ORIGINAL ARTICLE

Microalbuminuria : A New Biomarker for Cardiovascular Risk Among Stable COPD

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ABSTRACT

Background : Cardiovascular disease is one of the major causes of mortality in COPD patients. Microalbuminuria (MAB) has strong association with cardiovascular events and death as it reflects generalized endothelial vascular dysfunction and is also considered as a marker of systemic inflammation. Objectives of the study are-(a)To assess the prevalence of MAB in stable COPD patients. (b) To find out the relationship of microalbuminuria with clinical and physiological parameters in COPD patients.

Methods : This comparative cross-sectional study was carried out on COPD patients attending Outpatient department of Respiratory Medicine, Institute of Respiratory Diseases, SMS Medical College, Jaipur during the year 2018–2019. 40 stable COPD patients and 40 healthy controls were enrolled in the study. Spot urinary albumin/ creatinine ratio, smoking history, spirometry, arterial blood gas analysis, body mass index, kidney function tests and BODE index were assessed.

Results : Out of 40 cases and 40 controls, 23(56%) and 4(10%) had MAB respectively. There was a negative correlation between FEV1, PaO2 levels and 6 MWD with MAB levels. There was a positive correlation between BODE Index and mMRC grading with MAB levels.

Conclusion : COPD patients should be screened regularly with MAB to determine the risk of/and progression of cardiovascular consequences so that adequate decision of interventional strategies can be taken out to prolong survival in COPD patients.

Keywords-COPD, MAB, systemic inflammation, cardiovascular events, strategies.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is the fourth leading cause of death in the world but is expected to be the 3rd leading cause of death by 2020[1]. The pathological mechanisms and clinical manifestations of COPD are not only restricted to pulmonary inflammation and airway remodeling but also over the last decade it has been increasingly recognized as a systemic disease[2]. The best recognized systemic manifestations of COPD include systemic inflammation, cardiovascular comorbidities, cachexia, muscle dysfunction, osteoporosis, anemia, depression and anxiety.

Cardiovascular disease is a major cause of mortality in chronic obstructive pulmonary disease (COPD), particularly in patients with mild to moderate severity[3]. Cardiovascular conditions that have been reported to occur with a greater frequency in patients with COPD are coronary artery disease (CAD), heart failure (HF), peripheral vascular disease (PVD), and arrhythmias.

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The discovery of novel biomarkers helps identify cardiovascular risk in patients with COPD. Ideally, the biomarker should be inexpensive, noninvasive, and easily assessable. Microalbuminuria (MAB) is one such biomarker. It is a sensitive marker of cardiovascular risk[4]. Researchers hypothesize that microalbuminuria leads to hemodynamic strain and instability which thenleads to atherosclerotic process and eventually leads to adverse cardiovascular events such as Congestive Heart Failure, Acute Coronary Syndrome, Myocardial Infarction, Stroke etc.

In COPD, Hypoxia induces endothelial cells to release a number ofdifferent vasoactive agents including endothelin-1, platelet derived growth factor (PDGF), nitric oxide; that causes endothelial injury and lead to microalbuminuria. Limited number of studies that have investigated the presence of MAB among COPD patients reported a high prevalence in both acute exacerbations and alsoin stable state[5-8].

MATERIAL AND METHODS

The present study consisted of 40 stable COPD patients and 40 healthy controls of either sex, aged between 40 to 80 years who attended the outpatientdepartment of the Respiratory Medicine, IRD, SMS Medical college, Jaipur from July 2018 to June 2019. COPD patients and healthy controls for this study were randomly selected.

Patients were excluded based on the following criteria: (i) Pre-existing renal disease (ii) Acute exacerbation COPD (iii) Presence of Macroalbuminuria (UACR>300 mg/gm) (iv) Diabetes mellitus (v) Cardiovascular disease (vi) Other Respiratory diseases such as asthma, interstitial lung diseases,acute lung infections, lung malignancy (vii) Urinary tract infections. The control group consisted of apparently healthy volunteers with normal spirometry. Approval of the Institutional Ethical Committee was taken prior to the study.

Patients were examined clinically and radiologically to establish the diagnosis of COPD as per GOLD guidelines[9]. Routine blood investigations, Serum protein, Serum albumin and Urine microscopy, Chest x-ray, Spirometry, Electrocardiogram, 6-minute walk test, Arterial blood gas analysiswas done in all the participants. Body mass index (BMI) was calculated by measuring weight and height. Exercise capacity was assessed by 6-minute walk distance (6MWD) test according to American Thoracic Society (ATS) guidelines[10]. Dyspnea was assessed based on modified British Medical Research Council (mMRC) dyspnea scale[11]. The multi-dimensional BODE (body-mass index, airflow obstruction, dyspnea and exercise) index was calculated.

LABORATORY METHODS

The microalbumin (MALB) detection method is an in vitro diagnostic test based on a particle enhanced turbidimetricinhibition 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 concentration of albumin present in the sample, and the rate of aggregation was measured using bichromaticturbidimetric 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[12].

STATISTICALANALYSIS

Correlation of different parameters used to assess the clinical severity of COPD, like FEV1%,

BODE index, mMRC dyspnea grading, 6MWD and PaO2 values with UACR (microalbumin) were carried out using spearman's correlation analysis on Statistical Package for Social Sciences (SPSS) version 16.0 software. One-way analysis of variance (ANOVA) was used to compare the mean values of >2 sub-groups. p value <0.05 was considered statistically significant in all analysis.

RESULTS

Out of 40 cases,35 were males. Majority of cases(26) were seen over 50 years age contributing to 65% of the cases in cases group. Out of 40 controls, 36 were males.

Our study showed Microalbuminuria was present in 23(57.5%) cases out of 40 in cases group, while in controls, it was in 4 (10%) only. This association was statistically significant between two groups in our study.

Our study showed most of the cases in cases group 19cases(47.5%) had FEV1 in the range of 50% to 80% predicted; 14 cases (35%) in the range of 30% to 50%; and 7 (17.5%) had FEV1 <30%. In the control group, 36 (90%)had FEV1 >80% and 4 (10%) in the range of 50% to 80%.

Table 1 depicts that the comparison of mean value of PaO2, PaCO2, FEV1% predicted, FEV1/FVC ratio, BODE index, 6MWD (meter) & UACR (mg/g) were statistically significant whereas the mean value of PaCO2 was statistically not significant.

Table 2 depicts distribution of MAB with severity of COPD. Majority of the cases had MAB in severe and very severe COPD subgroup contributing to 71.4% cases respectively among cases group.

Table 3 depicts that majority of cases(19) were seen with FEV1 between 50% to 80% subgroup out of which 8 had MAB with 2(10.5%) in the range of 51-100 mg/g, 4 (21.0%) in the range of 101-150 mg/g and 2(10.5%) in the range of 151-200 mg/g. Similarly 25 cases were seen with BODE index 0-3 subgroup out of which 12 had MAB with 2(8%) in the range 51-100 mg/g, 5 (20%) in the range of 101-150 mg/g and 5(20%) in the range of 151-200 mg/g. Likewise 14 cases were seen in PaO2 levels between 61-70 mmHg subgroup out of which all 14 had MAB with 4 (28.57%) in the range of 101-150 mg/g, 8 (57.14%) in the range of 151-200 mg/g and 2(14.2%) had in the range of 201-300 mg/g. In the same manner 21 cases were seen in dyspnea grade 2 mMRC subgroup out of which 11 had MAB with 2(9.5%) in the range of 51-100 mg/g, 4(19.04%) in the range of 101-150 mg/g and 5 (23.80%) in the range of 151-200 mg/g. Similarly 19 cases were seen in 6 MWD of > 500 m subgroup out of which 8 had MAB with 2(10.5%) in the range of 51-100 mg/g, 4(21.05%) had it between 101-150 mg/g and 2(10.5%) had in the range between 151-200 mg/g.There was a negative correlation betweenFEV1%, PaO2 levels and 6 MWD with MAB levels and there was a positive correlation between BODE Index and mMRC grading with MAB levels among the 40 cases.The difference in mean MAB levels on one-way analysis of variance (ANOVA) among subgroups of cases with FEV1(50% to 80%, 30% to 50% and <30%), BODE index (0-3, 4-6 and 7-10), PaO2(>80 mmHg, 71-80 mmHg, 61-70 mmHg and 51-60 mmHg), Mmrc(grade 2, grade 3 and grade 4), 6MWD(>500m, 401-500 m, 301-400 m, and 201-300 m) were statistically significant.

DISCUSSION

COPD is a multicomponent disease in which structural and functional changes are seen in the lungs and extra-pulmonary organs. Many different inflammatory markers appear to be increased in the serum of stable COPD patients.MAB is a sensitive marker of cardiovascular risk and it has a stronger association with cardiovascular events and death.

We studied MAB in 40 stable COPD patients and similar number of healthy controls of same age group with MAB being correlated with severity of COPD and the severity was assessed using various

clinical and physiological parameters including arterial blood gas, spirometry, Bode Index, mMRC grading, 6 MWD. Our Study showed MAB is significantly increased in Stable COPD patients in comparison to healthy controls. We compared our study with Polatli et al[5] study who unlike our study compared the levels of Plasma von willebrand factor, Fibrinogen and 24 hour urine MAB in 33 AECOPD, 26 Stable COPD and 16 healthy controls of same age group. MAB showed significant increase in AECOPD(Acute excaberation of COPD) than stable COPD and healthy controls. However both studies showed significant correlation with disease severity.

Majority of the cases in both cases group and control group were above the age of 50 years. The mean age of cases group was 62.12 years and control group was 55.58 years. The comparison of mean value of age was statistically significant in between groups in our study. Male preponderance is seen in both cases group& control group which was similar to studyby Anand Kumar et al[13] who reported majority of cases in cases group [50(83%)] and control group[41 (82%)] were males with mean age of 58.4 years and 58.8 years in cases group and control group respectively. Majority of the cases in both cases group and control group were in age group between 61-70 years respectively. Similar observation is seen in another study by Rakesh Kumar[14] who reported majority of the cases in both cases group [41(80.39%]) and control group [30(75%)] were males. Most of the cases [16 (31.37%)] belonged to 61- 70 year of age group in cases group and 51-60 year age group [13 (32.5%)] in control group.

Our study showed that most of the cases in the cases group (19[47.5%]) had FEV1 in the range of 50% to 80% predicted and in the control group, 36 (90%) had FEV1 > 80% predicted which was in comparison with Anand Kumar et al[13] who reported majority of the cases in cases group (43[71.7%]) had FEV1 in the range of 50% to 80% predicted and in control group, 48 (96%) had FEV1 >80%.

Our study showed that the comparison of mean value of SPO2, PaO2, UACR (mg/g), CRP (mg/l), 6MWD (meter), BODE index, FEV1% predicted & FEV1/FVC ratio were statistically significant which was comparable to Anand Kumar et al[13] study.

Our study showed that the prevalence of MAB in COPD cases was around 56%, which was quite higher to the 24% reported by Casanova etal[7], Bulcun et al[8], Sanjay et al[15] found MAB prevalence of 39%, 38.27%, respectively in COPD cases in their studies.

Majority of the COPD cases with prevalence of MAB in our study were from severe and very severe COPD subgroups (71.4% respectively) which was similar to study done by Sanjay et al[15] who reported severe and very severe COPD cases had 51.62% and 22.58% MAB prevalence respectively.

Our study showed anegative correlation between FEV1%, 6MWD, PaO2 and MAB levels among the 40 cases which was similar to study done by Anand kumar et al[13] who reported a significant inverse relationship between UACR and PaO2, FEV1%, 6MWD. Similarly Casanova et al[7], Komurcuoglu et al[6], Mehmood and Sofi[16] reported a negative correlation between PaO2 and MAB levels in their respective studies.

Our study showed a positive correlation between MAB levels with BODE index and mMRC grading which was similar to study by Anand Kumar et al[13] who reported a positive relationship between UACR and BODE index and mMRC grading.

CONCLUSION

COPD patients should be screened regularly with MAB to determine the risk of/and progression of cardiovascular morbidity and mortality so that adequate decision of interventional strategies can be taken out to prolong the survival.

Table 1: Comparison of cases with COPD and controls

Parameters	Control group (Mean±SD)	Cases group (Mean±SD)	P-value
PaO2	93.05±5.188	74.90±10.04	<0.0001
PaCO2	40.30±3.480	42.15±5.066	0.0607 NS
FEV1%	89.40±7.500	53.88±19.46	<0.0001
FEV1/FVC	95.63±7.977	48.83±5.275	<0.0001
BODE index	0.4750±0.5057	2.900±1.985	<0.0001
6MWD (meter)	533.9±36.92	478.3±86.98	0.0004
UACR (mg/g)	14.63±4.253	92.18±70.61	<0.0001

Table 2: Distribution of MAB with Severity of COPD (GOLD criteria) in cases

Severity of COPD	MAB Present	Percentage (%)	(Mean±SD)
Mild (n=12)	4	33.73	97.5±22.64
Moderate (n=7)	4	57.14	148.5±12.68
Severe(n=14)	10	71.40	151.9± 23.62
Very severe(n=7)	5	71.40	179.8 ±29.39
Total(n=40)	23	57.50	147.95±34.32

Table 3: Association of MAB with FEV1, BODE index, PaO2, mMRC grade and 6MWD

Subgroups		Microalbumin Levels UACR (mg/g)						P-value (ANOVA test)	Spearman correlation(r) and P value
		30- 50	51-100	101-150	151-200	201-300	Mean±SD		
FEV^1 %	50-80% (n=19)	0	2	4	2	0	61.53±57.63	P=0.0230	r=-0.8660, p=0.001
	30-50% (n=14)	0	0	4	6	0	143.2±66.46		
	<30% (n=7)	0	0	0	3	2	173.3±82.99		
BODE index	0-3 (n=25)	0	2	5	5	0	74.64±65.51	P=0.0472	r=-0.9538, p=0.0194
	4-6 (n=14)	0	0	3	6	1	114.5±68.47		
	7-10 (n=1)	0	0	0	0	1	218.0		

PaO^2	>80 (n=14)	0	0	4	1	0	58.07±58.14	P<0.0001	r =-0.5754, p=0.0424
	71-80 (n=11)	0	2	0	1	0	41.45±48.34		
	61-70 (n=14)	0	0	4	8	2	161.9±29.07		
	51-60 (n=1)	0	0	0	1	0	152.0		
mMRC	Grade I (n=4)	0	0	0	0	0		P=0.0058	r= 0.9142, p=0.0458
	Grade II (n=21)	0	2	4	5	0	80.05±65.91		
	Grade III (n=13)	0	0	4	5	1	121.0±64.00		
	Grade IV (n=2)	0	0	0	1	1	188.0±42.43		
6MWD test	>500 (n=19)	0	2	4	2	0	61.53±57.64	P=0.0261	r =-0.9400, p=0.0400
	401-500 (n=14)	0	0	4	6	0	113.2±66.46		
	301-400 (n=5)	0	0	0	2	1	112.4±90.84		
	201-300 (n=2)	0	0	0	1	1	185.5±26.16		

REFERENCES

1. GOLD. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018. https://goldcoped.org/. Accessed June 25, 2019. 2019
2. P. J. Barnes and B. R. Celli, "Systemic manifestations and comorbidities of COPD," European Respiratory Journal, vol. 33, no. 5, pp. 1165–1185, 2009
3. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW etal. TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356:775–89.
4. Diercks GF, Van Boven AJ, Hillege JL, de Jong PE, Rouleau JL, van Gilst WH. The importance of microalbuminuria as a cardiovascular risk indicator:a review. Can J Cardiol. 2002;18:525–35.
5. Polatli M, Cakir Q, Cildag O, Bolaman AZ, Yenisey C, Yenicerioglu Y. Microalbuminuria, von Willebrand factor and fibrinogen levels as markers of the severity in COPD exacerbation. J Thromb Thrombolysis.2008;26:97–102.
6. Kömürcüoğlu A, Kalenci S, Kalenci D, Kömürcüoğlu B, Tibet G. Microalbuminuria in chronic obstructive pulmonary disease. Monaldi Arch Chest Dis.2003;59(4):269-72..
7. Casanova C, de Torres JP, Navarro J, Aguirre-Jaíme A, Toledo P. Microalbuminuria and hypoxemia in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010;182:1004–10.
8. Bulcun E, Mehmet E, Aydanur E, Ucler K.

Microalbuminuria in Chronic Obstructive Pulmonary Disease, Journal of Chronic Obstructive Pulmonary Disease, COPD.2013;10:186-92.

9. GOLD: Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease (updated 2014).
10. American Thoracic Society. ATS statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166:111–7.
11. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999;54:581–6.
12. De Jong PE, Curhan GC. Screening, monitoring and treatment of albuminuria: public health perspectives. J Am Soc Nephrol. 2006;17:2120–6.
13. Anand Kumar, Sanjay Kumar Verma, Achal Mehrotra, Avdhesh Kumar, Sudhir Chaudhri, C.M. Verma, Rajendra Prasad and Surya Kant. A Study on Microalbuminuria in Patients with Chronic Obstructive Pulmonary Disease at a Tertiary Care Centre in North India. Indian J Chest Dis Allied Sci 2017;59:17-21.
14. Kumar R. Study of Microalbuminuria in Patients with Stable COPD. Ann. Int. Med. Den. Res. 2016;2(3):95-8.
15. Sanjay Sahay, Mukesh Kumar Prasad. Microalbuminuria and COPD: A Clinical and Physiological Association. Int J Med Res Prof.2018 July;4(4):270-272
16. Mehmood K, Sofi FA. Microalbuminuria and Hypoxemia in Patients with COPD. J Pulm Respir Med. 2015;5:280.