Original Article

A Study on Microalbuminuria in Patients with Chronic Obstructive Pulmonary Disease at a Tertiary Care Centre in North India

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Abstract

Background. In chronic obstructive pulmonary disease (COPD), systemic effects of the disease result in structural and/or biochemical alterations in structures or organs other than the lungs. Microalbuminuria (MAB) is an important risk factor for cardiovascular disease, and it may be seen due to hypoxaemia in patients with COPD.

Objective. Present study was undertaken to find the presence of MAB in COPD and relationship of MAB with clinical and physiological parameters in stable patients with COPD.

Methods. Sixty patients with COPD and 50 healthy controls were enrolled in the study. Spot urinary albumin/creatinine ratio, smoking history, spirometry, blood gases, body mass index, kidney function tests and BODE index (body-mass index, airflow obstruction, dyspnoea and exercise) were assessed. Frequency of MAB was compared between cases and controls.

Results. Of 60 cases, 50 (83%) were males and 10 (17%) were females. In patients with COPD, MAB was found in all of them (100%) while in controls only 4 (10%) had MAB ($p<0.0001$).

Conclusion. In the present study, MAB was seen in all the patients with COPD and MAB levels were significantly high in COPD cases compared with asymptomatic smokers with normal spirometry.
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Key words: COPD, Microalbuminuria, Lung, Hypoxia.

Introduction

Chronic obstructive pulmonary disease (COPD) is an increasing public health problem. Currently, COPD is the second most common non-infectious disease and fourth leading cause of death in the world, causing some 2.75 million deaths annually which is predicted to more than double by 2020.[1] COPD is associated with an abnormal inflammatory response in the lungs, with important extra-pulmonary manifesta-tions and multiple co-morbidities.

Cardiovascular disease is a major cause of mortality in patients with COPD, particularly in patients with mild to moderate severity. The principal cause of hypoxaemia in patients with COPD is ventilation/perfusion (V/Q) abnormality resulting from progressive airflow limitation and emphysematous destruction of the pulmonary capillary bed.[2] Alveolar hypoxia is an important factor that leads to the development of pulmonary hypertension in patients with COPD. Hypoxia may also lead to the development of endothelial dysfunction, characterised by the loss of the physiological balance between vasodilation and vasoconstriction.[3]

The discovery of novel biomarkers to help identify cardiovascular risk in patients with COPD could help individualise therapy for that particular phenotype. Ideally, the biomarker should be inexpensive, non-invasive, and easily assessable. Microalbuminuria (MAB) is a sensitive marker of cardiovascular risk.[4] Presence of MAB is consistently associated with arterial stiffness assessed by pulse-wave velocity and worse cardiovascular outcomes in patients with diabetes and hypertension as well as in the general population.[5-7] MAB is believed to reflect a state of generalised endothelial dysfunction, and thus, a surrogate marker of endothelial dysfunction. Therefore, it is an emerging therapeutic target for primary prevention strategies. The limited number of studies that have investigated the presence of MAB

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in patients with COPD have reported a high prevalence in patients during acute exacerbations and, importantly, also in the stable state.[8-12]

Material and Methods

The present study consisted of 60 consecutive patients of either sex, aged between 30 to 80 years with clinically stable disease who attended the out-patient and in-patient Departments of the hospital from January 2014 to December 2015. Fifty healthy controls were included in the study. Patients with COPD and age- and sex-matched controls for this study were randomly selected as per OPD schedule.

Patients were excluded based on the following criteria: (i) pre-existing renal diseases, ruled out on the basis of past history of renal disease and blood biochemistry with elevated serum creatinine, blood urea nitrogen, potassium, calcium, phosphorous and depressed bicarbonate levels; ultrasonography showing small renal size or presence of MAB (urine albumin-to-creatinine ratio [UACR] ≥ 300 mg/g); (ii) COPD with acute exacerbation; and (iii) congestive heart failure. Patients having other respiratory diseases, such as, asthma, interstitial lung diseases, obstructive sleep apnoea, acute infections, uncontrolled co-morbidities, such as lung malignancy and systemic hypertension and diabetes mellitus were also excluded from the present study. Approval of the Institutional Ethical Committee has been taken prior to the study.

A detailed history and physical examination was carried out for every individual as per the pre-designed proforma. Patients were examined clinically and radiologically to establish the diagnosis of COPD, as per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[13-14] Blood biochemistry including haemoglobin, total leucocyte count (TLC), differential leucocyte count (DLC), fasting and post-prandial blood glucose, serum creatinine, liver enzymes, serum bilirubin, serum protein, serum albumin and urine microscopy, albumin and creatinine was done in all the participants. Echocardiography, spirometry, electrocardiogram, 6-minute walk test and other investigations were done, if required. Body mass index (BMI) was calculated by measuring weight and height. Exercise capacity was assessed by the 6-minute walk distance (6MWD) test according to American Thoracic Society (ATS) guidelines. Dyspnoea was assessed using the modified British Medical Research Council (mMRC) dyspnoea scale.[15] The multi-dimensional BODE (body-mass index, airflow obstruction, dyspnoea and exercise) index was calculated from BMI, forced expiratory volume in one second (FEV_1%), mMRC dyspnoea scale, and 6MWD.[16]

Laboratory Methods

The microalbumin (MALB) detection method is an *in vitro* diagnostic test based on a particle enhanced turbidimetric inhibition immunoassay (PETINIA) adapted to the Dimension Clinical Chemistry System® that allows direct quantitation of albumin in urine samples. MALB Flex reagent cartridge contains a particle reagent (PR) consisting of synthetic particles with human albumin bound to the surface and aggregates of these particles are formed when a monoclonal antibody (Ab) to human albumin is introduced. Albumin present in the sample competes with the particle for antibody, thereby decreasing the rate of aggregation. Hence, the rate of aggregation is inversely proportional to the concentration of albumin present in the sample, and the rate of aggregation was measured using bichromatic-turbidimetric reading at 340nm and 700nm. Creatinine levels were determined by the Jaffe method and were adjusted for sex and race using published formulae.

Urinary albumin/creatinine ratio was defined as [urine albumin (mg)]/k [urine creatinine (g)]], where k represents a sex- and race-dependent correction factor. Presence of MAB was defined as UACR between 20-299 mg/g in men and 30-299 mg/g in women.[11]

Statistical Analysis

Correlation of different parameters used to assess the clinical severity of COPD, like FEV_1%, BODE index, mMRC dyspnoea grading, 6MWD and PO_2 values with UACR (microalbumin) was carried out using Pearson's correlation analysis on the Statistical Package for the Social Sciences (SPSS) version 16.0 software. One-way analysis of variance (ANOVA) was used to compare the mean values of >2 sub-groups.

Results

Out of 60 patients with COPD, 50 were males. Their age ranged from 61-70 years (mean age=58.4±11.6 years). Out of 50 controls, 41 were males. The difference in mean of age between cases and controls was not statistically significant (p=0.858).

Majority of the cases (66.6%) were from rural background and 62.5% of controls were from urban area. The predominant symptom in cases with COPD was cough (n=60, 100%) and breathlessness (n=60, 100%) followed by chest pain (n=52, 86%), while in controls (n=40) 2 (5%) patients had cough and 2 (5%) had breathlessness. Majority of the patients amongst cases were smokers (83%) and all patients in the control group (100%) were smokers; 14 (35%) were tobacco addicts.

Most of the patients in the patients group (43 [71.7%]) had FEV_1 in the range of 50% to 80% predicted; 16 patients in the range of 30% to 50%; and 1 (1.7%) had FEV_1 <30%. In the control group, 48 (96%) had FEV_1 >80% and 2 (4%) in the range of 50% to 80%.

Microalbuminuria was present in all the patients in the patient group, while in controls, this was in 4 (10%) only. This association was statistically

significant (p<0.0001). Data of various other parameters are presented in table 1.

Table 1. Comparison of cases with COPD and controls

Parameter	Cases (n=60)	Controls (n=50)
Age (in years)	58.4±11.6	58.8±13.0
FEV_1% predicted	54.1±11.5	82.6±7.8
BODE INDEX	4.6±2.4	2.2±0.6
PaO_2 (mmHg)	63.8±8.8	82.3±8.1
UACR ratio (mg/g)	146.0±42.4	21.6±12.4

Data presented as mean±SD

Definition of abbreviations: COPD=Chronic obstructive pulmonary disease; FEV_1=Forced expiratory volume in one second; BODE=Body-mass index, airflow obstruction, dyspnoea and exercise; PaO_2=Partial pressure of arterial oxygen; UACR=Urinary albumin/creatinine ratio; SD=Standard deviation.

Amongst cases, of the 43 patients with FEV_1 in the range of 50% to 80%, 24 (56%) had MAB levels in the range 101-150 mg/g and 14 (33%) in the range of 151-200 mg/g table 2. Out of 16 (27%) patients who had FEV_1 in the range of 30% to 50%, 3 (10%) had MAB in the range of 101-150 mg/g; 9 (56.3%) had 151-200 mg/g; and 4 (25%) had MAB >200mg/g table 2. The only patient with FEV_1 <30% had MAB >200mg/g. There was a strong negative correlation (r=-0.834; p=0.001) between FEV_1% and UACR levels amongst the 60 cases (Table 2).

The mean UACR values on one-way analysis of variance (ANOVA) amongst the three groups of cases with FEV_1 50% to 80% (124.8±29.2), 30% to 50% (185.8±32.4) and <50 (M=199.3) were statistically significant (p=0.05) (Table 2).

Table 2. Association of microalbuminuria with FEV_1, BODE index, PaO_2, mMRC grade and 6MWD

Subgroup		Microalbumin Levels UACR (mg/g)						
		0-30	31-50	51-100	101-150	151-200	201-300	Mean ±SD
FEV_1(%)	50-80 (N=43)	0	0	5 (11.6%)	24 (55.8%)	14 (32.6%)	0	124.8±29.2
	30-50 (N=16)	0	0	0	3 (18.8%)	9 (56.3%)	4 (25%)	185.8±32.4
	<30 (N=1)	0	0	0	0	0	1 (100%)	199.3
BODE index	0-3 (N=21)	0	0	6 (28.6%)	14 (66.7%)	1 (4.8%)	0	100.9±21.1
	4-6 (N=24)	0	0	0	14 (58.3%)	10 (41.7%)	0	149.6±15.6
	7-10 (N=15)	0	0	0	0	10 (66.7%)	5 (33.3%)	198.6±28.6
PaO_2 (mmHg)	71-80 (N=18)	0	0	6 (33.3%)	12 (66.7%)	0	0	99.7±21.3
	61-70 (N=21)	0	0	0	12 (57.1%)	9 (42.9%)	0	142.6±13.9
	51-60 (N=18)	0	0	0	0	16 (88.9%)	2 (11.1%)	176.8±17.7
	<50 (N=3)	0	0	0	0	0	3 (100%)	244.6±8.8
mMRC grade	Grade-II (N=40)	0	0	6 (15%)	24 (60%)	10 (25%)	0(0%)	125.0±28.9
	Grade-IIII (N=16)	0	0	0	2 (12.5%)	12 (75%)	2 (12.5%)	182.8±19.1
	Grade-IV (N=04)	0	0	0	0	2 (50%)	2 (50%)	232.3±29.0
6MWD test (in metres)	>400(N=9)	0	0	5 (55.6%)	4 (44.4%)	0	0	91.0±13.1
	301-400 (N=28)	0	0	2 (7.1%)	22 (78.6%)	4 (14.3%)	0	130.3±23.8
	201-300 (N=12)	0	0	0	2 (16.7%)	10 (83.3%)	0	169.4±14.7
	101-200 (N=9)	0	0	0	0	6 (66.7%)	3 (33.3%)	194.6±21.9
	<100 (N=2)	0	0	0	0	0	2 (100%)	248.7±7.4

Definition of abbreviations: FEV_1=Forced expiratory volume in one second; BODE=Body-mass index, airflow obstruction, dyspnoea and exercise; PaO_2=Partial pressure of arterial oxygen; mMRC=modified British Medical Research Council; 6MWD=6-minute walk distance; UACR=Urinary albumin/creatinine ratio

The levels of MAB group with BODE index 0-3, 4-6, and 7-10 were 100.9±21.1, 149.6±15.6 and 198.6±28.6 mg/g, respectively (Table 2). There was a significant positive correlation between BODE index and UACR levels (r=0.921; p=0.001) amongst the cases. The difference in mean of UACR values was statistically significant (p=0.05) amongst the 3 groups of cases with BODE index 0-3 (100.9 ± 21.1), 4-6 (149.6±15.6) and 7-10 (198.6 ± 28.6) (Table 2).

Twenty-one (35%) patients amongst cases had PaO_2 levels between 61-70 mmHg and 12 (57.1%) of them had MAB in the range of 101-150 mg/g and in 9 (42.9%) it was between 151-200 mg/g. There was a significant negative correlation between PaO_2 and UACR levels (r=0.938; p=0.001) amongst the cases (Table 2). The difference in mean of UACR values was statistically significant (p=0.05) amongst 4 groups of cases with PaO_2 71-80 mmHg (99.7±21.3), 61-70 mmHg (142.6±13.9), 51-60 mmHg (176.8±17.7), and <50 mmHg (244.6±8.8).

Amongst cases, 40 (67%) patients had a dyspnoea of grade 2 on mMRC scale and 24 (60%) of them had MAB levels in the range of 101-150 mg/g. The difference in mean of UACR values amongst 3 groups of cases with mMRC grade 2 (125.0±28.9), grade 3 (182.8±19.1) and grade 4 (232.3±29.0) was statistically significant (p=0.05) (Table 2).

Twenty-two (78.6%) patients out of 28 patients who walked a distance in the range 301-400 m had UACR values in the range of 101-150 mg/g. There was a strong negative correlation (r=-0.910; p=0.001) between 6MWD and UACR values (Table 2). The difference in mean of UACR values amongst 5 groups of cases with 6MWD >400m (91.0±13.1), 300-400 m (130.3±23.8), 200-300 m (169.4±14.7),100-200 m (194.6±21.9), and <100 m(248.8±7.4) was statistically significant (p=0.05) (Table 2).

Discussion

Chronic obstructive pulmonary disease is a multi-component disease in which structural and functional changes are seen in the lungs and extra-pulmonary organs.[17] Therefore, systemic involvement in patients with COPD should certainly be considered. *To the best of our knowledge*, there are only a few studies reporting a higher prevalence of MAB in stable COPD patients compared with age-matched controls who were smokers and both the groups had no comorbidities, like cardiovascular, diabetes, hypertension, malignancy or renal disease.

Polatli *et al*[10], compared the levels of the plasma vWF, fibrinogen and 24-hour urine MAB[33] in stable COPD patients and with exacerbation in 26 patients and 16 controls. They observed that MAB increased significantly in patients with COPD (acute exacerbation group), compared to controls.[10] We studied stable COPD patients unlike Polatli *et al* who studied MAB in COPD exacerbation. However, MAB showed a positive correlation with severity in both the studies. In our study, severity was assessed using various clinical and physiological parameters and these parameters significantly correlated with MAB levels.

Another study by Cassanova *et al*[11] established the prevalence and relationship of MAB with clinical and physiological parameters in 129 patients with stable COPD and 51 smokers with normal spirometry without known cardiovascular disease. They reported that MAB was higher in patients with COPD than in control smokers. In patients with COPD, there was a negative correlation between PaO_2 and MAB. On multivariate analysis, MAB was only associated with the PaO_2 and with the systolic arterial blood pressure.[11] Our study also confirms the relationship of hypoxaemia and pulmonary hypertension with MAB levels in stable COPD patients.

Komurcuoglu *et al*[8] found that the BODE index has direct relationship with the levels of MAB while PaO_2 levels had an inverse relationship with MAB in urine.[8] We also found that BODE INDEX and PaO_2 levels had direct and inverse relationships with MAB levels, respectively. Bulcon *et al*[12] did a study to assess the prevalence and relationship of MAB with clinical and physiological parameters in 66 consecutive patients with COPD and 40 smokers with normal spirometry and UACR was calculated. They reported that the presence of MAB and UACR were higher in patients with COPD than smokers with normal spirometry and showed a significant inverse relationship between UACR and PaO_2, FEV_1%, forced vital capacity (FVC%). On the other hand, there was a positive relationship between UACR and BODE index and between the presence of MAB with PaO_2 and BODE index.[12]

Kaysoydu *et al*[19] found that patients with COPD and MAB were more hypoxaemic and hypercapnic compared to those with only MAB. They also observed that MAB levels were significantly higher in the patient group in which (CRP) was high and a relationship between elevated MAB levels and elevated CRP, indicating inflammation. The PaO_2 was found to be lower in the COPD group and a significant relationship was found between MAB level and PaO_2 and $PaCO_2$.[19] Contrary to this we observed that MAB had a significant correlation with spirometric parameters along with relationship with hypoxaemia and pulmonary hypertension. We found no relationship of $PaCO_2$ with MAB in our study.

Mehmood and Sofi[20] did a study to evaluate the practical role of MAB in 97 patients with stable COPD and 94 age-matched smokers with normal spirometry without any known cardiovascular disease. They observed that MAB was more frequent in patients with COPD compared to smokers without

obstruction (20.6% *versus* 7.4%, respectively; p=0.007) and there was an inverse association of the PaO_2 and MAB in patients with COPD (r=-0.35, p<0.0001).[20] Contrary to this we observed that all patients with COPD had MAB and not only PaO_2 but other clinical and physiological parameters like BODE INDEX, 6MWD, FEV_1% and mMRC grading showed significant correlation with UACR levels. Also COPD cases with MMRC grade 2 showed high MAB levels.

Harris *et al*[21] reported the association of systemic microvascular changes with lung function among 3397 patients aged 45 to 84 years without any clinical cardiovascular disease and had measured microvascular function including (retinal arteriolar and venularcaliber, urine albumin-to-creatinine ratio, low attenuation areas (LAA) in cardiac computed tomogram, myocardial blood flow on magnetic resonance imaging) and spirometry parameters. They observed that retinal venularcaliber was inversely associated with FEV_1 and FEV_1/FVC ratio (P=0.04). Albumin-to-creatinine ratio was inversely associated with FEV_1 (P=0.002) but not FEV_1/FVC. Myocardial blood flow (n=126) was associated with lower FEV_1 (P=0.02), lower FEV_1/FVC ratio (P=0.001) and greater percentage of low attenuation area (P=0.04).[21]

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