The relationship of microalbuminuria with left ventricular functions and silent myocardial ischemia in asymptomatic patients with type 2 diabetes

Tip 2 diyabetli asemptomatik hastalarda mikroalbüminüri ile sol ventrikül fonksiyonları ve sessiz miyokart iskemisi arasındaki ilişki

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Objectives: Recently, microalbuminuria (MA), a marker of advanced renal failure, has been shown to be related with cardiovascular disease especially in diabetic patients. This study was designed to investigate the relationship between MA and left ventricular functions and silent myocardial ischemia documented by exercise test in patients with type 2 diabetes mellitus.

Study design: The study included 50 asymptomatic patients (36 women, 14 men; mean age 63±7 years) with type 2 diabetes. All the patients underwent treadmill test and biochemical tests following transthoracic echocardiography. Microalbuminuria was diagnosed from a 24-hour urine sample on two different days and the patients were evaluated in two groups based on the presence (≥30 mg/dl) or absence (<30 mg/dl) of MA.

Results: Twelve patients (24%) were found to have MA. There were no significant differences between patients with and without (n=38; 76%) MA with regard to age, sex, blood pressure, cardiovascular risk factors, plasma glucose, cholesterol, and triglyceride levels, and parameters of renal function (p>0.05). The duration of diabetes was significantly longer in patients with MA (p=0.03). Echocardiographic findings showed no significant differences in left ventricular systolic and diastolic functions between patients with and without MA (p>0.05). Exercise test revealed ischemic changes in 21 patients (42%). The incidence of silent myocardial ischemia was significantly higher among patients with MA (9/12 and 75% vs. 12/38 and 31.6%, p<0.001).

Conclusion: Our data suggest that MA can be used as an important marker for coronary artery disease in patients with diabetes mellitus.

Key words: Albuminuria; cardiovascular diseases; coronary disease; diabetes mellitus, type 2/complications; exercise test; myocardial ischemia/etiology.

Amaç: Son yıllarda, ilerleyici böbrek yetersizliğinin bir belirteci olan mikroalbüminürinin (MA) özellikle diyabetik hastalarda kardiyovasküler hastalıkla da ilişkili olduğu gözlenmiştir. Bu çalışmada, tip 2 diyabetli asemptomatik hastalarda MA ile sol ventrikül fonksiyonları ve efor testinde saptanan sessiz miyokart iskemisi arasındaki ilişki araştırıldı.

Çalışma planı: Çalışmaya, kardiyak açıdan yakınmasız,tip 2 diyabet tanısı konan 50 hasta (36 kadın, 14 erkek; ort. yaş 63±7) alındı. Her hastaya transtorasik ekokardiyografik değerlendirmeyi takiben biyokimyasal değerlendirme ve egzersiz testi yapıldı. Her hastada iki ayrı günde 24 saatlik idrarda MA düzeyi ölçüldü. Hastalar MA miktarının 30 mg'nin üzerinde ve altında olmasına göre sırasıyla MA(+) ve MA(–) olarak gruplandırıldı.

Bulgular: On iki hastada (%24) MA saptandı. Mikroalbüminüri olan ve olmayan (n=38; %76) hasta grupları arasında yaş, cinsiyet, kan basıncı, kardiyovasküler risk faktörleri, plazma glikoz, kolesterol ve trigliserit düzeyleri ve renal fonksiyon parametreleri açısından anlamlı farklılık bulunmadı (p>0.05). Mikroalbüminürili hastalarda diyabet süresi anlamlı derecede daha uzundu (p=0.03). Ekokardiyografik değerlendirmede, iki grup arasında sol ventrikül sistolik ve diyastolik fonksiyonları açısından anlamlı farklılık bulunmadı (p>0.05). Egzersiz testinde 21 hastada (%42) iskemik değişiklikler gözlendi. Sessiz miyokart iskemisi görülen hasta sayısı MA(+) grupta (9/12; %75), MA(–) gruba (12/38; %31.6) göre anlamlı derecede fazla idi (p<0.001).

Sonuç: Mikroalbüminürinin, diyabetik hastalarda koroner arter hastalığını öngörmede başvurulabilecek önemli bir belirteç olarak kullanılabileceği düşünüldü.

Anahtar sözcükler: Albüminüri; kardiyovasküler hastalık; koroner hastalık; diabetes mellitus, tip 2/komplikasyon; egzersiz testi; miyokart iskemisi/etyoloji.

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Coronary artery disease (CAD) is the leading cause of mortality and morbidity in non-insulin dependent diabetes mellitus (NIDDM).[1] The incidence of sudden death, myocardial infarction (MI) and the risk of death following MI is 2-3 fold higher in diabetics compared to nondiabetics.[2,3] The risk of developing congestive heart failure is also 2-5 fold higher in diabetics.[4,5] CAD may be asymptomatic or may present with MI, sudden death, arrhythmia or heart failure in diabetics.

Urinary albumin excretion indicates glomerular permeability and the increase in the excretion of urinary albumin is an indication of increased renal impairment.[6] Microalbuminuria (MA) which is defined as the daily excretion of 30-300 mg urinary albumin is an early stage marker of progressive renal insufficiency with renal impairment and proteinuria.[7,8] Microalbuminuria is also an early indicator of cardiovascular mortality.[6] Studies have identified MA in 25% of diabetics[9] and have demonstrated an association between cardiovascular event and MA levels in patients with NIDDM.[10]

This study was designed to investigate the relationship between MA levels and silent myocardial ischemia and the effects of this relationship on left ventricular systolic and diastolic functions in asymptomatic diabetics.

PATIENTS AND METHODS

The study included 50 patients (36 women, 14 men; mean age 63±7 years) with NIDDM history without any cardiac symptoms.

The diagnosis of non-insulin dependent diabetes mellitus was based on using antidiabetics or a fasting blood glucose ≥126 mg/dL measured two times or ≥200 mg/dL blood glucose at any hour, which are the criteria of diabetes defined by the World Health Organization (WHO).[11-13]

The exclusion criteria were as follows: previous MI (typical history, presence of one of the criteria for enzymatic variation, pathological Q wave in two or more leads in electrocardiography), uncontrolled hypertension (blood pressure >180/100 mmHg), complaints of angina pectoris, findings of congestive heart failure, severe aortic stenosis, atrial fibrillation and left bundle branch block, digoxin treatment, renal insufficiency, infection and other inflammatory disease, rheumatological disease and presence of a known malignant disease.

All patients underwent a detailed physical examination, medications used were recorded and cardiovascular risk factors were established.

Hypertension was defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg or using antihypertensives according to the "Joint National Committee VII" guidelines.[14] On the other hand, hyperlipidemia was defined as total cholesterol >200 mg/dL or LDL cholesterol >130 mg/dL or using lipid lowering drugs according to the "National Cholesterol Education Program Adult Treatment Panel III" guidelines.[15] Low HDL cholesterol level was defined as <40 mg/dL in women and <50 mg/dL in men according to the "National Cholesterol Education Program Adult Treatment Panel III" guidelines.[15] Patients who quitted cigarette smoking within the past 2 years and those who were still smoking were categorized as "cigarette smokers".

Following a-12-hour fasting, a 10 mL blood sample was drawn from the brachial vein into dry BD vacutainer tubes which did not contain any additives and 2 mL blood sample was drawn into BD vacutainer tube containing 7.5% EDTA with low tourniquet pressure. Total cholesterol, LDL cholesterol, HDL cholesterol, very low density lipoprotein, triglycerides, fasting plasma glucose, hemoglobin A1c (HbA1c), blood urea nitrogen (BUN), creatinine, sodium, potassium, and uric acid levels were measured. Fasting plasma glucose was measured from the serum utilizing glucose oxidase technique (Opera Bayer) and after being centrifuged at 3500 cycle for 10 minutes. Following this procedure, blood urea nitrogen was measured by urease, while creatinine was measured by alkaline pitrate nondeproteinization endpoint. On the other hand, LDL cholesterol level was measured by direct method, and HbA1c level was measured by immunoturbidimetric tests (Integra 800 Roche).

Glomerular filtration rate (GFH) was estimated by evaluating BUN, creatinine, age and sex of the patients using the Modification of Diet in Renal Disease (MDRD) formula.[16]

Since urinary albumin excretion was shown to vary above 40% at different times measured, MA levels were checked by urine samples which were collected between 08:00 A.M. and 08:00 A.M. of the following day, on two consecutive days (a-24-hour urine sample).[3,17,18] Simultaneously, creatinine clearances of the patients were evaluated. Patients with microalbuminuria >30 mg were grouped as MA (+), whereas patients with microalbuminuria <30 mg were grouped as MA (-).

Electrocardiography. Standard 12-lead electrocardiography (ECG) was performed on all patients. Baseline ECG results of the patients were evaluated in terms of changes in ST-T segment and arrhythmia. Findings of ST-segment depression ≥0.5 mm and presence of a sharp symmetric T-wave negativity were interpreted as ischemic-type ECG change, and these patients were excluded from the study.

Transthoracic echocardiography. Transthoracic echocardiography was performed on all patients using the GE Vingmed Vivid 3 Expert (Horten, Norway) and Siemens Acuson Sequoia C256 (Mountain View, CA, USA) equipments, and 2.5 and 3.5 MHz transducers in the left lateral decubitus position, before treadmill test. M-mode assessment was performed using the parasternal win-

Table 1. Comparison of cardiovascular risks factors and clinic data of study groups

	Microalbuminuria (+) (n=12)			Microalbuminuria (-) (n=38)			
	Number	Percentage	Mean±SD	Number	Percentage	Mean±SD	*P*
Age			64±9			63±7	0.65
Sex							0.07
Female	6	50.0		30	79.0		
Male	6	50.0		8	21.1		
Hypertension	11	91.7		33	86.8		0.55
Hyperlipidemia	4	33.3		9	23.7		0.50
Cigarette smoking	3	25.0		5	13.2		0.38
Family history	8	66.7		16	42.1		0.14
Obesity	9	75.0		19	50.0		0.12
Low HDL cholesterol level	5	41.7		9	23.7		0.22
Duration of diabetes mellitus (years)			11.4±6.7			6.8±5.5	**0.03**
Systolic blood pressure (mmHg)			142.6±20.5			140.4±14.4	0.33
Diastolic blood pressure (mmHg)			80.8±9.8			77.5±7.2	0.28
Control of diabetes mellitus							
Diet	2	16.7		12	31.6		0.22
Oral antidiabetics	7	58.3		23	60.5		0.32
Insulin	3	25.0		3	7.9		0.21
Medications used							
Angiotension converting enzyme inhibitors	5	41.7		20	52.6		0.34
Beta-blockers	3	25.0		12	31.6		0.66
Angiotension enzyme inhibitors	2	16.7		10	26.3		0.49
Calcium channel blockers	5	41.7		9	23.7		0.22
Statin	9	75.0		24	63.2		0.45
Aspirin	10	83.3		33	86.8		0.76

dows, while two-dimensional and Doppler assessment was performed using the parasternal and apical windows. The ejection fraction and valvular functions were evaluated by means of the modified Simpson method using the left ventricular end-diastolic diameter, left ventricular end-systolic diameter, interventricular and posterior wall thicknesses.[19] The left ventricular diastolic functions were evaluated using early diastolic flow (E-wave), atrial systolic (A-wave) velocities, E/A ratio, deceleration time (DT), isovolumetric relaxation time (IVRT) and early diastolic flow (Ea) from assessment of tissue Doppler imaging obtained from the mitral annulus level, and E/Ea parameters, through the mitral flow obtained from the tip of the mitral valve of the apical four space image. Patients who have wall motion disorder in the echocardiographic evaluation were excluded from the study.

Exercise test. Exercise tests in the Bruce protocol were performed on all patients using the Cardiosis device. 12-lead ECG recordings were obtained during the test. Blood pressures of the patients were measured before the test, every three minutes during the test and after the test. Test interruption criteria were considered in case of a horizontal or vertical ST depression ≥1 mm, ST elevation ≥1 mm compared to baseline ECG, >10% decrease in systolic blood pressure, no increase in heart rate or presence of bradycardia, blood pressure above 250/130 mmHg, grade 3-4 angina, development of severe arrhythmia, attaining target heart rate and being too tired to sustain the test. Exercise test was considered positive in case of horizontal and vertical ST segment depression ≥1 mm, development of angina during the test, and ≥10% decrease in systolic blood pressure.

Statistical analysis. The SPSS 11.0 program was used to evaluate findings obtained. In addition to complementary statistical methods, Kruskal-Wallis test was used to compare multiple quantitative data, while Mann-Whitney U test was used for paired comparison and Chi-square and Fischer exact test were used to compare qualitative data. Results were also assessed with 95% confidence interval and $p<0.05$ significance level or with 99% confidence interval and $p<0.01$ high significance level.

RESULTS

Twelve patients (24%) were found as MA (+), while 38 (76%) were found as MA (-). There were no significant differences between patients with and without MA

Table 2. Comparison of laboratory parameters

	Microalbuminuria (+) (n=12)	Microalbuminuria (-) (n=38)	*P*
Blood urea nitrogen (mg/dL)	16.2±6.1	15.3±3.7	0.91
Creatinine (mg/dL)	0.9±0.2	0.8±0.1	0.52
Hemoglobin A1c (mg/dL)	7.5±2.0	6.9±1.4	0.43
Glomerular filtration rate (ml/min)	84.3±23.6	86.3±19.5	0.65
Fasting plasma glucose (mg/dL)	141.3±29.5	142.0±40.6	0.69
Total cholesterol (mg/dL)	207.7±44.6	194.7±31.6	0.40
LDL cholesterol (mg/dL)	125.6±32.0	113.5±27.5	0.22
Triglyceride (mg/dL)	145.0±59.6	143.3±76.5	0.76

with regard to age and sex. No significant difference was also found between groups regarding cardiovascular risk factors (hypertension, cigarette smoking, family history of cardiovascular diseases, obesity and low HDL cholesterol level) ($p>0.05$). Systolic and diastolic blood pressures did not also show any significant difference ($p>0.05$). However, the duration of diabetes was significantly longer in MA (+) patients, compared to MA (-) patients (Table 1).

Diet was used to control diabetes in 28% of the 50 patients (n=14) recruited to the study, while 60% (n=30) received oral antidiabetics and 12% (n=6) received insulin therapy. There was no significant difference between groups regarding the treatments received. No significant difference was neither found regarding medications used (Table 1).

BUN, creatinine levels and GFR values which were examined for the evaluation of renal functions were found within normal range (Table 2). Although HbA1c level was slightly higher in MA (+) patients,the difference was not significant ($p>0.05$). Moreover, there was no significant difference between groups regarding plasma glucose, cholesterol and triglyceride levels.

Comparison of echocardiographic data between the groups demonstrated that there was no significant difference in terms of left ventricular diameter, wall thickness, left ventricular ejection fraction, E/A ratio, IVRT and DT (Table 3).

Effort capacity, the percentage of maximum heart rate, the highest systolic and diastolic blood pressure responses were assessed by exercise test (Table 4). No significant difference regarding effort capacity and percentage of maximum heart rate was found between groups ($p>0.05$). Of all patients included in the study, 21 (42%) had ischemic changes during the effort test. The number of patients with ischemic changes was significantly higher in the MA (+) group compared to the MA (-) group ($p<0.001$). 75% (9/12) of the patients in MA (+) group had silent ischemia, whereas 31.6% (12/38) of the patients in the MA (-) group had silent ischemia.

DISCUSSION

In Western countries, the prevalence of NIDDM is about %3-5, whereas it is 7.2% in Turkey where the prevalence of impaired glucose tolerance is 6.7%. We have a higher prevalence compared to Western countries.[21] MA

Table 3. Comparison of echocardiographic findings

	Microalbuminuria (+) (n=12)	Microalbuminuria (-) (n=38)	*P*
Left ventricular end-diastolic diameter (cm)	4.70±0.26	4.65±0.25	0.52
Left ventricular end-systolic diameter (cm)	3.02±0.30	3.01±0.31	0.46
Wall thickness (cm)	1.39±0.04	1.39±0.01	0.49
Left ventricular ejection fraction (%)	63.1±1.4	64.4±2.3	0.10
E/A ratio	0.8±0.3	0.7±0.2	0.17
Isovolumetric relaxation time (msn)	137.1±31.9	144.4±26.2	0.70
Deceleration time (msn)	301.3±73.8	325.7±63.0	0.43

Table 4. Comparison of results of exercise test

	Microalbuminuria (+) (n=12)	Microalbuminuria (-) (n=38)	*P*
Effort capacity (METS)	8.1±1.5	8.4±2.2	0.95
The highest percentage of heart rate	93.4±10.2	95.5±9.2	0.66
The highest systolic blood pressure (mmHg)	170.0±24.9	179.2±24.7	0.31
The highest diastolic blood pressure (mmHg)	80.0±7.4	85.8±8.3	0.06
Incidence of ischemic change (%)	75.0	31.6	**<0.001**

is encountered in approximately 25% of patients with diabetes mellitus.[9] Microalbuminuria is a strong and independent marker of cardiovascular diseases in diabetic patients.[22] Furthermore, it is a predictor of macrovascular complications of diabetes.[23]

Although microalbuminuria is defined as urinary albumin excretion >30 mg/day, studies have shown that MA levels suggesting an increase in cardiovascular risk were found to be considerably lower.[24,25] In our study the threshold value of MA was detected in the range of 30-300 mg/day. Further studies are required to investigate the lower limit of microalbuminuria as a predictor of cardiovascular diseases.

Dinneen et al.[26] demonstrated that MA increased the risk of cardiovascular mortality by 2.4 fold in patients with type 2 diabetes. It was reported that not only the presence of microalbuminuria but also the gradual increase in time in MA levels were responsible for an increase in the risk of cardiovascular diseases.[27]

Silent myocardial ischemia is the presence of objective ischemic findings with or without angina or angina-like symptoms. The prognosis of silent myocardial ischemia is worse in diabetics compared to nondiabetics.[28,29] The prevalence of silent myocardial ischemia was found to be 9-57% in diabetics.[30,31] The sensitivity of exercise test in the detection of silent myocardial ischemia was 75%, while the specificity was 77%.[32] However, a negative effort test may be sufficient to exclude coronary artery disease in this patient group. In our study, silent ischemia was detected in 21 patients (42%) using the exercise test. The prevalence of silent myocardial ischemia was found to be 75% in asymptomatic diabetic patients with microalbuminuria. This rate is notably higher than the percentage cited in the literature. This may be due to a higher age group of patients compared to those involved in other studies. Although studies suggested an association between male gender and MA,[21] a significant difference between MA and silent ischemia in male and female patients was not found in our study.

In our study, there was no significant difference between groups in terms of left ventricular systolic and diastolic functions. Diastolic dysfunction was observed in 52% of all patients. Mbanya et al.[18] showed that there was a direct relationship between MA and left ventricular mass, while there was an inverse association between MA and systolic functions. Guglielmi et al.[4] found that the frequency of diastolic dysfunction and left ventricular hypertrophy was significantly high in NIDDM patients with MA. Hypertensive patients were excluded from these two studies. However, 82% of the patients had hypertension in our study. It suggested that MA cannot be the only reason for diastolic dysfunction in the patient group. Shim et al.[33] detected subclinical impairment in myocardial systolic and diastolic functions of diabetic patients, assessed by Doppler *strain*. We did not find any significant difference between the two patient groups in our study regarding systolic and diastolic functions. However, standard parameters which were used to assess echocardiographic findings in this study may not be sufficient to demonstrate subclinical systolic and diastolic dysfunction.

Our study showed that silent myocardial ischemia can be seen in 75% of the patients with NIDDM presenting MA. It was also shown that the rate of silent myocardial ischemia was high (31.6%) even in asymptomatic and MA (-) patients.

The limitations of this study included a small sample size, presence of hypertension in some patients included in the study, unevaluated left ventricular mass of the patients and utilization of *treadmill* test alone to assess silent ischemia. More significant results may be obtained when studies are conducted with a larger study population and when echocardiography is used as a supporting measure.

Consequently, MA in diabetic patients may be used in clinical practice as an important predictor of CAD.

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