

ORIGINAL RESEARCH

Microalbuminuria: A novel risk indicator for cardiac morbidity and mortality**¹Dr Atul Dubey, ²Dr Pranay Dhurvey, ³Dr RS Maniram, ⁴Dr Manuj Sharma**¹Resident, ²⁻⁴Associate Professor, Department of Medicine, Gandhi Medical College Bhopal, MP, India**Correspondence:**

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Abstract

Background: There is a relative paucity of data on the link between urine microalbumin and IHD in non-diabetics as well as non-hypertensives compared to diabetics. This study was meant to look for the association between urine microalbumin and cardiac morbidity and mortality among non-diabetic and non-hypertensives, which may further provide insight to the early diagnosis of microalbuminuria and its potential for predicting cardiac morbidity and thus needed inputs for better clinical management.

Aims and objectives: To assess the relationship between microalbuminuria and proven risk factors and markers of cardiovascular disease in non-diabetic & non-hypertensive 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 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. i.e., 107 (53.5%), followed by 44.5% with a 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. Microalbuminuria detected in 73.0% of the patients as per the criteria of 30-300 using urinary ACR. Out of 146 patients with microalbuminuria, 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 microalbuminuria 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 microalbuminuria. Among 26 patients with Serum cholesterol levels more than 200 mg/dl, 20 (76.9%) were having microalbuminuria. Among 63 patients with blood sugar levels above 126 mg/dl, 42

(66.6%) were having Microalbuminuria, 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: Microalbuminuria, cardiovascular, cardiac morbidity and mortality, non-diabetic and non-hypertensive.

Introduction

Cardiovascular disease (cvd) accounts for a 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 times from 1990 to 2020, with Ischemic heart disease (IHD) contributing the major share⁴⁻⁵.

Various new biomarkers of IHD such as, lipoproteins (a) levels, plasma homocysteine, elevated plasma fibrinogen levels, plasminogen activating inhibitor (PAI), C-reactive protein (CRP), different cytokines and microalbuminuria (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 Microalbuminuria. This range of albumin is not detected in routine tests of urine. Microalbuminuria is being associated with Diabetes Mellitus (DM) (Type 1 and 2) for a long time. Microalbuminuria is defined as the UAER between 30-300 mg/24 hour⁶. Microalbuminuria (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 subclinical increase in excretion of urinary albumin got attention but MA in non-diabetics still need to be studied. Greater excretion of urinary albumin leading to increased morbidity and mortality has been reported several years ago,⁸.

Microalbuminuria (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 30 mg/day. UAER 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 300 mg/day or more indicates microalbuminuria.

In clinically healthy subjects the atherogenic risk factors are raised when associated with microalbuminuria. 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 microalbumin is proportional to the size of infarct size¹⁴. A study by Bertoni et al. showed that microalbuminuria 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 closer relationship between MA and Coronary disease is greatly explained by the shared pathogenetic 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 microalbuminuria and proven risk factors and markers of cardiovascular disease in non-diabetic & non-hypertensive ischaemic 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, Gandhi Medical College & associated Hospitals (Hamidia Hospital) Bhopal, from December 2019 to August 2021.

Methodology

After approval of the study protocol by the Institutional Ethics Committee, written consent was taken. The study was done in Department of Medicine (cardiology), Gandhi Medical College & Hamidia Hospital Bhopal to investigate the course of microalbuminuria 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 of Hamidia Hospital, Bhopal 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 anti-hypertensive or lipid lowering drugs were regarded as hypertensives and hyperlipidic 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 not known case of hypertension and 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

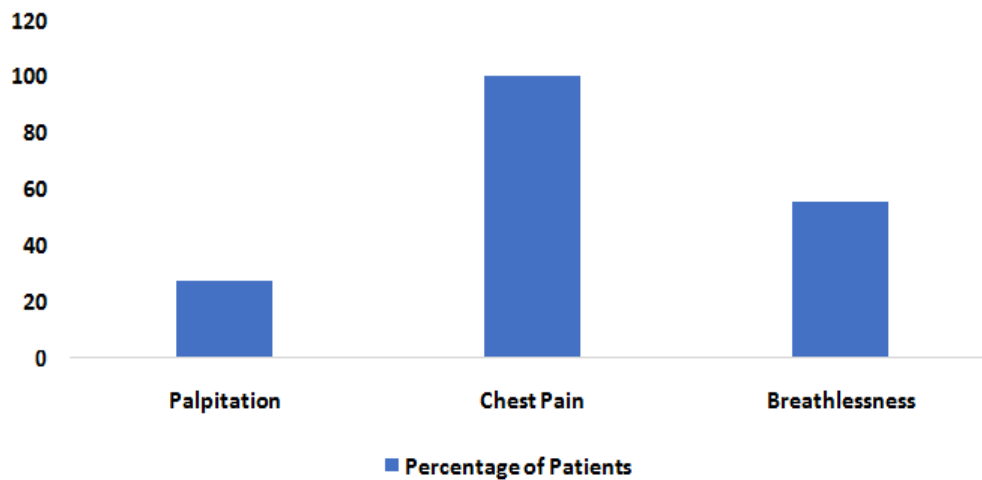
Data was analysed using appropriate statistical software. Frequency distribution and cross tabulation was used to prepare the tables. Quantitative variables were expressed as the mean and standard deviation. Categorical data was expressed as percentage. Microsoft Office was used to prepare the graphs.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

Observation and results

Table1 Distribution of patients according to age and gender

Age Group	Sex		Total n (%)	Chi Square statistic P Value
	Male	Female		
	n (%)	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 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.

Table 3 Distribution of patients according to Serum Urea and Microalbuminuria

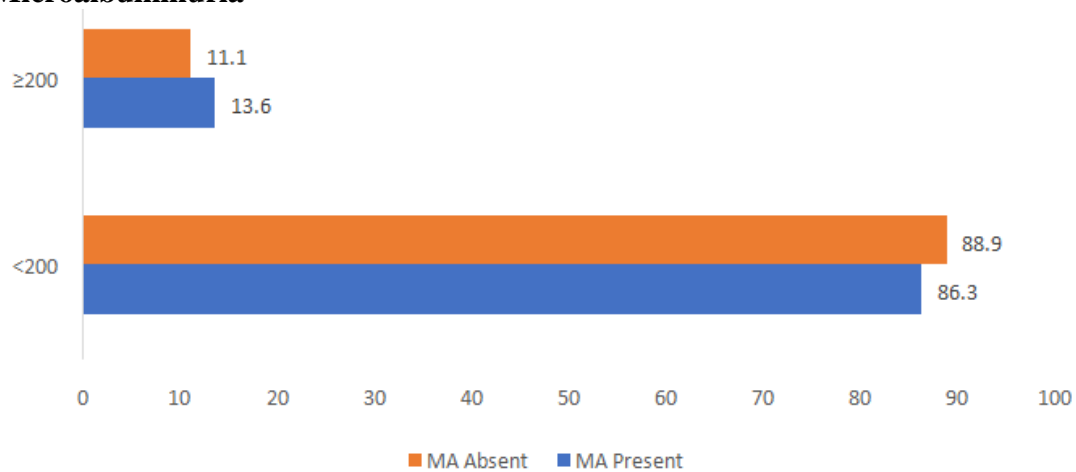
Serum Urea (mg/dl)	Microalbuminuria		Total n (%)	Chi Square statistic P Value
	Absent	Present		
	n (%)	n (%)		
<45	48 (88.9)	129 (88.4)	177 (88.5)	0.011 0.917
≥45	6 (11.1)	17 (11.6)	23 (11.5)	
Total	54 (100.0)	146 (100.0)	200 (100.0)	

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

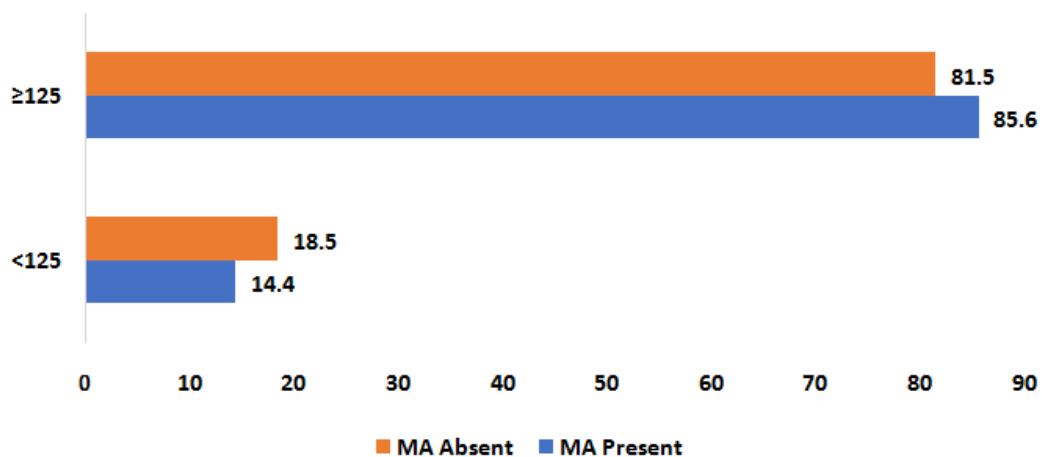
Table 4 Distribution of patients according to Serum Creatinine and Microalbuminuria

Serum Creatinine(In gm/dl)	Microalbuminuria		Total n (%)	Chi Square statistic P Value
	Absent n (%)	Present 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)	0.727

Among 52 patients with elevated serum creatinine, 37 i.e., 71.1% had microalbuminuria, while there were 15 (29.9%) patients having normoalbuminuria.

Fig 2 Distribution of patients according to Serum Cholesterol levels and Microalbuminuria

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 microalbuminuria.

Fig 3 Distribution of patients according to Serum Triglyceride levels and Microalbuminuria

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 microalbuminuria.

Table 5 Distribution of patients according to Blood Sugar levels and Microalbuminuria

Blood Sugar Level (in mmol/L)	Microalbuminuria		Total	Chi Square statistic P Value
	Absent	Present		

g/dl)	n (%)	n (%)	n (%)	Value
<126	33 (61.1)	104(71.2)	137(68.5)	1.872
≥126	21 (38.9)	42 (28.8)	63 (31.5)	
Total	54(100.0)	146(100.0)	200(100.0)	0.171

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	Microalbuminuria		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 microalbuminuria using unpaired t test, none of them were found to be significant statistically.

Table 7 Comparison of Means of various laboratory parameters

SNo	Parameter	Microalbuminuria		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	SerumCreatinine	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	SerumCholesterol	177.8(14.8)	176.2(18.9)	0.55
8	Serumtriglycerides	132.2(7.9)	131.4(10.8)	0.58
9	BloodSugarlevel	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, none of the parameters 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 perhaps proper to remark to evaluate microalbuminuria in the non-diabetic, non-hypertensive patients especially in India few studies have been conducted. In this study an attempt has been made to find if MA has an association with cardiovascular 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 **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 a 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 microalbuminuria 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 $X^2=3.41$, $P>0.05$ according to the study by **Abhijit Basu et.al²¹ (2015)**.

Mean serum cholesterol among patients was found to be 176.7 mg/dl, while mean serum TG was 131.7 mg/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 ± 40.5 mg/dl. Random Plasma Glucose concentration \pm 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 **Mustafa Taskiran et.al²⁸ (2010)**.

Microalbuminuria was associated with a similar risk of death as a left ventricle ejection fraction below 40%.

Microalbuminuria was present in 73.0% of the patients according to the criteria of 30-300 using urinary albumin creatinine ratio in the present study. **Abdul Ghaffar Memon et.al²⁰ (2015)** reported that after diagnosis out of 126 patients 77 patients were found with microalbuminuria, while in the study by **Dharmesh Gamit et.al¹⁸ (2017)** 79 (65.8%) of the cases were found with microalbuminuria and **Peter Kangwagye et.al²⁵ (2018)** estimated the prevalence of microalbuminuria as (ACR: 30–300 mg/g) was 59.3%. Contrary to our study were the findings of **H.L. Hillege et.al¹⁰ (2001)**, where the prevalence was 7.2%, **Yon Su Kim et.al²⁹ (2013)** with prevalence of 14.1% and **Hilal Bahjet Al-Saffaret.al¹⁷ (2015)** with 30%. **Pravin Kumar Jha et.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 microalbuminuria, 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 microalbuminuria, which shows the relation between urinary albumin excretion 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.al²⁰ (2015)**. Among 52 patients in this study with elevated serum creatinine, 37 i.e., 71.1% had microalbuminuria, while the rest 29.9% patients were having normoalbuminuria.

Statistically significant difference in serum total cholesterol and LDL cholesterol and urine microalbumin 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 microalbumin 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 microalbumin 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.al²⁶ (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 microalbuminuria. Clear association was also observed between level of serum urea and creatinine as well as MA. It's clearly evident that microalbuminuria 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 microalbuminuria was more with patient's having left ventricle EF $< 50\%$ which can be used to prognosticate patients of cardiovascular morbidity.

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