Relationship of Microalbuminuria with Ischemic Heart Disease in Non-Diabetic Subjects

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Abstracts: **Background and Objective:** Microalbuminuria is a well accepted marker for micro and macrovascular damage in patients with diabetes mellitus. There is growing evidence that microalbuminuria is an important risk indicator for development of ischemic heart disease. This study was conducted to establish a relationship between microalbuminuria and ischemic heart disease in non-diabetic subjects. **Methodology:** Fifty randomly selected non-diabetic patients with ischemic heart disease who fulfilled the criteria for the study were evaluated for traditional risk factors and microalbuminuria. **Results:** Microalbuminuria was detected in 36 (72%) patients with Ischemic Heart Disease ($p<0.05$). 77% patients with infarct pattern on ECG and 22% patients with ischemia pattern on ECG had microalbuminuria. Majority of patients had microalbuminuria levels between 30-100 mg/day (41% males and 64% females). 72.72% of female patients had microalbuminuria (MA) compared to 71.79% of the male patients. 71.79% of hypertensive patients had microalbuminuria compared to 72.72% of normotensive patients. 79.17% of smokers with microalbuminuria presented with myocardial infarction compared to 62.5% of non-smokers with microalbuminuria. MA level is also associated with ECG (LVH, QTc prolongation) and 2D ECHO findings. **Conclusion:** Our patients with ischemic heart disease had a significantly positive association with microalbuminuria. Hence, microalbuminuria can be regarded as an additional risk factor for ischemic heart disease. [Suthar N et al NJIRM 2014; 5(3) :51-56]

Key Words: Ischemic Heart Disease; Cardiovascular disease; Microalbuminuria; High Density Lipoprotein; Low Density Lipoprotein.

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Introduction: Ischemic Heart Disease which has an estimated prevalence of 6-9% in the general population in India may become the leading cause of mortality and morbidity in India by the year 2015.[1]

Since the pioneering work of the Framingham study, many prospective and clinical studies have identified a series of independent risk factors for ischemic heart disease among which age, male gender, a positive family history of premature atherosclerotic disease, smoking, diabetes mellitus, hypertension, hypercholesterolemia, hypertriglyceridemia and low HDL cholesterol are considered as classical risk factors.[2]

The interest in improving cardiovascular risk assessment, resulting from a better understanding of the pathogenesis of atherosclerosis and identification of new targets for anti-atherosclerotic drug therapy has stimulated the search for novel risk factors.

One such novel risk factor is microalbuminuria, which has emerged as an independent and robust risk factor. Microalbuminuria is a well-accepted marker for micro and macrovascular damage in patients with diabetes mellitus. However more and more evidence is accumulating that microalbuminuria is an important cardiovascular risk factor even in the general population.

The inclusion of microalbuminuria, which is an easy to obtain indicator along with the classical risk factors, may improve risk stratification.

The present study was conducted to define the prevalence of microalbuminuria in non-diabetic Ischemic Heart Disease patients admitted in ICCU and general wards at Sheth Vadilal Sarabhai General Hospital, Ahmedabad from June 2010 to October 2012. Our objective was to estimate microalbuminuria in non-diabetic patients with Ischemic Heart Disease and to study the relationship between microalbuminuria and Ischemic Heart Disease in these subjects.

Material and Methods: This was a hospital based prospective observational study involving 50 patients. Study was started after approval from NHLIEC (NHL Institutional Ethics Committee). Patients were recruited after taking informed consent. Study participants were fifty non-diabetic patients with Ischemic Heart Disease (IHD) attending the outpatient clinic or admitted as in-patients in the Medicine wards & ICCU at Sheth V.S. General Hospital, Ahmedabad fulfilling following inclusion criteria.

Inclusion Criteria: The diagnosis of Ischemic Heart Disease was based on the 12 lead ECG and cardiac enzyme estimation and 2D ECHO.

Exclusion Criteria:

1. Diabetic patients by ADA criteria (2010).
2. Congestive cardiac failure as presentation.
3. Urine showing
   - Macroalbuminuria (dipstick positive albuminuria)
   - RBCs > 50/µl
   - Leucocytes > 75/µl
4. Female patients with vaginal discharge.
5. Those patients who are not in follow up

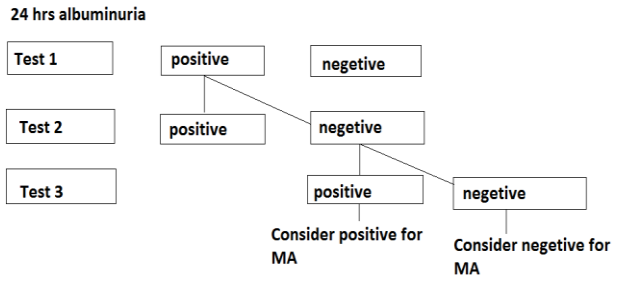
Method of Collection of Data: Data collection was by clinical history, examination and investigations. These details were recorded as per the proforma. The patients included in the study were first self-reported infarct/ischaemia by ECG/cardiac enzyme. The patients were given a container for collection of urine over 24 hours, which was then sent for estimation of microalbuminuria level by immunoturbidimetry method. The result was reported as x mg/day of albumin.

Whoever found to be positive for microalbuminuria (MA), MA level were repeated twice within next 3-6 months. If total 2/3 test found to be positive, patient was considered positive for MA.

A consensus conference in 1995 defined microalbuminuria (MA) in individuals with diabetes as an abnormal urinary excretion rate of albumin between the range of 20-200 µg/min or 30-299 mg/day.[3]

This is still the definition used today and is applicable to all people regardless of associated pathological condition. Following Viberti et al[4] the term MA has taken hold, although the so-called microalbuminuria levels are an artificial category carved out of continuum of values.

Statistical Analysis: The data is presented as Mean ±SD (95% confidence limit). The limit of significance was calculated using GraphPAD Quickcals. Microsoft word and Microsoft Excel, One note were used to generate graphs, tables, etc.



Result: Fifty (50) patients fulfilling the criteria for the study were included. The study was done over a period of one and half years.

In the present study, out of 50 patients, 39 were males and 11 were females. The mean age of the study population was 55.8±3.67 years. It was 53.37±4.17 years for male and 63.05±7.04 years for females.

Table 1: Gender Distribution

Age	Male	Female	Total
26-35	5	0	5
36-45	6	0	6
46-55	9	2	11
56-65	11	5	16
66-75	7	2	9
>75	1	2	3
Total	**39**	**11**	**50**

Subject in the age group 56-65 constituted 42% of the study group. Majority of females were aged above 55 years (81.8%). Younger one is 47 yrs.

Family history of IHD was present in 60% of the study subjects. There were 4(36.3%) female patient with history of smoking whereas 30(76.9%) of the male patients gave a history of smoking. Smoking

history was present in 78% of the study subjects (P<0.05) which was statistically significant.

The mean BMI was 25.87±0.96 in males and 26.10±0.82 in females. Majority of the patients were obese (80%). Female patients had a higher incidence, 81.8% of obesity in the present study.

Hypertension was present in 68% of the study subjects of which females had a higher percentage (Male to Female – 66.67% to 72.72%). The mean systolic BP was 144.36±4.75 in males and 144.18±9.1 in females. The mean diastolic BP was 86.26±2.09 in males and 84.55±5.51 in females.

Table 3: Abnormal Lipid Parameters

LIPID PARAMETER	M(n=39)	F(n=11)	TOTAL
TC (>200mg%)	4 (10.26%)	2 (18.18%)	6 (12%)
TG (>150mg%)	12 (30.77%)	1 (9.1%)	13 (26%)
HDL (M <40mg%, F <50mg%)	4 (10.25%)	10 (90.9%)	14 (28%)
LDL-C (>150mg%)	3 (7.7%)	1 (9.1%)	4 (8%)

The mean FBS was 97.4±1.97 mg% and mean PPBS was 137±2.51 mg% in this study group. Of the whole study the mean total cholesterol 167.4±3.80, mean triglyceride 132.8±3.91, mean HDL cholesterol 43.76±1.01 and mean LDL cholesterol 120.74±3.32. Mean total cholesterol and mean LDL-C was higher in females in this study.

In this study, the major dyslipidemia was hypertriglyceridemia (26%) and low HDL (28%) which is a typical Indian lipid profile pattern.

Table-4: Levels of Microalbuminuria (Mg/Day)

AvgMA	M	%	F	%	COMBINED	%
<30	11	28.20	3	27.27	14	28
30-100	11	28.20	6	54.54	17	34
>100	17	43.58	2	18.18	19	38

There was 31 males (79.49%) and 9 females (81.81%) with abnormal microalbuminuria levels in the present study. This shows that patients with microalbuminuria had a higher risk of developing ischemic heart disease (p<0.000) more female patients in the present study had abnormal microalbuminuria (72.72%) compared to male patients (71.79%). Youngest patient was male 25 years found to be positive for MA. The incidence of microalbuminuria increased with increasing age except in >75 years age group in the present study.

Relation of Microalbuminuria with Ischemia /Infarct pattern on ECG: The two-tailed P value is less than 0.05. Thirty six (36) patients (72%) of the study group had microalbuminuria which was statistically significant (p<0.05). There was significant increase in patients who presented with infarct pattern (77.77%) on ECG compared to ischemia pattern (22.22%) in patients having microalbuminuria.

Relation between Microalbuminuria, Hypertension and Ischemia/Infarct pattern: Out of the 39 patients with hypertension, 28 patients had microalbuminuria i.e.: 71.79% of hypertensive patients had abnormal microalbuminuria. 8 out of 11 normotensive patients also had microalbuminuria (72.72%).

Relation between Smoking, Microalbuminuria and Ischemia/Infarct: These were 34 patients with history of smoking out of which 24 patients (70.59%) had microalbuminuria compared to 75% (12/16) of non-smokers with microalbuminuria. 79.17% (19/24) of smokers with microalbuminuria presented with myocardial infarction compared to 62.5% (10/16) of non-smokers with microalbuminuria, who presented with myocardial infarction.

Relationship between Total Cholesterol Microalbuminuria, Ischemic/Infarct: Out of the 7 patients with abnormal total cholesterol, 5 (i.e.71.43%) had microalbuminuria ≥30 mg/day, whereas out of the 43 patients with normal cholesterol 31 patients (72.1%) had microalbuminuria.

Microalbuminuria is significantly associated with Echo findings can be seen in table below

Table-5 Cardiac measurements of Normoaibuminuric (NA) and Microalbuminuric (MA) Patients.

	MA(n=40)	NA(n=10)	P value
LVEF	48.56 ± 1.39	49.35 ± 2.12	0.7619
LVEDD	4.49± 0.04	4.50 ± 0.09	0.9068
IVS	12.95 ± 0.20	11.12 ± 0.515	<0.05
PWT	11.27 ± 0.10	9.6 ± 0.38	<0.05

LVM	204.67 ± 3.47	175.21 ± 7.84	<0.05
LVMI	78 ± 1.72	65.75 ± 2.41	<0.05
RIVS	0.057 ± 0.001	0.049 ± 0.002	<0.05
RPWT	0.050 ± 0.008	0.043 ± 0.001	<0.05

(mean±SEM (95%CI)) .IVS: inter-ventricular septum thickness, PWT: left ventricular posterior wall thickness, LVM: left ventricular mass, LVMI: left ventricular mass Index; RIVS: relative inter-ventricular septum thickness, RPWT: relative posterior wall thickness

Table 6: Relationship of ECG Findings (Except Those S/O IHD) and Microalbuminuria

	PATIENTS WITH MA						PATIENTS WITHOUT MA					
	MALE		FEMALE		TOTAL		MALE		FEMALE		TOTAL	
	28	%	8	%	36	%	11	%	3	%	14	%
LVH	19	67.85	5	62.5	25	69.44	4	36.36	0	0	4	5
LAE	17	60.71	5	62.5	22	61.11	6	54.54	1	33.33	7	50
BAE	1	3.57	0	0	1	2.77	1	9.09	1	33.33	2	14.28
QTc	14	50	3	37.5	17	47.22	3	27.27	0	0	3	21.42
AF	0	0	1	12.5	1	2.77	1	9.09	0	0	1	7.14
PAC	2	7.14	3	37.5	5	13.88	4	36.36	2	66.66	6	42.85
PVC	10	35.71	0	0	10	27.77	4	36.36	2	66.66	6	42.85
AVB-1 DEGREE	2	7.14	0	0	2	5.55	1	9.09	0	0	1	7.14
AVB-2 DEGREE	1	3.57	0	0	1	2.77	0	0	0	0	0	0
AVB-3 DEGREE	1	3.57	0	0	1	2.77	0	0	0	0	0	0
RBBB	4	14.28	1	12.5	5	13.88	3	27.27	1	33.33	4	28.57
LBBB	7	25	0	0	7	19.44	2	18.18	1	33.33	3	21.42
LAHB+RBBB	2	7.14	1	12.5	3	8.33	0	0	1	33.33	1	7.14
LPHB+RBBB	1	3.57	0	0	1	2.77	0	0	0	0	0	0

Relationship of ECG Findings (Except Those S/O IHD) and Microalbuminuria: In ECG, LVH was significantly more common in the subset with MA. There was also a significant positive correlation between MA and LVH (p=0.05). This finding was similar to the report of PREVEND study[5] which showed that MA was independently associated with ischemic electrocardiographic abnormalities in a large non-diabetic population.

It is also evident from this study that patients with MA had significantly longer mean QTc than their counterparts without MA. QTc prolongation was more frequent in the former than in the latter group. QTc also showed significant positive correlation with MA.

Discussion: Ischemic Heart Disease will become a major disease burden in India by the year 2015.[1] To target preventive strategies, risk stratification of the population should be effective. There are many reports emanating from the western literature about microalbuminuria as an independent risk factor for development of ischemic heart disease. Hitherto, microalbuminuria was considered as a marker of endothelial dysfunction in diabetes mellitus, but many studies have shown microalbuminuria is an effective marker of generalized vascular dysfunction even in non-diabetic population. This study was done to find out whether there is an association between IHD and MA in non-diabetic subjects.

In the present study, the diagnosis of IHD was made by ECG changes. de Bruyne MC et al[6] has shown that ECG can be used to determine the presence of IHD in a population at large. This study had 78% male patients compared to 22% female patients. This is in accordance with the knowledge that males are more prone for ischemic heart disease than females.

The mean age of the study population was 55.8±3.67 years. It was mean 63.05±7.04 for females. All the females were in the post-menopausal age group, which shows that sex hormones have a protective effect as far as cardiovascular risk is concerned.

In this study, history of smoking was present in 68% of the study subjects indicating that smoking is an important risk factor for IHD. Umesh N Khot et al[7] had found a prevalence of 76.9% in males and 36.3% in females in their study for smoking as a risk factor

The BMI was >25kg/m^2 in majority of the study group. This prevalence was much higher than that obtained by Singh R.B. et al[8] (11.0% in rural and 27.2% in urban). 68% of patients in the present study had hypertension (66.7% in males and 72.7% in females). This is much higher than the prevalence found by Umesh N Khot et al[7] (38.4% in males and 55.9% in females) but shows a similar trend.

26% of the patients had hypertriglyceridemia and 28% of patients had low HDL levels, which was similar to that obtained by Khot UN et al[7] (39.6% of females and 34.1% of males had abnormal lipid parameters). The present study showed that 72% of the patients with ischemic heart disease had

microalbuminuria which shows a positive association.

The PREVEND study[5] showed that in a multivariate model adjusted for established cardiovascular risk factors, microalbuminuria was independently associated with infarct pattern (7.1%) (OR-1.61), major ischemia (10.6%) (OR-1.43) and minor ischemia (15.1%) (OR-1.32).

Microalbuminuria was detected in 14.8% of those without Diabetes Mellitus at baseline in a cohort of Heart Outcomes Prevention Evaluation Study conducted between 1994 and 1999[9]. This showed that 20.4% of patients with microalbuminuria had a myocardial infarction, stroke or cardiovascular cause of death as compared to 13.8% of those without microalbuminuria.

In the PREVEND study[5], 32.8% of ischemic heart disease patients had microalbuminuria and in the HOPE study[9] cohort mentioned above, 20.4% of patients with a cardiovascular disease had microalbuminuria compared to 76% in this study. This was probably because, the present study had a cohort of IHD patients in whom microalbuminuria was estimated whereas the studies mentioned above was done on the general population.

Cardiovascular morbidity and mortality associated with MA in non-diabetic hypertensive patients. In fact, Dell'omo et al[10] concluded in their study that LVH explained, at least in part, the predictive power of MA for morbid events. The conferment of greater cardiovascular risk when LVH is associated with ST-T wave changes has been documented in many studies.[11,12] Opadijo et al[13] concluded that LVH with ST-T wave changes signified a higher coronary risk in adult Nigerians.

It is also evident from this study that patients with MA had significantly longer mean QTc than their counterparts without MA. QTc prolongation was more frequent in the former than in the latter group. QTc also showed significant positive correlation with MA. The significance of this finding is that hypertensive patients with MA are more likely to develop arrhythmias that are associated with QTc prolongation such as PVC and ventricular tachycardia. It also suggests that MA has additional value to conventional risk indicators in predicting cardiovascular events in non-diabetic hypertensive patients. Patients with MA are also more likely to have PVC than patients without MA. Major ECG abnormalities in hypertension may be as a result of pressure overload and atherosclerotic vascular damage and are considered predictors of future vascular events[13]. Pontremoli et al[14] also revealed that MA has a significant and independent role in target organ damage, particularly ECG abnormalities.

MA signifies ECG abnormalities such as LVH, QTc prolongation and ventricular arrhythmias in adult non-diabetic patients. It indicates excess cardiovascular morbidity and mortality. Hence, the subset of even non diabetic patients with MA constitutes a high risk group and needs close monitoring and follow-up. These patients may also benefit from antihypertensive drugs that have been proven to be effective in reducing albuminuria.

The present study showed that microalbuminuria can be used as an additional cardiovascular risk indicator even in non-diabetic patients.

Conclusion: Out of the 50 non-diabetic patients with IHD who were studied, 36 patients (72%) had microalbuminuria. Microalbuminuria is positively associated with Ischemic Heart Disease in non-diabetic subjects and can be regarded as an important additional risk factor for Ischemic Heart Disease.

Hence, screening for microalbuminuria in the general population is a worthwhile public health tool for cardiovascular risk stratification and targeting preventive strategies.

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