



ORIGINAL ARTICLE

STUDY OF GASTRO ESOPHAGEAL REFLUX DISEASE IN COPD PATIENTS

By

Adel Khattab,¹ Khaled El-Karmouty,² Tamer Aly,¹ Asmaa Abdel Azeem¹

¹Chest Department, Faculty of Medicine, Ain Shams University, ²Internal Medicine Department, Faculty of Medicine, Ain Shams University

This study included 30 COPD inpatients in chest and internal medicine departments in Ain Shams University Hospital, 15 of them with moderate COPD and 15 of them with severe COPD (by Gold 2007),⁽¹⁾ 25 were males and 5 were females (active or passive smokers).

The aim of the work was to study the prevalence of GERD in COPD patients and its effect on the number of exacerbations of COPD.

Both groups were subjected to history taking, full clinical examination, full laboratory investigations, radiography, spirometry, arterial blood gases and upper GIT endoscopy and biopsy.

Results revealed that the prevalence of GERD in COPD patients was 53.3% in the moderate group, 73.3 in the severe group (total= 63.3%) by endoscopy & was 66.6% in the moderate group, 93.3 % in the severe group ((total= 80 %) by biopsy being more prevalent in the severe group of COPD. GERD severity increases as the degree of COPD increases (there were more patients with advanced grades among severe COPD than the moderate group). GERD increases with increase in the smoking (pack/year) both in moderate & in the severe groups. Moreover, there was increase in the frequency of exacerbations of COPD in GERD patients both in moderate & in the severe groups.

From this study we conclude that GERD is common in COPD patients being more among severe COPD. Also GERD increases the number of exacerbations of COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality throughout the world; it is the fourth leading cause of death in the world.⁽²⁾ COPD is a preventable and treatable disease with some significant extra pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow

limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles and gases.⁽¹⁾ Gastro esophageal reflux disease (GERD) is the collective term used to describe abnormal reflux of gastric content into the esophagus as well as the symptoms and mucosal disease associated with it. Clinical manifestations of GERD include heart

burn, regurgitation, dysphagia, chest pain, cough and other esophageal symptoms. GERD is known to cause erosive esophagitis and Barrette esophagus. Currently upper GIT endoscopy is the main clinical tool for visualizing esophageal lesions.⁽³⁾

Micro aspiration of gastric contents and/or vagal nerve induced bronchospasm from gastric acid irritation of the esophagus may contribute to the observed association between GERD and pulmonary disease or symptoms.⁽⁴⁾

Gastroesophageal reflux disease (GERD) may cause, trigger, or exacerbate many pulmonary diseases. The physiologic link between GERD and pulmonary diseases has been extensively studied in asthma; however, in other pulmonary diseases, including interstitial pulmonary fibrosis (IPF), cystic fibrosis and COPD, the link has been less well studied.⁽⁵⁾

The prevalence of reflux symptoms is related to the degree of obstruction of airflow in patients with COPD.⁽⁶⁾

METHODS AND SUBJECTS

This work was conducted in chest and internal medicine units of Ain- shams university Hospital.

This study included 30 subjects with established diagnosis of COPD based on the criteria stated by Gold 2007 for diagnosis of COPD, 25 of them were males and 5 were females (active or passive smokers).

There exclusion criteria were:

1. Respiratory disorders other than COPD (such as asthma or IPF).
2. Known esophageal disease such as cancer, achalasia, stricture or active peptic ulcer.

All were subjected to the following:

1. Full history taking (questionnaire is included in the sheet) and clinical examination.
2. Routine laboratory investigations:
 - Random blood sugar (RBS).
 - Liver function tests (AST, ALT, total and direct bilirubin, total proteins and

albumin.).

- Kidney function tests (BUN, creatinine).
 - Complete blood count (CBC).
 - Prothrombin time and partial thromboplastin time (PT and PTT).
3. Chest X ray (postero- anterior view).
 4. Arterial blood gases analysis (ABG) with particular attention to PH, PaCO₂ & PaO₂ and O₂ saturation.
 5. Pulmonary function tests: in the form of spirometry including forced vital capacity (FVC) expressed as percent predicted, forced expiratory volume in 1st second (FEV₁) expressed as percent predicted, ratio of FEV₁ to FVC expressed as a percentage and average flow rate between 25% and 75% of the FVC (FEF 25 - 75).
 6. Upper GIT endoscopy and biopsy showed mucosal changes at the lower end of the esophagus, described by:

Los Angeles Criteria for classification of GERD.⁽⁶⁾

Grade	Description
A	One (or more) mucosal break not longer than 5mm that does not extend between the tops of two mucosal folds.
B	One (or more) mucosal break more than 5mm long that does not extend between the tops of two mucosal folds.
C	One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference.
D	One (or more) mucosal break which involves at least 76 % of the esophageal circumference.

Analysis of data was done by IBM computer using SPSS (statistical program for social science version 12).

RESULTS

This study included 30 subjects divided into 2 groups:

Group 1: 15 COPD patients with moderate chronic obstructive pulmonary disease.

Table 1. Description of different variables among moderate group.

Variables	Mean +SD	Range
Age	62.6+12	46-84
Gender		
Male	12	80%
Female	3	20%
Smoking (pack/year)	25+11	10-50
FVC%	87+15	64-116
FEV1%	62+7	51-79
FEV1/FVC	60.7+5.8	51-70
FEF25-75%	36.2+13.6	15-56
Duration of COPD in years	5.6+3	2-12

Group 2: 15 COPD patients with severe chronic obstructive pulmonary disease.

Table 2. Description of different variables among severe group.

Variables	Mean +SD	Range
Age	55.6±8	40-68
Gender		
Male	13	86.7%
Female	2	13.3%
Smoking (pack/year)	37±16	10-60
FVC%	65.2±14	45-92
FEV1%	36±8	22-48
FEV1/FVC	47.6±8	32-64
FEF25-75%	21±10	6-40
Duration of COPD in years	7±5	3-17

Table 3. Comparison between both groups as regard prevalence of GERD.

GERD	Total N=30	Moderate N=15	Severe N=15	P
No	11(36.7%)	7(46.7%)	4(26.7%)	>0.05
Yes	19(63.3%)	8(53.3%)	11(73.3%)	NS

This table shows no statistically significant difference could be detected between both groups as regard GERD by using Fisher exact test. However, the number of GERD patients among severe COPD is more than that in the moderate group & the overall prevalence of GERD in COPD patients (by endoscopy) in the taken sample was 63.3%.

Table 4. Comparison between both groups as regard GERD grades.

GERD Grades	Moderate N=15	Severe N=15	χ ²	P
No	7 (46.7%)	4 (26.7%)		
Grade A	2 (13.3%)	3 (20%)		
Grade B	4 (26.7%)	4 (26.7%)	1.8	>0.05
Grade C	1 (6.7%)	2 (13.3%)		NS
Grade D	1 (6.7%)	2 (13.3%)		

This table shows no statistically significant difference could be detected between both groups as regard GERD grades by using chi-square test.

Table 5. Comparison between GERD and non GERD cases as regard different variables among moderate group.

Variables	No GERD N=7	GERD N=8	T	P
Age	60±9	64±14	0.7	>0.05
BMI	25.8±4	30±5	1.8	>0.05
FVC	85.6±7	88.7±20	0.4	>0.05
FEV1	64.4±3.9	60±9	1	>0.05
FEV1/FVC	60±5	60.6±6	0.03	>0.05

BMI: body mass index.

This table shows no statistically significant difference could be detected between both groups (non GERD & GERD) among moderate COPD patients as regard different variables by using unpaired t-test.

Table 6. Comparison between GERD and non GERD cases as regard different variables among severe group.

Variables	No GERD N=4	GERD N=11	T	P
Age	57.8±5.6	54.8±9	0.6	>0.05
BMI	25±5	28.7±6	1.02	>0.05
FVC	69±14	52.5±8	2.3	<0.05
FEV1	38±6	32±11	1.3	>0.05
FEV1/FVC	49±10.5	47±7.5	0.6	>0.05

This table shows that FVC was lower among GERD cases with statistically significant difference in between both groups (non GERD & GERD) among severe COPD patients by using unpaired t-test. On the other hand there is no significant difference as regard other variables.

Table 7. Comparison between GERD and non GERD cases as regard smoking (pack / year) among moderate group.

Smoking (Pack /year)	No GERD N=7	GERD N=8	T	P
Mean +SD	16.7±4	32.1±4	3.2	<0.01

HS

This table shows that smoking (pack/year) was higher among GERD cases with statistically highly significant difference in between both groups by using unpaired t-test.

Table 8. Comparison between GERD and non GERD cases as regard smoking (pack / year) among severe group.

Smoking (Pack /year)	No GERD N=4	GERD N=11	T	P
Mean±SD	15±7	42±14	2.5	<0.01

HS

This table shows that smoking (pack/year) was higher among GERD cases with statistically highly significant difference in between both groups by using unpaired t-test.

Table 9. Comparison between GERD and non GERD cases as regard frequency of exacerbations among moderate group.

Frequency of exacerbations	No GERD N=7	GERD N=8	T	P
Mean ±SD	3±0.8	5+0.9	3	<0.01

HS

This table shows that frequency of exacerbations was higher among GERD cases with statistically highly significant difference in between both groups by using unpaired t-test.

Table 10. Comparison between GERD and non GERD cases as regard frequency of exacerbations among severe group.

Frequency of exacerbations	No GERD N=4	GERD N=11	T	P
Mean±SD	3±0.9	4+1.6	2.1	<0.05

S

This table shows that frequency of exacerbations was higher among GERD cases with statistically significant difference in between both groups by using unpaired t-test.

Table 11. Correlation between GERD grade versus other variables among moderate group.

Variables	GERD grade		Significance
	R	P	
Age	0.02	>0.05	NS
BMI	0.44-	<0.05	S
Pack/year	0.87	<0.01	HS
FEV1	0.34	>0.05	NS
Number of GERD symptoms /wk.	0.86	<0.01	HS
Duration of COPD in years.	0.03	>0.05	NS
Frequency of exc. In last year.	0.88	<0.01	HS

This table shows highly significant positive correlation between GERD grade versus smoking (pack/year), symptoms/week and frequency of exacerbations of COPD in last year and significant correlation versus BMI by using Spearman correlation test. On the other hand no significant correlation versus other variables.

Table 12. Correlation between GERD grade versus other variables among severe group.

Variables	GERD grade		Significance
	R	P	
Age	0.06	>0.05	NS
BMI	0.45-	<0.05	S
Pack/year	0.77	<0.01	HS
FEV1	0.30	>0.05	NS
Number of GERD symptoms /wk.	0.80	<0.01	HS
Duration of COPD in years.	0.05	>0.05	NS
Frequency of exc. In last year.	0.54	<0.05	S

This table shows highly significant positive correlation between GERD grade versus smoking (pack/year), symptoms/week and significant correlation versus BMI and frequency of exacerbations by using Spearman correlation test. On the other hand no significant correlation as regard other variables.

Table 13. Comparison between both groups (moderate & severe COPD) as regard different GERD symptoms.

Variables	Total	Moderate N=15	Severe N=15	X2	P
Heart burn					
No	2(6.7%)	1(6.7%)	1(6.7%)	0.0	>0.05 NS
Yes	28(93.3%)	14(93.3%)	14(93.3%)		
Regurgitation					
No	8(26.7%)	2(13.3%)	6(40%)	2.7	>0.05
Yes	22(73.3%)	13(86.7%)	9(60%)		NS
Vomiting					
No	18(60%)	8(53.3%)	10(66.6%)	3.2	>0.05
Yes	12(40%)	7(46.7%)	5(33.3%)		NS

This table shows no significant difference between both groups as regard different symptoms by using chi-square test. In general, there was 93% of COPD patients were complaining of heart burn, 73% of regurgitation & 40% of vomiting, other symptoms like haematemesis, melena, and dysphagia were 10%.

Table 14. Distribution of both groups as regard biopsy results.

Biopsy	Moderate N=15	Severe N=15	Total N=30
Negative	5 (33.3%)	1 (6.7%)	6 (20%)
Positive	10 (66.6%)	14 (93.3%)	24 (80%)

This table shows the prevalence of positivity in both groups (the overall prevalence of GERD by biopsy=80%).

DISCUSSION

Many studies have discussed the impact of gastroesophageal reflux disease on asthma, (especially in children). But few have done regarding COPD. Lopes et al (2002)⁽⁸⁾ has documented that only tiny amount of acids is necessary to trigger pronounced symptoms of cough, wheezes and airway obstruction evidenced by physiologic measurements such as spirometry; which may support the explanation of the possible association between GERD and COPD.

The aim of this work is to study the prevalence of GERD in COPD patients and its effect on the number of exacerbations of COPD that may show a possible modifiable risk factor that by control may improve health status and decrease the cost of health care and hospitalizations.

In this study 30 patients with known diagnosis of COPD by GOLD criteria; (2007)⁽¹⁾ were chosen from inpatient chest and internal medicine departments of Ain Shams University hospital. Patients were excluded if they have respiratory disorders other than COPD (such as asthma or IPF), or known esophageal disease (such as cancer, achalasia, stricture or active peptic ulcer); they were divided into 2 groups:

Group 1: with moderate COPD (15 patients).

Group 2: with severe COPD (15 patients).

Graded by spirometry. Both were asked to complete questionnaire then both underwent upper GIT endoscopy for assessment of the GERD state.

In this study there was no significant difference between moderate and severe COPD patients and between GERD and non GERD subjects regarding the age and there was no correlation between age and GERD grade either in moderate and in severe patients.

In the present study, there was no significant difference between moderate and severe COPD patients. However it is to some extent lower in severe group which is in agreement with a study done by Raafat (2006)⁽⁹⁾ denoting that BMI is lower

among COPD patients being more severely lowered in more advanced cases; that might be caused either by chronicity or by steroid induced myopathy which may affect diaphragmatic muscle mass and depresses diaphragmatic contractility. Also there was no significant difference between GERD & non GERD patients. In this study, (in either moderate or severe COPD) there was inverse relation between BMI & GERD grade (i.e. GERD increases while BMI decreases); which is against the fact that obesity is a risk factor for GERD denoted by Hampel et al., 2005.⁽¹⁰⁾ This means that in these COPD patients, the advanced GERD grades may be more related to the severity of COPD rather than obesity.

Regarding smoking (pack/year), there was significant difference between moderate and severe COPD patients being higher in severe group. Also there was highly significant difference between GERD and non GERD subjects being higher among GERD patients in either the moderate or the severe groups and it was found that in GERD subjects, there was positive highly significant correlation between smoking (pack/year) and GERD grade. i.e. increase in the smoking (pack/ year), increases the GERD grade; that correlates with the fact that smoking causes marked reduction in LESP by its content of nicotine which may block the cholinergic control mechanism and delay gastric emptying which predispose to gastroesophageal reflux.⁽¹¹⁾

Considering the frequency of exacerbations of COPD, there was highly significant difference between COPD patients with GERD and COPD patients without GERD being higher among GERD patients in either moderate or severe COPD. Within GERD patients, there was positive highly significant correlation between GERD & frequency of exacerbations of COPD in the moderate group & significant in the severe group; that correlates well with a study done by Ivan et al (2006)⁽¹²⁾ based on questionnaire Cross sectional survey on large number (91) outpatient clinics' patients with established diagnosis of COPD that noted that the rate of exacerbations of COPD was twice as high in patients with GERD symptoms compared to those without GERD symptoms. It

has the limitations of any cross sectional study; one of them was the recall bias, when patients responded to questions that required the use of long term memory, which is partially overcome in our study by a confirmatory investigation (upper GIT endoscopy).

Studying the symptomatology of GERD there was no significant difference in GERD symptoms in moderate and severe COPD patients, and the most common complaint was heartburn followed by regurgitation. It was obvious also that not all complaining patients showing evidence of GERD endoscopically. We noticed that 93.3% were complaining of heart burn, for example, while 63.3% were having GERD endoscopically among COPD patients. This may be explained by the possibility of the presence of non erosive GERD that can't be identified by endoscopy and appears by biopsy which revealed 80% prevalence.

There was no significant difference as regarding GERD grades in between moderate and severe COPD. However, there were more number of patients with more severe GERD grades in severe than in moderate COPD which means that GERD grade increases with increase severity of COPD.

Few other studies tried to find an association between COPD and GERD; a study done by Robert et al (2007) (13) on 41 COPD outpatients with a mean FEV1 OF 24% (advanced COPD) on their baseline medical regimen at the time of the study, using dual probe 24 h esophageal PH monitoring and manometry revealing that the prevalence of GERD was 57% and only one third of the patients reported symptoms (heart burn and/or regurgitation) and concluded that GERD is common in advanced COPD patients who were often asymptomatic and have a relatively high prevalence of isolated abnormal proximal reflux; but it has the limitation of that all the patients were advanced COPD patients and the findings might not be applicable to individuals with milder disease. The present study involved moderate & severe cases, the prevalence with endoscopy was; in the moderate group 53.3% & in the severe group 73.3 % (total =63.3%) & 93.3 % .60 % were complaining of GERD symptoms (heart burn and

regurgitation, respectively).

A study done by Mokhlessi et al (2001)⁽¹⁴⁾ using GERD questionnaire given to 140 patients and observed a high prevalence of GERD symptoms in patients with COPD with a trend to higher prevalence in severe COPD and increased use of acid suppressive medications among patients with COPD than the control; but this study had a limitation of not having objective measurements of acid reflux.

Upper GIT endoscopy identified only the erosive GERD therefore there may be still a portion of GERD patients who can't be identified by the upper GIT endoscopy (16.7%) and can be identified by biopsy.

Finally GERD is common in COPD patients, proved by upper GIT endoscopy, also GERD grade increases as the degree of obstruction of COPD increases and once diagnosed should be treated and followed for early detection of complications.

Also patients who have COPD and GERD are more likely to have an increased number of COPD exacerbations, when compared to non GERD group.

REFERENCES

1. GOLD. Global initiative for chronic Obstructive Lung Disease; Global strategy for diagnosis, management and prevention of chronic obstructive lung disease. Gold Website, WWW.gold COPD.org. 2007;2,3,33,35,36,37,69.
2. Lopez AD, Shibuya K, Held LS. Chronic obstructive pulmonary disease: current burden and future projections. *Eur Respir J.* 2006;27:397-412.
3. DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Am. J Gastrointerol.* 2005;100:190-200.
4. Weaver EM. Association between gastro esophageal reflux and sinusitis, otitis media, and laryngeal malignancy: a systematic review of the evidence. *Am J med.* 2003;115:81S-9S
5. Susan M, Harding MD. Pulmonary manifestations of GERD: pathophysiology and management, @www. google.com. 2004.

6. Andereu M, Delgado S, Seoane A. Gastroesophageal reflux (GER) symptoms in patients with chronic obstructive pulmonary disease (COPD). *Gut*. 2003;52:A124.
7. Lundell LR, Dent J, Bennett JR. Endoscopic assessment of esophagitis: clinical and functional correlates and further validation of the Los Angeles Classification. *Gut*. 1999;45:172-80.
8. Lopes FD, Alvarenga GS, Quiles R. Pulmonary responses to tracheal or esophageal acidification in guinea pigs with airway inflammation. *J Appl Physiol*. 2002;93:842-7.
9. Raafat RH. assessment of nutritional status of COPD and Bronchial asthma patients in relation to severity and duration of the disease. MSC thesis, chest department, Ain Shams University. 2006.
10. Hampel H, Abraham NS, El-Serage HB. Meta-analysis: and the risk for gastro esophageal reflux disease and its complications. *Ann. Int. Med*. 2005;143:199-211.
11. Richter JE, Castell DO. Drugs, foods and other substances in the cause and treatment of reflux esophagitis *Med. Clin N Am*. 1981;65:1223-34.
12. Ivan ER, Mark DO and Peter W. Role of gastroesophageal reflux symptoms in exacerbation of COPD, chest. 2006;130:1096-01.
13. Robert RK, Kay S and Joanne LB. High prevalence of proximal and distal gastroesophageal reflux disease in advanced COPD *Chest J*. 2007;06-2246 V1.
14. Mokhlesi B, Morris AL, Huang CH. Increased prevalence of gastroesophageal reflux symptoms in patients with COPD. *Chest*. 2001;119:1043-48.