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Effects of Aerobic Exercises on the Serum Paraoxonase 1/Arylesterase Activity and Lipid Profile in Non-Active Healthy Men

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Abstract. The purpose of this study was to investigate the effects of aerobic exercises on serum paraoxonase-1 (PON1) activity, arylesterase (ARE) activity, and lipoprotein profile. Forty-four non-active healthy men volunteered to participate in this research. They were randomly assigned into three groups: vigorous aerobic exercise group (VAE-group, n=15), moderate aerobic exercise group (MAE- group, n=17) and control group (n=12). Duration of training was 8 weeks, 3 sessions per week and each session lasted 30-45 minutes. VAE-group and MAE-group carried out exercises at 80-85 and 60-65 percent of maximal reserve heart rate. Dependent variables were measured in the three phases of the study, including pre-test, mid-test and post-test. Results did not show any significant changes in PON1 activity, ARE activity, low density lipoprotein cholesterol (LDL-c), or total cholesterol (TC) concentration after aerobic exercises. However, high density lipoprotein cholesterol (HDL-c), HDL-c/Total cholesterol ratios and maximal oxygen uptake (VO2max) significantly increased ($P<0.05$) and body mass index (BMI) conversely decreased ($P<0.05$) due to vigorous aerobic exercises. The lack of significant interaction between PON1/ARE activity and aerobic exercises in an Iranian group (with AA phenotype) along with low PON1 activity of our subjects probably confirm the concept of racial variability of PON1 activity.

Keywords: Antioxidant Enzymes, Lipid Indices, Aerobic exercise training

1. Introduction

Human serum paraoxonase (PON1) is located on one of the high density lipoprotein cholesterol (HDL-c) subfractions which contain APO A-I and clusterin [1]. PON1 is synthesized by the liver, and is stored in large amounts in mammals. It has been shown that PON1 is an enzyme with two type activity including paraoxonase activity (measurable toward paraoxon) and arylesterase activity (measurable toward phenylacetate) [2]. It is suggested that the activity toward paraoxon (PON) is more variable and is sensitive to different modulating factors, whereas arylesterase (ARE) is stable and better corresponds with enzyme concentration [3].

Enzyme PON1 has mainly been of importance in the field of toxicology where it appears capable of decreasing poisons through hydrolization of a various number of organophosphate compounds.[1] More importantly, studies show connections between PON1 activity and atherosclerosis, and it is believed that PON1 probably has a role in the antiatherogenic properties of HDL-c. In other words, PON1 can increase power of HDL-c in metabolizing lipid peroxides and reducing the extension of atherosclerotic lesions [4, 5]. Other reports have also pointed out that low density lipoprotein cholesterol (LDL-c) and a number of other oxidized phospholipids can be counted as appropriate physiological substrates for serum PON1 and that PON1 prevents the oxidative changes of lipoproteins, especially LDL-c [6, 7]. However, current reports pointed out that a high amount of HDL-c and a low amount of LDL-c can not solely guarantee cardiovascular health. In fact, whenever HDL-c becomes incapable of functioning properly, due to not

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having the supporting roles of enzyme PON1 and platelet activating factor acetylhydrolase (PAFAH), it is possible for lesions to appear in the vessels.[4,8] Lower PON1 enzyme activity has been reported frequently in myocardial infarction (MI) patients, advanced atherogen, family hypercholesteremia, diabetes mellitus and smokers [6, 7, 8]. Researchers believe that the level of PON1 activity is an etiological factor in causing cardiovascular problems and possibly other diseases. Thus, the study of the effects of both environmental (physical activity and nutrition) and genetic factors on PON1 activity is warranted.

It has been shown that PON1 genotype has an essential role in the PON1 response to exercise training [9]. In addition, it has been shown that the effects of physical activity on the lipid profile is dependent on PON1 polymorphism [10]. Results of the few reported studies show that acute exercises will inhibit the activity of PON1 [11]. However, based on another result, researchers have found that antioxidants like paraoxanase remained without any change after intensive aerobic exercise (running continuosly, mean distance 47.8 ± 7.4 Km), among 11 male athletes [12]. In addition, it is determined that PON1 activity did not demonstrate significant difference between active and inactive non-smokers [13], while it has found that in well trained rugby players, the activity of the anti-oxidant enzymes such as PON1, was higher than the non-active group [14]. However, the question still remains as to what is the effect of different levels of aerobic exercises (moderate and vigorous) on PON1/ARE activity and what is the interaction between this kind of physical exercise and lipoprotein profile in individuals with AA phenotype? These are the questions posed in this study.

2. Method

Forty four males aged 25-45 participated in this research. They were randomly divided into three groups: vigorous aerobic exercise (VAE-group) (n=15; 69.50±9.29/30.93±6.38/171.6±5.81 mean weight/age/heigh), moderate aerobic exercise (MAE-group) (n=17; 76.11±9.39/34.94±7.44/171.82±4.58 mean weight/age/heigh), and control (n=12; 75.54±7.46/29.75±5.31/175.33±4.59 mean weight/age/heigh) group. Participants had no previous record of cardiovascular disease, tobacco smoking, and regular physical activity. This information was collected using a health condition questionnaire and Baecke questionaire of habitual physical activity[15], respectively. Also, dietary intake of subjects during the 2 months of our study was recorded through a 24-hr dietary recall questionnaire.

Dependent variables were evaluated in three phases including pre-test, mid-test and post-test. Duration of training was 8 weeks and participants carried out exercise training for 3 sessions per week and each session lasted 30-45 minutes. VAE and and MAE groups performed vigorous aerobic exercise (at 80-85 percent of maximal reserve heart rate) and moderate aerobic exercise (at 60-65 percent of maximal reserve heart rate), respectively. The training heart rate was calculated by " Karvonen method " for every subject [16]. Vigorous aerobic exercise included running in various speeds. Similarly, the nature of moderate aerobic exercise was lifestyle training such as walking at various speeds (brisk & very brisk), stepping upstairs and downstairs.

2.1. Measurement methods

PON1 activity and lipoprotein profile of serum were measured by kinetic enzymatic reaction and CHOD-PAP enzymatic method, respectively. Blood samples were taken 24 hours before the start of protocol and 24 hours after the last session of exercise in the mid-test and post-test. Venous blood was obtained from subjects between 8-9 AM after a 12-14 hours fast.

2.2. Paraoxonase 1 activity

PON1 activity was measured by adding serum to 1 mL Tris/HCL buffer (100 mmol/L, pH 8.0) containing 2 mmol/L $CaCL_2$ and 5.5 mmol/L paraoxon. Then rate of generation of para-nitrophenol was followed at 405 nm and 25 °C with an autoanalyzer (Selectra2, Bieren, The Netherlands). Afterwards, absorption changes obtained per minute were used in conjunction with the molar extinction coefficient of paraoxon to determine paraoxonase enzyme activity [17].

2.3. Arylesterase activity

Arylesterase activity was measured by adding serum to 20 mM Tris-HCL buffer (20 mmol/l, pH=8.0) containing 1 mmol/l $CaCL_2$ and 1 mmol/l phenyl acetate. Then rate of generation of para-nitrophenol was followed at 270 nm and 25 °C in a countinuously recording spectrophotometer (Secoman 1000PC, Sarcelles, France). Afterwards, absorption changes obtained per minute were used in conjunction with the molar

extinction coefficient of phenylacetate to determine arylesterase enzyme activity [17].

2.4. Paraoxonase Phenotype Distribution:

The phenotypic distribution of paraoxonase activity was determined by the dual substrate method. Briefly, the ratio of the hydrolysis of paraoxon in the presence of 1 mol/l NaCL (salt-stimulated paraoxonase) to the hydrolysis of phenylacetate was used to assign individuals to one of the three possible phenotypes : AA (homozygous low activity), AB (heterozygous activity), or BB (homozygous high activity), which are defined by the ranges 1.21±0.19 for AA, 4.68±0.85 for AB, and 8.36 ± 0.70 for BB [18].

2.5. Lipid and lipoproteine concentration

Total cholesterol (TC), and HDL-c concentrations were measured by CHOD_PAP enzymatic method with a Pars Azmun kit [19]. LDL-c concentration was calculated with the Friedwald et al. formula for serum samples with TG values less than 400 mg/dl [20].

We estimated the maximal oxygen uptake (VO2max) by the Fax protocol on the ergometer (5 Min,150 Watt intensity and 60 RPM speed) [21].

2.6. Statistical Analysis

In order to evaluate the effect of exercise intensities (vigorous & moderate) on each of the dependent variables, we applied analysis of variance (ANOVA) test for repeated measures. Least significant difference (LSD) test was also used for coupled comparisons between times, groups and time-group interaction. Statistical significance was accepted if $P<0.05$.

3. Results

3.1. Paraoxonase 1 activity

Mean dependent variables including PON1 activity values are presented in Table 1. No significant differences were observed using repeated measures ANOVA in PON1 between times of measurement ($F=0.81$, $P>0.05$) and groups ($F=1.14$, $P>0.05$) and time–group interaction was not significant ($F=0.75$, $P>0.05$) as well (Table 2). These means that neither vigorous aerobic exercise nor moderate aerobic exercise did not have significant effect on PON1 activity.

3.2. Arylesterase activity

Mean ARE activity values presented in table 1. No significant differences were observed using repeated measures ANOVA in ARE activity between times of measurement ($F=0.54$, $P>0.05$) and groups ($F=0.75$, $P>0.05$) and time–group interaction was not significant ($F=2.01$, $P>0.05$) as well (Table 2). In other words, neither vigorous aerobic exercise nor moderate aerobic exercise did not have significant effect on ARE activity. We determined PON1 phenotype as well. The ratio of PON1 activity to arylesterase activity was in a range of 0.34 and 1.96, suggesting the all subjects had AA phenotype [18].

For HDL-c, results showed significant differences between groups ($F=3.63$, $P<0.03$) and also times of measurement ($F=4.12$, $P<0.01$), but time-group interaction was not significant ($F=0.91$, $P>0.05$)(Table 2). The LSD test indicated that HDL-c of the VAE-group is significantly higher than to control group ($MD=7.59$, $P<0.01$)(Table 3). In addition, HDL-c/total cholesterol (HDL-c/TC) ratio was significantly different between groups ($F=3.68$, $P<0.03$) and times of measurement ($F=13.52$, $P=0.000$), but time-group interaction was not significant ($F=1.69$, $P>0.05$)(Table 2). The LSD test indicated that HDL-c/TC ratio comparing VAE-group with both MAE-group ($MD=0.04$, $P<0.03$) and control group ($MD=0.05$, $P<0.01$) were significantly different (Table 3). In fact, vigorous aerobic exercise caused HDL-c/TC ratio not only become significantly higher than non-trained subjects (control group), but also than individuals with moderate aerobic exercise. These results are indicator of the specific role of vigorous aerobic exercise on the modification of HDL_c and TC concentrations. ANOVA also showed that HDL-c concentration and HDL-c/TC ratio changes occurred at least after 4 weeks of training, between mid-test to post-test ($MD=-3.54$, $P<0.002$; and $MD=-0.03$, $P=0.000$ respectively) and pre-test to post-test ($MD=-4.65$, $P<0.02$; and $MD= -0.04$, $P=0.000$ respectively)(Table 4).

Table 1: Descriptive data of dependent variables of study (Mean ± SD)

	Pre-test	Mid-test	Post-test
PON1 activity (U/L)			
VAE- group	92.26 ± 41.61	92.60 ± 41.00	93.06 ± 43.06
MAE- group	92.52± 46.65	87.00± 42.86	96.82± 44.99
Control group	70.66 ± 26.28	73.25 ± 36.79	73.37 ± 27.59
ARE activity(U/L)			
VAE- group	96.53 ± 37.24	85.53 ± 41.06	106.53 ±48.53
MAE_group	95.88 ±39.10	119.29 ±43.49	113.00± 62.91
Control group	110.75 ± 30.87	119.83 ± 39.49	100.25 ± 40.75
HDL_c (mg/dl)			
VAE_group	40.93 ± 12.74	43.20 ± 9.54	49.73 ± 11.62
MAE-group	38.94± 6.94	39.41± 8.13	44.35 ± 8.06
Control group	35.58 ± 6.41	40.16 ± 7.29	39.33 ± 7.32
LDL_c (mg/dl)			
VAE-group	126.73 ± 33.63	122.60 ± 29.05	107.73 ± 31.07
MAE-group	49.88± 41.56	137.76± 40.00	129.47 ± 27.29
Control group	136.75 ± 30.19	118.16 ± 29.13	121.41 ± 24.17
HDL_c/TC Ratio			
VAE-group	0.23 ± 0.08	0.22 ± 0.05	0.28 ± 0.09
MAE-group	0.18 ± 0.05	0.20 ± 0.06	0.23 ± 0.06
Control group	0.17 ± 0.04	0.20 ± 0.04	0.20 ± 0.04
TC (mg/dl)			
VAE-group	199.06± 39.03	190.53 ±30.45	177.60± 28.20
MAE-group	218.88± 45.78	204.11± 42.79	197.70 ±33.70
Control group	202.16 ±37.41	202.08±22.88	193.08± 24.61
VO2max (ml/kg/min)			
VAE-group	42.78± 4.89	48.61±5.42	50.80±6.77
MAE-group	37.90± 5.32	42.33±5.01	43.88±6.17
Control group	41.21± 5.88	42.57±5.57	42.98±5.87
BMI (kg/m^2)			
VAE-group	23.01±3.35	22.64±3.28	21.34±3.15
MAE-group	25.90±3.83	25.43±3.83	24.88±3.85
Control group	24.52±1.88	24.27±1.97	24.12±2.11

Note: VAE , MAE and BMI are indicators of vigorous aerobic exercise, moderate aerobic exercise and body mass index respectively.

Table 2 : Results of ANOVA test related to effects of training intensities on the dependent variables

Dependent Variables	Sources		
	Group	Times of Measurment	Time-Group intraction
PON1 activity	1.14 (0.33)	0.81 (0.44)	0.75 (0.55)
ARE activity	0.75 (0.47)	0.54 (0.58)	2.01 (0.09)
HDL-c	3.63 (0.03)†	4.12 (0.01) †	0.91 (0.45)
LDL-c	2.06 (0.14)	9.34 (0.000) †	0.80 (0.52)
TC	1.51 (0.23)	5.10 (0.008) †	0.41 (0.79)
HDL-c/TC Ratio	3.68 (0.03) †	13.52 (0.000) †	1.69 (0.15)

BMI	2.89(0.04) †	24.73(0.000) †	1.97(0.10)
VO2max	5.32(0.009) †	114.63(0.000) †	13.12(0.000) †

* Note : Numbers are indicators of F (P) values. † Significant effect (P<0.05) of aerobic exercises.

For LDL-c, significant differences were found between times of measurement (F=9.34, P=0.000) but not between groups (F=2.06, P>0.05) and time-group interaction (F=0.80, P>0.05)(Table 2). Similarly, there were significant changes for TC between times of measurement (F=5.10, P<0.008) but not between groups (F=1.51, P>0.05) or time-group interaction (F=0.41, P>0.05)(Table2).

Table 3 : Results of LSD test related to coupled comparisons between groups

Dependent Variables	Groups		
	VAE & MAE	VAE & Control	MAE & Control
HDL-c	5.05 (0.06)	7.59 (0.01)†	2.54 (0.37)
HDL-c/TC Ratio	0.04 (0.03) †	0.05 (0.01) †	0.01 (0.59)
BMI	-2.74(0.02) †	-1.83(0.04) †	1.10(0.36)
VO2max	6.02(0.004) †	5.17(0.02) †	-0.85(0.68)

* Note : Numbers are indicators of mean difference (P) values. † Significant difference (P<0.05) between groups. VAE, MAE and BMI are indicators of vigorous aerobic exercise, moderate aerobic exercise and body mass index, respectively.

For VO2max, we observed significant differences between groups (F=5.32, P<0.009) and times of measurement (F=114.63, P=0.000) and time-group interaction (F=13.12, P=0.000) was significant as well (Table 2). The LSD test indicated differences between the VAE-group with both control group (MD=5.17, P<0.02) and MAE-group (MD=6.02, P<0.004)(Table 3). These differences were significant between pre-test and mid-test (MD=-3.87, P=0.000), pre-test and post-test (MD=-5.22, P=0.000), and mid-test and post-test (MD=-1.35, P=0.000) (Table 4). Finally, results about BMI showed significant differences between groups (F=2.86, P<0.04) and times of measurement (F=24.73, P=0.000), but time-group interaction was not significant (F=1.97, P>0.05) (Table 2). The LSD test indicated differences between the VAE-group with both control group (MD=-1.83, P<0.04) and MAE-group (MD=-2.74, P<0.02)(Table 3). These differences were significant between pre-test and mid-test (MD=0.36, P=0.000), pre-test and post-test (MD=0.69, P=0.000), and mid-test and post-test (MD=0.33, P=0.000) (Table 4). Based on above, we can suggest that vigorous aerobic exercise beneficially modified VO2max and BMI after 4 weeks.

Table 4: Results of LSD test related to coupled comparisons between times of measurement

Dependent Variables	Times of Measurement		
	Pre _test & Mid_ test	Pre_ test & Post_ test	Mid_ test & Post_ test
TC	7.79 (0.14)	17.24 (0.008)†	9.44 (0.05)
HDL-c	- 1.10 (0.56)	- 4.65 (0.02) †	- 3.54 (0.002) †

LDL-c	11.61 (0.01) †	18.24 (0.000) †	6.63 (0.08)
HDL-/Tc Ratio	- 0.01 (0.19)	- 0.04 (0.000) †	- 0.03 (0.000) †
BMI	0.36(0.000) †	0.69(0.000) †	0.33(0.000) †
VO2max	-3.87(0.000) †	-5.22(0.000) †	-1.35(0.000) †

* Note : Numbers are indicators of mean difference (P) values. † Significant difference (P<0.05) between times of measurement.

4. Discussion

In the present study, PON1 and ARE activity did not affect significantly by vigorous and moderate aerobic exercises. However, we found significantly increases in the HDL-c, HDL-/TC, and estimated VO2max, and inversely significantly decrease in BMI after vigorous aerobic exercise at 80-85 percent of maximal reserve heart rate. In other hand, it is determined that although lipoprotein profile, VO2max and BMI of MAE-group modified beneficially, but they did not receive to the significance levels.

Data concerning the possible effect of exercise training on the anti-oxidant enzymes activity such as PON1/ARE are controversial, as differences and no changes in these parameters comparing active and non-active individuals have been described [9, 10, 13, 14, 22, 23]. It has been found that after performing 16 weeks of aerobic training people who carry the R allele showed reduction of PON1 activity, and people who carry the Q allele showed an increase (both significant), while in total group (Q & R allele) changes were not significant [9]. In another study, the activity of the anti-oxidant enzymes such as PON1, was higher in well trained rugby players than to non-active group [14]. Duration of our training protocol was 8 weeks and comparison between well-trained players and our subjects is not probably reasonable. It has been found that serum PON1 and ARE activity were significantly different (P<0.01) between subjects after chronic exercise (daily, for 6±2.5 year) and acute exercise (jogging-race and aerobic upstairs, 3 day/ week, and for 3 months) [22]. Results of above mentioned studies implicate that making changes in PON1 and ARE activity probably need to a long-term and chronic exercise–related stimulation. In addition, it has been shown that PON1 activity is not significantly different comparing active and inactive non-smokers, whereas it was significantly higher in active than non–active smokers [13]. Besides, some researchers found no significant differences in the physical exercise level (None, 1-5 h/week, and >5 h/week) in leisure time when participants were classified according to PON1 tertiles (high, medium, and low activity) [23]. These results [13, 23] are consistent to our research based on lack of significant different of PON1 and ARE activity between trained and non-trained subjects (both non- smokers). Other reports showed that physical activity in males with the R allele was associated with the increase of HDL-c and the reduction of triglyceride [10]. Similarly, we found in our research that HDL-c concentration, and HDL-c/TC ratio showed significantly increase in VAE-group, and there were inclination to decrease of LDL-c and TC concentration in both exercised groups. Generally, the existing results suggest that although some type of physical exercise has no direct and significant effects on PON1/ARE activity, improved physical fitness and adjust lipoprotein profile brings a control of cardiovascular risk factors in the people with low PON1 activity level (AA phenotype).

It has been suggested that acute exercise training can inhibit temporarily PON1 activity and aerobic training could attenuate this inhibitory effect of acute exercises on PON1 activity [9]. Decrease of rats PON1 activity due to both single race and parathionmetyl has been confirmed by another study [11]. In our study intensity of aerobic exercise training (vigorous vs. moderate) did not affect the PON1/ARE activity, but it seems that PON1/ARE activity usually decreases due to acute exercise which carry out on higher than the lactate threshold (anaerobic exercise) and to have an improved physical fitness can attenuate this inhibitory effect. We observed the level of Vo2max increased in VAE-group and this implies that improved physical fitness could guarantee maintenance of PON1 activity. Furthermore, concerning the reduction of PON1 activity after acute exercise, our results suggest that performing of vigorous aerobic exercise (up to 85 percent of maximal reserve heart rate) does not decreasingly affect on PON1 activity in people with AA phenotype. In other words, this kind of physical activity has beneficial effects on the risk factors and can at least maintain PON1/ARE activity in acute conditions.

To the best of our knowledge, our results constitue the first published report on the interaction between PON1 activity and physical exercise in Iranian descent. We found that our participants have lower PON1

activity than people in Western countries. The expression of PON1 enzyme activity in the serum is under genetic control and the polymorphism of the PON gene has been extensively recognized in different communities as a potential genetic determinant of PON1 activity [24]. In view of variability of genetic make up of different populations, the activity of PON1 shows great interethnic variability. European populations have been shown to have a bimodal distribution of PON1 activity, but in some non-European populations, low PON1 activity has been observed together with a unimodal curve of activity [25]. It is reported that there is variability as 10 to 40 fold in PON1 activity between populations [26]. Low PON1 activity observed in our study is consistent to another research performed in Iranian population [19]. The lack of significant interaction between PON1 activity and aerobic exercise in an Iranian group (with AA phenotype) along with low PON1 activity of our subjects probably confirm the concept of racial variability of PON1 activity. In addition, some of the inconsistent results are probably related to use of different designs of research (experimental vs. observational studies), and different nature (intensity and duration) of performed exercise training. Further studies are required to elucidate the interactions between exercise training, PON1 phenotype, and cardiovascular risk factors.

5. Conclusions

Although aerobic exercises did not significantly affect serum PON1/ARE activity, but they (especially vigorous aerobic exercise) became beneficially effective by (a) maintenance and stability of PON/ARE activity level, (b) modification of lipid profile (HDL-c and TC) and BMI and (C) improvement of physical fitness (VO2max). Antiatherogenic role of HDL-c is not only dependent on PON1 activity, but also to other enzymes and apolipoproteins associated HDL-c(lecitin cholesterol acylteransferase, PAFAH, APO AI). Thus, it seems that higher HDL-c is more important than PON1 activity individually. Therefore, it is necessary to concentrate on elevating of HDL-c concentration by prescription of feasible intensity (higher than 65 percent and up to 85 percent of maximal reserve heart rate) of physical activity. People with AA phenotype have a lower PON1 activity and considering the probable limitation of influence of environmental parameters, especially physical activity on PON1, these people need to pay more attention to performing regular physical activity. Finally, the change patterns of risk factors after moderate aerobic exercises showed that continuing of this type of training in long term will lead to significant changes in the risk factors and physical fitness.

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