Association of Gastroesophageal Reflux Disease Symptoms with Exacerbations of Chronic Obstructive Pulmonary Disease

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Abstract

Background: Symptoms of gastroesophageal reflux disease (GERD) are common in various chronic respiratory diseases, but little is known about GERD in the setting of chronic obstructive pulmonary disease (COPD). The aim of this study was to determine the effect of GERD symptoms on COPD exacerbations and subsequent hospitalization and drug usage.

Methods: This retrospective study was conducted from December 2008 to February 2009 in the Pulmonary Clinic of Dr. Shariati University Hospital, Isfahan, Iran. Consecutive patients who were diagnosed with COPD based on clinical features and pulmonary function tests were included. Patients were categorized in GERD positive and GERD negative groups based on the Mayo GERD questionnaire. Exacerbation of COPD, hospitalization, and drug usage were compared between the two groups.

Results: During the study period, 110 patients with COPD (mean age = 68.0 ± 8.4 years, 87.3% male) were included; 59 (53.6%) patients were GERD positive. There was no significant difference between the GERD positive and GERD negative patients in age, gender, tobacco use, or body mass index. GERD positive patients experienced significantly more acute exacerbations of COPD than patients who were GERD negative (p<0.001). The rate of hospitalization due to COPD exacerbations was significantly higher in GERD positive patients and they had a more severe COPD (p<0.05) and more concurrent use of multiple therapies as compared with GERD negative patients (p<0.05).

Conclusion: Patients with GERD symptoms have more COPD exacerbations and subsequent hospitalizations and drug usage. Clinical trials and preventive strategies for GERD in patients with COPD are warranted.

Key words


Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death with increasing prevalence and mortality rate worldwide [1]. Chronic obstructive pulmonary disease causes high resource utilization due to frequent clinician office visits, acute exacerbations and subsequent hospitalizations, and chronic therapy. Most of the COPD-related health care expenditure is for emergency department visits and hospital care. According to some reports, about half of those who are hospitalized for acute exacerbations require intensive care which demonstrates a high mortality rate as well as the use of healthcare resources in these patients [2].

Exacerbations, a prominent feature of the natural history of COPD, are commonly characterized by an acute increase in one or more of the following symptoms of COPD: cough frequency and severity; dyspnea; and change in the amount and/or character of sputum [1]. Patients frequently experience exacerbations with the median rates of 2.4-3 episodes per year [3]. The underlying mechanisms of acute exacerbations of COPD are still unclear. It is estimated that about 50-60% of the cases are due to respiratory infections (mostly viral and bacterial), 10% are due to environmental pollutions, and 25-35% are of unknown etiology [4].

One of the proposed risk factors for COPD exacerbations is gastroesophageal reflux disease (GERD). Gastroesophageal reflux disease is one of the most commonly diagnosed diseases seen in outpatient clinics [5] with the estimated prevalence of 14-20% in the adult general population [6, 7]. Patients with a variety of chronic respiratory diseases, including asthma [8], cystic fibrosis [9], and idiopathic pulmonary fibrosis [10] have a higher prevalence of GERD compared to general population. Also, upper respiratory symptoms are frequent among patients with GERD [11]. The exact mechanisms of the observed associations between GERD and pulmonary diseases or symptoms are still
unknown. Although evidence is available regarding the association between GERD and COPD, little is known about the effect of GERD on the course of COPD. This study was designed to test the relationship of GERD symptoms with the acute exacerbations of COPD and subsequent hospitalization and drug usage.

**Material and methods**

This retrospective study was conducted from December 2008 to February 2009 in Isfahan, Iran. Consecutive patients from the Pulmonary Clinic of the Dr. Shariati University Hospital who were diagnosed to have COPD based on clinical features and pulmonary function tests (PFTs) were included. The inclusion criteria were FEV1/FVC < 0.7, age ≥ 40 years, and a ≥ 20 pack-year history of smoking or history of exposure to occupational dusts or chemicals for ≥ 10 years. The severity of COPD was evaluated according to the GOLD criteria from mild (stage I) to very severe (stage IV) [12]. Patients with respiratory disorders other than COPD or known esophageal disease (e.g. cancer, achalasia, active peptic ulcer disease) were excluded from the study. The Ethics Committee of the Islamic Azad University, NajafAbad Branch, approved the study and informed consent was obtained from all patients.

A trained general physician interviewed patients regarding times of symptoms worsening, increased amount and purulence of sputum, hospitalization due to exacerbations and use of corticosteroids, bronchodilators, and oxygen therapy in the previous 12 months. Acute COPD exacerbation was defined by the increase in cough frequency and severity, increase in dyspnea, or change in the amount and/or character of sputum [1]. To evaluate symptoms of GERD, the Mayo gastro-oesophageal reflux questionnaire (GORQ) was completed for patients and those who had daily or weekly GERD symptoms were considered as GERD positive [13].

Data were analyzed using SPSS software version 16.0. Independent Sample t-test and Mann-Whitney and chi-square tests were used to compare GERD positive with GERD negative patients. General Linear Models (GLM) were used to find out any relationship between COPD severity and exacerbation and hospitalization frequencies as dependent variables and GERD as fixed factor adjusting for these variables. GLM analyses showed that GERD was significantly associated with exacerbation frequency (p=0.002), COPD severity (p=0.022), and hospitalization frequency (p=0.044) in adjusted models including sex, age, BMI, and smoking. Considering GERD symptoms frequency, the only significant association was found with exacerbation frequency (p=0.034) and this could not be used in models having COPD severity or hospitalization frequency as a dependent variable (p=0.482 and p=0.142, respectively).

**Results**

During the study period, 110 patients with COPD were included. The mean age was 68.0 ± 8.4 years and 87.3% (96/110) were males. According to GORQ, 59 patients (53.6%) were GERD positive; 39 (66.1%) had weekly and 20 (33.8%) had daily GERD symptoms. As presented in Table 1, there was no significant difference between GERD positive and GERD negative patients regarding age, gender, or tobacco use (p=0.05). GERD positive patients, however, had a slightly greater body mass index (BMI) compared with GERD negative patients (p=0.076).

GERD positive patients experienced significantly more acute exacerbations of COPD than patients who were GERD negative (Table I). Also, the rate of hospitalization due to COPD exacerbations was significantly higher in GERD positive patients. Moreover, based on GOLD criteria, GERD positive patients had a more severe COPD compared to GERD negative ones. Comparison of the drug history between the two groups showed that GERD positive patients needed oxygen therapy more frequently (Table I).

Bivariate analysis showed significant correlations between frequency of GERD symptoms and frequency of exacerbations (r=0.323, p=0.001), severity of COPD (r=0.331, p=0.001), frequency of hospitalization (r=0.258, p=0.006), and drug usage (r=0.295, p=0.002). Severity of GERD symptoms was, however, not correlated with these variables. GLM analyses showed that GERD was significantly associated with exacerbation frequency (p=0.002), COPD severity (p=0.022), and hospitalization frequency (p=0.044) in adjusted models including sex, age, BMI, and smoking. Considering GERD symptoms frequency, the only significant association was found with exacerbation frequency (p=0.034) and this could not be used in models having COPD severity or hospitalization frequency as a dependent variable (p=0.482 and p=0.142, respectively).

**Discussion**

As one of the leading causes of death, it is estimated that COPD will rise from the sixth to the third most common cause of death worldwide by 2020. Exacerbations...
are a significant cause of morbidity, mortality, and high resource utilization in COPD patients with unclear etiology in a considerable number of patients [1]. In the present study, we evaluated the association of GERD symptoms with COPD exacerbations and subsequent hospitalization and drug usage. The patients who had daily or weekly symptoms of GERD (GERD positive) were more likely to experience acute exacerbations of COPD. Findings also showed more severe COPD, increased number of hospitalizations, and increased drug usage in those who were GERD positive compared with GERD negative ones, confirmed after adjusting for sex, age, BMI, and smoking. Moreover, frequency but not severity of GERD symptoms was correlated with frequency of exacerbations, severity of COPD, frequency of hospitalization, and more drug usage. The prevalence of GERD symptoms in our sampled population was 53.6%, while population based studies in Iran estimated the prevalence of weekly GERD symptoms as about 20% in the general population aged > 50 years [14] and as 16% in those aged > 60 years [15] which confirms the association of GERD symptoms with COPD. Age, obesity, and smoking can decrease lower esophageal sphincter tone and predispose to GERD [16]. In our study, GERD positive and GERD negative groups were similar regarding these factors, though a slightly greater (not significantly) BMI was found in GERD positive patients.

Few reports are available on the effect of GERD symptoms on COPD severity and exacerbations. In a prospective study, a higher prevalence of weekly GERD symptoms, chronic cough, and dysphagia (based on a questionnaire) was found in patients with COPD (19%, 32%, and 17%) as compared to controls (0%, 16%, and 4%) [17]. The authors also found a trend toward higher prevalence of GERD symptoms in patients with more severe COPD: 23% in those with FEV1≤50% as compared to 9% in those with FEV1>50% of predicted. In our study, COPD was more severe in GERD positive patients than in the GERD negative ones. Moreover, we found a significant correlation between frequency of GERD symptoms and severity of COPD. In another prospective case-control study, using the Mayo GERD questionnaire, GERD symptoms were compared between 100 COPD patients and 150 controls. Similarly, a higher prevalence of GERD symptoms in COPD patients (25%) compared with controls (9%) was found [18]. Frequency of GERD symptoms was significantly associated with decreased FEV1. In both studies [17, 18], patients but not controls reported that respiratory symptoms were associated with reflux symptoms. Interestingly, a large study in the UK, found that patients with a diagnosis of COPD are at a significantly increased risk of receiving a new diagnosis of GERD compared with individuals with no COPD diagnosis and suggested that COPD predisposes patients to GERD rather than vice versa [19].

Regarding COPD exacerbations, in a retrospective questionnaire-based study, a higher rate of exacerbations in patients with GERD symptoms compared to those without GERD symptoms (3.2/yr vs. 1.6/yr, p = 0.02) was found [20]. It was also found that weekly GERD symptoms were associated with more hospitalizations and emergency department visits. Terada et al prospectively examined the association of GERD and its frequency with exacerbations in moderate to severe COPD patients [21]. They found GERD symptoms in 26.8% of COPD patients and in 12.5% of controls. The incidence of exacerbations was higher in patients with GERD symptoms (p<0.01). Also, they found a significant correlation between frequency of GERD symptoms and frequency of exacerbations that was similar to our findings.

Along with questionnaire-based studies, other investigations that were based on esophageal manometry and/or pH-metry also found a high prevalence of GERD (57%-62%) in COPD patients [22, 23]. These studies emphasized that a significant proportion of COPD patients with GERD are asymptomatic or do not have typical symptoms of GERD. Thus, subjective evaluations of patients may underestimate the association of GERD with COPD. It must be noted that none of these studies was based on objective data, though Terada et al measured Exhaled Breath Condensate pH and found it to be inversely correlated with GERD symptom frequency in both patients and controls [20]. Therefore, in contrast to the association of GERD and COPD which is based on objective data, the observed association of GERD with COPD exacerbations is only based on subjective symptoms and needs to be confirmed by further investigations using esophageal manometry and/or pH-metry.

The pathophysiology of the associations between GERD and various pulmonary diseases including COPD is not clear. The proposed mechanisms are microaspiration of the gastric contents leading to airway irritation and increased resistance, vagally mediated bronchoconstriction from esophago-bronchial reflex, and increased bronchial reactivity to other stimuli induced by esophageal acid exposure [24]. Another proposed mechanism is higher intra-abdominal pressure, caused by hyperinflation and respiratory muscle effort, which in turn changes the relationship between the diaphragm and the lower esophageal sphincter decreasing the esophageal sphincter tone [20, 22].

Conclusions

Both retrospective and prospective studies, using either subjective or objective data, demonstrated a high prevalence of GERD in patients with COPD. Our study indicated that having daily / weekly GERD symptoms is associated with an increase in acute exacerbations of COPD, in severity of COPD, in the number of hospitalizations, and drug usage. There is no clear evidence that treatment of GERD in COPD can lead to improvement in symptoms or reduction in respiratory medication usage. We strongly suggest a trial of medical anti-reflux therapy in COPD patients with GERD symptoms evaluating respiratory symptoms and function, exacerbations, hospitalization, and drug usage.
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Conflicts of interest

None to declare.

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