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INCIDENCE OF METABOLIC SYNDROME (METS) BASED ON HAEMATOLOGY, SEROLOGY & ACID BLOOD GAS ANALYSIS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE COPD PATIENTS AND ITS CORRELATION WITH SEVERITY OF COPD IN RURAL POPULATION OF NORTH INDIA: A CROSS-SECTIONAL STUDY.

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ABSTRACT

INTRODUCTION: The metabolic syndrome implies to the co-occurrence of various known cardiovascular risk factors that includes obesity, insulin resistance, atherogenic dyslipidemia and hypertension.

AIM: To detect prevalence of metabolic syndrome MetS in Chronic Obstructive Pulmonary Disease (COPD) patients and its correlation with severity of COPD.

MATERIALS AND METHODS: The current study was an observational cross-sectional study which was conducted on 62 COPD patients, from June 2018 to May 2020, diagnosis was based on Global initiative for Lung Disease (GOLD) guidelines and 62 age and sex matched control having no cardio-respiratory history.

All relevant investigations were conducted for all selected subjects and modified Medical Research Council (mMRC) dyspnoea grading was done in all the subjects. 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.

Standardised treatment modules were adhered to and spirometry and post-bronchodialater spirometry were 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).

Statistical Analysis: All records and data collection were analysed by using Statistical Package for the Social Sciences (SPSS) statistical version 25.0 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 sixty two patients along with age and sex matched sixty two healthy control in 1:1 ratio matched the inclusion criteria of the study, with mean age group of 50-70 years. On comparison of 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. 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: There were higher incidence of MetS among the COPD patient in age group of 50-70 years with mild to moderate airflow obstruction. More waist circumference i.e., central obesity, insulin resistance, dyslipidemia, increases the risk of cardiovascular complication in these patients. MetS is a vital comorbidity in patients of COPD that fastens 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

In accordance with GOLD 2020 report, COPD is one of the common preventable and treatable conditions which is characterised by continuous respiratory symptoms and airflow limitation either by airway and/or alveolar abnormalities typically caused by a significant exposure to harmful particles or gases and influenced by host factors which includes abnormal lung development [1]. COPD could be a growing explanation formorbidity and mortality worldwide, and will be the third leading reasons of death by 2020.

Previously, it was characterised by localised inflammation of airway and alveoli, however recently several studies had incontestable that that the marker of systemic inflammation are considerably raised in COPD patients. Peripheral lung inflammation might cause the "spill-over" of inflammatory markers into the systemic circulation, therefore result in extra-pulmonary complications such as CVD, musculoskeletal wasting, osteoporosis, psychological disorders, and MetS[2,3].

Alternatively, smoking that results in 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 doubtful[4]. Thanks to the emergence of those new finding in past few year, approaches of physicians treating COPD has been dynamical. Now COPD is not an airway disease anymore. Now-a-days, more no. of people are infavor of multisystem approach rather than tubular approach. COPD often co-exists with other diseases that might have a significant impact on prognosis.

MetSshows a cluster of risk factors which increases the risk of developing diabetes mellitus, non-fatal as well as fatal CVD [5]. The group of conditions including clustering of central obesity, hypertension, dyslipidemia, and hyperglycemia with systemic inflammation signifies 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 ranging from 21% to 53% [7]. Earlier studies have suggested that there is a robust association between the MetS and COPD and it is going to have an impact on quality of life, respiratory (lung) function, natural course of COPD (number of exacerbations) additionally will have an impact on co-morbidities in COPD patients [8-11]. The prevalence of MetS in COPD patients is increased in comparison to a control group as observed in studies by Funakoshi Y et al. and Marquis K et al., [7,10]. So, in this study, the authors aimed to evalaute the incidence of Metabolic Syndrome (MetS) based on Haematology, Serology & Acid Blood Gas Analysis in Chronic Obstructive Pulmonary Disease COPD

patients and its correlation with severity of COPD in Rural Population of North India.

MATERIALS AND METHOD

The present study was a cross-sectional and observational study that was conducted on sixty twoCOPD patients and sixty two age and sex matched control having no cardio-respiratory history from June 2018 to May 2020.

Inclusion Criteria:

Patients suffering fromCOPD based on GOLD guidelines,[1], based on history, clinical examination and investigations were included after taking informed consent.

Exclusion Criteria:

Subjects diagnosed with asthma or other chronic respiratory disorder, active pulmonary tuberculosis,malignancy, showing acute exacerbation of systemic corticosteroids in last three months or any known case of diabetes mellitus type II/ischemic heart disease/hypertension/ Chronic Renal Failure and those who did not give written informed consent were excluded from the study.

The cases were recorded documented for Chronic Obstructive Pulmonary Diseases with confirmationof post-bronchodilator pulmonary function test (FEV1/FVC less than 0.7) having irreversible airway obstruction and were thereafter screened for various other causes of breathlessness such as exacerbation of interstitial lung diseases, worsening of dyspnea due to heart failure, bronchial asthma, etc. by following strict protocols through detailed history, thorough physical examination and a channel of relevant serological and haematological investigations.

During hospital admission, patients were firstly treated with the standard protocol that consisted of short acting beta-2 agonist, inhaled corticosteroids and theophylline whichhas been warranted and governed by arterial blood gas analysis. They were accordingly included or excluded from the study, once the patients underwentpreliminary Pulmonary Function Test (PFT), reversibility testing and other relevant serological and haematological investigations.

All patients who met the inclusion criteria, underwent following investigations:

Complete Blood Count (CBC), HbA1C, renal & liver function tests, random blood sugar, High sensitivity C-Reactive Protein (HsCRP), Lipid Profile, Fasting insulin level , X-ray chest (PA view), PFT and Echocardiography (ECG). Echocardiography with 2D colour Doppler of heart, cardiac biomarkers (Creatinine Kinase (CK)-MTroponin T, B, Brain Natriuretic Peptide (BNP) and arterial blood gas (ABG) analysis,Treadmill Test (TMT), were done wherever necessary. mMRC dyspnoea grading was done by Body-mass index, airflow Obstruction, Dyspnea, and Exercise (BODE) Index [12], six minute walk test and Body Mass Index (BMI). High Resolution Computed Tomography (HRCT) thorax, Carotid artery Doppler, Coronary angiogram, 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/m2). According to BMI, all patients were classified as underweight (less than 18.5 kg/m2), normal (18.5 to 24.99 kg/m2), overweight (25 to 29.99 kg/m2) and obese (>30 kg/m2). Waist circumference was measured in accordance with the World Health Organisation (WHO) steps protocol[13]. The gathered data was then used for the diagnosis of MetSas per the criteria of National Cholesterol Education Programme: Adult Treatment Plan III [14].

Pulmonary function testing (PFT): For performing the spirometry, patients were instructed to withdraw the usage of short-acting β2-agonists for at least 6 hours, long-acting β2-agonist for at least twelve hours, long acting muscarinic antagonist for 24 hours and short acting muscarinic antagonist for twelve hours before the spirometry [15]. Post-bronchodilator spirometry testing was performed 15-30 min post inhalation of 400 mcg of Salbutamol as perrecommendations of European Respiratory Society (ERS) and American Thoracic Society (ATS) [15]. Pre and post values were then after obtained to estimate Forced Vital Capacity, Peak Expiratory Flow along with their difference. Global Lungs Initiative (GLI-2012) predicted values were used [16]. Patients obstruction was then classified as per the severity of airflow limitation on the basis of post-bronchodilator FEV1 as:

- GOLD Grade A : mild (≥80% predicted);
- GOLD Grade B: moderate (80>FEV1 ≥50% predicted);
- GOLD Grade C: severe(50% > FEV1 ≥30% predicted);
- GOLD Grade D: very severe (<30% predicted).

Data were collected for number of acute exacerbations and duration of the current hospital stay was also recorded. Similarly, the GOLD staging was done as per severity of symptoms and mMRC breathlessness for treatment purposes [1].

Statistical Analysis

After completing entire 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 25.0 software package. Discrete data were evaluated by cross tables by using descriptive method. Continuous data were evaluated evaluated by Univariate analysis. Means of both group patients (Cases and Control) were evaluated 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 sixty two subjects 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- 70 years age group. Age matched healthy control population were recruited from the hospital staff and patients attendants [Table/Figure-1]. In the present study, almost equal number of males and females were seen with slightly male predominance 54.8% in cases [Table/Figure-2].

Table/fig-1: Showing Age Distribution In Cases And Control Group (n=62 In Each Group).χ^2=0.314; P=0.957

Age group (years)	Cases (COPD patients)		Control (healthy population)	
	Frequency	Percentage	Frequency	Percentage
40-50	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-2: Showing Sex Distribution. X^2=0.807; P=0.369

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

To diagnose the prevalence of MetS in subjects of COPD as well as in healthy control population, the mean±SD of different parameters were calculated. On comparison, significantly raised triglyceride levels (TGL) and fasting blood sugar (FBS) in COPD cases (p-value was ≤0.001 and 0.005 respectively) has been 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 (46.85%) of COPD, much higher as compared to healthy control population where 19 people (30.6%) were positive for MetS [Table/Fig-4].

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

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-4: Prevalence Of Mets In Patients Of Copd (cases) And Healthy Population (control) Group. X^2 =3.399; P=0.065

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%**

Comparison Between The Copd With Mets And Copd Without Mets

MetS was present in mostly 50-70 years age group of patients. 20.7%and48.3%ofCOPDpatientswithMetSwereinagegroup of 41 to 50 years and 51 to 60 years respectively whereas it was lesscommoninolderage,only13.8%and17.2%werein61to70 years and more than70years respectively [Table/Fig-5].

Table/fig-5: Age Distribution In Cases Of Copd With Mets And Copd Without Mets. X^2=17.702; P=0.001

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%

MetS was seen more commonly 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].

Table/fig-6: Distribution Of Patients Of Copd With Mets And Copd Without Mets According To Airflow Limitation Severity (gold Stage). X^2 =23.428; P<0.001

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**

More than 90% of subjects who were included in the study had two or more than two mMRC grade of breathlessness, therefore they were in group B and group D that was an important guiding principle in selectingthe appropriate regimen for the treatment of COPD. 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]. 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 observations were statistically significant; suggesting higher prevalence of acute exacerbation in cases of COPD with MetS [Table/Fig-8].

Table/fig-7: Distribution Of Patients Of Copd With Mets And Copd Without Mets In Different Gold Grade A,b,c,d. X^2 =14.976; P<0.001

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-8: Number Of Patients Of Copd With Mets And Copd Without Mets With Different No. Of Acute Exacerbation X^2 =18.339; P<0.001

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**

DISCUSSION

It's a common known fact that COPD is a disorder of chronic airflow limitation and is considered to be the third most common cause of death worldwide and is known to be irreversible by bronchodialators. The knowledge and understanding of COPD has changed significantly in past few decades, from a simple airflow limitation to indeed a complex and heterogeneous condition surmounting to significant extra-pulmonary manifestations in heart, skeletal muscles as well as diabetic tendencies. Several cross-sectional and longitudinal studies have marked a connection between MetS and COPD [17,18]. and MetS is an independent risk factor for further worsening respiratory symptoms, increasing lung function impairment, pulmonary hypertension, and asthmatic condition. However, the extent of relationship of COPD with MetS and its individual components are still unclear, and it is likely to vary from population to population on a larger scale. 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 thoroughly investigated. In present study, these issues have been dealt withvia a case-control design. The present study had 54.8% male and 45.2% female in the study group which suggests 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 significant exposure of biomass fuel smoke as well as habit of bidi smoking amongst the women population in Northeastern region of Uttar Pradesh which is nevertheless one of the most backward and underdeveloped regions of the country as well as of south east Asian region. 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/m3 increase in particulate matter [9,21]. This observation was in accordance with a study done by Halbert R et al., according to which exposure of biomass fuels (e.g., use of wood for cooking and heating) significantly increases the risk of COPD by 3-4 times, contributing significantly to prevalence ofCOPD [22]. In the present study, prevalence of MetS in COPD patients was 46.8% which is in accordance with the previous studies suggestive of prevalence of MetS in COPD in the range of 21- 53%. In a study done by Watz H et al., prevalence of MetS in COPD was seen to be 47% in German population [10]. A study conducted by Marquis K et al., in Canada, inferred that 47% of COPD patients and 21% of control patients presented three or more determinants of the MetS [11]. This study also suggests that the prevalence of MetS in COPD patients was much higher when compared to general population. So screening of MetS in patients of COPD needs to be done to avoid the cardiovascular as well as blood (haematology) related complications. 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 observation was significant (p<0.001). In another study conducted by Minas M et al., also found that MetS is more prevalent in younger subjects with less severe COPD [23]. In a study done by Watz H et al that reported slightly higher prevalence of MetS in mild to moderate form of COPD [10].

In the present study, 58.6% of COPD cases with MetSshowed history of 2 or more than 2 number of acute exacerbation in previous year which was significantly higherwhen compared 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). Acute exacerbation further worsens the FVC of subjects and speeds up 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 subjects in the group of COPD with MetS had shown a history of two or more than two acute exacerbation per year and more than 90% of patients included in the study have two or more than two mMRC grade breathlessness, so in total 55.2% patients of COPD with MetSwere in group D in the GOLD grading system which is an important governing principle in the treatment of COPD.

CONCLUSION

MetS is thus more prevalent among the COPD patient in age group of 50-70 years with mild to moderate airflow limitation. COPD patients with MetS are usually obese with more waist circumference i.e., central obesity, impaired fasting glucose, dyslipidemia, in comparison to COPD without MetS which shoots up the risk of cardiovascular complication. MetS is an important co-morbidity factor in patients of

COPD which speeds up the natural course of disease by increasing the frequency of acute exacerbation.

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