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Original Article

Correlation of Paraoxonas1/Arylesterase Enzyme Activity with Microalbuminuria in Type 2 Diabetes Mellitus

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ABSTRACT

Objective: The aim of this study is to investigate the relationship between paraoxonase 1/arylesterase activity which have antioxidant properties and microalbuminuria in patients with type 2 diabetic.

Methods: The study included 48 patients (24 women and 24 men) with type 2 diabetes mellitus and microalbuminuria and 17 healthy volunteers as the control group (8 women and 9 men). Demographic data of the patients (age, gender, chronic disease); height-weight-body mass index (BMI), waist circumference, systolic and diastolic blood pressure and biochemical tests, fasting blood glucose (FBG), HbA1c, total cholesterol, triglyceride, LDL, HDL, CRP, urea, creatinine levels and spot urine albumin/creatinine ratios were recorded. In addition, serum paraoxonase (PON) and arylesterase (ARE) levels were studied.

Results: PON and ARE levels were found to be significantly lower in the type 2 diabetes with microalbuminuria ($p<0.05$). No statistically significant correlation was detected between ARE and PON and other parameters in the patient group (Spearman Correlation Analysis). Based on the ROC curve analysis, the laboratory cut-point used to obtain the best predictive results for differentiating the diabetic patients from the controls was PON 8.85 U/mL (sensitivity 95.83; specificity 47.06) and ARE 5.47 ng/mL (sensitivity 93.75; specificity 47.06).

Conclusion: PON and ARE levels were found to be significantly lower in type 2 diabetes mellitus patients with microalbuminuria, and there was no relationship between PON1/ARE activity and microalbuminuria.

INTRODUCTION

Diabetes is a chronic disease requiring continuous medical care, where the organism cannot sufficiently benefit from carbohydrate, fat and proteins due to deficiency or defects of insulin.[1] The most important reason of morbidity and mortality in diabetes mellitus is macro and microvascular complications involving every organ containing veins. In this sense, diabetes mellitus involves multiorgan failure spread over a long period of time.[2] Diabetic nephropathy is an important health problem due to the development of end-stage renal failure in increasing numbers of patients.[3] One of the findings in diabetic nephropathy is microalbuminuria.[4]

Paraoxonase1 (PON1) is an enzyme with 354 amino acid glycoproteins in its structure with three activities. These are paraoxonase, arylesterase and diazoxonase.[5] In human serum, the PON1 enzyme is associated with HDL and is an enzyme accepted as having antioxidant functions. Experimental studies have shown that the PON1 enzyme is associated with the Apo-A1 and Apo-J (clusterin) proteins of HDL-cholesterol.[6,7] Genes coding PON1's are located on the q21-22 region of the 7th chromosome. The PON gene family has three members - PON1, PON2 and

PON3. PON2 and PON3 do not have lysine residue in the 105th position so they do not hydrolyze PON and are not found in plasma.[8]

Though PON and ARE are perceived as two separate enzymes, studies and research have shown that in human serum the PON enzyme, a product of a single gene, has both ARE and PON activity.[9]

Many studies have shown that PON1 enzyme activity is reduced in myocardial infarctus, familial hypercholesterolemia, diabetes and chronic kidney disorders.[6,10,11] In our study, we aimed to research the relationship between HDL-paraoxonase 1/arylesterase activity in type 2 diabetic patients with microalbuminuria.

MATERIALS AND METHODS

48 patients (24 women and 24 men) and 17 healthy volunteers (8 women and 9 men) who were enrolled to the internal medicine outpatient clinics of GOP Education and Research Hospital between 10.10.2018–31.03.2019, and diagnosed type 2 diabetes mellitus with microalbuminuria were contained in the study. Each case participating in the study was informed, their consent was obtained and they were allowed to associated in the study voluntarily.

Exclusion criteria for the study were cardiovascular disease, antioxidant vitamin or drug use, chronic infectious and inflammatory disease, active infection, chronic autoimmune disease and cancer, along with pregnancy; those under 18 years or over 75 years were also excluded.

Patients included in the study had demographic features (age, sex, chronic disease, and continuous drug use), body mass index (BMI), waist circumference (at the central point of the distance between arcus costarum and spina iliaca anterior-superior), systolic and diastolic blood pressure and biochemical tests (fasting blood glucose (FBG), HbA1c, urea, creatinine, glomerular filtration rate (GFR), total cholesterol, triglycerides, LDL, HDL, and CRP levels) recorded and serum ARE and PON levels measured. The glomerular filtration rate of patients was calculated based on the MDRD formula. The MDRD study group formula is 186 x (serum creatinine) -1.154 x (age) -0.203 x (0.742 if female) x (1.21 if of African origin). To identify microalbuminuria, patients had albumin/creatinine values measured in spot urine. If the albumin/creatinine ratio was 30-300 mg/g, it was assessed as microalbuminuria.

In addition to these tests, for ARE and PON levels, blood samples from subjects were left in biochemistry tubes with gel clot activator until clotting occurred and were then centrifuged for 10 minutes at 4000g to separate the serum. The separated serum was portioned and placed in additive-free Eppendorf tubes. Samples were stored at -80 until the day of study. The stored samples were studied with a Sunred ELISA kit. On the day of study, samples were left to come to room temperature and studied with arylesterase measurements using a micro ELISA kit (Sunred Biotechnology Company Catalog No: 201-12-0728) and a DAR800 brand micro ELISA reader at 450 nm wavelength. PON measurements used a commercial micro ELISA kit (Bioassay Technology Laboratory Catalog No: E0931Hu) with a DAR800 brand micro ELISA reader at 450 nm wavelength.

The study protocol was permitted by the Health Sciences University Taksim Training and Research Hospital Clinical Research Ethics Committee on 03/10/2018, decision number 85.

Statistical Analysis

Descriptive statistical methods (mean, standard deviation, frequency, ratio, minimum, and maximum) were used to evaluate the study data. The chi-square (or if appropriate Fisher's exact test) test was used to investigate the correlation between categoric variables. Distributions of parameters assessed by the Kolmogorov – Smirnov Test. The Mann Whitney U test was used to compare two independent variables that did not display normal distribution. The student t-test was used to compare two variables, which were independent and normally distributed. Spearman correlation analysis was used to measure the degree of association between two variables. ROC analysis was used with the aim of calculating the cut-off point and area under the curve (AUC). A p-value of 0.05 was determined to be statistically significant. Analyses were completed using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013) Program.

RESULTS

The study included a total of 48 patients and 17 controls. The patients were 50% female, 50% male, with a mean age of 48±11 years. For the controls, 47.06% were female and 52.94% were male with a mean age of 46±5 years. There were statistically significant differences between the patients and controls in terms of comorbid diseases, oral antidiabetic and insulin use and smoking habits ($p<0.05$). There were no significant differences in the distribution of age, sex, antihyperlipidemic drugs and alcohol use between the patients and controls ($p>0.05$) (Table 1).

The PON level in the patient group was 2.52±3.29 U/mL, the the PON level in the controls was 11.00±14.76 U/mL, and the PON levels in the patient group were found to be significantly lower than the controls ($p=0.006$). The ARE level in the patients was 3.33±1.54 ng/mL, the ARE level in the controls was 8.58±9.21 ng/mL, and the ARE levels in the patients were found to be significantly lower than the controls ($p=0.002$). The HDL level in the patients was 45±13 mg/dl, the HDL level in the controls was 53±90 mg/dl, and the HDL levels in the patients were found to be significantly lower than the controls ($p=0.02$). When type 2 diabetics with microalbuminuria and controls were compared in terms of the recorded parameters, there were statistically significant differences identified between the groups in terms of systolic and diastolic blood pressure,

Table 1. Comparison of groups according to parameters

	Controls (n=17)		Patients (n=48)		
	N	%	N	%	p
Sex					
Male	9	52.9	24	50.0	1.000
Female	8	47.1	24	50.0	
Comorbid Disease					
None	17	100.0	36	75.0	0.027
Hyperlipidemia	0	0.0	12	25.0	
Oral antidiabetics					
No	17	100.0	15	31.3	<0.001
Yes	0	0.0	33	68.8	
Insulin					
No	17	100.0	31	64.6	0.003
Yes	0	0.0	17	35.4	
Antihyperlipidemic					
No	17	100.0	42	87.5	0.327
Yes	0	0.0	6	12.5	
Smoking					
No	17	100.0	33	68.8	0.007
Yes	0	0.0	15	31.3	
Alcohol					
No	17	100.0	45	93.8	0.561
Yes	0	0.0	3	6.3	

*Chi square test

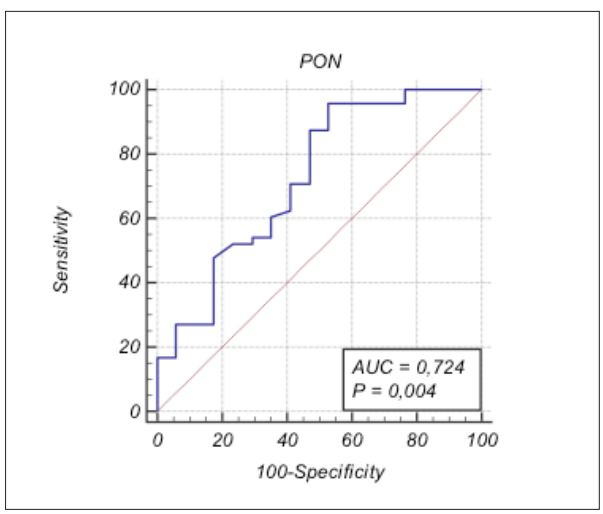

Figure 1. ROC curve analysis of serum PON.

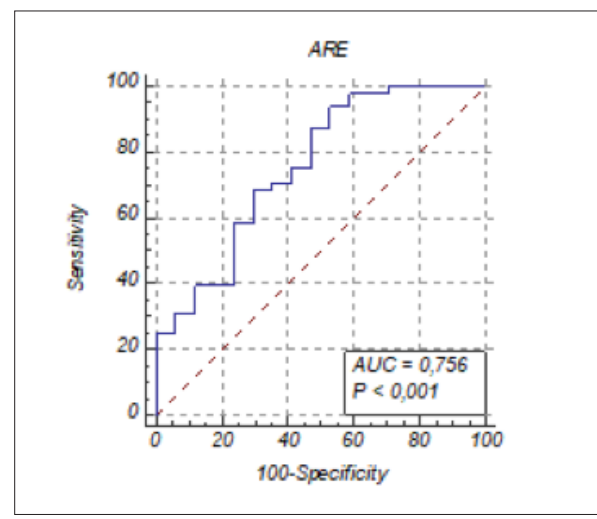

Figure 2. ROC curve analysis of serum ARE.

waist circumference, BMI, FBG, HbA1c, triglyceride, creatinine, and urine albumin/creatinine ($p<0.05$) (Table 2).

PON and ARE levels were significantly lower in the group with type 2 diabetes mellitus with microalbuminuria, but there was no direct relationship between PON1/ARE activity and microalbuminuria ($p>0.05$). The patients were not identified to have a statistically significant correlation between ARE and other parameters. In the patients, there was no significant correlation identified between PON1 and other parameters ($p>0.05$) (Table 3).

Table 2. Comparison of groups according to parameters

	Controls (n=17) Mean+SD Med. (Min.-Max.)	Patients (n=48) Mean+SD Med. (Min.-Max.)	p
Age (Years)	46±5.0	48±11	
	45 (31-52)	48 (28-68)	0.111
BMI (kg/m^2)	23.92±2.34	30.73±6.78	
	24.3(19.53-27.76)	29.4(22.66-64.06)	<0.001
Waist circumference (Cm)	84±11	104±11	
	86 (62-98)	103 (86-143)	<0.001
Systolic blood pressure (mmHg)	112±10	121±14	
	110 (100-130)	120 (100-170)	0.013
Diastolic blood pressure (mmHg)	72±11	78±10	
	70 (60-100)	80 (60-100)	0.031
Fasting glucose (mg/dl)	91±8.00	196±86	
	99 (89-132)	176 (78-399)	<0.001*
Hba1c (%)	5.1±0.60	9.0±2.4	
	5.6 (4-6.2)	8.8 (5.6-14.7)	<0.001*
Total cholesterol (mg/dl)	207±44	208±47	
	191 (140-298)	207 (111-354)	0.864*
Triglyceride (mg/dl)	121±76	238±204	
	96 (37-326)	204 (64-1416)	<0.001*
LDL (mg/dl)	130±34	122±38	
	126 (69-194)	121 (30-245)	0.420*
HDL (mg/dl)	53±9.0	45±13	
	53 (38-74)	43 (22-101)	0.002*
CRP (mg/l)	4.0±4.0	5.7±4.3	
	3 (0.4-14.9)	4.3 (0.6-17.7)	0.070*
Urea (mg/dl)	33±8.0	31±8.0	
	36 (16-46)	31 (15-51)	0.279*
Creatinine (mg/dl)	0.7±0.15	0.81±0.17	
	0.69 (0.44-1.16)	0.84 (0.56-1.1)	0.019*
GFR (ml/dk)	104±11	108±12	
	106 (84-120)	108 (76-134)	0.306*
Urine albumin/creatinine (mg/gr)	23.24±5.24	118.34±61.44	
	25 (11-29)	102 (41.1-300)	<0.001*
ARE (ng/mL)	8.58±9.21	3.33±1.54	
	8.58 (2.4-36.5)	3.33 (1.01-9.1)	0.002*
PON (U/mL)	11.0±14.76	2.52±3.29	
	11.0 (0.79-47)	2.52 (0.23-15.1)	0.006*

DM: Diabetes Mellitus; BMI: Body Mass Index; HbA1c: Hemoglobin A1c; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; CRP: C-Reactive Protein; GFR: Glomerular Filtration Rate; ARE: Arylesterase; PON: Paraoxonase Mann Whitney U test*. Student's t test.

Table 4. Receiver operating characteristic (ROC) curve for various cut off levels of PON and ARE in the differentiation of patients with DM patients from controls

Control vs. Patient	AUC	p-value	Cut-off	Sensitivity	Specificity
ARE	0.756	0.0004	≤5.47	93.75	47.06
PON	0.724	0.0042	≤8.85	95.83	47.06

ARE: Arylesterase; PON: Paraoxonase.

Table 3. Correlation of ARE and PON with other parameters (in the patient group)

Patients	ARE	PON
Age (Years)		
r	0.180	0.236
p	0.221	0.106
DM duration (years)		
r	-0.063	0.036
p	0.703	0.827
BMI (kg/m2)		
r	0.068	0.107
p	0.645	0.469
Waist circumference (cm)		
r	0.146	0.068
p	0.321	0.646
Systolic blood pressure (mmHg)		
r	0.077	0.095
p	0.604	0.519
Diastolic blood pressure (mmHg)		
r	0.070	-0.025
p	0.637	0.868
Fasting glucose (mg/dl)		
r	-0.212	-0.081
p	0.149	0.584
Hba1c (%)		
r	-0.108	-0.111
p	0.464	0.452
Total Cholesterol (mg/dl)		
r	0.081	0.100
p	0.585	0.499
Triglyceride (mg/dl)		
r	0.076	0.021
p	0.607	0.885
LDL (mg/dl)		
r	0.007	0.032
p	0.960	0.830
HDL (mg/dl)		
r	-0.058	0.040
p	0.697	0.787
CRP (mg/l)		
r	0.056	0.119
p	0.706	0.420
UREA (mg/dl)		
r	0.059	0.067
p	0.689	0.653
CREATININE (mg/dl)		
r	-0.088	-0.071
p	0.553	0.630
GFR (ml/dk)		
r	0.008	-0.051
p	0.956	0.729
Urine albumin/creatinine (mg/gr)		
r	-0.041	0.128
p	0.783	0.386

DM: Diabetes Mellitus. BMI: Body Mass Index. HbA1c: Hemoglobin A1c. LDL: Low Density Lipoprotein. HDL: High Density Lipoprotein. CRP: C-Reactive Protein. GFR: Glomerular Filtration Rate Spearman rank correlation test.

To identify whether ARE and PON1 levels were significant parameters for diabetes mellitus prediction, ROC analysis showed that the area under the curve (AUC) was significant. ARE and PON1 were significant parameters for diabetes mellitus prediction and it was determined that inclusion of values above or below the cut-off could be associated with diabetes mellitus (Figure 1, 2). Patients, who had ARE and PON levels lower than 5.47 ng/mL and 8.85 U/mL, were catching study group levels with a sensitivity of 93.75% and 95.83, a specificity of 47.06% and 47.06. (Table 4).

DISCUSSION

Some previous studies of diabetic patients have observed a significant reduction in PON1 serum concentration.[12-14] Additionally, diabetic patients had significantly reduced PON1 serum activity (arylesterase and paraoxonase) compared to healthy individuals.[12,15,16] A study by Susana Siewert et al.[17] found that type 2 diabetic patients had significantly lower PON1 activity compared to a controls. Changes in the antioxidative capacity of HDL particles in type 2 diabetic patients were seen to occur due to lower PON1 activity. In our study, the PON and ARE levels of the patients with diabetic microalbuminuria were significantly lower compared to those of the controls.

The increase of TG levels and simultaneous reduction in HDL concentration is consistent with the renowned relationship between the metabolism of lipoproteins rich in terms of TG with the maturation of HDL particles.[18] Given this relationship, current data prove that there is a significant increase in TG, VLDL and LDL levels, in addition to BMI, and a significant reduction in HDL in type 2 diabetic patients compared to those of controls. Additionally, the TG/HDL ratio and HOMA-IR recommended by McLaughlin et al.[19] as markers of insulin resistance and high atherogenic small and dense LDL particle ratios, is higher in type 2 diabetic patients. This situation is often associated with hypertriglyceridemia. All of these indicate that type 2 diabetes mellitus is marked by oxidative stress, reduced PON1/ARE activity and disrupted lipoprotein metabolism of TG, VLDL, HDL and LDL particles, and that type 2 diabetes is closely associated with vascular complications. In our study, the low HDL level, high TG level, increased waist circumference and BMI values in the patient group support the findings in these studies in the literature.

Additionally, in our study, increased smoking, and BMI and waist circumference measurements in the patient group may be considered to be connected to the low PON and ARE values. Ferretti et al.[20] compared the HDL-PON activity with HDL and low-density lipoprotein (LDL) within lipid peroxide levels between obese women and controls in a study of obese women. The results showed that obese individuals had significantly lower HDL-PON activity compared to the control group ($p<0.001$). Negative correlations between HDL-PON activity and HDL- and LDL-associated lipid peroxide levels confirm the correlation between PON activity and lipid peroxidation of lipo-

proteins. In conclusion, the study showed increased oxidative stress in LDL and HDL was associated with reduced HDL-PON activity in obese subjects. Lower PON activity and composition changes in HDL and LDL related to obesity may contribute to greater cardiovascular disease risk.

In our study, we investigated the correlation of changes in PON and ARE enzyme activities with microalbuminuria, a marker of nephropathy, which is one of the most common complications linked to type 2 diabetes mellitus. In the research, we analyzed enzyme activity in diabetic patients with microalbuminuria compared to that of controls. Some studies in the literature have proposed that PON may be connected with nephropathy. A study by Chengjiang Li & Qing Gu found that normoalbuminuric type 2 diabetic patients preserved HDL-PON1 activity; however, microalbuminuric or macroalbuminuric type 2 diabetic patients had significant reductions.[21] A 2017 study of type 1 diabetic children and adolescents by Ons Fekih et al.[22] showed that PON1 activity was inversely proportional to albumin excretion rate and that patients with nephropathy had reduced PON1 activity compared to that of patients without nephropathy. A study by Gawade et al.[23] in 2015 found a significant reduction in PON1 activity in patients with nephropathy compared to that in those without nephropathy and stated that PON1 may be used as a marker in the early period of diabetic nephropathy. Sabah et al.[24] found low serum PON1 enzyme activity in a diabetic patient group developing microvascular complications. The reduction in serum PON1 enzyme activity was concluded to be a determinative risk factor for microvascular complications in diabetes mellitus. Tabur et al.[25] grouped diabetic patients as normoalbuminuric and microalbuminuric and investigated PON and ARE enzyme activities along with oxidative stress causing diabetes, and concluded activity was lower in the microalbuminuria group.

In our study, the diabetic patient group with microalbuminuria had lower PON and ARE values compared to those of the healthy group. Based on the ROC curve analysis, the laboratory cut-point used to obtain the best predictive results for differentiating the diabetic patients from the controls was PON 8.85 U/mL (sensitivity 95.83; specificity 47.06) and ARE 5.47 ng/mL (sensitivity 93.75; specificity 47.06). Thus, a serum PON and ARE levels below 8.85 U/mL and 5.47 ng/mL may be used as a criterion to predict Diabetic patients. Correlation analysis found a positive correlation between PON and ARE, with no correlation identified between PON and ARE with microalbuminuria and other parameters. In this context, the lack of support in correlation analysis may be due to the low number of patients in the study group, variability of diabetic ages of patients and linked differences in the nephropathy development process, as well as antidiabetic and antihyperlipidemic treatments received by patients. Additionally, PON1 has genetic polymorphism and is an enzyme that exhibits variable activity with other antioxidant molecule levels and in the presence of inhibitory matter, which may have affected the results in our study. There is a need for further studies investigating groups containing more patients within the broader framework of the correlation between type 2 DM, dyslipidemia and nephropathy.

Study Limitations

The limitations of our study can be said to be single-center and the small number of patients. We believe that healthier results can be optained and gender differences can be evaluated, especially by increasing the number of patients.

Conclusion

In our study, the type 2 diabetes mellitus cases were determined lower PON1/ARE levels; however, there was relation found between microalbuminuria with PON1/ARE. Given this, although we did not show the direct relationship of PON and ARE with microalbuminuria, our analyses support other studies in the literature and we think microalbuminuria is linked to ARE and PON indirectly. ARE and PON1 are significant parameters for diabetes mellitus prediction. A decreased PON1/ARE activity may be a risk factor in the development of nephropathy in diabetes mellitus. PON1 is a newly-discovered molecule, and additional studies with larger sampling dimensions are required to better evaluate its role.

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Ethics Committee Approval

The study was approved by the Health Sciences University Taksim Training and Research Hospital Clinical Research Ethics Committee (Date: 03.10.2018, Decision No: 85).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: E.M.C.,B.B.; Design: O.M., E.M.C, BB; Supervision: O.M, B.B; Materials: E.M.C, O.Z, K.K ; Data collection &/or processing: E.M.C, O.Z, K.K, ; Analysis and/or interpretation: E.M.C, O.Z, K.K; Literature search: O.M, E.M.C, B.B; Writing: E.M.C, K.K; Critical review: O.M, B.B.

Conflict of Interest

None declared.

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Tip 2 Diyabet Mellitus'ta Paraoksonaz 1/Arilesteraz Enzim Aktivitesinin Mikroalbuminüri ile Korelasyonu

Amaç: Bu çalışmanın amacı tip 2 diyabetik hastalarda antioksidan özelliğe sahip paraoksonaz 1/arilesteraz aktivitesi ile mikroalbüminüri arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntem: Çalışmaya mikroalbuminürisi olan tip 2 diyabet 48 hasta (24 kadın ve 24 erkek) ve kontrol grubu olarak 17 sağlıklı (8 kadın ve 9 erkek) dahil edildi. Hastaların demografik verileri (yaş, cinsiyet, kronik hastalık); vücut kitle indeksi (BMI), bel çevresi, sistolik ve diyastolik tansiyonları ve biyokimyasal testler, açlık kan şekeri (AKŞ), HbA1c, total kolesterol, trigliserit, LDL, HDL, CRP, üre, kreatinin düzeyleri ve spot idrar albumin/kreatinin oranları kaydedildi. Ayrıca serum paraoksonaz (PON) ve arilesteraz (ARE) düzeylerine bakıldı.

Bulgular: Mikroalbüminürili tip 2 diyabetlilerde PON ve ARE düzeyleri anlamlı olarak düşük saptandı ($p<0.05$). Hasta grubunda ARE ile PON diğer parametreler arasında istatistiksel olarak anlamlı bir korelasyon saptanmadı (Spearman Korelasyon Analizi). ROC eğrisi analizine göre diyabet hastalarını kontrollerden ayırmada en iyi öngörücü sonuçları elde etmek için kullanılan laboratuvar kesim noktası PON 8.85 U/mL (duyarlılık 95.83; özgüllük 47.06) ve ARE 5 idi. 47 ng/mL (duyarlılık 93.75; özgüllük 47.06).

Sonuç: Mikroalbüminürisi olan tip 2 diyabet hastalarında PON ve ARE düzeyleri anlamlı olarak düşük bulundu ve PON1/ARE aktivitesi ile mikroalbuminüri arasında bir ilişki bulamadık.

Anahtar Sözcükler: Mikroalbuminüri; paraoksonaz/arilesteraz; tip 2 diyabet.