Original Article

Systemic inflammation in patients of chronic obstructive pulmonary disease with metabolic syndrome

Sufia Naseem[1], Ummul Baneen[2]

Departments of [1]Biochemistry, [2]Tuberculosis and Respiratory Medicine, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India

Abstract

Context: India has 18% of the global population and an increasing burden of chronic respiratory diseases. The prevalence of Metabolic syndrome (MS) was found to be as high as 39.7% among Indian population. Metabolic syndrome is found to be more common in Chronic Obstructive Pulmonary Disease (COPD) when compared to the general population. This study was done to assess the prevalence of metabolic syndrome in COPD and the association of systemic inflammation in COPD patients with metabolic syndrome. **Methodology:** This study enrolled 150 consecutive consenting patients of stable COPD attending the outpatient pulmonology department. Detailed history, clinical examination, spirometry, and relevant routine laboratory investigations including complete blood count, fasting blood sugar, and lipid profile were done. In addition, hsCRP, Serum lactate and Vitamin D level was assessed in all patients. Diagnosis of COPD and Metabolic syndrome was done according to GOLD guidelines, 2018 and the International Diabetes Federation criteria respectively. **Result:** The prevalence of metabolic syndrome was found to be 27.3% in our COPD patients. The frequency of metabolic syndrome in GOLD stage I, II, III, and IV was 75%, 32%, 17%, and 13.5%, respectively. Logistic regression analysis showed a significant relationship of blood leucocyte count (OR = 0.342, CI = 0.171-0.686), hs-CRP (OR = 0.020, CI = 0.003-0.122), pack years (OR = 1.083, CI = 1.026-1.14) and vitamin D levels (OR = 1.219, CI = 1.093-1.359) with metabolic syndrome in COPD patients. **Conclusion:** Metabolic syndrome is a co-morbidity that is very often overlooked in patients of COPD. Systemic inflammation which is a common characteristic of both COPD and Metabolic syndrome has been found to be an important contributor towards cardiovascular morbidity and mortality.

Keywords: Chronic obstructive pulmonary diseases, hsCRP, lactate, metabolic syndrome, pack years, spirometry, vitamin D

Introduction

The prevalence of Chronic Obstructive Pulmonary Disease (COPD) in India increased from 3·3% in 1990 to 4.2% in 2016.[1] Worldwide prevalence of Metabolic Syndrome (MS) ranges from <10% to as much as 84%, depending on the region, urban-rural environment, composition (sex, age, race, and ethnicity) of the patient, and the definition used. The prevalence of MS in India has been documented to be from 11% to 41% across this vast country with numerous socio-cultural varieties. A study in north India stated that the prevalence of Metabolic Syndrome[2] was more than 40% and its prevalence in <40 years age group is rapidly increasing.

The patients with COPD most often have associated chronic comorbidities. The systemic inflammatory process underlying COPD may lead to development or worsening of co-morbidities like type-2 diabetes mellitus (T2DM)[3] and metabolic syndrome (MS).[5] It has been shown that patients with COPD with MS present higher levels of insulin resistance compared to COPD patients without MS.[6] There is a complex interaction between COPD and metabolic syndrome.

Patients with COPD especially in severe cases or during exacerbations develop inflammatory responses and oxidative

Address for correspondence: Dr. Ummul Baneen, G-2, Azim Green Homes, New Sir Syed Nagar, Aligarh Muslim University, Aligarh - 202 001, Uttar Pradesh, India.
E-mail: ummulb8@gmail.com

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stress which also share a link with other diseases like metabolic syndrome. There is an interlinked mechanism for perpetuation of both inflammation and oxidative stress facilitating each other.[7] Inflammatory mediators such as TNFα and IL6 cause impaired insulin signaling thereby resulting in insulin resistance and hyperinsulinemia. Watz *et al.* found an association of higher levels of hs-CRP and IL-6 in patients of COPD with Metabolic Syndrome as compared with patients who had COPD without metabolic syndrome.[8] Another study found a strong association of metabolic syndrome with higher levels of TNFα and IL6 in COPD.[9]

Physical limitation is seen in patients of COPD owing to frequent respiratory symptoms during daily routine activities.[10] This symptom driven physical inactivity and sedentary lifestyle affects the metabolic pathways[11,12]

The objectives of this study were to find out the prevalence of metabolic syndrome in COPD patients in north India and the distribution of prevalence of metabolic syndrome among the COPD patients according to severity of COPD. We also aimed to assess the association of systemic inflammation with metabolic syndrome and COPD by assessing the levels of leucocyte counts, hs-CRP, Vitamin D, and lactate as independent predictors of Metabolic syndrome in COPD.

Methodology

This observational single centre case–control study was conducted on a total of 150 patients attending the Out Patient Pulmonology Department. Prior informed consent was taken from the patients.

Inclusion criteria were a diagnosis of COPD, stable state of disease (no exacerbations and no medication change in the preceding six weeks), while exclusion criteria were considered the presence of an inflammatory comorbidity (e.g., rheumatologic diseases, vasculitis, inflammatory bowel disease), acute infections (all acute infections e.g., infections of the respiratory, urogenital, gastrointestinal tract, and skin, within 6 weeks before enrolment to the study), respiratory diseases other than COPD, any kind of cancer within less than 5 years prior to the study and systemic corticosteroid treatment in less than 4 weeks prior to the study.

COPD was diagnosed according to the GOLD guidelines.[3] Spirometry was done according to the European Respiratory Society guidelines.[13] The staging of COPD was done based on spirometry using GOLD criteria.

For the diagnosis of metabolic syndrome International Diabetes Federation (IDF) criteria was followed. The IDF criteria of Metabolic Syndrome[4] uses (1) central obesity (waist circumference ≥90 cm for South Asian men or ≥80 cm for South Asian women) as a mandatory criterion and the presence of at least two of the other four criteria (2) triglycerides ≥150 mg/dL, (3) HDL cholesterol ≤40 mg/dL for men or 50 mg/dL for women, (4) systolic/diastolic blood pressure ≥130/85 mmHg or receiving drug treatment, and (5) fasting plasma glucose ≥100 mg/dL.

We recorded for each study participant the demographic characteristics, medical history, smoking status (current smokers, former smokers defined as those who had stopped smoking ≥1 year, non-smokers) and the number of pack-years (years of smoking x number of daily smoked cigarettes/20). All patients underwent a general examination, including the following measures: height, weight, BMI, waist circumference, arterial pressure and instrumental tests including spirometry. A venous blood sample was collected from each patient after a 12-hour fasting for estimation of Leucocyte count, serum lipid profile, estimation of blood glucose, serum vitamin D, and high sensitivity C-Reactive Protien (hs-CRP) estimation. Fasting and post prandial blood glucose level were measured by glucose oxidase peroxidase enzymatic method. Estimation of Lipid Indices Serum total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDLc), low density lipoprotein-cholesterol (LDLc) concentrations were determined using enzymatic spectrophotometric kits [Siemens Healthcare Diagnostics Inc, New York, USA] in the automatic analyzer in central facility. Serum level of hsCRP (Calbiotech, USA) concentrations were measured using sandwich enzyme-linked immunosorbent assay kit. The minimal detectable level was 0.05 mg/L for hsCRP. Serum Vitamin D level less than 20 ng/ml was considered as deficiency. All statistical analyses were performed using the IBM SPSS version 23 statistical software.

Results

A total of 150 patients of stable COPD were included in the study. Of them 72% were males. The mean age of the study participants was 58.59 ± 7.18 years. The mean age of males was 58.9 ± 7.31 years while the mean age of females was 57.76 ± 6.84 years. The difference was not found to be significant (P = 0.382). The demographic, clinical and biochemical characteristics are shown in Table 1. The prevalence of metabolic syndrome was found to be 27.3% in our COPD patients. The frequency of metabolic syndrome in GOLD stage I, II, III, and IV was 75%, 32%, 17%, and 13.5%, respectively.

The COPD patients were classified into two groups based on the presence or absence of metabolic syndrome as a comorbidity. The demographic, clinical, and lab characteristics of the two groups was compared. No significant difference was found in the age, sex distribution, and the number of pack years between the two groups. COPD patients with metabolic syndrome had a higher percentage of current smokers and a significantly higher mean FeV1% predicted as compared to patients with COPD alone. The waist circumference, fasting blood sugar, triglyceride level, systolic, and diastolic blood pressure was significantly higher in patients with metabolic syndrome. (P < 0.001) [Table 1]. Logistic regression analysis was used to assess the association

Table 1: Demographic, clinical and biochemical characteristics of the study participants

	All patients	COPD	COPD with Metabolic syndrome	*P*
Total patients	150	109 (72.7%)	41 (27.3%)	
Males (%)	108 (72%)	78 (71.56%)	30 (73.17%)	0.845
Age (years)	58.59±7.18	57.92±7.20	60.37±6.86	0.620
Current Smokers (%)	56 (37.33%)	32 (29.33%)	24 (58.5%)	0.001
Packyears	46.03±24.21	48.31±27.75	40.00±7.31	0.712
FeV1% predicted	48.69±18.76	44.47±16.9	59.92±18.9	0.000
Waist circumference (cm)	80.48±9.78	76.75±8.35	90.39±5.38	0.000
Fasting blood sugar (mg/dL)	102.73±16.6	96.39±13.55	119.59±11.37	0.000
Triglycerides (mg/dL)	167.05±37.97	156.69±35.36	194.59±30.39	0.000
HDL (mg/dL) males	39.31±6.31	42.01±4.21	32.3±5.41	0.000
HDL females (mg/dL)	44.79±8.48	46.64±8.57	39.55±5.77	0.000
Systolic BP (mm Hg)	125.93±15.41	119.65±11.07	142.63±12.64	0.000
Diastolic BP (mm Hg)	82.63±6.92	79.66±4.81	90.54±5.28	0.000
Leucocyte count ($\times 10^9$/L)	8.45±1.26	8.03±0.93	9.56±1.36	0.000
hsCRP (mg/L)	4.21±0.86	3.88±0.72	5.06±0.59	0.000
Lactate (mmol/L)	2.42±0.91	2.066±0.64	3.37±0.85	0.000
Vitamin D (ng/mL)	21.47±7.99	23.22±7.79	16.8±6.58	0.000

between inflammatory markers and metabolic syndrome in COPD patients. The Hosmer and Lemeshow goodness-of-fit test was conducted to assess whether each independent variable in the model significantly predicted metabolic syndrome. For this test, $P > 0.05$ indicates that the model predicts the dependent variable. The blood leucocyte count, hs-CRP, pack years and Serum Vitamin D level showed significant association with metabolic syndrome in our COPD patients ($P < 0.05$) [Table 2] Serum lactate level was initially included in the model. However, the Hosmer and Lemeshow test showed $P < 0.05$. Hence the variable Serum Lactate was excluded from the model. Linear regression analysis revealed that Metabolic syndrome in COPD is a predictor of blood leucocyte count, hsCRP, serum Lactate and Vitamin D level [Table 3].

Discussion

The prevalence of both metabolic syndrome and COPD is increasing worldwide. Metabolic syndrome and manifest diabetes are found to have a higher frequency in COPD.[3] The estimated prevalence of metabolic syndrome in COPD is more than 30%. In our study we found that 27.3% ($n = 41$) had metabolic syndrome. The prevalence of metabolic syndrome reported in various studies is quite variable. This may be because of the highly variable sociodemographic characteristics of the study population. It may depend upon the ethnicity, lifestyle, and socioeconomic status of the study participants. It also depends upon the inclusion criteria for diagnosing Metabolic Syndrome. We have used the IDF criteria. A study in Greece by Vasilios G *et al.*, used the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria found 21% prevalence of MS.[14] In another study by Hosny *et al.*, the prevalence of Metabolic Syndrome was found to be 40% among Egyptian COPD patients.[15] Vujic *et al.* studied the Serbian population and found the prevalence of metabolic syndrome as 37%.[16] G. Piazzolla and Castrovilli A have found that 62% of COPD patients had metabolic syndrome.[17] In their study they used the "harmonizing definition" of the syndrome by Alberti *et al.*[18] for diagnosing metabolic syndrome. An Indian study reported a prevalence of Metabolic Syndrome of 33% using the IDF criteria and a prevalence of 15.56% using NCEP ATP III criteria in the same study population.[19] Another study by Acharya A *et al.*, found a prevalence of 31% using the IDF criteria and 46% using the modified NCEP ATP III criteria for diagnosing Metabolic Syndrome.[20] In our study the prevalence of metabolic syndrome in COPD patients was slightly lower than in other studies. We also found that metabolic syndrome is less frequent in more severe forms of COPD. In our study we found that 50% of patients of mild to moderate airway obstruction had metabolic syndrome as compared to only 15.5% prevalence of Metabolic syndrome in patients with severe and very severe COPD. Akpinar *et al.*, in their study demonstrated a prevalence of metabolic syndrome of 38.5%, 52.8%, 30%, and 33.3% in GOLD stages I, II, III, and IV, respectively.[21] This prevalence of metabolic syndrome in severe and very severe COPD is much higher than the findings in our study. However in another study from Canada, the frequency of Metabolic syndrome in severe and very severe patients was about 10%.[22] The result of the study by Vujic *et al.* found that prevalence of 33.3%, 48.8%, 31.6%, and 23.1% in GOLD stages I, II, III, and IV, respectively.[16] Thus, metabolic Syndrome is more frequent in patients with mild and moderate disease.

We also found that COPD patients with metabolic syndrome had significantly greater systemic inflammation suggested by higher levels of blood leucocyte count, hsCRP, lactate, and lower levels of serum vitamin D level than those without metabolic syndrome. In our study, linear regression analysis showed that presence of metabolic syndrome in COPD patients is an independent predictor of high blood leucocyte count, hsCRP, lactate, and lower levels of serum vitamin D level [Table 3]. Vujic T *et al.* also found a significantly higher blood leucocyte count and CRP

Table 2:The relationship of blood leucocyte count, hsCRP, pack years and Serum Vitamin D level with Metabolic syndrome in COPD patientsby multiple logistic regression (*n*=150)

	Odds ratio	Standard error	95% confidence interval		*P*
			Lower	Upper	
Total leucocyte count ($\times 10^9$/L)	0.342	0.355	0.171	0.686	0.002
hsCRP (mg/L)	0.020	0.913	0.003	0.122	0.000
Packyears	1.083	0.028	1.026	1.144	0.004
Serum Vit D (ng/mL)	1.219	0.056	1.093	1.359	0.000

Table 3: Linear regression analysis showing Metabolic syndrome as a predictor of greater systemic inflammation and vitamin D deficiencyin COPD (*n*=150)

	R^2	*F*	*P*
Blood Leucocyte count ($\times 10^9$/L)	0.294	61.728	0.000
hsCRP (mg/L)	0.371	87.429	0.000
Lactate (mmol/L)	0.409	102.52	0.000
Vitamin D (ng/mL)	0.359	21.89	0.000

level in COPD patients with metabolic syndrome[16] Similar to our result, Therese Ghatas also found that CRP levels were higher in patients who had metabolic syndrome than in individuals who did not have metabolic syndrome in all GOLD stages of COPD patients.[23] Watz *et al*., also found that metabolic syndrome is an independent predictor of hs-CRP.[8] In contrast to our finding, in a study by Piazollo G, it was found that Serum vitamin D levels were not different among Metabolic syndrome, COPD and Metabolic syndrome with COPD groups.[17]

Lactate levels have been found to be raised with significant implications in individuals with metabolic syndrome. Wu LW *et al*., demonstrated a positive association between higher level of serum lactate and mortality from all causes in individuals with Metabolic Syndrome as compared to healthy control subjects.[24] Ahluwalia A *et al*., in their *in vitro* study, found significant interactions between adiposity and model complexity for lactate, meaning that the effect of adiposity is dependent on the level of lactate and vice-versa.[25] The lactate level in COPD patients with metabolic syndrome has not been well investigated. More studies are required to clearly delineate the association of lactate level with metabolic syndrome in COPD.

COPD patients with MetS had higher systemic inflammatory markers (↑TNFα, IL-6, leptin and ↑ adiponectin) than patients without MetS[26] This amplified systemic inflammation can feed forward to exacerbate metabolic abnormalities such as dyslipidaemia and insulin resistance.[27] Patients with COPD are at risk of developing diabetes. COPD is also found to be a common comorbidity of diabetes.[28] The correlation implies that components of the MetS particularly hyperglycaemia can give rise to pulmonary function impairment in COPD and vice versa.[29]

Glucocorticoids, that are used for therapeutic purposes in COPD, also increase lipolysis, muscle breakdown and gluconeogenesis. This decreases glucose utilization and promotes hyperglycemia. Prolonged consumption of glucocorticoids affects metabolism and insulin activity.[30] Its consumption enhances the risk of hyperglycemia even in patients without known diabetes and worsens glycemic state in diabetics, as a result of decreased production and resistance to insulin.[31] Repeated use of glucocorticoids in COPD may be another risk for metabolic syndrome.

Given the hazardous implications of coexistence of COPD and metabolic syndrome, general practitioners, and primary care physicians should be aware of the prevalence and consequences of metabolic syndrome in COPD patients. It will go a long way in curbing the dual threat at the primary care level. Both COPD and metabolic syndrome are preventable to a large extent. Lifestyle changes can be preventive and therapeutic at the primary care level. Both the entities are progressive in nature and may become refractory to treatment because one disease contributes to the progression of the other, forming a vicious circle. Physical inactivity, dyslipidemia, and use of glucocorticoids in COPD leads to increased adiposity, insulin resistance. Thus, judicious use of glucocorticoids is mandated at the primary care level.

Conclusion

This study revealed that metabolic syndrome is a common comorbidity especially in mild and moderate forms of COPD. Systemic inflammation is found to be more severe in COPD patients with Metabolic Syndrome as compared to patients with COPD alone. Total leucocyte count, hs-CRP level, and Vitamin D level were found to be independent predictors of metabolic syndrome in COPD. Both metabolic syndrome and COPD increase the risk of cardiovascular diseases several fold. COPD in itself is an adversely affecting determinant for cardiovascular health.[32] Both rural and urban areas are facing an increase in the prevalence of both COPD and Metabolic syndrome. Keeping in view the rising prevalence of both COPD and metabolic syndrome in India, it is important to prevent, diagnose and manage metabolic syndrome in COPD effectively at primary care level. This will also help in reducing the associated economic burden on already strained healthcare resources.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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