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Vitamin E differentially affects the short term exercise induced changes in oxidative stress, lipids, and inflammatory markers

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Introduction

Coronary artery disease (CAD) is the leading cause of mortality in the Western world. Oxidative stress and inflammation plays a major role in the pathogenesis of atherosclerosis induced CAD. Exercise reduces the risk of CAD, and may paradoxically promote free-radical formation, lipid peroxidation and vascular tissue injury [1–3]. Although trained athletes who received antioxidant supplements show evidence of reduced oxidative stress; until research fully substantiates that the long-term use of antioxidants is safe and effective, the recommendation for physically active individuals to ingest a diet rich in antioxidants will remain questionable [4–8]. The oxidation theory of cardiovascular disease appears to be widely accepted, yet there remains an obvious inconsistency between it and the benefits associated with exercise induced oxidative stress [4]. It is now generally recognized that regular exercise with minimum weight change has broad beneficial effects on lipoproteins profile [9–10]. Studies conducted on exercise with antioxidant supplementations failed to link the changes in lipid to vitamin E, but they documented attenuation in the levels of inflammatory and oxidative stress markers accompanied the exercise [11–13]. Data from our previous studies in humans have indicated that 30 minutes exercise at moderate intensity is sufficient oxidative stress to increase the susceptibility of low density lipoproteins (LDL) to oxidation. Additionally, exercise appeared to activate neutrophils, subsequently releasing myeloperoxidase (MPO) protein [14–15]. The purpose of this study is to examine the role played by exercise induced-oxidative stress and vitamin E supplementation on inflammation and oxidative stress markers.

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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 supplementation 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 disease, or physical inability to exercise were excluded from the study. 856 subjects filled the study questionnaire, however only 455 participants were found to be eligible and were enrolled for the study, 260 females (age 18–55) and 195 males (age 18–50). Enrolled subjects reflected the ethnic makeup of metropolitan Atlanta. The subject's compliance through the 8 weeks of the study was as follows: 227 F and 179 M completed 2 weeks of the exercise prescribed program, with 87.3 %, and 91.79% compliance, while 211 F, and 169 M continued through the end of the 4th week with 81.1%, and 86.6% compliance.

Dietary evaluations and vitamin E supplementation

To minimize the confounding effects of weight loss, subjects were counseled to maintain body weight, and not to make drastic changes in their daily diet. Subjects were also requested not to ingest other vitamins or dietary supplementations other than what supplied to them during the study. All participants were asked to complete dietary questionnaires indicating their typical daily food habits; one such questionnaire is filled at the first visit. Subjects were randomized to vitamin E (800 IU) or placebo; soft gelatin capsules 400 IU each providing the full biological potency of vitamin E (- tocopherol); placebo contain soft gelatin only without the active ingredients of - tocopherol. Subjects were advised to consume two capsules (400 IU) daily with normal meals throughout the period of the study. Capsules were obtained from J.R. Carlson Laboratories, Inc., Arlington Heights, IL, USA.

Exercise training

VO₂ peak was determined on a Marquette treadmill using a continuous progressive protocol [16]. 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. To evaluate the level of fitness, Subject VO₂, was measured before starting the exercise program and later after completion of the 8 week program: Participants were required to engage in at least 30 minutes, three times a week aerobic exercise for a total of 8 weeks. All subjects were followed by personal trainer to assess exercise behavior and compliance, and to provide encouragement; they were contacted every week either via email or telephone and could meet with personal trainer individually at any time during the study to go over the exercise routine. An activity log was used to record the subject's amount, type, duration and intensity of exercise performed; this information was used to identify variations between subjects training regimen.

Blood sample

Subjects were asked to give four blood samples, as follows, baseline sample (before they start to exercise at week 0), and then at week 2, week 4 and week 8. Heparinized blood

samples were obtained from the participant's forearm vein following a minimum 10 hours overnight fast. 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, USA) unless indicated otherwise.

Lipid analysis

Fasting plasma total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL-c), and low density lipoprotein (LDL-c) 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 markers in plasma, we measured a number of markers using commercially available enzyme-linked immunosorbent assay (ELISA) kits for the human MPO, 8-Isoprostane (immunoassay for 8-epi-Prostaglandin $\text{F}_{2\alpha}$), soluble vascular cell adhesion molecule-1 (sVCAM-1) monocyte chemotactic protein-1 (MCP-1) and Oxidized low density lipoprotein (OxLDL). Auto-antibodies to oxidized low density lipoprotein (AA-OxLDL) in plasma were determined using ELISA techniques as previously described [17].

Statistical analysis

The results were expressed as mean $\pm$ SD, and the significance of the differences between the mean values of both sexes was determined by the Student's t test. Pearson correlation was calculated to assess the association between the oxidative stress/inflammatory markers and lipids. Data were analyzed with S-plus 8 (Insightful-TIBCO Software Inc. Palo Alto, California) and SAS 9.1 (SAS Corporation, Cary, NC) packages.

Results

Total of 455 subjects, females (260) and male (195) were recruited for the study, their basic characteristics is described in Table 1A. The mean age for males and females were 32.4 ± 8.7 and 34.2 ± 10.0 respectively, males were slightly younger compared to females. The body mass index in males and females were 26.7 ± 5.0 and 27.0 ± 6.3 respectively showing slight over weight in both sexes. Subjects in both sexes have improved their fitness levels after they exercised. Females and males VO_2 levels after 8 weeks of exercise were significantly higher than their initial VO_2 levels ($P < 0.0007$, and $P < 0.0001$ respectively). Also males baseline, and after 8 weeks VO_2 levels were significantly higher than the corresponding females values ($P < 0.0001$), (Table 1B). The VO_2 max in males on placebo or vitamin E was 35.1 ± 7.7 and 34.5 ± 7.4 respectively whereas the corresponding female's values were 28.0 ± 6.4 and 27.8 ± 7.0 . The differences between the placebo and vitamin E groups VO_2 values within the same sex were not significant.

Effect of exercise on lipids

Lipoproteins in exercising subjects taking placebo or vitamin have not changed significantly. Vitamin E did not show beneficial effect on lipoproteins on both sexes after 8 weeks of exercise, this is well demonstrated by the fact that LDL-c levels in females taking vitamin E or placebo remained almost unchanged from its baseline levels. Whereas the males LDL-c increased on both groups with slight elevation among participants taking vitamin E, however the differences were not significant. HDL-c increased none significantly

with exercise among both sexes (Table 2A), these changes were not affected by either of the supplementations. Study population was further classified according to the level of VO₂, low<25, medium, high>35. The level of fitness did not show a significant effect on lipoproteins values among both sexes (Table 2B). Females who started with low VO₂ values showed slight decreases in their LDL-c values. Males on the other hand have shown increased HDL-c and LDL-c regardless of the VO₂ levels.

Oxidative stress markers

Table 3A and B describe the medium values for the oxidative stress markers measured in females and males respectively at the baseline and after the supplementation with the placebo or vitamin E to the subjects during the exercise regimen. Although the results did not establish a significant difference between either of the markers at the different time point, but trends were clear established in most makers.

MPO in both females and males tend to increase with increased level of exercise. Whereas MPO levels drop over time with progress in exercise regimen duration among those on placebo in both sexes, its levels remained higher compared to baseline among subjects taking vitamin E indicating that vitamin E may actually potentate the MPO levels. Isoprostane levels in females showed similar trends exhibited by MPO levels; however its levels in males decreased at the beginning of exercise and increased at the chronic phase of the physical activity among subjects taking placebo, and increased with level of fitness among males on vitamin E; furthermore males had higher Isoprostane levels compared to females. Soluble vascular molecule sVCAM decreased in females subjects taking placebo and increased in those on vitamin E; males on the other hand have shown opposite trends, as their sVCAM levels were obviously higher than that of females though not significantly. sVCAM increased among people taking placebo and decreased among those taking vitamin E. The differences between the levels of sVCAMs among females and males on placebo or vitamin E represent an interesting finding that demonstrates a sex differences in response to exercise vitamin E intakes. Monocyte chemotactic protein-1 (MCP-1) showed similar trends among males and females; it decreased at the initial level of the exercise and increased towards the chronic phase among subjects taking placebos; increased at the initial phase in both sexes and decreased by the end of two months.

Oxidative stress correlation studies

Several interesting correlations were observed in this study. Subjects duration time spent in the treadmill during the measurement of VO₂ was negatively correlated with age and BMI ($P<0.0001$), on the other hand VO₂ has shown negative correlation with hCRP among both placebo ($P<0.0004$), and vitamin E group ($P<0.01$) and also with MPO among females taking vitamin E ($P<0.0019$). Increased VO₂ levels associated with increased sVCAM in both groups ($P<0.0001$) and Isoprostane among vitamin E taking group (Table 4).

We assessed the effect of exercise and oxidative stress markers in changes in lipids; and as one would expect, VO₂ has shown negative correlation with total cholesterol (TC, $P<0.0001$), and LDL ($P<0.0001$). Higher MCP-1 at the beginning of the exercise tend to influence changes in LDL after two months of exercise ($P<0.02$); this changes diminished in the presence of vitamin E. Another very interesting finding is the association between OxLDL and lipid components, especially with LDL from subjects on placebo ($P<0.0001$) and those on vitamin E ($P<0.0028$). The negative association between HDL and sVCAM ($P<0.0001$) brings another interesting observation on the relationship between oxidative stress markers and lipids during exercise, sVCAM was lower among females compared to males.

Discussion

A growing body of evidence shows that oxygen radicals and other products of free radical reactions are involved in several disorders and diseases [8, 18, 19]. 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 cardiovascular benefits. Exercise may induce beneficial changes in lipid profile and thus reduce risk of cardiovascular disease [20]. Recent studies have suggested that exercise induced oxidative stress may potentially help lowering LDL and hCRP which are known to associate with cardiovascular disease [21, 22]. We examined effects of exercise training and supplementation of vitamin E on levels of oxidative stress and inflammatory markers. This study hypothesizes that supplementation of vitamin E might be counterproductive to the benefits associated with exercise induced oxidative stress. Vitamin E supplementation does not seem to be beneficial for the improvement of lipoproteins levels in both sexes. HDL-c increased in both sexes after two months of exercise among subjects taking placebo or vitamin E; on the other hand LDL-c did not seem to be affected by exercise or vitamin E supplementation however a sex dependent response was evident. Decreases in LDL-c was observed in an 8 weeks study among males and not females when the program included weight loss and dietary restriction [23], the current study did not intent to change the subjects dietary habit or the life style other than that requires the participants to refrain from vitamin supplementation and engage in a regular and prescribed exercise regimen. It is therefore unexpected to see drastic lipid change during such a short period of exercise Kraus et al., [24] had shown that exercise training had no significant effect on the total cholesterol or LDL cholesterol concentrations; they however shown that exercise had important effects on the concentrations of LDL sub-fractions. High-amount high-intensity exercise significantly reduced the concentrations of LDL and small LDL particles and increased the average size of LDL particles. The slight increases in HDL-c seen in this study suggest that aerobic exercise may actually increases HDL-C; as earlier reported [25]. Although the study could not establish significant differences between the level of oxidative stress and inflammation before and after exercise in both sexes on vitamin E or placebo, however there is a trend point towards the involvement of exercise in increasing the level of oxidative stress during the first two weeks of exercise as seen in the increased levels of MPO, Isoprostane and AA-OxLDL among females on placebos; and the increased MPO, AA-OxLDL, sVCAM, and OxLDL levels among males.

The increase in MPO can be interpreted as beneficial. Others and we had earlier suggested an exercise induced increase in MPO could be due to the increased degranulation of neutrophils and such oxidative stress could induce antioxidant defense [3]. Accordingly, we demonstrated an induction of catalase in animals subjected to exercise [26]. Recently, we suggested that enzymes such as MPO also could serve to oxidize lipid peroxidation derived aldehydes into carboxylic acids [27] and thus could be anti-atherogenic. However, in this study, only free plasma MPO protein was determined. We had also earlier suggested that vitamin E and estradiol might actually enhance the MPO catalyzed oxidations [28]. Such effects could explain the differences between men and women and could account for the increased isoprostanes and oxidation markers. In other words, these antioxidants could act as prooxidants when MPO is elevated. This could be one of the first suggestions for such effects in vivo.

One difference between males and females is the baseline fitness levels. The males could already be on the “defense” antioxidant phase of exercise induced benefits and thus could “resist” the oxidative stress as we early hypothesized [29].

Interestingly both sexes on both groups (Vitamin E/Placebos) have shown sharp hCRP drops after two weeks of exercise, however only females on vitamin E and males on placebo continued lowering their hCRP through the end of the exercise program, reflecting a sex and exercise extent dependent hCRP responses, to our understanding these findings have not been reported previously. Another finding in this direction is the decreased levels of MCP-1. Supplementations of antioxidants to exercisers have generated conflicting data [30–34]. The major findings of this study may be seen through the various correlations resulted between exercise, and lipid parameters on one hand and markers of oxidative stress and inflammation on the other hand. As one would expect elder participants have shown increased BMI (data not shown) and decreased duration time on the treadmill testing. This study also reports for the first time the association between MCP-1 and changes in LDL among both sexes and group, however to a lesser extend among vitamin E taking subjects, this finding shows that vitamin E supplementation may have counterproductive effects on reduction of LDL levels. The association between LDL and OxLDL ($P<0.001$) observed with exercise provide evidence that LDL levels may have been lowered through the oxidation induced by exercise and the positive correlation point out towards this direction; i.e in other word more LDL are oxidized into OxLDL and later cleared; furthermore this process slowed down by the supplementation of vitamin E, which may indicate that again supplementation of vitamin E may counter the effect induced by exercise as we earlier hypothesized. It may be worth mentioning that the weaker correlation between Ox-LDL and TG support the understanding that Ox-LDL is formed from LDLc epitope and not that of TG. The association between higher VO₂ and lower hCRP has provided evidence that CRP is an inflammatory marker that could be reduced through exercise.

The association between VO₂ and Isoprostane ($P<0.002$) confirm previous findings that exercise is an oxidative stress inducing activity [3], vitamin E seems to influence this correlation. A sex dependant correlation was observed between Isoprostane and VO₂, which could be attributed to the antioxidant effect of estrogen in females. Women tend to have negative correlation associated with oxidative stress than men; one in this direction is the decreased MPO levels among females on vitamin E.

It is also important to note that the duration of the exercise influences level of oxidative stress and, indeed, prolonged exercise may sustain the cardiovascular benefits [21].

In conclusion; this data strongly support the concept that exercise induces oxidative stress, and substantiate the benefits of oxidative stress associated with exercise might be blunted by the supplementation of vitamin E which did not show specific role during exercise. The association between exercise and reduction in hCRP provides promising insights on future studies focusing on cardiovascular risk reduction and mechanisms on how exercise may improve the cardiovascular outcome.

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Table 1A

Basic Characteristics of Subjects in the Study

Variables	Female		Females		Vitamin E		Males		Placebo		Males		Vitamin E	
	N		N		Mean $\pm$ SD		N		Mean $\pm$ SD		N		Mean $\pm$ SD	
AGE	130		130		34.2 $\pm$ 10.0		98		33.0 $\pm$ 8.8		97		32.4 $\pm$ 8.7	
BMI	127		127		27.0 $\pm$ 5.9		97		26.7 $\pm$ 5.0		94		27.1 $\pm$ 4.3	
Diastolic BP	118		122		76.7 $\pm$ 10.6		96		78.2 $\pm$ 8.4		91		78.6 $\pm$ 9.0	
Systolic BP	118		122		117.1 $\pm$ 12.9		95		123.8 $\pm$ 10.5		91		123.0 $\pm$ 11.4	
PULSE	112		110		83.6 $\pm$ 13.8		79		82.0 $\pm$ 10.3		80		82.3 $\pm$ 12.0	
Baseline VO2	116		124		27.8 $\pm$ 7.0		95		35.1 $\pm$ 7.7		96		34.5 $\pm$ 7.4	

Table 1B**VO2 Values in Females and Males**

Variables/Subjects	Females		Males		
Females Vs Males					
VO2 (ml/kg/min)	Mean (N)	SD	Mean (N)	SD	
VO2 Baseline	27.92 (240)	6.7	33.72 (195)	7.5	
				P<0.0001	
VO2 After 8 Weeks	30.25 (133)	8.5	39.06 (140)	8.8	
				P<0.0001	
Variables/Subjects	Females		Males		
Within the same Sex	Mean (N)	SD	Mean (N)	SD	
	VO2 (Baseline)	28.42 (127)	7.1	34.90(139)	7.7
	VO2 (8 Weeks)	30.05 (127)	8.0	39.03 (139)	8.9
	P	P<0.0007		P<0.0001	

Table 2A

Effect of vitamin E supplementation on lipoproteins

		Females				Males			
		HDL mg/dl	LDL mg/dl	VLDL mg/dl	N	HDL mg/dl	LDL mg/dl	VLDL mg/dl	N
Vitamin E	N								
Pre study	88	61.6±12.9	105.9±26.9	18.0±10.2	74	48.7±10.5	112.5±33.6	23.6±12.6	
Post Study	88	62.3±13.2	105.2±24.8	18.4±10.0	74	49.8±10.3	117.1±31.2	23.4±11.1	
Placebo									
Pre study	90	59.5±13.1	110.6±33.6	17.8±8.3	76	46.5±10.9	113.4±33.6	22.9±12.9	
Post Study	90	60.1±13.6	113.1±34.8	17.9±8.4	76	47.9±9.2	115.1±30.0	23.9±13.2	

Table 2B

Effect of level of fitness on lipoproteins

VO2 (ml/kg/min)	Females			Males		
	HDL mg/dl		N	LDL mg/dl		N
	Pre study	Post study		Pre study	Post study	
Low	62.2±14.7	62.9±13.3	49	120.7±31.6	117.4±28.5	52
Medium	61.4±14.8	62.1±15.2	57	103.1±23.9	105.7±27.6	46
High	59.2±10.6	59.4±11.2	63	102.9±33.3	104.8±33.8	51
				46.7±10.3	47.4±8.9	52
				46.5±11.9	48.1±10.8	46
				49.2±10.1	50.9±9.6	51
				118.3±32.4	119.5±28.8	52
				114.3±32.5	117.5±33.7	46
				105.5±34.5	111.1±29.3	51

Table 3A**Oxidative Stress and Inflammatory Markers in Females**

Females	Placebo	Vitamin E						
Variables	Baseline	2 w	4 w	8 w	Baseline	2 w	4 w	8 w
MPO (ng/ml)	2.89	2.93	3.36	2.98	3.10	2.96	3.54	3.34
Isoprostane (pg/ml)	13.19	13.57	14.05	13.82	13.12	12.80	12.55	11.34
SVCAM (ng/ml)	308.17	300.35	298.27	307.14	289.73	292.18	302.09	301.33
MCP1(pg/ml)	85.48	62.29	60.12	76.50	64.31	71.86	56.42	62.84
hCRP(ng/ml)	2.28	2.08	2.18	2.78	2.78	1.98	2.11	2.57
OxLDL (U/L)	21.23	20.98	21.25	22.25	21.49	22.80	21.83	20.50
AAOxLDL (OD)	0.19	0.21	0.21	0.20	0.20	0.21	0.21	0.23

Table 3B**Oxidative Stress and Inflammatory Markers in males**

Males		Placebo		Vitamin E				
Variables	Baseline	2 w	4 w	8 w	Baseline	2 w	4 w	8 w
MPO (ng/ml)	3.22	3.86	3.82	3.00	3.61	3.54	3.68	3.90
Isoprostane (pg/ml)	15.64	15.17	15.20	16.13	16.92	17.03	17.05	17.99
SVCAM (ng/ml)	467.96	530.56	499.10	510.94	510.88	514.60	513.21	477.62
MCP1(pg/ml)	93.20	71.82	80.73	86.18	84.36	91.33	89.23	77.70
hCRP(ng/ml)	1.14	1.05	0.98	0.94	1.00	0.91	1.62	1.24
OxLDL (U/L)	17.10	17.45	16.21	19.80	19.15	16.64	16.32	22.14
AAOxLDL (OD)	0.25	0.26	0.27	0.28	0.30	0.30	0.28	0.28

Table 4

Correlations studies

Variables	Variables	R (N)	P value
Duration Time	Age	−0.348 (217)	<0.0001
	BMI	−0.401 (428)	<0.0001
VO2	TC	−0.297 (220)	<.0001
	hCRP **	−0.307 (131)	<0.0004
	hCRP *	−0.220 (125)	<0.0100
	Isoprostane *	0.317 (131)	<0.0002
	Isoprostane (F-E)	0.301 (61)	<.01810
	sVCAM	0.5669 (431)	<0.0001
	MPO (F-E)	−0.389 (61)	<0.0019
HDL	sVCAM	−0.290 (430)	<0.0001
	Isoprostane	−0.195 (203)	<0.0052
MCP-1	Ch-LDL **	0.196 (197)	<0.0084
	Ch-LDL *	0.0167 (185)	<0.5673 (NS)
OxLDL	LDL *	0.203 (214)	<0.0028
	LDL **	0.281 (212)	<0.0001
	TG	0.192 (425)	<0.0001
	TC	0.321 (432)	<0.0001
MUFA	CRP	−0.151 (404)	<0.0022

** non-Vitamin E taking individuals,

* Vitamin E taking individuals E (On Vitamin E), F (Females), Ch-LDL change in LDL after 8 weeks