

The Evaluation Of Concurrent Supplementation With Vitamin E And Omega- 3 Fatty Acids On Plasma Lipid Peroxidation And Antioxidant Levels In Patients With Rheumatoid Arthritis

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Citation

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Abstract

Introduction: Rheumatoid Arthritis (RA) is a chronic inflammatory disorder which can cause oxidative stress [1]. The main characteristic of the disease is inflammation of synovial membrane with swelling and pain that ultimately leads to the destruction of cartilage and bone [2]. Routine clinical practices in management of rheumatoid arthritis aim at reducing the patients' pain and joint inflammation, minimizing loss of function and decrease the progression of joint damage. **Methods:** In this double blind-randomized clinical trial, 90 patients were included who were divided into three groups based on received drugs (group EO: one omega-3 capsule (1g/d of fish oil,) plus one vitamin E capsule (400 IU/d); group O: one omega-3 capsule plus placebo of vitamin E; group P: placebo of omega-3 and vitamin E). At the beginning and end of the study, all patients were examined, 72-h recall was completed and 10 ml of fasting blood sample was obtained to assess the serum levels of malondialdehyde (MDA), plasma antioxidant capacity (TAC) and C-reactive protein (CRP) as well as the activity of superoxide dismutase (SOD) and Glutathione peroxides (GPX). **Results:**

In group (EO), there was a significant decrease in lipid peroxidation (MDA concentration) compared with the other groups ($P=0.032$). None of the interventions could affect the activity of antioxidant enzymes, SOD and GPX, or total antioxidant capacity of serum. Also there was no significant improvement in the clinical outcomes of different groups. **Conclusion:**

Omega-3 and vitamin E supplements in the prescribed doses did not show any beneficial effect on clinical outcomes of the patients or activity of antioxidant enzymes, however adding vitamin E supplements to omega 3 fatty acid supplements could reduced MDA levels comparing to omega 3 fatty acids alone or placebo.

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic inflammatory disorder which can cause oxidative stress [1]. The prevalence of RA among adults is 1 to 2% worldwide and it is three times more prevalent in females than males [2, 3]. The main characteristic of the disease is inflammation of synovial membrane with swelling and pain that ultimately leads to the destruction of cartilage and bone [2]. Routine clinical practices in management of rheumatoid arthritis aim at reducing the patients' pain and joint inflammation, minimizing loss of function and decrease the progression of joint damage. However, some pharmacological therapies such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids have the potential to cause side-effects and rarely effective [3]. As a result, many studies have focused

on finding some complementary methods to reduce the dose of drugs or to improve the outcomes. One of these complementary treatments is supplementation with omega 3 fatty acids [4, 5]. Previous studies have shown Eicosapentaenoic acid (EPA) and Decosahexaenoic acid (DHA) effects on reduction of inflammatory cytokines [6]. In meta-analysis of randomized- controlled clinical trials (RCTs), it has been suggested that Omega-3 fatty acids can reduce pain, stiffness and the number of painful and swelling joints for 3 months [7]. However, the effect of these fatty acids on serum antioxidant levels is not well defined. In a study assessing the effect of Omega-3 fatty acids fed mice, a significant reduction of plasma vitamin E levels has been detected [8]. Another study on healthy people, who took the Omega-3 fatty acids supplements, showed an increase in

serum malondialdehyde (MDA) levels which is an indicator of lipid peroxidation [9]. Thus, combined supplementation with Omega-3 fatty acids and vitamin E can be a solution. In RA patients, reactive oxygen species (ROSs) such as superoxide, hydrogen peroxide and hydroxyl radicals are increased due to augmentation of inflammatory cytokines transcription. The antioxidant micronutrients like vitamin E are a part of antioxidant defense system in the body and can reduce ROSs which can result in integrity of cells and improvement of clinical outcomes of RA [10]. A recent molecular study reported an anti-inflammatory role for vitamin E supplements and the need for higher doses of analgesics was reduced when alfa-tocopherol supplements in addition to aspirin, were used [11]. In the present study, the effect of omega-3 fatty acids and vitamin E supplements were assessed on clinical outcomes, plasma lipid peroxidation and antioxidant levels of RA patients.

MATERIAL AND METHODS

This randomized double-blinded placebo controlled trial was conducted in a 12-week period on female patients with active RA, between April 2008 and November 2008. The study population was selected from 400 registered female RA patients in outpatient clinics of Sina and Sheikh Al-Raees educational clinics of Tabriz University of Medical Sciences in Tabriz, Iran. The inclusion criteria were ages between 20 -70 years, having RA based on 1987 American College of Rheumatology criteria [12] and having stable treatment protocols during the past 2 months.

The demographic characteristics and medical drug use history were obtained by face-to-face interview. Body mass index (BMI) of the patients was determined using Quetelet's index [BMI= Weight (Kg)/Height (m²)]. The exclusion criteria were no desire to participate in the study, history of diabetes mellitus, hypothyroidism, nephritic syndrome, abnormal hepatic or renal function, Cushing's syndrome, obesity, gastrointestinal disorders and fat mal absorption, taking vitamin E or Omega-3 fatty acids supplements and drugs such as β blockers, Angiotensin converting enzyme inhibitors (ACEI), Oral contraceptives and smoking. Ninety patients were randomly assigned to one of three groups receiving Omega-3 (group O, n = 30), vitamin E- Omega-3 (group EO, n = 30) or placebo (group P, n = 30). 1 g Omega-3 capsules were prescribed daily (180 mg EPA and 120 mg DHA). The daily dose of vitamin E (Alfa-tocopherol acetate) was 400 international units (IU). The participants didn't change their usual diet, physical activity and

medications throughout the study. All of the patients were examined by the same rheumatologist in every visit. Pain was measured by visual analog scale (VAS) using a 0-100 mm scale. The disease activity was determined by physical exams (morning stiffness, joint pain, tenderness and swelling) and biochemical analysis [high-sensitive C-reactive protein (hs-CRP) levels]. Disease activity score (DAS 28) was determined by LN-63 calculator, made by Bristol-Myers Squibb company. Plasma total antioxidant (TAO) of the patients was estimated by using Randox Total Anti Oxidant Status test kit in serum (Randox Laboratories Ltd, UK), Plasma superoxide dismutase (SOD) enzyme activity by Ransod spectrophotometric kit (Ransod, Randox Laboratories Ltd. UK), Plasma Glutathione peroxidase (GPX) enzyme activity by Ransel spectrophotometric kit (Ransel, Randox Laboratories Ltd. UK). Serum C-reactive protein was measured by two point immunoturbidimetric method using a kit produced by Parsazmun (Lot. No.83001). All of these procedures were completed using auto analyzer apparatus (Alcgon-Abbott, USA). Malondialdehyde (MDA) concentration was measured using MDA reaction with thiobarbituric acid followed by extraction with butanol. The optic density (OD) of the aqueous extract was measured spectrophotometrically at 532 nm wavelength and compared with standard curve [13]. Energy and nutrient intakes were measured using a 3-day 24-h recall (two week days and one weekend day). The information was obtained through face to face interview and standard food models. A variety of measuring tools were used to evaluate intake. Nutrients were analysed by Nutritionist III software, version 7.0 (N-Squared computing, Salem, OR, USA), which was modified for Iranian foods. A written informed consent was obtained from all participants. The research proposal was approved by both the institutional review board and the ethics committee of Tabriz University of Medical Sciences (ethics committee approval number 8071). The omega-3, vitamin E and placebo capsules did not have any side effects. Statistical analyses were done using SPSS Software (version 16.0). All values are expressed as mean standard deviation (SD). The normality of data distribution determined by Kolmogorov-Smirnoff test and P-P plot curve, Differences between three groups by one-way analysis of variance (ANOVA), differences before and after the intervention in each group by paired sample t-test. All tests were two-tailed, and p<0.05 was the significance threshold.

RESULTS

Of the 90 patients involved in the present study, 82 persons

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completed the study. Eight patients were excluded from the study due to either Unrelated medical problems (1 patients) or inaccessibility to rheumatologist’s office (5 patients) or lack of desire to complete the task (2 patients)(fig. 1). There were no significant differences among the three groups at the beginning of the study regarding age, disease duration, use of medication and body mass index (BMI). The used type and dose of medications were not significantly different between the three groups. Also, there were no significant difference in clinical outcomes (DAS-28, joint pain and swelling and VAS) between the three groups at the base line. After that intervention was completed, the changes in clinical outcomes were not significantly different among the three study groups and none of the interventions could improve the signs and symptoms (Table 2).The biochemical markers used in this study were SOD , GPX activity and TAC to assess anti oxidant capacity of plasma, MDA to test lipid peroxidation and CRP to evaluate inflammation. Among these biochemical markers, only MDA levels were significantly decreased in EO group comparing to two other groups after completion of the intervention. After intervention, there was neither a significant change in biochemical markers within each group compared with the beginning of the study (Table 3).

Figure 1

Figure 1: Flowchart of the patients participated in the study

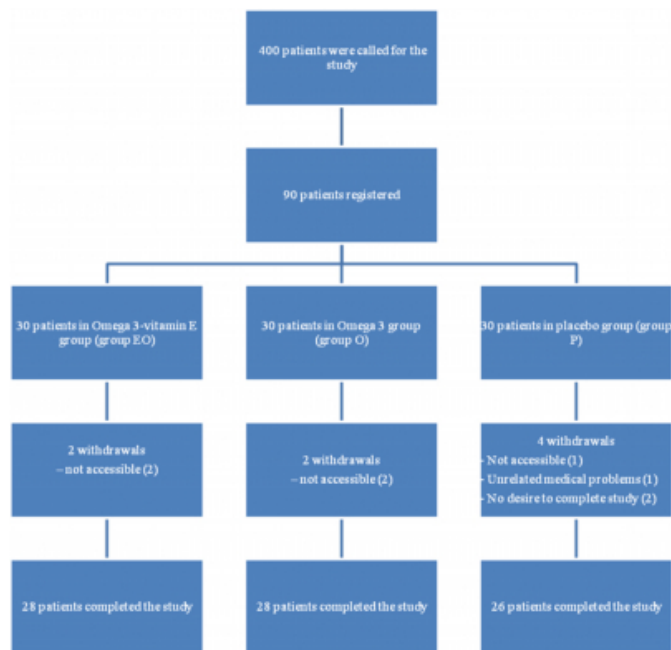


Figure 2

Table 1: Demographic and anthropometric characteristics and dietary intake of the patients at the baseline (n=90)

Variables	Group OE† n = 28	Group O‡ n = 28	Group P• n = 26	P
Age (years)*	45.3±13.5	48.3±12.9	48.7±15.0	0.599
Duration of disease (years)	7.4±6.7	8.8±9.1	8.4±7.8	0.784
Weight (kg)*	57.7±5.9	57.9±5.1	58.7±5.2	0.867
Height (m)*	155.2±7.1	156.1±5.3	156.4±5.5	0.865
BMI ¹ (kg/m ²)*	23.9±1.2	23.8±1.6	24.0±2.0	0.907
Energy intake (Kcal)*	1628±542	1595±676	1374±460	0.244
PUFA intake (g)*	18.04±11.5	16.52±10.73	14.4±8.51	0.408
Vitamin E intake (mg)*	27.33±16.8	28.9±15.8	24.66±13.04	0.683
Vitamin C intake (mg)*	89.37±71.6	65.82±56.6	79.98±80.73	0.373
Selenium (mcg)*	88±47	84±49	91±7	8.815
Prednisolone use **	30(100)	30(100)	28(93.3)	0.116
Methotrexate use **	29(96.7)	29(96.7)	29(96.7)	0.200
Sulfasalazine use **	9(30)	9(30)	6(20)	0.409
Chloroquine use **	17(56.7)	17(56.7)	20(66.7)	0.551

¹ - BMI: body mass index ^{*} - the data are expressed in mean ± SD ^{**} - the data are expressed in percentage (number) †-OE: omega-3-vitamin E ‡-O: omega-3 •-P: placebo

Figure 3

Table 2: Clinical symptoms of the patients before and after intervention and comparison the differences between the 3 groups

	Group OE† n = 28	Group O‡ n = 28	Group P• n = 26	p**
DAS 28 ^{1*} before	3.86±4.81	2.2±1.45	2.87±1.35	0.712
after	3.03±1.52	2.34±1.53	3.02±1.32	
VAS ^{2*} before	35.65±31.85	33.65±31.95	30.6±29.87	0.560
after	36.3±37.27	31.37±32.47	30±31.36	
Tender join count* before	2.83±4.29	2.38±3.43	3.48±5.66	0.470
after	3.35±4.65	3.8±6.29	3.68±6.8	
Swollen joint count* before	1.52±2.31	1.5±3.24	1.36±1.87	0.173
after	2.09±3.4	1.5±3.22	0.76±2.07	

- DAS: disease activity scale ² - VAS: visual analog scale ^{*} - The data are expressed in mean ± SD. †-OE: omega-3-vitamin E ‡-O: omega-3 •-P: placebo ^{**}- The p-values refer to differences between the EO, O and P groups concerning the change from baseline to week 12. Differences between the groups were analysed by ANOVA or Kruskal-Wallis tests. There was no statistically significant change from baseline to week 12. Withingroup differences at week 12 compared to baseline were evaluated by Paired t-test or Wilcoxon signed ranks test.

Figure 4

Table 3: Biochemical parameters in the patients before and after intervention and comparison of the differences between the 3 groups

Groups		Group OE†	Group O‡	Group P*	p**
Variables		n = 28	n = 28	n = 26	
MDA ¹ (mcml/L)*	before	3.9±1.7	3.1±0.9	3.2±1.4	0.032
	after	3.6±1.6	3.7±1.8	3.7±1.3	
CRP ² (mg/L) *	before	3.9±3.9	4.8±4.1	6.7±4.6	0.832
	after	4.3±3.6	5.1±4.4	6.2±4.1	
TAC ³ (mmol/L) *	before	0.9±0.2	0.9±0.1	0.9±0.9	0.685
	after	0.9±0.3	0.9±0.2	0.9±0.2	
GPX ⁴ (U/L)*	before	5162±407	5150±354	5152±443	0.684
	after	5227±423	5131±358	5093±357	
SOD ⁵ (U/ml) *	before	234.6±48.2	242.1±45.4	238±58.9	0.711
	after	220.8±51.3	232.3±53.4	239.2±47.7	

DISCUSSION

To the best of our knowledge, this randomized, double-blind, placebo controlled clinical trial was the first study to assess the effect of both omega-3 and vitamin E supplements on plasma antioxidant capacity in RA patients. In the present study intake of several nutrients such as vitamin E and C, selenium, PUFA, etc. which could have confounding effect on the data interpretation was assessed. Also we assessed the effects of omega-3 and vitamin E supplements on clinical outcomes and lipid peroxidation of RA patients. Although , the clinical outcomes of the patients were not improved significantly in any of groups, we found a significant reduction in MDA levels of EO group comparing with other groups. There are many types of reactive oxygen species (ROS) in the cellular environment of RA patients which can lead to lipid peroxidation and production of MDA. A recent study showed that vitamin E levels in RA patients were lower and MDA levels were higher than healthy control group [14]. Another study also showed that 2.4 g/d of fish oil consumption for 3 months in healthy women could decrease vitamin E levels after 1 month and increase lipid peroxidation and MDA production after 2 months [15]. Similar to other studies, the patients in this study had high levels of serum MDA and EO group was the only group with reduced MDA levels. A study by Palozza et al. [16] showed that human erythrocyte liability to lipid peroxidation depends on dose and duration of Omega-3 supplementation which results in changing of fatty acids composition and reducing erythrocyte vitamin E content that increases lipid peroxidation. In contrast to the present study, Trebble et al. showed that Omega-3 supplementation increased lipid

peroxidation, but vitamin E supplementation could not halt this increase [17]. This can be because of their low doses of vitamin E (30 mg/d) compared with this study (400 IU/d). Some previous studies suggested an antioxidant role for omega 3-fatty acids. They believe that fish oil supplementation may have free radical scavenger activity [18, 19]. On the other hand, some other studies found it as a peroxidant agent [20]. In the present study, we found neither antioxidant nor peroxidant effect for omega 3 fatty acids supplements in the prescribed dose. Plasma antioxidant enzymes (SOD and GPX) and plasma TAC levels were not significantly changed in any of the intervention groups. Also there was not a significant difference between the three groups. In a study by Sivriouglu et al. [21] on schizophrenic patients, the same doses of omega 3 fatty acids (1g) and vitamin E(400 IU) was prescribed and they found a significant reduction in SOD activity but GPX activity and levels of other plasma anti oxidants (vitamins C and E) was constant. In contrast, Erdugan et al. showed an increase in the activity of SOD after supplementation with omega 3 fatty acids in rats. The activity of GPX in their study was not changed significantly either [19]. In another study, supplementation with different doses of EPA could increase activity of both GPX and SOD [22]. A possible reason for these controversies in different studies can be differences in doses and types of supplements as well as the differences between the cell types. Along with the clinical outcomes, measurement of CRP concentration can be a good indicator of effectiveness of the intervention. Some previous studies found an anti-inflammatory effect for fish oil supplements in RA patients [23]. In the present study, hs-CRP concentration as a major inflammatory indicator did not change significantly and there were no significant differences between the study groups. Vega-Lopez et al. reported that serum levels of CPR was not significantly changed after 3 month supplementation with 1.5 g/d Omega-3 fatty acids [24]. Their finding is in agreement with the results obtained in the present study. In two other studies using higher doses of Omega-3 fatty acids (2 or 6.6 g/d) for 12 weeks and 4 g/d fish oil for 6 weeks did not affect serum hs-CRP concentration compared with control groups [25, 26]. However, anti or pro inflammatory effects of EPA and DHA were not studied in detail. In contrast, in GISSI study, supplementation with 1g/d Omega-3 fatty acids had positive effect on reducing inflammatory cytokines [27]. A comprehensive study in rats showed that when the ratio of EPA/DHA in supplements was 3 to 1, it could reduce the inflammation [28]. This ratio was 1.5 in our study; and was

0.67 in Vega-Lopez's study [24]. Therefore higher ratio of EPA/DHA may result in positive effects on inflammatory markers. During last 3 decades several investigations have been done on the effect of omega 3 fatty acids on clinical outcomes and inflammation in RA patients. However, there are still lots of controversies in this area and there is no agreement between systematic reviews and meta-analysis. For example, although Goldberg in his meta analysis study suggested a positive effect for omega 3 fatty acids on tender joint count, morning stiffness, VAS, NSAIDs use, etc. [7], another meta analysis found only a moderate effect on tender joint count and morning stiffness [29] and another one did not find any beneficial effect for omega 3 fatty acids supplements in RA patients [30]. In the present study, low doses of omega 3 fatty acids and its combination with vitamin E supplement did not show any beneficial effect on clinical outcomes of the patients such as tender joint count, swollen joint count, VAS and overall DAS-28. A possible reason for these controversies can be the differences in the doses and duration of the supplementation. Geusens et al. proposed that higher doses of Omega-3 can be more efficient than lower doses [31]. One possible reason that we could not find any beneficial effect for omega 3 supplementation on clinical outcomes, might be the use of lower doses (120 mg DHA & 180 mg EPA) compared with the most of the other similar studies. It should be mentioned that rheumatic patients took several medications for their disease and adding several tablets or capsules to their therapeutic regime could have caused a substantial increase in the loss of participants during the study and might have had some adverse effects on therapeutic outcomes. In the present study, adding vitamin E to Omega-3 supplements improved clinical signs and symptoms, but the difference was not statistically significant. Some studies denote that vitamin E has antioxidant, anti-inflammatory and analgesic role [32]. However, this role is not confirmed by other studies [33]. In a study by Edmonds et al. [32] 1200 mg of vitamin E was prescribed to RA patients and analgesic and its anti-inflammatory effects were assessed. They could not find any beneficial effect of vitamin E in terms of biochemical markers regarding inflammation or oxidation of proteins and fats. Several clinical symptoms except pain were not improved significantly either. The reduction of pain in their study can be attribute to the high dose of prescribed vitamin E. Despite using high doses of vitamin E in several clinical trials done by different researchers, there was no agreement in their results. Miehle et al. believe that the disparity is because of different stages of the disease in different studies

due to an association between disease activity score and the rate of free radical production [33]. Another reason for the difference between outcomes can be different forms of vitamin E isomers in different trials [34]. One limitation of the present study was that the stage or severity of the disease was not taken into account as an inclusion criterion; and we had patients with different stages in each group. Although random allocation can cover this confounder, in the future studies it is recommended to take it into consideration and work on a population with the same stage of disease. Eventually, as it is mentioned above, there are still lots of controversies in this area and the most important reasons for these inconsistent results for similar studies can be summarized as follows: difference in duration of intervention, difference in dose and types of supplements and variety of patients' characteristics. There is an obvious need for methodologically strong clinical trials with large sample sizes.

CONCLUSION

In conclusion, concurrent supplementation with Omega-3 fatty acids and vitamin E reduced oxidative stress, lipid peroxidation compared with fish oil alone or placebo in female RA patients. However, it did not affect the activity of antioxidant enzymes, TAC, clinical outcomes and disease activity score.

References

1. Peretz A, Siderova V, Nève J. Selenium supplementation in rheumatoid arthritis investigated in a double blind, placebo-controlled trial. *Scandinavian journal of rheumatology* 2001;30 4: 208-12.
2. Cerhan J, Saag K, Merlino L, Mikuls T, Criswell L. Antioxidant micronutrients and risk of rheumatoid arthritis in a cohort of older women. *American journal of epidemiology* 2003;157 4: 345.
3. Rennie K, Hughes J, Lang R, Jebb S. Nutritional management of rheumatoid arthritis: a review of the evidence. *Journal of Human Nutrition & Dietetics* 2003;16 2: 97.
4. Berbert A, Kondo C, Almendra C, Matsuo T, Dichi I. Supplementation of fish oil and olive oil in patients with rheumatoid arthritis. *Nutrition* 2005;21 2: 131-6.
5. Van der Tempel H, Tulleken J, Limburg P, Muskiet F, Van Rijswijk M. Effects of fish oil supplementation in rheumatoid arthritis. *British Medical Journal* 1990;49 2: 76.
6. Ariza-Ariza R, Mestanza-Peralta M, Cardiel MH. Omega-3 fatty acids in rheumatoid arthritis: An overview. *Seminars in Arthritis and Rheumatism* 1998;27 6: 366-70.
7. Goldberg R, Katz J. A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain. *Pain* 2007;129 1-2: 210-23.
8. Laganier S, Yu B, Fernandes G. Studies on membrane lipid peroxidation in omega-3 fatty acid-fed autoimmune mice: effect of vitamin E supplementation. *Adv Exp Med*

Biol 1990;262: 95-102.

9. Allard J, Kurian R, Aghdassi E, Muggli R, Royall D. Lipid peroxidation during n-3 fatty acid and vitamin E supplementation in humans. *Lipids* 1997;32 5: 535-41.
10. Sukkar S, Rossi E. Oxidative stress and nutritional prevention in autoimmune rheumatic diseases. *Autoimmunity Reviews* 2004;3 3: 199-206.
11. Abate A, Yang G, Dennerly P, Oberle S, Schröder H. Synergistic inhibition of cyclooxygenase-2 expression by vitamin E and aspirin. *Free Radical Biology and Medicine* 2000;29 11: 1135-42.
12. Arnett F, Edworthy S, Bloch D, Mcshane D, Fries J, Cooper N et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis & Rheumatism* 1988;31 3.
13. Yagi K. Lipid peroxides and related radicals in clinical medicine. In: Armstrong D ed. *Free radicals in diagnostic medicine* Plenum Press New York. 1994:1-15.
14. Vasanthi P, Ganesan N, Hariprasad C, Rajasekhar G, Meera S. Plasma lipophilic antioxidant and pro-oxidant levels in rheumatoid arthritis. *J Indian Rheumatol Assoc* 2004;12 2: 40-2.
15. Meydani M, Natiello F, Goldin B, Free N, Woods M, Schaefer E et al. Effect of long-term fish oil supplementation on vitamin E status and lipid peroxidation in women. *Journal of Nutrition* 1991;121 4: 484.
16. Palozza P, Sgarlata E, Luberto C, Piccioni E, Anti M, Marra G et al. n-3 fatty acids induce oxidative modifications in human erythrocytes depending on dose and duration of dietary supplementation. *American Journal of Clinical Nutrition* 1996;64 3: 297.
17. Trebble T, Arden NK, Stroud MA, Wootton SA, Burdge GC, Miles EA et al. Inhibition of tumour necrosis factor- α and interleukin 6 production by mononuclear cells following dietary fish-oil supplementation in healthy men and response to antioxidant co-supplementation. *British Journal of Nutrition* 2003;90 2: 405-12.
18. Barbosa D, Cecchini R, El Kadri M, Rodríguez M, Burini R, Dichi I. Decreased oxidative stress in patients with ulcerative colitis supplemented with fish oil [omega]-3 fatty acids. *Nutrition* 2003;19 10: 837-42.
19. Erdogan H, Fadillioğlu E, Ozgocmen S, Sogut S, Ozyurt B, Akyol O et al. Effect of fish oil supplementation on plasma oxidant/antioxidant status in rats. *Prostaglandins, Leukotrienes and Essential Fatty Acids* 2004;71 3: 149-52.
20. Song J, Fujimoto K, Miyazawa T. Polyunsaturated (n-3) fatty acids susceptible to peroxidation are increased in plasma and tissue lipids of rats fed docosahexaenoic acid-containing oils. *Journal of Nutrition* 2000;130 12: 3028.
21. Sivrioglu E, Kirli S, Sipahioglu D, Gursoy B, Sarandöl E. The impact of [omega]-3 fatty acids, vitamins E and C supplementation on treatment outcome and side effects in schizophrenia patients treated with haloperidol: An open-label pilot study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2007;31 7: 1493-9.
22. Li M, Kong Z, Liu Z. Antioxidant enzyme activities and lipid peroxidation induced by eicosapentaenoic acid (EPA) in PC12 cells. *Cell biology and toxicology* 2006;22 5: 331-7.
23. Venkatraman J, Chu W. Effects of Dietary {omega}-3 and {omega}-6 Lipids and Vitamin E on Serum Cytokines, Lipid Mediators and Anti-DNA Antibodies in a Mouse Model for Rheumatoid Arthritis. *Journal of the American College of Nutrition* 1999;18 6: 602.
24. Vega-López S, Kaul N, Devaraj S, Cai R, German B, Jialal I. Supplementation with 3 polyunsaturated fatty acids and all-rac alpha-tocopherol alone and in combination failed to exert an anti-inflammatory effect in human volunteers. *Metabolism* 2004;53 2: 236-40.
25. Chan D, Watts G, Barrett P, Beilin L, Mori T. Effect of atorvastatin and fish oil on plasma high-sensitivity C-reactive protein concentrations in individuals with visceral obesity. *Clinical Chemistry* 2002;48 6: 877.
26. Madsen T, Christensen JH, Blom M, Schmidt EB. The effect of dietary n-3 fatty acids on serum concentrations of C-reactive protein: A dose-response study. *British Journal of Nutrition* 2003;89 4: 517-22.
27. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *The Lancet* 1999;354 9177: 447-55.
28. Volker D, FitzGerald P, Garg M. The eicosapentaenoic to docosahexaenoic acid ratio of diets affects the pathogenesis of arthritis in Lew/SSN rats. *Journal of Nutrition* 2000;130 3: 559.
29. Fortin P, Lew R, Liang M, Wright E, Beckett L, Chalmers T et al. Validation of a meta-analysis: the effects of fish oil in rheumatoid arthritis. *Journal of clinical epidemiology* 1995;48 11: 1379-90.
30. MacLean C, Mojica W, Morton S, Pencharz J, Hasenfeld G, Tu W et al. Effects of omega-3 fatty acids on lipids and glycemic control in type II diabetes and the metabolic syndrome and on inflammatory bowel disease, rheumatoid arthritis, renal disease, systemic lupus erythematosus, and osteoporosis. Evidence report/technology assessment (Summary) 2004 89: 1.
31. Geusens P, Wouters C, Nijs J, Jiang Y, Dequeker J. Long-term effect of omega-3 fatty acid supplementation in active rheumatoid arthritis. *Arthritis Rheum* 1994;37: 824-9.
32. Edmonds S, Winyard P, Guo R, Kidd B, Merry P, Langrish-Smith A et al. Putative analgesic activity of repeated oral doses of vitamin E in the treatment of rheumatoid arthritis. Results of a prospective placebo controlled double blind trial. *British Medical Journal* 1997;56 11: 649.
33. Miehle W. Vitamin E in active arthroses and chronic polyarthritis. What is the value of alpha-tocopherol in therapy? *Fortschritte der Medizin* 1997;115 26: 39.
34. Brigelius-Flohe R, Kelly F, Salonen J, Neuzil J, Zingg J, Azzi A. The European perspective on vitamin E: current knowledge and future research. *American Journal of Clinical Nutrition* 2002;76 4: 703

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