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ORIGINAL ARTICLE

Metabolic Syndrome is associated with increased risk of acute exacerbation of COPD: a preliminary study

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Abstract Studies have confirmed correlation between metabolic syndrome (MetS) and chronic obstructive pulmonary disease (COPD). However, to date, no studies have analyzed correlation between exacerbations of COPD (ECOPD) and MetS. The aim of this preliminary study was to examine if presence of MetS increases the frequency and duration of ECOPD. Patients with COPD were prospectively enrolled and followed between March 2008 and September 2009. Medical records, pulmonary function tests, chest X-rays; laboratory test results were gathered to establish the presence of COPD and MetS. Patients were divided in two groups; with and without MetS. The ECOPD was defined as worsening of symptoms requiring increased use of rescue medications and/or need for either systemic steroids or antibiotics or that led to emergency room visit or hospitalizations during 12 months follow-up. A total of 106 patients were recruited, 29 with MetS and 77 without. The mean exacerbation of COPD frequency was 2.4 ± 0.8 in MetS group versus 0.68 ± 0.6 in the control group during the follow-up period ($P < 0.001$). Mean duration of each exacerbation was 7.5 ± 1.5 days in patients with MetS versus 5 ± 2.4 days in patients without. Serum C-reactive protein ($r = 0.31$, $P = 0.001$), fasting blood glucose ($r = 0.55$, $P < 0.001$), and triglycerides ($r = 0.251$, $P = 0.01$) were positively and significantly correlated with exacerbation frequency. This study demonstrates an association between ECOPD and its duration with the MetS. The systemic inflammation induced by common cytokines may explain the linkage between the two conditions.

Keywords Exacerbation of COPD · Metabolic Syndrome · Inflammation

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Introduction

Chronic obstructive pulmonary disease (COPD) is complicated by frequent exacerbations which are characterized by an increase in cough, sputum production, worsening dyspnea, or sputum purulence [1]. Although respiratory infections are suspected to be the main culprit for the exacerbations, other factors such as industrial pollutants, allergens, sedatives, congestive heart failure, and pulmonary embolism, have also been identified [1–4]. Despite the frequency and the consequences of the exacerbation of COPD (ECOPD), its underlying pathological mechanism remains poorly understood. Only a handful of studies have focused on the functional [5, 6] and inflammatory [6–9] aspects of the ECOPD. Nevertheless, there is compelling evidence that COPD can no longer be considered a disease limited only to the lungs [2]. Several studies have shown that it is associated with a wide variety of systemic consequences; most notably: systemic inflammation [10, 11]. Despite the fact that COPD is associated with significantly increased cardiovascular morbidity and mortality [11, 12], underlying mechanistic link between impaired lung function and cardiovascular risk is not well described.

Metabolic syndrome (MetS) is a complex disorder and an emerging clinical challenge, presenting with abdominal

obesity, elevated triglycerides (TG), atherogenic dyslipidemia, elevated blood pressure, high blood glucose levels, and/or insulin resistance [13]. The association between the MetS with inflammation is well documented; elevation of pro-inflammatory cytokine levels reflects their overproduction by the enlarged adipose tissue mass [14]. In this respect, COPD and the MetS share common pathophysiologic features; chronic systemic inflammation has been implicated as a major causative factor for both disorders. Recently, it has been shown that the presence of MetS is frequent in patients with COPD [15–17], nearly half of them having one or more components of the syndrome [18, 19]. Systemic inflammation, which is common among both the conditions, may increase the risk of ECOPD in MetS patients, yet while searching the literature for the terms "COPD exacerbation and metabolic syndrome," no study surfaces. The purpose of this preliminary study was to look for any relationship between the MetS and the frequency and the duration of ECOPD and a possible role of systemic inflammation in this linkage.

Results

A total of 112 patients were initially recruited. We were unable to establish mandatory four encounters in two patients with MetS and three without MetS during the study period and hence they were excluded from the study. Cause of loss for follow-up was one death in MetS group which was unrelated to the patient's respiratory status. Thus, the study included a total of 106 patients, 29 with MetS (M:F = 25:4) and 77 without (M:F = 67:10). Study population characteristics in both groups are depicted in Table 1. At the baseline, 68 (64%) of the patients were in mild-to-moderate stage (I and II) while 38 (36%) were severe and very severe stage (III and IV) of the disease (Table 2). All mild-to-moderate COPD patients were receiving inhaled long-acting β_2-agonists and/or anticholinergic agents while severe to very severe ones were receiving an additional oral theophylline and inhaled corticosteroid.

There was no statistically significant difference between the two groups with respect to age, gender, and smoking habits, baseline pulmonary function tests (PFTs), and the stage of COPD (Tables 1 and 2). Body mass index (BMI) and waist circumference were significantly higher in MetS group than in control group. Patients in the control group were overweight, yet not obese (BMI: 27.2 ± 5.7). Fasting blood glucose (FBG), TG, and C-reactive protein (CRP) levels were also higher and high-density lipoprotein cholesterol (HDL-C) was lower in MetS group. There was no significant difference between two groups in terms of total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels.

Table 1 Functional and biochemical parameters in patients with and without Metabolic Syndrome

	Patients with MetS $N = 29$	Patients without MetS $N = 77$	P
Gender (F/M)	5/24	10/67	0.57
Age	64.9 ± 6.7	67.3 ± 9.1	0.20
BMI (kg/m^2)	30.3 ± 5.6	27.2 ± 5.7	*0.014*
Smoking (pack years)	43.5 ± 20	47.5 ± 22	0.41
FEV_1 (L)	1.7 ± 0.7	1.5 ± 0.6	0.08
FEV_1 % Predicted	67 ± 24.8	61.2 ± 23.4	0.27
FVC (L)	3.1 ± 0.9	3.01 ± 0.85	0.64
FVC % Predicted	91.2 ± 23.5	91 ± 20.6	0.97
FEV1/FVC	57.2 ± 12.5	51.3 ± 13.9	0.055
FEF 25–75%	22.9 ± 14.8	23.3 ± 14	0.85
TLC (L)	5.9 ± 1.9	7.1 ± 1.9	0.21
IC (L)	1.9 ± 0.56	1.9 ± 0.4	0.86
SPO_2 (%)	91.1 ± 4.1	92.2 ± 4.2	0.20
FBG	121.9 ± 27.7	96.3 ± 15.9	*<0.001*
Total cholesterol	176.6 ± 57.8	180 ± 41	0.75
LDL	98.9 ± 37.8	101.7 ± 36	0.73
HDL	37 ± 12.3	48 ± 14.9	*0.001*
TG	169 ± 98.4	103.7 ± 39.7	*0.002*
CRP	14.4 ± 4	5.5 ± 2.4	*<0.001*
Exacerbation frequency (/ year)	2.4 ± 0.8	0.68 ± 0.6	*<0.001*

BMI Body mass index, *FBG*, fasting blood glucose level (mg/dl), *CRP* C-reactive protein, *LDL* low-density lipoprotein (mg/dl), *HDL* high-density lipoprotein (mg/dl), *TG* triglyceride (mg/dl)

$P < 0.05$: statistically significant

Table 2 Distribution of COPD stage and the Metabolic Syndrome

COPD stage (GOLD)	Patients with MetS $N = 29$	Patients without MetS $N = 77$	P
I	10 (34%)	19 (24.7%)	0.768
II	10 (34%)	29 (37.6%)	
III	7 (24%)	25 (32.4%)	
IV	2 (7%)	4 (5.2%)	

Of 106 patients, 32 (30.1%) were able to keep all four planned visits to the pulmonary department and had no exacerbations. Sixteen (15%) of patients had total of more than four visits during the study period including visits to emergency room (ER) or to their family physician for ECOPD. Twenty-nine (27.3%) patients had total of three; twenty-one (19.8%) had two, and remainder of eight patients (7.5%) had one clinical visit. If patients missed their scheduled appointment, they were contacted by the phone to collected required information for the study. All

Table 3 Number of exacerbations in patients with and without Metabolic Syndrome

Number of exacerbations	Patients with MetS *n* (%)	Patients without MetS *n* (%)
0	1 (3.4%)	31 (40.25%)
1	3 (10.3%)	39 (50.6%)
2	9 (31%)	7 (3.4%)
3	15 (51.7%)	0 (0%)
4	1 (3.4%)	0 (0%)

Table 4 Mean exacerbations according to the stage of COPD

COPD stage (GOLD)	Number of exacerbations in patients with MetS (mean)	Number of exacerbations in patients without MetS (mean)
I	2	0.4
II	2.4	0.5
III	2.7	0.9
IV	3.5	1.5

of the study patients kept at least one clinical visit to the pulmonary department.

The mean exacerbation frequency was 2.4 ± 0.8 (0–4) in patients with MetS and 0.68 ± 0.6 (0–2) in patients without MetS during the 12 months of follow-up period ($P < 0.001$) (Table 1). Mean duration of each exacerbation was 7.5 ± 1.5 days in patients with MetS versus 5 ± 2.4 days in patients without. Number of exacerbations during follow-up in both groups is shown in Table 3.

Number of unplanned visits to outpatient clinics in MetS group was significantly higher than the control group (4.8 ± 0.5 vs. 3.2 ± 0.9, $P = 0.015$). Similarly number of ER visits in MetS group was significantly higher than control group (2.4 ± 0.3 vs. 1.6 ± 0.4, $P = 0.018$). A total of 44 hospitalizations were recorded in the MetS group, while 39 hospitalizations in patients without MetS. Mean number of hospitalizations in MetS group was also higher than control group (1.5 ± 0.4 vs. 0.5 ± 0.4, $P < 0.001$). Mean duration of hospitalization was 5 ± 1.7 days in patients with MetS versus 4.5 ± 2.3 days in patients without ($P = 0.076$).

Use of steroids was left to the discretion of the primary physician and was prescribed on as needed basis. In other words, on several occasion ECOPD was treated without the use of steroids. A total of 25 scripts were written for steroid in MetS group while totally 40 scripts to patients without MetS. Mean number of prescription for either oral or intravenous steroids during exacerbations for patients with MetS was 0.86 ± 0.51, while that for the patients without MetS was 0.51 ± 0.57. The difference in the frequency of steroid use was statistically significant between the two groups ($P = 0.005$).

A positive correlation between exacerbation frequency and CRP, FBG, and TG levels was found using univariate analysis ($P = 0.001$; $r = 0.31$: $P < 0.001$; $r = 0.55$: $P = 0.01$; $r = 0.251$, respectively).

When the parameters of pulmonary functions were studied, there was a negative correlation between exacerbation frequency and the baseline post-bronchodilator forced expiratory volume at 1 second (FEV_1) (*L* and %) ($P = 0.043$; $r = -0.199$ and $P = 0.012$; $r = -0.244$, respectively). All other PFT parameters were not significantly related with exacerbation frequency. Measurement of baseline SpO_2 by pulse oximetry also negatively correlated with exacerbation frequency ($P < 0.001$; $r = -0.336$). Besides, there was a positive correlation between the stage of the disease and frequency of exacerbation for the entire group ($P = 0.012$, $r = 0.242$) as well as that for the patients with MetS ($P = 0.012$, $r = 0.462$) and without MetS ($P = 0.000$, $r = 0.439$) (Table 4).

Discussion

The role of systemic inflammation has been demonstrated in the pathogenesis of both stable and ECOPD by various studies [10, 20–24]. During ECOPD levels of serum cytokines (IL-6, TNF-α) and CRP are significantly increased [24–26]. How and why individuals with COPD develop systemic inflammation is uncertain, yet several potential mechanisms have been speculated: effect of tobacco [21], an inflammatory process spilling over into the systemic circulation [20, 22], tissue hypoxia [27], and effect of skeletal muscles, particularly during exercise [28, 29].

Inflammation has been proposed to be of major pathophysiological importance for the development of MetS [30]. Markers of inflammation, such as CRP, tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) have repeatedly shown to be elevated also in patients with MetS [31–37]. Based on these knowledge, it could be hypothesized that both conditions share similar inflammatory pathways involving IL-6 and TNF-α.

C-reactive protein is a sensitive marker for systemic inflammation and has been shown to up-regulate the production of pro-inflammatory cytokines. There is a linear increase in CRP levels with an increase in the number of metabolic disorders including MetS [38]. Circulating CRP levels are also higher in stable COPD patients and may thus be regarded as a valid biomarker of low-grade systemic inflammation [39, 40]. In our study, we found a significant difference in CRP levels among the COPD patients with and without MetS consistent with the literature. Therefore, we suspect that increased serum CRP level in stable COPD

patients indicate chronic subclinical systemic inflammation and could be a predictor for coexisting MetS.

The association between MetS and COPD has been previously described [15, 18, 19]. This study now demonstrates association between ECOPD and the MetS. We suspect that the systemic inflammation induced by the common cytokines may explain this linkage. The systemic inflammation of MetS seems to be a trigger for ECOPD. Even though, we did not study the cytokine levels in each group; it is not difficult to explain this relationship based on the involved cytokines.

In our study, CRP levels were significantly different between the two groups, suggesting that the degree of basic systemic inflammation was higher in COPD patients with MetS than without. Additionally, number of exacerbations, unplanned visits to our outpatient clinics and ER visits per patient during the follow-up period and the mean duration of each exacerbation were higher in patients with MetS. Mean hospitalization time was also longer in patients with MetS. Therefore, we suspect that the risk and the severity of exacerbations might have increased in patients with MetS due to the increased systemic inflammation. This hypothesis is further supported by more frequent use of steroids during ECOPD in patients with MetS than otherwise. Accordingly; medical approaches to the control MetS may help to decrease the severity and the frequency of ECOPD and need for systemic steroids.

There was no difference among PFTs, stages of COPD, and the presence or absence of MetS. For this reason, we considered that MetS could be a risk factor for the frequency and duration of exacerbations but not related to the severity of COPD. However, this belief needs to be further substantiated with larger studies as we had total of only 29 patients in the MetS group. Besides, there was a positive correlation between the stage of the disease and frequency of exacerbation for the entire group as well as for the patients with MetS and without MetS (Table 4). Incidentally, according to the stage of the disease number of patients in each group was too small to calculate any significant difference with adequate power. We did have much higher number of males in both groups, most likely reflecting popularity of smoking among men in our population.

In our study, exacerbation frequency was found to be increased in patients with DM as well. This finding could be attributed to hyperglycemia predisposing to infections [41–43].

Adipose cell enlargement in MetS leads to a pro-inflammatory state with increased secretion of IL-6 and TNF-α. The link between systemic inflammation and MetS may reflect an ongoing cytokine-mediated acute phase response initiated by the innate immune system [36, 44, 45]. In our study, BMI was significantly higher in MetS group which may have lead to frequent ECOPD. However, in any individual the effects of obesity on respiratory function depend on the mass and anatomical distribution of the excessive adipose tissue on the thorax and abdomen [46]. A relationship between COPD and obesity is increasingly recognized with the prevalence of between 18% and 54% [18, 47, 48], although the nature of this association remains unknown. The risk of developing obesity is increased in COPD as a result of either reduced physical activity or use of glucucorticoids [49]. Obesity may independently play a role in ECOPD, but to date there is no data to further substantiate this hypothesis.

There are some weaknesses in our study. We solely relied on the patients' declaration of symptoms which makes our study somewhat subjective. Second, we did not perform any specific tests to rule out other causes of ECOPD. However, we designed the study simple and as practical as possible without disturbing patient's routine life style.

In summary, we believe that our preliminary study suggests a relationship between MetS and ECOPD. We hypothesize that MetS may be a risk factor for increased number of exacerbation and its duration in COPD patients due to the shared inflammatory cytokine burden. A larger study using objective parameters of ECOPD and systemic inflammation predictors including IL-6 and TNF- α is required.

Materials and methods

Study population

This was a single-center, prospective case–control study involving patients with COPD. The Ethics Committee for Human Studies approved the protocol. All participants provided informed written consent. Patients with COPD who reported for regular follow-up at our Pulmonary Diseases Department, between March 2008 and September 2009 were consecutively recruited and followed. The study duration includes 7 months of enrollment and 12 months of follow-up periods. Medical records, PFTs, chest X-rays; biochemical laboratory test results of all patients were recorded to establish the diagnosis of COPD and MetS.

Diagnosis of COPD was based on current Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1], based on past smoking history, clinical evaluation and PFTs (FEV1 $< 80\%$ of predicted value and FEV1/forced vital capacity [FVC] $< 70\%$), showing irreversible or partial airflow obstruction (a FEV_1/FVC $< 70\%$, and with a response to 200 ml and 12% to a bronchodilator test with salbutamol) [50].

Patients who suffered with ECOPD and received systemic corticosteroids within prior 2 months, those who

could not properly perform the PFTs, those with symptoms of any infections or using anti-inflammatory medications were excluded from the study.

Exacerbation of COPD was defined as a sustained (lasting 48 h or more) worsening of dyspnea, cough, or sputum production leading to an increase in the use of rescue medications and/or supplementation with additional medications [1, 51]. Actual management of the ECOPD was left to the discretion of the primary physician.

End of COPD exacerbation was defined as (1) when the frequency of use of rescue medications and patients' symptoms had returned to the base line or (2) when patients were ready to be discharged from the hospital. Length of steroid therapy was not considered in this definition because the patients were to complete 2–3 weeks course of the medication irrespective of resolution of their symptoms.

All patients were advised to be followed-up in our COPD clinic at an interval of every 3 months. Patients who were unable to visit our clinic periodically were contacted by phone calls during the 12 months follow-up period to investigate any additional information related to the study. An unplanned visit to the doctor's office or to the ER where there was a complete access to the medical records was considered as a follow-up visit. Patients were questioned about any symptoms suggestive of exacerbations by and their duration by a daily diary between the out patients visits. Patients were to note the answers to the questions related to increasing dyspnea, sputum production or purulence, use of rescue medications, oral steroids, antibiotics or visits to doctor's office, ER, or hospitalizations. All patients were followed for a minimum period of 12 months after the enrollment.

A minimum of four encounters during the study period were required for a patient to complete the study, last encounter being in the last month of the study. An outpatient visit, a telephone contact initiated by the physician, unplanned visit to the primary physician or the ER for ECOPD were satisfactory medical record were available and hospitalization for the each episode of exacerbation was consider as an "patient encounter." If we were unable to establish four encounters during the study period on a given patient, that individual was excluded from the analysis.

Frequency rate for the ECOPD was calculated for 12 months. Diagnosis of ECOPD was based on a thorough review of patient's symptoms. Frequency and duration of hospitalization, if took place during the study period was also recorded.

The diagnostic criteria proposed by the Adult Treatment Program III (ATP III) of the National Cholesterol Education Program (NCEP) has been used for the definition of MetS [52]: (1) abdominal obesity, defined as a waist circumference in men $>$ 102 cm and in women $>$ 88 cm; (2) serum triglycerides $\geq$ 150 mg/dl or greater; (3) serum high-density lipoprotein in men $<$ 40 mg/dl and in women $<$ 40 mg/dl; (4) blood pressure $\geq$ 130/85 mm Hg; and (5) fasting plasma glucose $\geq$ 110 mg/dl. Measurements of subjects' height, weight, and waist circumference were recorded by the same physician in all patients. Waist circumference was measured with a folding tape at the level of the umbilicus in a horizontal plane. BMI was obtained by dividing the body weight (kg) to the square of height (m).

Patients with COPD were divided in two groups; patients with MetS and without MetS (control group).

Pulmonary function testing

A clinical spirometer (SensorMedics Vmax spectra 229, Bilthoven, The Netherlands) was used for all tests, and each respiratory maneuver was demonstrated by the same laboratory technician for the subject before testing. Each subject performed a maximal expiratory flow maneuver in the sitting position. FEV_1 and FVC were measured and then FEV_1/FVC was calculated. Standard PFTs including spirometry and lung volumes were obtained according to the previously described guidelines [53, 54]. These results were used to define disease severity according to the GOLD classification [1]. Oxygen saturation (SpO_2) was measured in all patients on room air at the time of enrollment.

Laboratory analysis

Each venous sample was drawn after a minimum fasting period of 12 h. All samples were collected between 08.00 and 09.00 am. Serum concentrations of FBG, HDL-C, LDL-C, TG, and CRP were measured. Serum glucose was measured by the glucose oxidase technique (Roche Diagnostics GmbH, Mannheim, Germany). The serum insulin level was assayed with a solid-phase competitive chemiluminescent enzyme immunoassay (Diagnostic Product Corp., Los Angeles, CA). Total cholesterol, HDL-C, and TG triglyceride concentrations were measured by enzymatic assay (Boehringer, Mannheim, Germany). LDL-C was calculated using Friedewald's formula [LDL-C = total cholesterol − (HDL-C + triglyceride/5)]. Serum CRP was assayed by a particle-enhanced immunoturbidimetric assay, using a Hitachi Modullar PP Analyzer according to the manufacturer's specifications (Roche Diagnostics GmbH, Mannheim, Germany).

Statistical analysis

All continuous data were expressed as the mean ± SD. Data were analyzed with SPSS software (Statistical

Package for the Social Sciences, version 15.0, SSPS Inc., Chicago, IL, USA). Statistical comparisons were performed by means of independent-samples *t*-tests for data with a normal distribution and χ^2 tests. Chi-square test and *t*-test were used to compare the parameters of the patients with and without MetS. All parameters were expressed as mean values ± standard derivation (SD). Pearson's correlation analysis was used to explore the relationship between parameters. A P value < 0.05 was considered statistically significant.

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