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Urinary Albumin to Creatinine Ratio and the Degree of Coronary Artery Narrowing in Patients Undergoing Coronary Angiography

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Coronary artery disease (CAD) is one of the major causes of death and disability in both developed and developing countries. Microalbuminuria is regarded not only an indicator of global endothelial dysfunction but also an antecedent to atherosclerotic coronary artery disease. A cross-sectional study was done on 57 patients of both sexes undergoing coronary angiography at Cardiac Medical Unit, Yangon General Hospital in order to associate urinary albumin to creatinine ratio (UACR) and the degree of coronary artery narrowing. The mean age was 57.9±9.8 years with M:F ratio of 1.7:1. UACR was measured by immunoturbidimetry method using UACR 30mg/g as cut-off value for having microalbuminuria. The severity of coronary artery narrowing was recorded as normal, one vessel narrowing, two vessels narrowing and three vessels narrowing. Microalbuminuria was present in 31.6% of total cases. There were 21.1% CAD negative (normal) patients and 78.9% CAD positive (stenosis ≥50%) patients. Microalbuminuria was detected in 16.7% of patients with one vessel narrowing, 22.2% with two vessels narrowing and 61.1% with three vessels narrowing. None of the patient with normal angiogram result had microalbuminuria. There was a significant association between UACR and degree of coronary artery narrowing (p=<0.001). This showed that patients with microalbuminuria (raised UACR) have greater atherosclerotic burden and more severe coronary artery disease than those without microalbuminuria.

Key words: Urinary albumin to creatinine ratio, Coronary artery disease, Coronary angiography

INTRODUCTION

Coronary artery disease (CAD) is a well-known cause of death and disability worldwide. Atherosclerosis is responsible for almost all cases of CAD. It is a multifactorial disorder with several different risk factors. Advancing age, male sex, hypertension, diabetes mellitus, cigarette smoking and dyslipidemia are the major and independent well-known risk factors for CAD.[1] There are also many new biomarkers relating cardiovascular risk, including C-reactive protein (CRP) levels,[2] B-type natriuretic peptide,[3] fibrinogen,[4] D-dimer[5] and homocystine.[6]

The high volume of fluid filtered across the glomerular endothelium (140-180 L/day) markedly amplifies the functional consequence (increase albumin filtration) of early endothelial injury in the glomerulus in contrast to the systemic endothelial bed in which early atherosclerotic injury is undetectable. The emergence of microalbuminuria unmasks systemic endothelial injury likely occurring simultaneously in other vascular beds, progressively from silent to overt disease later years.[7] It is thought to be an indicator of glomerular endothelial dysfunction and of macromolecular hyperpermeability.[8]

Increasing prevalence of microalbuminuria in various clinical conditions, such as

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diabetes mellitus, acute ischemic heart disease, acute stroke[9], arterial hypertension[10] and carotid atherosclerosis,[11] strengthens the link between microalbuminuria and vascular diseases. Although a 24-hour urine collection is the gold standard for the detection of microalbuminuria, several studies have found that a urinary albumin to creatinine ratio (UACR) is equally sensitive, specific, and can be easily utilized on a daily basis.[12]

In this study, urinary albumin to creatinine ratio was done in patients undergoing coronary angiography aiming to detect the association of microalbuminuria in terms of UACR and the degree of narrowing of coronary artery.

MATERIALS AND METHODS

The study was a cross-sectional, hospital- and laboratory based analytical study. Fifty-seven patients admitted to Cardiac Medical Unit (CMU) of Yangon General Hospital (YGH) for coronary angiography were included.

The patients with overt proteinuria, hematuria, urinary tract infection detected by routine urinalysis and renal insufficiency with abnormal urea and creatinine result were excluded. Patient with blood pressure above 140/90 mmol/l or patient taking anti-hypertensive drug was recorded as having hypertension.[13] Patient with fasting blood sugar ≥126 mg/dl (7.0 mmol/l) or 2HPP (two-hour post-prandial glucose) ≥200 mg/dl (11.1 mmol/l) or random blood sugar ≥200 mg/dl (11.1 mmol/l) in patient with symptoms of hyperglycaemia or HbA_{1C} ≥6.5%[14] or patient taking anti-diabetic drugs was recorded as having diabetes mellitus.

Patient with fasting lipid profile showing one of the following values: Total cholesterol ≥240 mg/dl, Triglyceride ≥200 mg/dl, LDL cholesterol ≥160 mg/dl, HDL cholesterol <60 mg/dl was recorded as having dyslipidemia. Patient who had history of smoking; either current smoker or ex-smoker was recorded as smoker.

Five milliliters of random urine sample were taken for determination of microalbuminuria in terms of urinary albumin to creatinine ratio. It was measured by DCA 2000+ Microalbumin/Creatinine assay with: albumin reagent: 3.3-10% purified poly-clonal goat anti-human albumin antiserum in 50 mM TRIS; 8.6% w/v non-reactive ingredients (15 ul dried in each cartridge), creatinine alkaline reagent: 28% potassium hydroxide, 5% non-reactive ingredients (30 ul dried in each cartridge) and buffer solution: 0.22% w/v 3, 5-dinitro-benzoic acid, 4% polyethylene glycol in 25 mM HEPPS buffer, with 2% non-reactive ingredients (0.57 ml in each cartridge).

The ratio of urinary albumin to creatinine ratio (UACR) was used to define micro-albuminuria. The patients with urinary albumin to creatinine ratio of 30-300 mg/g were defined as having microalbuminuria. In this study, the stenosis ≥50% in a main coronary artery or in one of the other branches was recorded as having significant coronary disease.[15] The <50% stenosis was recorded as non-significant or normal.

Statistical analysis was performed using Statistical Package for Social Science (SPSS) 16.0. The data were described in terms of mean and standard deviation, while categorical variables were expressed as numbers and percentages when appropriate. Associations between two categorical variables were tested using Pearson Chi-Square, as appropriate. A 'p' value of ≤0.05 was considered statistically significant.

RESULTS

Demographic characteristics

Within the study group, the youngest patient was found to be 30 years and the oldest age was 77 years. The mean age was 57.91±9.86 years. The majority of the patients (52%) were in 56-70 years age group. There were 36 men (63.2%) and 21 women (36.8%). Male to female ratio was found to be 1.7:1.

Urinary albumin to creatinine ratio (UACR) among patients undergoing coronary angiography

In this study, UACR was studied with cut-off value at 30-300 mg/g as raised UACR and 18(31.6%) out of 57 patients had raised UACR.

Degree of coronary artery narrowing in patients undergoing coronary angiography

The results of coronary angiography showed that there were 12(21.1%) CAD negative (normal) patients and 45(78.9%) CAD positive (stenosis ≥50%) patients. Among the CAD positive patients, 21(46.7%) had one vessel involvement, 9(20.0%) had two vessels and 15(33.3%) had three vessels involvement.

Association between UACR and degree of coronary artery narrowing in patients undergoing coronary angiography

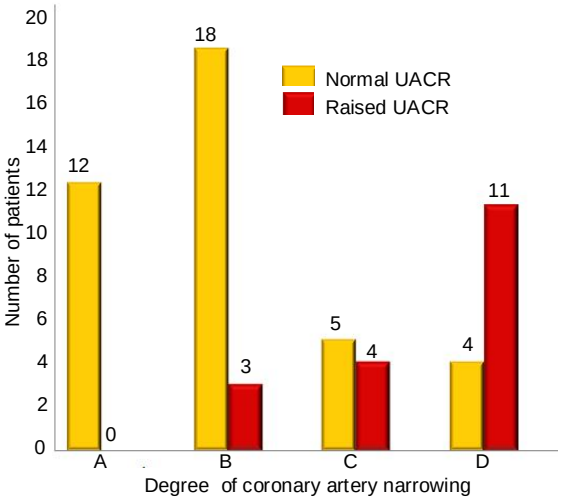
In the patients with normal UACR, 12(30.8%) patients had normal angiogram result, 18(46.2%) had one vessel narrowing, 5(12.8%) had two vessels narrowing and 4(10.2%) had three vessels narrowing. On the other hand, in patients having raised UACR, there was no normal angiogram result and 11(61.1%) patients had three vessels narrowing while 3(16.7%) and 4(22.2%) had one vessel and two vessels narrowing, respectively.

Association between CAD risk factors and UACR in patients undergoing coronary angiography

In the study population, the mean age in the group of patients with normal UACR was 55.69±9.91 years ranged from 30-77 years, and in those with raised UACR was 62.72±8.07 years ranged from 46-72 years. In normal UACR group, there were 25 males (64.1%) and 14 females (35.9%). In raised UACR group, there were 11 males (61.1%) and 7 females (38.9%). The association between smoking, DM, hypertension, dyslipidemia and UACR in studied population were not found to be significant as shown in Table 1.

Table 1. Association between CAD risk factors and UACR in patients undergoing coronary angiography

	Number of patients		p value
	Normal UACR n=39(68.4%)	Raised UACR n=18(31.6%)	
Age			
Range	30-77	46-75	0.101
Mean	55.69	62.72	
SD	9.91	8.07	
Sex			
Male	25(64.1%)	11(61.1%)	0.828
Female	14(35.9%)	7(38.9%)	
Family history of CAD			
Yes	18(46.2%)	3(16.7%)	0.032
No	21(53.8%)	15(83.3%)	
Smoking			
Yes	24(61.5%)	8(44.4%)	0.227
No	15(38.5%)	10(55.6%)	
Diabetes mellitus			
Yes	12(30.8%)	7(38.9%)	0.546
No	27(69.2%)	11(61.1%)	
Hypertension			
Yes	27(69.2%)	14(77.8%)	0.504
No	12(30.8%)	4(22.2%)	
Dyslipidemia			
Yes	14(35.9%)	10(55.6%)	0.162
No	25(64.1%)	8(44.4%)	



A= Normal
B= ≥50% narrowing in one vessel
C= ≥50% narrowing in two vessels
D= ≥50% narrowing in three vessel

Fig 1. Association between UACR and degree of coronary artery narrowing in patients undergoing coronary angiography

Association between traditional CAD risk factors and degree of coronary artery narrowing in patients undergoing coronary angiography

The mean age of patients with normal or <50% narrowing was 54.67±12.34 years and in those with ≥50% narrowing in one

Table 2. Association between traditional CAD risk factors and degree of coronary artery narrowing in patients undergoing coronary angiography

	Number of patients				p value
	Normal or <50% narrowing n=12(21.1%)	≥50% narrowing in one vessel n=21(36.8%)	≥50% narrowing in two vessels n=9(15.8%)	≥50% narrowing in three vessels n=15(26.3%)	
Age					
Range	30-77	41-75	41-71	46-72	0.115
Mean	54.67	55.71	58.89	63	
SD	12.34	8.42	11.25	7.19	
Sex					
Male	7(58.3%)	14(66.7%)	6(66.7%)	9(60%)	0.952
Female	5(41.7%)	7(33.3%)	3(33.3%)	6(40%)	
Family h/o CAD					
Yes	5(41.7%)	8(38.1%)	2(22.2%)	6(40%)	0.795
No	7(58.3%)	13(61.9%)	7(77.8%)	9(60%)	
Smoking					
Yes	7(58.3%)	14(66.7%)	3(33.3%)	8(53.3%)	0.404
No	5(41.7%)	7(33.3%)	6(66.7%)	7(46.7%)	
DM					
Yes	4(33.3%)	6(28.6%)	3(33.3%)	6(40%)	0.916
No	8(66.7%)	15(71.4%)	6(66.7%)	9(60%)	
Hypertension					
Yes	7(58.3%)	16(76.2%)	7(77.8%)	11(73.3%)	0.693
No	5(41.7%)	5(23.8%)	2(22.2%)	4(26.7%)	
Dyslipidemia					
Yes	4(33.3%)	6(40.0%)	24(42.1%)	6(40%)	0.876
No	8(66.7%)	9(60.0%)	33(57.9%)	9(60%)	

vessel was 55.71±8.42 years, ≥50% narrowing in two vessels was 58.89±11.25 years and ≥50% narrowing in three vessels was 63±7.19 years. In each group the percentage of male was apparently higher than female (Fig. 1). The association between family history of CAD, smoking, DM, hypertension, dyslipidemia and the degree of coronary artery narrowing were not found to be significant as shown in Table 2.

Association between UACR and degree of coronary artery narrowing in patients undergoing coronary angiography

Table 3. Association between UACR and degree of coronary artery narrowing in patients undergoing coronary angiography

Total	A n=12 (21.1)	B n=21 (36.8)	C n=9 (15.8)	D n=15 (26.3)	P value
UACR					
Normal	12(100)	18(85.7)	5(55.6)	4(26.7)	<0.001
Raised	0(0)	3(14.3)	4(44.4)	11(73.3)	

A= Normal or <50% narrowing
B=≥50% narrowing in one vessel
C=≥50% narrowing in two vessels
D=≥50% narrowing in three vessel

UACR was raised in none of the patient with normal coronary artery. Only 3(14.3%) of patients with one vessel disease had raised UACR while UACR was raised in 4(44.4%) of patients with double vessel disease and 11(73.3%) of patients with triple vessel disease. There was a significant association between UACR and the degree of coronary artery involvement. The higher the vessel involvement, the more is the chance of having raised UACR (Table 3).

DISCUSSION

The traditional risk factors of coronary artery disease do not entirely explain the variation of CAD incidence and mortality in individual and populations. This fact has led to studies on nontraditional cardiovascular risk factors and microalbuminuria appears as one of these factors.

In this study, 31.6% of patients had raised UACR (microalbuminuria). This finding was more or less comparable to the studies done by Sadaka, *et al.*,[16] Rein, *et al.*,[17] Deveci, *et al.*[18] and Hashim, *et al.*,[21] in which the prevalence were 34%,[16] 24%,[17] 28%[18] and 37%,[21] respectively.

In the study population, the coronary angiographies were done in cases with post-acute myocardial infarction (57.9%), post-NSTEMI (10.5%), unstable angina (14.1%) and positive exercise tolerance test (17.54%). The results of coronary angiography showed that 21.1% of patients had normal coronary artery while 36.8% had one vessel narrowing, 15.8% had two vessels narrowing and the rest (26.3%) had three vessels narrowing.

Association between UACR and degree of coronary artery narrowing

In the patients having normal UACR, 12(30.8%) had normal angiogram result, 18(46.2%) had one vessel narrowing, 5(12.8%) had two vessels narrowing and 4(10.2%) had three vessels narrowing. On the other hand, in patients having raised UACR, there was no normal angiogram result and most 11(61.1%) patients had three vessels narrowing while 3(16.7%) and 4(22.2%) had one vessel and two vessels narrowing, respectively. This finding was statistically significant with the p value of <0.001. According to the study, the patients with microalbuminuria had a greater atherosclerotic burden and a more severe coronary artery disease in the forms of total number of vessels affected than those without microalbuminuria.

These results supported many studies. In the study of Sadaka, *et al.,* microalbuminuria was observed in 34% of patients and these patients were found to have more severe angiographic CAD compared to those without microalbuminuria. That study also concluded that microalbuminuria could be utilized as an independent risk factor for CAD. Similar results were presented by Hoseini and Rasouli who performed a study consisting of 153 non diabetic patients who underwent coronary angiography.[19] In the study of Sukhija, *et al.,* the patients with microalbuminuria have more severe angiographic CAD showing microalbuminuria is independent of other risk factors and is particularly evident in patients with DM.[22]

The study performed by Parvizi, *et al*., showed that the urinary albumin/creatinine ratio of the patients with confirmed coronary atherosclerotic lesion was higher than that of the control (p=0.00). It indicates the existence of a significant correlation between the extension of atherosclerotic lesions and UACR.[23]

Hashim, *et al.,* found that the frequency of microalbuminuria was elevated in the study population (37%) which is significantly higher as compared to the general population which ranges from 2.2% to 10.2% in various studies. That study also highlights that MA is more frequent in non-diabetic patients with CAD than the general population and thus may be an important emerging risk marker for CAD.[21]

According to the study, although statistically not significant, microalbuminuria (Raised UACR) was seemed to be more common in older age group (mean age 62.72±8.06 years *vs.* 55.69±9.91 years) (p=0.101). This finding was in accordance with the findings of Rein, *et al.*,[19] Ei Ei Shwe[24] and Sandar Soe.[25]

Among 18 patients with raised UACR, 11(61.1%) patients were men and 7(38.9%) women. Therefore, microalbuminuria was found to be common in male although statistically not significant (p=0.828). It was found to be similar to the result of Sadaka, *et al.,* in which raised UACR was accounted for 73.5% men and 26.5% women.[16] Yin Mon Thant[26] stated that the occurrence of microalbuminuria between men and women had ratio of 1.77:1 when studied in Myanmar patients with AMI.[26] In the study of Parsa, *et al*., among 16 patients with microalbuminuria, there were 12 men (35.3%) and 4 women (9.3%) and there was a significant difference between the genders regarding the prevalence of micro-albuminuria (OR of male/ female=5.3, 95% CI: 1.53-18.5, p<0.005).[20]

Patients with diabetes mellitus are at high risk of suffering renal damage. Early detection of diabetic nephropathy is one of

the important steps in the management of diabetic patients. Microalbuminuria is common in diabetic patients than those without diabetes. In HOPE study, 32.6% of participants with DM and 14.8% of participants without DM were detected to have microalbuminuria at baseline.[27] In the study of Ei Ei Shwe, 43% of patients with DM had microalbuminuria.[24]

In the current study, 19 patients (33.3% of study population) had diabetes and 7 diabetic patients (12.9% of the study population and 36.8% of diabetic patients) were found to have microalbuminuria. This might be due to the small study population and the selected diabetic patients under-going coronary angiography had good glycemic control and renoprotective drugs like ACEI and ARB were already given to the patients. The patients with advanced nephropathy and macroalbuminuria were also excluded from the study by exclusion criteria.

Out of 57 patients, 21 patients had family history of CAD. Microalbuminuria was present in 3 patients among those having family history. There were 32 patients who had smoking history, in which 8 patients had microalbuminuria. Hypertension was observed in 41 patients out of 57 and 14 hypertensive patients had microalbuminuria. Dyslipidemia was present in 24 patients and 10 of those had microalbuminuria. There was no obvious significant association between the CAD risk factors and UACR in the study population except with family history of CAD.

In the study of Sadaka, *et al.*, there was no significant difference in the prevalence of hypertension and hypercholesterolemia between the patients with or wi thout microalbuminuria.[16] Sukhija, *et al.*, studied the relationship of microalbuminuria and coronary artery disease in patients with or without DM and stated that there were no significant differences in the prevalence of hypertension, hypercholesterolemia and current smoking across the 4 groups of patients (DM+ MA+, DM+ MA-, DM- MA+, DM- MA-).[22] The patients were categorized according to the degree of coronary artery narrowing as following: patients with normal coronary artery (normal or <50% narrowing), those with ≥50% narrowing in one vessel, two vessels and three vessels.

The mean age of study population according to status of coronary artery narrowing were 54.67±12.3 years in patients with normal artery while 55.71±8.4 years, 58.89±11.2 years and 63±7.1 years in patients with one vessel, two vessels and three vessels narrowing, respectively. It could be concluded that the older the age, the more is the possibility of having multiple vessels involvement although not significant statistically (p=0.115). In the study of Bildirici, *et al.*, as well, those with CAD were older than those without CAD (59±11years *vs.* 55±9 years).[28]

In each category, the number of male exceeded that of female (p=0.952). This observed finding strengthened the fact that male sex is the risk factor for CAD although not significant statistically. This finding was consistent with the findings of Sadaka, *et al.*,[16] Hoseini, *et al.*,[19] Bildirici, *et al.*,[28] and Rein, *et al.*[17]

Family history of CAD was present in 41.7% of normal patients, 38.1% of patients with one vessel disease, 22.2% of patients with double vessel disease and 40% of patients with triple vessel disease. There was no statistically significant association between the present or absent of family history of CAD and degree of coronary artery narrowing in this study (p=0.795).

Smokers were found to have more risk of having CAD than non-smokers although statistically not significant (p=0.404). This study revealed 66.7% of one vessel disease patients, 33.3% of double vessel disease patients and 53.3% of triple vessel disease patients were smokers. Similar finding were observed in the studies of Hoseini, *et al.*,[16] Bildirici, *et al.*,[28] and Rein, *et al.*,[17] Diabetes was present in 28.6% patients with one

vessel disease, 33.3% of double vessel disease and 40% of triple vessel disease patients (p=0.916).

In this study, 76.2% of patients with one vessel disease, 77.8% of those with double vessel disease and 73.3% of triple vessel disease patients had hypertension. Although hypertensive patients are majority of the CAD patients, hypertension was not found to have statistical association with degree of coronary artery narrowing (p=0.693).

Dyslipidemia was observed in 40% of one vessel disease patients, 42.1% of double vessel disease and 40% of triple vessel disease patients (p=0.876). In the study of Sadaka, *et al*., there were no significant differences in the prevalence of hypertension and hypercholesterolemia between the patients with or without CAD.[16] Furthermore, Bildirici, *et al.*, also found out that baseline clinical and laboratory characteristic of patients with or without CAD, including the statuses of hypertension, DM, smoking, dyslipidemia and family history, were not different in his study.[28]

There are several limitations to the present study. The most important limitations are small sample size and short duration of study period. This study solely relied on only one sample of UACR and a consecutive assay could have provided additional information. Another limitation is that as most of the patients were already optimized for the confounding factors before angiography, like blood pressure optimization, sugar control and reno-protective drugs like ACEI and ARB were already given, these could have some effect on the patients' UACR status. Since the study was conducted on a limited number of patients, there is a need for further investigations on larger group of patients in order to support these results.

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