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PROGNOSTIC IMPLICATIONS OF MICROALBUMINURIA IN NON-DIABETIC, NON-HYPERTENSIVE PATIENTS WITH ACUTE CORONARY SYNDROME

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ABSTRACT

Background: Microalbminuria is a major risk factor predisposing to cardiovascular morbidity and mortality but very limited evidence are there to suggest it's use as a prognostic tool to determine in-hospital morbidity and mortality. The aim of this study was to examine the presence of microalbuminuria as a predictor of major adverse cardiac events in non-diabetic,non-hypertensive patients with acute coronary syndrome.

Methods: Fifty five non-diabetic, non-hypertensive patients with acute coronary sydrome were studied prospectively. A comparison of in-hospital mortality and major non-fatal in-hospital events between microalbuminuric and normoalbuminuric patients was done.

Results: In the study group 52.7% patients developed an in-hospital event (fatal or non-fatal). Microalbuminuric had a higher mortality rate in comparison with normoalbuminuric but it was not significant (p=0.146). The incidence of arrhythmias (p=0.029) and cardiogenic shock (p=0.042) were significantly higher in patients with microalbuminuria. The combined end-point of the total number of fatal and non-fatal events was significantly higher in patients with microalbuminuria (p=0.002). In multiple logistic regression analysis, microalbuminuria (p=0.030) was independently related to the occurrence of major in-hospital events.

Conclusions: Microalbuminuria is a significant predictor of in-hospital morbidity and mortality in non-diabetic, non-hypertensive patients with acute myocardial infarction.

KEYWORDS : URINE MICROALBUMIN, A:C RATIO, MYOCARDIAL INFARCTION, MACE

INTRODUCTION

Microalbuminuria happens more often in diabetic patients with acute myocardial infarction (AMI)[1] but it has been reported even in non-diabetic, non-hypertensive patients with AMI. The microalbuminuria is a considerable predictive factor in intra-hospital mortality [2,3] coronary incidents and the death over longer periods after myocardial infarction [4]. A considerable higher and severe degree of coronary disease has been registered in patients with AMI and microalbuminuria than in patients with AMI but without microalbuminuria[5]. From clinical practice point of view the investigation of microalbuminuria as a prognostic factor is of considerable importance since a lot of studies show that the microalbuminuria is a factor that could be modified. Some medications, especially the inhibitors of Angiotensin Converting Enzyme, Angiotensin receptor blockers and statins [6,7,8] can decrease its level, which can turn out to be a value in finding therapeutic strategies about diminishing the cardiovascular disease mortality, including patients with myocardial infarction.

Limited studies are there regarding the prognostic significance and pathophysiological mechanism of microalbuminuria in non-diabetic, non-hypertensive patients with ACS. Hence, the present study is undertaken to find out the correlation between urine albumin level and the severity and complications of patients admitted with acute coronary syndrome to the general medicine department of our hospital.

METHODS

Patient Characteristics

Consecutive patients admitted to our hospital for suspected ACS from December 2014 to October 2016, were eligible in this prospective follow-up study. All hospitalized patients are screened for suspected ACS on the basis of admission diagnoses. The whole spectrum of ACS, including unstable angina, non–ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation MI (STEMI), was studied. The diagnosis of ACS was based on American College of Cardiology (ACC)/American Heart Association (AHA) guidelines. Patients with chronic kidney disease and macroalbuminuria, urinary tract infection, traumatic event, acute kidney injury, PSGN, h/o rheumatic and other inflammatory disease, high grade fever and malignancy were excluded from the study.

Urine samples were collected from morning first urination within 24 hours of admission. Urine for microalbuminuria was tested using SIEMENS CLINITEK MICROALBUMIN 2 REAGENT STRIPS with SIEMENS CLINITEK STATUS+ ANALYZER

Data Collection

Demographic data and past medical history, including card iovascular (CV) risk factors and comorbidities, were collected. The investigation results including blood tests and electroc ardiogr aphic findings were also recorded. All patients were followed up till discharge.

Endpoints

The composite primary endpoints of this study were the correlation of microalbuminuria with major adverse cardiac events (MACE) during hospital stay. MACE included CV mortality, malignant arrhythmia, cardiogenic shock, congestive heart failure. Cardiogenic shock was defined as systolic blood pressure <90 mm Hg or a drop of mean arterial pressure >30 mm Hg with a pulse >60 beats per minute to exclude shock secondary to bradycardia and/or low urine output (<0.5 mL/kg/h) with or without evidence of organ congestion. Malignant arrhythmia was defined as symptomatic sustained ventricular tachycardia and also ventricular fibrillation, irrespective of symptoms or hemodynamic stability.

Statistical Analysis

We used SPSS version 20.0 (SPSS Inc., Chicago, IL) for statistical analysis. For the purpose of present analysis, patients were divided into 2 groups based on urine microalbumin: group 1, with microalbuminuria and group 2, without microalbuminuria.

Continuous variables were presented as mean ± SD and categorical variables were presented as number of patients and percentage. Baseline characteristics of the 2 groups were compared using the $\chi 2$ test or the Fisher exact test for categorical variables and the Student unpaired t test for continuous variables, as appropriate. Association of various risk factors with MACE were analysed and significant variables were entered in a bivariate logistic regression analysis to determine independent predictability of risk factors.

OBSERVATIONS

The baseline patient characteristics are shown in Table 1.

TABLE 1: COMPARISON OF BASELINE CHARACTERISTICS IN NON-DIABETIC, NON-HYPERTENSIVE PATIENTS WITH AND WITHOUT MICROALBUMINURIA

Base Line Characteristics	With MA N=35	Without MA N=20	P Value
Age in Years (Mean)	61.86±10.90	63.85±8.39	0.4840
Sex (Male : Female)	22:13	13:7	1.0000
H/O IHD	5(14.2%)	3(15%)	1.0000
Family History	5(14.2%)	2(10%)	1.0000
H/O Smoking	9(25.7%)	3(15%)	0.5025
H/O Alcoholism	4(11.4%)	2(10%)	1.0000
BMI (Mean)	25.46±1.77	24.80±1.43	0.1610
Admission Blood Sugar (Mean)	148.40±31.76	148.75±42.58	0.9725
Total Cholesterol (Mean)	165.20±28.32	156.05±33.65	0.2868
Triglyceride(Mean)	179.86±43.70	134.35±37.72	**0.0003**
LDL(Mean)	110.34±27.61	87.00±23.50	**0.0025**
HDL (Mean)	40.20±7.34	40.00±7.42	0.9232
Haemoglobin (Mean)	11.71±1.50	11.65±1.78	0.8945
TLC (Mean)	10.11±1.49	9.10±1.44	**0.0177**
Diagnosis (STEMI:NSTEMI)	25:10	14:6	1.0000
LV Ejection Fraction (Mean)	46.94±7.21	53.65±7.55	0.0019
Trop I	2.51±2.73	0.60±0.68	**0.0034**

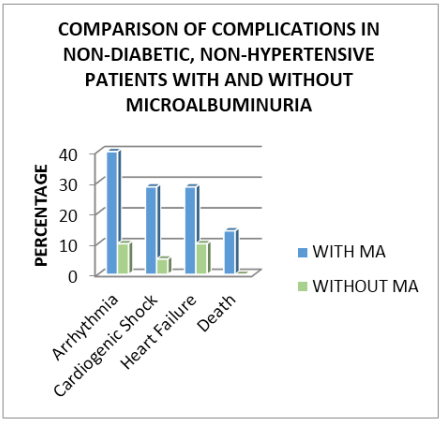
Among the parameters significant difference was found between the means of TG, LDL, TLC, LV ejection fraction and Trop I between the two groups.

Incidence of complications in both groups are shown in Table 2 & Figure 1.

TABLE 2 COMPARISON OF COMPLICATIONS IN NON-DIABETIC, NON-HYPERTENSIVE PATIENTS WITH AND WITHOUT MICROALBUMINURIA

Complication	Patients With MA		Patients Without MA		P Value
	No.	%	No	%	
Arrhythmia	14	40.0	2	10	**0.0293**
Cardiogenic Shock	10	28.5	1	5	**0.0420**
Heart Failure	10	28.5	2	10	0.1756
Death	5	14.2	0	0	0.1465

FIGURE 1



Complications like arrhythmia and cardiogenic shock were seen in significantly higher number of patients with microalbuminuria. Although there was higher incidence of heart failure and mortality in patients with microalbuminuria but it was not statistically significant.

To study the relationship between MA and MACE, Fisher's exact test was performed using a contingency table (table 3) and the p value was calculated to be 0.0002 which is significant.

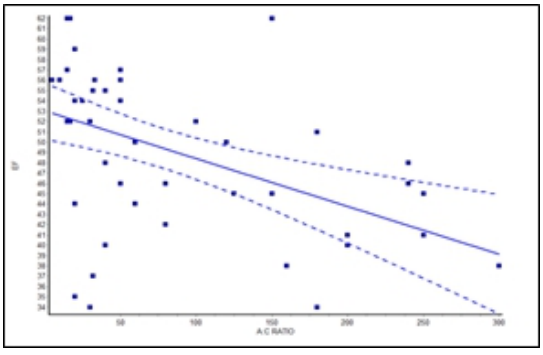
TABLE 3 RELATIONSHIP BETWEEN MICROALBUMINURIA AND MACE

	NO MACE	MACE
MA –VE	15	5
MA +VE	11	24

To correlate the A:C ratio and ejection fraction, **Pearson's correlation coefficient (r)** is calculated which is a measure of linear dependence or the strength of association between the two variables.

In our study the correlation coefficient (Figure 2),r = -0.4589, p value = 0.0004 which means that there is an extremely significant inverse correlation between the two variables and the negative r value indicates that EF decreases as the value of A:C ratio (Albumin: creatinine ratio) increases.

FIGURE 2. CORRELATION BETWEEN A:C RATIO AND EF



Association of risk factors with MACE is shown in Table 4.

TABLE 4 ASSOCIATION OF RISK FACTORS WITH MACE (MAJOR ADVERSE CARDIAC EVENTS) IN NON-DIABETIC, NON-HYPERTENSIVE PATIENTS

Base Line Characteristics	No Mace N=27	Mace N=28	P Value
Age in Years (Mean)	61.37±11.21	63.75±8.77	0.3835
Sex (Male : Female)	21:6	14:14	**0.0496**
H/O IHD	4(14.81%)	4(14.28%)	1.0000
Family History	1(3.70%)	6(21.42%)	0.1012
H/O Smoking	7(25.92%)	5(17.85%)	0.5279
H/O Alcoholism	4(14.81%)	2(7.14%)	0.4216
BMI (Mean)	24.33±1.44	26.07±1.43	**<0.0001**
Admission Blood Sugar (Mean)	144.0±40.21	152.89±30.80	03604
Total Cholesterol (Mean)	149.70±30.13	173.61±26.11	**0.0027**
Triglyceride(Mean)	138.07±36.84	187.64±42.72	**<0.0001**
LDL(Mean)	83.0±18.77	120.04±23.84	**<0.0001**
HDL (Mean)	38.70±8.77	41.50±5.35	0.1571
TLC (Mean)	9.85±1.65	9.64±1.44	0.6168
Microalbuminuria	11(40.74%)	24(85.71%)	**0.0007**
Trop I	1.52±2.86	2.11±1.85	0.3660
EF	53.22±6.76	45.67±7.33	**0.0002**

Only female sex, BMI, total cholesterol, triglyceride, LDL, presence of MA and Ejection fraction were associated with MACE.

From bivariate logistic regression analysis (Table 5) presence of microalbuminuria was found to be an independent predictor of MACE (odds ratio 17.126, 95% CI 1.317 to 222.716 and p value 0.030).

The other independent predictor is LDL (odds ratio 0.037, 95%CI 1.006 to 1.198 and p value 0.037).

TABLE 5 BIVARIATE LOGISTICS REGRESSION ANALYSIS

Risk Factors	Odds Ratio	95% Confidence Interval		P Value
		Lower	Upper	
Female sex	4.976	0.452	54.801	0.190
BMI	1.729	0.912	3.277	0.093
Total Cholesterol	0.999	0.941	1.060	0.972
Triglyceride	0.966	0.925	1.009	0.121
LDL	1.098	1.006	1.198	**0.037**
Microalbumiuria	17.126	1.317	222.716	**0.030**
EF	0.963	0.865	1.073	0.494

DISCUSSION

To identify high risk patients of ACS is still one of the challenging issues. There are multiple clinical variables to assess these patients. Urinary albumin excretion increases significantly during initial days of ACS. But less importance has been given to this parameter as prognostic indicator in patients of ACS, especially in non-diabetic, non-hypertensive patients.

From our study it was found that in non-diabetic, non-hypertensive patients level of total cholesterol, triglyceride, LDL, TLC and Trop I were significantly higher in patients with MA. Left ventricular ejection fraction is also significantly lower in patients with MA. Among the non-diabetic, non-hypertensive patients the complications were seen in higher number of cases with MA but only arrhythmia and cardiogenic shock were significantly increased.

In the study by **Abdul Ghaffar Memon et al.**[9] in non-diabetic, non-hypertensive patients majority of the deaths was seen in the patients with MA 12.8% while in the patients with MA were with mortality of 7.5% but there was no statistical significance of the difference between the two mortality rates which is similar to the finding in our study.

In the study by **Lekatsas, Ioannis et al.**[10], Patients with microalbuminuria had a higher mortality rate in comparison with normoalbuminuric patients (p=0.01). For non-fatal events, the incidence of pulmonary edema and ventricular arrhythmias was significantly higher in patients with microalbuminuria (p<0.001 and p=0.01, respectively). The combined end-point of the total number of fatal and non-fatal events was significantly higher in patients with microalbuminuria (p<0.001).

It was also found that among the non-diabetic, non-hypertensive patients female sex, BMI , total cholesterol, triglyceride, LDL, presence of MA and Ejection fraction were associated with MACE. From logistic regression analysis presence of microalbuminuria and LDL found to be an independent predictor of MACE. A significant inverse correlation was also found between A:C Ratio and Ejection Fraction.

In the study by **Lekatsas, Ioannis et al.**[10], from multiple logistic regression analysis, microalbuminuria (p<0.001) and ejection fraction (p=0.01) were independently related to the occurrence of major in-hospital events.

Previous studies have proved MA to be a predictor of MACE in patients with ACS but very few studies are there showing the correlation of MA with MACE in non-diabetic, non-hypertensive patients.

Microalbuminuria is a widely identified marker of endothelial dysfunction and it's presence markedly increases the risk for cardiovascular morbidity and mortality among diabetics and nondiabetics.[11,12] In general, most studies in non-diabetic hypertensives indicate a two- to three-fold increase in cardiovascular risk. Furthermore, among hypertensives without diabetes followed prospectively, microalbuminuria is associated with a four-fold increased risk for ischemic heart disease.[13,14] It has been postulated that MA indicates increased vascular endothelial permeability not restricted to renal vessels. This could promote foam cell formation and atherogenesis by increased leakage of lipoprotein particles into the vessel wall, an increased trans-capillary albumin excretion rate, an increased plasma level of VWF, and an attenuated endothelium dependent response to vasodilator stimuli in subjects with MA[15]. Therefore, these individuals are at increased risk of enhanced progression of atherosclerosis and subsequent mortality. The ability of MA to predict adverse cardiovascular events is not restricted to high risk populations. In a low risk population for CVD, this fact was supported by Hillege et al. They demonstrated that MA can predict CVD and non-CVD mortality in a general population[16].

Different theories have been postulated to explain the increase in the albumin excretion rate during acute myocardial infarction. During the first days after acute myocardial infarction, heart failure seems to be the main determinant of urinary albumin, as shown by the good correlation of the albumin:creatinine ratio with aldosterone[17]; inflammation seems to play the key role from the third day. Normally cubilin plays an important role in proximal tubule endocytic reabsorption of filtered albumin and megalin may be involved in albumin reabsorption directly as a receptor for albumin, and/or indirectly by affecting the expression and/or endocytic function of cubilin.[18] TGF-β, released as a result of inflammation acts in a feedback mechanism increasing albumin filtration[19] and at the same time inhibiting megalin- and cubilin-mediated albumin endocytosis,[20] both leading to increased albuminuria.

Thus, since low-level urinary albumin may be easily measured during the hospital stay, the albumin:creatinine ratio may constitute a suitable method for an adequate assessment of outcome in patients with acute coronary syndrome and patients with MA can be closely followed up for development of adverse cardiac events, so that timely intervention can be done to prevent mortality.

CONCLUSION

Non-diabetic, non-hypertensive patients with ACS having MA had more incidence of short term complication but no significant increase in mortality. From the regression analysis it was found that microalbumiuria is an independent predictor of MACE in non-diabetic, non-hypertensive patients with acute coronary syndrome.

Microalbuminuria estimation is a simple and inexpensive test. Hence, it can be measured along with other routine investigations during screening and regular follow up of the non-diabetic,non-hypertensive population, so that, patients can be stratified as low or high risk depending on A:C ratio and preventive measures like life style modification and dietary restriction can be strictly advised.

LIMITATIONS OF THE STUDY

The sample size of the study was small mostly due to unaffordability of patients. A larger sample size would have yielded better outlook towards the association of MA with prognosis of patients with acute coronary syndrome. The follow-up period was short because of illiteracy and non-compliance of the patients and their attendants. A longer follow up would have allowed us to get more information regarding the long term prognostic implications of MA in patients of acute coronary syndrome. Information regarding angiography and patients who underwent revascularization procedures like PTCA or CABG could not be gathered. The information would have helped us to examine the association between microalbuminuria and number of vessel blocked and also would have helped us in analysing the predictive effect of microalbuminuria on the outcome following revascularization. Assay of other proinflammatory markers like hsCRP not included in the study which could have affected the independent predictive value of microalbuminuria.

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