## Original Research Article

# Metabolic syndrome in chronic obstructive pulmonary disease

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## ABSTRACT

**Background:** COPD (Chronic obstructive pulmonary disease) is considered as a systemic disease due to associated systemic inflammation which can manifest as metabolic syndrome or its component illnesses. This study was undertaken to determine the proportion of metabolic syndrome in patients with COPD.
**Methods:** 51 patients with COPD were compared with equal number of age and gender matched controls. GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria were used for diagnosing COPD. Metabolic Syndrome (MS) was diagnosed based on modified NCEP:ATP III criteria (National cholesterol education Program Adult Treatment Panel III). Subjects were evaluated for hypertension, WC, FBS, and serum triglycerides and serum HDL (High-density lipoprotein) to diagnose MS.
**Results:** Metabolic syndrome was diagnosed in 16 (31.4%) patients with COPD and in 8 (15.7%) controls. The proportion of individual parameters of MS in cases and controls was as follows: DM in 19 (37.3%) cases and 13 (25.5%) controls, hypertension in 21(41.2%) cases and 9 (17.6%) controls, low serum HDL in 31 (60.7%) cases and 22 (43.1%) controls increased WC in 14 (27.5%) cases and 7 (13.7%) controls and elevated serum TG in 12 (23.5%) cases and an equal number of controls.
**Conclusions:** Metabolic syndrome and its parameters are more prevalent in COPD patients. Early detection and treatment of MS in COPD patients can prevent development of complications due to the combined effects of both diseases.

**Keywords:** Body Mass Index, Chemo attractant protein, COPD, Forced expiratory volume in one second, Forced vital capacity, GOLD, HDL, MS, NCEP: ATP III

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality. It is the 4th leading cause of death in the world and a further increase in its prevalence and mortality is predicted in the coming decades.[1] Globally, COPD is expected to rise to the 3rd position as a cause of death and 5th position as a cause of disability adjusted life years (DALY'S) according to the base line projections made in Global Burden of Disease Study (GBDS).[2]

COPD is not only disease of lung, but it affects other systems beyond the lungs. Hence, it is now considered as

a systemic disease.[3] In patients with COPD a significant relationship exists between respiratory impairment and the presence of comorbid cardiovascular disease, diabetes mellitus and hypertension, respiratory impairment is more likely to have at least two of these conditions and a significantly higher risk of death and hospitalizations, especially when comorbid disease is present.[4]

The metabolic syndrome (syndrome X, insulin resistance syndrome) consists of a constellation of metabolic abnormalities that confer increased risk of cardiovascular disease (CVD) and cerebrovascular disease.[5] The criteria for the metabolic syndrome have evolved since the original definition by the World Health Organization in 1998, reflecting growing clinical evidence and analysis by a variety of consensus conferences and professional organizations. The major features of the metabolic syndrome include central obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, hyperglycemia, and hypertension.[5]

Metabolic syndrome was found to be more common in COPD when compared to the general population. Several studies from different parts of the world have shown a prevalence of metabolic syndrome and COPD patients.[6-9]

In a study conducted by, Watz H et al on COPD patients states that metabolic syndrome was found in almost half of the patients having COPD irrespective of disease stage and was associated with markers of systemic inflammation, particularly the pro inflammatory cytokines Tumor necrosis factor-α (TNF-α) and interleukin (IL-6) C-reactive protein (CRP) and fibrinogen.[6]

An epidemiological study conducted in China in 2010 shows strong association between metabolic syndrome and COPD. The researchers also concluded that metabolic syndrome was identified in approximately 20% of patients with COPD, and this correlated most closely with central obesity.[7]

## METHODS

This was a prospective observational cross-sectional study which was carried out on Chronic Obstructive Pulmonary Disease patients and healthy controls.

### Inclusion criteria

- Patients diagnosed with COPD based on GOLD guidelines, on history, clinical examination, and pulmonary function test (FEV1/FVC <0.7)
- Healthy controls.

### Exclusion Criteria

- Presence of asthma or other chronic respiratory diseases

- Presence of malignancy or serious comorbidities that would prevent the study completion
- Patients with active pulmonary tuberculosis
- Patients with acute exacerbation of COPD requiring ICU admission.

### Study methods

Both cases and controls were interviewed to obtain relevant data. Based on inclusion and exclusion criteria, about 51 cases of chronic obstructive pulmonary disease patients were compared with an equal number of healthy controls. Global initiative for chronic obstructive pulmonary disease (GOLD) guidelines were used for diagnosing COPD and Metabolic Syndrome diagnosed based on Modified NCEP: ATP III criteria.[5,10]

After taking a history and performing relevant clinical and laboratory evaluations, the following parameters were compiled in a structured clinical proforma:

Clinical history and demographic data, Weight, height, BMI (wt in kg/ht in meter$^2$), waist circumference, blood pressure, spirometry report, fasting blood sugar, serum triglyceride level and serum high density lipoprotein).

### Spirometry

Spirometry was done on a computerized spirometer (Spirobank G). The test was performed when patients were clinically stable. Spirometry was performed before and after post-bronchodilator short acting β-agonist.

### Sample size

Sample size was 102, calculated using N-master software with 51 cases and 51 controls. A study carried up by Marquis et-al on Metabolic Syndrome in COPD, showed that 47% of COPD patients as compared to controls had 3 or more parameters of metabolic syndrome. A statistically significant difference of Metabolic Syndrome at a power of 80% and α-level of 5%, It was required to include 51 subjects in each group thus a total of 102 subjects were included for study.

### Statistical analysis

All quantitative variables in the present study such as age, BMI, waist circumference, abdominal obesity, blood pressure, fasting blood glucose level, hypertriglyceridemia, low HDL were summarized in terms of descriptive statistics such as mean, standard deviation, median and range. All the qualitative variables were expressed in terms of frequencies and proportions. Student T test/Mann-Whitney test was used as indicated to compare the difference between the mean values in cases and controls. Chi-square test was used to find the association between the metabolic syndrome components and COPD. P value <0.05 was considered to statistically

significant. SPSS Version 20 software was used for statistical analysis.

## RESULTS

### Demographic and anthropometric features

The present study was done on 51 cases of COPD and an equal number of age and sex matched healthy controls. The mean age was 57.3 years in cases and 57.4 years in controls. Among each group there were forty-three (84.3%) males and eight (15.7%) females. The mean BMI in COPD patients was $24\pm5.32$ kg/m$^2$ compared to $22.59\pm4$ kg/m$^2$ in controls (p = 0.120). Among cases, 4 (7.8%) cases had BMI <18.5, 22 (43.1%) had normal BMI (18.5-23), 11 (21.6%) had BMI 23-25, 8 (15.6%) had BMI 25-30 and 6 (11.8%) had BMI>30. The mean waist circumference among patients was $92.63\pm8.1$cm and $90.22\pm7.78$ cm in controls (p = 0.128). Among these parameters, waist circumference of ≥102 cm or in male subjects and ≥88 cm in female subjects was considered as one of the defining features for metabolic syndrome according to the NCEP ATP III criteria. All the demographic and anthropometric parameters are depicted in Table 1. Among cases, 43 male patients (84.3%) gave a history of smoking. This included 31(72%) patients who smoked cigarettes and 13 (30%) who smoked beedis. Thirty patients were ex-smokers 30 (69.7%) and 13 (30.3%) were current smokers.

It was found that majority of the smokers had history of smoking more than 10 beedis/cigarette per day with a mean smoking index of 316.8 and mean pack years (of smoking) of 11.

**Table 1: Demographic and anthropometric parameters.**

| Parameter | Cases (n=51) | Controls (n=51) |
|---|---|---|
| Age (years) | 57.29±8.97 | 57.37±8.88 |
| Male:female | 43(84. %) / 8 (15.7%) | 43 (84.3%) / 8 (15.7%) |
| Smokers | 43 (84.3%) | 0 |
| BMI (kg/m$^2$) | 24.05±5.32 | 22.59±4.01 |
| Waist circumference | 92.63±8.10 | 90.22±7.78 |

All 8 female patients included in the study were non-smokers but had a history of exposure to biomass fuel. All controls were non-smokers and did not have any underlying pulmonary or systemic illness.

### Spirometry

As mentioned in the 'methods' section, a spirometry with bronchodilator reversibility was performed in all cases and severity of COPD was categorized based on GOLD guidelines. A baseline spirometry alone without reversibility testing was done in controls.

**Table 2: Spirometry values in COPD patients and controls.**

| | Cases | Controls | P value |
|---|---|---|---|
| FEV1/FVC | 57.92±8.87 | 82.12±5.58 | <0.001** |
| FEV1 | 57.71±17.03 | 100.90±12.4 | <0.001** |
| FVC | 79.75±18.24 | 103.31±12.87 | <0.001** |

**Table 3: GOLD stage and spirometry values in COPD patients.**

| | Gold staging | | | |
|---|---|---|---|---|
| | Mild (n = 7) | Moderate (n = 30) | Severe (n = 12) | Very severe (n = 2) |
| FEV1/ FVC | 63.93±3.32 | 59.59±8.58 | 51.63±8.36 | 50.60±6.51 |
| FEV1 | 84.14±2.67 | 60.77±10.64 | 39.75±4.69 | 27.00±0.00 |
| FVC | 99.43±5.16 | 84.07±12.90 | 63.92±14.64 | 41.00±2.83 |
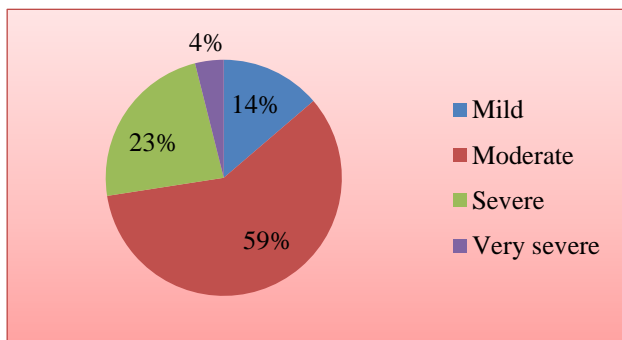


**Figure 1: GOLD stage among COPD patients**

**Table 4: Biochemical parameters in cases and controls.**

| | Cases | Controls | P value |
|---|---|---|---|
| TG (mg/dl) | 141.61±51.05 | 136.35±31.79 | 0.534 |
| HDL (mg/dl) | 41.22±11.73 | 47.61±12.35 | 0.009** |
| FBS (mg/dl) | 95.04±11.820 | 92.88±15.213 | 0.426 |

Among subjects in the COPD group, 7 (13.7%) patients had mild, 30 (58.8%) had moderate, 12 (23.5%) had severe and 2 (3.9%) had very severe COPD. Mean

spirometric values recorded in cases and controls are shown in Table 2. Categorisation of COPD (according to GOLD guidelines) are depicted in Table 3 and Figure 1.

Biochemical investigations pertaining to the diagnosis of metabolic syndrome (Table 4). The mean values of Fasting Blood Sugar (FBS), High density lipoprotein (HDL) and Triglyceride (TG) in cases and controls have been detailed in the Table 4.

### *Metabolic syndrome in cases and controls*

Using NCEP ATP III criteria, metabolic syndrome was diagnosed in 16 (31.4%) patients with COPD and in 8 (15.7%) controls (Figure 2).
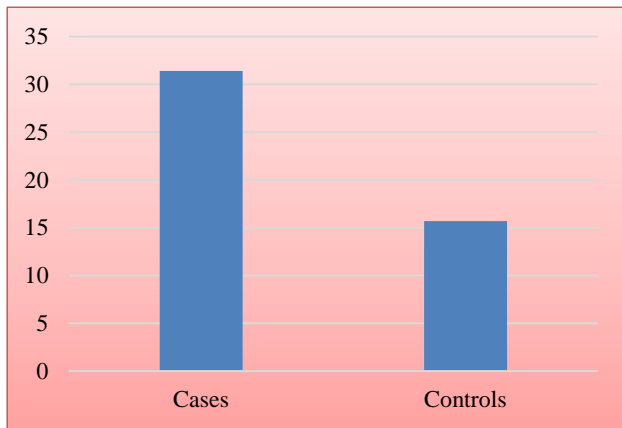


**Figure 2: Prevalence of metabolic syndrome.**

The proportion of metabolic syndrome in patients with COPD with respect to the stage of COPD has been depicted in Table 5. It was observed that 14 (96.5%) of COPD patients with metabolic syndrome had either moderate or severe COPD while the remaining 2 (3.5%) had mild and very severe COPD respectively.

**Table 5: Metabolic syndrome in various stages of COPD.**

| Gold stage | Metabolic syndrome |
|------------|--------------------|
| Mild | 1 (6.3%) |
| Moderate | 7 (43.8%) |
| Severe | 7 (43.8%) |
| Very severe | 1 (6.3%) |

### *Components of metabolic syndrome in study subjects*

#### *Cases*

Sixteen (31.4%) cases had 3 or more features of metabolic syndrome, thus qualifying for a diagnosis of MS while 35 did not meet criteria for MS. Out of the 16 patients with metabolic syndrome, 10 (62.5%) patients had 3 qualifying parameters and the remaining 6 (37.5%) had four qualifying parameters; the combination of parameters is depicted in Table 6.

Among those who did not meet the criteria for MS (n-35), 10 (28.5%) patients had no features of metabolic syndrome while 7 (20%) had at least one parameter of metabolic syndrome and 18 (42%) had 2 parameters of metabolic syndrome. The qualifying abnormalities in patients with one parameter included DM in 2 (28.5%), HTN in 1 (14.2%), low HDL in 4 (57.1%).

**Table 6: Parameters constituting MS in cases and controls.**

| | Cases | Controls | P value |
|---|-------|----------|---------|
| Hypertension | 21 (41.2%) | 9 (17.6%) | 0.408 |
| Diabetes mellitus | 19 (37.3%) | 13 (25.5%) | 1.000 |
| Waist circumference | 14 (27.5%) | 7 (13.7%) | 0.128 |
| Elevated serum triglycerides | 12 (23.5%) | 12 (23.5%) | 0.53 |
| Low serum HDL | 31 (60.8) | 22 (43.1) | 0.009 |

#### *Controls*

Six (11.7%) control subjects had 3 parameters of metabolic syndrome while 2 (3.9%) had four parameters of metabolic syndrome. Twenty-three (45%) control subjects had at least one parameter of metabolic syndrome and 8 (15%) had 2 parameters of metabolic syndrome. Twelve patients had no features of metabolic syndrome.

### *Comparison of frequency of components of metabolic syndrome in cases and controls*

Further statistical analysis was done with respect to individual parameters of metabolic syndrome. Hypertension was diagnosed in twenty-one (41.2%) patients as compared to nine (17.6%) in controls. Nineteen (37.3%) patients had diabetes mellitus as compared 13 (25.5%) controls. Fourteen (27.5%) patients had waist circumference above the cut-off value as compared to seven (13.7%) in controls with mean WC of 92.6 cm in cases as compared to 90.2 cm in controls.

Twelve (23.5%) patients each in the COPD and control group had elevated triglycerides; the mean level being 141.6 mg/dl in COPD patients and 136.3 mg/dl in controls. Thirty-one (60.7%) patients with COPD and 22 (43.1%) controls had decreased HDL; mean level was 41.2mg/dl in COPD patients and 47.6 mg/dl in controls. A statistically significant difference was found in serum HDL level between cases and controls as shown in Table 6.

### DISCUSSION

In this prospective study which included 51 COPD subjects and an equal number of matched controls who were screened for MS, it was found that the prevalence of metabolic syndrome was 31.4% in patients with COPD

and 15.7% in controls. (p = 0.062). This is in concurrence with the statistics reported in the literature. Studies have proved the association of COPD with various components of the metabolic syndrome. However, literature linking metabolic syndrome as a whole with COPD is scarce. It has also been proven that the prevalence of metabolic syndrome is higher in patients with COPD than in the general population [6-9]

In a study conducted by Watz H et-al on chronic bronchitis and COPD patients, it was reported that half of the patients included had metabolic syndrome irrespective of disease stage and severity. Besides, an association with markers of systemic inflammation, particularly the pro-inflammatory cytokines namely; Tumor necrosis factor-α (TNF- α), Interleukin (IL-6) C-reactive protein (CRP) and fibrinogen was demonstrated.[6]

A study conducted by Karine M et al concluded that 47% of COPD patients and 21% of control participants exhibited 3 or more determinants of the metabolic syndrome. They have emphasized in their results that a sedentary life style and physical de-conditioning in COPD patients predisposed them to developing MS, which in turn increased the risk for development of cardiovascular disease.[9]

A study by Funakoshi et al on 7,189 Japanese males aged 45-88 years found a high prevalence of metabolic syndrome in COPD patients particularly GOLD stage II - IV with an Odds ratio (OR) of 1.33.[11] The authors concluded that waist circumference and hypertension were the predominant components of metabolic syndrome in COPD patients.

An epidemiological study conducted in China showed a prevalence of metabolic syndrome in COPD patients approximately 20%.[7] They have concluded that obesity was the central component of metabolic syndrome in their patients. This study also correlated the occurrence of metabolic syndrome with smoking history and also to exposure to passive smoking and environmental dust.

### Age and gender distribution

In the present study, mean age cases and controls was 57.3 years with a male to female ratio of 5.3:1. Higher proportion of males compared to females could be attributed to increased frequency of smoking among males and exposure to various dusts and allergens at the workplace.

In males, metabolic syndrome was diagnosed in 12 (27.9%) cases and 6 (14%).controls while among females, 4 (50%) subjects and 2 (25%) controls had MS. This is comparable to the study conducted in China which showed higher prevalence of metabolic syndrome in females (22.9%) than in males (12.4%).[7] They found that men included in study had low TG level and lower waist circumference as compared to female participants.

However, the authors quoted there was no evidence from the heterogeneity of effect across strata that the association of lung function status and metabolic syndrome varied with sex.

### Smoking status

In the present study, all male 43 (84.3%) cases were smokers and all 8 (15.7%) female cases were non-smokers with history of exposure to biomass fuel. Among smokers, majority were 31 (72%) cigarettes smokers than 13 (30%) who smoked beedis with a mean smoking index of 316.8. and mean pack years (of smoking) of 11.

As mentioned in earlier studies, smoking is an important contributory factor for systemic inflammation and its consequences in COPD. Some of these studies have been reviewed below.[12-14]

Fabbri et al and Lone et al suggest that the term 'Chronic Systemic Inflammatory Syndrome' (comprising age >40 years, smoking for >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.[14,15]

Smoking induces systemic inflammation even in absence of COPD. Systemic inflammation in smokers contributes significantly to atherosclerosis.[16,17] Smoking triggers a local inflammatory response in lungs and it also causes systemic inflammation that results in comorbidities like cardiovascular or metabolic disorders.[12]

### Individual diseases and MS

In the present study, the occurrence of hypertension was not significantly different between cases and controls. The incidence of hypertension can vary from 6-50% and depends upon the severity of airflow of obstruction. The pathological mechanisms responsible for hypertension in COPD are hypoxia related vasoconstriction, free radical injury, endothelial dysfunction and arterial stiffness.[18]

A study conducted by Watz H, et al concluded that there was a high prevalence of hypertension in all stages of COPD; being as high as 70%.[6] Study conducted by Karine M et al states 59% of COPD cases had raised blood pressure. A health survey conducted several years.[9]

Present study has showed that hypertension was 31.7% in patients with GOLD stage II and III. These findings are consistent with other studies showing higher prevalence of hypertension in advanced stage of COPD.

In the present study, the mean FBS and DM were not significantly different between cases and controls. However, it was observed that our study has demonstrated a higher prevalence of DM in contrast with prevalence reported in other studies.[6,9,19]

The prevalence of diabetes in COPD is approximately about 3-12%. A study by Engstrom et al described that reduced lung function is an important risk factor for the development of diabetes in COPD.

An epidemiological study conducted in China showed results that metabolic syndrome (22.6 versus 19.8%), central obesity (34.1 versus 33.1%) and raised blood pressure (56.7 versus 53.4%) were more common in individuals with airflow obstruction than in those with normal lung function, the opposite was seen for raised fasting glucose level (34.3 versus 36.9%), raised triglyceride level (29.6 versus 33.4%) and reduced HDL–cholesterol level (15.9 versus 16.6%). [7]

Present study exhibited significant level of HDL component of metabolic syndrome with 31 (60.7%) patients having low HDL level as compared to 22 (43.1%) controls which was statistically significant. (p = 0.009). This is in concordance with various studies as mentioned above.[7]

A study conducted by Karine M et al has concluded that 24% had low HDL-C levels.[9] The CONSISTE study showed that COPD subjects had the highest prevalence of IHD (12.5% vs 4.7%) when compared to controls. Dyslipidemia was found in 48.3% of COPD patients and 31.7% among controls.[19]

In the present study, twelve (23.5%) patients each in the COPD and control group had elevated triglycerides; the mean level being 141.6 mg/dl in COPD patients and 136.3 mg/dl in controls. (p = 0.53) which was not in concordance with studies showing prevalence of high triglyceride level in COPD patient than in control groups.[7,19]

A study conducted by Karine M et al concluded that 63% of the COPD patients and 32% of controls had elevated triglycerides.[9]

In the present study, the difference in waist circumference in cases and controls was not statistically significant although mean values were higher in COPD patients. This is consistent with study done by Karine M et al which showed higher mean of WC in cases of COPD than in control group.[20]

### Combinations of diseases and MS

Ten (62.5%) patients had 3 parameters of metabolic syndrome among them combination of parameters hypertension, increased TG, and low HDL was found more frequent 4 (40%). Six (37.5%) patients had 4 parameters of metabolic syndrome

Six (37.5%) patients had 4 parameters of metabolic syndrome. The combination of parameters DM, hypertension, low HDL, and increased WC was found more common in this group of patients 4 (66.6%).

### Severity of COPD and MS

Present study showed higher prevalence of metabolic syndrome in COPD cases than in control group. It was observed that 14 (96.5%) of COPD patients with metabolic syndrome had either moderate or severe COPD while the remaining 2 (3.5%) had mild and very severe COPD respectively. Thus, there was a higher prevalence of metabolic syndrome in moderate and severe COPD patients than in very severe disease.

These results are in in accordance with study done by Watz H, et al which showed higher prevalence of metabolic syndrome in mild to moderate stage of COPD.[6] These observations may be explained by the fact that patients with severe to very severe COPD would have frequent exacerbations and hospitalizations with resultant loss of muscle mass, osteoporosis and weight loss. Watz H et al has observed that might be best explained by weight loss, which frequently occurs in patients who are the later stages of the disease.[6]

### CONCLUSION

The present study has demonstrated that there is higher prevalence of metabolic syndrome and its parameters among COPD patients, particularly those with moderate disease. Thus, considering COPD as a systemic disease and screening for components of metabolic syndrome could form a part of routine work-up of these patients.

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