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Gastroesophageal reflux disease: A review

S Mahmood Alqallaf*; Ahmed Abdulmohsin Zaid; Ahmed Abdulnabi Shamtoot; Ahmed Ali Alhamali; Hussain Baqer Alzaki; Mohammed Ali Alsari

Pharmacy program, College of Health Sciences, University of Bahrain, Kingdom of Bahrain.

***Corresponding Author: Sayed Mahmood Alqalaf**
Pharmacy program, College of Health Sciences, University of Bahrain, Kingdom of Bahrain.
Email: smalqallaf@uob.edu.bh

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Abstract

Gastro-esophageal reflux disease (GERD) is a common digestive disorder characterized by the backward movement of the stomach contents including acid into the esophagus. The main etiological factor of the disease is believed to be a defect in the lower esophageal sphincter. Different types of food found to be highly associated with increasing GERD symptoms among the patients including fried food, spicy food, soft drinks, citrus foods and drinks in addition to tea and coffee. Although most patients suffer from mild symptoms of the disease that can be controlled with modification of their lifestyle habits and avoiding certain drugs, many patients could have severe atypical symptoms that might lead to complications. Diagnosis of the disease is based on obtaining a full medical and drug history of the patient to discover the main precipitating factors that could be adjusted. Some invasive diagnostic tool might be needed such as upper gastrointestinal endoscopy and pH monitoring. Many patients can be managed pharmacologically with over the counter medications such as the antacids, but some patients might need potent acid suppressing drugs such as the proton pump inhibitors and the less potent histamine-2 receptor blockers. Raising patients knowledge about the disease is a key factor in the management of the disease as many precipitating factor of the disease are know and can be easily identified in the patient, hence educational programs to raise patients awareness level of the disease is necessary.

Introduction

Gastroesophageal reflux disease (GERD) is a quite common disease, with over 5.6 million medical visits every year [1]. Over the past several decades, the incidence of GERD symptoms has increased by around 4% each year, coinciding with rises in obesity rates and a decrease in the prevalence of Helicobacter pylori [1]. Patients with objective signs of GERD, such as erosive esophagitis or Barrett esophagus may not have symptoms [2,3]. In 2015, the overall direct economic impact of GERD and its consequences was reported to be over $18.1 billion with the usage of proton pump inhibitors (PPIs) accounting for $12.4 billion and indirect expenses resulting from lower work productivity estimated to be $75 billion [4].

GERD is a disorder that occurs when stomach contents reflux into the esophagus, causing unpleasant symptoms with or without complications. It was reported that the disease affects up to 16% of the population in the United States, with 6% reporting clinically significant heartburn [3,5].

However, GERD may cause a variety of symptoms. Lying recumbent, especially after a meal might aggravate GERD symptoms. Dysphagia can be a symptom of uncomplicated GERD,

but its presence necessitates a more thorough evaluation and possible intervention because it might be caused by strictures, rings, cancer, or esophageal dysmotility among other factors. Although, chest discomfort is a common symptom of GERD, a cardiac etiology should be excluded before GERD is addressed. Dyspepsia, nausea, bloating, sore throat, globus feeling, and epigastric discomfort are among GERD symptoms [3].

Elderly patients are less likely to suffer from GERD symptoms [6]. However, the severity of the illness once occurred was shown to be higher in the elderly than in younger individuals on average. As a result, older patients have a lower prevalence of recorded GERD than younger patients, but indeed the underlying GERD incidence is likely to be similar between the two age groups [3]. Extra-esophageal symptoms such as chest discomfort, tooth erosions, persistent cough, laryngitis, or asthma can also occur in an atypical manner [7]. GERD is divided into three phenotypes based on endoscopic and histopathologic findings: non-erosive reflux disease (NERD), erosive esophagitis (EE), and Barrett esophagus (BE). NERD is the most common phenotype, accounting for 60-70 percent of GERD patients, followed by erosive esophagitis and BE, which account for 30 percent and 6-12 percent of GERD patients respectively [8]. Over the years, lifestyle changes and proton pump inhibitors have been the mainstays in the treatment of GERD [8]. Patients with relapsed or refractory GERD is becoming more widespread, necessitating a personal approach to GERD management depending on each GERD type and severity and each case [8].

Epidemiology

Gastroesophageal reflux disease (GERD) is a prevalent medical condition that affects people all around the world. GERD is the fourth most prevalent chronic illness seen in primary care and because of its great prevalence, negative impact on quality of life and high cost, GERD is considered a serious healthcare issue [9,10]. According to the recent studies, the highest prevalence of GERD in the worldwide found to be in Southeast Europe and South Asia (>25%). On the other hand, France, Canada and southeast Asia recorded the lowest prevalence of GERD in the worldwide (less than 10%) [11,12]. The prevalence of GERD was reported to be about 20% of adults in Western countries and about 18.1% - 27.8% in United States. Nevertheless, these statistics might not be accurate because high percentage of patients tend to treat themselves with over-the-counter medications [13,8]. Some studies estimated the prevalence of typical symptoms of the disease (heartburn and acid regurgitation) in different regions in the world such as in Middle East at 8.7%–33.1%, 11.6% in Australia, 8.8% in Europe, 20% in Turkey and 8.7% - 21.2% in Tehran – Iran [13]. In addition, a recent study estimated the prevalence of GERD at 28.7% in Saudi Arabia [14]. GERD symptoms found to be more prevalent in women compared to men. However, these women were found to suffer mostly from Non-erosive reflux disease (NERD) while erosive esophagitis is more common among men. Additionally, Barrett's esophagus found to be more common in males with long-lasting GERD symptoms than females [8,11,15].

Regarding the relationship between helicobacter pylori (H. pylori) infection and GERD, recent studies showed no correlation between these bacteria and GERD. Findings from these studies revealed that H.pylori and GERD appear to have inverse relationship and it's still subject of debate as the disease determined by many concomitant factors and the relationship needs to be confirmed by studies which combine all the factors such as patient factors, lifestyle habits and H. pylori infection [16].

Pathophysiology, clinical manifestation and diagnosis

In the previous decades, the prevalence of gastroesophageal reflux disease (GERD) has risen, making it one of the most frequent chronic illnesses. The understanding of the pathophysiology of GERD has shifted dramatically over time, owing to new research methodologies. It was found that the etiology of GERD has multifactorial causes as it is increasingly regarded as a complex disorder. However, the GERD pathophysiology needs further investigation since the incidence of proton pump inhibitor-refractory GERD symptoms is still common [8].

Factors that are suspected of playing a major role in the etiology of GERD include stimulation of inflammatory mediators in the esophagus, changes in esophageal mucosal integrity, enhanced biochemical and mechanical sensation in the esophagus, and both peripheral and central sensitization. The symptoms of GERD are highly exacerbated by several factors including stress, central sensitization, anxiety and hypervigilance [17,18]. A relationship was elucidated between high-fat diet and stimulation of free radicals in the esophagus causing inflammation and damage to the lower esophageal sphincter [18].

The prevalence of aberrant esophageal acid exposure times, as defined by 24-hour pH monitoring, is escalating across the GERD spectrum [19]. Firstly, following meal intake, the persistence of a highly acidic "pocket" during a period when the stomach's pH actually increases. If the individual has either a faulty barrier mechanism or a higher predisposition to transitory relaxation of the lower esophageal sphincter, the contents of this pocket is expected to poise to reflux. Acid may be the catalyst for the production of microscopic alterations in the squamous epithelium that allow acid access to sensitive submucosal neurons resulting in the onset of symptoms [19]. Secondly, the fundamental mechanism of reflux in health and illness is known to be spontaneous and leads to protracted relaxations to the baseline of lower esophageal sphincter (LES) pressure. Hiatal hernias, that happen when a portion of the stomach squeezes up into the chest through a diaphragm hole (hiatus) have resurfaced as a major factor in GERD. A nonreducible hernia disturbs sphincter function, increases acid reflux and hinders acid clearance resulting in more reflux episodes and extended acid exposure [19]. Thirdly, is the "nocturnal acid breakthrough" which is the term firstly introduced by Peghini and colleagues, who defined it as stomach acid recovery to a pH level of <4 lasting at least 60 minutes in the nighttime period (10:00 PM to 6:00 AM) [19]. Peghini and colleagues were intrigued by certain GERD patient's apparent resistance to very high dosages of proton pump inhibitors, therefore they investigated stomach pH profiles in these patients and recorded the common incidence of nocturnal acid breakthrough (NAB). A nighttime dosage of proton pump inhibitor was ineffective, whereas histamine H2-receptor antagonists were effective. Many GERD patients, particularly those with severe signs of the illness, such as Barrett's esophagus, were prescribed these medicines as a result of the NAB [8,20].

Furthermore, some pathological factors or underlying structural problems are other causes of GERD development. Changes in the action of the esophageal muscles, which govern natural peristalsis. For example, it might cause increased regurgitation of stomach secretions and contribute to the disease's development. Similarly, anatomical abnormalities of the lower esophageal sphincter (LES) result in its malfunction, which usually acts as a lid for the stomach, preventing stomach content from moving back into the esophagus. The development of a large-sized hiatal hernia can potentially cause LES problems. Furthermore, continuous exposure of the mucosal lining to acidic chemicals may cause the protective properties of the internal lining to deteriorate, resulting in the appearance of GERD symptoms. The mucosal lining is a well-known host of the human body's defensive mechanisms. Abnormalities in these mucosal lining processes might potentially play a significant role in the disease's development [21].

The presence of typical symptoms (such as heartburn and acid regurgitation) or atypical symptoms (such as nausea, vomiting, chest pain, chronic cough, asthma-like symptoms, and sinusitis) is used to diagnose GERD. The diagnosis can be guided by the GERD questionnaire (GERDQ). Patients can start a PPI study if they don't have any warning signs (dysphagia, anemia, weight loss, upper gastrointestinal hemorrhage, or persistent vomiting) [22]. Upper gastrointestinal endoscopy should be explored in individuals who have not seen any relief with PPI trial in their reflux symptoms. For individuals having alarming symptoms, upper gastrointestinal endoscopy should be the first port of call. If no anomalies are discovered during an upper gastrointestinal endoscopy, pH monitoring should be done to get more information. If the GERD phenotype is unknown after traditional pH monitoring, high-resolution impedance manometry with or without pH impedance can give further information [23].

Treatment

The pharmacologic management of GERD is subdivided into five categories: antacids (such as calcium carbonate and sodium bicarbonate), alginate-based barriers, sucralfate, adjunctive therapies (prokinetic agents and reflux inhibitors [bethanechol, as off-label use]), and medications that suppress gastric acid secretion (H2-receptor blockers and PPIs). The acid-suppressive drugs alleviate GERD symptoms by lowering stomach acid production (goal of increasing gastric pH to more than 4). These drugs form the cornerstone of pharmacologic GERD management [24,25].

In all adults with GERD, a trial of lifestyle changes should be considered first. In the light of lifestyle changes, guidelines urge a dietary restriction from a certain type of foods known to exacerbate the reflux of the disease. These may include: Avoidance of tomato products, carbonated beverages, alcohol, fried or fatty foods, chocolate, coffee, citrus products and spicy foods. Whereas, weight loss has a great impact in reducing the symptoms and the relapse of the disease. In addition, smoking cessation, avoiding large meals especially 2 hours before bedtime, raising the head of the bed at least 6-8 inches and avoiding wearing tight clothes around the waist should also be considered. All of these techniques are deemed safe and have been found to be effective [25].

H2-receptor antagonists (H2RAs) reduce pepsin output and gastric acid volume by inhibiting histamine which is involved in stomach acid production. H2RAs were the first class of acid-suppressive medicines. Cochrane systematic reviews indicated that H2RAs are useful in the treatment of GERD with and without esophagitis [26,27]. Example of the H2RAs available in the market are: Cimetidine, famotidine, nizatidine, and ranitidine. All four drugs are considered to be equal when given in equipotent doses. They work better on baseline acid secretion than on postprandial secretion and should be given 30 to 60 minutes before meal [28,25]. The most effective acid suppressants are the proton pump inhibitors (PPIs). They function by inhibiting the last stage in acid secretion; the stomach H+/K+-adenosine triphosphatase (ATPase) that causes K+ ion absorption and H+ ion secretion. PPIs, as compared to H2RAs and placebo, give faster and more effective symptom alleviation and are more helpful in treating erosive esophagitis [29,25]. Throughout the treatment of daily PPI usage, 10% to 40% of individuals will continue to suffer reflux symptoms [24]. In the event of a failure in response to a PPI trial, it is critical to both reaffirm the diagnosis of GERD (while focused on excluding out warning symptoms) and guarantee correct PPI delivery 30 minutes before meal [25]. Antacids available include calcium carbonate, sodium bicarbonate, aluminum, and magnesium hydroxide that might be used separately or in combination. They offer immediate but short-term symptom alleviation by buffering stomach acid and are equally effective as H2RAs in large doses [29].

Furthermore, surgical management should be included whenever patient remains unresponsive to drug therapy [3]. The Nissen fundoplication, primarily conducted in 1955 by Dr. Rudolph Nissen, gained prominence in the 1970s and is today the most often performed anti-reflux surgery. To repair the LES barrier, the hiatal hernia must be minimized, and the gastric fundus must be wrapped partially or fully around the lower esophagus [3]. Presence of a big hiatal hernia, reflux esophagitis or GERD symptoms that have not responded to medical treatment, or unfavorable consequences of medical therapy are all indications for the surgery [3]. However, anti-reflux surgery should be used with caution since it can cause serious side effects including dysphagia, gas bloat syndrome, and flatulence, and the desired impact may only be transitory, as up to 60% of patients will need anti-reflux drugs on a daily basis for the next decade [3]. A less invasive option is the Linx treatment (magnetic sphincter augmentation). It entails the laparoscopic placement of a magnetic bead band around the LES, which enables food to pass but then shuts to avoid acid reflux. The technique is linked to a reduction in symptom severity and the requirement for PPI treatment, but not to a consistent decrease in esophageal acid exposure [3,30]. For excessively obese individuals, the Roux-en-Y gastric bypass is a surgical option. A prospective study of 53 patients found that after bypass, GERD symptoms, reflux esophagitis, and esophageal acid exposure improved for more than 3 years [3,31].

Awareness

The importance of awareness of diseases and their treatments cannot be overstated. Collaboration in this aspect would produce favorable results in the community, including more research, more education programs and better patient care. GERD has an impact on the patient's quality of life which is considered a worldwide pervasive medical problem that affects practically everyone in the world. In Western countries, it is believed that 20% of the population are having this illness [8]. The number of cases recorded in poor nations is lower, due to the absence of awareness, which leads to mild GERD symptoms being overlooked. A cross-sectional survey-based study in the United States revealed the need for population-specific educa-

tional initiatives to improve awareness about the symptoms of GERD in populations with different cultural backgrounds [32]. Moreover, other studies were undertaken in industrialized nations, including Sweden, Canada, Switzerland, Norway, and the United Kingdom, to describe epidemiology, prevalence, risk factors, and the effect of public awareness of GERD and related lifestyle changes, these studies reported increasing rate of recently diagonosed patients with GERD year by year resulting in considerable burdens and costs [21,33,34].

In addition, several studies have been conducted in Asian countries to determine various elements of GERD, such as general public knowledge and its effects on local population health outcomes. One of these was a study that was done in United States and found a lack of awareness and information regarding the early signs and symptoms of GERD among Asians [32]. In a Taiwanese investigation, the prevalence of GERD was shown to be significantly increasing. The findings of this study further highlighted the significance of raising GERD awareness among the Asian community [35]. Moreover, increased awareness and knowledge concerning GERD in the local populace was also highlighted in an Indian research. According to this study, the recent increase in the incidence of GERD in India might be linked to increasing awareness, resulting in an increase in the number of cases recorded [36]. Similarly, a research in Japan found similar results, indicating an increase in GERD prevalence due to increased public awareness and the availability of improved diagnostic tools [37]. On the other hand, a research including 1,010 Pakistani patients with typical GERD symptoms found a lack of knowledge and risky habits [38]. Likewise, GERD prevalence and awareness in local communities have been assessed in certain Middle Eastern studies. According to a Turkish study, there are a lot of undiagnosed and untreated GERD patients. Due to a lack of understanding and following poor lifestyles and habits, the study's findings revealed a very high incidence of GERD among economically deprived populations [39]. Due to a lack of knowledge and misdiagnosis, a research from the United Arab Emirates found a high prevalence of gastrointestinal illnesses, including GERD [40]. Various studies in Saudi Arabia have found a significant incidence of GERD due to a lack of knowledge and the existence of multiple modifiable lifestyle factors [41]. In the Arar area of Saudi Arabia, unhealthy eating habits, stress, excessive coffee intake, smoking, more spices in food and long-term use of non-steroidal anti-inflammatory medicines (NSAIDs) were all linked to an increased occurrence of GERD [42]. Regarding the prevalence and incidence of GERD among Saudi Arabia's local population, a recent study revealed a lack of knowledge about the disease's etiology, symptoms, prevention, and management measures [42].

It is important to raise awareness of the predisposing factors for GERD in order to reduce the disease's prevalence, symptoms, and consequences. Studies have shown that the majority of patients opting for non-medical treatment [43]. Those who see a physician are much more likely to have distinct features than those who do not, including a higher burden of disease and more disease-related problems [44]. Although, GERD remains a prevalent condition in the gulf region including Bahrain, knowledge of the predisposing factors and symptoms is lacking. A study in Saudi Arabia which is close to Bahrain and other Gulf countries in its culture, education and health system has shown this. It is expected that promoting awareness of GERD to be a key factor in preventing and managing GERD in the community and reduce its financial burden. To promote awareness of GERD, healthcare education programs need to be implemented. These programs could include social media to reach the widest possible audience [42].

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