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Original article

Effects of aerobic training on serum paraoxonase activity and its relationship with PON1-192 phenotypes in women

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Abstract

Background: Paraoxonase 1 (PON1) is an antioxidant enzyme that protects high-density lipoprotein (HDL) and low-density lipoprotein against oxidation. Limited studies have addressed the influence of exercise on PON1 activity and its relationship with PON1 phenotypes. We investigated relationships between PON1-192 phenotypes, PON1 activity, aerobic exercise, and blood lipid and lipoprotein concentrations in middle-aged women. Methods: An exercise group (n = 50) engaging in regular aerobic exercise and a control group (n = 41) were selected from a subset of 300 Caucasian women that met the inclusion criteria. Serum PON1, salt-stimulated PON1 (SSPON1), and arylesterase (ARE) activities; cholesterol levels and ARE activities of total HDL and HDL subgroups (HDLs) (supernatants obtained by polyethylene glycol); and blood lipid and lipoprotein concentrations were determined by standardized enzymatic methods. PON1-192 QQ (low activity), QR (moderate activity), and RR (high activity) phenotype groups were defined using serum SSPON1/ARE activity ratios. The R-carries (RC) phenotype group consisted of the QR and RR groups combined. Results: All lipid and lipoprotein concentrations were greater in the exercise group than in the control group. Regardless of phenotype, no significant differences were observed between the exercise and control groups in terms of serum PON1, SSPON1, or ARE activity associated with HDLs (p > 0.05), whereas PON1 activities in QQ-phenotyped women in the exercise group were significantly higher than those in the control group (p < 0.01), but not the RC group. A statistically significant interaction between PON1 phenotypes (QQ and RC groups) and exercise (exercise and control groups) on PON1 activity was found.

Conclusion: These results showed that a regular aerobic exercise program can improve PON1 activity depending on PON1-192 phenotype, but not on lipid and lipoprotein levels, in middle-aged Turkish women.

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Keywords: Aerobic exercise program; Arylesterase; Lipids; Lipoproteins; Paraoxonase; PON1-192 phenotype; Women

1. Introduction

Atherosclerosis is the main cause of death in developed countries. Regular aerobic exercise program reduces the risk of developing cardiovascular disease (CVD) by increasing serum high-density lipoprotein cholesterol (HDL-C) levels. Paraoxonase 1 (PON1) prevents the oxidation of both HDL and low-density lipoprotein (LDL), impeding the development of atherosclerosis. The anti-oxidative property of HDL has been partly attributed to serum PON1 enzyme. ²

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PON1 enzyme hydrolyzes both paraoxon and phenylacetate substrates, which are referred to in the literature as paraoxonase and arylesterase (ARE) activities, respectively. PON1 can hydrolyze the oxidized lipids of LDL and HDL, which are known to promote atherosclerosis. PON1 enzyme is produced mainly in the liver and is released into the blood.^{2,3} HDL facilitates the secretion of PON1 from the liver into the blood and stabilizes the enzyme. PON1 is located on HDL and its subfractions (HDLs: HDL₂ and HDL₃) were found in the blood.⁴

PON1 activity can be affected by genetic factors, life style choices, disease status, and HDL-C levels;⁵ however, its activity is mainly determined by polymorphisms in the *PON1* gene. The *PON1* gene has several genetic polymorphisms, 1 set of which occurs in codon 192 (referred to as PON1-192 polymorphisms),

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whose Q and R alleles are associated with low and high PON1 activity, respectively.⁶

It was reported that PON1 activity, HDL₂-C, and HDL₃-C are related to CVD⁵⁻⁷ and that both serum PON1^{7,8} and ARE activities^{8,9} are lower in individuals with CVD than in controls. Similarly, it was found that blood HDL-ARE activities are lower in women with CVD than in controls and that these parameters are more predictive for CVD than HDL-C levels.¹⁰ In addition, ARE activity was shown to be polymorphism-independent.¹¹

Exercise is another major factor that affects PON1 activity. 9,12,13 Therefore, to protect against CVD, it is important to monitor one's serum PON1 and HDLs-ARE activities as well as cholesterol levels, with the goal of improving these activities through an appropriate exercise program.

Tomás and coworkers¹³ reported that acute and 4-month exercise programs did not affect salt-stimulated PON1 (SSPON1) activity in a group of healthy Spanish men and women athletes, regardless of PON1-192 polymorphism. However, when PON1-192 polymorphism was considered, both types of exercise increased SSPON1 activity, and the effects of exercise on SSPON1 activity were modulated by PON1-192 polymorphism. Results from a separate study showed that PON1 activity increased significantly after maximal exercise independently of PON1-192 polymorphisms in rugby players, but ARE activity was not affected by exercise. 12 In a crosssectional study, blood SSPON1 and ARE activities, as well as the distribution of PON1-192 genotypes, did not differ between endurance athletes and controls.¹⁴ Conflicting effects of genotype and exercise on PON1 activity and their relationships with PON1-192 polymorphisms were seen among athletes. Moreover, conflicting results were also observed with non-athlete women and men with CVD.9 The reasons underlying such discrepancies are unclear, as only a single study investigating the influence of PON1-192 phenotypes on PON1 activity is found in the literature.¹⁴

In addition, in both humans and mice, it was shown that PON1 activity is greater in women than in men, 9,15 and it was reported that PON1 is regulated at the mRNA level in a gender-specific manner by some pro-inflammatory and anti-inflammatory substances. 15

In parallel, it was also reported that estradiol may regulate the specific activity and/or stability of cell surface PON1. In most studies, 8.9,14 blood ARE activities has been measured, which are known to be independent of PON1-192 polymorphisms. Thus, ARE and PON1 measurement methods and gender differences may influence the interpretation of results when examining the effects of PON1-192 phenotypes.

PON1 activity varies widely between individuals within the same genotype group and across ethnic variations.^{5,17} Therefore, similar studies may yield different results with healthy women and Turkish populations with a different ethnic group, although no such study has been published yet.

Furthermore, it is reported that the effect of physical activity on HDL-C concentration is related to PON1-192 polymorphisms. ¹⁸ However, some studies have failed to demonstrate associations between PON1-192 phenotype and lipoprotein changes, ^{19,20} while Hegele and coworkers²¹ found significant

associations between PON1-192 genetic variants and plasma HDL-C and triglyceride levels. Thus, the relationships between PON1 phenotypes and all blood lipid and lipoprotein concentrations are unclear, and these relationships have not been reported for Turkish subjects. Our hypothesis was that a regular aerobic exercise program can increase PON1 activity and lipid and lipoprotein concentrations depending on PON1-192 phenotype in middle-aged Turkish women. To test our hypothesis, we planned this cross-sectional study to investigate the relationships between PON1-192 phenotypes and regular aerobic exercise, PON1 and ARE activities, and all lipid and lipoprotein concentrations in middle-aged women.

2. Methods

2.1. Subjects

Three hundred women volunteers completed an anamnesis questionnaire providing information regarding their basic demographics, medical history, medication usage, frequency of smoking and alcohol consumption, and amount of physical activity. One hundred and sixty women met the inclusion criteria and were selected for medical examination. These criteria included (a) being ≥32 years of age and having regular menstrual cycles; (b) not being anemic or actively infected; (c) being free of illnesses predisposing to CVD; (d) not being a smoker and/or an alcohol user; (e) not taking medication affecting lipid, lipoprotein, or antioxidant metabolism; and (f) agreeing to participate in an exercise group (EG, n = 50) for 1 h for 3 days per week for at least 3 months, involving a supervised aerobic exercise program (step aerobics). The control group (CG, n = 41) included habitually active women (exercising less than 1 h/week) that were not engaged in a structured training program, nor had they been so engaged for at least 3 months prior to the study. Following medical history inquiries, physical examinations, and blood testing, 91 women met the inclusion criteria (Table 1).

Participants were informed about the details of the study and the probable risks and all provided written informed consent. The study was approved by the Ege University Medical Faculty's Ethics Committee.

2.2. Physical and physiological measurements

Physical examination consisted of anamnesis, ECG, anthropometry (height, weight, and body mass index (BMI)), and percentage of body fat (%BF). Body density and %BF values were calculated using widely recognized equations included in the book of Ratames and American College of Sports Medicine.²²

Physiological measurements included resting heart rate (HR), blood pressure (BP), and maximum oxygen consumption (VO_{2max}). VO_{2max} was determined by respiratory gas analysis (Quark b²; COSMED, Rome, Italy) on a cycle ergometer (Monark, Varberg, Sweden), using gradually increasing loads. VO_{2max} measurements were confirmed when 3 or more of the following criteria were met: (1) a plateau in VO₂ despite an increase in workload, (2) a respiratory exchange ratio higher than 1.2, (3) a peak HR at least equal to 90% of the age-predicted maximum, and/or (4) visible exhaustion.²³

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