



# A study of metabolic syndrome in chronic obstructive pulmonary disease patients attending out-patient department of a medical college

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## ABSTRACT

**Introduction:** Metabolic syndrome (MetS) occurs as co-morbidity in chronic obstructive pulmonary disease (COPD) and requires evaluation.

**Methods:** MetS was studied in 336 patients of COPD (NCP-ATP III guidelines). TNF- $\alpha$ , IL-6 and C reactive protein were analysed. Patients were divided into metabolic (n=89) and non-MetS (n=247) groups and further divided into mild to very severe COPD category as per Global Initiative for Chronic Obstructive Lung Disease.

**Results:** The 89 patients (26.49%) had MetS. Waist hip ratio (WHR) was more in 80.89% (72/89). Triglycerides and HDL derangements were found in 63 and 75 patients. Fasting blood glucose, systolic and diastolic blood pressure criterion were met by 58 (65.17%), 20 (22.47%) and 32 (35.95%) patients respectively. In non-MetS group, the derangement in above parameters were found in 41, 53, 109, 47, 43 and 46 patients respectively. Compared to MetS group, significant difference was found in WHR, lipid profile and blood pressure. Significant difference was found in waist circumference, triglycerides, HDL, fasting blood glucose and diastolic blood pressure between COPD groups with and without MetS. Moderate COPD patients had highest MetS. Difference in results as per severity of disease was found to be non-significant. Inflammatory markers between COPD groups with and without MetS were non-significant with levels more in latter group. Within COPD group (as per severity of disease) with MetS their levels were significantly raised.

**Conclusion:** MetS occurs as co-morbidity in COPD and requires evaluation which will help in better management and prevent cardio metabolic complications.

### Keywords:

COPD  
Metabolic syndrome  
Inflammation  
Lipid profile  
Blood pressure  
Blood glucose

## Introduction

Metabolic syndrome is diagnosed by presence of three out of five of following criterion i.e. central obesity, increased triglycerides, low density lipoprotein (LDL) cholesterol, elevated blood sugar and increase in blood pressure (Thakur et al., 2013). Globally, the prevalence

of metabolic syndrome as an extra pulmonary manifestation in chronic obstructive pulmonary disease (COPD) is reported to be between 26-61% (Gupta et al., 2017) and is considered to be risk factor for diabetes and cardio vascular events (Vitezova et al., 2015). The exact mechanisms are unknown but there appears a

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link between the two. Triad of obesity, lipid profile derangement and inflammation (due to stress induced serum cortisol elevation) in COPD leads to metabolic syndrome (Naik et al., 2014). Both obesity and metabolic syndrome may co-exist in COPD (James et al., 2018). COPD induced hypoxia of adipose tissue results in inflammation and there appears association between lung functions decline, adipose tissue dysfunction, inflammation and metabolic manifestations in COPD (Bianco et al., 2013; Choudhary and Jan, 2016). COPD is associated with decrease in physical activity and smoking is considered to be a major risk factor for COPD. (Boyer et al., 2018). Interestingly, both smoking and physical inactivity are risk factors for metabolic syndrome (Cebon Lipovec et al., 2016). Thus, in light of the above literature, smoking, obesity and inflammation appears to be interconnections between COPD and metabolic syndrome, both of which have deleterious effect on health. However, not all smokers develop COPD; duration and intensity of smoking are important (Siafakas and Tzortzaki, 2002). Results of earlier study show that there is no significant increase or decrease in incidence of metabolic syndrome in smokers and no correlation between the quantity smoked and metabolic syndrome. Importantly, results indicated that vulnerable period for developing metabolic syndrome was two years after cessation of smoking which was attributed to weight gain following cessation of smoking (Dedinska et al., 2014). Air pollution, pulmonary infections, low socioeconomic status, poor nutrition and genetic factors are considered as risk factors in COPD (Terzikhan et al., 2016). Genetics, sedentary life style, diet, gender, stress, alcohol, tobacco and socio economic status are considered to be risk factors associated with metabolic syndrome (Pasdar et al., 2017; Chakraborty et al., 2015; Mohanan, 2016). Thus, there are common links between the two and both being syndromes of public health importance require attention. Keeping it in view, the present study was undertaken to find the presence of metabolic syndrome in patients of COPD, which would help reduce the future complications and consequences.

## Materials and methods

The present cross-sectional study was conducted in the Department of Physiology, Jawaharlal Nehru Medical College (JNMC), AMU, Aligarh, Uttar Pradesh, India. The study period was from January 2009 to February

2010 during which 336 COPD patients were selected (after permission from the Department and ethics and research committee) from tuberculosis and respiratory diseases out-patient department (OPD). The study was self-financed without any external source of funding. On the basis of Modified National Cholesterol Education Program (NCEP), Adults Treatment Panel III (ATP III) (Thakur et al., 2013) guidelines, subjects were divided into two groups i.e. COPD with metabolic syndrome (n=89) and COPD without metabolic syndrome (n=247).

All the participants included were more than 18 years and less than 65 of age. Patients with history of chronic cough or sputum production on most days for at least 3 months of the two consecutive years were included. Patients having FEV1 (forced expiratory volume during first second) % predicted <70% and FEV1/FVC % <70% (where FVC is forced vital capacity) on the basis of pulmonary function test (the results of MIR Spirolab in tuberculosis and chest diseases department JNMC) were included in the study. On the basis of pulmonary function test, patients were divided into mild to very severe disease category as per Global Initiative for Chronic Obstructive Lung Disease (Waseem et al., 2012). All the patients gave history of smoking in one form or other and some were even current smokers. Subjects not giving consent, pregnant females, subjects with renal disease and liver cirrhosis, diagnosed cases of diabetes mellitus, bronchial asthma and chronic diseases other than COPD were excluded from the present study. Metabolic syndrome was diagnosed on the basis of Modified NCEP ATP III criterion (three out of five) i.e. triglycerides  $\geq 150$  mg/dl, high density lipoprotein (HDL) cholesterol  $\leq 40$  mg/dl for male or 50 mg/dl for female, fasting blood glucose  $\geq 100$  mg/dl, abdominal obesity which is a component of syndrome rather than prerequisite for diagnosis  $\geq 90$  cm for Asian men or  $\geq 80$  cm for Asian women, blood pressure  $\geq 130$  (systolic)/85 (diastolic) mmHg or receiving drug treatment (Thakur et al., 2013). Waist circumference (in centimetres) was measured using an inelastic tape in a horizontal plane. Blood pressure was measured using standard protocol with the help of mercury sphygmomanometer (readings were expressed as millimetre of mercury). Fasting blood samples were used to analyze blood glucose (GOD-POD method), HDL (PEG-CHOD-PAP method) and triglycerides (GPO-Trinder method) and inflammatory markers like interleukin-6 (IL-6 in pg/ml), tumor necrosis factor- $\alpha$

(TNF- $\alpha$  in pgm/ml) and C reactive protein (CRP in mgm/dl) were analysed using commercially available kits (Waseem et al., 2013; Waseem et al., 2015).

### Statistical analysis

The data were analysed, using R software and prism graph. Values were expressed as mean $\pm$ SD. Number and percentage of subjects with and without metabolic syndrome were mentioned. Similarly, number and percentage of subjects with and without metabolic syndrome in mild, moderate, severe and very severe COPD were also mentioned. The normality of the data was analysed using Shapiro Wilk statistical tests. The data of the study groups were compared using Chi square, analysis of variance (ANOVA) and Students unpaired t tests. *P* value of <0.05 was taken as significant.

## Results

In the present study data of 336 patients of COPD reporting in the OPD of tuberculosis and chest diseases from January 2009 to February 2010 was analysed. After analysis, they were divided into two groups'

i.e. with and without metabolic syndrome. Out of 336 patients, metabolic syndrome was found in 89 patients i.e. 26.49%. Out of total 89 patients having metabolic syndrome, 41.57% were males and 58.43% were females. In patients with metabolic syndrome (both males and females) the waist hip ratio (WHR) met the metabolic syndrome diagnosis values in 80.89% (72 patients out of total 89). Similarly, triglycerides and HDL derangements as per metabolic syndrome definition were found in 63 and 75 patients respectively. Fasting blood glucose, systolic and diastolic blood pressure criterion were met by 58 (65.17%), 20 (22.47%) and 32 (35.95%) patients respectively.

The 247 patients belonged to non-metabolic syndrome group. In this group 41 patients i.e. 16.60% (41/247) had WHR as per the metabolic syndrome criteria. Similarly, triglycerides and HDL criteria were met by 53 and 109 patients respectively. Fasting blood glucose ( $\geq 100$  mgm/dl), systolic and diastolic blood pressure of more than equal to 130/85 mmHg were found in 47, 43 and 46 patients respectively. As compared to metabolic syndrome group significant difference were

**TABLE 1:** Number and percentage of COPD patients with (3/5 criteria met) and without metabolic syndrome

Parameter	Metabolic syndrome in COPD patients		P value
	Present (n=89/336) i.e. 26.49% (%) Number	Absent (n=247/336) (%) Number	
<b>Gender</b>			
Males	(41.57%) 37	(63.97) 158	0.001>
Females	(58.43%) 52	(36.03%) 89	
<b>WHR</b> ( $\geq 90$ cm in males and $\geq 80$ cm in fe- (males	(80.89%) 72	(16.60%) 41	0.001>
<b>Lipid profile</b>			
-Triglycerides( $\geq 150$ mgm/dl)	(70.79%) 63	(21.46%) 53	0.001>
<b>HDL-</b>			
[Males ( $\leq 40$ mgm/dl)	(84.27%) 75	(44.13%) 109	0.001>
Females ( $\leq 50$ mgm/ dl)]			
<b>Fasting blood glucose</b>			
(mgm/dl $100 \leq$ )	(65.17%) 58	(19.03%) 47	0.001>
<b>Blood pressure</b>			
SBP ( $\geq 130$ mm Hg)	(22.47%) 20	(17.40%) 43	0.294
DBP ( $\geq 85$ mm Hg)	(35.95%) 32	(18.62%) 46	0.001

COPD: chronic obstructive pulmonary disease, WHR: waist hip ratio, HDL: high density lipoprotein, SBP: systolic blood pressure, DBP: diastolic blood pressure

**TABLE 2:** Values of study parameters in COPD group with and without metabolic syndrome

Parameter	Metabolic syndrome in COPD patients		P value
	Present (n=89)	Absent(n=247)	
	Mean±SD	Mean±SD	
Waist circumference (cm)	89.77 ±6.47	81.11 ±7.70	<0.001
<b>Lipid profile</b>			
Triglycerides(mgm/dl)	156.71 ±13.94	132.97±22.47	<0.001
HDL (mgm/dl)	42.35 ±5.60	44.24± 5.29	<0.05
<b>Fasting blood glucose</b> (mgm/ dl)	105.65±12.11	92.13±12.59	<0.001
<b>Blood pressure</b>			
SBP(mm Hg)	121.15±12.33	118.82±13.28	0.148
DBP(mm Hg)	81.60±6.57	79.56±6.54	0.01

COPD: chronic obstructive pulmonary disease, HDL: high density lipoprotein, SBP: systolic blood pressure, DBP: diastolic blood pressure

**TABLE 3:** Distribution as per severity [\* In COPD group with metabolic syndrome majority of patients had moderate severity of disease i.e. 31.97 % (47/147)].

severity	Metabolic syndrome		P value
	Present	Not present	
	Number (%)	Number (%)	
<b>Mild (n=128)</b>	31 (24.22)	97 (75.78)	Chi Square=4.866
<b>Moderate (n=147)</b>	47 (31.97)*	100 (68.03)	df=03
<b>Severe (n=40)</b>	07 (17.50)	33 (82.50)	P=0.182
<b>Very severe (n=21)</b>	04 (19.05)	17 (80.95)	

**TABLE 4:** Serum markers in COPD patients with and without metabolic syndrome

Serum marker	Metabolic syndrome in COPD patients		P value
	Present	Absent	
	Mean±SD	Mean ±SD	
Interleukin 6 (pgm/ml)	3.99±0.78	4.79±0.48	No-Significant
<b>Tumor necrosis factor-α (pgm/ml)</b>	92.66±2.63	96.41± 2.67	Non-Significant
<b>C reactive protein (mgm/dl)</b>	35.88± 2.05	38.30± 1.89	Non-Significant

found in WHR, lipid profile and blood pressure levels (Table 1). Significant difference were found in waist circumference ( $P<0.001$ ), triglycerides ( $P<0.001$ ), HDL ( $P<0.05$ ), fasting blood glucose ( $P<0.001$ ) and diastolic blood pressure ( $P=0.01$ ) values between COPD groups with and without metabolic syndrome (Table 2). Results of Table 3 show that out of total 336 patients, mild, moderate, severe and very severe COPD were present in 128, 147, 40 and 21 patients respectively. The results show that the maximum percentage of patients having metabolic syndrome belonged to moderate COPD

group. However, the overall difference in results as per the severity of disease was found to be non-significant ( $P=0.182$ ). The differences in levels of inflammatory markers like IL-6, TNF-α and CRP between COPD groups with and without metabolic syndrome were non-significant with values higher in latter group. However, within COPD group (as per severity of disease) with metabolic syndrome their levels increased with increase in severity and the difference was significant (Tables 4 and 5).

**TABLE 5:** Markers of inflammation within the COPD group (as per disease severity) with metabolic syndrome

Serum marker	COPD group with metabolic syndrome				P value
	Mild COPD Mean±SD	Moderate COPD Mean±SD	Severe COPD Mean±SD	Very Severe COPD Mean±SD	
Interleukin-6 (pgm/ml)	3.79 ±0.86	3.99±0.56	4.06±0.95	4.12±0.82	<0.05
Tumor necrosis factor- $\alpha$ (pgm/ml)	86.67±3.09	90.45±2.71	94.72±3.08	97.52±3.19	<0.05
C reactive protein(mgm/dl)	33.89±2.50	36.35±1.99	38.80±2.05	40.01±2.99	<0.05

## Discussion

In COPD group with metabolic syndrome, 58.43 % and 41. 57% were females and males respectively but in non-metabolic syndrome group majority were males; the difference was significant. Results of systematic review done earlier found that metabolic syndrome in COPD was more prevalent in females and elevated blood pressure, elevated blood sugar and abdominal obesity were commonly associated derangements (Cebren Lipovec et al., 2016). Higher prevalence in females could be attributed to high body mass index (BMI), elevated triglycerides, decrease in HDL and impaired blood sugar as was found in earlier study (Singh et al., 2015). However, there are contradictory studies, which have found higher prevalence in males owing to more pack years smoked by them as compared to females (Lazovic et al., 2012). Smoking which is a major risk factor in COPD results in hyperlipidaemia. On the other hand, low quality of life associated with COPD, contributes to obesity, which in turn is expected to up-regulate the inflammatory cytokines. The link between obesity, COPD and inflammation is central to pathophysiology of metabolic syndrome (Waseem et al., 2015; Mantoo et al., 2017). As per the National Health and Nutrition Examination Survey III (NHANES III), active smoking is risk factor for developing metabolic syndrome irrespective of gender. Smokers are more likely to have lower BMI and increase abdominal obesity due to visceral fat deposition, both of which lead to development of metabolic syndrome (Kolovou et al., 2016).

In our study we found metabolic syndrome in 26.49 % of COPD patients and majority had moderate COPD. Metabolic syndrome in 15.7% of COPD patients with

majority having moderate to severe disease. Similarly, another study reported metabolic syndrome in 31.4% COPD patients with higher prevalence among moderate to severe COPD patients, the reasons for which were attributed to cachexia or weight loss associated with increase in severity of disease (Pasha et al., 2018).

In our study, the waist circumference of patients with metabolic syndrome was significantly higher than those without it. The results assume importance in the light of scientific data which highlighted the importance of visceral obesity as an important risk factor for cardio-metabolic disease (Despres et al., 2008). In our study, the levels of triglycerides were significantly higher in metabolic syndrome patients and values of HDL were lower. Impaired lipid profile in terms of high triglycerides and cholesterol results in increase airway resistance and lung function impairment (Rafie et al., 2018) and thus requires serious evaluation.

In our study, blood pressure and fasting blood glucose were found to be higher in COPD patients with metabolic syndrome. The results are in accordance with previous research in which authors found that COPD was associated with metabolic syndrome only when NCEP ATP III criterion was used. Authors argued that the association is dependent upon the definition used for metabolic syndrome (Acharyya et al., 2016). In our study, modified NCEP ATP III criterion was used for diagnosing metabolic syndrome in COPD patients.

Although, we did not analysed the result as per severity of smoking but it (being the risk factor for development of COPD) cause an increase in waist circumference, blood pressure and triglycerides and decrease in HDL levels. Smoking increases secretions of cortisol and growth hormone and also stimulates sympathetic

nervous system (Sun et al., 2012) which is further expected to cause derangements of the parameters analysed. Diabetes mellitus and elevated blood pressure level has been found as co-morbidities in COPD patients (Kane et al., 2018).

Assessment of lipid profile and evaluation of metabolic risk factors are very important in COPD patients. Doehner et al. (2011), in their review article concluded that body size and lipid profile play an important role in guiding the management of COPD patients with co-morbidities like diabetes and cardiovascular disorders. With lipid profile derangement and central obesity, the levels of anti-inflammatory cytokine adiponectin are reduced. Cardiovascular and metabolic derangements are also reported to be associated with plasminogen activator-1 increase due to decline in adiponectin levels in hypoxia. Interestingly, COPD patients with lower BMI have higher levels of adiponectin which provide protection against mortality from cardio vascular diseases (Mirrakhimov, 2012). Thus, assessment of waist circumference, lipid profile and blood pressure assume significance in patients with COPD for better management and reducing complications from associated co-morbidities. Although, we have not evaluated the adiponectin levels but recently, it has attracted the attention of researchers worldwide due to its implication in inflammation, immunity, lipid and glucose metabolism and insulin resistance. Interestingly, adiponectin by the virtue of its ability to inhibit TNF- $\alpha$  production from macrophages is also being debated as having anti-inflammatory properties. Its levels are shown to correlate inversely with lung function decline (Jaswal et al., 2018). Lower levels of adiponectin have been reported in metabolic syndrome, obesity and type II diabetes (Huang, 2009) and these conditions may co-exist with COPD (Verma et al., 2015; Houssaini et al., 2018; Waseem et al., 2017).

In the present study, the levels of adiponectin and its correlation with lung function decline were not done but other markers of inflammation like IL-6, TNF- $\alpha$  and CRP were analysed. The results showed that in patients having metabolic syndrome, the levels were significantly raised with increase in lung function decline (i.e. with increase in the severity of COPD). However, the values were non-significantly higher in patients without metabolic syndrome as compared to those with it. The possible explanation could be that

the number of patients and those suffering from severe to very severe disease were more in the group without metabolic syndrome.

In metabolic syndrome group the interrelation between metabolic syndrome, obesity and inflammation could possibly be attributed to variety of adipocytokines like IL-6, 8, 10, 12, transforming growth factor- $\beta$  and TNF- $\alpha$  (Castro et al., 2017). Mantoo et al. (2017), conducted a study on 55 stable COPD patients of mild to very severe grade and found that patients with metabolic syndrome had higher grades of inflammation as indicated by elevated levels of CRP and TNF- $\alpha$ . They concluded that inflammation plays an important role in disease progression. Smoking increases macrophages which results in increased production of TNF- $\alpha$  and free radicals, resulting in oxidative stress and systemic inflammation which are central to the pathophysiology of COPD (Barnes, 2014). Increase in the levels of CRP in COPD has been reported in other studies also (Ragulan et al., 2017).

## Conclusion

Metabolic syndrome occurs as co-morbidity in COPD patients. Smoking being a major risk factor for COPD is expected to result in inflammation, which in turn affects lipid and sugar levels and results in elevated blood pressure as well. Assessment of metabolic syndrome in patients of COPD is expected to prove beneficial for management of patients and also prevent cardio metabolic complications. Inflammatory markers may act as a novel target for therapeutics in COPD and associated co-morbidities like metabolic syndrome and thus further evaluation and studies are required. In the present study patients were not classified on the basis of severity of smoking. Analysis of study parameters on the basis of smoking severity would improve results. Although, smoking is a risk factor in COPD but not all smokers develop COPD and thus further evaluation of the results after including other risk factors of COPD is required. Metabolic syndrome is co-morbidity in COPD patients but at the same time analysis of associated risk factors is required.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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