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Physical Inactivity and Cardiovascular Risk: Baseline Observations from Men and Premenopausal Women

Mahdi Garelnabi,[1] Emir Veledar,[2] Jerome Abramson,[3] Jill White-Welkley,[4] Nalini Santanam,[5] William Weintraub,[6] and Sampath Parthasarathy[7]*

[1]*Department of Clinical Laboratory and Nutritional Sciences, University of Massachusetts Lowell, Massuchusetts*

[2]*Division of Cardiology, Emory University School of Medicine, Atlanta, Georgia*

[3]*School of Public Health, Emory University, Atlanta, Georgia*

[4]*Department of Health and Physical Education, Emory University, Atlanta, Georgia*

[5]*Department of Pharmacology, Joan C. Edwards School of Medicine, Marshall University, Medical Center Drive, Huntington, West Virginia*

[6]*Center for Heart and Vascular Health, Christiana Healthcare System, Newark, Delaware*

[7]*Division of Cardiothoracic Surgery, Ohio State University, Columbus, Ohio*

Introduction: Physical activity or exercise is a proven deterrent of cardiovascular (CV) diseases. *Purpose*: In this study, we examined the relationships between baseline values of parameters related to physical activity and known markers of CV disease, including markers of oxidative stress. *Methods*: A total of 455 healthy men and women between the ages of 18 and 50 were recruited to participate in the study. Levels of lipids/lipoproteins and markers of oxidative stress and inflammation were measured along with the VO_2 and duration time spent on treadmill. *Results*: Women, in general, had a significantly ($P<0.0001$) higher plasma high density lipoprotein (1.51 ± 0.30 mmol/l), decreased ($P<0.0001$) low density lipoprotein (LDL) (2.75 ± 0.66 mmol/l), and decreased ($P<0.0001$) triglycerides levels (2.09 ± 0.85 mmol/l), compared with males (1.21 ± 0.23 mmol/l, 2.92 ± 0.81 mmol/l, and 3.02 ± 1.34 mmol/l, respectively). There was a direct correlation between the levels of plasma LDL and the levels oxidized LDL levels ($P<0.0001$) in both men and women. Despite a better antiatherogenic lipid profile, the levels of C-reactive protein in women were significantly ($P<0.0001$) elevated (3.78 ± 3.66 ng/ml) as compared with those in men (1.82 ± 2.37 ng/ml). *Conclusion*: These results suggest intrinsic sex differences between men and women in relation to atherogenic risk. J. Clin. Lab. Anal. 24:100–105, 2010.

Key words: exercise; oxidative stress; sex; inflammatory markers; atherosclerosis

INTRODUCTION

Exercise reduces the risk of coronary heart disease in men and women (1–3). It is now generally recognized that regular exercise with minimum weight change has broad beneficial effects on lipoproteins profile (4–7). Exercise mode, intensity, and duration are important determinants of plasma lipid profile (8–11). Exercise has been suggested to increase high density lipoprotein (HDL) levels (12,13), but controversy persists (5,14). In addition to promotion of an antiatherogenic lipid profile, exercise also has been suggested to reduce markers of inflammation (15,16), including that of C-reactive protein (CRP). We recently reported that exercise also caused a significant regression of atherosclerosis in atherosclerotic mice as compared with low fat diet alone (17).

Oxidative stress has been implicated in cardiovascular (CV) disease (18,19). Practically every facet of the development of the vulnerable atherosclerotic plaque

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*Correspondence to: Sampath Parthasarathy, Division of Cardiothoracic Surgery, N-850 Doan Hall, 410 W 10th Ave, Ohio State University, Columbus, OH 43210 1292. E-mail: spartha@osumc.edu

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development, fatty streak lesion formation, (20) smooth muscle cell proliferation (21), inflammation (22), and matrix destabilization via activation of matrix metallo proteinases (23) have been attributed to be associated with oxidative stress. Markers of oxidative stress (plasma TBARS, lipid peroxides, isoprostanes, oxidized low density lipoprotein (Ox-LDL), autoantibodies to Ox-LDL and CV disease markers (soluble form of vascular cell adhesion molecule-1 (sVCAM-1), CRP, myeloperoxidase (MPO), and monocyte chemotactic protein-1 (MCP-1) are elevated in subjects with established atherosclerosis (19). Many of these proteins/genes are intimately connected with oxidative stress (9). Beginning exercise, paradoxically, may also promote free radical formation, lipid peroxidation, and vascular tissue injury (2,24,25). Exercise depletes plasma antioxidant levels, 26, and increases the propensity of isolated LDL to undergo oxidation during the transition from a sedentary state to intense physical activity. Data from our earlier studies in humans have indicated that 30 min exercise at moderate intensity is sufficient oxidative stress to increase the susceptibility of LDL to oxidation (26). Additionally, exercise appeared to activate neutrophils, subsequently releasing MPO protein (25). We, and others also, reported that sustained long-term exercise might be required and essential to maintain a body's antioxidant protection (10,27,28). Serendipitously, studies in women showed as originally suggested in animal experiments that females were more resistant to exercise-induced changes compared with a male's counterparts, perhaps represented by an active estradiol hormonal status (24,29). Yet, younger premenopausal females appear to be protected against CV risk as compared with men of similar age group (24). These results prompted us to examine the sex differences related to inflammation and oxidative stress markers in seemingly healthy sedentary subjects. We hypothesize that men and premenopausal women may intrinsically differ in their CV risk factor markers, particularly those associated with oxidative stress.

METHODS AND STUDY DESIGN

Recruitment and analysis were completed at Emory University School of Medicine, Atlanta, GA, USA. The research protocol was reviewed and approved by Emory University institutional Review Board.

Study Population

All subjects completed an approved human consent form explaining the voluntary nature of the study. Subjects were recruited from Emory University and the surrounding community through advertisements, flyers, and a website created for the study. Sedentary participants who were not involved in regular exercise, and who were otherwise healthy and not taking vitamins or dietary supplements, were chosen for the study after completing a detailed medical history and physical activity questionnaire. Those who reported a history of heart disease, diabetes, hypertension, hypercholesterolemia, smoking, chronic infection, or physical inability to exercise were excluded from the study. Of the 856 subjects screened, 455 participants were found to be eligible, 260 females (age 18–55) and 195 males (age 18–50). Enrolled subjects reflected the racial makeup of metropolitan Atlanta.

VO_2 peak was determined on a treadmill (Marquette Electronics, Jupiter, FL), using a continuous progressive protocol (30). Intensity of exercise was assessed by continuous monitoring of heart rates (using polar heart rate monitor) and self-reported ratings of perceived exertion every minute during the test. Criteria for test termination included subject request to stop the test, attainment of 95% of age-predicted maximal heart rate, or attainment of a respiratory exchange ratio G 1.1.

Blood Sample

Baseline samples were obtained from the participant's forearm vein following a minimum 10 hr overnight fast. Blood was drawn in two vacutainer® tubes (~10 ml) and placed immediately on ice. Each sample was centrifuged at 2,500*g* for 10 min and plasma was extracted and distributed in aliquots. Plasma lipids were measured immediately and the remaining aliquots were frozen at −80°C for subsequent analysis.

Biochemical Procedures

All chemicals were obtained from Sigma Chemical Co. (St. Louis, MO), unless indicated otherwise.

Lipid Analysis

Fasting plasma total cholesterol (TC), triglycerides (TG), HDL, and LDL measurements were determined using the Cholestech L*D*X analyzer (Cholestech Corporation, Hayward, CA).

Markers of Inflammation and Oxidative Stress

To determine the levels of inflammation and oxidative stress in plasma, we measured a number of markers using commercially available enzyme-linked immunosorbent assay (ELISA) kits. Human MPO and 8-Isoprostane (immunoassay for 8-epi-Prostaglandin F2L) were measured using kits (Catalog No. 21013 and 21019, respectively) obtained from OXIS International Inc. (Portland, OR). Quantitative determination of human sVCAM-1 concentrations in plasma was

performed using a kit (Catalog No. DVC00) from R&D Systems, Inc. (Minneapolis, MN). Human MCP-1 was measured using a kit (Catalog No. 019-EL-MCI) purchased from ALPCO Diagnostics (Windham, NH). Ox-LDL concentration was measured using a kit (Catalog No. 10- 1143–01) manufactured by Mercodia AB (Uppsala, Sweden). High-sensitivity CRP was measured using a kit (Catalog No. DSL-10-42100) purchased from Diagnostic Systems Laboratories, Inc. (Webster, TX). AA-Ox-LDL in plasma was determined using ELISA techniques as earlier described (31).

Statistical Analysis

Data were analyzed with computer software (S-plus 6 for Windows and SAS Software Release 8.2 packages).The results were expressed as mean $\pm$ SD, and the significance of the difference between the mean values of both sexes was determined by the Student's *t*-test employing ANOVA program. Spearman's rank correlation was calculated to assess the association between the oxidative stress/inflammatory markers and lipids.

Linear regression models were run to examine the relationship between oxidative stress/inflammatory markers and VO_2, duration time, and marker of oxidative stress and inflammation after adjustment for other factors.

RESULTS

Total of 455 subjects, females (260) and male (195) were recruited for the study. The basic characteristics of the subjects are given in Table 1. The means age (years) for females and males were 33.87 ± 10.22 and 32.40 ± 8.46, respectively. The body mass index in males and females were 26.3 ± 5.23 and $26.27 \pm 3.40\,kg/m^2$, respectively, showing slight overweight in both sexes. The females have shown fair VO_2 max (27.76 ± 6.02 ml/kg/min), whereas sedentary males have shown generally accepted VO_2 max for their age range (33.92 ± 6.26 ml/kg/min) and level of fitness. The difference between the VO_2 levels among the two sexes was significant ($P < 0.0001$). Females spent shorter time on treadmill for the measurement of VO_2 (484.46 ± 139.90 sec) compared with males (500.11 ± 95.98 sec).

To determine if changes in plasma lipoproteins is sex based or related to the level of fitness across the study population, we measured the plasma lipoprotein profile in both groups (Table 1). Women had a significantly lower LDL ($P < 0.01$), TG ($P < 0.0001$), VLDL ($P < 0.0001$), and higher HDL ($P < 0.0001$) than men. There was a slight increase in the levels of TC among men compared with women (4.76 ± 1.11 mmol/l and 4.71 ± 0.76 mmol/l, respectively), and obviously the TC/HDL ratio was also slightly elevated among men (3.9) as compared with women (3.1). Generally, both groups have shown acceptable average for the lipid profiles for their age, sex, and level of fitness, as determined by VO_2 measurement. Lipid results comply with the acceptable lipid profile criteria set for enrolment in this study.

TABLE 1. Baseline Values of Subjects

	Females $N = 260$	Males $N = 195$	
Variables	Mean $\pm$ SD	Mean $\pm$ SD	*P* value
Age (yr)	33.87 ± 10.22	32.40 ± 8.46	
Systolic BP (mmHg)	117.13 ± 11.63	123.76 ± 9.34	
Diastolic BP (mmHg)	76.39 ± 9.75	80.88 ± 6.17	
BMI (kg/m^2)	26.30 ± 5.23	26.27 ± 3.40	
Duration time (sec)	484.46 ± 139.90	500.11 ± 95.98	
VO_2 (ml/kg/min)	27.76 ± 6.02	33.92 ± 6.26	$P < 0.0001$
TC (mmol/l)	4.71 ± 0.76	4.76 ± 1.11	
LDL (mmol/l)	2.75 ± 0.66	2.92 ± 0.81	$P < 0.01$
HDL (mmol/l)	1.51 ± 0.30	1.21 ± 0.23	$P < 0.0001$
TG (mmol/l)	2.09 ± 0.85	3.02 ± 1.34	$P < 0.0001$
VLDL(mmol/l)	0.41 ± 0.16	0.55 ± 0.23	$P < 0.0001$

Markers of Oxidative Stress and Inflammation

Levels of oxidative stress and inflammatory markers in both groups are shown in Table 2. Females had significant lower levels of autoantibodies to oxidatively modified proteins ($P < 0.0007$), isoprostanes ($P < 0.0001$), MCP-1 ($P < 0.0001$), and sVCAM ($P < 0.0001$) suggesting a lower oxidative stress. Plasma MPO levels tended to be lower in females (3.23 ± 1.50) than males (3.51 ± 1.67); women, on the other hand, had a significant increase in CRP ($P < 0.0001$) and Ox-LDL ($P < 0.01$) levels compared with males. The lower levels of autoantibodies to oxidatively modified proteins combined with increased Ox-LDL might suggest a lower immune clearance of Ox-LDL. A decrease in isoprostanes with an increase in Ox-LDL (which is recognized owing to its oxidatively tailored lipids) in females might suggest an increased degradation of oxidized lipids to a

TABLE 2. Oxidative Stress and Inflammatory Markers

	Females $N = 260$	Males $N = 195$	
	Mean $\pm$ SD	Mean $\pm$ SD	
Autoantibody—Ox-LDL (OD units)	0.23 ± 0.14	0.28 ± 0.13	$P < 0.0007$
Ox-LDL (U/l)	23.28 ± 14.22	20.13 ± 11.48	$P < 0.0007$
Isoprostane (pg/ml)	13.18 ± 5.17	16.60 ± 7.15	$P < 0.01$
MCP-1 (pg/ml)	85.63 ± 66.45	131.68 ± 86.45	$P < 0.0001$
sVCAM (ng/ml)	297.87 ± 79.82	544.65 ± 233.25	$P < 0.0001$
MPO (ng/ml)	2.23 ± 1.50	3.51 ± 1.67	NS
CRP (ng/ml)	3.78 ± 3.66	1.82 ± 2.37	$P < 0.0001$

NS: Not significant.

TABLE 3. Spearman's Rank Correlation Coefficients

	BMI	LDL	HDL	TG
CRP	0.295 ($P<0.0001$)*	0.248 ($P<0.0005$) F	NS	NS
sVCAM	NS	NS	−0.296 ($P<0.0001$)*	0.253 ($P<0001$)*
Ox-LDL	NS	0.284 ($P<0.0001$)*	NS	0.204 ($P<0.001$) F 0.249 ($P<0.002$) M

F, females; *M*, males; NS, not significant.
*Table 3 shows results of the correlation studies. Values shown with asterisks (*) were calculated from the entire study population.

shortened chain moiety in females as compared with males.

The multivariable regression analysis for Spearman's rank correlation is shown in Table 3. Level of fitness as measured by VO_2 max have shown significant association with increases in isoprostane ($P<0.0001$) and inversely correlated with levels of CRP ($P<0.0001$). CRP also correlated with BMI ($r = 0.295$) in both groups and with LDL ($r = 0.248$) in women. Subjects, however, differed in their fitness levels correlations with sVCAM; although males had a strong significant inverse correlation between VO_2 and sVCAM ($r = -0.310$), this association was not significant among females. sVCAM also correlated with TG levels ($r = 0.270$) and inversely correlated with HDL ($r = -0.284$) among both groups. Males have shown strong correlations between the levels of Ox-LDL and LDL ($r = 0.508$) and TG ($r = 0.249$) compared with females $r = 0.216$ and $r = 0.204$, respectively.

DISCUSSION

A growing body of evidence shows that oxygen radical and other products of free radical reactions are involved in several disorders and diseases (28,32–35). Epidemiological studies have demonstrated considerable benefits of habitual vigorous activity, both at work and during leisure time. There are many benefits at all ages and for all levels of fitness, but particular emphasis is being placed on the CV benefits. Exercise may induce beneficial changes in lipid profile and thus reduce risk of CV disease. Recent studies have suggested that exercise-induced oxidative stress may potentially offer benefit by inducing body's antioxidant defense and by lowering LDL and hCRP (7). We examined effects of levels of fitness among sedentary women and men subjects on oxidative stress and inflammatory markers and their role on conventional CV risk markers. As evident from Table 1, the lipoproteins profiles of subjects have shown a distinctive sex difference. Females had significantly decreased LDL, VLDL, and TG and increased HDL levels compared with males. These differences do not seem to be related to the level of fitness among participants as males had significantly higher VO_2 max. There are no data yet that sufficiently describe whether or not females may be different than males in lipoproteins pertaining to level of fitness in sedentary subjects; however, earlier cross-sectional studies have pointed toward the advantages of women having lower TG and LDL, and higher HDL. Women are also shown to have large non-atherogenic LDL particle compared with men (36,37). We have earlier shown that women subjects were more resistant to exercise-induced changes in lipids and that their baseline lipids, which were already better in terms of the CV risk advantages, do not change dramatically as compared with males (24,29). This may be attributed to the active estradiol hormonal status.

Markers of oxidation and inflammations (Table 2) are the major findings of this study. Sedentary females have generally shown decreased levels of oxidative stress and inflammatory markers; plasma autoantibody to oxidatively modified protein, soluble vascular cellular adhesive molecule, and monocyte chemotactic protein (1) were significantly decreased among women compared with men. Although MPO was also decreased among females, the difference between the two groups was not significant. Females had significantly elevated Ox-LDL and CRP levels compared with males. Recent studies have reported increased CRP levels among female subjects compared with males and inverse association between CRP and physical activity (38,39). This indicates that females may have increased inflammation and oxidative stress levels associated with sedentary life style. Multivariate linear analyses, in this study, have shown several interesting relationships between the level of fitness and markers of oxidation and inflammation (Table 3). CRP inversely correlated with VO_2 (Fig. 1) and positively correlated with BMI. We also found that VO_2 significantly correlated with isoprostanes (Fig. 2) and inversely correlated with sVCAM. These findings demonstrate that increased level of physical activity may induce oxidative stress and decreases the levels of the adhesion molecule. Levels of sVCAM pointed in the same direction and correlated with increased levels of TG and inversely correlated with increased levels of HDL in both groups. Although only LDL in women

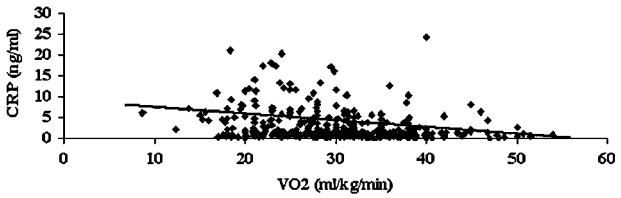

Fig. 1. VO_2 and CRP correlations in both sexes $r = -0.283$ ($P < 0.0001$).

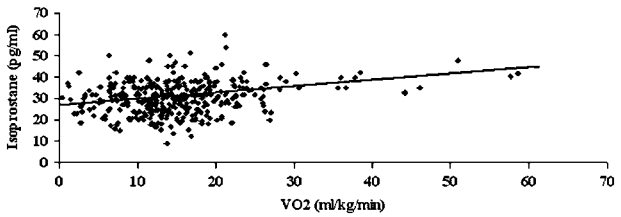

Fig. 2. VO_2 and isoprostane correlation between males and females $r = 0.200$ ($P < 0.0001$).

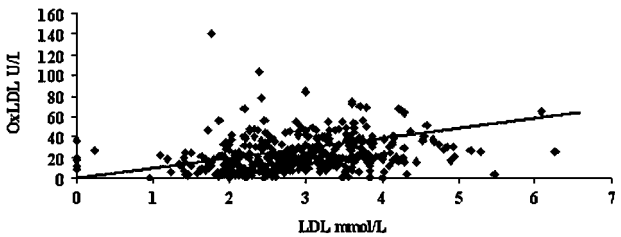

Fig. 3. Correlation between LDL and Ox-LDL in both sexes $r = 0.284$ ($P < 0.0001$).

correlated with Ox-LDL, in men TG levels correlated with increased Ox-LDL as well (Fig. 3). As one would expect, CRP was associated with increased LDL levels in females. It is well understood that exercise induces oxidative stress and sustained exercise results in an elevation of antioxidant defense and results in the reduction of inflammatory markers. These data strongly point toward the fact that physical activity helps decreasing levels of inflammation; this may, however, differ between the two sexes. The association between exercise and reduction in hCRP, as seen in this study, provides promising insights on CV risk reduction. Premenopausal sedentary women had better lipid profile and overall greater oxidative stress and inflammatory markers index compared with men; this raises the question on the mechanisms through which younger females may have CV benefits associated with exercise, despite the increased inflammation as demonstrated by the increases in CRP levels. Sex-based studies are needed to further investigate mechanisms by which both sexes may derive fitness-based beneficial CV protections.

Strengths of this study include a large number of healthy women participants with comprehensive measurements of both novel and traditional CV biomarkers.

Additionally, detailed information on CV risk factors was available, allowing for the control for potential confounding by these factors. Finally, few earlier studies have examined level of fitness among sedentary subjects jointly with regard to their influence on CV biomarkers. In conclusion, both lower levels of physical activity and higher levels of BMI were strongly associated with CRP in a large population of healthy women and men. Sedentary healthy women have increased CRP and Ox-LDL levels and overall decreased levels of oxidative stress and inflammatory markers. These findings demonstrate a sex-based difference in relation to physical inactivity and CV risk.

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