

Serum arylesterase activity is negatively correlated with inflammatory markers in patients with acute coronary syndromes

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ABSTRACT

الأهداف: لمعرفة ما إذا كان نشاط مصل (PON1) ونشاط (ARE) مرتبط مع العلامات الحيوية الالتهابية (بروكالسيتونين وسلسلة الخمائر الناقلة للبروتين (hs-CRP) وسلسلة تفاعل البروتين C - عالي الحساسية) لدى المرضى الذين يعانون من متلازمات شريانية تاجية حادة (ACS).

الطريقة: أجريت دراسة على شريحة مقطعية بقسم القلب والكيمياء الحيوية بجامعة يولوداج - بورصة - تركيا، خلال الفترة ما بين 11 أبريل 2007م وحتى 30 ديسمبر 2007م. تم فحص 78 مريض يعانون من متلازمات شريانية تاجية حادة (ACS) و 39 شخصا سليما كمجموعة التحكم. تم تقسيم المرضى الذين يعانون من متلازمات شريانية تاجية حادة (ACS) إلى ثلاث مجموعات وفقا لحالاتهم السريرية: ذبحة صدرية غير مستقرة UAP Braunwald III-B, n=25 مريض، إحتشاء غير منتظم في عضلة القلب NSTEMI 18 مريض وإحتشاء منتظم في عضلة القلب STEMI (35) مريض. تم قياس أنشطة مصل (PON1/ARE). كما تم قياس مستويات بروكالسيتونين وسلسلة الخمائر الناقلة للبروتين (hs-CRP) بواسطة المقاييس المناعية.

النتائج: كانت مستويات مصل (PON1/ARE) أقل بشكل ملحوظ لدى جميع المرضى في جميع المجموعات مقارنة مع مجموعة التحكم. لم يلاحظ وجود علاقة بين أنشطة مصل (PON1/ARE) ومستويات (كوليسترول HDL) من بين المرضى المصابين بمتلازمات شريانية تاجية حادة (ACS)، كان هنالك صلة عكسية لنشاط مصل (ARE) مع الخط القاعدي وبروكالسيتونين 48-ساعة ($r = -0.577, p = 0.009$ - $r = -0.642, p = 0.019$) وعلى التوالي، ومستويات (hs-CRP) ($r = -0.614, p = 0.03$ - $r = -0.719, p = 0.044$) على التوالي.

خاتمة: ينخفض نشاط مصل (ARE) لدى المرضى المصابين بمتلازمات شريانية تاجية حادة (ACS) ولديه علاقة عكسية مع العلامات الالتهابية.

Objectives: To examined whether serum paraoxonase (PON1) and arylesterase (ARE) activities are

correlated with inflammatory biomarkers (procalcitonin and high sensitivity C-reactive protein (hs-CRP) in patients with acute coronary syndrome (ACS).

Methods: This cross-sectional study was conducted at the Departments of Cardiology and Biochemistry, Uludag University School of Medicine, Bursa, Turkey, from April 2007 to December 2007. Seventy-eight consecutive patients with ACS and 39 healthy controls were investigated. Acute coronary syndrome patients were divided into 3 groups according to their clinical presentation: unstable angina pectoris (UAP) (Braunwald III-B, n=25), non-ST elevation myocardial infarction (NSTEMI) (n=18), and ST-elevation myocardial infarction (STEMI) (n=35). Serum PON1/ARE activities were measured spectrophotometrically. Levels of procalcitonin and hs-CRP were measured by immunoassay.

Results: Paraoxonase/ARE activities were significantly lower in all patient groups compared to controls. No correlation between PON1/ARE activities and high-density-cholesterol levels was seen. Among ACS patients, serum ARE activity correlated inversely with baseline and 48-hour procalcitonin ($r = -0.577, p = 0.009$, and $r = -0.642, p = 0.019$) and hs-CRP levels ($r = -0.614, p = 0.03$, and $r = -0.719, p = 0.044$).

Conclusion: Serum ARE activity is reduced in ACS patients and inversely correlated with inflammatory markers.

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It is generally accepted that oxidative stress and inflammation play a central role in atherosclerosis.^{1,2} Previous data have shown that oxidative modification of lipids associated with low-density lipoprotein (LDL) contributes to mechanisms of atherogenesis.³ Human serum paraoxonase (PON1) and arylesterase (ARE) are esterase enzymes that have lipophilic antioxidant characteristics.^{4,5} Paraoxonase and ARE activities are lower in diseases prone to development of premature atherosclerosis and are reduced in inflammatory diseases.⁶⁻⁸ Notably, PON1 null mice have been found to be susceptible to lipoprotein oxidation and atherosclerosis.⁹ Increased levels of high sensitivity C-reactive protein (hs-CRP) have been linked to atherosclerosis. Moreover, procalcitonin (PCT) level in the serum is an inflammatory marker, which has been associated with the extent of coronary artery disease.^{9,10} Acute coronary syndromes (ACS) are heterogeneous with respect to pathophysiology, presentation, prognosis, and response to therapy. The clinical spectrum of ACS comprises ST-segment elevation acute myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina pectoris (UAP).¹¹ ST-segment elevation acute myocardial infarction is caused by acute total coronary occlusion, whereas NSTEMI has been associated with the presence of vulnerable atherosclerotic plaque and sub-occlusive thrombosis.¹²⁻¹⁴ Previous studies have shown that mean levels of hs-CRP show a different pattern in the 3 ACS groups. Specifically, while baseline hs-CRP values were similar, a 3/4-fold increase has been observed in the STEMI group compared to either the NSTEMI or UAP groups.¹⁵ It is also an important finding that elevated plasma hs-CRP level confers a significantly increased risk of future fatal or nonfatal ischemic complications in STEMI or NSTEMI patients.¹⁶⁻¹⁸ Several studies have shown reduced serum PON1 and ARE activities in ACS patients.^{19,20} Although PON1 has been shown to inhibit the pro-inflammatory responses of macrophages and endothelial cells to oxidized and minimally modified LDL,²¹ little is known on the association between PON1/ARE activities and inflammatory markers in ACS patients. The aim of this study was to examine whether PON1/ARE activities are correlated with inflammatory biomarkers in patients with STEMI, NSTEMI, and UAP.

Methods. The study was conducted at the Departments of Cardiology and Biochemistry, Uludag University School of Medicine, Bursa, Turkey, between April and December 2007. A total of 78 consecutive patients with ACS were investigated. Acute coronary syndromes patients were divided into 3 groups according to their clinical presentation: unstable angina

pectoris (UAP) (Braunwald III-B, n=25), non-ST elevation myocardial infarction (NSTEMI) (n=18), and ST-elevation myocardial infarction (STEMI) (n=35). Acute coronary syndromes were defined according to the consensus document from the Joint European Society of Cardiology/American College of Cardiology Committee.²² The diagnosis of STEMI was defined as the concurrence of prolonged chest pain or discomfort with persistent ST-segment elevation of greater than 1 mm in 2 or more contiguous leads or with presumed new left bundle-branch block with cardiac enzymes (total creatine kinase and creatine kinase MB fraction [CK-MB]) above twice the upper normal limit. ST-segment elevation acute myocardial infarction locations (anterior, antero-septal, inferior, and inferior-posterior) were defined according to electrocardiographic and echocardiographic criteria. The diagnosis of non-STEMI included the presence of typical angina at rest associated with acute and transient ST-segment or T-wave changes with cardiac enzymes above twice the upper normal limit, raised troponin I levels to at least "high risk" values (>0.6 ng/mL), or both. Unstable angina pectoris was defined as resting chest pain occurring within the previous 48 hours without a recent myocardial infarct (according Braunwald class IIIB).²³ The control group (n=39, mean age: 54.0±10.1 years) was enrolled from the laboratory and hospital staff. All controls showed no clinical signs of ischemic cardiac or cerebrovascular disease. Exclusion criterion were as follows: presence of the New York Heart Association (NYHA) class IV heart failure or cardiogenic shock, severe bradycardia (heart rate <45 bpm), hypotension (systolic blood pressure <90 mm Hg), presence of second-degree or third-degree (complete) heart block, left bundle branch block, severe valvular disease, renal failure, hepatic dysfunction, known malignancy or other severe diseases or pregnancy. Patients who had undergone percutaneous transluminal coronary angioplasty or coronary artery bypass grafting upon admission were excluded. All ACS patients were treated with various cardiovascular drugs, including intravenous or oral nitrates, β -blockers, aspirin, heparin, angiotensin-converting enzyme inhibitors and statins. All STEMI patients were received thrombolytic therapy with tissue plasminogen activator (tPA).

The study protocol was approved by Uludag University Ethics Committee in accordance with the ethical principles of the Declaration of Helsinki. Informed consent was obtained from each patient.

Serum PON and ARE activities of ACS patients were determined upon emergency room admission. Procalcitonin and hs-CRP levels were measured on admission and 48 hours thereafter. The mean time between the onset of symptoms until blood sampling was 6 hours. Blood samples for determination of

procalcitonin, hs-CRP and serum PON1 activities were drawn from a cubital vein into plastic tubes. Serum was isolated by centrifugation and aliquots were kept frozen at -80°C for measurement of PON1 and ARE activities. Paraoxonase activity was measured by the rate of hydrolysis of paraoxon (diethyl-p-nitrophenylphosphate) by monitoring the increase in absorbance at 412 nm at 25°C. The amount of generated p-nitrophenol was calculated from the molar absorptivity coefficient at pH 10.5, which was 18 290 M⁻¹ cm⁻¹.²⁴ Serum ARE activity was determined by using phenylacetate as substrate. The reaction mixture contained 1.0 mM phenylacetate and 0.9 mM calcium chloride in 9.0 mM Tris-HCl buffer, pH 8.0. Enzymatic activity was calculated from the molar extinction coefficient 1310 M⁻¹ cm⁻¹. One unit of ARE activity is defined as 1 µmol phenol generated per minute under the above conditions and expressed as kU/l serum.²⁴ Serum levels of TC, HDL-C and triglycerides were determined using enzymatic assays (Abbott) on an Aeroset autoanalyzer. Low-density lipoprotein concentrations were calculated according to Friedewald's formula for serum samples with triglyceride values <400 mg/dL.²⁵

Measurement of procalcitonin and hs-CRP. High sensitivity C-reactive protein was measured by a latex-based immunoassay using the Dade-Behring BNII nephelometer (Dade Behring, Liederbach, Germany). The minimum detection limit of the method was 0.2 mg/dL and the reference range was <0.5 mg/dL. Levels of procalcitonin were determined using an

immunoluminometric assay (LUMI test PCT, Brahms Diagnostica, Berlin, Germany). The minimum detection limit of the method was 0.08 ng/dL and the reference range was < 0.5 ng/mL.

Statistical analysis. Variables are reported as percentages or means and standard deviations, as appropriate. Categorical variables were compared by the χ^2 test and continuous variables by the t-test or the Mann-Whitney U-test. Statistical comparisons between the 3 groups were performed by analysis of variance and the Kruskal-Wallis test. Spearman's correlation coefficients were used for examining the correlation between the study variables. Statistical analysis was performed using the SPSS version 13.0 software for Windows. A 2-tailed p value <0.05 was regarded as statistically significant.

Results. General characteristics of the study participants. The general characteristics of the study participants are summarized in Table 1. Seventy-eight patients (mean age 52.1 ± 9.62 years; 45 males and 33 females) and 39 healthy control subjects (mean age 54 ± 10.1 years; 22 males and 17 females) were included in the study. There were no significant intergroup differences in terms of demographic characteristics. Among patients with STEMI, 6 had antero-septal, 10 had anterior, 7 had inferior, and 12 had inferior-posterior myocardial infarction.

Enzymatic activities. Serum PON1 and ARE activities did not differ significantly in STEMI (113.5

Table 1 - Demographic and clinical characteristics of the study participants.

Variable	Controls (n = 39)	STEMI (n = 35)	NSTEMI (n = 18)	UAP (n = 25)	P-value
Age* (years)	54.0 ± 10.1	51.5 ± 9.7	52.1 ± 14.6	53.2 ± 10.2	0.26
Gender†					0.04†
Man	22 (56.4)	18 (59.3)	9 (55.5)	18 (55.9)	
Woman	17 (43.6)	12 (40.7)	7 (44.5)	14 (44.1)	
Hypertension†	14 (35.8)	11 (34.3)	7 (38.9)	12 (35.2)	0.33
Diabetes mellitus†	6 (15.3)	4 (12.5)	3 (16.7)	8 (23.5)	0.29
Smoking†	16 (41)	15 (46.8)	7 (38.9)	16 (46.7)	0.41
BMI* (kg/m ²)	26.6 ± 3.2	27.1 ± 3.1	26.7 ± 3.2	27.4 ± 2.8	0.38
Killip class*	-	1.8 ± 1.0	1.6 ± 0.9	1.5 ± 0.8	0.46
Treatment during hospital					
Aspirin†	-	32 (100)	18 (100)	34 (100)	0.82
Beta blockers†	-	29 (90.6)	16 (88.8)	30 (88.2)	0.71
Nitrates†	-	32 (100)	18 (100)	34 (100)	0.76
Heparin†	-	32 (100)	16 (88.8)	33 (97)	0.66
Lipid-lowering agents†	-	26 (81.2)	14 (77.7)	31 (91.1)	0.19

STEMI - ST elevation myocardial infarction, NSTEMI - non-ST elevation myocardial infarction, UAP - unstable angina pectoris, BMI - body mass index. Values are means ± SDs or numbers of patients (percentages) *Kruskal-Wallis test. †Chi-squared test.

The ratio of women in STEMI and NSTEMI groups was lower than in other groups.

Table 2 - Paraoxonase/arylesterase activities and lipid variables in the study participants.

Variable	Controls (n = 39)	STEMI (n = 35)	NSTEMI (n = 18)	UAP (n = 25)	p value*
Total-cholesterol (mg/dl)	205.0 ± 65.0	195.5 ± 37.2	198.6 ± 43.2	200.7 ± 40.8	0.39
HDL-cholesterol (mg/dl)	47.1 ± 11.6	47.0 ± 8.9	44.2 ± 11.5	42.4 ± 9.0	0.29
LDL-cholesterol (mg/dl)	129.5 ± 59.5	121.0 ± 31.0	135.2 ± 47.0	130.0 ± 32.0	0.55
Triglyceride (mg/dl)	144.1 ± 86.4	133.4 ± 77.4	149.2 ± 57.6	146.7 ± 60.7	0.47
Paraoxonase (U/L)	162 (98.2 - 302.1)	113.5 (64.2-236)	117.4 (81.1-224)	93.7 (72.4-241.1)	0.009 [†]
Arylesterase (kU/L)	78.5 (53.9 - 87)	52.1 (42.3-78.9)	50.8 (39.5-68.9)	47.2 (33.4-59.6)	<0.001 [‡]
Paraoxonase/HDL-C	5.34 ± 2.1	3.15 ± 2.08	3.31 ± 2.21	3.22 ± 2.19	<0.001 [‡]

*STEMI - ST elevation myocardial infarction, NSTEMI - non-ST elevation myocardial infarction, UAP - unstable angina pectoris, HDL - high density lipoprotein, LDL - low density lipoprotein. Values are means ± SDs, or medians (ranges), Kruskal-Wallis test, [†] $p=0.004$ for control versus STEMI; $p=0.001$ for control versus UAP, $p=0.004$ for control versus NSTEMI, $p<0.001$ for control versus STEMI, NSTEMI, and UAP.

Table 3 - Baseline and 48-hour (in percentage) concentrations of hs-CRP and procalcitonin across the ACS spectrum.

Variable	STEMI	NSTEMI	UAP	P value*
<i>hs-CRP (mg/dl)</i>				
Baseline	1.79 ± 1.50	1.34 ± 0.83	1.12 ± 1.71	0.036 [†]
48-hours	6.66 ± 4.19 ^c	4.44 ± 4.27 ^a	2.55 ± 2.41 ^b	0.004 [‡]
Percentage change	4.87 ± 4.07	3.10 ± 3.93	1.43 ± 2.04	0.010 [§]
<i>Procalcitonin (ng/ml)</i>				
Baseline	0.15 ± 0.06	0.14 ± 0.06	0.14 ± 0.05	0.91
48-hours	0.22 ± 0.04 ^a	0.22 ± 0.07 ^a	0.19 ± 0.08 ^a	0.21
Percentage change	0.07 ± 0.05	0.08 ± 0.04	0.05 ± 0.05	0.14

STEMI - ST elevation myocardial infarction, NSTEMI - non-ST elevation myocardial infarction, UAP - unstable angina pectoris, hs-CRP - high sensitivity C-reactive protein, ACS - acute coronary syndromes.

Values are expressed as means ± SD, *Kruskal-Wallis test, [†] $p=0.019$ for STEMI versus UAP; $p=0.041$ for NSTEMI versus UAP,

[‡] $p=0.001$ for STEMI versus UAP, [§] $p=0.002$ for STEMI versus UAP,

^a $p<0.01$ for within-group comparison between baseline and 48 hour,

^b $p<0.001$ for within-group comparison between baseline and 48 hours

^c $p<0.0001$ for within-group comparison between baseline and 48 hours

U/L), NSTEMI (117.4 U/L), and UAP patients (93.7 U/L). Compared with the controls, serum PON1 and ARE activities were lower in each patient group (Table 2). The PON1/HDL-C ratio was significantly higher in controls (5.34±2.1) compared to the STEMI (3.15±2.08), NSTEMI (3.31±2.21), and UAP groups (3.22±2.19). There was no correlation between serum PON1/ARE activities and HDL-C levels in both patients and controls ($p>0.05$). No difference in serum PON1/ARE activities was seen in STEMI patients according to myocardial infarction localization. Serum PON1 and ARE activities were not influenced by cardiovascular drugs ($p=0.35$).

Serum procalcitonin and hs-CRP levels. Baseline and 48-hour procalcitonin levels were similar in the entire ACS spectrum (STEMI, NSTEMI, and UAP). A significant increase in procalcitonin levels was seen at 48 hours in the STEMI (0.15 ± 0.06 versus 0.22 ± 0.04 ng/ml), NSTEMI (0.14 ± 0.06 versus 0.22 ± 0.07 ng/ml), and UAP groups (0.14 ± 0.05 versus 0.19 ± 0.08

ng/ml). The percentage changes in serum procalcitonin levels were similar across the ACS spectrum (Table 3). Changes in baseline and 48-hour hs-CRP levels were lower in the UAP group (1.43 ± 2.04 mg/dl) compared with either STEMI (4.87 ± 4.07 mg/dl) or NSTEMI groups (3.10 ± 3.93 mg/dl). As shown in Table 3, 48-hour hs-CRP values were significantly increased compared with baseline levels in each patient group.

Correlation between serum PON1/ARE activities and inflammatory markers. Among ACS patients, serum ARE activity correlated inversely with the baseline and 48-hour procalcitonin ($r=-0.577$, $p=0.009$ and $r=-0.642$, $p=0.019$) and hs-CRP levels ($r=-0.614$, $p=0.03$ and $r=-0.719$, $p=0.044$). No significant correlation was seen between serum PON1 activity and inflammatory markers in any of the study groups.

Discussion. The main findings of this study are 2-fold. First, ACS patients had reduced serum PON1/ARE activities compared with controls, and serum PON1

activity was not related to HDL-C levels. Second, the present study demonstrates for the first time that serum ARE activity is negatively associated with inflammatory markers in ACS patients. The onset of ACS may be explained by several physiopathological mechanisms.¹²⁻¹⁴ Most cases of acute STEMI are due to the sudden and complete obstruction of a coronary artery, whereas only a partial obstruction is generally found in NSTEMI and UAP.¹³ In the present study, serum PON1/ARE activities were similar across the entire ACS spectrum, thereby suggesting that serum PON1/ARE may not play a major role in relation to clinical presentation of ACS. It should be noted, however, that ACS patients had significantly lower serum PON1/ARE activities compared with controls. Our results paralleled those of previous studies,^{19,20} showing reduced serum PON1 activity in ACS individuals. Ayub et al¹⁹ have reported low PON1 concentrations and activities immediately after myocardial infarction compared with those of age and gender-matched controls. Previous studies have shown that, at the 42 days of infarction, serum PON1 activity was still significantly lower than controls, although it increased slowly.^{19,20} Van Lenten et al³ found that serum PON1 activity was reduced during the acute-phase reaction and suggested that HDL-C cannot protect LDL-C from oxidation during acute inflammation. In our study, low serum PON1/ARE activity might be due to the acute phase reaction occurring in patients with STEMI and NSTEMI. Since a lowered PON1/ARE activity was also found in UAP patients, who did not display an acute phase response, it is suggested that a reduced PON1 activity should be regarded as a predisposing factor rather than an acute phase reactant. In the present study, the ratio of female to male in the STEMI and NSTEMI groups was insignificantly lower than other patient groups. Kleemola et al²⁶ have previously shown that females display a slightly higher mean PON1 activity than males. Serum PON1 activity depends on the number of PON1 molecules associated with HDL-C rather than serum HDL-C levels.⁸ The reduced serum ARE activity in ACS patients might reflect a decrement in the enzyme protein synthesis. Notably, no correlation was seen between serum PON1 activity and HDL-C levels, thereby suggesting the existence of other factors influencing serum PON1 activity. There are several factors that may influence PON1 activity including PON1 gene polymorphisms, dietary and life-style factors such as vitamin C and E intake, smoking and alcohol intake.²⁷⁻³⁰ Paraoxonase-containing HDL-C particles constitute a very small fraction of total plasma HDL-C, and serum PON1 activity depends on the number of PON1 molecules associated with HDL-C rather than the serum HDL-C levels.^{8,29} Mackness et

al³⁰ have previously shown that the decrease in PON1 observed in diabetic patients is independent of changes in HDL-C. In the present study, we have shown that serum ARE activity is decreased in subjects with ACS and is inversely correlated with inflammatory biomarkers, thereby suggesting a potential modulatory role of this enzyme on vascular inflammation.

Several limitations are inherent in the present study. First, our study included a relatively small number of patients. Another limitation is that PON1 activities were only measured upon admission. Paraoxonase/ARE activities were measured in the control group, but inflammatory indexes were not determined in controls. Serum PON1/ARE activities in ACS patients were lower than controls. Our study was cross-sectional in nature, and thus we cannot establish whether the reduction of serum PON1/ARE activities was a cause or a consequence of ACS. Sequential blood sampling may be needed to investigate this issue. Additionally, oxidative stress markers were not investigated in the present study. Finally, the PON1 allele distribution was not determined.

In conclusion, the present study suggests that reduced serum PON1/ARE activities and increased levels of inflammatory markers might reflect different facets of early pathophysiological mechanisms involved in ACS. Further studies are warranted to shed more light on the therapeutic implications of our observations.

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