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Role of Microalbuminuria as a Predictor of Severity of Coronary Artery Disease - A Prospective Cohort Study

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Abstract
Background: *Coronary Artery Disease is one of the most important causes of disability and death. Microalbuminuria is a biomarker that has been related to cardiovascular risk.[1,2] Microalbuminuria is defined as urine albumin between 30-300 mg/24 hours or urine albumin creatinine ratio between 30-300 mg/gm creatinine.*
Objective: *To determine whether microalbuminuria can be used as a predictor of severity of Coronary Artery Disease in patients with chronic stable angina.*
Methods: *All patients admitted for elective coronary angiography, included. Detailed medical history and thorough clinical examination done. Microalbuminuria detected on the basis of spot urine albumin creatinine ratio. Sample size calculated to be 88. Subjects divided into two equal groups, group A with Urine albumin creatinine ratio less than 30mg/dl and group B with more than 30 mg/dl. All patients underwent coronary angiography and severity of coronary artery disease calculated using SYNTAX scoring system.*
Results: *Both groups did not show statistically significant difference in the distribution of variables like age (p=0.122), sex (p=0.286), smoking (p=0.503), systemic hypertension (p=0.135) and dyslipidemia (p=0.165). There was a higher distribution of diabetes mellitus in the group with microalbuminuria (p=0.03). No statistically significant association was obtained between microalbuminuria and severity of coronary artery disease (p=0.08).*
Conclusion: *According to this study, there is no evidence to suggest that microalbuminuria could be a predictor for severity of coronary artery disease in chronic stable angina.*
Keywords: *coronary artery disease, chronic stable angina, microalbuminuria.*

Introduction

Cardiovascular diseases have been on the rise in Indian population over the past few decades with a prevalence of 8-10% in population based surveys. The spectrum of coronary artery disease comprises of chronic stable angina, unstable angina and acute coronary syndromes. Owing to the high disease burden, there is a growing necessity of an ideal biomarker, that will aid clinicians in categorizing patients for therapeutic and prognostic purposes. But such a maker till date is unavailable. So other alternatives including combination of markers have been comprehensively studied.

Micro albuminuria has been extensively evaluated as a cardiac biomarker and in many other conditions.[1,3] A transient increase in the urinary albumin excretion rate has been noted in acute myocardial infarction. This has been attributed to the increased vascular permeability following the inflammatory process in infarction.[4] Urinary microalbuminuria has been noted to be a predictor of complications including death in patients with acute myocardial infarction.[2]

Even though there is surmounting evidence establishing the association of acute myocardial infarction and albumin excretion, studies using microalbuminuria as a predictor of severity of coronary artery disease in chronic stable angina are few in India. Therefore this study was planned to evaluate the possibility of using microalbuminuria to predict the extent of coronary artery diseasein patients with chronic stable angina.

Aim of the study

This study was aimed at examining whether the presence of microalbuminuria can predict the severity of coronary artery disease.

Objectives

1. To identify and prognosticate patients with chronic stable angina using microalbuminuria levels.
2. To find any correlation between diabetes, microalbuminuria and SYNTAX score.

Review of literature

Chronic stable angina

Stable coronary artery disease (SCAD) is characterized by episodes of reversible myocardial ischaemia. Because the transition from unstable to stable syndromes is a continuum, angina at rest may also be regarded within the scope of SCAD.

The prevalence of angina in population-based studies increases with age in both sexes. Conventional risk factors for the development of coronary artery disease (CAD) are hypertension, hypercholesterolaemia, diabetes, sedentary life-style, obesity, smoking and family history.[5]

Symptoms and signs

A careful history remains the cornerstone of the diagnosis of chest pain (angina pectoris). Definitions of typical and atypical angina have been summarized in Table 1.[6]

Table 1: Definitions of typical and atypical angina

Types of angina	Characteristics
Typical angina	1.Substernal chest discomfort of characteristic quality and duration 2.provoked by exertion or emotional stress 3.relieved by rest and or nitrates within minutes
Atypical angina	Meets two of the above characteristics
Non anginal chest pain	Meets one or none of the above characteristics

The Canadian cardiovascular society classification is widely used as a grading system for stable angina[7], to quantify the threshold at which symptoms occur in relation to physical activities

Stratification for risk of events

The long-term prognosis of SCAD depends on factors like clinical and demographic variables, left ventricular function, results of stress testing and coronary angiography. Even though there are several clinical, biochemical and invasive diagnostic tests for risk stratification, there is no single test with high sensitivity and specificity to predict a cardiac event. The extent, severity of luminal obstruction and location of coronary disease on coronary arteriography, have been demonstrated to be important prognostic indicators in patients with CSA.[8]

SYNTAX score[9]

Optimal revascularization strategy in patients with CAD remains a subject of debate. Numerous large scale randomized trials addressed this issue comparing CABG with percutaneous coronary intervention (PCI) in patients with multi vessel disease (MVD). Initially these trials compared multi vessel balloon angioplasty with CABG and in a later period multi vessel stenting with CABG.

The SYNTAX (synergy between PCI with TAXUS™ and cardiac surgery) study was

organized as a study for patients with significant lesions in the left main stem and or the three epicardial coronary arteries. The SYNTAX score has been developed to prospectively characterise the coronary vasculature with respect to the number of lesions and their functional impact, location, and complexity. Higher SYNTAX scores, indicative of more complex disease are hypothesized to represent a bigger therapeutic challenge and to have potentially worse prognosis.

Biomarkers

Epidemiological and clinical studies have shown strong and consistent relationships between markers of inflammation and risk of future cardiovascular events. It is important to understand the nature of association between the presumed risk indicators and cardiovascular disease. In our study we are trying to find out the nature of association between microalbuminuria and severity of cardiovascular disease.

Microalbuminuria

Microalbuminuria (MA) is defined as a small amount of urinary albumin excretion (30–300 mg/24 hours). Since there is a large variability in individual samples measured for urinary microalbumin, the urinary albumin-to-creatinine ratio (ACR) calculated using spot urine sample is recommended. MA is strongly associated with risk for cardiovascular disease, but the nature of this link remains controversial and poorly understood.

Pathophysiology

The pathophysiologic processes that link MA and CAD are unclear. MA could be a cause or a consequence of vascular disease. In view of this, endothelial dysfunction and chronic inflammation have been suggested as possible candidates to explain the association between MA and CAD. Some studies found that markers of inflammation such as CRP, IL-6, and TNF, is associated with the occurrence and the progression of MA, which results in increased risk for atherosclerotic disease. However, other studies indicate that although endothelial dysfunction and low-grade inflammation are linked, they are independently associated with risk for cardiovascular death (CVD).

Many cross-sectional and a few prospective studies indicated that MA is associated with several cardiovascular risk factors such as aging, male gender, hypertension, diabetes, smoking, obesity and dyslipidemia. It is clear that these explain part of the association between MA and atherosclerotic events. Another theory is that some individuals are born with varying degrees of vascular function within a physiologic range and therefore, excrete a variable amount of albumin[10] This inherent variability as determined by urinary albumin excretion, may be associated with susceptibility to subsequent organ damage.[10]

Epidemiologic and clinical evidence has established a pathophysiologic link between MA and CVD in patients with diabetes and hypertension and in the general population. This correlation is observed even at levels of albuminuria below the conventional threshold for microalbuminuria. Screening for urine albumin can help clinicians estimate a patient's CVD risk.

Hoseini et al found that patients with CAD had higher incidence of MA and that patient with MA had higher burden of atherosclerosis in the form of three vessel disease.[11] MA predicts cardiovascular events and renal insufficiency in hypertensive patients. They found out that diabetic patient with MA had four to six fold increase in risk of cardiovascular mortality.

However, some studies have shown that the association of MA with CAD is independent of hypertension, diabetes and renal function. The underlying mechanisms are abnormal vasodilatation, endothelial dysfunction, inflammation, insulin resistance or abnormal coagulation.

Wang y et al[12] concluded that MA was significantly higher in older age groups ($p<0.01$), in the presence of DM ($p<0.01$) and systemic hypertension ($p<0.01$). There was a significant association between MA and a major cardiovascular event or congestive heart failure ($p<0.01$).

Yagi H et al[13] found that MA is also common in nondiabetic, nonhypertensive population and is an independent indicator of cardiovascular morbidity.

They noted that association between MA and CAD was statistically significant ($p<0.05$).

Methodology

After getting approval from ethical committee, all patients who got admitted for elective coronary angiography, during the period of January 2016 to December 2016, were selected for the study. After getting a written consent from the subject, the investigator took the medical history and did a thorough clinical examination. Blood and urine samples were collected from the patient for examination. Sample size calculated for the study was 88 and the subjects were divided into two equal groups: group A with urine ACR less than 30mg/dl and group B with urine ACR more than 30 mg/dl. All 88 patients underwent coronary angiography and severity of CAD was calculated using SYNTAX scoring system. Data collected were statistically analyzed.

Inclusion criteria

1) Patients who got admitted for elective coronary angiogram for SCAD
2) CAD diagnosed by typical history with or without ECG or echocardiography changes.

Exclusion criteria

1) Patients who underwent percutaneous coronary intervention or coronary artery bypass graft earlier
2) Patients with liver diseases
3) Patients with renal diseases
4) Patients with history of urinary tract infection in the last 3 months

Urine albumin creatinine ratio

Albumin-to-creatinine ratio (ACR) is the first method of preference to detect elevated protein. The recommended method to evaluate albuminuria is to measure urinary ACR in a spot urine sample. ACR is calculated by dividing albumin concentration in milligrams by creatinine concentration in grams.

Coronary angiogram

Elective coronary angiogram was performed using the conventional technique through femoral artery. The angiography images were saved into the computer and later reviewed by the cardiologist to calculate the SYNTAX score.

Severity of coronary artery disease

Severity of CAD was assessed by the SYNTAX scoring method, a web based algorithm consisting of sequential and interactive self-guided questions. Patients were angiographically divided based on the SYNTAX scoring system into severe and non severe CAD. Score calculation was done with the help of a cardiologist, who was blind to the other parameters.

Results

Among 88 patients who satisfied the inclusion criteria, urine was collected and sent for urine ACR prior to the procedure.

Age distribution

Mean age in group A was 56.95, which ranged from 39 years to 75 years and mean age in group B was 60.32, which ranged from 40 years to 82 years. There was no statistically significant difference between the groups.(Table 2)

Table. 2: Age distribution in group A and group B

Microalbuminuria	Number of patients	Age		P value
		Mean	SD	
Absent	44	60.32	11.16	0.122
Present	44	56.95	8.94	

Sex distribution

In group A, there were 20 males (45.5%) and 24 females (54.5%) and in group B, there were 25 males (56.8%) and 19 females (43.2%). These groups did not show any statistically significant difference. (p value 0.286)

Correlation of smoking with microalbuminuria

In this study, 31 patients were smokers and 57 patients were non-smokers. Out of 31 smokers, 17 patients were in group A and 14 patients were in group B. 27 patients were nonsmokers in group A and 30 patients were in group B. On comparison, it did not show any statistical significance ($p= 0.503$) between groups (Table 3)

Table 3: Correlation of smoking with microalbuminuria

Smoking	Microalbuminuria		P value
	Absent	Present	
Absent	27 (61.4%)	30 (68.2%)	0.503
Present	17 (38.6%)	14 (31.8%)	

Correlation between systemic hypertension and microalbuminuria

There were 41 hypertensive patients, out of which 17 patients (38.6%) were in group A and 24 patients (54.5%) in group B. There were 47 patients who were not hypertensive and out of which 27 patients (61.4%) in group A and 20 patients (45.5%) in group B. (Table 4)

Table 4: Correlation between systemic hypertension and microalbuminuria

Systemic hypertension	Microalbuminuria		P value
	Absent	Present	
Absent	27 (61.4%)	20 (45.5%)	0.135
Present	17 (38.6%)	24 (54.5%)	

Correlation between diabetes mellitus and microalbuminuria

There were 36 diabetic patients, out of which 13 patients (29.5%) were in group A and 23 patients (52.3%) in group B. 52 patients were non diabetic and among those, 31 patients (70.5%) were in group A and 21 patients (47.7%) in group B. There was a statistically significant difference (p=0.030) in the prevalence of diabetes between the two groups. (Table 5)

Table 5: Diabetes mellitus and microalbuminuria

DM	Microalbuminuria		P value
	Absent	Present	
Absent	31 (70.5%)	21 (47.7%)	**0.030**
Present	13(29.5%)	23 (52.3%)	

Correlation between dyslipidaemia and microalbuminuria

Among 88 patients, 71 patients [mean ±SD (52.36 ± 67.04)] were found to have dyslipidaemia. No statistical significance noticed between dyslipidaemia and microalbuminuria.

Correlation between SYNTAX score and microalbuminuria

On comparing SYNTAX score of group A (12.39 ± 11.99) and group B (8.52 ± 8.31) with microalbuminuria, no statistical significance (p= 0.08) obtained. (Table 6)

Table 6: Correlation between SYNTAX score and microalbuminuria

Microalbuminuria	SYNTAX score			P value
	Number of patients	Mean	SD	
Absent	44	12.39	11.99	0.083
Present	44	8.52	8.31	

Correlation between SYNTAX score and diabetic patients with and without microalbuminuria

On comparing SYNTAX score to diabetic patients with and without MA, there was no statistically significant (p value 0.689) correlation between these groups.(Table 7)

Table 7 : Correlation between SYNTAX score and diabetic patients with and without microalbuminuria

Diabetes Mellitus & Microalbuminuria	Number of patients	SYNTAX score		P value
		Mean	SD	
DM+ & MA +	23	9.26	8.16	0.689
DM+ & MA -	13	12.13	11.05	

Discussion

CAD is a major health issue in this era. Cardiovascular disease has been well recognised as the leading cause of morbidity and mortality worldwide. The economical burden due to CAD is enormous and it has got a negative impact on indices of an economically developing country. It is prudent to have a risk predictor, which will give us a glimpse into the severity of CAD.

Previous studies have proven that presence of chronic angina doubles the risk of major cardiovascular events. So it is better to prevent a major cardiovascular event rather than treating it. And it is also important in identifying the persons

who have higher burden of atherosclerosis and risk of cardiac event.

Even though multiple risk factors are identified, none of them have got a linear correlation with the severity of CAD. The purpose of the study was to find out whether MA values could be used as a predictor of severity in SCAD. Only few studies were done on chronic SCAD patients to use MA as a predictor of degree of involvement of coronary arteries.

The mean age of the patients in the study was 58.63 which was in fact almost in line with other studies.[13]Montalescot et al stated that prevalence of angina in population-based studies increases with age in both sexes, from 5–7% in women aged 45–64 years to 10–12% in women aged 65–84 and from 4–7% in men aged 45–64 years to 12–14% in men aged 65–84. [14] Interestingly, angina is more prevalent in middle-aged women than in men, probably due to the higher prevalence of functional CAD such as microvascular angina in women [15], whereas the opposite was true in the elderly. In our study 45 of the subjects were males and 43 were females. There was a slight higher incidence of chronic SCAD in men than in women which is contrary to other studies. A higher prevalence of MA in men and on increasing age was reported earlier.[12,16,17]

In our study, variables like age (p=0.122), sex (p=0.286), smoking (p=0.503), systemic hypertension (p=0.135) and dyslipidemia (p=0.165) had similar representation in both groups. There was a statistically significant difference in the occurrence of diabetes mellitus between the groups (p=0.03). There was higher occurrence of DM in the group with MA. Our study did not show any association between MA and severity of CAD (p=0.08). As we selected all patients undergoing elective coronary angiogram for SCAD, we could not exclude patients with DM and patients who were on angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB). MA might be present in diabetic patients. The rate of albuminuria would be less in patients who are on ACEIs and ARBs. All these factors might be the reasons why we did not obtain statistical significance between microalbuminuria and SYNTAX scoring.

In contrary to our observation, there are several studies establishing MA as an indicator for predicting cardiovascular events. Hillege et al [18] showed clearly that urinary albumin is a continuous risk marker with no lower limit.

The clinical relevance of MA as a common independent risk indicator in the absence of diabetes and hypertension is still unestablished. Ibsen h et al[19] stated that a reduction in albuminuria translates to a reduction in cardiovascular events in hypertensive patients.

For determining MA as a predictor of SCAD, further randomized studies should be undertaken.

Limitations of the study

1) This study had included patients with CSA, who were diabetic and on treatment with ACEIs and ARBs. These factors which affect microalbuminuria might have influenced the final result.
2) Small sample size

Conclusion

In our study there is no evidence to suggest that microalbuminuria could be a predictor for CAD in chronic stable angina patients. The prevalence of microalbuminuria was higher in patients with diabetes mellitus which was expected. Further studies should be undertaken to substantiate the results, after excluding diabetic patients and patients on angiotensin converting enzyme inhibitors or angiotensin receptor blockers.

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The heading of the Acknowledgment section and the References section must not be numbered.

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