

## **Effect of Eicosapentaenoic Acid (EPA) and Vitamin E on the Blood Levels of Inflammatory Markers, Antioxidant Enzymes, and Lipid Peroxidation in Iranian Basketball Players**

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### **Abstract**

**Background:** Exercise can change the release of numerous cytokines and modulate their receptor systems. Dietary  $\omega$ -3 lipids may decrease the levels of inflammatory cytokines and prostaglandins (PGs). Therefore, in this study, we investigated the effects of exercise and eicosapentaenoic acid (EPA) supplementation, with or without vitamin E, on the blood levels of IL-2, TNF- $\alpha$ , catalase, glutathione reductase, and MDA in male basketball players.

**Methods** Thirty-four well-trained male basketball players were enrolled into the study. Venous blood samples were obtained from all subjects between 5:00 and 6:00 p.m., after intensive endurance exercising for 2 hours, at the baseline and after intervention. Subjects received 2g EPA and/or 400 IU vitamin E or placebo depends on their groups for 6 weeks.

**Results** There were significant fall (paired *t*-test) in TNF- $\alpha$  in group1 ( $P < 0.05$ ), and in MDA in group 3 ( $P < 0.05$ ), whereas there were significant increase in glutathione reductase in groups1 and 3 ( $P < 0.05$ ), and in MDA in group2 ( $P < 0.05$ ). There were significant differences (Tukey) in glutathione reductase between groups 2 and 3 ( $P < 0.05$ ), and in IL-2 between groups 1 and other groups ( $P < 0.01$ ), but there were no significant differences in MDA, CAT, and TNF- $\alpha$ , among groups after 6 week of intervention.

**Conclusion:** Six weeks of EPA+vitamin E supplementation enhances the plasma levels of IL-2 and erythrocytes glutathione reductase, whereas it reduces TNF- $\alpha$ , and 6 weeks of EPA supplementation alone enhances only the serum level of MDA.

**Keywords:** *EPA, Vitamin E, Inflammation, Antioxidant enzymes, Lipid peroxidation*

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### **Introduction**

Exercise can alter the release of numerous cytokines and modulate their receptor systems. Such changes may trigger inflammatory and acute phase responses. Inflammation in athletes may be caused by mechanical stress, local ischemia, and/or free radical generation in the active skeletal muscle. After high-intensity exercise, the immune system becomes involved in tissue repair processes. Increases in IL-1 and TNF- $\alpha$  production are reported after exercise (1-3). Physical exercise, including enteric muscle contractions, induces increases in the production of cytokines (4).

Specific fatty acids can lower the levels of certain pro-inflammatory cytokines. These fatty acids may have a protective role to defend against the inflammatory responses caused by exercise (5).

Dietary  $\omega$ -6 fatty acids generally increase the levels of pro-inflammatory cytokines and inflammatory prostaglandins (PGs), whereas  $\omega$ -3 fatty acids may decrease the levels of these cytokines and inflammatory PGs (6).

Research evidence has accumulated in the past decade indicating that strenuous aerobic exercise is associated with oxidative stress and tissue damage. It is therefore conceivable that die-

tary supplementation with specific antioxidants would be beneficial (7). During severe oxidative stress, the enzymatic and nonenzymatic antioxidant systems of skeletal muscle are not able to cope with the massive free radical formation, which results in an increase in lipid peroxidation. Exercise and training, however, appear to augment the body's antioxidant defense system (8). Whether this augmented defense system can keep up with the increase in lipid peroxidation with exercise is not known. Vitamin E is reported to decrease exercise-induced lipid peroxidation. The exercise may increase superoxide anion generation in the heart, and the increase in the activity of superoxide dismutase (SOD) in skeletal muscle may be indirect evidence for exercise-induced superoxide formation (5).

However, incorporation of the highly unsaturated fatty acids in membranes may increase the membranes' susceptibility to lipid peroxidation, especially in combination with exercise (9).

Therefore, we investigated the effects of exercise and eicosapentaenoic acid (EPA) supplementation, with or without vitamin E, on the blood levels of IL-2, TNF- $\alpha$ , catalase, glutathione reductase and MDA in male basketball players.

## Materials and Methods

The present study was a randomized double blind placebo-controlled clinical trial. Thirty-four apparently healthy, well-trained male basketball players (aged 17-35 yr) were enrolled into the study between May 4 and 19, 2006. Participants were instructed not to take any antioxidant supplements during and 2 weeks preceding the study. Exclusion criteria included the existence of pathologies interfering with immune functions (i.e. inflammatory diseases) and hemophilia.

Venous blood samples were obtained from all subjects between 5:00 and 6:00 p.m., after intensive endurance exercising for 2 h, at the baseline and after intervention. Subjects received 2g EPA and/or 400 IU vitamin E or placebo depends on their groups.

For 6 weeks, eight subjects took a daily EPA supplement together with vitamin E (group 1), nine an EPA supplement together with vitamin E placebo (group 2), nine an EPA supplement placebo along with vitamin E (group 3), and finally, eight subjects received an EPA supplement placebo along with vitamin E placebo (group 4).

EPA and EPA placebo soft gels were supplied by Minami Nutrition (Belgium). The vitamin E and their placebo soft gels were obtained from Zahravi Pharmaceutical Inc. (Iran). N7505 NADPH, GSSG, and F6625 FAD were purchased from Sigma (USA), and K<sub>2</sub>HPO<sub>4</sub>, NaCl, NaHCO<sub>3</sub>, EDTA, NaOH, KH<sub>2</sub>PO<sub>4</sub>, Na<sub>2</sub>HPO<sub>4</sub>·2H<sub>2</sub>O, H<sub>2</sub>O<sub>2</sub>, trichloro acetic acid (TCA), H<sub>2</sub>SO<sub>4</sub>, n-butyl alcohol, NaSO<sub>4</sub>, T5500 thio-barbitutic acid (TBA) and tetramethoxypropane were obtained from Merck (Germany).

The serum MDA levels were determined using the method described by Satoh k. in 1978 (10). Erythrocytes catalase levels were measured by Abei method (11). glutathione reductase was determined with sauberlich method (12). IL-2 and TNF- $\alpha$  ELISA kits were obtained from Bender Medsystems GmbH (Vienna, Austria). Excel was used for data handling and graph generation, and SPSS (version 10; SPSS Inc., Chicago, IL, USA) and Stata (version 7; Stata Corp., College Station, TX, USA) were used for statistical analysis. Values are expressed as means with their standard errors for each group.

## Ethical consideration

Ethical approval was obtained from the Medical Ethics Committee of Tehran University of Medical Sciences and informed consent was obtained from all subjects.

## Results

Thirty-seven subjects were recruited with a median (range) age of 24 (17-35) years. Thirty four of them completed the 6 wk intervention. The groups were well matched for gender, and age. Some of characteristics of subjects are seen in Table 1. Withdrawal from the study were due

to personal reasons, unrelated to the protocol. Body weight were statistically similar in all groups (group 1: 86.7±8.5; group 2: 91.5±7.3; group 3: 83.5±6.5; group 4: 88.2±7.6 kg, respectively) throughout the study.

Mean (SD) plasma levels of IL-2, TNF- $\alpha$ , serum MDA and catalase and glutathione reductase of erythrocytes are shown in table2. There were significant falls (paired *t*-test) in TNF- $\alpha$  in group1 ( $P<0.05$ ), and in MDA in group 3 ( $P<0.05$ ),

whereas there were significant increases in glutathione reductase in groups1 and 3 ( $P< 0.05$ ), and in MDA in group2 ( $P< 0.05$ ) (Table 2).

There were significant differences (Tukey) in glutathione reductase between groups 2 and 3 ( $P< 0.05$ ), and in IL-2 between groups 1 and other groups ( $P< 0.01$ ), but not in MDA, CAT, and TNF- $\alpha$ , among groups after 6 weeks of intervention (Table 3).

**Table 1:** Age and anthropometric characteristics of subjects ( $\bar{x} \pm SD$ )

Characteristics	group 1(n=8) (EPA+vitamin E)	group 2 (n=9) (EPA+placebo)	group 3 (n=9) (Vitamin E +placebo)	group 4 (n=8) (placebo+placebo)
Age(yr)	27.5±5.3	23.7±3.3	23.5±2.4	21.2±2.2
Weight(kg)	88.4± 5.6	89.8 ± 5.4	88.1 ± 5.5	87.9 ± 4.8
Height(m)	1.91±0.07	1.94±0.03	1.93±0.07	1.92±0.05
BMI(kg/m <sup>2</sup> )	24.1±1.1	23.7±1.3	23.5±0.8	23.8±0.7

**Table 2:** Comparisons of parameters in the groups before and after 6 wk supplementation

Parameters	Group1			Group2			Group3			Group4		
	Baseline values	change	<i>P</i> value (paired <i>t</i> -test)	Baseline values	change	<i>P</i> value (paired <i>t</i> -test)	Baseline values	change	<i>P</i> value (paired <i>t</i> -test)	Baseline values	change	<i>P</i> value (paired <i>t</i> -test)
IL-2 (pg/ml)	25.12±13.33	6.25±8.06	0.06	19.11±8.7	2.88±9.8	0.5	20.66±12.14	5.44±13.6	0.2	31.5±23.64	1.5±10.65	0.7
TNF- $\alpha$ (pg/ml)	10.87±6.1	3.5±2.4	0.02	10.44±5.05	0.88±4.45	0.4	7.77±2.63	1.44±3.6	0.2	8.75±5.14	0.37±3.62	0.7
MDA (nmol/l)	3.24±1.4	0.48±1.99	0.1	3.51±1.06	1.41±1.27	0.01	4.2±1.35	1.75±1.98	0.03	3.78±1.93	1.36±2.05	0.1
Catalase (u/l)	230.27±71.4	56.91±90.26	0.2	189.23±95.92	21.01±111.23	0.6	187.85±55.22	6.23±57.6	0.7	197.47±104.28	41.78±103.66	0.29
Glutathione reductase (u/l)	3.92±1.7	1.04±1.36	0.01	3.38±1.47	0.65±1.47	0.2	5.38±1.58	2±1.95	0.01	3.98±1.53	0.22±1.65	0.7

**Table 3:** Multiple comparisons of parameters among groups after 6 wk supplementation

Parameters	Group1	Group2	Group3	Group4
IL-2(pg/ml)*	18.87±9.24	16.22±4.68	15.22±4.73	33±17.07
TNF- $\alpha$ (pg/ml)	7.37±4.37	9.55±6.82	6.33±3.4	9.12±5.02
MDA(nmol/l)	2.76±0.94	2.1±0.66	2.45±0.98	2.41±0.4
Catalase(u/l)	173.36±74.2	168.22±46.12	181.62±60.82	155.68±25.08
Glutathione reductase(u/l)**	2.88±1.4	2.74±0.99	3.37±1.3	3.75±1.93

Results were expressed as the Mean±SD

\* Significant differences between group 1 and other groups ( $P< 0.01$ ) (Tukey)

\*\* Significant differences between groups 2 and 3 ( $P< 0.05$ ) (Tukey)

## Discussion

The present study examined the effects of EPA and vitamin E supplementation on plasma levels of IL-2, TNF- $\alpha$ , catalase, glutathione reductase, and MDA in male basketball players.

EPA is an omega-3 (n-3) polyunsaturated fatty acids (PUFA) derived from fish oil that competitively inhibits n-6 PUFA arachidonic acid (AA) metabolism and thus reduces the generation of inflammatory 4-series LT and 2-series PG mediators (13), and the production of cytokines from inflammatory cells (14). Consuming fish oil results in partial replacement of AA in inflammatory cell membranes by EPA (13, 14). This response alone is a potentially beneficial anti-inflammatory effect of n-3 PUFA.

Many studies have shown that exercise may result in oxidative damage (15, 16) that can be inversed with vitamin E.

Cytokines are a group of low molecular weight regulatory proteins secreted by white blood cells and a variety of other body cells in response to a number of inducing stimuli.

Cytokines generally function as intercellular messenger molecules that evoke particular biological activities after binding to a receptor on a responsive target cell.

Exercise is accompanied by an increase in pro-inflammatory and inflammation responsive cytokines, reactions having some similarities to sepsis and trauma (1, 17, 18).

This randomized double blind placebo-controlled clinical trial study in male basketball players, demonstrated an increase in IL-2 levels ( $P < 0.05$ ) and a fall in TNF- $\alpha$  levels ( $P < 0.01$ ) in group1 following 6 weeks of EPA supplementation, suggesting that EPA along with vitamin E can induce the production of anti-inflammatory cytokines, and decrease the pro-inflammatory cytokines production.

These findings confirm those of Endres et al. (19), on the other hand, Venkatraman et al.(20) found no effect of  $\omega$ -3 fatty acids on the induction and reduction of anti- and pro-inflammatory cytokines production.

Some investigators have shown that dietary supplementation with n-3 PUFA results in decreased monocyte synthesis of TNF- $\alpha$  and IL-1 $\beta$  in healthy subjects (21). However, Hodge et al. (22) demonstrated reductions in TNF- $\alpha$  production after fish oil supplementation.

The mechanism involved is probably that exercise causes release of pro-inflammatory cytokines that in turn will trigger the production of anti-inflammatory cytokines such as IL-2 and IL-10 (23-30). The sources of these cytokines are the skeletal muscle and peripheral blood mononuclear cells (23, 31). The sequence of production of these pro- and anti-inflammatory cytokines appears to be initial production of TNF- $\alpha$  and IL-1 $\beta$  by the peripheral blood leukocytes and muscle. Meanwhile, EPA has anti-inflammatory actions; however, the exact mechanism is not known.

In this study, there were significant differences (Tukey) in glutathione reductase ( $P < 0.05$ ) between groups 2 and 3, and these enzyme levels were higher (paired *t*-test) after intervention in groups1 and 3 ( $P < 0.05$ ), whereas there were no significant differences (ANOVA) in catalase among the groups and in any of groups (paired *t*-test) after 6 weeks of intervention.

A decrease in plasma antioxidant concentrations after fish oil supplementation has been reported by Nair et al.(32), but this was not confirmed in the present study or by other workers (33).

The results of several studies suggest that increased consumption of n-3 fatty acids may result in an increased potential for oxidative stress in vivo. These studies were based primarily on the results of the TBA assay (34). The results of the present study, also showed increased oxidative stress during EPA supplementation, as the plasma MDA levels in group2 increased after intervention ( $P < 0.01$ ). The plasma MDA levels, however, were lower after supplementation in group3 ( $P < 0.05$ ).

Data from this study indicate that EPA and vitamin E in well-trained basketball players have

variable effects on the immune system, some of which are suppressive, such as the plasma TNF- $\alpha$  levels, and some of which may be anti-inflammatory, such as IL-2 levels.

This is the first study to assess the effect of EPA and vitamin E supplementation on inflammatory markers and antioxidant enzymes and lipid peroxidation in basketball players.

In conclusion, this study shows that 6 wk of EPA+ vitamin E supplementation enhances the plasma levels of IL-2 and erythrocytes glutathione reductase, whereas it reduces TNF- $\alpha$ , and that 6 wk of EPA supplementation alone enhances only the serum level of MDA, and finally that 6 wk of vitamin E supplementation alone reduces the serum level of MDA and enhances the glutathione reductase of erythrocytes.

The differences between reports on the effect of EPA and vitamin E supplementation on inflammatory markers and antioxidant status are probably methodologic. The small number of studies and the different methods used for the assessment of inflammation and antioxidant status, call for further trials (35-37). In addition, due to the fact the present study's findings are in contrast with some other studies, further investigations are warranted.

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