Study of microalbuminuria in chronic obstructive pulmonary disease patients at tertiary care teaching hospital

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ABSTRACT

Background: Hypoxemia-induced endothelial dysfunction leads to microalbuminuria. Microalbuminuria (MAB) has also been used as a parameter to assess the risk of cardiovascular events in an individual. The aim of this study was to observe the relationship of MAB in patients with chronic obstructive pulmonary disease (COPD) and to correlate MAB with different stages of COPD.

Materials and Methods: This cross sectional study included 140 patients with COPD selected according to GOLD guidelines based on COPD test assessment score and the number of exacerbations who had smoking pack years of more than 10 years. Urine albumin creatinine ratio (UACR) more than 30 mg/gm represents MAB. Results: The UACR increases as the severity of groups of COPD increases with significant differences in UACR values among different COPD groups. Significant differences were seen among various groups of COPD when compared for different clinical parameters such as SPO2, PaO2, PaCO2, pH, and C-reactive protein (CRP). Pearson correlation analysis revealed that UACR was significantly inversely related with PaO2 ($r = -0.514, P < 0.001$), SPO2 ($r = -0.397, P < 0.001$) and FEV1 ($r = -0.441, P < 0.001$) and it was significantly positively correlated with PaCO2 ($r = 0.675, P < 0.001$).

Conclusion: This study indicates that there is strong relationship of MAB in patients with COPD and the levels of MAB increase as the severity of COPD increases due to hypoxia and endothelial dysfunction. As MAB is a marker for cardiovascular risk, patients with COPD can be routinely evaluated for the urine test of MAB specially who are at increased risk for cardiovascular events.

Keywords: Chronic obstructive pulmonary disease, microalbuminuria, urine albumin creatinine ratio

Introduction

COPD is a disease having systemic inflammation. Circulating pro-inflammatory cytokines and C-reactive protein (CRP) are important markers of systemic inflammation.9,8 Cardiovascular disease is most common cause of mortality in COPD.8,4

Microalbuminuria (MAB) is the condition in which excretion of albumin in the urine is elevated at amounts not detectable by conventional semiquantitative tests. MAB is now measured by albumin (µg) and creatinine (mg) ratio in a random urine sample.9

Currently, the National Kidney Foundation recommends to use spot urine albumin/creatinine ratio in the first voided, morning, and midstream specimen to detect albuminuria.9

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MAB is defined as the urine albumin creatinine ratio (UACR) between 20 mg/g in men and 30 mg/g in women and the upper threshold of 299 mg/g for both sexes.\cite{11}

More recently, MAB is used to screen people who are at a high risk for cardiovascular events and the progression of kidney disease.\cite{10}

During exacerbation of COPD-MAB was increased in recent researches.\cite{12} The link between lower forced expiratory volume in 1 s (FEV₁) and emphysema severity with endothelial dysfunction was also endorsed by researchers.\cite{13,14} Furthermore, MAB may point toward endothelial dysfunction.\cite{15} It was studied that decreased oxygen concentration in blood during exacerbation episodes of COPD will lead to increased glomerular filtration and hence more protein leakage in the form of MAB.

Till now there has been very few studies on the association of MAB in different groups of patients with COPD based on Global Initiative for Obstructive Lung Disease (GOLD) criteria including COPD assessment test scores (CAT) and the number of exacerbations; therefore, our study was conducted to investigate the relationship of MAB in patients with COPD and to correlate MAB with different stages of COPD.

**Materials and Methods**

The cross-sectional study was done in the Department of Internal Medicine, King George’s Medical University, Lucknow after getting approval of Institutional ethical committee of KGMU. All patients with COPD diagnosed by history, examination, and spirometry (GOLD guidelines) who gave written informed consent were included in the study. The study excluded patients who did not give consent or had well-documented chronic history of heart failure, kidney failure, and liver cirrhosis. It also excluded patients who were pregnant, or who were suffering from urinary tract infection, HIV, diabetes mellitus, and ischemic heart disease.

A total of 140 patients with COPD were taken and they were divided into four different groups, namely A, B, C, and D based on the CAT score and number of exacerbations. A CAT score of more than 10 denoted a patient as having more symptoms and a history of exacerbation of 2 or more than 2 in a year denoted that the patient had more risk of COPD. Group A included patients having less symptoms and less risk, group B had patients of more symptom less risk, group C had patients of more risk less symptom group D had patients having more symptoms and more risk.

All subjects were evaluated by taking a detailed clinical history. All subjects in the study had smoking pack years of more than 10 years. The duration of COPD, number of exacerbations, symptoms and treatment history was enquired from each patient enrolled in the study with detailed systemic examination of each patient. Routine blood investigations were done with specific investigations such as urine routine microscopy, MAB, UACR, spirometry, CRP, arterial blood gas (ABG) analysis, skiagram of chest in posterior anterior view. For the diagnosis of MAB, care was taken when collecting samples for the urine UACR. An early morning sample was preferred. The patient was instructed to avoid heavy exercises 24 h before the test. In our study we labelled a patient to have MAB when the urine ACR was more than 30 mg/gm.

Patients with COPD of different groups were compared with urine ACR values. Further, these urine ACR values were also correlated with different physiological parameters such as SpO₂, pH, PaCO₂, CRP, and PaO₂.

Data were analyzed using SPSS (Statistical Package for the Social Sciences) software program, version 21.0. The values were represented in number (%) and mean ± SD. To test the significance of two means, Student t test was used. Chi-square test and analysis of variance (ANOVA) test were also used. To assess the correlation between continuous variables, Pearson correlation coefficients (r) were used. The r value <0.3 denoted weak correlation, r value between 0.3 and 0.5 denoted mild correlation, between 0.5 and 0.7 denoted moderate correlation, and >0.7 denoted strong correlation. The level of statistical significance was set at P < 0.05.

**Results**

The study included a total of 140 patients with COPD who met the selection criteria. Of these 22 (15.7%) subjects were in Group A, 30 (21.4%) subjects were in Group B, 36 (25.7%) subjects Group C, and 52 (37.1%) subjects were in Group D. The characteristics of the subjects are mentioned in Table 1. The mean age of patients with COPD was 66.60 ± 11.69 years and 84.3% were male. The MAB was present in 18.6% of patients with COPD. Proportion of patients having high urine ACR (urine ACR >30 mg/gm) was 9.1% in Group A, 13.3% of Group B, 16.7% of Group C, and 26.9% of Group D. Maximum percentage of patients having high urine ACR were present in Group D, pH, PaO₂, and SpO₂ levels of Group D cases were lowest, whereas those of Group A were highest. Urine ACR, PaCO₂, and CRP of Group D cases were maximum, whereas those of Group A were minimum. A significant difference was observed between various groups of COPD (A-D) when they were compared in terms of values of urine ACR (P < 0.001). The urine ACR values were highest in Group D (67.5 ± 98.16 mg/gm) and lowest in Group A (8.82 ± 12.68 mg/gm). Urine ACR values of Group B was 17.7 ± 25.1 mg/gm and Group C was 31.8 ± 39.88 mg/gm. PaCO₂ values were highest in Group D (61.35 ± 11.21 mm Hg) and lowest in Group A (40.18 ± 4.7 mm Hg) and the difference was statistically significant. PaO₂ values were highest in Group A (74.09 ± 7.6 mm Hg) and lowest in Group D (61.35 ± 11.21 mm Hg). SpO₂ values were highest in Group A (93.55± 0.51%) and lowest in Group D (85.6 ± 2.8%), whereas CRP was highest in Group D (5.62 ± 0.99) and lowest in Group A (2.97 ± 1.15) and difference among different groups was statistically significant (P < 0.005) [Table 1 and Figure 1].
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COPD patients having MAB were more hypoxic (mean PaO2 60 ± 6.56) and more hypercapnic (mean PaCO2 64.23 ± 13.45) as compared to COPD patients without MAB (mean PaO2 69.26 ± 7.36 and mean PaCO2 47.49 ± 9.46) (P < 0.001). There was a significant difference between COPD patients having MAB and COPD patients without MAB when they were compared for values of pH (P < 0.03) and SpO2 (P < 0.001) but values for nonsignificant for CRP [Table 2].

The urine ACR had positive significant correlation with PaCO2 (r = 0.675, P = <0.001) and negative significant correlation with PaO2 (r = −0.512, P = 0.001). There was mild level of negative correlation of urine ACR with FEV1 (r = −0.441, P < 0.001) and SpO2 (r = −0.397, P < 0.001). There was weak negative correlation of urine ACR with pH (r = −0.258, P = 0.002) and it weakly positive with CRP (r = 0.258, P < 0.002) [Table 3; Figures 2 and 3].

**Discussion**

Our study aimed to investigate the relationship of MAB in patients with COPD and to correlate MAB with different stages of COPD.

Our study revealed that MAB was present in 18.6% of patients with COPD which is similar to the result of previous study done in 2015 (24%).[14] Urinary ACR was increased in the subjects who were more symptomatic and had high risk (26.9%) as compared to the patients who had less symptoms with low risk (9.1%) which was similar to the study done in 2017.[16] There was a significant difference in the urine ACR between the groups when they were categorized on the basis of FEV1, history of exacerbations and CAT.

The aforementioned results of our study are supported by previous studies who found that smoking induces albuminuria.[16-18] Smoking decreases renal blood flow, causing decline in the glomerular filtration rate (GFR). A decrease in the GFR will enhance the renovascular resistance causing renal arteries to be thickened and hence further decreasing the renal blood flow. Therefore, in persons exposed to cigarette smoke with a normal GFR, the filtration rate decreases. These transient multiple renal hypoperfusion episodes damage some glomeruli leading to structural changes such as hyperfiltration leading to MAB along with hypertrophy of remaining glomerulus.

As per our knowledge, till now there has been no study done to compare the values of pH, SpO2, PaO2, CRP, and PaCO2 in various groups of COPD according to GOLD criteria based CAT score and number of exacerbations. Our study reveals that pH, PaO2, and SpO2 levels of Group D cases were lowest, whereas those of Group A were highest. Urine ACR, PaCO2, and CRP of Group D cases were maximum, whereas those of Group A were minimum. Thus, hypoxemia increases from stage A to stage D which as a result causes a decline in SpO2, PaO2, pH as we move from stage A to stage D. Due to hypoxemia-induced endothelial dysfunction and increased inflammation from cigarette smoking urine ACR, CRP, and PaCO2 increases as we move from stage A to stage D. As we know, CRP is an inflammatory marker and associated with lung inflammation, hence Group D patients (those with greater

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**Table 1: Characteristics of study population**

| Group | n=22 | n=30 | n=30 | n=52 | ANOVA |
|-------|------|------|------|------|-------|
| Group A | 64.00±7.41 (43-65) | 65.53±12.54 (48-85) | 67.50±9.05 (52-85) | 67.69±14.09 (43-95) | 0.664 | 0.75 |
| Group B | 20 | 26 | 30 | 22 | 0.713 |
| Group C | 8.82 ±12.68 | 17.7±25.1 | 31.8±39.88 | 67.5±98.16 | 6.2 | 0.001 |
| Group D | 40.18±4.7 | 45.2±7.03 | 45.94±7.9 | 61.35±11.21 | 43.3 | 0<.001 |
| Group C | 74.09±7.6 | 71.2±4.5 | 66.9±6.06 | 63.35±8.12 | 15.9 | <0.001 |
| Group A | 93.55±5.1 | 91.80±2.55 | 87±4.18 | 85±2.8 | 52.6 | <0.001 |
| Group A | 7.43±0.04 | 7.42±0.04 | 7.40±0.05 | 7.38±0.05 | 7.52 | <0.001 |
| Group A | 2.97±1.15 | 4.34±0.82 | 5.18±1.34 | 5.62±0.99 | 34.02 | <0.001 |
| FEV1% | <30% | - | - | - | 12 |
| 30%-49% | - | - | 12 | 28 |
| 50%-79% | 10 | 30 | 24 | 12 |
| >80% | 12 | - | - | - |

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**Figure 1:** Comparison of urine ACR, pH, PaCO2, PaO2, and SpO2 between groups of COPD
disease severity) had CRP values higher than Group A (with lesser disease severity).

Bozkus et al. found a moderate negative correlation of urine ACR with PaO2 which was statistically significant ($r = -0.60$).

Some patients who were hypoxic did not show MAB suggesting there may be a role of genetic susceptibility to oxidative stress.[19]

Thus, we observed that patients with COPD who were more hypoxic and more hypercapnic had more MAB than compared to COPD patients without MAB which was statistically significant because hypoxia results in endothelial dysfunction due to loss of physiological equilibrium of vasodilation and vasoconstriction which results in loss of peritubular capillaries in tuberculosis. [20] As MAB is now used as a screening tool for patients of cardiovascular risk, patients with COPD should be regularly advised for urine routine microscopy to detect MAB which will alert them for development of further cardiovascular events and hence take necessary precautions and treatment for the same. There is a possibility to assess a therapeutic role of blockers of RAAS system in reducing cardiovascular events in COPD.[21] Our study had few limitations. First the sample size is small which may not depict the COPD burden in general population. Secondly the number of pack years and BODE index between different groups of COPD were not evaluated in our study. As our study was not prospective, we could not assess the long-term impact of MAB on the clinical outcome in patients with COPD.

### Conclusion

We conclude that patients with COPD have more prevalence of MAB and the levels of MAB increase as the severity of COPD increases due to hypoxia and endothelial dysfunction. MAB is a simple noninvasive, inexpensive test which can be performed without much resources. Previous studies have already evaluated the importance of MAB as a marker for cardiovascular events. Hence, patients with COPD can be routinely evaluated for the urine test of MAB especially who are at high risk for cardiovascular events. Further multicentric studies should be done with larger population of patients with COPD to:

(a) assess the clinical importance of MAB in these patients
(b) evaluate for further therapeutic treatments in patients with COPD while keeping MAB as a marker of disease activity.

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Conflicts of interest
There are no conflicts of interest.

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