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Correlation of Spot Urine Protein Creatinine Ratio with Angiographic Disease Severity in Non-Diabetic Stable Coronary Artery Disease

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Abstract: ***Background: Coronary artery disease (CAD) is a major cause of death and disability. Microalbuminuria, a marker of atherogenesis and early endothelial damage has been an emerging risk factor. This study aimed to correlate urine spot protein creatinine ratio with angiographic disease severity in non-diabetics with stable coronary artery disease. Methods: This was a single center prospective observational study which included 100 non-diabetic patients with stable CAD. Spot urine protein creatinine ratio was used to define Microalbuminuria (MA) (30-300mg/g creatinine), and severity of CAD was estimated using SYNTAX score and Modified Gensini score. Patients were divided into two groups: one group included patients without MA and another group included patients with MA. Results: Out of 100 non-diabetic patients with stable coronary artery disease, 56 (56%) were in MA negative group and 44% were in MA positive group. The mean age of the study population was 58.65±9.7 years with majority of them being males (75%). The prevalence of double vessel CAD and triple vessel CAD was significantly higher in MA positive group compared with the MA negative group (79.54% vs 26.78% p <0.00002). MA positive group when compared with the MA negative group had majority of them with High SYNTAX score (77.27% vs 8.9% p <0.00001) and also high Modified Gensini score were observed in MA positive group compared to MA negative group (84.8% vs 25% p < 0.00001). Statistically significant positive correlation was seen between urine protein creatinine ratio and SYNTAX score (r = 0.650, p <0.0001) and even with Modified Gensini score (r = 0.697, p <0.0001). Conclusion: This study concludes that non-diabetic patients with microalbuminuria have more severe angiographically detected CAD than with outmicroalbuminuria, hence enlightening the role of microalbuminuria as an independent risk factor for CAD in non-diabetics.***

Keywords: Coronary artery disease, Microalbuminuria, SYNTAX score, Modified Gensini score

1. Introduction

Coronary artery disease (CAD) is a major cause of death and disability in both developed and developing countries. There are various traditional independent risk factors for CAD[1], but they do not entirely explain the variation in cardiovascular disease incidence and mortality. Therefore, additional risk factors have been proposed to better identify patients potentially at risk of CAD. Many individual new biomarkers have been identified related to cardiovascular risk, including high sensitive C-reactive protein (hs CRP), B-type natriuretic peptide (BNP), Fibrinogen, D-dimer and Homocysteine. Among these new biomarkers is microalbuminuria, which is gaining recognition as a marker of atherogenesis, owing to its association with several atherosclerotic risk factors and early systemic endothelial damage[2].

Microalbuminuria is a common phenomenon in patients with cardiovascular disease worldwide. An increasing number of studies in different patient populations have reported that microalbuminuria is independently associated with cardiovascular morbidity and mortality in patients with diabetes, hypertension and in general population[3]. The term microalbuminuria is defined as urinary albumin levels between 30- 300 mg/24 h in 24-h urine collection or albumin/creatinine ratio (ACR) of more than 30 mg/g creatinine in random spot urine sample.

Although a 24 hr urine collection is the gold standard for the detection of microalbuminuria, several studies have found that a urinary protein to creatinine ratio is equally sensitive, specific and can be easily utilized on a daily basis.[4]Our aim in the present study is to assess the protein to creatinine ratio as a new predictor for coronary artery disease and to correlate it with its severity apart from other traditional CAD risk factors.

2. Materials and Methods

It is a single centre, prospective, observational study conducted in the department of Cardiology, Sri Venkateswara Institute of Medical Sciences, Tirupati, India, from July 2018 to August 2019. The study was approved by institutional ethics committee on 3rd july 2018. Each participant provided written, informed consent.

A total of 100, Non diabetic patientssuspected to have stable CAD and who underwent elective coronary angiography are included in the study after informed consent. Patients with Diabetes, Recent history of acute myocardial infarction or percutaneous transluminal coronary angioplasty, Congestive heart failure, Malignant diseases, Presence of active infection, Renal failure, Serum creatinine level over 2 mg/dl or glomerular filtration rate (GFR) below 30 ml/min, Patients not willing to participate in the study and Pregnant women were excluded from study.

Detailed history and clinical examination was performed and recorded in preformed data collection sheet. Baseline laboratory investigations, e.g. complete blood count, serumcreatinine, serum electrolytes, fasting blood sugar, fasting lipid profile, electrocardiogram, and 2D-echocardiography was be obtained from all patients before Conventional coronary angiography. Morning random mid stream urine sample was collected before coronary artery catheterization and spot urine protein to creatinine ratio was estimated. The patients underwent diagnostic Coronary Angiography (CAG) and assessment of angiographic lesion severity was done by Modified Gensini score and SYNTAX score.

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Measurement of urine protein to creatinine ratio was done in a morning random mid stream urine sample collected before coronary artery catheterization. Urine Protein (mg/dl) was estimated using Perkin Elmer Lambda 25 spectrophotometer by Sulphosalicylicacid method.

Urine Creatinine (mg/dl) was estimated using Beckman Coulter AU 680 auto analyzer, U.S.A by Modified Jaffe's rate kinetic method.Urine protein to creatinine ratio was calculated and reported as mg/g creatinine. Patients with albumin levels less than 30 mg/g of creatinine are defined as having normoalbuminuria, those with albumin levels 30 - 300 mg/g as having microalbuminuria.

All patients underwent CAG using transradial or transfemoral approach. CAG was evaluated by two experienced interventional cardiologists who were blinded to the clinical characteristics and laboratory results of the patients. The SYNTAX score is an anatomical based risk score that takes into account features such as bifurcations, total occlussions, thrombus, calcification and small vessels. Each coronary lesion with a >50% luminal obstruction in vessels >1.5mm is scored separately and the scores summated to provide the overall SYNTAX score, using online SYNTAX score algorithm.[5]The SYNTAX score is divided into three tertiles as follows: low- risk tertile is ≤ 22, intermediate risk -22-32 and high-risk tertile is > 32.The Modified Gensini score takes into consideration the geometrical severity of lesions determined by angiography, the cumulative effects of multiple obstructions and the significance of jeopardized myocardium.[6] Modified Gensini score is divided as: low score (< 20), Intermediate score (20 – 160) and high score (> 160).

3. Statistical Analysis

All continuous variables weretested for normal distribution with the Kolmogorov–Smirnov test. Normally distributed values werepresented as mean ± standard deviation, whereas non normally distributed values werepresented as median (inter quartile range). Categorical values arepresented as numbers and percent. Pearson correlation analysis was used to asses correlation between variables as appropriate .Data was collected in pre-designed Microsoft excel spread sheets. The collected data was analysed with **IBM.SPSS statistics software 23.0 Version**. All results were considered statistically significant at the level of p-value of ≤0.05

4. Results

A total of 100 patients were included in the study. As per the results of spot urine protein creatinine ratio patients were classified into two groups. Microalbuminuria negative group (MA negative) – patients having spot urine protein creatinine ratio less than 30mg/g. Microalbuminuria positive group (MA positive) – patients having spot urine protein creatinine ratio between 30-300mg/g.

Microalbuminuria negative group included 56 (56%) patients and Microalbuminuria positive group included 44 (44%) patients. The mean age of the study population was 58.65±9.7 years with majority of the patients in the age group of 50 to 60 years. Males were predominanat constituting 75% of study group. Baseline characteristics and major risk factor distribution among study population is shown in **table 1.**

Table 1: Major risk factor distribution among study population

Variable	MA Negative Group	MA Positive Group	p-value
Age (Years)	55.2 (8.2)	56.65 (9.7)	0.224
Sex			0.104
Males, n%	39 (68.4)	36 (83.7)	
Females, n%	18 (31.6)	7 (16.3)	
Hypertension, n%	26 (45.6)	25 (58.1)	0.215
Smokers, n%	21 (38.2)	24 (55.8)	0.082
Dyslipidemia, n%	18 (31.6)	14 (32.6)	0.917
Family History, n%	11 (19.3)	7 (16.3)	0.697
Serum Creatinine (mg/dl)	0.87	0.84	0.345

Prevalance of double vessel CAD and triple vessel CAD was higher in microalbuminuria positive group compared to negative group. 36.36% of patients in MA positive group had double vessel disease compared to 16.07% in MA negative group and triple vessel disease constituted 43.18% in MA positive group compared to 10.71% in MA negative group. (**table 2**). These results were statistically significant with p value 0.00002.

Table 2: Prevalance of coronary artery disease

Coronary Artery Disease	MA Negative Group (n=56)	MA Positive Group (n=44)
Normal Coronaries	11 (19.60%)	5 (2.27%)
SVD	30 (53.57%)	8 (18.18%)
DVD	9 (16.07%)	16 (36.36%)
TVD	6 (10.71%)	19 (43.18%)
X^2=21.42 p=0.00002		

*p value of <0.05 is statistically significant. SVD- single vessel disease, DVD- double vessel disease, TVD- tripple vessel disease

The median protein creatinine ratio in MA negative group was 22 and in MA positive group was 151, which was statistically significant (p<0.00001) when Mann Whitney U test was performed.

SYNTAX score and microalbuminuria:

In both the groups severity of coronary artery disease was evaluated using SYNTAX score. Patients were divided as: score < 22 – low score, 22 – 32 as intermediate score and with score > 32 as high score.91.07% of patients in microalbuminuria negative group had low SYNTAX score compared to 22.07% in microalbuminuria positive group. Patients in microalbuminuria positive group had majority of patients with intermediate score (43.18%, n=19) and high score (34.09%, n=15), compared to patients in microalbuminuria negative group which constituted 8.9% (n=5) of patients with intermediate score. These results were statistically significant (p < 0.00001). (**table 3**).When median SYNTAX score was calculated patients with microalbuminuria had high SYNTAX score with median of

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28.25 compared to microalbuminuria negative group which had median score of 9

Table 3: SYNTAX score and microalbuminuria

	Low Score (<22)	Intermediate Score (22-32)	High Score (>32)
MA Negative Group	51 (91.07%)	5 (8.9%)	
MA Positive Group	10 (22.70%)	19 (43.18%)	15 (34.09%)
X^2=48.85 p<0.00001*			

*p value of <0.05 is statistically significant

Modified Gensini score and microalbuminuria:

In both the groups severity of coronary artery disease was also evaluated using Modified Gensiniscore. Patients were divided as: low score (< 20), Intermediate score (20 – 160) and high score (>160). Majority of patients in microalbuminuria negative group (75%) had low modified Gensini scores compared to positive group (25%). Microalbuminuria positive group had majority of patients with intermediate score (65.9%, n=29) and high score (18.18%, n=8), compared to patients in microalbuminuria negative group which had only 25% (n=14) of patients with intermediate score. These results were statistically significant (p < 0.00001). (**table 4**) When median Modified Gensini score was calculated, patients with microalbuminuria had high Modified Gensin**i** score with median of 86 compared to microalbuminuria negative group which had median score of 12.

Table 4: Modified Gensini score and microalbuminuria

	Low Score (<20)	Intermediate Score (20-160)	High Score (>160)
MA Negative Group	42 (75%)	14 (25%)	
MA Positive Group	7 (15.9%)	29 (65.9%)	8 (18.18%)
X^2=35.61 p<0.00001*			

* p value of <0.05 is statistically significant.

When correlation was done using Pearson's correlation test between urine protein creatinine ratio and SYNTAX score, a significant positive correlation was seen (r = 0.650) which was statistically significant. (p <0.0001). Similar results were seen when pearson's correlation test was performed between urine protein creatinine ratio and Modified Gensini score (r = 0.697) which was statistically significant. (p <0.0001). (**table 5**)

Table 5: Correlation between spot urine protein creatinine ratio and severity of coronary artery disease using SYNTAX and Modified Gensini scores

Spot Urine Protein Creatinine Ratio Vs	Correlation Coefficient (r)	P Value
SYNTAX Score	.650	<0.0001*
MODIFIED Gemini Score	.697	<0.0001*

Pearson's correlation test: * indicates significant p value

5. Discussion

Study subjects were divided into two groups based on based on urine protein-creatinine ratio (urine PCR). Subjects with urine PCR < 30mg/gm as microalbuminuria negative group (n=56, 56%) and those with urine PCR 30 -300mg/gm as microalbuminuria positive group (n=44, 44%). We found that frequency of microalbuminuria was high i.e 44% in our study, compared to general population which ranges from 5% to 7%.[7]Hence this study highlights the importance of microalbuminuria in non diabetics and may be an important emerging risk factor for CAD.

Majority of study population was contributed by patients aged between 51-60 years (n=40, 40%) in both the groups, MA negative n= 24, 42.8%) and MA positive group (n=16, 36.3%). Males predominated the study with 75% (n=75%) compared to females (n=25, 25%), and in both the groups males were predominant (MA negative- male: female = 39:17) (MA positive- male: female = 36:8).Above findings are supported by data from INTERHEART study[8] which showed three fold rise in CAD incidence in males compared to females and increased incidence with aging.

In our study we could not find any statistical differences in prevalence of HTN, smoking, dyslipidemia, family history of CAD and serum creatinine between the two groups. This is in contrast to gou et al[9]which found association between HTN, dyslipidemia and microalbuminuria.

Prevalence of double vessel CAD and triple vessel CAD was significantly higher in MA positive group compared to MA negative group (79.48% in MA positive group vs 28.8% in MA negative group). Hence this study highlights the importance that patients with microalbuminuria have a greater atherosclerotic burden and more severe CAD in terms of number of vessels affected than patients without microalbuminuria.

Presence of Microalbuminuria also exhibits significant correlation with severity of CAD (p < 0.001).These results are in accordance with previous studies by Guo et al [9], Hoseni et al [10], and Al saffer et al[11] which also concluded positive correlation between severity of CAD and microalbuminuria in non diabetics.

Median protein creatinine ratio in our study was 22 in MA negative group and 151 in MA positive group which was significant (p < 0.0001).similar to our study, Hashim et al [12] in their study found median protein creatinine ratio of 131 in MA positive group.

In the present study patients in MA positive group had a greater intermediate and high SYNTAX score (77.27%), compared to MA negative group (8.9%), with a median SYNTAX score of 28.25 in MA positive group. Hence this findings suggest more complex coronary artery disease in patients having microalbuminuria than those with outmicroalbuminuria. These results matched with previous studies by sukhija et al [13], Hashim et al [12] and Hoesini et al [12] which showed that patients with microalbuminuria had high SYNTAX score.

Patients with microalbuminuria in our study also had higher modified Gensini score, 84.08% in MA positive group had intermediate and high modified Gensini score, compared to 25% in MA negative group, with a median score of 86 in patients with microalbuminuria. These results were in agreement with studies done by El sheriff et al [14] and Parsa

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et al [15]who concluded that Gensini score was significantly high in patients with microalbuminuria than in patients with outmicroalbuminuria.

Significant positive correlation was seen with microalbumiuria and SYNTAX score ($r = 0.650$ and $p < 0.0001$) and also positive correlation was observed with microalbuminuria and modified Gensini score ($r = 0.697$ and $p < 0.0001$)

Gosling et al [16]and Haffner et al [17] in their studies concluded microalbuminuria as an emerging cardiovascular risk factor in non diabetic patients. This study also had findings similar to above studies as it showed significant microalbuminuria in non-diabetics and microalbuminuria correlated significantly with severity of CAD, hence suggesting microalbuminuria as an emerging risk factor.

6. Conclusion

In this study we found significantly high microalbuminuria (44%) in non diabetic patients, hence enlightening the importance of microalbuminuria in non diabetics. Non diabetic patients with microalbuminuria had more extensive and complex coronary artery disease (i.e they had high SYNTAX and Modified Gensini scores) compared to those with outmicroalbuminuria. Since detection of microalbuminuria is simple and relatively inexpensive investigation, early identification of microalbuminuria may influence the aggressiveness of management and outcome of disease.

7. Limitations

The study population is relatively small to generalize the results, Single center study, Sampling method was not random rather purposive so there is a risk of selection bias, Quantification of lesions was based on visual interpretation.

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