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Relationship of Microalbuminuria with Chronic Obstructive Pulmonary Disease and its Severity-An observational study

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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.

Aims and Objective: Present study was undertaken to find the presence of MAB in COPD and relationship of MAB with severity of COPD by $FEV_{1(\%predicted)}$, BODE Index, PaO_2, mMRC grade and 6MWD test.

Material and Method: 100 patients with COPD(50 with acute exacerbation and 50 with stable COPD) and 30 healthy controls were enrolled in the study. Spot urinary albumin creatinine ratio(MAB), spirometry, arterial blood gases, body mass index, renal 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 100 COPD patients, (87%) were male. MAB was present in all COPD patients (100%), while in control in 2(6.6%) subjects only(p=0.001).

Conclusion: In the present study,MAB was found in all COPD patients and MAB levels were significantly high in COPD cases compared with control.Increased MAB was associated with acute exacerbation and also increasing with severity of COPD.

Keywords: COPD, Microalbuminuria, Lung, Hypoxia.

Introduction

Chronic obstructive pulmonary disease (COPD) is defined as a disease state characterized by persistent respiratory symptoms and airflow limitation that is not fully reversible[1] . COPD is an increasing public health problem. Currently, COPD is the second most common

non-infectious disease and third leading cause of death in the world.[2]

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. 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, characterized by the loss of the physiological balance between vasodilatation and vasoconstriction.[3-4]

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. [5]

Presence of MAB is consistently associated with arterial stiffness and worse cardiovascular outcome in patients with diabetes and hypertension. MAB is believed to reflect a state of generalized endothelial dysfunction, and thus, a surrogate marker of endothelial dysfunction. Therefore it is an emerging therapeutics target for primary prevention strategies. The limited numbers of studies that have investigated the presence of MAB in patients with COPD have reported a high prevalence in patients during acute exacerbations and also in stable state.[6-10]

Materials and Methods

The present study included 100 COPD patients of either sex, >30 years of age, who attended OPD and IPD of the Hospital from february 2018 to september 2019 and 30 healthy controls. In 100 COPD patients, 50 with acute exacerbation and 50 with stable COPD included. So in our study there were 3 groups.

1. 50 patients with acute exacerbation of COPD.

1. 50 patients with stable COPD.
2. 30 healthy controls.

Patients were excluded based on the following criteria-

1. Preexisting renal disease were rule out on the basis of past history and blood biochemistry with elevated serum creatinine, BUN, K^{+}, Ca^{+2}, phosphorus, USG showing small renal size or presence of MAB (UACR >300mg/g).
2. CHF (Congestive Heart Failure)
3. Patient having other respiratory disease such as asthma, interstitial lung disease, obstructive sleep apnoea, acute infection, uncontrolled co-morbidities such as lung malignancy and systemic hypertension, diabetes mellitus were excluded from study.
4. Diabetes mellitus, Hypertension.
5. Viral fever, dengue, malaria
6. Any hematological disease & drugs which affects the platelet count.

Approval of the Institutional Ethical Committee has been taken prior to the study. Detailed history and physical examination was carried out for every individual as per proforma. Patients were examined clinically, radiologically and ABG analysis to establish diagnosis of COPD, as per GOLD guideline. PFT(Spirometry) was done in stable COPD patients (in acute exacerbation after stabilization of patients) using European Respiratory and American Thoracic Society guideline 2005.Routine Blood investigations 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 was done in all the participants.Electrocardiogram,echocardiogram and ultrasonography 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. The multi-dimensional BODE (body-mass index, airflow obstruction, dyspnoea and exercise) index was calculated from BMI, forced expiratory volume in one second (FEV1 %), mMRC dyspnoea scale, and 6MWD. Microalbuminuria Laboratory Method- An early morning spot urine sample was collected in a sterile urine container from each participant and analysis of this urine sample was carried out within 4 hour of sample collection.Then estimation of urine albumin was carried out by immunoturbidimetric test and urine creatinine level was determined by Jeffe's method. By using obtained values the urine albumin to creatinine ratio (UACR) was calculated.The value of UACR from 30 – 300 mg/g was considered as microalbuminuria.

Statistical analysis for the above parameters were done using SPSS version 20.0 Windows software program. The analysis of variance (ANOVA) with post hoc Bonferroni test was used for quantitative data comparison, t-test was used for correlation coefficient, while Chi-square test and fisher exact test were used for qualitative data comparison.

Results and Discussion

Mean age of COPD patients was 60.43±9.42 years and that in control group was 59.76±7.26 years and difference between mean age of cases and control was not statistically significant (p value=0.72).Age distributed between 40-77 years. In our study, out of 100 COPD patients, 31(31%) patients were <60 years. So majority of patients lie in elderly age group.Out of 100 COPD patients 13 were female and 87 were male. In 30 control group 4 were female and 26 were male. So majority were male in our study.

MAB in COPD (Table 1 and 2)

In our study results we found-1.MAB was present in all COPD patients, while in control group MAB was found in 2 subjects only.2.Mean value of MAB (UACR) in acute ex COPD, stable COPD and Control were 178.46±41.80 , 125.4 ±27.27 and 20.2±6.15 respectively. 3.Mean value of acute ex COPD was comparatively higher than stable COPD ($p<0.001$).Mean value of MAB in Acute ex COPD was comparatively higher than control group ($p<0.001$).Mean value of MAB in stable COPD was comparatively higher than control group ($p<0.001$).4.Mean value of MAB in 100 COPD patients was 151.95±44.08 and in 30 control group it was 20.2±6.15. Difference of mean value was statistically significant (p value=0.001).

Kaysoydu et al found increased MAB in COPD exacerbation. In their study mean UACR value in COPD and control group were 64.8±91.8 and 10.6±6 respectively.[11] 2. Casanova et al found higher MAB in COPD patients than control smoker.[9] 3. Polatli et al also observed that MAB increased significantly in patients with COPD(Acute exacerbation group) compared to controls.[8] 4. Anand kumar et al found MAB was seen in all the patients with COPD and MAB levels were significantly higher in COPD cases compared with asymptomatic smokers with normal spirometry.[12] So our study corresponds to above studies.

Table 1: Inter-group comparison of MAB (UACR)

	Mean	SD	Minimum	Maximum	P value
stable COPD	125.4400	27.27873	60.00	168.00	0.001 (S)
acute ex COPD	178.4600	41.80578	110.00	280.00	
control	20.2333	6.15144	10.00	40.00	
Total	121.5538	67.84868	10.00	280.00	

Table 2: Comparison of COPD cases and Control

		N	**Mean**	**SD**	**P value**
Age	Case	100	60.4300	9.42193	0.72
	Control	30	59.7667	7.26676	
FEV1 (%Pred)	Case	100	57.2200	13.35345	0.001 (S)
	Control	30	89.0000	2.42117	
BMI	Case	100	20.9820	1.94782	0.39
	Control	30	21.3100	1.49421	
PaO_2	Case	100	64.9200	9.68669	0.001 (S)
	Control	30	89.8000	3.23131	
BODE	Case	100	4.5800	2.44611	0.001 (S)
	Control	30	.8667	.77608	
mMRC	Case	100	2.4000	.63564	0.001 (S)
	Control	30	.1667	.37905	
6MWD	Case	100	238.4300	103.89109	0.001 (S)
	Control	30	363.9000	28.25908	
MAB	Case	100	151.9500	44.08197	0.001 (S)
	Control	30	20.2333	6.15144	

Severity of COPD- For severity of COPD correlation of different parameters like FEV1% predicted, BODE index, PaO2, mMRC dyspnoea scale, 6MWD values with UACR (microalbuminuria) and MPV was carried out using Pearson's correlation analysis on the Stastical Package for Social Sciences(SPSS) version 20.0 software.

Table 3: Comparison of UACR with COPD severity parameters

			UACR (MAB)					
			51-100	101-150	151-200	201-300	Total	Mean ±SD
FEV1 (% pred)	51-80	N	8	40	24	0	72	138.23±31.36
	(GOLD stage-2)	%	11.10%	55.60%	33.30%	0.00%	100.00%	

	30-50 (GOLD stage-3)	N	0	6	14	4	24	172.45±40.38
		%	0.00%	25.00%	58.30%	16.70%	100.00%	
	<30 (GOLD stage-4)	N	0	0	0	4	4	275.75±4.34
		%	0.00%	0.00%	0.00%	100.00%	100.00%	
Bode Index	0-3	N	8	24	0	0	32	111.4±23.41
		%	25.00%	75.00%	0.00%	0.00%	100.00%	
	04-Jun	N	0	18	24	0	42	157.42±19.6
		%	0.00%	42.90%	57.10%	0.00%	100.00%	
	07-Oct	N	0	4	14	8	26	193±49.78
		%	0.00%	15.40%	53.80%	30.80%	100.00%	
PaO2	71-80	N	8	22	0	0	30	109.56±23.01
		%	26.70%	73.30%	0.00%	0.00%	100.00%	
	61-70	N	0	24	10	0	34	144.41±13.41
		%	0.00%	70.60%	29.40%	0.00%	100.00%	
	51-60	N	0	0	28	2	30	180.16±20.87
		%	0.00%	0.00%	93.30%	6.70%	100.00%	
	<50	N	0	0	0	6	6	265.5±16.53
		%	0.00%	0.00%	0.00%	100.00%	100.00%	
mMRC	2	N	8	46	14	0	68	129.85±25.65
		%	11.80%	67.60%	20.60%	0.00%	100.00%	
	3	N	0	0	24	0	24	178.2±8.11
		%	0.00%	0.00%	100.00%	0.00%	100.00%	
	4	N	0	0	0	8	8	261±16.32
		%	0.00%	0.00%	0.00%	100.00%	100.00%	
6MWD	301-400	N	8	24	0	0	32	111.4±23.41
		%	25.00%	75.00%	0.00%	0.00%	100.00%	
	201-300	N	0	16	4	0	20	142.15±12.24
		%	0.00%	80.00%	20.00%	0.00%	100.00%	
	101-200	N	0	6	34	8	48	183.06±39.01
		%	0.00%	12.50%	70.80%	16.70%	100.00%	

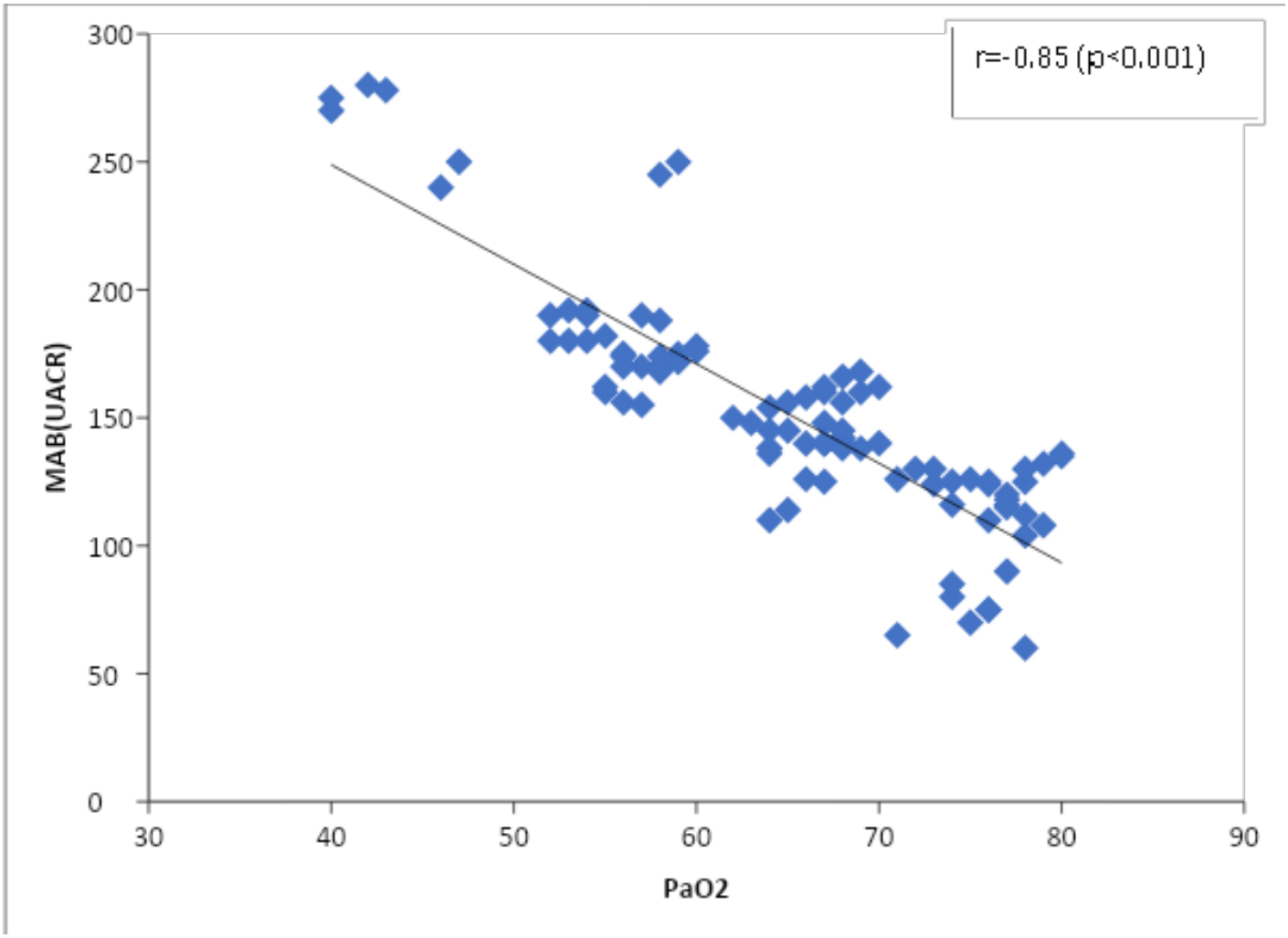

Figure 1

MAB (UACR) with severity of COPD (Table 3)

UACR and FEV1% predicted: In 100 COPD patients 72 (72%) patients had FEV1% predicted in the range of 51-80% predicted, 24(24%) patients in the range of 30-50% and 4(4%) patients had FEV1 <30%. In the control group, 30(100%) had FEV1>80%.

Amongst cases, of the72 patients with FEV1 in the range of 51-80%, 8 (11.1%) had MAB in the range of 51-100 mg/g, 40(55.6%) in the range of 101-150, and 24(33.3%) in the range of 151-200. Out of 24 patients, who had FEV1 in the range of 30-50%, 6(25%) had MAB in the range of 101-150, 14(58.3%) had 151-200, and 4(16.7%) had MAB 201-300. 4 patients with FEV1 <30% had MAB in the range of 201-300. There was a strong negative correlation (r=-0.79, p<0.001) between FEV1(%pred) and UACR levels amongst 100 cases.

The mean UACR values on one way analysis of variance (ANOVA) amongst the three group of cases with FEV1% predicted 51-80%(138.23±31.36), 30-50%(172.45±40.38) and <30% (275.75±4.34) were statistically significant (p=0.001).

UACR and BODE index: In 100 COPD patients 32 (32%) patients had BODE in the range of 0-3, 42(42%) patients in the range of 4-6 and 26(26%) patients had BODE 7-10. In the control group, 30(100%) had BODE 0-3.

Amongst cases, of the32 patients with BODE 0-3, 8 (25%) had MAB in the range of 51-100 mg/g, 24(75%)

in the range of 101-150. Out of 42 patients, who had BODE in the range of 4-6, 18(42.9%) had MAB in the range of 101-150, 24(57.1%) had 151-200. Out of 26 patients with BODE 7-10, 4 (15.4%) had MAB in the range of 101-150, 14(53.8%) had 151-200 and 8(30.8%) patient had MAB 201-300. There was a significant positive correlation between BODE index and UACR levels ($r=0.83$, $p<0.001$) amongst cases.

The difference in mean of UACR values was statistically significant ($p=0.001$) amongst the 3 group of cases with BODE index 0-3(111.4±23, 41), 4-6(157.42±19.6) and 7-10(193±49.78).

UACR and PaO2: In 100 COPD patients, 30(30%) patients had PaO2 in the range of 71-80mmHg, 34(34%) patients in the range of 61-70mmHg, 30(30%) patients had PaO2 51-60mmHg and 6(6%) had PaO2<50mmHg. In the control group, 30(100%) had PaO2>80mmHg.

Amongst cases, of the 30 patients with PaO2 in the range of 71-80mmHg, 8(26.7%) had MAB in the range of 51-100, 22(73.3%) had 101-150. Out of 34 patients with PaO2 61-70 mmHg, 24(70.6%) had MAB in the range of 101-150 and 10(29.4%) had 151-200. Out of 30 patients with PaO2 in the range of 51-60, 28(93.3%) had MAB 151-200, 2(6.7%) had MAB 201-300. Remaining 6 patients with PaO2<50mmHg all had MAB in the range of 201-300. There was a significant negative correlation between PaO2 and UACR levels ($r=-0.85$, $p<0.001$) amongst the cases.

The mean UACR values on one way analysis of variance(ANOVA) amongst the four group of cases with PaO2 71-80mmHg (109.56±23.01), 61-70 mmHg (144.41±13.41), 51-70mmHg (180.16±20.87) and PaO2<50mmHg (265.5±16.53) were statistically significant ($p=0.001$).

UACR and mMRC: In 100 COPD patients 68 patients had mMRC= 2, 24 patients had mMRC=3 and 8 patients had mMRC=4. In the control group, 30(100%) had mMRC<2.

Amongst cases, of the 68 patients with mMRC=2, 8(11.8%) had MAB in the range of 51-100 mg/g, 46(67.6%) in the range of 101-150, and 14(20.6%) in the range of 151-200. Out of 24 patients, who had mMRC=3, all (100%) had MAB in the range of 151-200. 8 patients with mMRC=4 had MAB in the range of 201-300. There was a strong positive correlation ($r=0.85$, $p<0.001$) between mMRC and UACR levels amongst 100 cases.

The mean UACR values on one way analysis of variance (ANOVA) amongst the three group of cases with mMRC=2(129.85±25.65), mMRC=3(178.2±8.11) and mMRC=4 (261±16.32) were statistically significant ($p=0.001$).

UACR and 6MWD test : In 100 COPD patients 32(32%) patients had 6MWD in the range of 301-400m, 20(20%) patients in the range of 201-300m and 48(48%) patients had 6MWD 101-200m. In the control group, 30(100%) had 6MWD>300m.

Amongst cases, of the 32 patients with 6MWD in the range of 301-400 m, 8 (25%) had MAB in the range of 51-100 mg/g, 24(75%) in the range of 101-150. Out of 20 patients, who had 6MWD in the range of 201-300, 16(80%) had MAB in the range of 101-150, 4(20%) had 151-200. Out of 48 patients with 6MWD 101-200, 6(12.5%) had MAB in the range of 101-150, 34(70.8%) had MAB 151-200 and 8(16.7%) patients had MAB 201-300. There was a strong negative correlation ($r=-0.75$, $p<0.001$) between 6MWD and UACR levels amongst 100 cases.

The mean UACR values on one way analysis of variance (ANOVA) amongst the three group of cases

with 6MWD 301-400(111.4±23.41), 201-300(142.15±12.24) and 101-200 (183.06±39.01) were statistically significant (p=0.001).

Bulcan et al[10] evaluated significant inverse relationship between UACR and PaO2, UACR and FEV1%. On the other hand there was positive relationship between UACR and BODE index. So our study corresponds to this study.

Our study concordance with study done by Bozcus F et al[13] where Pearson correlation analysis revealed that UACR was significantly inversely correlated with FEV1% predicted (r=-0.56, p=0.001), PaO2 (r=-0.60,p=0.001)

Our study concordance with study done by-(1) Casanova et al[9], where in COPD patients, there was a negative correlation between PaO2 and MAB (r=-0.40, p<0.001).(2) J Sujay and G S Gajanan[14] also found negative association between hypoxemia and MAB.(3) S Agrawal et al[15] showed significant negative correlation between MAB and PaO2(p<0.001).(4) Poonam Gupta et al[16]study concluded that patients with severe COPD with hypoxemia or hypercapnia were significantly associated with microalbuminuria.(5) Komurcuoglu A et al[6]found negative correlation between MAB at admission and arterial pO2(p=0.031,r=-0.433). (6) Mehmood and Sofi[17] observed that MAB was more frequent COPD patients compared to smokers without obstruction (20.6% vs 7.4%, respectively: p=0.007) and there was an inverse association of the PaO2 and MAB in patients with COPD(r=-0.35, p<0.0001). Contrary to Mehmood and Sofi study in our study all patient with COPD had MAB.

Contrary to above studies in our study not only PaO2, but other clinical and physiological parameters like BODE index, FEV1%pred, 6MWD, mMRC grading showed significant correlation with UACR levels.

Harris et al[18] observed that UACR was inversely associated with FEV1(p=0.002)

Our results accordance with Solfrid Romundstad et al[19] and Sanjay Sahay et al[20] who found positive association trend of MAB with severity of COPD by GOLD staging.

Rakesh Kumar[21] found significant correlation of UACR values with FEV1%(r=-0.83, p=0.001), BODE index (r=0.92,p=0.001), 6MWD values(r=-0.91, p=0.001), PaO2(r=-0.938, p=0.001) and mMRC grading (r=0.224, p=0.001) and concluded that MAB could be a promising biomarker to identify COPD patients at increased cardiovascular risk. Our study corresponds to this study.

MAB is believed to reflect a state of generalized endothelial dysfunction, and thus, a surrogate marker of endothelial dysfunction. Therefore it is an emerging therapeutics target for primary prevention strategies[6-10].

Conclusion

1. Microalbuminuria (MAB) was present in all COPD patients. Increased MAB was associated with acute exacerbation of COPD .
2. Microalbuminuria was increasing with severity of COPD by FEV1% predicted, BODE index, PaO2, mMRC grade and 6MWD test. So, MAB may be useful as a marker of acute attack and severity of COPD.

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