Positive Correlation between Microalbuminuria and Severity of Coronary Artery Stenosis in Patients with Type 2 Diabetes Mellitus

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Abstract- Diabetes mellitus (DM) is the most prevalent metabolic disease worldwide and is associated with coronary artery disease (CAD). Therefore it is very important to find a clue to diagnose the presence of CAD as early as possible in DM patients. The aim of this study was to find any correlation between microalbuminuria (MAU) and the severity of CAD in patients with DM type 2. This was a cross sectional study that included 77 DM type 2 patients with suspected CAD that all of whom were performed coronary angiography in our hospital (from 2010 to 2011). Patients were divided into two groups, the case group (group 1) that includes patients with MAU and the control group (group 2) that include patients without MAU. Severity of CAD was estimated by using Gensini score and MAU was defined as the ratio of urine albumin to urine creatinine. Of 77 patients forty three (55.8%) were female, mean ± SD of their ages was 55.8 ± 10.3 and sixteen (21%) of them had MAU. Gensini score of case group was significantly higher than control group (94.94 ± 12 versus 33.25 ± 25.4, $P<0.001$). The linear regression analysis revealed urinary albumin to creatinine ratio (UA/CR) as an independent predictor for the severity of CAD ($P<0.001$). Based on the ROC curve, 10.25 was the best albumin level cut off point for differentiating Gensini score over and below 70. Area under curve was 0.9; sensitivity and specificity were 72% and 80%, respectively ($P<0.001$). According to this study, in patients with DM type2, MAU is an independent predictor of severity of coronary artery stenosis and reveals a positive correlation between MAU and the Gensini score.

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Key words: Coronary artery stenosis; Microalbuminuria; Diabetes mellitus type 2; Gensini score

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease widespread through the world which has provoked considerable worrisome for public health care workers. Despite the fact that there has been great progression in the treatment of diseases, prevalence and complications of DM is increasing (1). Cardiovascular disease is the major cause of death in these patients (2). Many of diabetic patients with coronary artery disease (CAD) don't have any other classic risk factor for coronary disease and half of them have normal lipid profile (3), thus researchers in this field are looking for new risk factors to identify patients whom are prone to CAD.

Microalbuminuria (MAU) is a marker of endothelial dysfunction and vascular damage which could be a predictor for coronary artery atherosclerosis (5,6) and early mortality in patients with DM type2, independent of renal function (7). Many studies have shown positive relationship between increased MAU and CAD in diabetic patients (8-11), but there isn't a known specific cut off point for the level of MAU which may accompany with considerable increase in coronary artery stenosis. A few studies have suggested that the predictive level of MAU for vascular disease may be lower than threshold for diabetic nephropathy (2,12). This study was designed to determine the correlation between MAU and the severity of coronary artery atherosclerotic disease in diabetic patients whom have been undergone coronary angiography and to determine the MAU cut off point level that best predicted the risk of coronary artery atherosclerosis in diabetic patients.

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Materials and Methods

This is a cross sectional prospective study that enrolled 77 DM type 2 patients who were suspected for CAD and whom underwent elective coronary angiography in our hospital during years 2010 and 2011 (inclusion criteria). All patients had WHO criteria for DM type2 (13).

Coronary angiography and assessment of MAU were done at the same time. Exclusion criteria were; macroalbuminuria over 300 mg/g creatinine, existence of specific disorders or conditions such as acute myocardial infarction (MI), congestive heart failure (CHF), malignancies, active infection, renal failure, serum creatinine level over 2 mg/dl or glomerular filtration rate (GFR) below 30 dl/min, using angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs).

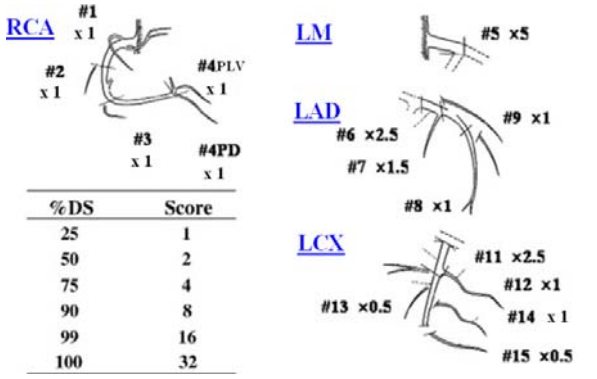
Clinical characteristics: Patients' age, sex, smoking status and blood pressure were recorded. Diastolic and systolic blood pressures were measured with a standard mercury sphygmomanometer after at least 15 min rest after getting patients to the hospital. Hypertension was defined as systolic blood pressure over or equal to 140 mmHg and/ diastolic blood pressure over or equal to 90 mmHg, or using antihypertensive drugs.

Measurement of MAU: Albumin (Alb) and creatinine levels were measured in a single urine specimen. Diagnostic kit (Diyazim, Germany) was used to measure creatinine (Jaffe method) and Alb (Bromocresol green method). The apparatus was Alcyon, 3001 & auto-analyzer system (made in USA)

Laboratory tests: Blood samples were taken after 12 hours fasting. Routine laboratory tests were done including fasting plasma glucose (FPG), glycosylated hemoglobin ($HgbA_{1C}$) total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and serum creatinine (Cr).

Coronary angiography (Assessment for coronary artery atherosclerotic disease): The diagnostic procedure was performed by an experienced interventional cardiologist by using a Siemens high core system (Seldinger's technique) via right femoral artery after performing local anesthesia with xylocaine. For better displaying the lesions, in order to make grading assessment possible, angiographies were performed in several views. Intra-arterial systolic and diastolic pressures of the ascending aorta were measured during cardiac catheterization. In patients with creatinine level 1.5 mg/dl or less and significant coronary artery disease, abdominal aortography was performed by using a pigtail catheter with a pump injector for evaluating and/ruling out renal arteries stenosis (14,15). In case of having difficulty to evaluate the degree of stenosis of renal arteries , selective renal arteriography was done with a right 6 or 7 French Judkin's catheter in the anterior-posterior, and if necessary, in oblique projections. All images were recorded digitally.

Functional significance score (FSS) of coronary arteries.



%DS	Score
25	1
50	2
75	4
90	8
99	16
100	32

Figure 1. Calculation of Gensini score, (Gensini score X FSS); LM =Left main, LAD= left anterior descending, LCX=left circumflex, RCA=right coronary artery, DS= degree of stenosis.

Assessment of the severity of coronary artery disease (using Gensini score): Gensini score was calculated by sum of stenosis score multiply functional significance score (Figure 1). Stenosis score was determined as below:

Statistical analysis

Data were statistically described in terms of mean, standard deviation (SD) for quantitative and frequencies and percentages (prevalence) for qualitative variables. Comparison between the study groups was done using independent t-test and Mann Whitney U-test for numerical, Chi-square and Fisher's exact test for categorical data variables. Correlation between two numerical various variables was done using Pearson correlation coefficient (Spearman rank correlation equation for non-normal variables). *P*-values less than 0.05 were considered statistically significant. Statistical calculations were done using SPSS (version 11).

Results

Demographic and clinical characteristics of all diabetic patients included in this cross sectional study are shown in table 1 and 2. The patients' ages ranged between 30–80 years with mean age of 55.8±10.3 years. They

included 43 females (55.8%) and 34 males (44.2%). The average of Gensini score was 46.6±34.24. Thirty one percent of patients had Gensini score between 0-20, 11.7% between 21-40, 27.3% between 41-60, 9% between 61-80, 15.6% between 81-100, while 4% between 101-120 and 1.3% of patients had Gensini score between 121-140.

MAU was seen in 16 patients (21%) and 61 (79%) of patients were normal regarding albuminuria. In MAU group (group 1), there were 12 men (35.3%) and 4 women (9.3%) and there was a significant difference between the two genders regarding the prevalence of MAU ($OR_{male/female}$=5.3, 95% CI: 1.53-18.5, P<0.005). Results have been presented in table 3.

Gensini score and albuminuria were correlated significantly (P<0.001) with a correlation coefficient (r) of 0.57 which means there is a good correlation between them.

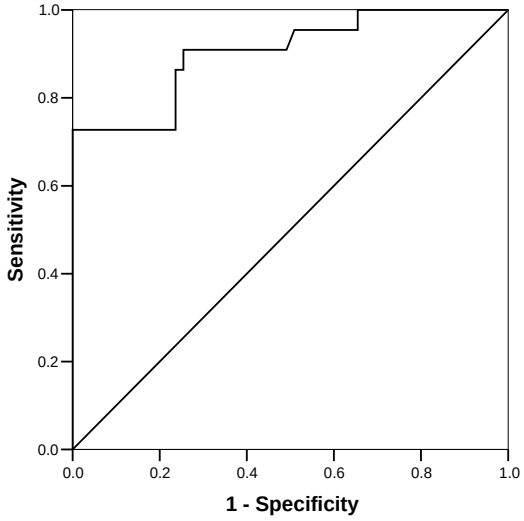


Figure 2. ROC curve for albuminuria level in patients with Gensini score above and below seventy.

Gensini score and age were correlated significantly (P<0.01) but with a correlation coefficient (r) of 0.3. Albuminuria and age also were correlated significantly (P<0.039) but with a correlation coefficient (r) of 0.24 which means that there isn't a good correlation between them.

Based on ROC curve (Figure 2), 10.25 was the best albumin level cut off point for differentiating Gensini score over and below 70. Area under curve was 0.9; sensitivity and specificity were 72% and 80%, respectively (P<0.001). Linear regression equation (Stepwise method) for finding relationship between Gensini score and albuminuria was obtained as: Gensini score= 36.416+0.335 (albuminuria).

Table 1. Demographic and clinical characteristics of all patients enrolled in the study.

Variable	Mean	SD
Age (years)	55.8	± 10.3
TC× (mg/dl)	190.5	± 43.2
TG (mg/dl)	166.7	± 89.8
LDL-C (mg/dl)	106.0	± 36.8
HDL-C (mg/dl)	46.9	± 12.0
FBS	174.7	± 67.5
Gensini score	46.0	± 34.2

×TC=Total cholesterol, TG=Triglyceride, LDL-C=Low density cholesterol, HDL-C=High density cholesterol, FBS=Fasting blood sugar

Table 2. Demographic and clinical characteristics of all patients enrolled in the study.

Variable	Frequency (Number)	Prevalence (%)
Sex		
Male (%)	34	44.2
Female (%)	43	55.8
Hypertension	21	27.3
Dyslipidemia	58	68.8
Smoking (%)	6	8.1

Table 3. Results of comparing normoalbuminuria and microalbuminuria groups.

Variable	Normoalbuminuria group 2	Microalbuminuria group 1	*P*-value
Sex			
Male [number (%)]	22 (64.7%)	12 (35.3%)	*<0.005
Female [number (%)]	39 (90.7%)	4 (9.3%)	
HDL-C [Mean (SD)]	46.6 (12.15)	47.5 (12)	0.177
LDL-C [Mean (SD)]	109 (39.7)	97.44 (25.9)	0.187
TG [Mean (SD)]	171 (89.6)	152.8 (92)	0.669
Systolic pressure [Mean (SD)]	129 (19.8)	122.5 (16.9)	0.918
Diastolic pressure [Mean (SD)]	76.3 (9)	74.4 (9.8)	0.241
Gensini score [Mean (SD)]	33.25 (25.4)	94.94 (12)	* <0.001

* P<0.05 is significant

Discussion

In presents study the presence of MAU was accompanied with higher Gensini score which was statistically significant. This finding was in agreement with previous reports (8,9,17-19).

Aging had positive correlation with MAU and Gensini score which was consistent with El Sherif *et al.* (17) and Guo *et al*. (18) findings.

MAU was significantly different between men and women (higher in men) like Guo *et al.* (18) and Luo *et al.* (20) studies, but Gensini score was similar in two sexes which was contrary to these two studies.

Differ from Gou *et al*. (18) and Luo *et al*. (20) surveys, we didn't find any relation between MAU or Gensini score with LDL-C, TG, cigarette smoking and systolic or diastolic hypertension. This diversity could be due to differences in sample size, survey period, race, medications and geographic or nutritional factors.

With regard to ROC curve, the best cut off point for albumin level in patients with Gensini score over 70, was 10.25 µg which is close to 11.275 µg/min obtained from Guo *et al.* study (18). In conclusion, based on this study, MAU could be considered as a risk factor for predicting the severity of coronary artery stenosis in DM type2 patients (especially in older male patients). Thus diabetic patients may be advised to check for MAU periodically and if it's over 10.25, performing more study for detecting CAD seems to be reasonable. Conversely, in patients who undergo angiography, if Gensini score is over 70, it's reasonable to check urine for MAU for diagnosing and preventing renal involvement as soon as possible.

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