proton pump inhibitors (PPI) (1). A considerable increase in PPI use occurred worldwide over the last two decades as well. Such,

in the UK general practice PPI use increased from 0.2% in 1990 to 15% in 2014 (3).

GERD emerged as a separate entity in the 1960s and 1970s, initially led by surgeons and then gastroenterologists, interested in this pathology (4). The term "gastroesophageal reflux disease (GERD)" was first introduced in the English literature by Krejs *et al.* in 1976 (5). Since that time GERD has become a well-recognized entity with increased burden of the disease in the population and a high health care resource utilization (6). Numerous medications and various surgical interventions have been introduced for the treatment of this condition. Currently, it is the most common chronic disease with an estimated direct and indirect cost exceeding 75 billion dollars annually and expenditures continue to increase (7). The disease has significant impact on patient quality of life and leads to substantial morbidity in the general population (8).

Definition of GERD

According to the Montreal Definition and Classification, GERD is defined as a condition, that develops when the reflux of stomach contents causes troublesome symptoms and/or complications (9). It has been postulated that symptoms become troublesome when they affect patient quality of life. All symptoms are subdivided into esophageal and extra esophageal syndromes. Esophageal syndromes include such symptomatic syndromes as typical reflux syndrome, reflux chest pain syndrome and syndromes with esophageal injury, particularly reflux esophagitis, stricture, Barrett's esophagus and adenocarcinoma. Extraesophageal syndromes include those with well-established associations with GERD, such as reflux-associated cough, laryngitis, asthma, dental erosion and proposed associations such as pharyngitis, sinusitis, idiopathic pulmonary fibrosis (IPF) and recurrent otitis media (9). Whereas it remains in the hands of the patients to determine the degree of affliction by the condition, diagnosis is sometimes difficult and convoluted even with the typical esophageal syndromes. In an analysis of 308 patient with GERD, neither assessment with the Reflux Disease Questionnaire (RDQ) by PCP, endoscopy by gastroenterologist, or a trial of esomeprazole therapy were sensitive or specific enough for the diagnosis of GERD (8).

Pathophysiology

Imbalance between aggressiveness of the gastric refluxate on the one hand and antireflux mechanism on the other leads to the development of symptoms of GERD (10). Anatomical structures, such as circular muscle thickening at the low esophageal sphincter (LES), the diaphragmatic crura and valve mechanism of the angle of His and functional mechanisms, such as esophageal peristalsis, saliva production and epithelial integrity play a protective role in the development of GERD. Western diet with high volume meals leads to chronic over distention of the stomach and shortening of the LES, similar to the shortening of the neck of an air balloon, resulting in stretching of the phrenoesophageal membrane and development of the hiatal hernia (11,12). Hiatal hernia leads to separation of the LES from diaphragmatic crura and its proximal displacement, transposing it into the negative pressure environment of the chest, decreasing its effective strength (13-15).

Certain foods that cause either an increase in the acidity of the gastric content or relaxation of the LES, as well as an inhibition of gastric motility and gastric stasis contribute to the reflux (16). Incidence and severity of GERD are likely related to the degree of anatomical derangements of the gastroesophageal junction (GEJ) in patient with hiatal hernias. Analyzing a group of 175 patients with GERD diagnosed based on the 24-hour pH-metry, Schlottman *et al*. identified a direct relationship between size of the hiatal hernia and severity of GERD, including frequency of cough, wheezing, decrease of the LES pressure and peristalsis as well as severity of the acid reflux on the pH-metry and degree of the esophagitis on endoscopy (17). However, silent GERD prevalence, assessed by the presence of esophageal injury in the patient with absent GERD symptoms, ranges from 2% to 23% (18,19). Many different factors were implemented in the development of GERD. Obesity is one of the most prominent risk factors for GERD (20,21). Obesity, leading to a rise in intraabdominal pressure and chronic lung diseases with decreased in intrathoracic pressure, result in increase of the transdiaphragmatic pressure gradient, promoting the development of the GERD (10,22). Data from The National Health and Examination Survey (NHANES) estimated a prevalence of obesity at 42.8% and severe obesity at 9.2% in adults with no difference among men and women and it had progressively increased over the last two decades (23). Baik *et al*. have demonstrated a statistically significant increase in the prevalence of Barrett's esophagus in patients with obesity, defined by the abdominal diameter index. These findings have been corroborated by numerous

other authors especially for the development of the GEJ adenocarcinoma (20,24,25).

Prevalence of GERD

GERD is one of the most common conditions of the GI tract affecting over 60 million people in the United States (1). It has a profound impact on patient's quality of life and comprises a significant proportion of patient concerns at many primary care practices (7,10). Unfortunately, the significance of the problem is universally underestimated (26).

True prevalence of the GERD is hard to determine, however it is estimated to affect approximately 11–14% of the population world-wide, with rising prevalence with increase in body mass index (BMI) and abdominal diameter (7). In the systematic review, El-Serag *et al.* analyzed 30 studies addressing prevalence and incidence of GERD in the general population from various parts of the world. Astonishingly, GERD prevalence was estimated at 18–28% in North America, 9–26% in Europe, 3–8% in East Asia, 9–33% in the Middle East, 12% in Australia and 23.0% in South America (27). There has also been a steady statistically significant increase in the prevalence of GERD since 1995 worldwide (3).

The prevalence of GERD is also increasing with age. In a survey of 1,859 employees and their families in Japan, Okimoto *et al.* identified an increasing prevalence of GERD in adults compared to children. Defining the presence of GERD on the GERD calculator questionnaire (GerdQ) as a score >8, GERD was present in 4.4% of subjects under 20 years of age compared to 11.6% of adults. Moreover, the prevalence continued to increase with age and reached 18.4% at age of 60 and 21.1% at the age of 80. Again, the authors noted an increasing incidence of GERD with a rise in BMI. The prevalence of GERD in adults with BMI ≥25 was 18.7%, compared to 9.3% in those with the BMI <25 (28). Risk factors have significant implications in the development of GERD. In the surveillance of over a thousand subjects in Russia with a validated 72-point questionnaire, Bor *et al.* identified a total GERD prevalence at 23.6%. Notably, it was higher in females (29.5% *vs.* 15.4%) and also increased with age. Particularly, GERD was present in 20.4% of smokers, 24.2% of coffee drinkers, 21.5% of alcohol consumers and 45.9% of stressed participants (29).

Meta-analysis, including 102 published reports and almost half a million patients, revealed various incidence of the GERD throughout the world, ranging from 2.5% in China to 51.2% in Greece. Pooled prevalence was 13.3% with an increase with age (OR 1.26), in smokers (OR 1.32), nonsteroidal anti-inflammatory drugs (NSAIDs) users (OR 1.44) and in obese individuals (OR 1.73) (30). In another meta-analysis of 102 papers, representing 37 countries and all regions of the UN geoscheme, the global pooled prevalence of GERD was 13.98%. This prevalence varied greatly according to a region (12.88% in Latin America and the Caribbean to 19.55% in North America) and a country (4.16% in China to 22.40% in Turkey) with an estimated prevalence of GERD globally at 1.03 billion (31). The prevalence of GERD in the USA adult population in one study was estimated as high as 45% (32).

Presentation and symptoms

Classic symptoms of GERD, also known as "typical" are heartburn, retrosternal chest pain and regurgitation. Development of dysphagia in patient with GERD might signify development of reflux related stricture and should rise a concern for malignancy. These symptoms are described as an "esophageal syndromes". Other, less common, "atypical" symptoms are part of so called "extraesophageal syndromes" and may include reflux related chronic cough, laryngitis, asthma, dental erosions, pharyngitis, sinusitis, IPF and recurrent otitis media (9).

GERD can have a profound impact on a patient's quality of life. In a systematic review Liker *et al.* analyzed 23 papers, assessing the impact of GERD on a patient's quality of life. Analysis of the results of the short form 36 (SF-36) survey of GERD patients demonstrated significant impairment in the domains of vitality, bodily pain, general health, physical and emotional role, mental health and physical and social functioning (26). In a mail survey of over 130 thousand respondents, the majority of GERD patients reported reduced enjoyment of food (more than 80%), disturbed sleep (more than 60%) and difficulties concentrating at work (over 40%). Heartburn affected a wide range of daily activities, including exercise, playing with children, hobbies and enjoying intimacy and sex. Nearly half of GERD patients avoided physical activities that might precipitate heartburn symptoms, one third reported restrictions in some activities, and 16% limited sporting activities and exercise (26). Sleep disturbances were observed in over 55% of patients with severe GERD. Even in the well-controlled symptoms group, up to 25% of patient reported waking up at night and up to 65% of patient with GERD reported an

inability to get a good night sleep (26). Additionally, 40% reported that their daily activities were compromised by their symptoms (26).

Functional esophageal disorders (functional heartburn, chest pain and dysphagia, globus and reflux hypersensitivity) are defined by Rome IV criteria as conditions with typical symptoms in the absence of objective evidence of corresponding abnormalities (33,34). Frequently, patients with functional esophageal disorders fail to respond to initial medical treatment and careful evaluation is required to distinguish these individuals from typical GERD patients (35).

Risk of GERD complications

GERD can lead to the development of numerous esophageal and extraesophageal complications. Esophagitis, esophageal ulcers, Barrett's esophagus and esophageal cancer are well established GERD related complications (18,36). Other, less acknowledged conditions are cough, chronic sinusitis, laryngitis, bronchitis, asthma and IPF, pneumonia, dental caries and others (9,37-39). Large population-based studies from Europe have demonstrated five to eight-fold increase in the rate of adenocarcinoma in patients with GERD (40,41). Among over a million patients in Europe, absence of GERD on endoscopy was associated with 55% reduction in incidence of upper GI malignancy and 61% decrease in mortality (42). A group of authors analyzed 13 studies with nearly 40 thousand patients, focusing on the risk of head and neck cancers in patient with GERD. There was a statistically significant increase in the rate of malignancies, especially laryngeal carcinoma in these patients (OR =1.86, 95% CI: 1.27–2.74) (43). In a recent study, medical therapy and surgical interventions for reflux led to a decreased risk of esophageal adenocarcinomas in patients with GERD, especially those with Barrett's esophagus, although the risk still remained about 10 times elevated compared to the general population (44). Various pulmonary complications can develop due to "reflux", including direct aspiration of the acidic gastric secretions or "reflex" (refluxate-triggered, vagally mediated airway spasm) mechanisms. This may lead to restrictive pulmonary disease and altered respiratory mechanics that can contribute to a worsening of the reflux (45).

Management of GERD

Initial management of the patient with a typical presentation of GERD starts with diet and lifestyle modification. Avoidance of the foods, that can precipitate reflux symptoms can improve patient quality of life. Citrus and other acidic foods, such as fruits, tomatoes, juices, coffee and carbonated drinks trigger reflux symptoms, by having slower distal esophageal transit than neutral fluids, leading to worsening of reflux symptoms (16,46). Predominantly non-vegetarian diet, greasy food and chocolate have been associated with increased GERD symptoms, possibly by causing low esophageal sphincter pressure (LESP) relaxation (46-48). Fruits and vegetables have a protective effect on the GERD and Barrett's esophagus development (36). Use of alcohol and tobacco was associated with increased risk of GERD and Barrett's esophagus (36). In a cross-sectional study of 817 participants, the Mediterranean diet (composite/traditional dishes, fresh fruit and vegetables, olive oil, and fish) was associated with a statistically significant 57% decrease of the risk of GERD, even after adjustment for age, sex, socioeconomic factors, lifestyle and eating habits (49). Increased fiber intake (psyllium 5 g TID) led to a significant increase in the minimal resting LES pressure, decrease in the number of reflux episodes and heartburn symptoms in a study group of 36 patients (50).

Lifestyle modifications have also enjoyed increased scientific attention since the recognition of a side effects profile of medical therapy. Several studies have demonstrated that weight loss leads to decrease in the severity and duration of reflux episodes (51). In a trial of 332 patients enrolled in a supervised weight management program, average weight loss of 13±7.7 kg resulted in the decrease of overall prevalence of GERD from 37% to 15% ($P<0.01$) with the mean GERD symptom score decreasing from 5.5 to 1.8 ($P<0.01$). The authors reported an overall 81% reduction, including 65% complete resolution of reflux symptoms with significant correlation between the degree of weight loss and a reduction in GERD symptom scores (52). In a large Norwegian population-based study involving nearly 30,000 individuals, a decrease in BMI of over 3.5 points or more resulted in a significant reduction of (50–70%) of GERD symptoms (53).

Abdominal, or diaphragmatic breathing exercise is a simple office-based intervention that has been shown to decrease acid exposure in GERD patients and improve quality of life. It is postulated that this intervention actively trains diaphragmatic crura, contributing to the competency of the LES, directly affecting severity of GERD. In one RCT, published by Eherer *et al.*, acid exposure was shown to decrease by nearly 50% after just 4 weeks of training,

improving Quality of Life (QoL) scores. After 9 months of ongoing training, QoL scores improved by 36% and PPI usages decreased by 75% (54). In another RCT, Halland et al showed that postprandial esophageal acid exposure reduced by 56% in patients randomized to diaphragmatic breathing (55).

Tobacco cessation has been shown to lead to decrease in symptoms of GERD. However, the effect was more prominent in normal weight individuals. In obese patients it did not result in a meaningful outcome, probably due to more significant role of obesity in the pathogenesis of GERD (51). A randomized controlled study of 30 patients revealed significantly higher supine reflux symptoms in those who had late evening meals, obese individuals and those with presence of a hiatal hernia (56). Elevating the head of bed during sleep was shown to be an effective method of decreasing distal esophageal exposure to reflux and shortening the acid clearance time compared to a flatbed position (57).

Medical therapy

Medical therapy is a mainstay in the management of the majority of GERD cases. In a typical GERD presentation empiric therapy with a PPI is frequently initiated first without additional confirmatory studies. In cases where symptoms are not improved over a course of several weeks, patients are referred for additional studies and evaluation by specialists.

PPI have been shown to be the most effective agents in the treatment of GERD (58). In the Cochrane database systematic review including 134 trials with over 35,000 patients with esophagitis, Khan *et al.* unequivocally demonstrated superiority of PPI treatment over other agents in healing erosive esophagitis (EE) (59). Five randomized controlled trials (RCTs) with a total of 965 patients demonstrated a statistically significant improvement in healing of esophagitis over placebo (RR =0.22; 95% CI: 0.15–0.31). Ten RCTs, including 1,241 participants reported a statistically significant benefit of H2 receptor antagonist (H2RA) over placebo (RR =0.74, 95% CI: 0.66–0.84). There was no statistically significant benefit to prokinetic therapy versus placebo in three RCTs, involving 198 participants (RR =0.71, 95% CI: 0.46–1.10). Twenty-six RCTs, involving 4,032 participants reported on outcomes of PPI versus H2RA with or without prokinetic agents and demonstrated a statistically significant benefit of PPI therapy (RR =0.51, 95% CI: 0.44–0.59) (59). However, therapeutic gain of PPI over placebo was only 30–50% in reflux control and was higher in patient with EE than in non-erosive reflux disease (NERD) (37% *vs.* 56%) (58). As many as 45% of patient with GERD do not respond to PPI therapy (35). Even lower response rates are observed in controlling regurgitation (25–60%) or atypical symptoms (60,61). Functional esophageal disorders may play a role in failure of standard medical antireflux therapy (33-35).

Side effects of PPI

PPI have become a "go to" therapy in the current practice of GERD management and are now widely available without a prescription. As a result, over-prescription and over-utilization of the PPI has taken a significant prevalence in the current medical practice. Continued overprescribing and over-the-counter use of PPI medications is ubiquitous worldwide. In the analysis of over 1,800 patients, Jones *et al.* demonstrated that only half of them were formally diagnosed with GERD. Of these, 65% were taking over the counter medications. Among patients undiagnosed with GERD, 97% were taking over the counter PPI medications (62).

This is a concerning trend, as these medications carry significant side effect risk and complications. Numerous studies have called attention to various adverse health outcomes of the chronic use of PPI. These include acute nephritis and chronic kidney injury, dementia, along with an increased mortality in patient with dementia, fatal hypomagnesemia, clostridium difficile infection, osteoporosis and fractures, community acquired pneumonia and cardiovascular events (63-69). However, in the recent metanalysis including over three hundred thousand patients Desai *et al.* failed to show association of PPI use and dementia or Alzheimer's disease (70). In the metanalysis of 24 observational studies involving over 2 million patients taking PPI from 1990 to 2018, Poly *et al.* demonstrated an increased risk of 20 % for hip fractures (71). The risk of prosthetic joint infection was 2.4 times higher in PPI users (72). The risk was further increased in patients with high dose PPI (30%) or long-term therapy (24%). In the analysis of over six million patient records from the US Department of Veterans Affairs administrative database with 5.7 years of follow up, Xie and co-authors demonstrated a statistically significant 25% increase in mortality in PPI users *vs.* H2 blocker users (HR 1.25, 95% CI: 1.23–1.28) (73). Recently, PPIs were associated with increased severity and mortality in patients with COVID-19 infection (74,75). To

the contrary, in the large placebo controlled randomized trial Moayyedi *et al.* found that pantoprazole was not associated with any adverse events, except for enteric infections during a three-year therapy (76). Analyzing published data on PPI complications Vaezi *et al.* pointed out to predominantly observational nature of these studies. Acknowledging the problem with universal over prescription of PPI, minimal absolute risk increase of complications and enormous benefit for patient with GERD, authors called for pragmatic, "common sense" approach to PPI prescribing at the lowest effective dose (77).

De-escalation of PPI therapy

De-escalation of PPI therapy might be considered in clinical practice. In response to the formulary changes in the Tennessee Medicaid program, attempt at tailoring PPI use was undertaken in 129 patients of internal medicine clinic. Eighteen (14%) of patient discontinued the PPI therapy, 40 (31%) continued it and 71 (55%) were switched to H2 blockers. At eight months follow-up, 81% of these patients remained on H2 blockers or were completely off acid suppression therapy (78). Experience of another family medicine clinic in the underserved area of rural Minnesota demonstrated success in the discontinuation of PPI therapy. Of the 126 patients, 21% were willing to undergo the trial. Of these, 86% successfully discontinued PPI use, 9% decreased the dose and 5% remained on the current dose (79). However, in the metanalysis of six trials involving 1,758 subjects aimed at discontinuation of the PPI therapy either abruptly, or to "on demand" use, lack of symptom control favored continuation of the PPI therapy in five of those trials (80).

Failure of initial therapy and escalation of care

Whereas PPI hold a dominant role in the management of the GERD, they do not affect anatomical relationship and pathophysiological mechanisms of reflux. By decreasing acidity of the gastric refluxate and alleviating heartburn they simply mask the ongoing problem of continued reflux (81). Various anti-reflux interventions, on the other hand, address the anatomic basis of the disease and have shown promise in the management of GERD (13,82,83). Further refinements of the technology in the field brought to the forefront numerous less invasive surgical and endoscopic options. Laparoscopic and robotic procedures are now a standard of care (14). Magnetic sphincter augmentation procedure (LINX) is a new device aimed at reflux control that is implanted laparoscopically (84). Endoscopic interventions such as transoral incisionless fundoplication (TIF), Stretta, Medigus Ultrasonic Surgical Endostapler (MUSE), antireflux mucosectomy (ARMS) and others are designed to address GERD completely via endoscopic approach without surgical incisions (85,86). These procedures reduce the magnitude of the intervention and facilitate patient's recovery and return to normal activities after anatomically corrective intervention.

Conclusions

GERD is a ubiquitous condition, affecting over a billion of adult population across the globe and its prevalence is steadily increasing as a result of the western diet and rising rates of obesity. It has a profound impact on patients' quality of life and is associated with high healthcare resource utilization and societal cost. Diagnosis and management of the condition is convoluted. First line interventions, such as diet and lifestyle modifications, carry limited success. PPI are the most effective medical agents and commonly are a mainstay of the initial medical therapy. However, they are frequently over prescribed and overutilized, especially with over-the-counter availability. Chronic use of PPI is associated with a wide range of complications. De-escalation of PPI therapy might be successful in some patients. In cases of failure of initial intervention and medical therapy, early referral to specialist with expertise in the management of GERD is indicated for selection of appropriate management strategy and improvement of patients' outcomes.

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Footnote

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