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2012

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The Effects of Aerobic Training and Age on Plasma sICAM-1

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Key words

- systemic inflammation
- age
- endurance training
- physical inactivity
- adhesion molecules

Abstract

Chronic low-grade systemic inflammation plays a role in the development of cardiovascular (CV) disease. Habitual endurance exercise training reduces the risk of CV disease in part through anti-inflammatory mechanisms. The purpose of this study was to investigate the effects of age, endurance training status, and their interaction on pro-inflammatory plasma cytokines involved in the pathogenesis of CV disease. Subjects were BMI-matched young (25±3 years; endurance trained: n=9, sedentary: n=11) and older (62±5 years; endurance-trained: n=12, sedentary: n=11) men. Plasma cytokine concentrations were determined by multiplex cytometric bead

assay. Soluble intercellular adhesion molecule-1 (sICAM-1) levels were 40% higher in sedentary older men compared to young sedentary subjects ($P=0.048$), but they were not different between the young and older trained men. Furthermore, sICAM-1 levels were negatively correlated with maximal oxygen uptake ($\dot{V}O_{2\max}$; $r=-0.38$, $P=0.01$) across all subjects. There were no significant differences among the groups in plasma concentrations of monocyte chemoattractant protein-1 (MCP-1), soluble tumor necrosis- α receptor (sTNFR), soluble CD40 ligand (sCD40L), or resistin. We conclude that habitual endurance training is associated with an attenuated age-related increase in plasma sICAM-1.

Introduction

Regular physical activity is associated with a reduced incidence of cardiovascular (CV) and all-cause mortality [2]. However, traditional CV disease risk factors (obesity, hypertension, hyperglycemia, hyperlipidemia, etc.) explain only ~60% of the reduced risk of CV mortality among physically active individuals [23]. There is evidence that chronic physical inactivity is associated with low-grade systemic inflammation [6,25], which increases the risk of developing CV disease [19,20]. Circulating levels of several pro-inflammatory cytokines, including monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor- α (TNF- α), soluble intercellular adhesion molecule-1 (sICAM-1), soluble CD40 ligand (sCD40L), and resistin have been implicated in age-related increases in CV disease risk [7,18,21,22,31].

Regular physical activity has been suggested to attenuate the chronic systemic inflammation that occurs with age [4]. Investigation of associations between habitual endurance training and

pro-inflammatory cytokines known to damage the vascular endothelium and contribute to the pathogenesis of atherosclerosis may further clarify the role by which physical activity reduces inflammation-related CV disease risk. Accordingly, the purpose of this investigation was to quantify the associations between endurance exercise training, age, and their interaction on systemic markers of inflammation. We hypothesized that habitual endurance training would be associated with attenuated age-related increases in these pro-inflammatory cytokines.

Methods

Subjects

All subjects provided written informed consent prior to participation and all protocols were approved by the Institutional Review Board at the University of Maryland. We confirmed that our study complied with the ethical standards of the International Journal of Sports Medicine [9]. Plasma samples of subjects from previous studies

accepted after revision
May 07, 2012

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DOI <http://dx.doi.org/10.1055/s-0032-1316317>
Published online:
September 12, 2012
Int J Sports Med 2013; 34:
253–257 © Georg Thieme
Verlag KG Stuttgart · New York
ISSN 0172-4622

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in our laboratory were assayed for the purposes of the present study [13, 15, 16, 32]. Subjects were healthy defined as having no history of smoking, cancer, bleeding disorders, liver, kidney, lung or CV disease, \geq Stage I hypertension, or diabetes, and not taking any medications. 22 age- and BMI-matched sedentary male subjects (young: $n=11$, older: $n=11$) and 19 active male subjects (young: $n=9$, older: $n=12$) were enrolled. Young subjects (25 ± 4 years) were classified as endurance-trained if they reported engaging in regular endurance type activities (e.g., running, cycling, or swimming) for >4 hr/wk and for >3 years. Older subjects (62 ± 2 years) were classified as endurance-trained if they reported participating in regular endurance training on >3 days/wk for >20 years. Young and older sedentary subjects reported performing regular exercise for <20 min/day, <2 days/wk. Physical activity status was assessed via a leisure time physical activity questionnaire as used previously in our laboratory [13, 16, 32]. Young and older subjects refrained from alcohol, vitamins, caffeine, antioxidants and anti-inflammatory medications for 24 and 48 h prior to testing, respectively. All testing was performed after a 12-h overnight fast. Subjects were instructed not to make any changes to their dietary habits before testing and to maintain a low nitrate diet 2–3 days prior to testing.

Cardiovascular and anthropometric assessments

Fasting blood samples were obtained using standard venipuncture techniques. Glucose, triglycerides, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol concentrations were measured in serum samples (Quest Diagnostics, Baltimore, MD). Plasma samples were prepared in EDTA-anticoagulated tubes for measurement of circulating cytokines. A maximal treadmill exercise test was performed to assess maximal oxygen uptake ($\dot{V}O_2\text{max}$) as described by our laboratory previously [13, 16, 32]. Body composition was assessed by dual x-ray absorptiometry (Hologic; Bedford, MA) in the older subjects. In the younger subjects, body composition was assessed using the seven-site skinfold method [12]. Trained subjects refrained from exercise 16 to 24 h prior to testing.

Cytokine assay

Plasma cytokines levels (resistin, sTNF-R, sCD40L, sICAM-1, and MCP-1) were measured in duplicate by a multiplex cytometric bead assay according to the manufacturer's instructions (Bender MedSystems; Vienna, Austria) on a FACSCalibur™ System (BD Biosciences; San Jose, CA). Briefly, a master mixture containing beads coated with antibodies specific for the different cytokines (resistin, sTNF-R, sCD40L, sICAM-1, MCP-1) was prepared and labeled with a biotin-conjugate mixture. The beads were then washed to remove unbound protein and fluorescently labeled with streptavidin-PE prior to cytometric analysis. The beads used in this assay can be differentiated by their sizes and by their distinct spectral addresses. A mixture containing multiple coated beads for all analytes was incubated with plasma samples or cytokine standards. A standard curve generated from the fluorescence intensities of the cytokine standards was used to calculate the plasma cytokine concentrations.

Statistics

A 2-way ANOVA was used to examine the main and interactive effects of physical activity status and age group on peripheral cytokine levels, followed by Fisher's Least Significant Difference post hoc test for pairwise differences between groups. The sta-

tistical significance criterion was $P \leq 0.05$. The initial study from which these samples were derived was statistically powered to detect training status effects on other circulating biomarkers [13, 16]. Based on these calculations, this study was appropriately powered to detect a main effect of physical activity of ~ 0.5 standard deviations, or $\sim 30\%$ differences between groups, on plasma cytokine concentrations ($\alpha=0.05$, $1-\beta=0.8$).

Results

Subject characteristics

Cardiovascular and body composition-related parameters of the subjects are presented in **Table 1**. The four groups were successfully matched for BMI. Young endurance-trained subjects had a $\sim 25\%$ higher $\dot{V}O_2\text{max}$ compared to young sedentary subjects, and older endurance-trained subjects had a $\sim 44\%$ higher $\dot{V}O_2\text{max}$ compared to older-sedentary subjects ($P < 0.001$).

Plasma cytokines

All cytokine concentration data conformed to the assumptions of normality and homogeneity of variances. There were no significant effects of training status on plasma cytokine levels in young and older groups. However, there was a significant age \times training status interaction effect on sICAM-1 levels ($P < 0.05$) (**Fig. 1a**). Post hoc tests indicated an effect of age on sICAM-1 levels where the older sedentary group had significantly higher plasma sICAM-1 concentrations than the young sedentary group ($P < 0.05$), whereas there was no significant difference between young and older endurance trained groups (**Fig. 1a**). Additionally, $\dot{V}O_2\text{max}$ (L/min) significantly correlated with sICAM-1 levels across all groups ($r = -0.38$, $P = 0.01$; **Fig. 1b**). There were no interactive or main effects of age or training status on plasma concentrations of resistin, sTNF-R, sCD40L, or MCP-1 ($P > 0.05$; **Table 2**), and these cytokine concentrations did not significantly correlate with any standard CV risk factors or body composition variables. However, sICAM-1 levels were positively correlated with sCD40L, MCP-1, and sTNFR across all groups (all $P < 0.05$; **Table 3**). There were no significant correlations between plasma cytokine level and percent body fat (resistin: $r = -0.13$, sICAM-1: $r = 0.03$, MCP-1: $r = -0.05$, sTNFR: $r = 0.02$, sCD40L, $r = 0.01$; all $P > 0.05$) and, therefore, percent body fat was not included as a covariate in statistical analyses.

Discussion

The major finding of this study is that endurance exercise training is associated with attenuated age-related increases in plasma sICAM-1 levels. Importantly, these data were obtained from a carefully recruited and screened cohort consisting of very healthy, lean, BMI-matched, and disease-free young and older sedentary and endurance-trained men. Therefore, although our cross-sectional study design does not allow for definitive cause-effect conclusions, we believe that we have isolated the effects of long-term endurance exercise training on the plasma concentrations of the pro-inflammatory cytokines examined.

Elevated plasma levels of sICAM-1 have been suggested to directly contribute to the pathogenesis of atherosclerosis [10] and are positively associated with subclinical markers of CV disease such as systemic inflammation, low-grade inflammation, and arterial stiffening [30]. Endurance training is suggested to

	Endurance-Trained		Sedentary	
	Young (n=9)	Older (n=12)	Young (n=11)	Older (n=11)
age (yr)	25 ± 1 ^a	62 ± 2 ^b	26 ± 1 ^a	64 ± 2 ^b
body mass (kg)	76.0 ± 4.4	70.7 ± 3.1	77.7 ± 4.4	74.7 ± 2.4
BMI (kg/m ²)	23.6 ± 1.2	22.9 ± 0.7	23.3 ± 1.1	24.3 ± 0.6
body fat (%)	12.7 ± 2.0 ^a	18.0 ± 1.3 ^b	14.8 ± 1.8 ^{a,b}	23.5 ± 1.8 ^c
fat-free mass (kg)	65.8 ± 2.8 ^a	57.6 ± 1.8 ^b	65.5 ± 2.6 ^a	56.8 ± 1.4 ^b
fat mass (kg)	10.2 ± 2.0 ^a	13.1 ± 1.5 ^a	12.2 ± 2.0 ^{a,b}	17.9 ± 1.7 ^b
glucose (mg/dL)	82.6 ± 3.1 ^a	93.8 ± 2.1 ^b	80.5 ± 2.0 ^a	100.7 ± 2.6 ^c
cholesterol (mg/dL)	153.1 ± 7.2 ^a	199.2 ± 8.9 ^b	161.5 ± 11.1 ^a	194.2 ± 10.6 ^b
HDL-C (mg/dL)	56.4 ± 3.3 ^a	71.2 ± 3.3 ^b	49.5 ± 2.8 ^a	51.0 ± 4.6 ^a
LDL-C (mg/dL)	83.7 ± 6.5 ^a	114.8 ± 8.4 ^b	93.6 ± 10.1 ^a	122.5 ± 11.4 ^b
TG (mg/dL)	64.9 ± 6.9 ^a	66.2 ± 8.4 ^a	91.6 ± 10.5 ^{a,b}	103.0 ± 13.5 ^b
SBP (mm Hg)	118.3 ± 1.8 ^a	122.4 ± 3.3 ^{a,b}	119.8 ± 1.9 ^a	128.5 ± 2.6 ^b
DBP (mm Hg)	74.7 ± 3.1 ^a	79.2 ± 1.9 ^{a,b}	78.1 ± 1.9 ^a	84.8 ± 1.6 ^b
MAP (mm Hg)	89.2 ± 2.3 ^a	93.6 ± 2.1 ^a	92.0 ± 1.8 ^a	99.3 ± 1.6 ^b
VO ₂ max (L/min)	4.72 ± 0.2 ^a	3.52 ± 0.2 ^b	3.61 ± 0.1 ^b	2.08 ± 0.12 ^c
VO ₂ max (mL/kg/min)	63.0 ± 2.5 ^a	50. ± 1.9 ^b	47.1 ± 1.6 ^b	28.1 ± 1.7 ^c
VO ₂ max (mL/kg FFM/min)	72.0 ± 1.9 ^a	61.1 ± 2.3 ^b	55.3 ± 1.4 ^b	36.7 ± 1.9 ^c

Data are presented as mean ± SEM. Values with different superscripts are statistically significantly different ($P < 0.05$). BMI, body mass index; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TG, triglycerides; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; VO₂max, maximal oxygen uptake; FFM, fat-free mass

Table 1 Subject characteristics.

attenuate systemic inflammation through the increased secretion of anti-inflammatory cytokines into the circulatory system [5]. Hence, the observed reductions in plasma sICAM-1 levels may be due to local and/or systemic attenuation of pro-inflammatory signaling pathways that promote ICAM-1 cleavage [29]. Additionally, increased sICAM-1 shedding from cultured endothelial cells has been observed in response to pro-atherogenic shear stress [28]. Thus, an important area for future work is to determine whether the age-related increases in pro-inflammatory/pro-atherogenic vascular hemodynamics might be mechanistically linked to increases in endothelium-derived sICAM-1 concentrations in human plasma.

Although we found no significant age- or exercise training-related effects on the other cytokines we investigated, sCD40L, MCP-1 and sTNFR were all positively and significantly correlated with plasma concentrations of sICAM-1. Correlations between the plasma levels of these pro-inflammatory cytokines are possibly suggestive of underlying systemic inflammation in individuals with elevated sICAM-1 levels. Additionally, it is possible that an age-related increase in all of the cytokines examined would be observed by expanding the study sample size.

Our finding of higher sICAM-1 levels with age in sedentary individuals is consistent with previous results indicating a positive relationship between age and sICAM-1 levels in Caucasian men and women ages 18–75 years [22]. Our data are also consistent with findings from the Physicians' Health Study, which reported positive associations between plasma sICAM-1 and age ($r = 0.15$) in 948 healthy middle-age men. Further, results from the Physicians' Health Study agree with our findings of attenuated sICAM-1 levels with habitual endurance training, as individuals grouped in higher sICAM-1 quartiles were less likely to exercise more than one time per week [27]. The positive relationship between exercise frequency and plasma sICAM-1 levels is also supported by lifestyle intervention studies reporting decreases in sICAM-1 levels with moderate intensity endurance training and dietary lifestyle interventions designed to reduce body mass in overweight to obese individuals [8,26] and patients with chronic heart failure [1]. In contrast, there have been other reports of no effect of endurance exercise on plasma sICAM-1

levels in patients with chronic heart failure and healthy controls [24]. Discrepancies among studies may be due to differences in exercise intensity and program lengths. Further, in these previous studies, the effects of endurance training on plasma sICAM-1 may be confounded by large differences in changes in fat mass between intervention groups.

Although our subjects were matched for BMI, there were significant differences among the groups in percent body fat and total fat mass. On the basis of previous data indicating that adipose tissue can produce sICAM-1 [3], it is possible that differences in body composition contributed to the higher sICAM-1 levels in our sedentary older subjects. However, it is important to point out the pairwise correlations between percent body fat and total fat mass and sICAM-1 levels were not statistically significant in our study. These findings differ from previous studies that have shown correlations between body fatness and sICAM-1 levels in specific subject populations. For example, sICAM-1 was significantly correlated with percent body fat, (e.g., Pima Indians [31] and obese women [11]). Thus, it appears that the amount of adipose tissue may not necessarily drive increased circulating sICAM-1 levels in normal weight young and older endurance-trained and sedentary men. Alternatively, it is possible that the adipose tissue itself becomes inflamed with chronic sedentary behavior [25], and adipose-derived sICAM-1 increases with a sedentary lifestyle during aging. This is supported by animal studies observing endurance training-induced decrements in adipose tissue macrophage infiltration and TNF α expression without changes in fat mass [17]. We did not observe an effect of training on plasma cytokines in the younger cohort. It is possible that this study was underpowered to detect significant differences in plasma cytokines between the younger age groups and an effect of age on the other cytokines measured. An additional explanation for the lack of a training effect in the younger cohort may be that in normal weight individuals, sedentary behavior may gradually lead to changes in adipocyte biology that result in adipocyte inflammation that do not manifest in the form of increased circulating levels until later in life. This is supported by the recent observation that adipose tissue hypoxia and oxidative stress increase with age [33]. Findings from our study support

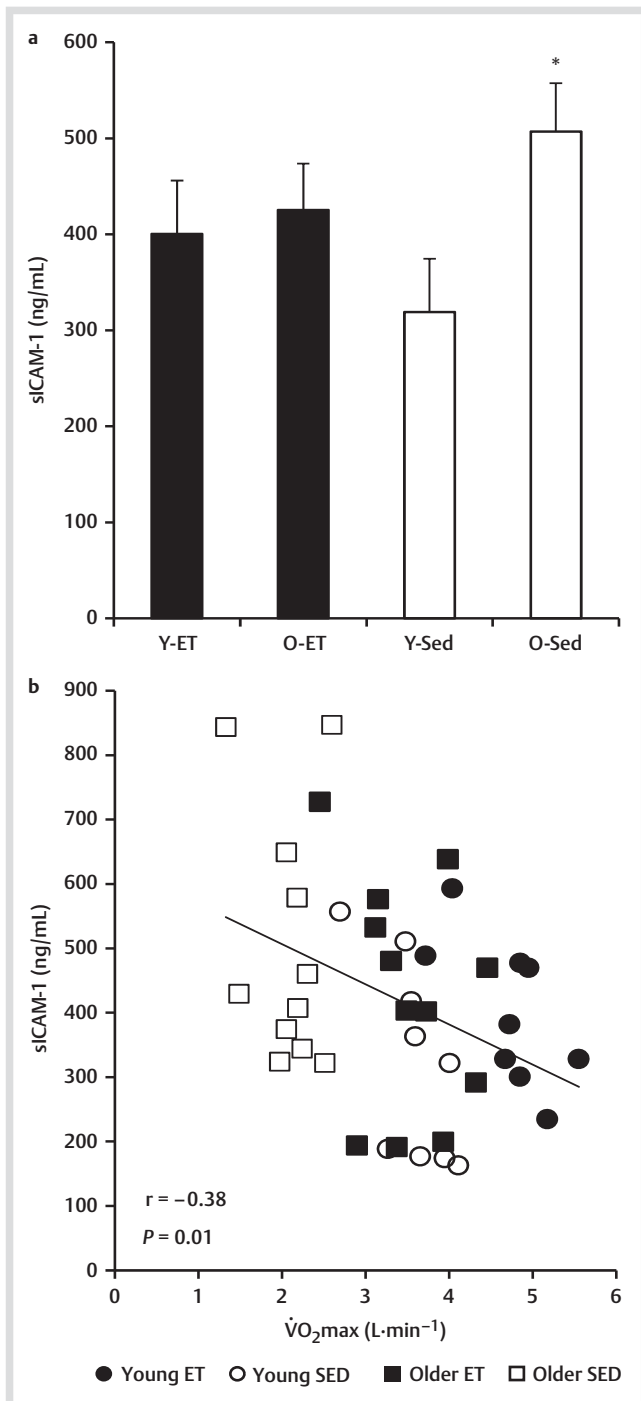


Fig. 1 Influence of exercise training and age on plasma soluble intercellular adhesion molecule-1 (sICAM-1) concentrations. **a** Concentrations of sICAM-1 in young endurance-trained (Y-ET), older endurance-trained (O-ET), young sedentary (Y-Sed), and older sedentary (O-Sed) men. *Significantly different from Y-Sed ($P < 0.05$). **b** Correlation between maximal oxygen uptake ($\dot{V}O_2\text{max}$) and sICAM-1 levels across all subjects.

the notion that habitual endurance training may combat such increases in adipose tissue inflammation.

Limitations

There are several important limitations of our study that must be considered. First, as mentioned above, it is possible that we

Table 2 Plasma cytokine concentrations.

	Endurance-Trained		Sedentary	
	Young	Older	Young	Older
sCD40L (pg/mL)	431 ± 291	165 ± 252	103 ± 263	633 ± 263
sTNFR (ng/mL)	1.1 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	1.2 ± 0.2
MCP-1 (pg/mL)	391 ± 49	352 ± 42	312 ± 44	352 ± 44
resistin (ng/mL)	9.1 ± 0.7	8.4 ± 0.6	9.0 ± 0.6	8.5 ± 0.6

Data are presented as mean ± SEM

Table 3 Correlations between plasma cytokine concentrations.

	sCD40L	sTNFR	MCP-1	Resistin
sICAM-1	0.345*	0.489**	0.302*	-0.250
sCD40L	-	0.854**	0.497**	-0.446**
sTNFR	-	-	0.518**	-0.342*
MCP-1	-	-	-	0.080

Correlation (r values) between cytokine concentrations across all subjects. *Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed)

were underpowered to detect significant differences among groups in the cytokines examined, as evidenced by the large variability in the cytokines studied (particularly sCD40L) and also significant correlations between some cytokines but lack of statistically significant differences among groups for cytokines besides sICAM-1. Second, by design our study did not have a large range of body fatness, as groups were matched for BMI and even the sedentary groups were quite lean (although statistically their body fatness was greater than the trained group). Thus, without a large range of body fatness within our cohort, we were unable to examine the full spectrum of possible relationships between body composition and plasma cytokine levels. However, we also regard this aspect of our study as a strength, in that we achieved our primary aim of identifying the influences of age, training status, and their interaction on plasma cytokine concentrations while controlling for other factors such as body weight or composition to the extent possible with a cross-sectional study design. Third, owing to the complexities of appropriately controlling for variations in the menstrual cycle of young and older women, we chose to recruit only men for these initial studies. Our data should, therefore, not be extrapolated to women, and future studies should examine whether sex differences exist in the effects of endurance training and age on circulating inflammatory cytokines. Fourth, it is possible that some cytokines may be elevated by the previous bout of exercise for longer than the 16–24h rest period used in our trained groups, and this may have influenced our results. However, we recently found that circulating microparticles expressing the cell surface antigen E-selectin, a molecule expressed on vascular endothelial cells exclusively upon activation by inflammatory insult, were increased >2 fold with as little as 1 day of inactivity in individuals who regularly perform endurance exercise [14]. Thus, it appears that removal of regular exercise bouts acutely increases inflammatory signaling to the vasculature, and accordingly, we do not believe that rest periods of greater than 24h are necessary for examination of the influence of regular endurance exercise on inflammatory factors.

Conclusions

In summary, our findings suggest that regular endurance exercise training is associated with attenuated age-related increases in sICAM-1 levels. Additionally, our findings suggest that sICAM-1 levels are correlated to other pro-inflammatory and atherogenic cytokines in young and older endurance-trained and sedentary men.

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