The relationship between metabolic syndrome and chronic obstructive pulmonary disease

Therese Ghatas

Background Metabolic syndrome is a condition frequently found among individuals. It predisposes affected individuals to systemic inflammation and physical inactivity. The aim of the present study was to investigate the frequency of metabolic syndrome and C-reactive protein (CRP) levels as markers of systemic inflammation in stable chronic obstructive pulmonary disease (COPD) patients with different severity levels and in an age-matched and sex-matched control group.

Patients and methods One hundred COPD patients and 50 controls were included in this study. The severity level in patients with COPD was determined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages I–IV, we measured the characteristics of the metabolic syndrome and systemic inflammation (high-sensitivity C-reactive protein).

Results The frequency of metabolic syndrome was found to be higher in the patient group than in control individuals, especially in GOLD stages I and II. Abdominal obesity, hypertension, and hyperglycemia components of metabolic syndrome were significantly more prevalent in the patient group ($P<0.05$ for all). Increased CRP levels were higher in control and patient groups in all GOLD stages, with metabolic syndrome than without metabolic syndrome. *P*-values for control group and GOLD stages I–IV were 0.044, 0.483, less than 0.01, 0.048, and 0.076, respectively.

Conclusion Metabolic syndrome is substantial among stable COPD patients, especially in the early stages (GOLD stages I–II). Abdominal obesity, hypertension, and hyperglycemia were significantly more in COPD patients with metabolic syndrome. An impaired profile of CRP levels was found in patients and control groups with metabolic syndrome than in individuals without metabolic syndrome.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease, and is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients [1].

Systemic inflammation and physical inactivity have been identified as relevant extrapulmonary markers of the severity of COPD, as both conditions are related to exacerbations, hospitalizations, and mortality in this patient population [2].

The origin of systemic inflammation in patients with COPD is unclear [3]. In the general population, physical inactivity and metabolic syndrome are important determinants of systemic inflammation [4]. These two determinants of systemic inflammation have not been investigated in detail in patients with COPD so far. Watz *et al*. [5] found higher values of systemic inflammation associated with reduced physical activity in patients with COPD; however, the complex relationship of metabolic syndrome, physical inactivity, and the severity of lung disease with systemic inflammation in patients with COPD is unknown. Approximately 40–50% of the individuals greater than 60 years of age in industrialized countries meet the criteria for metabolic syndrome [6]. Metabolic syndrome represents a cluster of risk factors (abdominal obesity, atherogenic dyslipidemia, hypertension, and insulin resistance) that predispose affected patients to systemic inflammation [7], cardiovascular disease [6], and physical inactivity [8]. The frequency of metabolic syndrome and its role in systemic inflammation and physical inactivity in patients with COPD is unknown. As hypertension, diabetes, and/or dyslipidemia can be found frequently in patients with COPD, the frequency and associated consequences of metabolic syndrome need further study in this population [9].

Aim

To investigate the prevalence of metabolic syndrome in COPD patients with different the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages and control individuals. High-sensitivity C-reactive

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protein (hs-CRP) levels were also evaluated in patient and control groups to define the level of systemic inflammation and its correlation with the presence of metabolic syndrome.

Patients and methods

Study population

The study was designed as a case–control study. The work was carried out on 100 stable outpatients with stable COPD with different levels of severity (86 men and 14 women), who were admitted from the outpatient clinic of Al-Sahel Teaching Hospital. The diagnosis of COPD was made according to GOLD 2013 criteria [1]. The study was approved by the local ethics committee of general organization of Teaching Hospital and Institutes (GOTHI). Written informed consent was obtained from each participant.

Fifty participants were selected as the control group; age and sex were matched with the patient group, with normal spirometry and without any infectious or inflammatory diseases that could increase C-reactive protein (CRP) levels. The criteria for exclusion included patients having an acute exacerbation (an increase in cough, sputum production, worsening dyspnea, or sputum purulence within 3 weeks) as per GOLD 2013 [1], any infectious or inflammatory diseases such as collagen vascular diseases, or inflammatory bowel disease that could cause an increase in CRP levels.

Pulmonary function testing

Spirometry was performed using a Pulmonary Spirometry Instrument (Micro Medical Limited, Rochester, Kent, UK) by the same technician using the same spirometer. The staging of COPD was made using GOLD criteria: GOLD I (mild): forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC)<70% and FEV1≥80%; GOLD II (moderate): FEV1/FVC<70% and FEV1<80 and ≥50%; GOLD III (severe): FEV1/FVC<70% and FEV1<50 and ≥30%; GOLD IV (very severe): FEV1/FVC<70% and FEV1<30% GOLD 2013 [1].

Blood sampling and analyses

A venous blood sample was collected from each individual after a 12-h fasting. Blood samples were taken in the stable phase of COPD patients. Plasma glucose, triglyceride (TG), and high-density lipoprotein (HDL) were measured using Hitachi 912 (Hitachi; Hitachi, Ltd., Tokyo, Japan). hs-CRP levels were measured using Hitachi 912 (CRP levels >5 μg/l were accepted as 'high', and otherwise 'low').

The diagnosis of metabolic syndrome

Body weight and height were measured and the BMI was calculated by dividing the weight by the height squared (kg/m^2). The blood pressure was measured according to the American Heart Association's recommendations. Blood pressure measurements were obtained from both arms in the supine position after a 15-min resting period and the highest measurement was used for analysis [10]. The waist circumference was measured according to the procedures of Airlie Conference [11]. The National Cholesterol Education Program's Adult Treatment Panel III (Table 1) was used in the diagnosis of metabolic syndrome [12]. If the participants were using antihypertensive or antidiabetic drugs, they were considered to have had high blood pressure or high fasting glucose.

Statistical analysis

A review of data and coding was performed; results were analyzed through the SPSS program software (SPSS; version 17, SPSS Inc., Chicago, IL, USA). Results were expressed as mean±1 SD and categorical variables as percentages. The χ^2-test was used to determine associations between categorical variables. Continuous variables were examined for normality by the Shapiro–Wilks test and homogeneity of variances by the Levene test. For normally distributed variables, differences between the groups were determined by an independent samples *t*-test. The Mann–Whitney *U*-test was used for abnormally distributed variables. *P*-values less than 0.05 were considered statistically significant.

Results

This work was carried out on 100 stable COPD patients with different levels of severity diagnosed and classified according to the GOLD criteria (86 men and 14 women), with a mean age of 62.6±7.8 years and a smoking history of 52.4±22.3 pack-year. Fifty participants (42 men and eight women) (*P*=0.932) with a mean age of 63.4±8.6 years

Table 1 The National Cholesterol Education Program's Adult Treatment Panel III criteria for the diagnosis of metabolic syndromea

Abdominal obesity, given as the waist circumference	
Male	>102 cm (>40 inch)
Female	>88 cm (>35 inch)
Triglycerides	≥150 mg/dl
HDL cholesterol	
Male	<40 mg/dl
Female	<50 mg/dl
Blood pressure	≥130/≥85 mmHg
Fasting glucose	≥110 mg/dl

HDL, high-density lipoprotein. [a]The presence of three of the five criteria explained above was diagnostic for metabolic syndrome.

(P=0.623) were selected as the control group (Table 2 and Fig. 1).

The distribution of COPD patients according to GOLD criteria was as follows: stage I was presented in 15%, stage II in 58%, stage III in 20%, and stage IV in 7% of the patients (Table 3).

The prevalence of metabolic syndrome in the patient group was found to be much higher than in the control group (45 vs. 18%) (P=0.009) (Table 4). The distribution of the prevalence of metabolic syndrome between GOLD stages was as follows: stage I in 40%, stage II in 53.4%, stage III in 30%, and stage IV in 28.5% (Table 5).

High CRP levels increased in 54% of the COPD patients, whereas high CRP levels were found only in 24% of the control group (P=0.004) (Table 4).

CRP levels were higher in both the patient and the control groups with metabolic syndrome than in those without metabolic syndrome (84 vs. 29%, 55 vs. 17%). The difference between CRP levels in patients with metabolic syndrome and without metabolic syndrome was highly significant, whereas the difference in the control group was not statistically noticeable (P<0.000 and P=0.044, respectively) (Table 6).

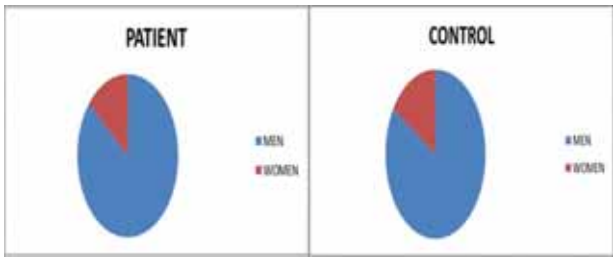
The parameters of metabolic syndrome were evaluated in both the patient and the control groups. Ratios were abdominal obesity 51.1 against 22% (P=0.003), hypertension 70.50 against 46% (P=0.021), hyperglycemia 42.60 against 19% (P=0.036); components of metabolic syndrome were significantly higher in the patient group (P<0.05 for all). In contrast, TG and HDL components were higher in the control group: the ratios were TG 24.4 against 33. % and HDL 33.3 against 44%, but the difference was not significant (P=0.732 and 0.412) (Table 7).

CRP levels were higher in patients who had metabolic syndrome than in individuals who did not have metabolic syndrome in all GOLD stages. Increased CRP levels were also higher in control participants with metabolic syndrome than in individuals without metabolic

Table 2 Demographic properties of patients and control participants

	Patients	Controls	P-value
Men (n)	86	42	>0.05
Women (n)	14	8	
Mean age (years)	62.6±7.8	63.4±8.6	>0.05

Figure 1



The percentage of men and women in the patient and the control groups.

Table 3 The distribution of chronic obstructive pulmonary disease patients according to the Global Initiative for Chronic Obstructive Lung Disease stages

Stage I	15% of COPD patients
Stage II	58% of COPD patients
Stage III	20% of COPD patients
Stage IV	7% of COPD patients

COPD, chronic obstructive pulmonary disease.

Table 4 The prevalence of metabolic syndrome and high C-reactive protein levels in patients and controls

	COPD (%)	Control (%)	P-value
Metabolic syndrome	45	18	0.009
High CRP level	54	24	0.004

COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein.

Table 5 The distribution of metabolic syndrome between the Global Initiative for Chronic Obstructive Lung Disease stages

Stage I	40%
Stage II	53.40%
Stage III	30%
Stage IV	28.50%

Table 6 Comparing high C-reactive protein levels in individuals with metabolic syndrome and those without metabolic syndrome with regard to chronic obstructive pulmonary disease and control

High CRP	With metabolic syndrome (%)	Without metabolic syndrome (%)	P-value
COPD	84	29	0
Control	55	17	0.044

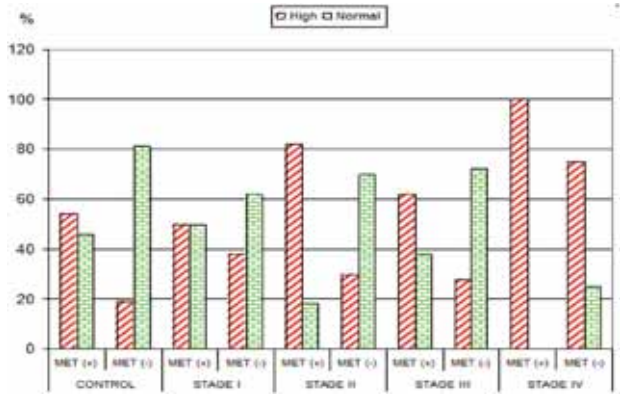
COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein.

Table 7 The parameters of metabolic syndrome in patients and controls

	Patient (%)	Control (%)	χ^2	P-value
Abdominal obesity	51.10	22	8.408	0.003
Hypertension	70.50	46	16.16	0.021
Hyperglycemia	42.60	19	12.43	0.036
Triglyceride	24.40	33	0.777	0.732
HDL	33.30	44	0.673	0.412

HDL, high-density lipoprotein.

Figure 2



The comparison of the ratios of high (>5 μg/l) and low (≤5 μg/l) C-reactive protein in the control and the patient groups according to the Global Initiative for Chronic Obstructive Lung Disease stages, with metabolic syndrome and without metabolic syndrome.

syndrome. The difference was significant only in the control group and patients with GOLD stage II and nearly significant in stage III. *P*-values for the control group and GOLD stages I–IV were 0.044, 0.483, less than 0.01, 0.048, and 0.076, respectively (Fig. 2).

Discussion

COPD is characterized by chronic airway inflammation, but there is increasing evidence that the disease is not restricted to the lungs. Smoking is a major risk factor not only for the development of COPD, but also many other chronic diseases. It triggers a local inflammatory response in lungs, and it also causes systemic inflammation that results in comorbidities such as cardiovascular or metabolic disorders. It is not clear yet as to whether this inflammation spreads from the lung to the systemic circulation, or multiple organ systems including the lung are affected due to a systemic inflammatory response [13].

The main finding of our study was that a considerable number of patients with COPD of different severities have a coexisting metabolic syndrome; serum CRP levels, as a marker of systemic inflammation, were higher in the COPD group than in the control group. In addition, patients with metabolic syndrome had higher CRP levels than COPD patients without metabolic syndrome. When the parameters of metabolic syndrome were evaluated one by one, abdominal obesity, hypertension, and hyperglycemia were more prevalent, especially in the patient group.

An epidemiologic study from Germany performed by Moebus *et al.* [14], using the criteria of International Diabetes Federation, found the prevalence of metabolic syndrome in individuals between 60 and 65 years of age to be 55% in men and 45% in women. This is in agreement with this study, where the prevalence of metabolic syndrome was 45% in all COPD patients. Furthermore, these frequencies are in line with epidemiologic data from the Third National Health and Nutrition Examination Survey in the USA [6].

Markers of systemic inflammation have consistently been found to be elevated in stable patients with COPD [15]. Several potentially relevant mechanisms, such as smoking, hypoxia, genetics, local inflammation spilling over to the systemic compartment, and exacerbations, are currently thought to play a role in the presence of systemic inflammation in patients with COPD [16]. Airway obstruction failed to show substantial associations with systemic inflammation in previous studies [17] on patients with COPD.

Several markers of systemic inflammation such as hs-CRP and interleukin 6 (IL-6) were found to be higher in stable COPD patients than in control participants, suggesting low-grade systemic inflammation even during clinical stability. CRP, one of the most widely used serum markers of systemic inflammation [18], showed that higher levels of CRP were associated with decreased lung volumes in a general population over a wide range of age. In this study, hs-CRP levels were also higher in stable COPD patients than in the control group [18].

Moreover, CRP levels were higher in patients with metabolic syndrome than in individuals without metabolic syndrome. This result may indicate that the presence of metabolic syndrome in COPD patients is associated with more intense systemic inflammation than it is in patients with COPD, but without metabolic syndrome. Similarly, Watz *et al.* [5] also found that the presence of metabolic syndrome in patients with COPD was associated with significantly higher levels of hs-CRP. CRP levels were not significantly different between GOLD stages in our study. In contrast, Watz *et al.* [5] showed that the clinical stage of COPD was an independent factor predicting the levels of hs-CRP. Our study also revealed hs-CRP levels that were higher in patients with COPD and metabolic syndrome than in patients with COPD without metabolic syndrome.

The presence of metabolic syndrome was associated with higher levels of hs-CRP and IL-6. Adipocytes of the visceral adipose tissue have been identified as an important source of IL-6. IL-6 induces the synthesis of hs-CRP by hepatocytes [19]. In epidemiologic studies

[20], adiposity as a prerequisite for metabolic syndrome has consistently been found to be an important predictor of systemic inflammatory markers. A recent study performed by Poulain *et al.* [21] revealed systemic inflammation to be higher in 16 obese patients with moderate COPD compared with 12 patients of normal weight with severe COPD. In the past 2 years, it has been suggested that the term chronic systemic inflammatory syndrome, consisting of the components age greater than 40 years, smoking for greater than 10 pack-years, symptoms and abnormal lung function compatible with COPD, chronic heart failure, metabolic syndrome, and increased CRP, be added to the diagnosis of COPD [22].

Conclusion

We found that the presence of metabolic syndrome is substantial among stable COPD patients, especially in early stages (GOLD stages I–II). When the components of metabolic syndrome were evaluated separately, abdominal obesity, hypertension, and hyperglycemia were significantly more in the patient group, and the presence of this coexisting condition was associated with an impaired profile of CRP levels in these patients and control groups with metabolic syndrome than in those without metabolic syndrome.

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Conflicts of interest

There are no conflicts of interest.

References

1 Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2013; **187**:347–365.

2 Groenewegen KH, Postma DS, Hop WC, Wielders PL, Schlösser NJ, Wouters EF, COSMIC Study Group. Increased systemic inflammation is a risk factor for COPD exacerbations. *Chest* 2008; **133**:350–357.

3 Agustí A. Systemic effects of chronic obstructive pulmonary disease: what we know and what we don't know (but should). *Proc Am Thorac Soc* 2007; **4**:522–525.

4 Mora S, Lee IM, Buring JE, Ridker PM. Association of physical activity and body mass index with novel and traditional cardiovascular biomarkers in women. *JAMA* 2006; **295**:1412–1419.

5 Watz H, Waschki B, Boehme C, Claussen M, Meyer T, Magnussen H. Extrapulmonary effects of chronic obstructive pulmonary disease on physical activity: a cross-sectional study. *Am J Respir Crit Care Med* 2008; **177**:743–751.

6 Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA* 2002; **287**:356–359.

7 Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R. Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation. *Circulation* 2005; **111**:1448–1454.

8 Ford ES, Kohl HWIII, Mokdad AH, Ajani UA. Sedentary behavior, physical activity, and the metabolic syndrome among US adults. *Obes Res* 2005; **13**:608–614.

9 Crisafulli E, Costi S, Luppi F, Cirelli G, Cilione C, Coletti O, *et al.* Role of comorbidities in a cohort of patients with COPD undergoing pulmonary rehabilitation. *Thorax* 2008; **63**:487–492.

10 Perloff D, Grim C, Flack J, Frohlich ED, Hill M, McDonald M, Morgenstern BZ. Human blood pressure determination by sphygmomanometry. *Circulation* 1993; **88**(Pt 1):2460–2470.

11 Lohmann T, Roche ARM. *The Airlie (VA) consensus: standardization of anthropometric measurements*. Champaign, IL: Human Kinetic Publishers; 1988. 39–80.

12 Grundy SM, Brewer HB, Cleeman JI, Smith SC, Lenfant C, for the Conference Participants. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. *Circulation* 2004; **109**:433–438.

13 Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur Respir J* 2009; **33**:1165–1185.

14 Moebus S, Hanisch JU, Aidelsburger P, Bramlage P, Wasem J, Jöckel KH. Impact of 4 different definitions used for the assessment of the prevalence of the metabolic syndrome in primary healthcare: The German Metabolic and Cardiovascular Risk Project (GEMCAS). *Cardiovasc Diabetol* 2007; **6**:22.

15 Pinto-Plata VM, Müllerova H, Toso JF, Feudjo-Tepie M, Soriano JB, Vessey RS, Celli BR. C-reactive protein in patients with COPD, control smokers and nonsmokers. *Thorax* 2006; **61**:23–28.

16 Wouters EF, Groenewegen KH, Dentener MA, Vernooy JH. Systemic inflammation in chronic obstructive pulmonary disease: the role of exacerbations. *Proc Am Thorac Soc* 2007; **4**:626–634.

17 Broekhuizen R, Wouters EF, Creutzberg EC, Schols AM. Raised CRP levels mark metabolic and functional impairment in advanced COPD. *Thorax* 2006; **61**:17–22.

18 Gläser S, Ittermann T, Koch B, Völzke H, Wallaschofski H, Nauck M, *et al.* Airflow limitation, lung volumes and systemic inflammation in a general population. *Eur Respir J* 2012; **39**:29–37.

19 Fantuzzi G. Adipose tissue, adipokines, and inflammation. *J Allergy Clin Immunol* 2005; **115**:911–919; quiz 920.

20 Thorand B, Baumert J, Döring A, Herder C, Kolb H, Rathmann W, *et al.* KORA Group. Sex differences in the relation of body composition to markers of inflammation. *Atherosclerosis* 2006; **184**:216–224.

21 Poulain M, Doucet M, Drapeau V, Fournier G, Tremblay A, Poirier P, Maltais F. Metabolic and inflammatory profile in obese patients with chronic obstructive pulmonary disease. *Chron Respir Dis* 2008; **5**:35–41.

22 Fabbri LM, Luppi F, Beghé B, Rabe KF. Complex chronic comorbidities of COPD. *Eur Respir J* 2008; **31**:204–212.