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Effects of exhaustive training with L-arginine consumption on inflammation and oxidative stress biomarkers in young bodybuilders

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Abstract

***Background & Aims*:** The acute exercise causes induction of oxidative stress and inflammatory responses. Considering anti-inflammatory and antioxidant properties of L-arginine, in this study we have investigated effects of L-arginine consumption on inflammatory and oxidative stress biomarkers following exhaustive training in young bodybuilders.

***Materials & Methods*:** In an interventional study, 30 young bodybuilders were divided into two equal groups, placebo (consuming L-arginine) and supplementation (consuming dextrose). Each individual received 3 g/day of L-arginine or dextrose for one week. During the supplementation, all participants performed one week exhaustive training according the specific protocol. Blood samples were collected before (at baseline) and immediately after first training session (for evaluating acute effects) and also after one week training. Finally serum levels of C-reactive protein (CRP), interleukin-6 (IL6), malondialdehyde (MDA) and activity of superoxide dismutase (SOD) were determined in all samples by ELISA.

***Results*:** The results showed that exhaustive training caused a significantly increase in levels of CRP, MDA and IL6 ($p<0.05$). Our results revealed that the L-arginine consumption could prevent exercise-induced increasing in concentration of these factors following trainings. Also, positive correlations were observed between CRP with IL6, CRP with MDA and IL6 with MDA before the training.

***Conclusions*:** Performing acute and chronic exhaustive training even in athlete causes increasing in inflammatory and oxidative biomarkers and consumption of L-arginine could modulate chronic and acute exhaustive exercise-induced oxidative stress and inflammatory responses.

***Keywords*:** Inflammation, Oxidative stress, Exercise trainings, Arginine

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Introduction

Physical activities especially acute exercises in addition to maintaining health can induce oxidative stress and also inflammatory responses (1-3). So, hard and exhaustive aerobic and anaerobic trainings can increase oxidation of macromolecules such as lipids and

proteins (1,4). The incidence of such condition which is associated with oxidative stress can has adverse effects such as cell membranes damage or/and DNA and RNA damages (1,4,5). On the other hand it has been observed that the acute short or long-term high-intensity exercises associated with metabolic stress and increased inflammatory markers such as C-reactive protein (CRP), interleukin -1 and -6 (IL1 and 6), colony stimulating factor (CSF) (2,6,7). Human body has enzymatic (such as catalase, superoxide dismutase, glutathione peroxidase and reductase) and non-enzymatic (such as vitamins A, E and C, glutathione, L-arginine, and beta-carotene) antioxidants to deal with oxidative stress (8). Nevertheless it has been documented that in acute and exhaustive exercise, the natural antioxidant system activity is not enough (1-3). Therefore, for inhibition of oxidative stress and inflammatory conditions during the intense exercise suitable approaches are required. One of these approaches is using L-arginine as a dietary supplement. Arginine (Arg) is considered as semi-essential amino acid and despite of its endogenous synthesis, in some conditions such as growth and stress, body can not produce enough amount of the Arg (9,10). Previous studies have shown that arginine supplement could improve immune function and reduce mRNA expression of inflammatory cytokine (9-11). Arginine has beneficial effects on endothelial function and insulin sensitivity in healthy individuals (12,13) and nowadays it is used for enhance immune function and some sever clinical conditions (14). Moreover, L-arginine can be a substrate of nitric oxide synthesis (NOS) and consequently play a role in NO synthesis (15). On the other hand antioxidant and anti-platelet effects of NO have been reported (16,17). However studies have documented that arginine could apply its antioxidant and anti-inflammatory effects independent of NO (9,10). Wells et al. (18) have reported an inverse association between receiving dose of arginine and blood CRP levels. In another study also it has been found that L-arginine inhibits secretion of tumor necrosis factor (TNF), IL 1 and 6 from macrophages and other muscles inflammatory cells19. Besides, significant increases in superoxide dismutase (SOD) activity and reduction in xanthine oxidase (XO) activity and MDA concentrations have been indicated following L-arginine supplementation for 15 days (20).

Considering the reports about effects of arginine on inflammatory and antioxidant systems20,21 and also lack of proper study about effects of L-arginine supplementation on oxidative stress and inflammatory conditions following intense exercise, in this study we have examined the effects of exhaustive exercise for 7 days on inflammatory (CRP and IL6) and oxidative stress (SOD and MDA) factors as well as possible beneficial influences of L-arginine supplementation on these parameters in young bodybuilders.

Materials and Methods

In this prospective study, effects of one week exhaustive exercise and L-arginine supplementation on levels of MDA, CRP, IL6 and SOD activity were investigated. The studied population included healthy young bodybuilders with at least two years training. Thirty bodybuilders were selected, considering criteria of age 30 ± 5 years, body mass index (BMI) 24 ± 3, avoiding the use of antioxidant supplements and other supplements, non-smoking and lack of metabolic diseases. The study was approved by the Ethical Committee of Urmia University and was conducted according to the Helsinki declaration. Also all recruited subjects gave written informed consent according to the ethical committee criteria. Subjects were randomly divided into two equal groups, placebo (n=15) and supplementation (n=15). The supplementation group received daily 3 grams of L-arginine (Karen Pharmaceutical Co, Yazd-Iran) for 7 days and the placebo group received daily 3 grams of dextrose during same period. All participants carried out exhaustive exercise according to specified protocols for a week. The training program includes a week of exhaustive incremental exercise on treadmill.

Each training session consisted of warm-up, the main training and cooling down steps. The warm-up step consisted of stretching movement for 5 to 7 minutes and the main training included running on the treadmill at speed of 6 to 8 km/h for 3 minutes, one minute active

rest (at speed of 3 km/h) and then running at speed of 8 to 10 km/h until exhaustion. Colling down step also contained 2-minute walk slowly (at speed of 3 km/h) on the treadmill and then stretching movements. Blood samples were collected before (at baseline) and immediately after first training session (for evaluating acute effects) and also after one week training. The sera were isolated using centrifugation and stored at -20 °C until laboratory experiments. To determine the concentration of SOD and MDA in serum, Biospes ELISA kits (China) were used. The serum concentrations of IL6 and CRP were investigated by ELISA kit (Bender MedSystems, Austria and Cortez Diagnostics, USA respectively) according to the procedures provided by the manufacturer.

Statistical analysis:

The data were analyzed using statistical software SPSS19. Due to the small sample size, non-parametric statistical tests were used. For comparison of quantitative parameters between two different times in a group Wilcoxon test and between two different groups Mann-Whitney U test were used. Also to evaluate the association between various parameters Spearman test was used. $p=0.05$ was considered as significance level.

Results

Demographic characters of both placebo and L-arginine supplementation groups are listed in table 1. The results showed no significant difference in age, height, weight, BMI, and maximum oxygen consumption between the two groups. The data about comparison of CRP, IL6, MDA levels and SOD activity between the supplementation and placebo groups and also between different times of trainings are shown in Table 2. The results demonstrated that one session of exhaustive exercise caused significant increase in CRP and MDA concentrations in both supplementation and placebo groups, although after one week of training in the group with L-arginine supplementation the concentrations returned to basic levels. In the placebo group after one week training the MDA and CRP concentrations still were higher than before training. It was observed that one session of exhaustive training did not affect the IL6 level in studied groups. Although after a week of training IL6 level in the placebo group was significantly higher than the supplementation group and also the level was higher than before training in this group. SOD activity in both groups showed no significant changes during the study. Evaluating possible relations between various blood parameters before exhaustive exercise in supplementation and placebo groups showed positive correlations between IL6 with CRP (r=0.72, p=0.022 and r=0.61, p=0.043 respectively), MDA with CRP (r=0.69, p=0.041 and r=0.58, p=0.048 respectively) and MDA with IL6 (r=0.63, p=0.047 and r=0.74, p=0.036 respectively) levels (Table 3). After one-week exhaustive exercise a positive correlation was observed between concentrations of IL6 and CRP (r=0.68, p=0.042) in the supplementation group. In placebo group in addition to a positive correlation between CRP and IL6 levels (r=0.89, p=0.014), we found also a significant correlation between MDA and CRP levels (r=0.56, p=0.049) (Table 4).

Table 1 Demographic characters of placebo (n=15) and L-arginine supplementation (n=15) groups

	Supplementation	Placebo	p-Value
Age (year)	28.4±1.96	28.7±2.5	0.77
Height (cm)	178.7±4.9	180.7±6.33	0.44
Weight (kg)	79.6±7.53	79.7±7.68	0.98
Body mass index (kg/m^2)	24.93±2.11	24.41±1.96	0.56
Body total lipid (%)	12.68±6.41	11.78±5.29	0.74
Maximum oxygen consumption (ml/kg/ml)	36.1±1.37	36.1±1.45	1

All data are expressed as mean ± SD

Table 2 Comparssion of C-reactive protein (CRP), interleukin 6 (IL6), malondialdehyde (MDA) levels and superoxide dismutase (SOD) activity in supplementaion (L-arginine) and placebo groups

	Groups	**Before training**	**After 1st session**	**After one week training**
CRP (mg/l)	placebo	4.13±2.06	6.67±3.16[a]	6.58±2.75[b]
	supplementaion	4.52±2.10	7.05±3.15[a]	4.20±2.22[b, d]
IL6 (pg/ml)	placebo	4.74±1.84	6.14±2.05	7.24±1.89[b]
	supplementaion	3.96±2.04	5.40±1.86	4.48±0.94[d]
MDA (mmol/l)	placebo	0.35±0.06	0.50±0.12[a]	0.49±0.09[b]
	supplementaion	0.37±0.05	0.59±0.15[a]	0.40±0.10[c, d]
SOD (IU/ml)	placebo	4.02±0.59	3.78±2.78	4.15±2.70
	supplementaion	4.10±1.42	3.91±1.29	4.19±1.39

Statistical differences: [a] 1st session vs. before training; [b] one week vs. before training; [c] 1st session vs. one week; [d] placebo vs. supplementation. All data are presented as mean ± SD.

Table 3 Correlation between inflammation and oxidative stress markers before exhaustive exercise in supplementation (L-arginine) and placebo groups

	CRP (mg/l)		IL6 (pg/ml)		MDA (mmol/l)		SOD (IU/ml)	
	r	p	r	p	r	p	r	p
Supplementation group								
CRP (mg/l)	-	-	0.72	0.022	0.69	0.041	-0.37	0.34
IL6 (pg/ml)	0.72	0.022	-	-	0.63	0.047	0.46	0.23
MDA (mmol/l)	0.69	0.041	0.63	0.047	-	-	-0.19	0.67
SOD (IU/ml)	-0.37	0.34	0.46	0.23	-0.19	0.67	-	-
Placebo group								
CRP (mg/l)	-	-	0.61	0.043	0.58	0.048	0.39	0.42
IL6 (pg/ml)	0.61	0.043	-	-	0.74	0.036	-0.37	0.85
MDA (mmol/l)	0.58	0.048	0.74	0.036	-	-	-0.20	0.71
SOD (IU/ml)	0.39	0.42	-0.37	0.85	-0.20	0.71	-	-

CRP, C-reactive protein; **IL6**, interleukin 6; **MDA**, malondialdehyde; **SOD**, superoxide dismutase

Table 4 Correlation between inflammation and oxidative stress markers after one week exhaustive exercise training in supplementation (L-arginine) and placebo groups

	CRP (mg/l)		IL6 (pg/ml)		MDA (mmol/l)		SOD (IU/ml)	
	r	p	r	p	r	p	r	p
Supplementation group								
CRP (mg/l)	-	-	0.68	0.042	0.41	0.068	-0.24	0.57
IL6 (pg/ml)	0.68	0.042	-	-	0.034	0.253	0.022	0.721
MDA (mmol/l)	0.41	0.068	0.034	0.253	-	-	0.017	0.881
SOD (IU/ml)	-0.24	0.57	0.022	0.721	0.017	0.881	-	-
Placebo group								
CRP (mg/l)	-	-	0.89	0.014	0.56	0.049	0.027	0.82
IL6 (pg/ml)	0.89	0.014	-	-	0.50	0.057	-0.09	0.73
MDA (mmol/l)	0.56	0.049	0.50	0.057	-	-	-0.17	0.63
SOD (IU/ml)	0.027	0.82	-0.09	0.73	-0.17	0.63	-	-

CRP, C-reactive protein; **IL6**, interleukin 6; **MDA**, malondialdehyde; **SOD**, superoxide dismutase

Discussion

Considering that acute exercise induces stress and inflammatory responses and on the other hand, due to the damaging effects of inflammation and oxidative stress on the body, it is necessary to find new approaches to prevent these harmful effects during exercise (1,3,4). For this purpose some studies have examined the effect of vitamin and antioxidants supplements in preventing inflammation and acute stress caused by intense exercise (3,22,23). In this study, in addition of investigating the effects of exhaustive exercise for 7 days on some inflammatory and oxidative stress markers in young bodybuilders, we studied possible beneficial and inhibitory effects of L-arginine supplementation.

The results of our study showed that both one session and one week of exhaustive exercise caused a significant increase in CRP concentration, but IL6 level increased after one week training. Previous studies have also reported elevated levels of CRP serum after short-term high-intensity exercise (16,24). Previously it has been suggested that increase in levels of inflammatory cytokines and mediators such as granulocyte-colony stimulating factor (G-CSF), IL 1 and 6 possibly cause exercise-induced CRP elevation (2,6,7). However, our findings indicated that increase in CRP level occurred after a training session without significant change in concentration of IL6. So it can be concluded that other inflammatory mediators or other mechanisms are also involved in this process. In contrast to our results in a study conducted on elderly men, a significant increase of IL6 after a session of acute exercise has been reported3. Such differences may be due to various studied population, since it has been well-documented that elevation of inflammatory factors immediately after exercise is more common in those without history of regular exercise (2). Our results revealed that acute exercise increased MDA level but did not change SOD activity in serum. In consistence with our findings Fogarty et al. (24) have also reported an increase in MDA levels after exhaustive aerobic exercise. However, some studies have mentioned that aerobic exercises had no effect on oxidative stress markers in young men with history of exercise (25,26). Considering that in this study we did not find any decrease in antioxidant enzyme activity, it can be inferred that elevation of MDA level was due to increase in free radicals and reactive oxygen species rather than antioxidant capacity reduction. In support of this hypothesis, it has been described that one of the possible mechanism in

increasing MDA levels following exercise is high activity of xanthine oxidase enzyme (27).

Due to anti-inflammatory and antioxidant effects of arginine it can possibly be a good supplement for preventing the effects of acute exercise. Our results revealed that supplementation with L-arginine could inhibit elevation of inflammatory factors such as CRP and IL6 following exercise. Inhibitory effects of L-arginine on inflammatory responses have been documented by previous studies, as Martina and colleagues showed that arginine supplementation together with N- acetylcysteine could reduce inflammatory markers in patients with high blood pressure and type 2 diabetes (28). Wallas et al. (18) have also reported an inverse correlation between amount of orally received arginine and blood CRP levels. In addition, they mentioned a 47% decrease in IL6 levels after 6 months of L-arginine supplementation. Various mechanisms have been suggested for L-arginine in reducing inflammation, of which can mention the effect of L-arginine in reducing serum lipids (29). Another possible mechanism is increasing some anabolic hormones such as prolactin, growth hormone and insulin-like growth factor 1 which can reduce the inflammation (30,31). Also it is possible that L-arginine increases level of tissue inhibitor of the metalloproteinase 1 (TIMP-1) via elevating adiponectin and therefore reduces vascular inflammation (32). Considering that in this study we did not investigate the possible mechanisms of L-arginine in reducing inflammation and on the other hand the exact mechanism is not clear, further investigation is needed.

In consist with our findings Huang et al. (33) have reported that L-arginine supplementation during exhaustive exercise decreased the MDA level in rats. Moreover, in a study on healthy and patients with heart disease, reduction in level of MDA after 7 and 15 days L-arginine supplementation with dose of three grams daily have been reported, which is concurred with our results (20). One of the possible mechanisms which through it the L-arginine decreases oxidative stress and MDA levels is elevating the amount of NO as an antioxidant factor(15). However some studies have reported that the antioxidant and anti-inflammatory effects of arginine are independent of NO production (9,10). Another possible mechanism is inflammatory factors reduction following L-arginine supplementation which finally decreases oxidative stress markers. In support of this hypothesis our results showed a positive correlation between inflammatory markers (CRP and IL6) and MDA. However, contrary to our results, Walker et al. (34) have demonstrated that L-arginine supplementation for 2 weeks had no effect on oxidative stress indicators. Probably such a result was due to consumption of high dose of L-arginine (15 grams daily), since it has been seen that high dose of L-arginine increased NO too much, while low concentration of NO can act as antioxidant agents and excessive NO reacts with superoxide radicals and increases toxic radicals of proxy nitrite (35).

Conclusions

İn conclusion results of this study showed that acute and chronic exhaustive exercise increase the oxidative and inflammatory markers even in athelet with history of well regular exercise. Also it was found that L-arginine supplementation could prevent elevation of inflammation and oxidative stress markers Sresulted from acute and chronic exhaustive exercise.

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