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Original Article

Cardiovascular disease in type 2 diabetes mellitus: Relationship between microalbuminuria and cardiovascular risk factors

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Abstract

Aim: In this study, the relationship between cardiovascular disease (CVD) risk factors and microalbuminuria (MAU) in patients with type 2 diabetes mellitus (DM) was investigated.

Materials and Methods: The data of type 2 DM patients without CVD were evaluated retrospectively. Anthropometric measurements were made using calibrated standard devices. Biochemical data of the patients were obtained from the hospital information processing system. Patients with type 1 DM, history of CVD and diseases that may affect the MAU level were excluded from the study. Statistical analysis was done using SPSS 22.0.

Results: The study included 300 type 2 DM patients with the mean age of 58.9±10.1. 56.7% of the cases (n=170) were female, and 43.3% (n=130) were male. 12.7% of the cases were obese (BMI>30 kg/m^2). Body mass index, blood pressure (BP), LDL, glycated hemoglobin (HbA1c) and lipoprotein (a) levels were detected to be higher in patients with MAU ($p<0.05$). In the multivariate model, lipoprotein (a) (OR=1.015 p=0.004) and systolic BP (OR=1.052 p=0.000) increase the risk of MAU.

Conclusion: Dyslipidemia and impaired glycemic control are closely related to microalbuminuria. MAU follow-up should be done regularly in every diabetic patient as it can prevent and reduce the clinical and economic burden of diabetes complications.

Keywords: Diabetes mellitus; lipoprotein (a); microalbuminuria; risk factor

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder with complex pathophysiological mechanisms characterized by hyperglycemia, a physiologically abnormal condition represented by high plasma glucose levels. Hyperglycemia is caused by anomalies in insulin secretion and/or insulin effect, and manifests as carbohydrate, fat and protein metabolic dysfunctions (1). DM is associated with long-term dysfunction of many organs such as the kidneys, heart and blood vessels, eyes, nervous system (2). DM prevalence is increasing rapidly all over the world due to unhealthy dietary habits, physical inactivity and urbanization (3).

Cardiovascular disease (CVD) is one of the most important causes of mortality and morbidity in patients with DM worldwide. CVD risk increases progressively as fasting plasma glucose (FPG) increases (4). With the increasing DM prevalence in Framingham Heart Study, DM-associated CVD risk was detected to be increased from 5.4% in 1952–1974 to 8.7% in 1975-1998 (5).

Microalbuminuria (MAU) is a well-known predictor of chronic kidney disease (CKD), CVD and mortality in DM patientsMAU is a simple method for assessing the risk of diabetic nephropathy and is very useful as it represents the first stage of diabetic kidney disease (6). Because MAU is reversible, regular MAU screening and timely therapeutic intervention have become standard therapy around the world (7). Microalbuminuria has been associated with vascular abnormalities such as endothelial dysfunction and reduced vascular dilatation (8).

Evaluation of factors associated with MAU development in patients with DM is important to determine whether such changes are due to underlying kidney pathology or associated with functional changes. Routine follow-up of

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microalbuminuria in diabetic patients is a cost-effective method to prevent complications that may develop. This study examined the relationship between MAU and other factors that are risk factors for CVD.

MATERIALS and METHODS

Our study was approved by Istanbul Training and Research Hospital Clinical Trials Ethics Committee with the decision numbered 926 and dated 23.06.2017. In our study, 300 type 2 DM patients without CVD who admitted to Istanbul Training and Research Hospital Diabetes Outpatient Clinic and Internal Diseases Outpatient Clinic between 01.07.2016 and 02.07.2017 were assessed retrospectively based on the findings and data at the time of admittance from the hospital's automation system and diabetes outpatient clinic follow-up files. The consents of the patients included in the study were obtained. Exclusion criteria were as following: Type 1 DM, monogenic DM sub-types, history of coronary angiography, vascular heart disease, other cardiopathies such as myocardial dysfunction and pericarditis; active infection, kidney failure; diabetic ketoacidosis; diabetic non-ketotic hyperosmolar coma, hypertensive attack, active cancer, hematological malignancies, rheumatic diseases, macroalbuminuria, urinary infections, nephrotic syndrome, secondary glomerular disease, kidney stones and tuberculosis and history of systemic steroid use.

Patients' height and weight measurements were taken using devices calibrated regularly in the outpatient clinic. Weight and Height measurements were measured with calibrated devices. Body mass index (BMI) was calculated as the weight (kg) divided by the square of height in meters (m^2). Blood pressure was measured at sitting position using standard mercury sphygmomanometer and properly sized cuff, and recorded in mmHg. Patients with blood pressure of >140/90 mmHg or currently using anti-hypertensive medication were labelled as hypertensive. Waist circumference (WC) was measured in the horizontal plane with a standard tape measure.

Biochemistry results were blood analysis data studied in the biochemistry lab after at least 8 hours of overnight fasting. Fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), uric acid, low-density lipoprotein (LDL), gamma glutamyl transferase (GGT), Lp(a) were documented from the hospital's data processing system. MAU was defined as urinary albumin-creatinine ratio being 30-300 mg/gr. All patients with DM were divided into two groups stratified by the presence or absence of microalbuminuria.

Statistical Analysis

Minimum and maximum, mean and median, standard deviation, frequency and ratio values were used for the descriptive statistics of data. Distribution analysis of the variables was performed using the Kolmogorov-Smirnov test. The analysis of the quantitative independent data was performed using sample t-test and mann-Whitney U test. The analysis of the qualitative independent data was performed using Chi-square test and Fisher's test when the conditions for Chi-square test were not met. The effect level was examined using univariate and multivariate logistic regression. Statistical analysis was done using SPSS 22.0.

RESULTS

The study included a total of 300 patients with the mean age of 58.9±10.1 years. Study subjects were divided into two groups stratified by the presence or absence of MAU. Age, sex, WC, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), GGT, uric acid, FPG, HbA1c, Lp(a), LDL levels were compared between the study and control group. The study population had more females than males (56.7%). 12.7% of the patients were in the obese (BMI>30) group. Table 1 shows all demographic data and laboratory data of the patients.

Table 1. Anthropometric and metabolic characteristics of the study group

Age (Year)	58.9 ± 10.1
Gender	
Male	43.3% (130)
Female	56.7% (170)
Waist Circumference (cm)	87.4 ± 8.8
BMI (kg/m²)	27.5 ± 2.5
<25	21.0% (63)
25-30	66.3% (199)
>30	12.7% (38)
SBP (mmHg)	127.1 ± 12.9
DBP (mmHg)	71.1 ± 12.2
FPG (mg/dL)	177.8 ± 71.0
Uric Acid (mg / dL)	5.1 ± 1.5
<6	75.3% (226)
>6	24.7% (74)
LDL (mg/dL)	154.4 ± 94.2
<70	5.7% (17)
70-100	18.7% (56)
>100	75.7% (227)
GGT (U/L)	32.0 ± 32.3
<55	91.0% (273)
>55	9.0% (27)
HbA1c (%)	12.8 ± 6.1
MAU (mg/g Cr)	63.7 ± 227.4
Lp(a) (mg/dL)	28.0 ± 29.2
<30	70.0% (210)
>30	30.0% (90)

Table 2 shows the comparison of CVD risk factors between microalbuminuric and normoalbuminuric groups. Both groups were similar in terms of age and gender distribution (p>0.05). While BMI, blood pressure, LDL levels were detected to be significantly higher in patients with MAU than the patients without MAU (p<0.05), waist circumference measurements, uric acid, GGT were similar for both groups. When the groups were compared for DM, FPG was detected to be similar for both groups, HbA1c was detected to be higher in diabetic patients with MAU (p<0.05). Being an important risk factor for CVD, Lp(a) is significantly higher in patients with MAU compared to the control group (p<0.05) (Figure 1).

In the univariate model between microalbuminuric and normoalbuminuric groups, BMI, Lp(a), SBP and DBP were observed to have significant (p<0.05) effect. In the multivariate model, Lp(a) and SBP value was observed to have independent significant (p<0.05) effect (Table 3).

Table 2. Comparison of CVD risk factors between microalbuminuric and normoalbuminuric groups

Age (Year)	Normoalbuminuria	Microalbuminuria	p
Gender	58.5 ± 10.0	59.4 ± 10.2	0.385
Male	47.9% (67)	39.4% (63)	0.741
Female	59.3% (83)	54.4% (87)	
Waist Circumference (cm)	86.4 ± 8.7	88.4 ± 8.8	0.057
BMI (kg/m^2)	27.1 ± 2.5	27.8 ± 2.5	0.012
<25	28.6% (40)	14.4% (23)	0.024
25-30	68.6% (96)	64.4% (103)	
>30	10.0% (14)	15.0% (24)	
SBP (mmHg)	123.1 ± 11.3	131.0 ± 13.2	0.000
DBP (mmHg)	68.4 ± 10.2	73.8 ± 13.4	0.000
Uric Acid (mg / dL)	5.1 ± 1.4	5.1 ± 1.5	0.677
<6	81.4% (114)	70.0% (112)	0.789
>6	25.7% (36)	23.8% (38)	
LDL (mg/dL)	95.5 ± 19.8	169.7 ± 45.3	0.000
<100	54.3% (38)	0% (0)	0.000
>100	45.7% (32)	100% (70)	
GGT (U/L)	31.8± 38.7	32.2 ± 24.4	0.179
<55	98.6% (138)	84.4% (135)	0.545
>55	8.6% (12)	9.4% (15)	
FPG (mg/dL)	173.4 ± 67.3	182.1 ± 74.5	0.249
HbA1c (%)	11.8 ± 4.9	13.7 ± 5.9	0.000
MAU (mg/g Cr)	9.1 ± 7.1	178.3 ± 93.2	0.000
Lp(a) (mg/dL)	22.3 ± 25.1	33.7 ± 31.9	0.000
<30	89.3% (125)	53.1% (85)	0.000
>30	17.9% (25)	40.6% (65)	

Table 3. Logistic regression analysis of MAU and independent variables

	Single Variable Model			Multivariate Model		
	OR	95% CI	p	OR	95% CI	p
Age (Year)	1.008	0.986 - 1.031	0.465			
Waist Circumference (cm)	1.026	0.999 - 1.053	0.057			
BMI (kg/m^2)	1.124	1.025 - 1.233	0.013			
FPG (mg/dL)	1.002	0.999 - 1.005	0.286			
Uric Acid (mg / dL)	0.997	0.853 - 1.165	0.965			
LDL (mg/dL)	1.000	0.998 - 1.003	0.895			
GGT (U/L)	1.000	0.993 - 1.007	0.919			
HbA1c (%)	1.001	0.996 - 1.005	0.753			
Lp (a) (mg/dL)	1.016	1.006 - 1.026	0.001	1.015	1.005- 1.025	0.004
SBP (mmHg)	1.054	1.032 - 1.075	0.000	1.052	1.052 – 1.074	0.000
DBP (mmHg)	1.038	1.018 - 0.059	0.000			

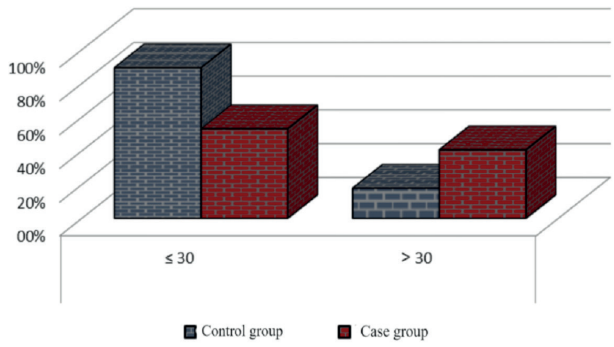

Figure 1. Comparison of Lp (a) level between microalbuminuric and normoalbuminuric groups

DISCUSSION

This study was performed to assess the relationship between MAU and CVD risk factors in patients with DM. We found that MAU risk is strongly correlated with hyperglycemia level, BMI and LDL. Furthermore, Lp(a) was found to be an independent risk factor in the logistic regression analysis.

MAU is accepted as the earliest detectable indicator of diabetic nephropathy, and is an independent risk factor for proteinuria progression n(9). Moreover, reducing albumin excretion is a therapeutic target in diabetic nephropathy (10). MAU prevalence varies between 14.2% and 36.3% in different ethnic groups. United Kingdom Prospective Diabetes Study (UKPDS) shows that progression to MAU is seen in approx. 2% of the normoalbuminuric DM patients, and progression to macroalbuminuria is seen in 2.8% of the patients with MAU (11).

Obesity is associated with MAU development in both type 1 and type 2 DM. The Australian Diabetes, Obesity and Lifestyle Study identified the BMI as an independent risk factor for albuminuria (12). In a study performed in patients with type 2 DM, MAU prevalence was detected to be 27.2% and WC measurement was found to be a risk factor for MAU with no relating being found with BMI (13). Similarly, in their study, Afkhami et al. did not detected an association between BMI and MAU (14). The fact that no correlation was detected between BMI and MAU in these studies was linked to patients' weight loss due to catabolic process caused by poorly controlled diabetes. Similar contradictory results are also present in the studies examining the relationship between BMI and MAU in non-diabetic patients. In a study performed by Minoo et al. in non-diabetic individuals, no increase was detected in MAU in subjects with a BMI of >30 kg/m^2 (15). In our study, BMI was detected to be higher in patients with MAU compared to the control group.

Studies support the opinion that intraglomerular pressure increase is the leading factor causing MAU (16). In their study in hypertensive individuals, Bavikar et al. demonstrated that there is a strong correlation between hypertension and MAU (17). In another study, however, this correlation between hypertension and MAU could not be shown (18). In our study, both SBP and DBP values in patients with MAU were detected to be higher than the control group. It can be concluded that this contradictory results are because of the fact that the duration during which the patients were hypertensive and the exact blood pressure levels during this time could not be clearly detected.

The pathogenesis of diabetic nephropathy is complex and yet to be elucidated. In animal models, it was shown that hyperuricemia may cause low-grade kidney damage without the accumulation of uric acid crystals (19). In the studies performed in diabetic mice, it was shown that allopurinol treatment reduces uric acid levels and improves tubulointerstitial damage (20). In a study in diabetic patients, serum uric acid level and MAU were found to be associated with nephropathy development (21). In our study, no significant difference was detected in terms of uric acid levels between microalbuminuric and normoalbuminuric groups. In their study in male diabetic patients, Fukui et al. detected higher serum uric acid level in patients with MAU(22). The fact that only male patients were included in this study might have affected the results due to muscle mass. The lack of difference between the groups could also be due to the use of serum uric acid lowering medications such as losartan, fenofibrate and atorvastatin in the patients in our study group.

Dyslipidemia correlates well with CVD both in diabetic and non-diabetic patients, and frequently accompanies to diabetic nephropathy. Studies have shown that dyslipidemia increases macrophage infiltration and excessive extracellular matrix production in glomeruli under diabetic conditions leading to the development of diabetic nephropathy(23). Many studies on dyslipidemia in type 2 DM have found that the LDL cholesterol levels are within normal range in patients with diabetic nephropathy (24). In the study by Tseng, no correlation was detected between LDL and albuminuria (25). In our study LDL level was found to be higher in the microalbuminuric group compared to the control group.

Epidemiological and genetic evidence suggests a correlation between lipoprotein Lp(a) and CVD (26). Nonetheless, while the Lp(a) metabolism is yet to be fully understood, a correlation was observed between renal dysfunction including diabetic nephropathy and higher Lp(a) levels in various sectional studies(27,28). In a prospective, observational cohort study Lp(a) level was demonstrated to be an independent prognostic factor for future development of CKD in patients with type 2 DM (29). In our study, Lp(a) levels in the microalbuminuric group were significantly higher. This positive correlation explains the high risk of current residual cardiovascular disease despite reaching target lipid levels.

The underlying risk factors for MAU are high blood pressure and poor glycemic control. HbA1c is a blood glucose control marker in diabetic patients (30). Higher HbA1c levels have been associated with the increased risk of microangiopathy development. In a study examining the relationship between MAU and HbA1c, microalbumin

levels have been found to be linearly correlated with diabetes duration and HbA1c(31). In their study, Memon et al. found that FPG and HbA1c levels are positively correlated with albuminuria level (32). Improvement from microalbuminuria and normoalbuminuria is also possible by strict glycemic control (33). While no significant difference was detected in terms of FPG between the groups in our study, HbA1c levels were detected to be significantly higher in the microalbuminuric group. The non-significant correlation between FPG and MAU might have occurred due to intra-day fluctuations.

LIMITATIONS

There are several limitations to this study. First, this study is cross-sectional study identified risk factors and therefore, establishes a definite cause and effect relationship between interaction and MAU is not possible. Second, we only obtained one microalbumin measurement. Lastly, the sample size is small; therefore, these results cannot be applied to all type 2 DM population. Therefore, large clinical studies are needed to establish a relationship between high MAU levels and type 2 DM.

CONCLUSION

MAU is a marker which allows early detection of diabetic nephropathy and also shows CVD risk. Annual MAU screening in DM patients is the most efficient method for detecting and treating diabetic nephropathy. Our study demonstrated that modifiable risk factors such as hypertension, LDL, Lp(a) and HbA1c are correlated with MAU in type 2 DM. Strict control of these factors will be protective against future development of diabetic nephropathy and CVD.

Competing Interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical Approval: Our study was approved by Istanbul Training and Research Hospital Clinical Trials Ethics Committee with the decision numbered 926 and dated 23.06.2017.

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