Original Article

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Internal Medicine Section

Prevalence of Metabolic Syndrome in Chronic Obstructive Pulmonary Disease in Rural Population of Developing Country- A Cross-sectional Study

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ABSTRACT

Introduction: Metabolic Syndrome (MetS) is characterised by the clustering of central obesity, hypertension, dyslipidemia, and hyperglycemia that predisposes patients to Cardiovascular Disease (CVD). It is a representative group of conditions with systemic inflammation, which is a potential mechanism responsible for both Chronic Obstructive Pulmonary Disease (COPD) and MetS.

Aim: To detect incidence of MetS in COPD patients and its correlation with severity of COPD.

Materials and Methods: The present study was an observational cross-sectional study which was conducted on 62 COPD patients in SS Hospital, BHU, Varanasi, Uttar Pradesh, India, from June 2015 to June 2017, diagnosed on basis of Global initiative for Lung Disease (GOLD) guidelines. 62 age and sex matched control having no cardio-respiratory history were included. All relevant investigations were done for all selected subjects and modified Medical Research Council (mMRC) dyspnoea grading was done in all the subjects. Standardised treatment modules were followed and spirometry and post-bronchodialater spirometry was performed 15-30 mins after inhalation of 400 mcg Salbutamol. Patients obstruction was classified according to the severity of airflow limitation based on post-bronchodilator Forced Expiratory Volume in one second (FEV1) as follows: mild (≥80% predicted); moderate (80>FEV1 ≥50% predicted); severe (50%> FEV1 ≥30% predicted); very severe (<30% predicted). Complete work-up and data collection were analysed by using Statistical Package for the Social Sciences (SPSS) version 23.0 software, descriptive cross tables, univariate and multivariate analysis. Independent Student's t-test was used to compare the means of cases and controls. The p-value <0.05 was considered statistically significant.

Results: Total 62 patients along with age and sex matched 62 healthy control in 1:1 ratio have been taken in the study, majority were in age group of 50-70 years. On comparing the mean values of different parametres of MetS in COPD cases and controls, significantly raised triglyceride level and fasting blood sugar in COPD cases (p-value <0.001 and 0.005 respectively) were observed. MetS was present in 29 cases (46.8%) of COPD whereas in healthy control population only 19 people (30.6%) were positive for MetS. Total of 55.2% cases of COPD with MetS was in group D whereas 84.8% cases of COPD without MetS were in group B of GOLD staging. Statistically significant (p<0.001) higher incidence of acute exacerbation was observed in cases of COPD with MetS.

Conclusion: MetS was more prevalent among the COPD patient in 50-70 years age group with mild to moderate airflow limitation. More waist circumference i.e., central obesity, impaired fasting glucose, dyslipidemia, increases the risk of cardiovascular complication in these patients. MetS is an important co-morbidity in patients of COPD which fasten the natural course of disease by increasing the frequency of acute exacerbation.

Keywords: Airflow obstruction, Chronic obstructive pulmonary disease, Global initiative for lung disease, Morbidity, Spirometry

INTRODUCTION

According to Global Initiative for Lung Disease (GOLD) 2020, COPD is a common preventable and treatable condition, characterised by continuous respiratory symptoms and airflow limitation by airway and/or alveolar abnormalities usually caused by significant exposure to harmful particles or gases and influenced by host factors including abnormal lung development [1]. COPD is a growing cause of morbidity and mortality worldwide, and will be the third leading cause of death by 2020. Previously, it was characterised by localised inflammation of airway and alveoli, but recently many studies had demonstrated that the marker of systemic inflammation are significantly raised in COPD patients. Peripheral lung inflammation may cause the "spill-over" of inflammatory markers into the systemic circulation, thus lead to extra-pulmonary complications such as CVD, musculoskeletal wasting, osteoporosis, psychological disorders, and MetS [2,3]. Alternatively, smoking which causes systemic inflammation, and COPD and the genetic response to such changes may also trigger these responses [2,3]. So, the origin of systemic inflammation in patients with COPD is unclear [4]. Due to emergence of these new finding in past few year approaches of physicians treating COPD has been changing. Now COPD is not just an airway disease. Now-a-days, more people are in favor of multisystem approach rather than tubular approach. COPD often co-exists with other diseases that may have a significant impact on prognosis.

Metabolic Syndrome (MetS) represents a cluster of risk factors that increases the risk for developing diabetes mellitus, non-fatal and fatal CVD [5]. The representative group of conditions clustering of central obesity, hypertension, dyslipidemia, and hyperglycemia with systemic inflammation, is a potential mechanism responsible for both COPD and MetS [6].

MetS is common in patients with COPD. According to the previous study by Mekov E et al., the prevalence of MetS in COPD patients varies between 21-53% [7]. Many previous studies suggest that there is a strong association between the MetS and COPD and it may have impact on quality of life, lung function, natural course of COPD (number of exacerbations) as well as to affect co-morbidities

in COPD patients [8-10]. The prevalence of MetS in COPD patients is increased when compared to a control group as observed in studies by Funakoshi Y et al., and Marquis K et al., [8,11]. So, in this study, the authors aimed to detect the incidence of MetS in COPD patients and its correlation with severity of COPD in rural Indian Population.

MATERIALS AND METHODS

The present study was an observational, cross-sectional study which was conducted on 62 COPD patients and 62 age and sex matched control having no cardio-respiratory history from the Chest Department of SS Hospital, BHU, Varanasi, Uttar Pradesh, India, from June 2015 to June 2017. Permission of Departmental Ethical Committee (Diary no: Dean/2015-16/EC/223) as well as Institutional Ethical Committee was obtained (number- ECR/526/Inst/UP/2014 Dt. 31.1.14).

Inclusion criteria: Patients diagnosed with Chronic Obstructive Pulmonary Disease (COPD) based on GOLD guidelines, [1], on the basis of history, clinical examination and investigations were included after taking informed consent.

Exclusion criteria: The patients with asthma/other chronic respiratory disorder, malignancy, active pulmonary tuberculosis, acute exacerbation/systemic corticosteroids in last three months or known case of ischaemic heart disease/hypertension/ diabetes mellitus type II/Chronic Renal Failure and those who did not gave consent were excluded from the study.

The cases were documented for COPD with post- bronchodilator pulmonary function test confirmation (FEV1/FVC <0.7) with irreversible airway obstruction and were screened for other causes of breathlessness like exacerbation of bronchial asthma, interstitial lung diseases, worsening of dyspnoea due to heart failure etc., by channeling through detailed history, thorough physical examination and a battery of relevant investigations.

During hospital admission, patients were first treated with the standard protocol consisting of short acting beta-2 agonist, inhaled corticosteroids and theophylline as warranted and guided by arterial blood gas analysis. Once the patient underwent, Pulmonary Function Test (PFT) and reversibility testing and other relevant investigations were done they were accordingly included/excluded from the study.

All selected patients underwent following investigations Complete Blood Count (CBC), renal and liver function tests, random blood sugar, HbA1c, Lipid Profile, High sensitivity C-Reactive Protein (HsCRP), Fasting insulin level, X-ray chest (PA view), PFT and Echocardiography (ECG). ECG with 2D colour Doppler of heart, Treadmill Test (TMT), cardiac biomarkers (Troponin T, Creatinine Kinase (CK)-MB, Brain Natriuretic Peptide (BNP) and arterial blood gas analysis were performed wherever necessary. mMRC dyspnoea grading was done by Body-Mass Index, airflow Obstruction, Dyspnoea, and Exercise (BODE) Index [12], six minute walk test and Body Mass Index (BMI). High Resolution Computed Tomography (HRCT) thorax, Coronary angiogram, Carotid artery Doppler and Polysomnography were also performed for the grading wherever required. Body weight and height were measured and the BMI was calculated by dividing weight by height squared (kg/m^2). According to BMI, all patients were classified as underweight (<18.5 kg/m^2), normal (18.5-24.99 kg/m^2), overweight (25-29.99 kg/m^2) and obese (>30 kg/m^2). Waist circumference was measured according to the World Health Organisation (WHO) steps protocol [13]. The collected data was used for diagnosis of MetS according to the criteria of National Cholesterol Education Programme: Adult Treatment Plan III [14].

Pulmonary function test: For performing the spirometry, patients were instructed to withdraw using short-acting β2-agonists for atleast six hours, long-acting β2-agonist for atleast 12 hours, long acting muscarinic antagonist for 24 hours and short acting muscarinic antagonist for 12 hours before the spirometry [15]. Post-bronchodilator spirometry testing was performed 15-30 min after inhalation of 400 mcg Salbutamol according to European Respiratory Society (ERS)/American Thoracic Society (ATS) recommendations [15]. Pre and post values were obtained for Forced Vital Capacity (FVC), FEV1, FEV1/FVC, FEV6, FEV1/FEV6, (Peak Expiratory Flow) PEF, FEF2575, FEV3, FEV3/FVC along with their difference. Global Lungs Initiative (GLI-2012) predicted values were used [16]. Patients obstruction was classified according to the severity of airflow limitation based on post-bronchodilator FEV1 as: mild (≥80% predicted); moderate (80>FEV1 ≥50% predicted); severe (50% > FEV1 ≥30% predicted); very severe (<30% predicted). Data were collected for number of acute exacerbations and duration of the current hospital stay was recorded. The subjects were divided into GOLD groups based on the FEV1 measured as: those with mild FEV1 to be in GOLD Grade A, moderate in GOLD Grade B, severe in GOLD Grade C and very severe in GOLD Grade D [1]. Similarly the GOLD staging was done according to severity of symptoms and mMRC breathlessness for treatment purposes [1].

STATISTICAL ANALYSIS

After the complete work-up, prevalence of MetS was calculated in COPD cases and control group as well as in different COPD GOLD groups. All data were analysed and calculated by using SPSS statistical version 23.0 software package. Discrete data were analysed by cross tables by using descriptive method. Continuous data were analysed by Univariate analysis. Means of both group patients (Cases and Control) were analysed by Independent Student's t-test. Multiple variables were analysed by multivariate analysis. Differences with p-value <0.05 were considered as statistically significant.

RESULTS

Total 62 patients along with age and sex matched 62 healthy control in 1:1 ratio were included in the study, majority of the study population were in 50 to 70 years age group. Age matched healthy control population were taken from the hospital staff and patients attendants [Table/Fig-1]. In the present study, almost equal number of males and females were seen with slightly male predominance 54.8% in cases [Table/Fig-2].

	Cases (COPD patients)		Control (Healthy population)	
Age group (years)	Frequency	Percentage	Frequency	Percentage
41-50	7	11.3%	9	14.5%
51-60	19	30.6%	18	29.0%
61-70	22	35.5%	22	35.5%
>70	14	22.6%	13	21.0%
Total	62	100	62	100

[Table/Fig-1]: Showing age distribution in cases and control group (N=62 in each group).
χ^2=0.314; p=0.957

	Cases (COPD patients)		Control (Healthy population)	
Sex	Frequency	Percentage	Frequency	Percentage
Male	34	54.8%	29	46.8%
Female	28	45.2%	33	53.2%
Total	62	100	62	100

[Table/Fig-2]: Showing sex distribution.
χ^2=0.807; p=0.369

To diagnose the incidence of MetS in cases of COPD as well as in healthy control population, the mean±Standard Deviation (SD) of different parameters were measured. On comparing, significantly raised triglyceride level and fasting blood sugar in COPD cases (p-value ≤0.001 and 0.005 respectively) was observed. Waist circumference, systolic blood pressure, diastolic blood pressure were also higher in cases of COPD in comparison to healthy control but was not significant (p-value >0.05 in all the cases). HDL level was lower in COPD cases which was statistically not significant (44.11±7.786 vs. 46.48±7.846, p-value=0.094) [Table/Fig-3].

Out of 62 cases of COPD, MetS was present in 29 cases (46.8%) of COPD, much higher as compared to healthy control population where 19 people (30.6%) were positive for MetS [Table/Fig-4].

Parameters	Cases (Mean±SD)	Control (Mean±SD)	t-value	p-value
Age (years)	64.19±9.715	61.98±9.069	1.309	0.193
Waist circumference (cm)	84.56±8.502	83.61±8.141	0.637	0.526
SBP (mm Hg)	126.90±18.062	123.90±13.504	1.047	0.297
DBP (mm Hg)	79.65±8.466	79.65±7.712	0.000	1.000
FBS (mg/dL)	99.16±23.029	88.68±17.142	2.875	0.005
TG (mg/dL)	156.69±27.753	137.23±30.838	3.695	<0.001
HDL (mg/dL)	44.11±7.786	46.48±7.846	-1.689	0.094

[Table/Fig-3]: Comparison of mean of parameters of MetS between Cases (COPD Patients) and controls (Healthy population).
SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBS: Fasting blood sugar; TG: Triglycerides; HDL: High density lipoprotein

MetS	Cases (COPD patients)		Control (Healthy population)	
	Frequency	Percentage	Frequency	Percentage
Present	29	46.8%	19	30.6%
Absent	33	53.2%	43	69.4%
Total	62	100%	62	100%

[Table/Fig-4]: Prevalence of MetS in patients of COPD (Cases) and healthy population (Control) group.
χ^2=3.399; p=0.065

Comparison between the COPD with MetS and COPD without MetS

MetS was present in mostly 50-70 years age group of patients, with 20.7% and 48.3% of COPD patients with MetS were in age group of 41 to 50 years and 51 to 60 years, respectively whereas it was less common in older age, only 13.8% and 17.2% were in 61 to 70 years and more than 70 years respectively [Table/Fig-5].

Age (years)	COPD with MetS		COPD without MetS	
	Frequency	Percentage	Frequency	Percentage
41-50	6	20.7%	1	3.0%
51-60	14	48.3%	5	15.2%
61-70	4	13.8%	18	54.5%
>70	5	17.2%	9	27.3%
Total	29	100%	33	100%

[Table/Fig-5]: Age distribution in cases of COPD with MetS and COPD without MetS.
χ^2=17.702; p=0.001

MetS was more common in COPD with mild to moderate airflow limitation, 72.4% cases of COPD were in GOLD stage I and II whereas only 20.7% and 6.9% cases were in GOLD stage III and GOLD stage IV respectively [Table/Fig-6].

GOLD stage	COPD with MetS		COPD without MetS	
	Frequency	Percentage	Frequency	Percentage
GOLD I	5	17.2	3	9.1
GOLD II	16	55.2	2	6.1
GOLD III	6	20.7	14	42.4
GOLD IV	2	6.9	14	42.4
Total	29	100	33	100

[Table/Fig-6]: Distribution of patients of COPD with MetS and COPD without MetS according to airflow limitation severity (GOLD STAGE).
χ^2=23.428; p<0.001; GOLD: Global initiative for lung disease

More than 90% of patients included in the study had 2 or more than 2 mMRC grade breathlessness, hence were in group B and group D which was an important guiding principle in choosing the regimen for the treatment of COPD. Total of 55.2% cases of COPD with MetS was in group D whereas 84.8% cases of COPD without MetS were in group B. The difference was statistically significant [Table/Fig-7].

GOLD grade	COPD with MetS		COPD without MetS	
	No.	%	No.	%
A	0	0	0	0
B	11	37.9	28	84.8
C	2	6.9	0	0.0
D	16	55.2	5	15.2
Total	29	100	33	100

[Table/Fig-7]: Distribution of patients of COPD with MetS and COPD without MetS in different gold grade A,B,C,D.
χ^2=14.976; p<0.001

In 17 patients i.e., 58.6% cases of COPD with MetS had history of 2 or more than 2 number of acute exacerbation in previous year whereas only 3 case i.e., 9.1% cases of COPD without MetS had history of 2 or more than 2 number of acute exacerbation in previous year. These finding were statistically significant and suggesting the higher incidence of acute exacerbation in cases of COPD with MetS [Table/Fig-8].

Number of acute exacerbation	COPD with MetS		COPD without MetS	
	Frequency	Percentage	Frequency	Percentage
0	3	10.3	13	39.4
1	9	31.0	17	51.5
2	12	41.4	2	6.1
3	5	17.2	1	3.0
Total	29	100	33	100

[Table/Fig-8]: Number of patients of COPD with MetS and COPD without MetS with different no. of acute exacerbation.
χ^2=18.339; p<0.001

DISCUSSION

Chronic Obstructive Pulmonary Disease (COPD) a disorder of chronic airflow limitation, is the third most common cause of death worldwide and is irreversible by bronchodialators. The understanding of COPD has changed from a simple airflow limitation to a complex and heterogeneous condition with significant extra-pulmonary manifestations in heart, skeletal muscles as well as diabetic tendencies. Several cross-sectional and longitudinal studies have established a link between MetS and COPD [17,18], and MetS is an independent risk factor for worsening respiratory symptoms, increasing lung function impairment, pulmonary hypertension, and asthma. However, the extent of association of COPD with MetS and its individual components are still an unsettled issue, and it is likely to vary from population to population. Both COPD and MetS are common in South Asian Indians [19,20], but the association between the two disorders and their common determinants have not been properly investigated. In this study, these issues have been addressed through a case-control design.

The present study included 54.8% male and 45.2% female in the study group suggesting almost equal prevalence of COPD amongst male and female population which was against the existing fact that COPD is more prevalent amongst the male population due to habit of smoking, but it can be explained by the high exposure of biomass fuel smoke as well as habit of bidi smoking amongst the women population in North-eastern region of Uttar Pradesh which is one of the most backward and underdeveloped regions of India as well as of South East Asia. This observation is supported by many previous studies, according to which exposure to outdoor and indoor air pollutants increases the prevalence of COPD by an estimated 2% for each 10 g/m^3 increase in particulate matter [9,21]. This observation was also supported in a study by Halbert R et al., according to which exposure of biomass fuels (e.g., use of wood for cooking and heating) increases the risk of COPD by three to four times, contributing significantly to COPD prevalence [22].

In the present study, prevalence of MetS in COPD patients was 46.8% which is in accordance with the previous studies which suggest prevalence of MetS in COPD in the range of 21 to 53%. In a study conducted by Watz H et al., prevalence of MetS in COPD was found to be 47% in German population [10]. A study

conducted by Marquis K et al., in Canada, concluded that 47% of COPD patients and 21% of control participants presented three or more determinants of the MetS [11]. This study also suggests that the prevalence of MetS in COPD patients was much higher in comparison to general population. So, screening of MetS in patients of COPD should be done to avoid the cardiovascular complication.

MetS was more common in COPD cases with mild to moderate grade of airflow limitation since 55.2% and 17.2% cases of COPD with MetS were within the GOLD stage II and GOLD stage I respectively, when they are classified according to airflow limitation severity. On statistical analysis this finding was significant (p<0.001). Study done by Minas M et al., also found that MetS is more prevalent in younger patient with less severe COPD [23]. In a study done by Watz H et al., also reported slightly higher frequency of MetS in mild to moderate form of COPD [10].

According to Kupeli E et al., and Abdelghaffar HB et al., the presence of MetS in patients with COPD increases with the frequency of exacerbations (2.4 vs 0.7) and their duration - (7.5 vs 5.0 days; 8 vs 5.5 days) [17,18]. The present study found a similar finding, 58.6% cases of COPD with MetS were having history of 2 or more than 2 number of acute exacerbation in previous year which was significantly high in comparison to COPD without MetS group in which only 9.1% cases have history of 2 or more 2 exacerbation in previous year (p<0.001). This finding is further supported by the study done by Mekov E et al., in Bulgaria in which study reported that the presence of MetS was significantly related to the number of acute exacerbations [7]. Acute exacerbation further deteriorates the FVC of patients and fastens the natural progress of disease. So COPD with MetS are at more risk of rapid deterioration in FVC due to frequent acute exacerbations. Since 58.6% of patients in the group of COPD with MetS had history of 2 or more than 2 acute exacerbation per year and more 90% of patients included in the study have 2 or more than 2 mMRC grade breathlessness, so total 55.2% patients of COPD with MetS are in group D in GOLD grading system which is an important guiding principle in the treatment of COPD.

Limitation(s)

Firstly, it was a cross-sectional analysis. Therefore, causal relationships cannot be inferred on the descriptive level. Secondly, it is a study that was performed in a single centre. The observed results of the studies needs confirmation by further studies to be generalised. Sample size for cases was small and also the control population may not be representative of general population.

CONCLUSION(S)

Metabolic Syndrome (MetS) is more prevalent among the COPD patient in 50-70 years age group with mild to moderate airflow limitation. Chronic Obstructive Pulmonary Disease (COPD) patients with MetS are obese with more waist circumference i.e., central obesity, impaired fasting glucose, dyslipidemia, in comparison to COPD without MetS which increases the risk of cardiovascular complication. MetS is an important co-morbidity in patients of COPD which fasten the natural course of disease by increasing the frequency of acute exacerbation.

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