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A study on urine micro albuminuria as an isolated risk factor for cardiac morbidity and mortality in non-diabetics and non-hypertensives

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Abstract---Background: There is a relative paucity of data on the link between urine micro albumin and IHD in non-diabetics as well as non-hypertensive's compared to diabetics. This study was meant to look for the association between urine micro albumin and in cardiac morbidity and mortality among non-diabetic and non-hypertensive's, which may further provide insight to the early diagnosis of micro albuminuria and its potential for predicting cardiac morbidity and thus needed inputs for better clinical management. Aims and objectives: To assess the relationship between micro albuminuria and proven risk factors and markers of cardiovascular disease in non-diabetic & non-hyper extensive ischaemic heart disease patients. Materials and methods: Among the 200 patients which were taken in the study, 141 (69.8%) were males and the rest 29.2% were females. 34.5% each were from the age of 41-50 years and 51-60 years respectively. Only 26 (13.0%) patients were from the age group of more than 60 years. Results: The mean age of patients was 50.66 with a SD of 9.33. Majority of males were from the age group of 41-50 years (38.3%), while 42.4% of females were from the age group of 51-60 years. Mean age of male patients was found to be 49.41±9.16, while female patients was of 52.44±9.57. Chest pain remains the most

common complaint among the patients (100%), followed by breathlessness in 55% and palpitation in 27.5%. Most of the patients were having a BMI of more than 23 kg/sq.m., 107 (53.5%), followed by 44.5% with normal value. Mean serum cholesterol among patients was 176.7 mg/dl, while mean serum TGs was 131.7 mg/dl. Mean blood sugar level was around 118.9 mg/dl. Ejection fraction of less than 50% was observed in 132 patients, constituting to 66.0% of the total study subjects. Micro albuminuria detected in 73.0% of the patients as per the criteria of 30-300 using urinary ACR. Out of 146 patients with micro albuminuria, 102 (69.9%) were males and the rest 44 (30.1%) were females. Among the patient having MA, 129 (88.4%) were from less than 60 years of age and the rest were above 60 years of age. 45.9% of the patient having micro albuminuria were having normal BMI. Around 74% of the patients with raised serum urea had incidence of micro albuminuria. Among 52 patients with elevated serum creatinine, 37 i.e., 71.1% had micro albuminuria. Among 169 patients with TG levels more than 125 mg/dl, 125 (73.9%) were having micro albuminuria. Among 26 patients with Serum cholesterol levels more than 200 mg/dl, 20 (76.9%) were having micro albuminuria. Among 63 patients with blood sugar levels above 126 mg/dl, 42 (66.6%) were having Micro albuminuria, EF of less than 50% was observed in 132 (66%) of the patients. In 146 patients with micro albuminuria, 98 (67.1%) were having EF of less than 50%. Conclusion: Urinary MA can be used as an important isolated indicator for assessing morbidity and mortality and survival in cardiovascular diseases amongst the patients who are not a known case of HTN and diabetes and develop Ischaemic heart disease.

Keywords---micro albuminuria, cardiovascular, cardiac morbidity, mortality, non-diabetic, non-hypertensive.

Introduction

Cardiovascular disease (cvd) account for large proportion of deaths and disabilities around the globe. Ischemic heart disease (IHD) has now become one of the leading causes of death worldwide, which accounts for more than 7.3 million deaths in 2008 alone¹. Moreover, around 80% of cardiovascular deaths now occur from low- and middle-income countries². As India is in the transition stage, facing burden of both communicable and non-communicable diseases and 24% of deaths in India accounts to cardiovascular etiology³. Currently 31.8 million Indians are living with IHD, and the death rate from cardiovascular diseases in India has rose 111 time from 1990 to 2020, with Ischemic heart disease (IHD) contributing the major share⁴⁻⁵.

Various new bio-markers of IHD such as, lipoproteins (a) levels, plasma homocysteine, elevated plasma fibrinogen levels, plasminogen activating inhibitor (PAI), C-reactive protein (CRP), different cytokines and micro albuminuria (MA) have emerged over a period of time. The excretion of albumin in urine, in the range of 20-200 µg/min (30-300 mg/day) is often called as Micro

albuminuria. This range of albumin is not detected in routine tests of urine. Micro albuminuria is being associated with Diabetes Mellitus(DM)(Type 1 and 2) for a long time. Micro albuminuria is defined as the UAER between 30-300mg/24hour⁶. Micro albuminuria (MA) as a marker now a day is also considered a risk factor for IHD in diabetic and non-diabetic individuals. Patients with MA and concomitant diabetes have higher deaths due to IHD development. Since the first description in 1974,⁷ the presence of sub clinical increase in excretion of urine albumin got attention but MA in non diabetics still needs to be studied. Greater excretion of urinary albumin leading to increased morbidity and mortality has been reported several years ago,⁸. Micro albuminuria (MAU) can also be defined as urine albumin excretion at rates that are more than normal but less than values detected by conventional methods like dipsticks⁹. In clinical practice MAU helps to know about kidney impairment in patients suffering from hypertension (HTN) and diabetes (DM). MAU is associated with cardiovascular disease (Cvd) factors such as age, smoking, hypertension, diabetes, dyslipidaemia and lack of physical activity¹⁰⁻¹².

In healthy individuals, the normal range for urinary albumin excretion is usually less than 30mg/day. UAE rate increases with exercise, protein intake, pregnancy and urinary tract infection. Albumin excretion on an average is 25% higher during the day than at night, with 40 % day to day variation. Albuminuria of 300mg/day or more indicates micro albuminuria. In clinically healthy subjects the atherogenic risk factors are raised when associated with micro albuminuria. It is also observed that the patients with MA have more severe angiographic CAD than those without MA¹³. MA is evaluated as an early response to myocardial infarction (MI) and urinary excretion of micro albumin is proportional to the size of infarct size¹⁴. A study by Bertone et al. Showed that micro albuminuria occurs in AMI and predicts early mortality¹⁵. Moreover, MA is independently associated with Cvd morbidity, after adjusting the known risk factors of the prevalence of CAD in men and women. The close relationship between MA and Coronary disease is greatly explained by the shared pathogenic mechanisms of endothelial dysfunction, systemic inflammation and vascular injury¹⁶; it is reasonable to assume that such a relationship should exist regardless of the simultaneous presence or absence of diabetes.

Aims and objectives

To assess the relationship between micro albuminuria and proven risk factors and markers of cardiovascular disease in non diabetic & non hypertensive ischemic heart disease patients.

Materials and Methods

A Prospective(Hospital based) Observational Study was conducted on 200 patients. Non diabetic and non-hypertensive adults aged between 28-70 years in the Department of Medicine, from December 2019 to August 2021.

Methodology

After approval of the study protocol by the Institutional Ethics Committee, written consent taken. The study was done in Department of Medicine to investigate the course of micro albuminuria and its relation with CVD in a large group drawn from the general population. All the patients fulfilling the inclusion criteria were subjected to detailed clinical history, systemic examination, routine investigation, and ECG and ECHO. Patients from the cardiology department aged 28-70 years around 200 subjects were given a questionnaire and a vial to collect early morning urine sample and the administered questionnaire provided information whether established risk factors for cardiovascular disease and morbidity were present.

Subjects were considered being diabetic and they had physician diagnosis of diabetes whether on medication or not and were excluded. Those who reported taking antihypertensive or lipid lowering drugs were regarded as hypertensive's and hyper lipidic respectively and were excluded. Myocardial infarction (MI) was considered present if subject reported with ECG and ECHO findings consistent with myocardial infarction and were included if they were no taken own case of hypertension an diabetes. All the relevant data was then entered in MS Excel.

Inclusion criteria: -Patients of Ischaemic heart disease(diagnosed by ECG and ECHO findings), Non-Diabetic Patients, Non-Hypertensive Patients

Investigation: CBC(Hb,TLC), LFT, RFT, Lipid Profile, Blood Sugar, Blood Pressure, Renal Function test, ECG, ECHO.

Statistical analysis

Data was analyzed using appropriate statistical software. Frequency distribution and cross tabulation was used to prepare the tables. Quantitative variables were expressed as the mean and standard deviation. Categorical data was expressed as percentage. Microsoft office was used to prepare the graphs. Student t- test is being used to compare the means. Chi Square test has been used to compare the categorical data. P value of <0.05is considered as significant.

Observation and Results

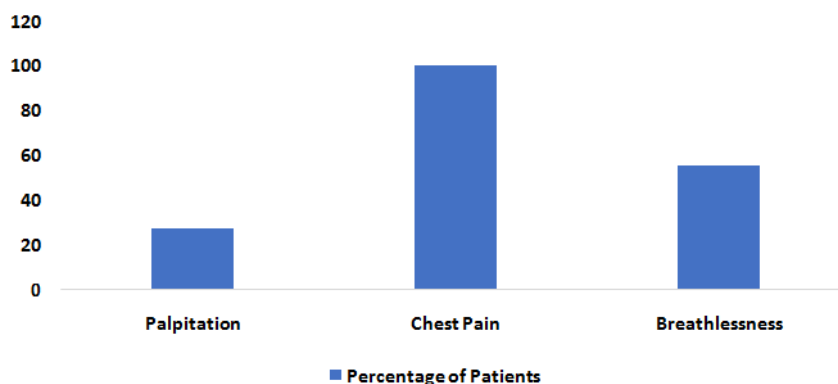
Table1 Distribution of patients according to age and gender

Age Group	Sex		Total n (%)	Chi Square statistic PValue
	Male n (%)	Female n (%)		
≤40	26 (18.4)	10 (16.9)	36 (18.0)	3.88 0.275
41-50	54 (38.3)	15 (25.4)	69 (34.5)	
51-60	44 (31.2)	25(42.4)	69 (34.5)	
>60	17 (12.1)	9 (15.3)	26 (13.0)	
Total	141(100.0)	59(100.0)	200(100.0)	

Distribution of patients according to age and gender reveals that majority of males were from the age group of 41-50 years (38.3%), while 42.4% of females were from

the age group of 51-60 years. The above distribution of patients according to age and gender was found to be statistically insignificant (p value >0.05)

Fig1 Distribution of patients according to presenting complaints



Chest pain remains the most common complaint among the patients (100%), followed by breathlessness in 55% and palpitation in 27.5% of the study subjects

Table 2 Distribution of patients according to findings in cardiovascular system examination

SNo	Parameter	Mean(S.D)	Median(IQR)	Range
1	Pulse Rate	75.79(7.69)	75(68-82)	99-47
2	SBP	109.1(11.84)	110(90-130)	140-80
3	DBP	69.75(2.54)	70	90-50

The mean PR of the patient's was 75.7 with a SD of 7.7 beats/min. Mean SBP was found to be 109.1mmHg, while mean DBP was 69.7 mmHg.

Table 3 Distribution of patients according to Serum Urea and Micro albuminuria

SSerum Urea(ingm/dl)	Micro albuminuria		Total	Chi Square statistic P Value
	Absent	Present		
	n(%)	n(%)	n(%)	
<45	48 (88.9)	129(88.4)	177(88.5)	0.011
≥45	6 (11.1)	17 (11.6)	23 (11.5)	
Total	54(100.0)	146(100.0)	200(100.0)	

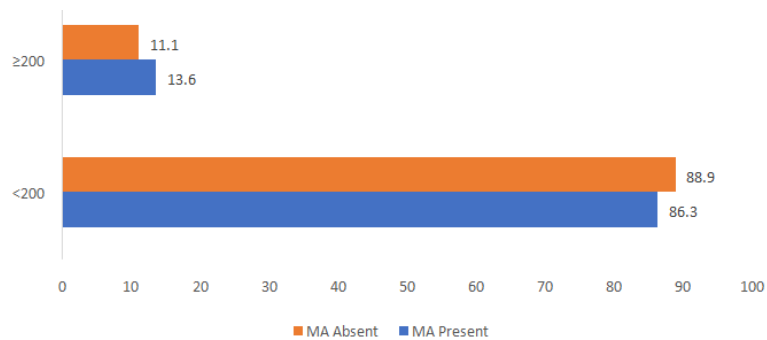
Around 74% of the patients with elevated serum urea had incidence of micro albuminuria, which shows the relation between urinary albumin excretions with renal markers.

Table 4 Distribution of patients according to Serum Creatinine and Micro albuminuria

Serum Creatinine(In gm/dl)	Micro albuminuria		Total n (%)	Chi Square statistic P Value
	Absent	Present		
	n (%)	n (%)		
<1.2	39 (72.2)	109(74.7)	148(74.0)	0.122
≥1.2	15 (27.8)	37 (25.3)	52 (26.0)	
Total	54(100.0)	146(100.0)	200(100.0)	

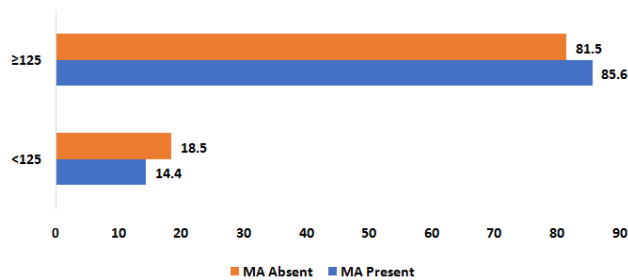
Among 52 patients with elevated serum creatinine, 37 i.e.,71.1% had micro albuminuria, while the rest 29.9% patients were having normoalbuminuria

Fig 2 Distribution of patients according to Serum Cholesterol levels and Micro albuminuria



87.0% of the patients were having cholesterol levels below 200 mg/dl. Among 26 patients with levels more than 200 mg/dl, 20 (76.9%) were having micro albuminuria

Fig 3 Distribution of patients according to Serum Triglyceride levels and Micro albuminuria



85.6% of the patients were having triglyceride levels above 125 mg/dl. Among 169 patients with levels more than 125 mg/dl, 125 (73.9%) were having micro albuminuria,

Table 5 Distribution of patients according to Blood Sugar levels and Micro albuminuria

Blood Sugar Level(inmg/dl)	Micro albuminuria		Total n (%)	Chi Square statistic P Value
	Absent	Present		
	n (%)	n (%)		
<126	33 (61.1)	104(71.2)	137(68.5)	1.872 0.171
≥126	21 (38.9)	42 (28.8)	63 (31.5)	
Total	54(100.0)	146(100.0)	200(100.0)	

Among 63 patients with blood sugar levels above 126 mg/dl, 42 (66.6%) were having Micro albuminuria, which clearly depicts the role of elevated blood sugars in albuminuria.

Table 6 Comparison of Means of various parameters

SNo	Parameter	Micro albuminuria		P value
		Absent	Present	
		Mean (SD)		
1	Age	50.9(10.1)	50.5(9.1)	0.81
2	PulseRate	75.11(6.9)	76.0(7.9)	0.42
3	SBP	110.8(11.8)	108.4(11.9)	0.20
4	DBP	69.8(1.36)	69.7(2.9)	0.77
5	BMI	22.7(2.1)	24.5(1.8)	0.24

On comparison of various parameters in patients with and without micro albuminuria using unpaired t test, none of them were found to be significant statistically.

Table 7 Comparison of Means of various laboratory parameters

SNo	Parameter	Micro albuminuria		P value
		Absent	Present	
		Mean (SD)		
1	Hb	11.8(1.4)	11.8(1.4)	0.95
2	TLC	8386.9(1469.6)	8073.4 (1456.4)	1.34
3	SerumUrea	34.5(6.7)	33.9(8.0)	0.54
4	Serum Creatinine	0.9(0.2)	0.9(0.3)	1.81
5	SerumSGOT	47.2(3.9)	46.5(6.9)	0.47
6	SerumSGPT	47.393.6)	46.9(4.9)	0.58
7	Serum Cholesterol	177.8(14.8)	176.2(18.9)	0.55
8	Serum triglycerides	132.2(7.9)	131.4(10.8)	0.58
9	BloodSugar level	121.1(12.9)	118.0(14.4)	0.15
10	LVEF	44.7(7.0)	45.1(5.9)	0.78

On analysis of various lab parameters pertaining to the patients, who were having/ not having Micro albuminuria by using appropriate statistical tests, no one of the parameter showed any significant difference in between two groups.

Discussion

Studies of previous researchers concluded independent role of MA and its connection with cardiovascular morbidity and mortality in patients with diabetes mellitus and HTN. It is per haps proper to remark to evaluate micro albuminuria in the non-diabetic, non-hypertensive patients especially in India few studied have been conducted. In this study an attempt has been made to find if MA has an association with cardio vascular morbidity even in non-diabetic, non-hypertensive IHD patients.

Baseline Characteristics

Patient's mean age was 50.66 with a SD of 9.33 in the present study. The findings were similar to the studies conducted by Johan Arnlov et.al¹⁶ (2005), where the 55 was the mean age and in the study by Hilal Bahjet Al-Saffar et.al¹⁷(2015) mean age was 56 ± 12 years. Dharmesh Gamit et.al¹⁸ (2017) reported the mean age to be 51.32 ± 11.25 years, while Md Jahirul Haque et.al¹⁹ (2020) reported it to be 57.17 ± 11.2 years. A finding of study by G Berton et.al⁴¹ (2000) was contrary to ours.

Abdul Ghaffar Memon et.al²⁰ (2015) reported the patients age distribution to be 42.5 ± 10.8 , while Abhijit Basu et.al²¹ (2015) reported mean to be (48.76 ± 6.97) and Marwa Kamal Abdo Khairallah et.al²²(2016) as 42.93 ± 15.60 years. 34.5% each patient was from the age group of 41-50 years and 51-60 years in the present study. Marwa Kamal Abdo Khairallah et.al²²(2016) reported that 26, 18, 18, 19, 13, and 5% patients were in the age range less than 30 years old, from 30 to less than 40 years old, from 40 to less than 50 years old, from 50 to less than 60 years old, and from 60 years to less than 70, and more than 70 respectively. In the present study, the range of age of participants was found to be 28 to 75 years of age. Abdul Ghaffar Memon et.al²⁰ (2015) reported the range of age to be 20 to 80 years, while Dharmesh Gamit et.al¹⁸ (2017) as range of 30 to 70 years.

69.8% patients were males and rest 29.2% were females in the present study. Male predominance was observed in studies by Hilal Bahjet Al-Saffar et.al¹⁷(2015) and Abdul Ghaffar Memon et.al²⁰(2015). Dharmesh Gamit et.al¹⁹(2017) reported the gender distribution as 97 males (80.8%) and 23 females (19.2%). Findings contrary to the present study were reported by Aida Jimenez Corona et.al²⁴ (2005) and Johan Arnlov et.al¹⁷ (2005). Marwa Kamal Abdo Khairallah et.al²² (2016) described that men represent 33% of the studied group while women represent 67%, while Peter Kangwagye et.al²⁵ (2018) reported that 208 (62.3%) of the patients were females in their study. The mean age of male patients was 49.41 ± 9.16 , while that of female patients was 52.44 ± 9.57 in the present study.

Clinical Presentation

Chest pain was the most common complaint among the patients (100%), followed by breathlessness in 55% and palpitation in 27.5% of the study subjects.

Description of salient variables

The mean PR of the patients was 75.7 with a SD of 7.7 beats/min. Mean SBP was found to be 109.1 mmHg, while mean DBP was 69.7 mmHg. Most of the patients were having a BMI of more than 23 kg/sq. i.e., 107(53.5%), followed by 44.5% with a normal value. MA is associated with IHD irrespective of BMI. 36 people with BMI >25 of these 72.22% (n=26) fall among cases and only 27.77% (n=10) were controls. There were 26 people with micro albuminuria and BMI >25. Of these 80.76% (n=21) were among cases and only 19.23% (n=5) among controls. This was not significant statistically $\chi^2=3.41$, $P>0.05$ according to the study by Abhijit Basuet.al²¹ (2015).

Mean serum cholesterol among patients was found to be 176.7 mg/dl, while mean serum TGs was 131.7mg/dl. Mean blood sugar level was found to be 118.9 mg/dl in the present study. While in the study by Sowjanya Naha et.al²⁶(2016) the Mean fasting blood glucose (mg/dL) was 107.31±13.8 and Mean triglycerides (mg/dL) was 107.21±46.7. Mean serum cholesterol was reported to be 176.53±40.5mg/dl. Random Plasma Glucose concentration ± standard deviation (SD) of 104.54 ± 21.64, ranging from 78 mg/dl to 141 mg/dl was reported by Asif Mustafa²⁷ (2020).

Ejection fraction of less than 50% was observed in 132 patients, constituting to 66.0% of the total study subjects. No statistically significant differences found in gender, systolic or diastolic BP, left ventricle ejection fraction, smoking status, or diabetes was reported in the study by MustafaTaskiranet.al²⁸ (2010). Micro albuminuria was associated with a similar risk of death as a leftventricleejectionfractionbelow40%.

Micro albuminuria was present in 73.0% of the patients according to the criteria of 30-300 using urinary albumin creatinine ratio in the present study. AbdulGhaffar Memonet.al²⁰(2015)reported that after diagnosis out of 126 patients 77 patients were found with micro albuminuria, while in the study by Dharmesh Gamit et.al¹⁸ (2017) 79 (65.8%) of the cases were found with micro albuminuria and PeterKangwagyeet.al²⁵(2018) estimated the prevalence of micro albuminuria as (ACR:30–300mg/g) was 59.3%. Contraryto our study were the findings of H.L.Hillegeet.al¹⁰(2001),where the prevalence was 7.2%, Yon Su Kim et.al²⁹ (2013) with prevalence of 14.1% and Hilal BahjetAl-Saffaret.al¹⁷(2015)with30%.PravinKumarJhaet.al(2017)³⁰ reported that out of 90 CAD patients who were not a known case of DM, 62 (68.9%) belonged to group I (MAU negative) and 28 (31.1%) belonged to group II (MAU positive).

Among 146 patients with micro albuminuria, 102 (69.9%) were males and the rest 44 (30.1%) were females. The distribution according to gender and urinary albumin excretion was found to be insignificant statistically in this study. 129(88.4%) were from the age group of less than 60 years and the rest were

above 60 years of age. Around 74% of the patients with elevated serum urea had incidence of micro albuminuria, which shows the relation between urinary albumin excretions with renal markers. Blood urea was raised in 20 patients from them 17/13.4% having MA. Raised serum creatinine was found in 16 of cases, out of them 12/9.5% were noted with MA according to the study by Abdul Ghaffar Memon et al.²⁰(2015). Among 52 patients in this study with elevated serum creatinine, 37 i.e., 71.1% had micro albuminuria, while the rest 29.9% patients were having normoalbuminuria.

Statistically significant difference in serum total cholesterol and LDL cholesterol and urine micro albumin between cases and controls was seen. A trend towards higher fasting blood glucose was also observed in the cases as compared to the controls, and the number of individuals with impaired fasting glucose was significantly higher among the cases (OR: 4.70; 95% CI, 1.93–11.42; $P < 0.001$). Binary logistic regression confirmed urine micro albumin to be associated with IHD independent of fasting blood sugar, total and LDL-cholesterol ($P = 0.015$). 100% specificity but only 32% sensitivity of urine micro albumin for the presence of concomitant IHD when using the conventional cut-off of 30 mg/g was demonstrated on ROC curves as per the study by Sowjanya Naha et al.²⁶(2016).

Conclusion

In the present study, micro albuminuria was found in 73.0% of the non-diabetic and non-hypertensive individuals presenting with cardiac morbidity. The level of serum cholesterol and Serum Triglycerides along with blood sugar was on higher side in individuals with micro albuminuria. Clear association was also observed between level of serum urea and creatinine as well as MA. It's clearly evident that micro albuminuria and the established risk indicators of cardiovascular morbidity have a positive correlation and can also be used to assess cardiovascular morbidity. Cardiac morbidity was stratified in terms of the ejection fraction findings in echocardiography. Patients with ejection fraction (EF) $> 50\%$ have a better prognosis in terms of survival and treatment response when compared with the patients having EF $< 50\%$ who have a comparatively bad prognosis. It was clearly evident that micro albuminuria was more with patient's having left ventricle EF $< 50\%$ which can be used to prognosticate patients of cardiovascular morbidity.

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