



## Does gastroesophageal reflux increase chronic obstructive pulmonary disease exacerbations?



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### ABSTRACT

**Background:** The relationship between chronic obstructive pulmonary disease (COPD) exacerbations and gastroesophageal reflux (GER) has been investigated less than asthma-GER. We aimed to evaluate the presence of GER in patients with COPD and its impact on exacerbations.

**Methods:** We included 24 patients with stable mild-moderate stage COPD and 19 volunteers as the control group. We conducted a gastroesophageal reflux disease (GERD) symptom questionnaire, gastroscopy, manometry, and an ambulatory 24-h pH-impedance study.

**Results:** According to the GERD questionnaire, only 5 (20.8%) patients with COPD had typical GER symptoms. According to the 24-h pH-impedance study, the mean DeMeester score (DMS) was  $38.1 \pm 34.6$  in the COPD group and  $13.3 \pm 16.8$  in the control group ( $p = 0.01$ ). The acid reflux (DMS > 14.7) rate was higher in patients with COPD than in controls (73.9% vs 26.3%,  $p = 0.01$ ). The symptom association probability positivity rate was 17.4% ( $n = 4$ ) in the COPD group, which was similar to the controls ( $p = 0.11$ ). The mean proximal extension rate of reflux (Z 17 cm) was  $26.4 \pm 12.9\%$  in the COPD group. The proximal extent of reflux was positively correlated with the number of COPD exacerbations per year ( $p = 0.03$ ,  $r = 0.448$ ). In the motility results, only 2 (20%) patients in the control group had a minor motility disorder. Seventeen (70.8%) patients in the COPD group had a minor motility disorder, and 4 (16.7%) had major motility disorders ( $p < 0.001$ ).

**Conclusion:** In our study, gastroesophageal reflux was frequent in patients with COPD, but only a quarter had typical reflux symptoms. The proximal extent of reflux may trigger frequent exacerbations of COPD.

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### 1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease characterized by progressive persistent airflow limitation [1]. COPD prevalence, morbidity, and mortality rates differ between countries. The World Health

Organization (WHO) reports that there are 63.6 million patients with symptomatic COPD worldwide [2]. There is ongoing research aimed at treating the disease and preventing exacerbations, which may prevent the progression of COPD or its morbidity and mortality. Exacerbations impair quality of life, cause loss in pulmonary function, and have socioeconomic costs [3–5]. Most exacerbations are due to infections or environmental factors, but 30% are related with nonidentified factors [6]. In a number of studies, the prevalence of gastroesophageal reflux (GER) was found to be higher in patients with COPD [7,8]. A recent large-scaled prospective study by Donaldson et al. [9] analyzed frequent and infrequent exacerbations of COPD over a 2-year period in 1832 patients. This study reported that reflux/heartburn was more common in patients with infrequent exacerbations of COPD than patients with frequent exacerbations [9]. Other studies reported high COPD exacerbation

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rates in patients with GER [7,10–13]. However, most studies in the literature were retrospective or used symptom-based questionnaires to evaluate the presence of GER [7,9–13]. The aim of our study was to evaluate the prevalence of GER in patients with COPD using esophageal manometry and 24-h pH impedance study results, and to analyze the relationship between GER and exacerbations of COPD.

## 2. Material and methods

### 2.1. Patients and procedures

The study was conducted between January 2015, and May 2015, in our pulmonology department's outpatient clinic and our gastroenterohepatology clinic. All patients who presented to our pulmonology outpatient clinic during this period and were eligible for the study according to inclusion/exclusion criteria were included into the study. We analyzed 24 patients with mild-moderate COPD and 19 healthy volunteers as controls. The control group comprised volunteers with no known comorbidities, respiratory or dyspeptic symptoms, or antireflux treatment. The data of the control group were taken from a prior study of the affiliated gastroenterology clinic [14].

The patients with COPD had had COPD for at least one year and were taking inhaler therapy in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline criteria [1]. The inclusion criteria for patients with COPD were as follows: being aged 18–85 years, mild-moderate COPD, and stable COPD for at least 4 weeks prior to admission. The exclusion criteria were use of long-term oxygen therapy and noninvasive mechanical ventilation therapy at home, systemic corticosteroid therapy or current anti-biotherapy, COPD exacerbation during the four weeks prior to admission, regular use of proton pump inhibitor, H<sub>2</sub>-receptor blockers, and current use of anti-acid tablets/solutions. All patients enrolled in the study gave informed consent. All patients underwent spirometry in accordance with approved standards (MasterScope PC, CareFusion, Germany) [15]. The patients were questioned for demographic features, comorbid diseases, medications used for COPD, smoking history, number of COPD exacerbations, and exacerbation-related hospitalizations during the previous year. An exacerbation of COPD is an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication [1,16,17]. Frequent exacerbation of COPD was defined as  $\geq 2$  exacerbations or  $\geq 1$  hospitalization for COPD exacerbation in the previous year [1]. To evaluate the severity of dyspnea and severity of symptoms associated with COPD, we used the modified Medical Research Council (mMRC) dyspnea scale (scoring 0–4) and COPD assessment test (CAT) (scoring 0–40) [18,19]. In accordance with GOLD 2015, we defined a patient with COPD as being more symptomatic if they had an mMRC score  $\geq 2$  or CAT score  $\geq 10$  [1].

Body mass index (BMI) was calculated using the formula  $\text{weight [kg]} / \text{height}^2 [\text{m}^2]$ . Also, the patients were asked to complete a gastroesophageal reflux disease (GERD) questionnaire (GerdQ) scoring 0–18. GerdQ is a self-administered 6-item questionnaire designed for symptom-based diagnosis of GER and has been validated in Turkish [20,21]. The scoring of the questionnaire was as follows: 0–7 was defined as *Low likelihood of GERD* and 8–18 as *High likelihood of GERD*.

Twenty-three patients with COPD underwent high resolution esophageal manometry (HRM) and an ambulatory 24-h pH-impedance study. One patient was excluded because he did not tolerate the fitting of the 24-h pH-impedance study equipment and had nasal bleeding. When we detected any pathology with these studies, we also performed gastroesophageal endoscopy under

local anesthesia with lidocaine oral spray and mild sedation with intravenous midazolam (23 patients in COPD group). Esophagitis was classified in accordance with the Los Angeles system (normal, LA-A, LA-B, LA-C, and LA-D) [22].

The control group underwent conventional dry system esophageal manometry (10 patients), an ambulatory 24-h pH-impedance study, and gastroesophageal endoscopy.

### 2.2. Ambulatory 24-h pH-impedance and manometry

Esophageal manometry and 24-h esophageal pH-impedance monitoring were performed in the participants. The location of the lower esophageal sphincter (LES) was determined using manometry (Medical Measurement Systems (MMS) conventional-balloon dry system for controls, MMS high resolution solid state manometry for COPD patients). The manometry results were classified as normal, minor motility disorders (ineffective motility, fragmented peristalsis), and major motility disorders (distal esophageal spasm, Jackhammer esophagus, absent contractility) [23].

pH-impedance was performed using a mobile recording device (Ohmega Impedance-ambulatory pH-meter, MMS, Enschede, Netherlands); the catheter had eight impedance rings and 1 antimony pH measurement loop (Versa Flex Z-Impedance pH meter disposable catheters, Alpine bio Med, Fountain Valley, CA, USA). pH-impedance catheters were passed transnasally under topical anesthesia and positioned 5 cm from the LES to record pH, and impedance at 3, 5, 7, 9, 15, and 17 cm proximal to the LES in the esophageal body. The catheter was not removed until the following day at 08:00 a.m. All participants were encouraged to maintain their normal activities. Event markers on the pH-impedance data logger recorded posture changes. After a 24-h investigation, recordings were uploaded onto a personal computer. Analysis of esophageal pH-impedance was performed by one expert (F.A.). The 24-h trace analysis was conducted manually and automatically using the MMS system. A 50% decrease in impedance compared with the baseline starting 3 cm above the LES and propagation for at least 3 impedance circles was accepted as GER.

- Acid reflux: Defined as reflux below pH 4 for at least 4 s
- Weak acid reflux: Defined as a period of at least 4 s in which there was at least a 1 unit decrease; reflux remains between pH 4–7.
- Alkaline reflux: Defined as reflux with pH above 7 [24].

For each reflux episode, the associated gas-liquid pattern was classified as liquid reflux, gas reflux, and mixed reflux of liquid and gas, as determined by the pH-impedance. For each patient, we measured the total number of reflux events (acid, weak acid, alkaline), percent of time spent at pH < 4, and the total number of episodes at pH < 4 throughout 24 h while upright, supine, and at nighttime. The number and percentage of reflux episodes extending to the proximal esophagus (the number of reflux episodes extending Z 17 cm above the esophageal sphincter), bolus exposure time (BET), DeMeester score (DMS), and symptom association probability (SAP) were also evaluated. SAP positivity was accepted as  $p < 0.05$  with automatic analysis. Zerbib et al.'s studies in healthy people were taken as normal values [25].

### 2.3. Statistical analysis

The Statistical Package for Social Sciences (SPSS) version 22.0 for Windows (IBM SPSS Statistics Data Editor) was used for statistical analysis of the data. Descriptive data were given as number of participants and frequency. Categorical variables were expressed as

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