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Original Contribution

Paraoxanase as an indicator of myocardial ischemia and its utility in determining extension of ischemia☆,☆☆

Ali Kemal Erenler, MD [a,*], Ramazan Kocabaş, MD [b], Tolga Doğan, MD [c], Hacı Kemal Erdemli, MD [b], Mücahit Yetim, MD [c]

[a] Department of Emergency Medicine, Hitit University, Çorum Education and Research Hospital, Çorum, Turkey
[b] Department of Biochemistry, Hitit University, Çorum Education and Research Hospital, Çorum, Turkey
[c] Department of Cardiology, Hitit University, Çorum Education and Research Hospital, Çorum, Turkey

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ABSTRACT

Background: The aim of this study was to investigate Paraoxanase 1 (PON-1) activity in patients with ST-elevated and non–ST-elevated acute myocardial infarction (AMI) and to determine its correlation with Gensini scores (GSs).

Methods: A total of 109 patients with AMI and 58 healthy subjects as control group were included in the study. Patients were divided into 2 subgroups as ST-elevated and non–ST-elevated AMI patients (Group I and II, respectively). Controls were named as Group III. PON-1 activity was determined on admission to emergency department for each group. In addition, GSs for patient groups were determined. Then, groups were compared according to their results.

Results: PON-1 levels in Group I and II were significantly lower when compared to Group III. Median GSs for Group I and II were 60 and 64, respectively. The cut-off value of PON-1 for diagnosis of AMI was ≤180 U/L, which was identified by receiver characteristics receiver curve analysis. However, we could not determine a significant relationship between serum PON-1 levels and GSs in patients with AMI.

Conclusion: PON-1 levels measured on admission to emergency department may be used to rule out AMI. PON-1 levels in AMI patients are found to be inefficient in determining extension of ischemia measured by GS.

1. Introduction

Atherosclerosis and acute myocardial infarction (AMI) is a leading cause of death worldwide. Inflammatory process has been known to play an important role in the initiation, progression, and destabilization of atherosclerosis [1]

Paraoxanases (PONs) compose a family with three members (Paraoxanase 1, 2, 3) that have various roles in multiple biochemical pathways including inflammation [2]. Paraoxanase 1(PON-1) is the most studied enzyme of the family. It is synthesized primarily in the liver and appears mainly in serum, where is associated to high-density lipoproteins (HDL) [3]. HDL is a well characterized protective factor for cardiovascular disease [4]. An increased level of HDL has been reported to be associated with a decreased risk for coronary artery disease. This protective effect of HDL against atherosclerosis has been at least partly attributed to enzymes (such as PON-1) associated with HDL [5]. An interaction of myeloperoxidase–apoAI-PON-1 on HDL surface that seems to be associated with atherogenesis [6].

PON-1 plays a significant role in delaying/inhibiting the oxidation of both low-density lipoprotein (LDL) and HDL particles. By virtue of its actions like prevention of accumulation of lipid peroxides in LDL, stimulation of breakdown by hydrolysis of lipid peroxides, and protection against lipoprotein oxidation, PON-1 has a protective role against atherosclerosis and cardiovascular disease [3,7–10].

In this study, we aimed to investigate PON-1 activity in patients with AMI and sought its relationship with Gensini scores (GS).

The GS is an angiographic scoring system that assesses the severity and extension of coronary artery disease (CAD) [11]. It is calculated for each coronary stenosis based on the degree of luminal narrowing and its localization [12].

2. Materials and methods

After ethical approval from local ethics committee, we prospectively collected medical history, current medical data and blood samples of 109 (79 males and 30 females) consecutive patients with AMI admitted to our emergency department due to chest pain. Age- and gender-matched 58 healthy individuals were selected as control group. According to electrocardiogram and cardiac marker results, patient group was divided into 2 subgroups as patients with ST-elevated MI (group I) and patients with non–ST-elevated MI (group II). Control group was given the name group III.

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* Corresponding author at: Bahçelievler Mah. Çamlık Cd, No:2, Çorum, Turkey. Tel.: +90 5324475563; fax: +90 364 223 03 23.
E-mail addresses: akerenler@hotmail.com (A.K. Erenler), ramazankocabas@gmail.com (R. Kocabaş), tolga_dogan80@yahoo.com (T. Doğan), hkemal@hotmail.com (H.K. Erdemli), mucahityetim@hotmail.com (M. Yetim).

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Blood samples of the patients for PON-1 activity were taken on admission after confirmation of MI. ST-elevated MI was diagnosed if there was ST-segment elevation (greater than or equal to) 0.1 mV in 2 or more contiguous leads, and non–ST-elevated MI was diagnosed if electrocardiogram was non-diagnostic and cardiac troponin I (cTnI) was positive (>0.1 ng/ml). Then, patients with AMI have undergone coronary angiography.

The severity of CAD was evaluated by GS assessment system, which was defined according to stenosis severity as 1 point for <25% stenosis, 2 points for 26% to 50% stenosis, 4 points for 51% to 75% stenosis, 8 points for 76% to 90% stenosis, and 32 points for total occlusion. The score was then multiplied by a factor that represents the importance of the lesion's position in the coronary arterial system. For example, 5 for the left main, 2.5 for the proximal left anterior descending or proximal left circumflex, 1.5 for the mid-region, and 1 for the distal left anterior descending arteries [13].

All patients underwent serial cTnI testing at presentation and 6 h later as per institutional protocol for management of acute chest pain patients.

Routine serum biochemical variables including glucose, HDL, LDL, triglycerides, and albumin were analyzed using standard laboratory methods (Beckmann Coulter AU5800 Autoanalyser, Beckmann Coulter Inc, Brea, California, US).

Patients with MI (either ST-elevated or non–ST-elevated) in all ages were included into the study. Patients with co-morbidities that might elevate cTnI levels were excluded (eg, renal diseases, pulmonary embolism, sepsis, heart failure, exercise, pericarditis/myocarditis, cardiotoxic chemotherapy).

Serum PON-1 levels were measured using commercially available kits (Relassay, Gaziantep, Turkey). PON-1 activity was determined using paraoxon substrate. The rate of hydrolysis of paraoxon was measured by monitoring the increase in absorbance at 412 nm and 37°C due to the formation of p-nitrophenol. PON-1 activity was expressed as U/L and defined as 1 mmol p-nitrophenol generated per minute under well-established conditions.

All statistical analyses were made using the Statistical Package for the Social Sciences (SPSS) for Windows version 21.0 (SPSS, Inc, Chicago, IL) software program. Normal distribution of data was detected by Kolomogorov-Smirnov test. All the study variables were presented as median (95% confidential interval). Mann–Whitney *U* test (for independent samples) were used to compare the groups. Spearman's correlation coefficient was used to test the strength of association between the variables. Stepwise multivariate linear regression analysis was undertaken to determine factors affecting serum PON-1 levels. To determine a cut-off value for PON-1 in AMI, Receiver operating characteristic (ROC) analysis was performed. $P < .05$ was accepted as statistically significant.

3. Results

Our study revealed that PON-1 levels in Group I and II were significantly lower when compared to Group III. We also determined that type of AMI (ST-elevated or non–ST-elevated) did not affect PON-1 levels. Similarly HDL levels in group I and II were significantly lower than in group III.

In our study, serum albumin and Ca levels were lower in MI Groups when compared to controls.

While Alanine transaminase (ALT) was significantly lower in non–ST-elevated MI group (group II), AST was significantly lower in the ST-elevated group (group I).

Clinical and laboratory findings of the patients are summarized in Table 1.

We also demonstrated that there is a positive correlation between PON-1 and HDL and albumin.

Mean GSs for Group I and II were 60 and 64, respectively.

We could not determine a significant relationship between serum PON-1 levels and GSs in patients with AMI.

The cut-off value of PON-1 to rule out diagnosis of AMI was ≥180 U/L, which was identified by ROC analysis. The area under the curve was 0.676 (0.599–0.746, $P < .001$, sensitivity: 86.4%, specificity: 44.8%), which indicates good discriminative power. In Figure, ROC curve for PON-1 is shown.

In patients with AMI, PON-1 level was correlated with LDL and cholesterol. We also determined a negative correlation between PON-1 levels and age. When regression analysis was performed for correlated variables, it was determined that serum PON-1 levels were associated with LDL and AMI (R^2-adjusted = 0.099, $P < .001$). Results for regression analysis are summarized in Table 2.

4. Discussion

This study revealed that PON-1 activity in patients with AMI may be used in diagnosis of both ST-elevated and non–ST-elevated MI. However, its usefulness in predicting extension of ischemia is limited.

Relationship between PON-1 activity and MI was assessed in a number of studies in literature.

In their study, Shenekwar et al reported that a decreased PON-1 activity might be a risk factor for CAD, which is likely to be explained by derangement of PON-1 activity towards lipid peroxidation. They also suggested that serum antioxidant activity of PON-1 was an important factor which provided protection from oxidative stress and lipid peroxidation in CAD [14].

Mackness et al reported that low PON-1 activity was associated with coronary heart disease presence [15]. In another study, the mean serum PON activity was found to be lowest in AMI patients when compared to CAD patients and controls [16].

Our results revealed that PON-1 indicates MI with a cutoff value of 180 U/L. In patient groups (Groups I and II) PON-1 levels were significantly lower than that of control group. However, any statistical significance between Group I and II could not be determined in respect to PON-1 levels.

The PON family inhibits oxidative modification of LDL and suppresses the differentiation of monocytes into macrophages, which is the first stage in the development of atherosclerosis. There is a certain relation between PON-1 polymorphism and HDL and LDL particles. The PON1192RR genotype is associated with lower HDL levels and higher LDL levels. Lower concentrations of LDL in people with genotype PON155LL have been noted[17].

Accordingly in our study, HDL and LDL levels in Group I and II were lower when compared to control group. While this finding demonstrates strong relationship with HDL and MI, it may also indicate that LDL level may not be associated with CAD.

The severity of CAD was assessed using angiographic Gensini score (GS) [11]. The GS was calculated for each coronary stenosis based on the degree of luminal narrowing and its localization. Mild atherosclerosis was classified as a GS ≤10, moderate atherosclerosis as a GSS >10 and ≤40, and severe atherosclerosis as a GS >40 [18]. In our study, patients in AMI groups were in the severe group. However, any correlation between PON-1 levels and GS could not be determined. Results of our study suggest that PON-1 levels do not predict extension of ischemia in patients with AMI.

In a study, it was reported that elevated apoA-I glycation and reduced serum and HDL-associated PON activities, and their interaction were associated with the presence and severity of stable CAD in patients with type 2 diabetes mellitus. Severity of coronary disease was assessed by number of diseased coronary arteries, extent index, and cumulative coronary stenosis score even after adjusting for possible confounding factors [19]. In another study with 89 patients, Sentürk et al investigated PON-1 level and its correlation with GS in patients with acute coronary syndrome. They reported that, in patients with acute coronary syndrome, the GS correlated inversely with serum PON levels [20]. The study of Zhou et al indicated that PON-1 activity in different CAD groups was significantly lower than that of non-CAD patient group. This finding