

# Metabolic syndrome; frequency and its relationship with variable parameters in chronic obstructive pulmonary disease

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**Background** Chronic obstructive pulmonary disease (COPD) has many extrapulmonary comorbidities, and metabolic syndrome (MetS) is one of them. Scant data are available on MetS in Egyptian patients with COPD.

**Objective** The purpose of the current research was to determine the frequency and clinical characteristics of MetS among Egyptian patients with stable COPD.

**Patients and methods** A prospective study including 70 (64 males and six females) patients with stable COPD was conducted. Clinical assessment, pulmonary function, and other laboratory studies were performed.

**Results** MetS was present in 31 patients with COPD (44.3%). BMI and high-sensitivity C-reactive protein were significantly higher in patients with COPD with MetS than those without MetS ( $P=0.02$  and  $0.01$ , respectively). Age of the patients, duration of COPD, grade of dyspnea, and pulmonary function tests had no significant difference between those with MetS versus those without it.

There was a significant negative correlation between plasma triglyceride level, as the only one of the variables of MetS, and some of parameters of pulmonary function test.

## Introduction

Metabolic syndrome (MetS) is a state of chronic low-grade inflammation as a consequence of a complex interplay between genetic and environmental factors. Insulin resistance, visceral adiposity, atherogenic dyslipidemia, endothelial dysfunction, genetic susceptibility, elevated blood pressure, hypercoagulable state, and chronic stress are the several factors that constitute the syndrome [1].

In 2002, the National Cholesterol Education Progress devised a definition for the MetS [2]. According to this definition, MetS is present if there are three or more of the following five criteria: waist circumference exceeding more than or equal to 102 cm for men and at least 88 cm for women, fasting triglycerides (TGs) of at least 150 mg/dl, high-density lipoprotein-cholesterol (HDL-c) less than 40 mg/dl for men and less than 50 mg/dl for women, blood pressure at least 130/85 mmHg, and fasting plasma glucose of at least 110 mg/dl.

Chronic obstructive pulmonary disease (COPD) is accompanied by chronic inflammation of the airways and lung parenchyma [3].

Systemic inflammation is responsible for most of extrapulmonary manifestations of COPD. Spirometry is not the only method to determine the clinical severity

**Conclusion** MetS is relatively frequent among patients with COPD. Plasma triglyceride level is the only parameter of MetS to have a significant correlation with pulmonary function tests. Apart from BMI and high-sensitivity C-reactive protein, no other parameter among patients with COPD has a significant relationship with MetS.

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**Keywords:** chronic obstructive pulmonary disease, high-sensitivity C-reactive protein, metabolic syndrome, pulmonary function tests

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of COPD, as it the clinical severity can also be detected by concomitant comorbidities. These comorbidities include affection of cardiovascular system, bronchogenic carcinoma, osteoporosis, weight loss, MetS, myopathy, and depression [4].

Although the pathobiology of COPD has not been well explained, systemic inflammation has been involved in the mechanism of most of its systemic effects [5], to the point that some authors have suggested that COPD is a part of a chronic systemic inflammation [6].

Approximately half of the patients with COPD had one or more criteria of the MetS [7]. Many reports have been published on the prevalence of the MetS in the Middle East among the general population, but limited one on its prevalence among patients with COPD, especially in our locality.

In this work, we aimed to assess the frequency of MetS in patients with stable COPD, and the relationships of

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MetS with some clinical, inflammatory, and spirometric indices of COPD were also evaluated.

## Materials and methods

### Study population

This prospective study was done on 70 (64 males and six females) patients with stable COPD attending chest clinic of Cardiothoracic Minia University Hospital from October 2015 up to October 2016. This study was approved by the Ethical Committee of Faculty of Medicine, Minia University, and an informed consent was obtained from all participants.

Diagnosis of COPD was based on GOLD definition in the form of presence of risk factors like smoking, biomass fuel exposure, and occupational exposure in addition to presence of chronic cough and/or expectoration and dyspnea, with post-bronchodilator forced expiratory volume in first (FEV<sub>1</sub>)/forced vital capacity (FVC) less than 0.7 (GOLD guidelines) [8].

Stable COPD was defined by the lack of hospitalization, urgent care visits, antibiotic use, or changes in medications within 4 weeks before the study.

Patients with an acute exacerbation of COPD within 1 month of the study as well as patients with a history of collagen vascular diseases and inflammatory bowel disease were excluded.

### Clinical assessment

Patient demographics were recorded, including age, sex, smoking status, and duration of illness. Grading of dyspnea was done using modified Medical Research Council scale.

Clinical parameters like BMI were calculated [9]. Blood pressure and waist circumference were also measured. Waist circumference was measured using an inelastic tape [10].

### Pulmonary function tests

Spirometry was done using 2130 spirometer (V max; SensorMedics, USA). Results were obtained for FVC, FEV<sub>1</sub>, FEV<sub>1</sub>/FVC percentage, forced expiratory flow at 25–75% of FVC, and peak expiratory flow rate. All parameters were calculated as percentages of predicted values.

Patients who had FEV<sub>1</sub>/FVC less than 70% underwent post-bronchodilator spirometry, 20 min following two puffs of salbutamol 200 µg.

### Laboratory assessment

Fasting blood glucose (FBG) and lipid profile in the form of plasma TGs and HDL-c after 12 h fasting using automated chemistry analyzer were measured.

Measurement of high-sensitivity C-reactive protein (hs-CRP) was also done; 3 ml venous blood samples were collected and centrifuged within 2 h of sampling. The serum was separated and was frozen and stored at -20°C until analyzed for measurement of hs-CRP by enzyme immunoassay kits supplied by European Authorized Representative (Immunospec Corporation).

### Assay of high-sensitivity C-reactive protein by enzyme immunoassay

The assay system uses a unique monoclonal antibody directed against a distinct antigenic determinant on the hs-CRP molecule.

A goat anti-C-reactive protein (CRP) antibody is the antibody-enzyme (horseradish peroxidase) conjugate solution. The test sample is allowed to react simultaneously with the two antibodies, resulting in the CRP molecules being sandwiched between the solid phase and enzyme-linked antibodies. After 45-min incubation at room temperature, the wells are washed with water to remove unbound labeled antibodies.

A tetramethylbenzidine reagent is added and incubated for 20 min, resulting in the development of blue color. The color development is stopped with the addition of stop solution, and the color is changed to yellow. The concentration of hs-CRP is directly proportional to the color intensity of the test sample, which is read a microtiter well reader within 15 min.

### Statistical analysis

Data entry and analysis were done using SPSS, version 19. The Student's *t*-test was employed for comparative analysis of the quantitative variables. For the qualitative variables, either  $\chi^2$ -test or Fisher's exact test was used. Correlation test (Pearson's test) was used. The probability of less than 0.05 ( $P < 0.05$ ) \* was used as a cutoff point for all significant values.

## Results

### Patient characteristics

Demographics and clinical features of patients with COPD are presented in Table 1. Based on NECT ATP III definition of MetS [2], we found that 31 (44.3%) patients with COPD had MetS, whereas 39 (55.7%) patients were without MetS. It was found that

**Table 1 Comparison of clinical characteristics of patients with chronic obstructive pulmonary disease with and without metabolic syndrome**

Data	Patients with COPD with MetS (N=31)	Patients with COPD without MetS (N=39)	P
Age (mean±SD)	59.03±6.5	62.4±7.9	0.06
Sex			
Male	27 (87.1)	37 (94.9)	0.2
Female	4 (12.9)	2 (5.1)	
Duration of illness (years)	12.4±7.2	11.6±6.8	0.9
Current smoker			
Smoking	6 (19.4)	13 (33.3)	0.4
Ex-smoker	19 (61.3)	19 (48.7)	
Nonsmoker	6 (19.4)	7 (17.9)	
Pack/year	20.7±5.7	24.5±10.9	0.1
BMI	30.6±5.1	27.8±4.9	0.02*
GOLD stage			
1	4 (12.9)	5 (12.8)	0.2
2	13 (41.9)	12 (30.7)	
3	12 (38.7)	12 (30.7)	
4	2 (6.5)	10 (25.6)	
mMRC	2.15±0.71	1.5±0.62	0.4
hs-CRP (mg/l)	210.4±45.6	130.2±30.5	0.01*

Data are presented as *n* (%), mean±SD. COPD, chronic obstructive pulmonary disease; hs-CRP, high-sensitivity C-reactive protein; MetS, metabolic syndrome; mMRC, modified Medical Research Council. \**p*< 0.05 which means significant value.

**Table 2 Comparison of metabolic syndrome criteria among patients with chronic obstructive pulmonary disease with and without metabolic syndrome**

Data	COPD patients with metabolic syndrome (N=31)	COPD patients without metabolic syndrome (N=39)	P
WC	107.4±6.8	104.7±7.1	0.1
SBP	121.2±8.4	120.2±8.4	0.6
DBP	80±7.3	74.3±12.5	0.03*
TG	168.1±77.1	124.4±66.6	0.01*
HDL-c	51.2±28.8	75.5±36.1	0.003*
FBG	205.1±110.2	132.6±88.8	0.003*

Data are represented as mean±SD. COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-c, high-density lipoprotein-cholesterol; SBP, systolic blood pressure; TG, triglycerides; WC, waist circumference. \**p*< 0.05 which means significant value.

BMI in patients with COPD with MetS was significantly higher than in patients with COPD without MetS (30.6 vs. 27.8, *P*=0.02, respectively). In addition, hs-CRP was also higher in patients with MetS than those without, with no significant difference in other parameters.

#### Measurements and laboratory assessments

There is a higher significant value of diastolic blood pressure in patients with COPD with MetS than those without MetS (80 vs. 74.3, *P*=0.03). Besides TGs and FBG are significantly higher in patients with COPD with MetS versus those without MetS (168.1 vs. 124.4, *P*=0.01) (205.1 vs. 132.6, *P*=0.003, respectively); on the contrary, HDL-c is significantly higher in patients

with COPD without MetS than those with MetS (75.5 vs. 51.2, *P*=0.003; Table 2).

We found that 18 (25.6%) patients with COPD had one criterion of MetS; 21 (30%) patients had two criteria of MetS; 28 (40%) patients of COPD had three criteria of MetS, which were increased waist circumference, elevated TG level, and increased FBG; and three (4.4%) patients had four criteria of MetS (Fig. 1).

No significant difference was found regarding all parameters of spirometry between patients having COPD with and without MetS (Table 3).

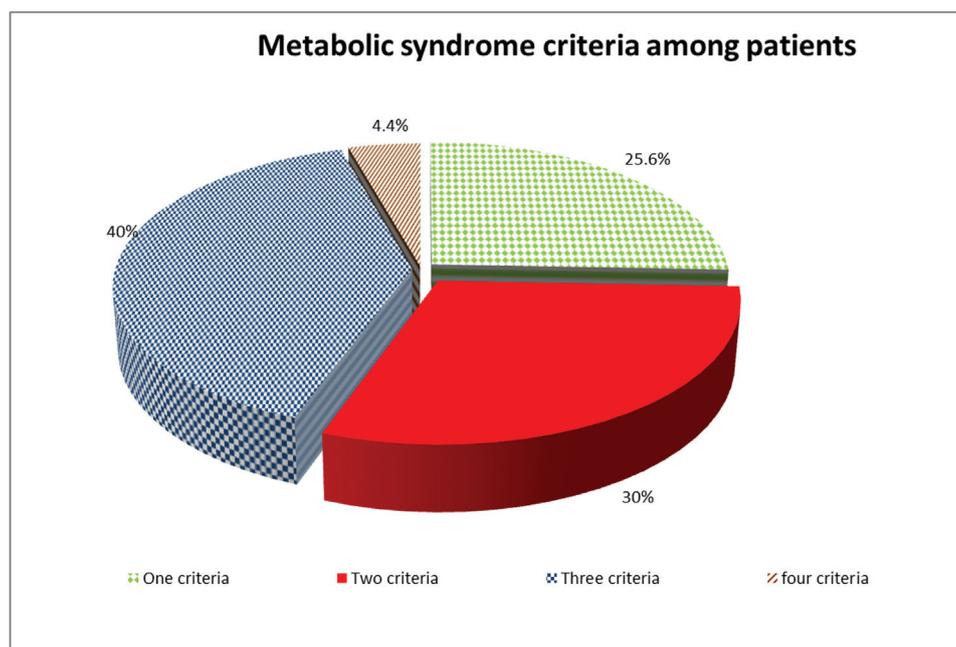
#### Correlation of spirometry and metabolic parameters

Plasma TG as one of the components of MetS presented a significant negative correlations with both of FEV<sub>1</sub> and FVC% predicted (Figs 2 and 3, respectively) whereas there was no significant correlation between other parameters of spirometry and MetS criteria (Table 4).

#### Discussion

A relation between MetS and COPD has been observed in some studies, and the syndrome has been identified as an independent risk factor for worsening respiratory symptoms, increasing lung function impairment, and pulmonary hypertension [11]. From this important point of view, this work was designed to detect first, the frequency of MetS in

Figure 1



Metabolic syndrome criteria among patients with chronic obstructive pulmonary disease.

**Table 3 Results of spirometry between patients with chronic obstructive pulmonary disease with and without metabolic syndrome**

Variables	COPD patients with MetS (N=31)	COPD patients without MetS (N=39)	P
FVC%	67.09±20.6	69.4±22.2	0.6
FEV <sub>1</sub> %	48.6±15.5	50.07±21.7	0.7
FEV <sub>1</sub> /FVC	52.6±6.4	52.8±9.3	0.9
FEF 25–75%	21.9±9.4	24.9±12.9	0.2
PEER%	37.7±13.3	36.7±17.5	0.9

Data are represented as mean±SD. COPD, chronic obstructive pulmonary disease; FEF, forced expiratory flow; FEV<sub>1</sub>, forced expiratory volume in first; FVC, forced vital capacity; MetS, metabolic syndrome.

patients with COPD, and we found that 44.3% of patients with COPD had MetS based on NECT ATP III definition [2]. In the literature, reports of prevalence of MetS in patients with COPD have rates ranging from 23 to 61% [7,12,13]. These considerable variations in frequency found in studies on MetS can be explained by different geographical origins of the study and the use of different diagnostic criteria for defining MetS. In addition, this prevalence of MetS did not determine if patients with COPD were studied in periods of acute exacerbations or in stable state.

COPD often results in a sedentary lifestyle and physical deconditioning, which could explain the presence of MetS in patients with COPD [7].

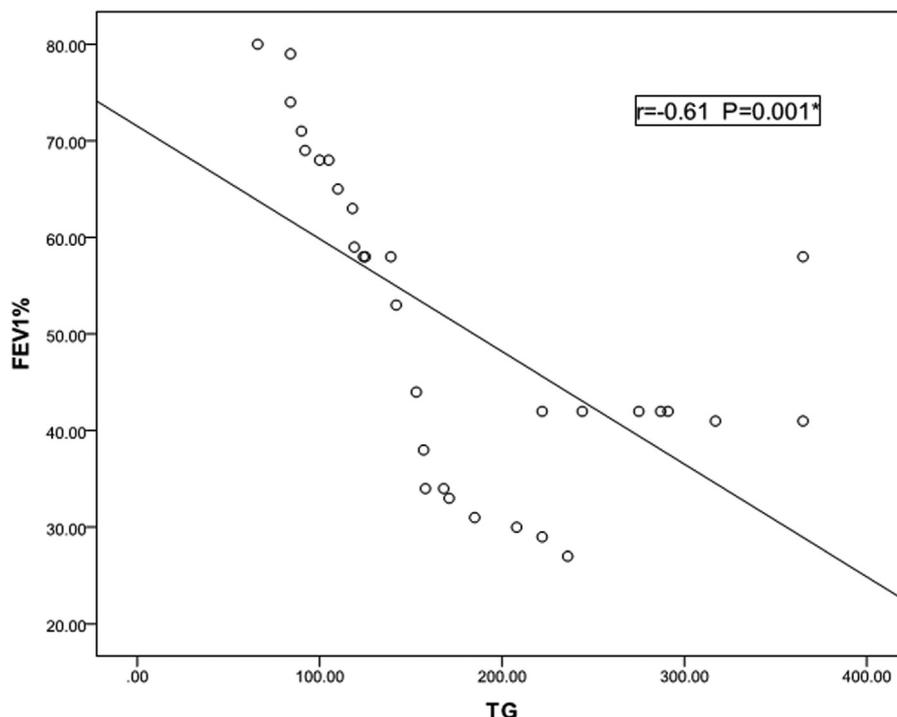
When components of MetS were evaluated one by one, we found that abdominal obesity was present in 78.6% of patients with COPD, elevated FBG in 65.7%, low HDL-C levels in 34.3%, elevated TG in 31.4%, and raised blood pressure in 2.9% (data not shown). So, abdominal obesity had the highest frequency as one criterion of MetS in patients with COPD. However, in the study by Ghatas [14], abdominal obesity, hypertension, and hyperglycemia were more prevalent in patients with COPD in descending order.

The second commonest parameter of MetS in patients with COPD included in our study was FBG more than 110 mg/dl, which was present in 46 (65.7%) patients. Of 46 patients, 13 (28.2%) had impaired fasting glucose (IFG) which is defined as a FBG that is higher than the upper limit of normal, but not high enough to be classified as diabetes mellitus. We used WHO criteria of definition of IFG which means fasting plasma glucose level from 110 to 125 mg/dl [15]. The remaining 33 (71.8%) of 46 patients with COPD had diabetes mellitus, as their FBG levels were more than 126 mg/dl, 22 (66.6%) of them among those with MetS.

Impaired fasting glucose is one form of prediabetes; many newly identified IFG patients progress to diabetes in less than 3 years [15].

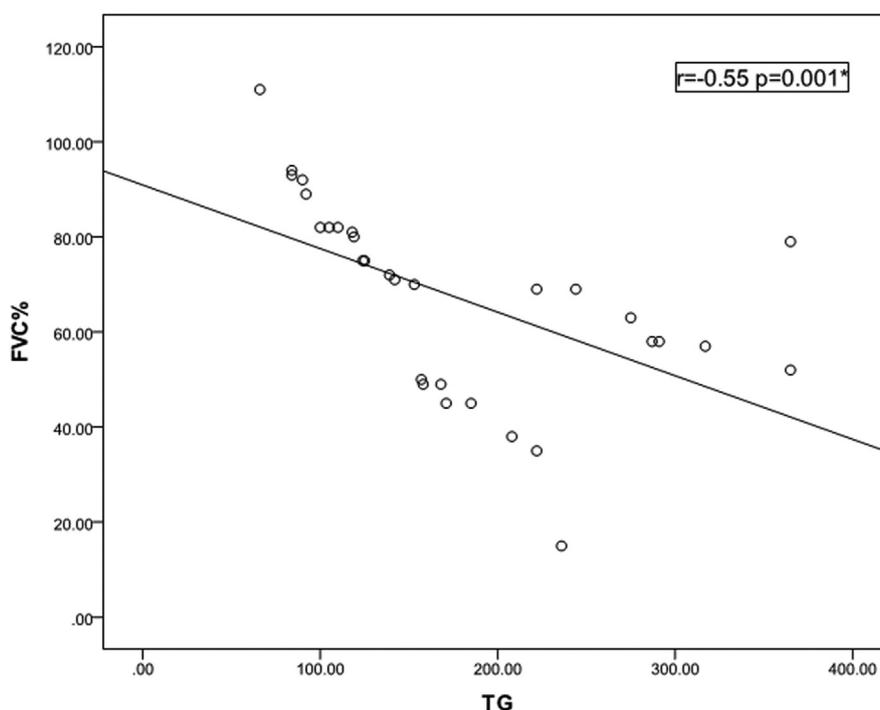
The second objective of this study was to determine the relationship of MetS with clinical, inflammatory and

Figure 2



Correlation between FEV<sub>1</sub>% and TG among patients with metabolic syndrome. FEV<sub>1</sub>, forced expiratory volume in first second; TG, triglyceride.

Figure 3



Correlation between FVC% and TG among patients with metabolic syndrome. FVC, forced vital capacity; TG, triglyceride.

pulmonary function parameters in patients with COPD.

On analysis of the baseline data of patients with COPD with MetS versus those without MetS, we found that

there was no significant difference regarding age between patients with COPD with and without MetS (59.03 vs. 62.4,  $P=0.06$ ). This agrees with the results of Díez-Manglano *et al.* [16]. We found also that sex, duration of COPD, dyspnea grade, and

**Table 4 Correlation between spirometry and metabolic syndrome criteria among patients with metabolic syndrome**

Data	FVC%		FEV <sub>1</sub> %		FEV <sub>1</sub> /FVC		FEF 25–75%		PEEFR%	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Waist circumference	-0.01	0.9	-0.02	0.8	-0.06	0.7	-0.08	0.6	0.07	0.6
Systolic blood pressure	0.03	0.8	-0.02	0.8	-0.04	0.8	-0.06	0.7	0.002	0.9
Diastolic blood pressure	-0.002	0.9	-0.006	0.9	-0.02	0.9	-0.05	0.7	0.04	0.8
TG	-0.55	0.001*	-0.61	0.001*	-0.19	0.2	0.28	0.1	0.23	0.2
HDL-c	0.35	0.05	0.15	0.5	-0.11	0.4	0.06	0.7	0.20	0.2
FBG	-0.15	0.5	-0.15	0.4	0.03	0.8	-0.05	0.7	-0.11	0.5

FBG, fasting blood glucose; FEF 25-75% of FVC, forced expiratory flow; FEV<sub>1</sub>, forced expiratory volume in first second; FVC, forced vital capacity; PEF, peak expiratory flow rate; HDL-c, high-density lipoprotein-cholesterol; TG, triglycerides. \**p*< 0.05 which means significant value.

GOLD stage had no significant difference in those with or without MetS.

In the current study, BMI was significantly higher in patients with COPD with MetS versus those without (30.6 vs. 27.8, *P*=0.02), and this coincides with the results of Breyer *et al.* [17].

Patients with COPD experience a systemic inflammation even in stable state which can be assessed by measuring inflammatory mediators like CRP [18]. Serum hs-CRP was significantly higher in patients with COPD with MetS versus those without MetS (210.4±45.6 vs. 130.2±30.5, *P*=0.01). Our results were in accordance with previous studies [18–20]. However, Hotamisligil [21] concluded that it is not clear yet whether systemic inflammation associated with COPD causes metabolic disorders or metabolic signals trigger inflammatory response. We did not find a significant difference in all parameters of pulmonary function test among patients with COPD with and without MetS; on the contrary, Stanciu *et al.* [19] noted that patients with COPD with MetS show a significance difference than patients with COPD without MetS regarding FEV<sub>1</sub> and the 6-min walk test. Alpaydin *et al.* [22] found that FEV<sub>1</sub> and FEV<sub>1</sub>/FVC were higher in patients with COPD with MetS compared with those without MetS. No obvious explanation was found for these discrepancies.

Regarding correlation of pulmonary function parameters and MetS criteria in patients with COPD (Table 4), we found a significant inverse correlation of TG only with FVC% and FEV<sub>1</sub>% (*r*=-0.55, *P*=0.001 and *r*=-0.61, *P*=0.001, respectively). Ameen *et al.* [23] showed significant inverse (negative) relation between severity of COPD (FEV<sub>1</sub>) and all parameters of MetS except HDL which showed linear (positive) relation with FEV<sub>1</sub>. Popović-Grle *et al.* [24] found that FVC and FEV<sub>1</sub> correlated negatively with waist circumference; however, the correlation was weak and statistically

nonsignificant, and this is in line with our results of FEV<sub>1</sub> and FVC correlations with waist circumference.

The present study has some limitation; one of them is the small sample size of studied patients. Second, we have no data on the rate of exacerbation of patients with MetS versus those without MetS. Lastly, no follow-up information on the prognosis of patients with COPD with MetS is provided regarding the changes of lung function, impaired health-related quality of life, and increase mortality.

## Conclusion

We found that 44% of patients with COPD have MetS, so MetS in our locality is frequent. With the exception of BMI and serum level of hs-CRP, no other clinical indicator for the presence of MetS is found. Increased serum level of TGs, as one of the components of MetS, is associated with more impairment in FEV<sub>1</sub> and FVC. Abdominal obesity, impaired glucose level, and diabetes mellitus are the most frequent components of MetS found in patients with COPD.

So, an effort to throw light on MetS in patients with COPD should be undertaken in our locality. In addition, we recommend that preventive approaches to patients with COPD should be taken in the form of weight reduction and diet control with exercise; these lifestyle modifications can reduce the more frequent components that lead to the development of MetS.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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