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ORIGINAL ARTICLE

Prevalence and Consequences of Gastroesophageal Reflux Disease on COPD

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ABSTRACT

Background The main determinants for COPD exacerbations are previous history of exacerbation, the severity of the disease, and the presence of comorbidities. However, the role of GER in this setting remains unclear. This study aimed to assess the impact of GER on COPD severity and exacerbation frequency.

Methods: Stable COPD patients were included. Diagnosis of GER was done by GERD questionnaire. Patients were classified into two groups (COPD with GERD & COPD without GERD). Associations of GERD with degree of airway obstruction, frequency of exacerbation. ICU admission and mechanical ventilation in the previous year were assessed. Factors associated with exacerbation were analysed by regression analysis.

Results: The current study included 233 COPD patients and were classified into two groups; Group A: COPD with GERD including 56 patients (24%) and Group B : COPD without GERD including 177 patients (76%).Group A had more ICU admission and mechanical ventilation events in the last year (P= 0.01 & 0.009 respectively).COPD patients with GERD had more severe degree of airway obstruction measured by FEV1 % (56% versus 62% in COPD patients without GERD. When comparing rate of COPD exacerbation in the last year before inclusion, 60% of COPD patients with GERD gave history of two or more exacerbations while in those without GERD, only 33% were exacerbators. Current smoking, GERD and Severity of airway obstruction were the three independent predictors of excaerbation in the studied population.

Conclusions: The frequency of GER in COPD was 24%. COPD with GERD had lower FEV1%, more exacerbation and mechanical ventilation than those without GERD.

Keywords: COPD; GERD; Exacerbation; ICU; Reflux; Mechanical ventilation

INTRODUCTION

COPD is considered one of the leading causes of morbidity and mortality worldwide especially during episodes of exacerbation [1]. Recent studies have suggested that the main determinants for COPD exacerbations are a previous history of exacerbations, a low level of physical activity, the severity of the disease, [2-4] and the presence of comorbidities, such as Gastroesophageal Reflux (GER), congestive heart failure, coronary artery disease, and chronic renal/liver failure [3,5-6]. However, the role of GER in this setting remains unclear especially in our locality with high prevalence of both disease entities. So, the current work was conducted to assess the impact of GER on COPD severity and exacerbation frequency.

METHODS

A cross sectional study was conducted at the outpatient clinics of Tropical Medicine & Chest Departments, Faculty of Medicine, Zagazig University Hospitals, Egypt, from December 2018 to May 2020. The study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Association (Declaration of Helsinki) for studies involving humans. Written informed consent was taken from participants.

Patients: Stable COPD patients (free from exacerbations 4 weeks prior recruitment) were followed up in outpatient clinics of Tropical Medicine & Chest Diseases Departments during the period of the study were included. COPD was diagnosed according to GOLD (2018**)** [7] on the basis of: Presence of risk factor (e.g. smoking) & symptoms suggesting COPD (progressive persistent dyspnea, cough and expectoration) and supported by spirometric evidence of airflow obstruction.

All participants were subjected to the followings:
Complete history taking including comorbidities, smoking status, COPD treatment and number of ICU admission or mechanical ventilation in the last year. Spirometric pulmonary function testing.
Diagnosis of GER by GerdQ questionnaire. The questionnaire was translated into Arabic by a professional translator. Internal consistency was done with Cronbach's α coefficient. A cut-off of 8 (those with a score of 8 or more have a high likelihood of having GER) [7]
Scoring: How many times per week do each of the following symptoms occur per week Answers: Score 0: Occurs on 0 days. Score 1: Occurs on 1 day. Score 2: Occurs on 2-3 days. Score 3: Occurs on 4-7 days.
Questions (Score 0-3 for each based on above)
Burning feeling behind the Breast bone (Heartburn)?
Stomach contents moving up to the throat or mouth (regurgitation) middle of the upper Stomach area?
Nausea?
Trouble getting a good night's sleep because of Heartburn or regurgitation?
Need for over-the-counter medicine for Heartburn or regurgitation?
Interpretation :Total score of 0-2 points (likelihood of GERD: 0%).Total score of 3-7 points (likelihood of GERD: 50%).Total score of 8-10 points (likelihood of GERD: 79%).Total score of 11-18 points (likelihood of GERD: 89%)
Incomplete or invalid responses, patients already on anti-reflux measures, Obesity, those with uncontrolled comorbidities or on long term oxygen therapy were excluded.

STATISTICAL ANALYSIS

Minitab 17.1.0.0 for windows (Minitab Inc., 2013, Pennsylvania, USA) was used. Continuous data was presented as mean (± SD) , and categorical data as number, (%). Independent t-test was used for comparison between two groups of continuous data, and chi square test for comparison between categorical data. Paired t-test used to compare between two means before and after intervention. Multiple linear regressions used to estimate the effect of factors that affecting the number of disease exacerbation. P considered significant if < 0.05.

RESULTS

The current study included 233 COPD patients. The prevalence of GERD in the studied population was 56 out 233 patients (24%), Figure 1 Both groups were matched as regards age, sex, comorbidity profile and smoking status. Group A had more ICU admission and mechanical ventilation episodes in the last year (P= 0.01&0.009 respectively). COPD patients with GERD had more severe degree of airway obstruction measured by FEV1 % (≈56% versus ≈62% in COPD patients without GERD (figure 2). When comparing rate of COPD exacerbation in the last year before inclusion, 60% of COPD patients with GERD gave history of two or more exacerbations while in those without GERD, only 33% were exacerbators **(**figure 3**).**
Factors associated with exacerbation concluded by regression analysis were shown in table 2. Current smoking, GERD and Severity of airway obstruction were the three independent predictors of excaerbation in the studied population.

Table (1): General characteristics of the studied patients

	COPD with GERD (n=56)	COPD without GERD (n= 177)	P
Age (mean, SD)	52.9±6.2	52.76±4.7	0.32
Sex (n, %)			
Male	38 (67.8%)	119 (67.2%)	0.43
Female	18 (32.2%)	58 (32.8%)	
BMI (Kg/m^2) (mean, SD)	22.91±2.05	22.76±2.23	0.13
Smoking status (n, %)			
Current smoker	32(57.1%)	62(35%)	0.053
Ex-smoker	24 (42.9%)	115 (65%)	
Co morbidity (n, %)			
Hypertension	21(37.5%)	66(37.3%)	0.64
Diabetes Mellitus	28(50%)	91(51.4%)	
Ischemic heart disease	13(23.2%)	45(25.4%)	
HCV	4(7.14%)	9 (5.1%)	
FEV1% (mean, SD)	55.8%±2.65%	61.6%±3.32%	0.032

	COPD with GERD (n=56)	COPD without GERD (n= 177)	P
ICU admission last year	12(21.4%)	17(9.6%)	0.01
Mechanical ventilation last year	7(12.5%)	6(3.4%)	0.009

Table (2): Factors associated with exacerbation using regression analysis

Factors	Coefficient	SE	P-Value
GERD	0.041	0.02	0.01
Degree of obstruction (FEV1)	0.37	0.43	0.03
Current smoker	0.41	0.19	<0.001
Use of oral steroids	0.21	0.46	0.34

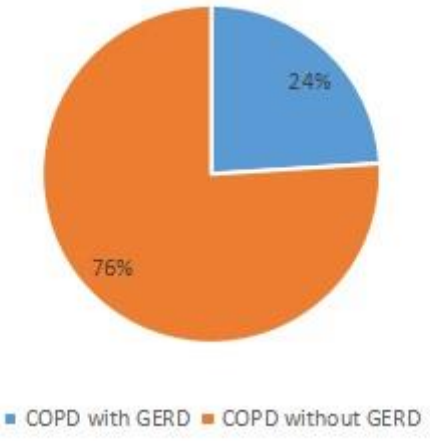

Figure 1: Frequency of GERD in the studied population

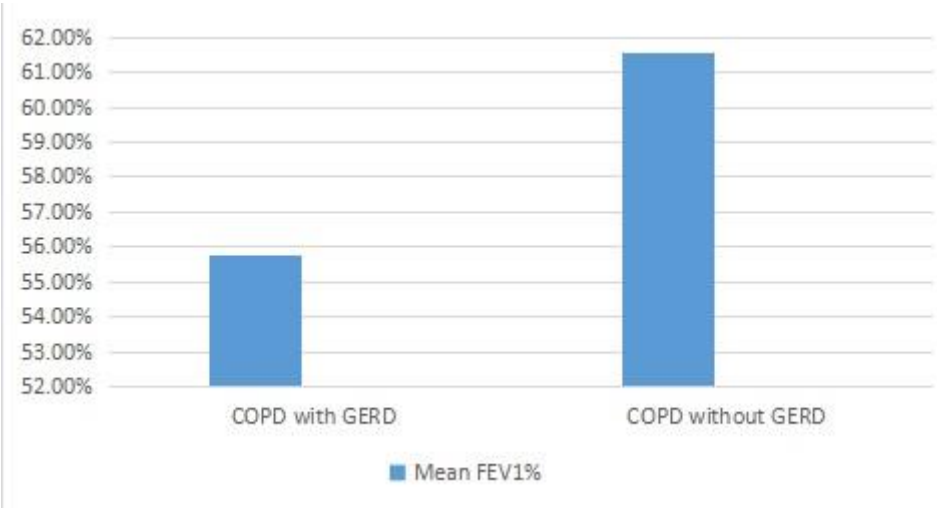

Figure 2: FEV1% in both groups

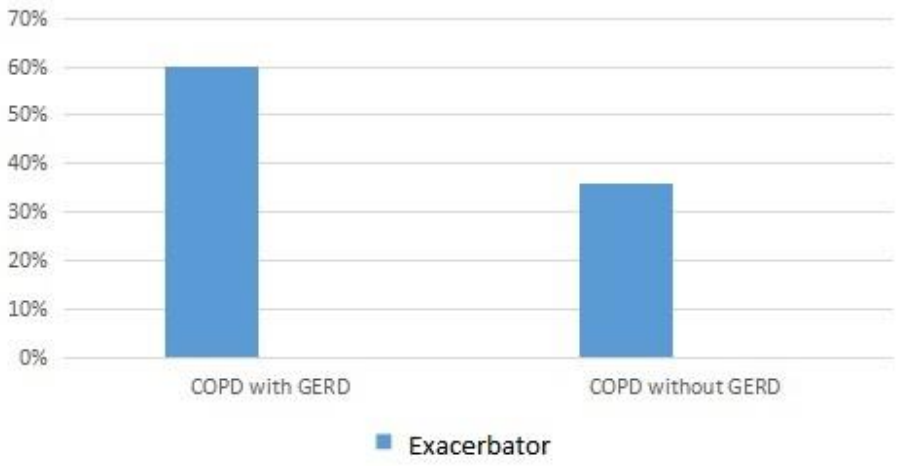

Figure 3: Frequency of exacerbator in both groups

DISCUSSION

The current study included 233 COPD patients after applying GERD questionnaire 56 patients (24%) was diagnosed to have GERD and 177 (76%) patients without GERD. Figure 1**,** so GERD was documented in the studied COPD patients similarly as well as previously found by some studies in Japan [6,8] and by kim et al, [9] and was less than others, as it was 32%–37% in the USA and 53.6% in Iran [10-12]

GERD in COPD patients was found to be more prevalent than general population [13]. GERD in COPD patients was prevalent by a range around 17-54% as found by questionnaires; GerdQ & Gastrointestinal Short Form Questionnaire (GSFQ) [14,15]. When pH monitoring in the oesophagus was done, pulmonary micro aspiration was found to range from 19% to 78% [5-16]. The reported prevalence was greatly varied due to many factors such as the criteria used to diagnose GERD, method used or even history of medications for GERD. Even asymptomatic reflux is prevalent by a rang around 20-74% in COPD patients [17].

In our stud, no significant difference between COPD patients with GERD and COPD patients without GERD as regard age, sex, and comorbidities. Regarding smoking status current smokers were more in COPD group with GERD than COPD without GERD (57% versus 35% respectively) but without significant difference Table 1.

Smoking is common risk factor for both COPD and GERD. Nicotine is associated with decrease in lower esophageal sphincter (LES) tone as relaxation of circular muscle was found to be caused by nicotine. increased acid exposure in upright position was evident after smoking, frequent reflux events and decreased acid clearance due to decreased salivation [9, 18]. Also cough due to tobacco smoking causes the diaphragm to contract and pushing contents of the stomach upwards leading to GERD. Irritation and esophageal inflammation may be induced by nicotine and other contents in the smoke. Delayed gastric emptying is also caused by nicotine which in turn increase incidence of GERD. It was evident that there is decrease in esophageal motility along with decreased both the upper and lower esophageal sphincter pressures caused by the effects of nicotine in COPD patients [19, 20].

In the current study, patients with GERD had more severe COPD in comparison to patients without GERD (lower FEV1 %; 56% vs 62%) (figure 2). This is consistent with many reports [11,12] concluded a declined lung functions in COPD patients with GERD.

Increased severity of COPD by GERD may be explained by two possible mechanisms one of them is bronchoconstriction induced by vagal reflex this reflex bronchoconstriction occurs due to the same autonomic innervation of the tracheobronchial tree and the esophagus. Airway irritation and inflammation is induced by esophageal acid present in the distal esophagus, with release of potent mediators of bronchoconstriction. pulmonary micro-aspiration is the other mechanism that is associated with GERD and badly affect the respiratory disease. During micro-aspiration, there is proximal extension of the refluxed gastric material to the esophagus and then reaching the hypopharynx, causing direct laryngeal or tracheal response, which making patients complaining of coughing, wheezing, or a sensation of breathlessness. [21]

When comparing rate of exacerbation of COPD of the studied patients in the last year before inclusion in the study we found that 60% of COPD patients with GERD gave history of two or more exacerbations while in COPD patients without GERD only about 33% were exacerbators (figure

3). Also in regression analysis, it was revealed that GERD is one of the factors associated with exacerbation in addition to FEV1% & current smoker (table.2).

This is in accordance with a meta-analysis done **by** Huang et al. [23] who found that patients with COPD & GERD were more exacerbated (OR = 5.37; 95% CI: 2.71 to 10.64), (WMD: 0.48 times per year; 95% CI: 0.31 to 0.65).

Also, our results were consistent with another meta-analysis done by Sakae et al [24] who also found that one of the risk factors for COPD exacerbations is association with GERD (RR = 7.57; 95% CI: 3.84 to 14.94), with increased the annual rate of exacerbations (mean difference: 0.79; 95% CI: 0.22 to 1.36).

Some studies explained the possible pathological mechanisms thought to be responsible for acute exacerbation in COPD patients with GERD. The main pathophysiological mechanism depends on the fact that significant airway irritation and injury as a result of reflux of duodeno- gastric contents increasing bronchial reactivity changes and account for respiratory symptoms for example tracheal or bronchial cough reflex [25, 26]. Another to take in consideration is the oesophagus and tracheal bronchus are both innervated by the vagus nerve [27], either of which when stimulated lead to bronchoconstriction through esophago-bronchial reflex and augment cough reflex [28, 29]. In addition, one of the significant contributing factors to increased exacerbations of COPD is pulmonary infection [2]. Aspirations of non-infectious chemicals or bacteria that occurred as a result of reflux or its related swallowing difficulties lead to pulmonary inflammation and should be taken in consideration as a factor increasing exacerbations significantly [10, 30].

Also, in this current study history of admission to ICU and mechanical ventilation in the last year were found to be more in COPD patients with GERD than COPD patients without GERD (Table1) this was in accordance with Tsai et al [31] who reported that COPD patients with subsequent development of GERD during the first year after being diagnosed to have GERD, these patients admitted more to ICU with more mechanical ventilation than those COPD patients who did not develop GERD.

This may be in the same way of the results of our study that showed that COPD patients with GERD were having more exacerbation rate and lower FEV1% these factors which in turn are indicators of more severe exacerbation with bad outcome and poor prognosis .but this was in disagreement with Kim et al [9] who reported that no relation between ICU admission due to COPD exacerbation and the association with GERD.

CONCLUSIONS

The frequency of GERD in the studied population was 24% with more frequent exacerbation, ICU admission and mechanical ventilation and lower FEV1%. Current smoking, degree of obstruction and GERD were factors associated with exacerbation.

Limitation of the current study was the diagnosis of GERD by questionnaire due to limited resources and costy invasive investigations which are not convenient for COPD patients. However, diagnosing GERD in COPD patients by symptoms-based questionnaire as of a great value in the clinical practice as sensitivity, specificity and positive predictive value of GerdQ compared to the gold standard were 72%, 72% and 87%, respectively. In another Korean study GerdQ was found to have a sensitivity of 64.9% and a specificity of 71.4% for the diagnosis of GERD [32,33].

Conflict of Interest: None.

Financial disclosure: None.

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