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A M E R I C A N C O L L E G E O F
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Role of Gastroesophageal Reflux Symptoms in Exacerbations of COPD*

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Background and aims: The impact of gastroesophageal reflux disease (GERD) on exacerbations of COPD has never been evaluated. The aims of this investigation were to determine the prevalence of gastroesophageal reflux (GER) symptoms in COPD patients and the effect of GER on the rate of exacerbations of COPD per year.

Methods: A questionnaire-based, cross sectional survey was performed. Subjects were recruited from the outpatient pulmonary clinics at the University of Florida Health Science Center/Jacksonville. Included patients had an established diagnosis of COPD. Exclusion criteria were respiratory disorders other than COPD, known esophageal disease, active peptic ulcer disease, Zollinger-Ellison syndrome, mastocytosis, scleroderma, and current alcohol abuse. Those meeting criteria and agreeing to participate were asked to complete the Mayo Clinic GERD questionnaire by either personal/telephone interview. Clinically significant reflux was defined as heartburn and/or acid regurgitation weekly. Other outcome measures noted were frequency and type of COPD exacerbations. Statistical analysis was performed using the Fisher exact test for categorical data and the independent *t* test for interval data.

Results: Eighty-six patients were enrolled and interviewed (mean age, 67.5 years). Male patients accounted for 55% of the study group. Overall, 37% of patients reported GER symptoms. The mean FEV₁ percentage of predicted was similar in those with or without GER. The rate of exacerbations of COPD was twice as high in patients with GER symptoms compared to those without GER symptoms (3.2/yr vs 1.6/yr, *p* = 0.02).

Conclusions: The presence of GER symptoms appears to be associated with increased exacerbations of COPD. (CHEST 2006; 130:1096–1101)

Key words: COPD; exacerbations; gastroesophageal reflux disease

Abbreviations: ED = emergency department; GER = gastroesophageal reflux; GERD = gastroesophageal reflux disease; PFT = pulmonary function test; PPI = proton pump inhibitor

Gastroesophageal reflux disease (GERD) is a common esophageal disorder; 40% of the US adult population have symptoms monthly.¹ Microaspiration of gastric contents and/or vagal nerve-induced bronchospasm from gastric acid irritation of the esophagus may contribute to the observed asso-

ciation between GERD and pulmonary disease or symptoms. In this regard, pulmonary diseases associated with GERD may include pneumonia, pulmonary fibrosis, asthma, or chronic bronchitis.^{2–4} The latter may be a manifestation of COPD, suggesting that GERD may be a risk factor for acute exacerbation of COPD.

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Acute exacerbations of COPD are a major cause of morbidity and mortality in patients with COPD.^{5,6} An acute exacerbation of COPD is defined by the presence of worsening dyspnea, increased sputum production, or the development of purulent sputum, and may be accompanied by hypoxemia and worsening hypercapnia.⁷⁻¹⁰ Patients with COPD have, on average, 2.4 to 3 acute exacerbations per year.⁹⁻¹¹ Risk factors for acute exacerbations include airway irritation from active smoking,^{3,12} environmental factors,¹³⁻¹⁵ and/or upper respiratory tract infection.¹³ In this regard, microaspiration of gastric contents and/or vagal irritation from gastroesophageal reflux (GER) may constitute airway irritants and thus represent a potential pathogenic mechanism for acute exacerbations of COPD. On this basis, we theorized that in patients with COPD, GER may represent a risk factor for acute exacerbations of COPD. To test this question, we classified COPD patients according to the presence or absence of GER symptoms, and assessed the number of COPD exacerbations for the previous year.

MATERIALS AND METHODS

Patients

From January 2003 through January 2004, 91 patients with a diagnosis of COPD were recruited from the pulmonary specialty clinics at the University of Florida Jacksonville. All patients with a diagnosis of COPD presenting to pulmonary clinic for routine health care during the study period were eligible for inclusion. Two investigators (I.R.A. and M.P.) attended pulmonary clinic sessions on a random basis determined monthly by other clinical responsibilities, and approached consecutive patients with a diagnosis of COPD for study inclusion. All patients approached (n = 91) during the clinic sessions to participate agreed to do so.

This study was approved by the University of Florida Jacksonville Institutional Review Board, and all patients provided in-

formed consent. Inclusion criteria were as follows: FEV₁/FVC ratio \leq 70% on pulmonary function tests (PFTs),¹⁰ age \geq 40 years, and a \geq 20 pack-year history of smoking. Patients were excluded if the following disorders were present: respiratory disorders other than COPD; known esophageal disease such as cancer, achalasia, stricture, active peptic ulcer disease, Zollinger-Ellison syndrome, mastocytosis, scleroderma; or current abuse of alcohol defined as more than three alcoholic drinks per day.

Protocol

Eligible patients with a known diagnosis of COPD by PFTs were asked to complete a standardized questionnaire. This questionnaire queried for GER symptoms and COPD exacerbations (Fig 1). GER symptoms were derived from completion of the previously validated Mayo Clinic GERD questionnaire.¹⁶ In brief, each patient was asked to classify and characterize the frequency of either reflux or heartburn symptoms over the past year. Those patients that had weekly symptomatic reflux were classified as GERD(+). Patients were also asked about the number and type of acute COPD exacerbations in the past year. An acute COPD exacerbation was defined as worsening dyspnea, increasing volume of sputum, or purulent sputum in conjunction with physician-initiated use of corticosteroids or antibiotics, hospitalization, or emergency department (ED) visit during the previous 12 months. The questionnaire was written at a fourth-grade reading level and was thus easily understood by all patients.

Statistical Analysis

All data are expressed as the mean \pm SD. Groups were compared using the Fisher exact test for categorical data and the independent *t* test for interval data. A multiple regression model was used to control for unequal distributions of patient characteristics between with and without GER symptoms.

RESULTS

The patient demographics are shown in Table 1. Ninety-one patients participated in the investigation, 5 were unavailable for follow-up, and 1 was disqualified once for enrolling twice (Fig 1). The mean age

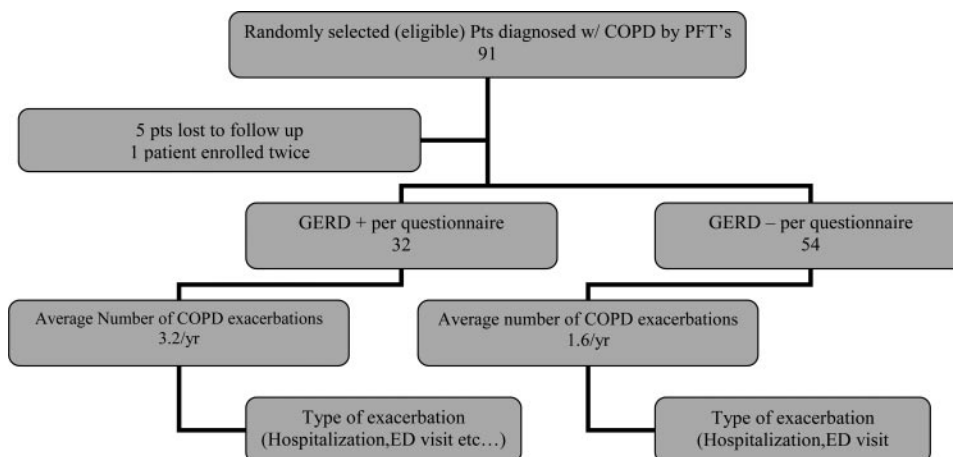


FIGURE 1. Patient selection diagram. pts/Pts = patients; w/ = with.

Table 1—Patient Demographic Data*

Variables	GERD(+), n = 32	GERD(-), n = 54	p Value
Mean age, yr	66.0 ± 9.9	68.8 ± 7.0	0.16
Male gender	59.0 (19)	53.7 (29)	0.65
Tobacco use	25.0 (8)	18.5 (10)	0.58
Mean FEV ₁ , % predicted	45.9 ± 16.0	40.7 ± 17.6	0.16
Mean body mass index, kg/m ²	27.4 ± 6.2	26.3 ± 5.9	0.41
Alcoholic drinks, per wk	1.2 ± 0.80	1.3 ± 0.75	0.62
Coffee, 240 mL/wk	1.5 ± 2.1	1.0 ± 1.1	0.25

*Data are presented as mean ± SD or % (No.).

was of 67 ± 8.3 years. Forty-eight patients (55%) were male. Thirty-two of the eligible surveyed patients (37%) were categorized as GERD(+) or having weekly symptomatic reflux over the past year. The groups were similar in gender, age, FEV₁ percentage of predicted, continued smoking, body mass index, alcoholic drinks per week, and weekly coffee consumption.

Figure 2 indicates the number of COPD exacerbations between GERD(+) and GERD(-) groups. GERD(+) patients had significantly more exacerbations than the GERD(-) group (3.2 ± 3.1 exacerbations/yr vs 1.6 ± 1.6 exacerbations/yr, p = 0.02). A multiple regression model with the number of COPD exacerbations as the response variable showed that the presence of weekly GERD symptomatology was associated with the number of exacerbations (p = 0.007) controlling for age (p = 0.004), severity of airflow obstruction (p = 0.7), gender (p = 0.36), and tobacco use (p = 0.154) [R² = 0.24]. This means that GERD is a possible predictor of the number of exacerbations, but this study was not designed to demonstrate causality. Patients had an

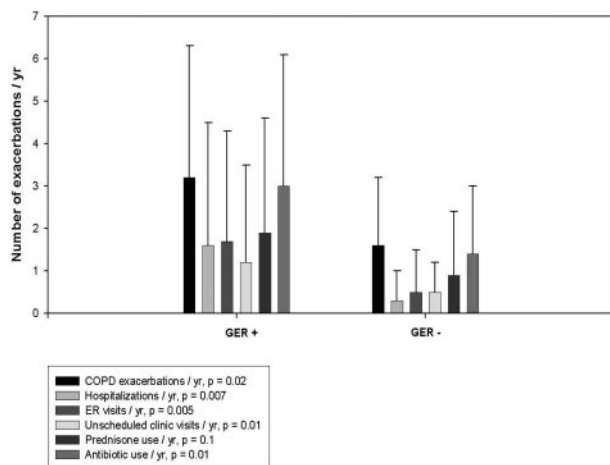


FIGURE 2. Average number and type of exacerbations in GERD(+) and GERD(-) groups.

average of 1.56 more exacerbations (95% confidence interval, 0.44 to 2.69) with weekly GER symptoms compared with no GER symptoms adjusting for the other factors.

Figure 2 compares weekly GERD(+) and GERD(-) patients with regard to exacerbation frequency, type of exacerbation (hospitalization, ED, or unscheduled clinic visit), and either prednisone or antibiotic use for the exacerbation in the past year. Patient who had weekly GER symptoms had significantly more hospitalizations related to their COPD than those without weekly GER symptoms (p = 0.007). All types of exacerbations were also significantly increased in the weekly GERD group with the exception of prednisone use, which showed only an increased numerical trend in usage.

As can be seen on Table 2, the majority of patients received a type of antireflux therapy. A subanalysis of the patients receiving antireflux therapy (Table 3) demonstrated that the number of COPD exacerbations in the patients who were receiving proton pump inhibitors (PPIs) and had controlled or non-symptomatic GERD had an average of 1.6 ± 0.9 (mean ± SD) exacerbations per year compared with the symptomatic GERD group receiving PPIs (3.7 ± 3.3 exacerbations; p = 0.09), indicating a trend toward more yearly exacerbations. Twenty-nine of the total 86 patients were receiving a combination of at least two different types of antireflux medications (Fig 3).

The number of exacerbations stratified by severity per the Global Strategy for the Diagnosis, Management, and Prevention of COPD (Global Initiative for Chronic Obstructive Lung Disease criteria) are shown on Table 3.¹⁷ These data indicate that patients with symptomatic GERD had more exacerbations independent of the severity of airflow obstruction. With regard to smoking, 8 of the GERD(+) patients (25%) smoked and 10 of the GERD(-) patients (18%) smoked. Further analysis of this subgroup of current smokers is shown on Table 3 and depicts a trend in the frequency of COPD exacerbations between the GERD(+) smokers and GERD(-) smokers. Also noted is that both smokers and non-

Table 2—Medication Use in the Study Population*

Variables	GERD(+), n = 32	GERD(-), n = 54	p Value
PPIs (n = 33)	16 (48)	17 (54)	0.11
H2RA (n = 19)	10 (52)	9 (47)	0.17
Antacids (n = 44)	23 (52)	21 (47)	0.03
No therapy (n = 25)	4 (15)	21 (86)	< 0.011

*Data are presented as No. (%). H2RA = histamine H₂-receptor antagonist.

Table 3—Annual Exacerbations of COPD Stratified by Therapy, Severity, and Smoking Status*

Variables	Exacerbations		p Value
	GERD(+), n = 32	GERD(-), n = 54	
GER treatment			
PPI (n = 33)	3.7 ± 3.3	1.6 ± 0.9	0.09
No PPI (n = 53)	2.6 ± 3.0	1.6 ± 1.9	0.1
H2RA (n = 19)	2.3 ± 2.3	1.1 ± 1.0	0.3
No H2RA (n = 67)	3.6 ± 3.4	1.7 ± 1.7	0.02
Antacid (n = 44)	3.3 ± 2.9	1.7 ± 1.3	0.4
No antacid (n = 42)	3.0 ± 3.9	1.5 ± 1.8	0.08
Airflow obstruction severity			
Moderate (n = 2)	2.7	1.2	0.1
Severe (n = 29)	3.9	2.7	0.1
Very severe (n = 55)	3.1	2.0	0.1
Smoking status			
Nonsmoker (n = 68)	3.6 ± 3.3	1.6 ± 1.7	0.01
Current smoker (n = 18)	2.0 ± 2.3	1.6 ± 1.2	0.9

*Data are presented as mean ± SD or mean.

smokers had a greater number of yearly exacerbations if they had concomitant symptomatic GERD.

DISCUSSION

The aims of this study were as follows: (1) to demonstrate the prevalence of symptomatic GERD in our sampled population, and (2) to determine if there was an epidemiologic association between GER symptoms and exacerbations of COPD. The most significant finding in this study is that patients with the diagnosis of COPD and weekly GER symptoms have more acute exacerbations of COPD than

patients with COPD without GER symptoms. We also found that in our sampled population, a prevalence of 36% of COPD patients had weekly GER symptoms despite frequent use of antireflux medications. This is higher than estimates of weekly GER symptoms in the general US adult population of 14 to 19%.^{18–20} This phenomenon of increased prevalence of GER symptoms has been previously observed in patients who have asthma and also in patients with COPD.^{3,12} Other significant observations were the increased number of hospitalizations, ED, and unscheduled clinic visits as well as antibiotics usage was greater in the weekly GERD COPD population compared with the GERD(-) population.

Patients with more severe COPD are well known to have a higher risk of exacerbation than those who have less severe COPD.¹² A subanalysis of the number of exacerbations stratified by severity as per the Global Initiative for Chronic Obstructive Lung Disease criteria¹⁷ showed that the patients who were GERD(+) had a trend toward more exacerbations independent of severity although not statistically significant (Table 3). The majority of our patients were ex-smokers. Smokers were allowed to participate in this study to see if there existed a difference in the number of exacerbations between weekly GERD(+) smokers and GERD(-) smokers. As seen in Table 3, there is a numerical trend toward a higher number of exacerbations in the smokers with weekly GER symptoms than in those smokers who have no symptoms of GERD, further supporting the association between GER symptoms and exacerbations of COPD.

Finally, patients who were receiving antireflux medications were permitted to participate in this study in order to see if the use of such medications would be protective in the exacerbations of COPD. Our data have shown that there is a trend toward more exacerbations of COPD in the GERD(+) groups whether they were receiving antireflux therapy or not (Tables 1–3). At this point, we cannot conclude that the use of antireflux therapy was or was not protective against exacerbation. The majority of our GERD(+) population was consuming a form of antireflux therapy but still had more exacerbations than patients without GER symptoms. This of course is expected since they are, after all, having symptomatic reflux. The question is why they are still having symptomatic reflux despite therapy. Does this mean they were being inadequately treated for their reflux symptoms? Or were noncompliant with therapy? Further research will be needed to answer this question.

Although a statistically significant association between GER symptoms and exacerbations of COPD

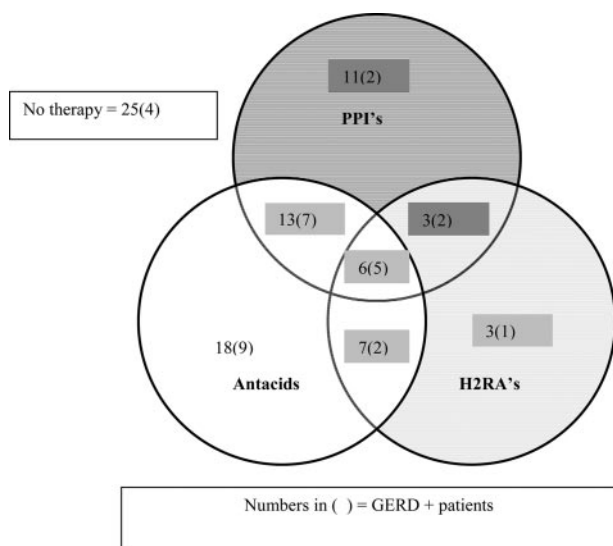


FIGURE 3. Use of antireflux medication by each group.

was observed, our major limitation was that we cannot establish a cause-and-effect association from the cross-sectional data gathered. This can be said for most observational studies^{18,21} that have identified GERD as a potential trigger for respiratory disorders. Other limitations were the possibility of recall bias when patients responded to questions that required the use of long-term memory; also, the design of our study is cross-sectional, which limits our results to a specific point in time. Finally, a sample size of 86 was used because this was a sufficient enough number to reach statistical significance when comparing the average number of yearly COPD exacerbations between the GERD(+) and GERD(-) groups, although not enough for other *post hoc* analysis, which showed only a numerical trend to support our hypothesis.

A limited number of studies have found a link between GERD and COPD, El-Serag and Sonnenberg²² noted in a retrospective study an increased risk of COPD as well as other pulmonary diseases in patients with reflux esophagitis. Andersen and Jensen³ found an increased prevalence of esophageal disease in patients with self-reported COPD. Mokhlesi et al⁴ identified COPD patients per American Thoracic Society guidelines¹⁶ and found a trend toward an increased prevalence of GER symptoms in patients with severe COPD as opposed to those who did not have COPD, although this difference did not reach statistical significance. And more recently, Casanova et al²³ found that patients with severe COPD have a high prevalence of asymptomatic GER.

Presently, there are no other published studies that have examined the association between GER symptoms and exacerbations of COPD. The findings of this study suggest a possible modifiable risk factor in exacerbations of COPD. The implications of this link may not only be of clinical significance but also of economic significance, considering the cost of a single hospitalization, and taking into account that in the year 2000 there were 726,000 hospitalizations, 1.5 million ED visits, and 8 million office visits all due to exacerbations of COPD.²⁴

CONCLUSIONS

We conclude that patients who have COPD and also have reflux symptoms at least once a week are more likely to have an increased number of COPD exacerbations when compared to COPD patients who are either asymptomatic or have GER symptoms less than once a week. This is true despite no significant difference in FEV₁ percentage of predicted between the two groups. We also conclude

that COPD patients with weekly GER symptoms and COPD are twice as likely to be hospitalized, have an ED visit, or unscheduled clinic visit when compared with COPD patients with less frequent GER symptoms.

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