The relationship between paraoxonase-1 activity and coronary artery disease in patients with metabolic syndrome

Metabolik sendromlu olgularda koroner arter hastalığının paraoksonaz-1 aktivitesi ile ilişkisi

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ABSTRACT

Objectives: We investigated the correlation of serum paraoxonase-1 (PON-1) activity with coronary artery disease (CAD) in patients with metabolic syndrome (MetS).

Study design: The study included 21 patients (mean age 55±9 years) with MetS, stable angina pectoris, and angiographically shown CAD, 24 patients (mean age 51±10 years) with MetS and angiographically normal coroner arteries, and 28 healthy controls (mean age 49±12 years). Demographic and clinical characteristics, insulin levels, homeostasis model assessment of insulin resistance index, and PON-1 activity were assessed in all the groups. Severity of CAD was assessed using the Gensini score.

Results: Paraoxonase-1 activity was significantly lower in patients with MetS compared to the control group (p=0.02). The two MetS groups with and without CAD exhibited similar characteristics in all the parameters including PON-1 activity (p>0.05). Univariate correlation analysis performed in MetS-CAD patients showed a significant negative correlation between the Gensini score and PON-1 activity (r=-0.48, p=0.02). The overall PON-1 activity of all the subjects showed no correlation with the parameters examined.

Conclusion: Decreased PON-1 activity in patients with MetS compared to the control group suggests increased oxidative stress in MetS. Detection of similar PON-1 activity levels in MetS groups with and without CAD suggests that disturbance of oxidative-antioxidative balance occurs before the development of CAD. The negative correlation between the Gensini score and PON-1 activity implies that decreased PON-1 activity may be one of the etiologic causes of atherosclerotic progress in MetS.

ÖZET

Amaç: Bu çalışmada, metabolik sendrom (MetS) olan hastalarda serum paraoksonaz-1 (PON-1) aktivitesinin koroner arter hastalığı (KAH) ile ilişkisi araştırıldı.

Çalışma planı: Çalışmaya, MetS, kararlı angina pektoris ve anjiyografik olarak KAH bulunan 21 hasta (ort. yaş 55±9), anjiyografide koroner arterleri normal bulunan MetS'li 24 hasta (ort. yaş 51±10) ve 28 sağlıklı birey (ort. yaş 49±12) alındı. Hasta ve kontrol gruplarında demografik ve klinik özellikler, insülin düzeyi, homeostaz modeliyle değerlendirilen insülin direnci indeksi ve PON-1 aktivitesi değerlendirildi. Koroner arter hastalığının ciddiyeti Gensini skoruyla değerlendirildi.

Bulgular: Kontrol grubuyla karşılaştırıldığında, MetS'li hastalarda PON-1 aktivitesi anlamlı derecede daha düşük bulundu (p=0.02). Buna karşın, KAH'li ve KAH'siz MetS gruplarında PON-1 aktivitesi de dahil, incelenen hiçbir parametrede anlamlı fark saptanmadı (p>0.05). Koroner arter hastalığı olan grupta yapılan tekdeğişkenli korelasyon analizinde, Gensini skoru ile PON-1 aktivite düzeyi arasında anlamlı negatif ilişki gözlendi (r=-0.48, p=0.02). Tüm olguların alındığı analizde ise, PON-1 aktivitesi incelenen hiçbir parametre ile anlamlı ilişki göstermedi.

Sonuç: Kontrol grubuyla karşılaştırıldığında, MetS'li hastalarda PON-1 aktivitesindeki azalma oksidatif stres artışını düşündürmektedir. İki MetS grubunda (KAH'li ve KAH'siz) PON-1 aktivitesinin benzer bulunması, oksidatif-antioksidatif dengenin KAH oluşumu öncesinde bozulduğunu düşündürmektedir. Gensini skoru ile PON-1 aktivitesi arasındaki negatif ilişki ise, düşük PON-1 aktivitesinin MetS'li hastalarda ateroskleroz gelişmesinden sorumlu olan nedenlerden biri olduğunu akla getirmektedir.

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Metabolic syndrome is defined as a cluster of cardiometabolic abnormalities that increases an individual's risk for type 2 diabetes mellitus, coronary artery disease, and cardiovascular disease. The core components of MetS are glucose intolerance or diabetes, obesity, hypertension, and dyslipidemia specifically hypertriglyceridemia and low level of high-density lipoprotein cholesterol.[1]

Paraoxonase-1 is a protein composed of 354 amino acids.[2] The site of synthesis is the liver, and it is located on HDL-C in the serum.[3] Studies have shown that PON-1 confers protection of low-density lipoprotein cholesterol from oxidation by removing oxidized phospholipids on LDL-C.[4] Several studies have demonstrated decreased PON-1 activity in patients with CAD and MetS.[5-7] In the present study, we assessed PON-1 activity in patients with MetS and CAD.

PATIENTS AND METHODS

Patients

The study included 45 patients with MetS who underwent coronary angiography between May 2006 and January 2007. Of these, coronary angiography performed due to stable angina pectoris revealed at least one significant lesion in at least one major epicardial coronary artery in 21 patients (MetS-SAP, mean age 55±9 years), and 24 patients (mean age 51±10 years) underwent coronary angiography for chest pain and positive treadmill test and were found to have angiographically normal coronary arteries. Twenty-eight healthy subjects (mean age 49±12 years) comprised the control group. The control group included subjects who had a normal resting electrocardiogram and normal metabolic parameters, but presented with complaints suggestive of cardiac disease in the absence of a previous history of CAD. The study protocol was approved by our local ethics committee and written informed consent was obtained from all participants.

Exclusion criteria were the presence of the following: previously known CAD, SAP with normal coronary arteries or with <70% stenosis in major coronary arteries, acute coronary syndrome, cerebrovascular disease, diabetes mellitus, use of lipid-lowering drugs, known renal, hepatic, or immunologic disorders, obesity secondary to hypothyroidism or Cushing's disease, severe debilitating diseases, malignancy, and pregnancy or lactation.

Abbreviations:

CAD	*Coronary artery disease*
HDL-C	*High-density lipoprotein cholesterol*
LAD	*Left anterior descending*
LDL-C	*Low-density lipoprotein cholesterol*
MetS	*Metabolic syndrome*
NCA	*Normal coronary artery*
PON-1	*Paraoxonase-1*
SAP	*Stable angina pectoris*

Patients with a history of diabetes mellitus and/or hyperglycemia defined by the World Health Organization criteria were accepted as having diabetes mellitus. Patients with at least one first-degree relative having a history of CAD at an early age (<55 years for males, <65 years for females) or sudden cardiac death were considered potential candidates for CAD. Patients who were using tobacco products at the time of referral to our hospital and those who quitted smoking within the past year were considered smokers. Patients who used antihypertensive drugs or those who did not have a history of hypertension but had arterial pressure over 140/90 mmHg after three consecutive measurements were considered hypertensive patients. Body mass index was calculated by dividing body weight to the square of height (kg/m^2). Central obesity was defined as waist circumference ≥94 cm in men and ≥80 cm in women, according to the 2005 definition of the International Diabetes Federation.

Coronary angiography

All patients except those in the control group underwent diagnostic coronary angiography through the femoral artery and using standard images. Angiographic images were assessed by two independent cardiologists who were blind to clinical and laboratory findings of the patients. Any stenosis of ≥70% in at least one major coronary artery was considered significant.

The severity of coronary stenotic lesions was assessed with the Gensini score assigned based on the degree of luminal narrowing and its geographic importance. Reduction in lumen diameter and roentgenographic appearance of concentric lesions and eccentric plaques were evaluated. Reductions of 25%, 50%, 75%, 90%, 99%, and complete occlusion were rated with Gensini scores of 1, 2, 4, 8, 16, and 32, respectively. A multiplier was assigned for each main vascular segment based on the functional significance of the myocardial area supplied by that segment: 5 for the left main coronary artery; 2.5 for the proximal segment of the left anterior descending coronary artery; 2.5 for the proximal segment of the circumflex artery; 1.5 for the mid-segment of the LAD; 1.0 for the right coronary artery, the distal segment of the LAD, the

posterolateral artery, and the obtuse marginal artery; and 0.5 for other segments.[8] The Gensini score was expressed as the sum of the scores for all the coronary arteries.

Definition of metabolic syndrome

The diagnostic criteria of the International Diabetes Federation released in 2005 were used for the diagnosis of MetS, which include central obesity (waist circumference ≥94 cm for Europid men and ≥80 cm for Europid women, with ethnicity-specific values for other groups) plus any two of the following four factors: *(i)* increased triglyceride level (≥150 mg/dl) or specific lipid-lowering treatment; *(ii)* reduced HDL-C (<40 mg/dl in males and <50 mg/dl in females) or specific treatment for that lipid abnormality; *(iii)* raised blood pressure (systolic ≥130 mmHg or diastolic ≥85 mmHg) or treatment of previously diagnosed hypertension; *(iv)* raised fasting plasma glucose (≥100 mg/dl) or previously diagnosed type 2 diabetes.[9] However, as mentioned for the selection criteria, we excluded subjects with diabetes (fasting plasma glucose >125 mg/dl and two-hour plasma glucose >200 mg/dl in glucose tolerance test).

Laboratory tests and measurement of paraoxonase-1 activity

Fasting blood samples were obtained from the patients in the morning for the measurement of blood glucose, hemoglobin A_{1c} (HbA_{1c}), total cholesterol, triglycerides, LDL-C, and HDL-C. Total cholesterol, HDL-C, and triglyceride levels were measured using enzymatic colorimetric methods (Cobas Integra 800, Roche Diagnostics, Mannheim, Germany). For HbA_{1c}, hemolyzed blood samples were assayed by an immunoturbidimetric method (Cobas Integra 800, Roche). Fasting blood samples for PON-1 activity and insulin level were obtained in the morning before coronary angiography, stored at –70 °C, and analyzed collectively. PON-1 activity was measured spectrophotometrically as an activity increase in the rate of hydrolysis of paraoxon (diethyl-p-nitrophenylphosphate) as a substrate monitored at 25 °C and 412 nm wavelength. The activity was calculated

Table 1. Clinical and laboratory parameters of individuals with and without metabolic syndrome

	Metabolic syndrome (n=45)			Control (n=28)			*p*
	n	%	Mean±SD *or* Median (range)	n	%	Mean±SD *or* Median (range)	
Age (years)			54±11			49±12	0.30
Gender							0.49
Male	23	51.1		12	42.9		
Female	22	48.9		16	57.1		
Body mass index (kg/m^2)			29.7±4.1			26.1±2.3	**<0.001**
Waist circumference (cm)			99±7			86±4	**<0.001**
Hypertension	28	62.2		–			
Smoking	19	42.2		13	46.4		0.72
Family history	9	20.0		4	14.3		0.54
Fasting blood glucose (mg/dl)			100±15			79±8	**<0.001**
Impaired fasting glucose/ glucose tolerance	19	42.2		–			
Total cholesterol (mg/dl)			238±33			113±22	**<0.001**
HDL cholesterol (mg/dl)			40±9			45±6	**0.039**
LDL cholesterol (mg/dl)			118±30			92±24	**<0.001**
Triglyceride (mg/dl)			238±94			113±22	**<0.001**
Hemoglobin A_{1c} (%)			5.8±0.4			5.2±0.2	**<0.001**
Insulin (μIU/dl)			17.6 (9.4-45.5)			5.6 (4.0-8.5)	**<0.001**
HOMA-IR index			4.9 (0.2-15)			1.1 (0.1-2.1)	**<0.001**
Paraoxonase-1 (U/l)			72 (56-92)			123 (65-170)	**0.02**

HOMA-IR: Homeostasis model assessment of insulin resistance.

Table 2. Clinical and laboratory parameters of metabolic syndrome patients having normal coronary arteries and significant stenosis on coronary angiography

	Normal coronary artery (n=24)			Significant stenosis (n=21)			
	n	%	Mean±SD *or* Median (range)	n	%	Mean±SD *or* Median (range)	*p*
Age (years)			51±10			55±9	0.53
Gender							0.18
Male	10	41.7		13	61.9		
Female	14	58.3		8	38.1		
Body mass index (kg/m^2)			30.2±4.2			29.3±4.1	0.92
Waist circumference (cm)			100±7.9			97±7	0.91
Hypertension	14	58.3		14	66.7		0.56
Smoking	9	37.5		10	47.6		0.49
Family history	4	16.7		5	23.8		0.55
Fasting blood glucose (mg/dl)			100±14			100±17	0.94
Impaired fasting glucose/ glucose tolerance	11	45.8		8	38.1		0.60
Total cholesterol (mg/dl)			204±37			204±29	0.94
HDL cholesterol (mg/dl)			40±9			39±9	0.92
LDL cholesterol (mg/dl)			120±35			116±25	0.92
Triglyceride (mg/dl)			225±86			253±102	0.77
Hemoglobin A_{1c} (%)			5.8±0.4			5.8±0.4	0.91
Insulin (μIU/dl)			19.2 (6.3-48.9)			17.6 (10.8-34.4)	0.90
HOMA-IR index			5.0 (1.7-13)			4.7 (2.5-8.8)	0.88
Paraoxonase-1 (U/l)			81 (55-104)			70 (56-91)	0.36

HOMA-IR: Homeostasis model assessment of insulin resistance.

as the amount of p-nitrophenol generated at basal conditions using the molar absorption coefficient of 18.29 M^{-1} cm^{-1} and the results were expressed as U/l. Insulin levels were measured using the electrochemiluminescense immunoassay method (Moduler E-170, Roche Diagnostics). Homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated by the formula: fasting plasma glucose (mg/dl) x fasting plasma insulin (μIU/dl)/405.

Statistical analysis

All variables were tested for normal distribution using the Kolmogorov-Smirnov test. Variables with normal distribution were presented as mean ± standard deviation, whereas non-normally distributed variables were presented as median and range. Categorical variables were expressed as percentages and compared with the chi-square test or Fisher's exact test. In the comparison of continuous variables, differences between the groups of diagnosis were analyzed with one-way analysis of variance (ANOVA). Differences between the groups in continuous variables with or without normal distribution were determined using the Student's t-test or Mann-Whitney U-test, respectively. Univariate correlations of the Gensini score and PON-1 activity with other variables were analyzed using the Spearman's correlation coefficient. A *P* value of less than 0.05 was considered to be statistically significant. All analyses were performed using the SPSS software package version 11.5.

RESULTS

General characteristics of the MetS patients and control subjects are shown in Table 1. There were no significant differences between the two groups with respect to age, gender, smoking, and family history, but other risk factors weighed heavily against patients with MetS. Paraoxonase-1 activity was significantly lower in patients with MetS (p=0.02).

Table 3. The results of univariate correlation analysis

	r	*p*
Age	0.24	0.21
Body mass index	0.30	0.17
Waist circumference	0.06	0.80
Hypertension	-0.17	0.44
Fasting blood glucose	0.25	0.26
Impaired fasting glucose/ glucose tolerance	0.23	0.31
Total cholesterol	-0.10	0.68
HDL cholesterol	0.19	0.39
LDL cholesterol	0.09	0.67
Triglyceride	-0.26	0.24
Hemoglobin A_{1c}	0.16	0.51
Insulin	-0.19	0.46
HOMA-IR index	-0.04	0.87
Paraoxonase-1	-0.48	**0.02**

HOMA-IR: Homeostasis model assessment of insulin resistance.

Clinical and laboratory parameters of the two study groups with MetS are shown in Table 2. The two groups exhibited similar characteristics in all the variables examined including PON-1 activity.

Univariate correlation analysis performed in the MetS-SAP group showed a negative correlation between the Gensini score and PON-1 activity (r=-0.48, p=0.02) (Table 3). There was no correlation between the Gensini score and age, hypertension, anthropometric measurements, biochemical parameters, HOMA-IR, and insulin level. On the other hand, the overall PON-1 activity of all the subjects showed no correlation with HDL-C, triglycerides, insulin, HOMA-IR, smoking, and other parameters.

DISCUSSION

In the present study, patients with MetS exhibited significantly lower PON-1 activity than the control group and the two subgroups with MetS (MetS-SAP and MetS-NCA) had similar PON-1 activity. A negative correlation was found between the Gensini score and PON-1 activity in the MetS-SAP group.

An inverse relationship between HDL-C and CAD is already known. High-density lipoprotein cholesterol, which plays an anti-atherogenic role apart from inverse cholesterol transport, protects LDL-C against oxidative modification, which is attributed to PON-1 enzyme located on HDL-C. Paraoxonase-1 activity is determined by genetic, diet, life-style, and environmental factors.[10-12] In the study by Taskıran et al.[13] PON-1 M/L 55 polymorphism was found to be closely related with CAD, whereas no susceptibility to CAD was detected in subjects having PON-1 Q/R 192 polymorphism. Serum PON-1 activity in patients with type 1 and type 2 diabetes mellitus was reported to be lower independent of genotype.[14,15] Mackness et al.[16] demonstrated that measurement of PON-1 activity was a better predictor than genotype in terms of CAD. Considering this, genotype was not determined in patients with MetS and the control group.

There are a limited number of studies investigating PON-1 activity in patients with MetS. Sentí et al.[7] assessed antioxidant capacity and PON-1 activity in patients with MetS and found that antioxidant/oxidant balance was impaired progressively as severity of MetS increased. Consistently, increased oxidative stress and low antioxidant enzyme activity were detected in patients with MetS. Garin et al.[17] found a significantly lower PON-1 activity in patients with MetS compared to the control group. The findings of our study were consistent with those studies showing lower PON-1 activity in patients with MetS. However, there are studies not supporting those observations. Yılmaz et al.[18] evaluated PON-1 activity in female patients with MetS and found no difference in PON-1 activity compared to the control group. In addition, there was no difference in PON-1 activity between diabetic and nondiabetic patients with MetS. Tabur et al.[19] found that PON-1 activity was not affected in patients with MetS and obesity, both without diabetes. We think that these conflicting results regarding PON-1 activity might have originated from the higher number of female patients enrolled in these two studies. Mackness et al.[20] showed in a mouse model of MetS that PON-1 activity increased as a result of human PON-1 gene overexpression, resulting in decreases in the volume of atheromatous plaques, number of macrophages in the plaque, and oxidized LDL level. In addition to this experimental observation, many studies showed that PON-1 activity decreased as the severity of CAD increased. Gür et al.[21] demonstrated that the highest decreases in total antioxidant capacity of PON-1 activity and free sulphydryl groups occurred in CAD patients with three-vessel disease. They also detected that the Gensini score showed negative correlations with PON-1 activity and free sulphydryl groups and positive correlations with HDL level and diabetes. Granér et al.[22] investigated the association of PON-

1 activity and concentration with the severity and dimension of angiographic CAD. Paraoxonase-1 activity and concentration in patients with severe CAD were found lower and this association was confirmed by quantitative coronary angiographic assessment. Our study supports these observations with the finding of a negative correlation between the Gensini score and PON-1 activity in the MetS-SAP group.

Some studies found correlations between serum PON-1 activity and several lipid and lipoprotein parameters (HDL-C, triglyceride).[23,24] In the present study, PON-1 activity showed no correlations with metabolic parameters, HDL-C, triglyceride, insulin, and HOMA-IR index in the MetS group. We think that this may be related to broad genetic polymorphisms in the PON-1 gene and various factors such as sex, age, diet, medications, etc. Although many parameters were standardized in our study, it was impossible to standardize factors such as genetic polymorphism, diet, and drug use.

Limitations of the study

The most important limitations of the present study may be listed as small number of patients, lack of genotyping for PON-1 activity, and lack of examination of other oxidative stress markers.

In conclusion, we found that PON-1 activity decreased in patients with MetS. Although further studies with greater number of patients are needed to illuminate the subject, we think that decreased PON-1 activity may be one of the antioxidant parameters responsible for the progress of atherosclerosis in patients with MetS.

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Key words: Angina pectoris; aryldialkylphosphatase/blood; coronary artery disease; metabolic syndrome X.

Anahtar sözcükler: Angina pektoris; arildialkilfosfataz/kan; koroner arter hastalığı; metabolik sendrom X.