Efficacy of omega-3 fatty acid supplementation on serum levels of tumour necrosis factor-alpha, C-reactive protein and interleukin-2 in type 2 diabetes mellitus patients

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INTRODUCTION Consumption of omega-3 fatty acids can alter the inflammatory response in diabetic patients. This study aimed to determine the effects of omega-3 fatty acid supplementation on the serum levels of C-reactive protein (CRP), interleukin (IL)-2 and tumour necrosis factor-alpha (TNF-α) in type 2 diabetes mellitus patients.

METHODS A randomised, double-blind, placebo-controlled clinical trial was conducted on 84 subjects aged 45–85 years with at least a two-year history of type 2 diabetes mellitus. Participants were randomly assigned to the treatment or control group. Each subject in the treatment group received three omega-3 capsules per day (eicosapentaenoic acid 1,548 mg; docosahexaenoic acid 828 mg; other omega-3 fatty acids 338 mg), while each subject in the control group received three placebo capsules (sunflower oil 2,100 mg) for a period of eight weeks. At the beginning of the study and post intervention, fasting blood samples were taken and serum concentrations of IL-2, TNF-α and CRP were assessed and compared.

RESULTS Serum IL-2 and TNF-α levels were significantly reduced in the treatment group compared to the controls ($p < 0.01$). There was no significant change in serum CRP levels.

CONCLUSION Short-term omega-3 fatty acid supplementation (3 g/day for eight weeks) can decrease the serum levels of TNF-α and IL-2 in diabetic patients, with no change in CRP levels. Consumption of omega-3 fatty acid supplements is highly recommended to alleviate inflammation caused by type 2 diabetes mellitus.

Keywords: CRP, diabetes mellitus type 2, IL-2, omega-3 fatty acid, TNF-α
Singapore Med J 2012; 53(9): 615–619

INTRODUCTION

Diabetes mellitus is one of the most prevalent non-communicable chronic diseases.[1] Globally, it is estimated that about 2.5%–3.0% of people are suffering from diabetes mellitus.[2] Its rapidly increasing global prevalence is a noticeable cause for concern.[3] Huge amounts of national investments and diabetic patients' incomes are spent on disease control and healthcare services annually in countries around the world.[2] Strong correlations between enhanced inflammatory biomarkers, including C-reactive protein (CRP), interleukin (IL)-2 and tumour necrosis factor-alpha (TNF-α), and the occurrence of diabetes mellitus have been reported through extensive studies by many researchers.[2,4,5]

Recent studies indicate that polyunsaturated fatty acids (PUFAs), including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and anti-inflammatory agents can potentially decrease inflammation through several mechanisms, including inhibition of tissue inflammation induced by arachidonic acid (AA) pathway,[6,7] prevention of AA release by lipoprotein lipase,[8] reduction in AA contents of cell membranes[9] and inhibitory effects on activation of cyclooxygenase-2 pathway, an enzyme that converts AA to prostaglandin E2 and thromboxane A2.[10,11] Immunologic studies have shown the inhibitory effects of omega-3 fatty acids on the production of different cytokines by immune cells.[12] It has been proposed that a defined period of administration time is required for emerging anti-inflammatory effects of these fatty acids.[13] However, in some unique situations, such as Alzheimer's disease, these effects have not been observed at all.[14] *In vitro* and *in vivo* studies on omega-3 and omega-6 fatty acids have revealed that these fatty acids could inhibit the production of inflammatory cytokines, including IL-1, IL-2 and TNF-α, by stimulated human lymphocytes.[15] Findings of other studies have shown that the administration of diets supplemented with omega-3 fatty acids may lead to a noticeable reduction of CRP levels in the sera of normal populations.[16,17] Several investigations have been carried out to confirm reducing the effect of omega-3 fatty acids on inflammatory biomarkers among type 2 diabetes mellitus patients, but the findings have not been consistent.[18,19] There is also no strong evidence about the effect of omega-3 fatty acids on inflammation in Iranian type 2 diabetes mellitus patients. The purpose of the current study was to investigate the potential effects of eight weeks of omega-3 fatty

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acid supplementation on the serum levels of CRP, IL-2 and TNF-α in Iranian type 2 diabetes mellitus patients.

METHODS

This was a randomised, double-blind, placebo-controlled clinical trial conducted in 84 subjects aged 45–85 years with type 2 diabetes mellitus. All the patients had been diabetic for at least two years and had been taking medications in order to control the disease. Diabetes mellitus was confirmed (by a professional physician) if the patient had a fasting or random plasma glucose concentration ≥ 140 mg/dL (7/8 mmol/L) or ≥ 200 mg/dL (11/1 mmol/L), respectively, or if the patient was undergoing treatment with hypoglycaemic medication.[20]

The inclusion criteria were as follows: patients who were not consuming omega-3 fatty acids, multivitamin-mineral supplements or pharmaceutical products that may interact with their lipid profile; patients not diagnosed with digestive, renal, hepatic, cardiovascular, thyroid, respiratory or inflammatory diseases, or cancer; non-pregnant women; non-alcoholics; non-smokers; and those with no past history of drug abuse. Participants who met the above criteria provided a written informed consent and were enrolled in the trial. They were fully informed about the scope, procedures and probable risks of the study. The Ethics Committee on Human Experimentation of Tehran University of Medical Sciences approved the research protocol. The sample size was calculated such that a difference of at least 0.25 mg/L in serum concentration of CRP after supplementation with omega-3 fatty acids would be detected.

The patients were randomly assigned into two groups (treatment and control), with 42 patients (21 female and 21 male) in each group. Anthropometric data, including weight and height to calculate body mass index (BMI), as well as information on past medical and drug history, were collected through face-to-face interviews and physical examinations. Based on previous studies,[3,21] a total dose of 2,714 mg of omega-3 fatty acids per day (EPA 1,548 mg; DHA 828 mg; and other omega-3 fatty acids 338 mg) in the form of three capsules for eight weeks was used. Omega-3 supplements were purchased from PBL Co. (Philadelphia, PA, USA). The placebo package contained three capsules, including 2,100 mg of sunflower oil (12% saturated fatty acid, 65% linoleic acid, 23% monounsaturated fatty acid). The placebo capsules had an identical appearance to the omega-3 fatty acid capsules and were prepared for this trial by Zakaria Tabriz Pharmaceutical Co. (Tehran, Iran).

Venous blood samples (10 mL) were obtained from all patients between 8 am and 10 am after 12–14 hours of overnight fasting, prior to the administration of any oral hypoglycaemic agent, at the beginning and after eight weeks of intervention. Blood samples were aliquoted into plasma (with ethylenediaminetetraacetic acid [EDTA]) and serum (without EDTA), and immediately stored at –70°C for further analyses.[3] A commercially available enzyme-linked immunosorbent assay (ELISA) kit (Bender MedSystems Diagnostics GmbH, Vienna, Austria) was used for the measurement of TNF-α and IL-2. Serum CRP levels were measured using a solid-phase capture sandwich ELISA kit (Pars Azmun, Tehran, Iran).

Table I. Age, BMI, and daily energy and nutrient intakes of treatment (n = 42) and control (n = 42) groups at baseline and post intervention.

Variable	Mean ± SD		p-value*
	Treatment group	Control group	
Age (yrs)			
Baseline and post-intervention	55.36 ± 9.88	52.96 ± 10.72	0.21
BMI (kg/m²)			
Baseline	27.72 ± 3.47	27.51 ± 3.16	0.77
Post-intervention	27.19 ± 3.43	27.22 ± 3.31	0.90
Total energy (Kcal/d)			
Baseline	1212.63 ± 261.51	1317.47 ± 307.14	0.09
Post-intervention	1150.85 ± 453.64	1303.35 ± 508.46	0.18
Total carbohydrate (g/d)			
Baseline	175.50 ± 48.00	190.94 ± 64.00	0.29
Post-intervention	164.03 ± 64.69	187.62 ± 83.53	0.12
Total fibre (g/d)			
Baseline	21.83 ± 8.57	24.51 ± 12.77	0.25
Post-intervention	17.46 ± 9.93	21.74 ± 12.19	0.07
Total fat (g/d)			
Baseline	37.33 ± 15.26	38.23 ± 12.57	0.71
Post-intervention	37.78 ± 28.76	37.78 ± 14.58	1.00
Total protein (g/d)			
Baseline	58.72 ± 17.24	63.73 ± 11.78	0.13
Post-intervention	55.54 ± 20.61	64.24 ± 26.29	0.09

*Significant at $p < 0.05$ for age and gender.
SD: standard deviation; BMI: body mass index

The nutrient intake of the subjects was estimated using the 24-hour dietary recall questionnaire at the beginning and at the end of the period. The Food Processor software version 2 (Esha Research, Salem, OR, USA) was used to calculate nutrient intakes. The subjects were advised not to change their usual diet, drug regimen and physical activity throughout the study. Furthermore, alterations in their routine medications were discouraged. All the patients were closely followed up weekly by phone to make sure that they were following the procedure as well as to resolve probable complications. Data were expressed as mean ± standard deviation. Differences between the two groups were determined using Student's *t*-test. Association between variables was determined by Pearson's correlation coefficient. Data was analysed using the Statistical Package for the Social Sciences version 16.0 (SPSS Inc, Chicago, IL, USA). A p-value < 0.05 was considered to be statistically significant.

RESULTS

Table I shows the participants' age, BMI, and daily intake of energy and nutrients before and after the intervention. The intervention and control groups had similar age and BMI at the beginning of the clinical trial; data showed that there was no change during the trial, and thus, any change at the end of the study would be attributed to the supplementation. There was also no significant difference in the mean age, BMI, as well as energy, carbohydrate, fibre, protein and fat intakes of participants in the treatment

Table II. Fasting serum CRP, IL-2 and TNF-α concentrations before and after 8 weeks of omega-3 supplementation in the treatment and control groups.

Variable	Mean ± SD		p-value
	Treatment group	Control group	
TNF-α (pg/mL)			
Before treatment	37.52 ± 6.41	38.68 ± 9.53	0.5
After treatment	34.46 ± 6.40	40.67 ± 11.01	0.002*
IL-2 (pg/mL)			
Before treatment	42.47 ± 13.85	42.46 ± 19.78	0.9
After treatment	35.25 ± 11.28	51.52 ± 19.71	0.0001*
CRP (mg/L)			
Before treatment	25.68 ± 27.38	18.67 ± 16.75	0.1
After treatment	20.35 ± 24.19	18.17 ± 11.33	0.5

*Statistically significant at $p < 0.05$.
SD: standard deviation; TNF-α: tumour necrosis factor-alpha; IL-2: interleukin-2; CRP: C-reactive protein

Table III. Relationships among CRP, IL-2 and TNF-α in the treatment and control groups at the end of study.*

Pearson's correlation coefficient	CRP	TNF-α	IL-2
Treatment group			
CRP	-	+0.1	−0.2
TNF-α	+0.1	-	−0.2
IL-2	−0.2	−0.2	-
Control group			
CRP	-	+0.4	−0.1
TNF-α	+0.4	-	−0.4
IL-2	−0.1	−0.4	-

*$p < 0.05$ for all measurements.
CRP: C-reactive protein; TNF-α: tumour necrosis factor-alpha; IL-2: interleukin-2

and control groups, at the beginning and end of the trial. Table II shows the initial and final serum concentrations of the inflammatory biomarkers, including TNF-α, IL-2 and CRP, in the treatment and control groups. At the end of the study, TNF-α concentration in the treatment group decreased significantly as compared to that in the control group ($p < 0.01$). Likewise, the IL-2 level in the treatment group decreased drastically ($p < 0.001$) post intervention in comparison with that in the control group. There were no statistically significant differences between the two groups with regard to the two biomarkers at the beginning of the trial. The initial and final CRP concentrations also did not differ significantly between the treatment and control groups. Table III shows the Pearson's correlation coefficients among the different variables (CRP, TNF-α and IL-2) in the control and treatment groups at the end of the intervention.

DISCUSSION

The findings of this clinical trial indicate that omega-3 fatty acid supplementation drastically decreases the serum concentrations of inflammatory biomarkers, including TNF-α and IL-2. It also results in a decrease in the serum CRP levels, although this was not statistically significant. The non-significant detectable changes in CRP levels could be due to the small sample size in this study compared to other studies. Our data, however, confirms the results of studies that show that omega-3 fatty acids can potentially decrease inflammatory biomarkers in different types of inflammation. Some studies have reported the anti-inflammatory effects of omega-3 fatty acids in patients with cardiovascular diseases.[22,23] Others have demonstrated that supplementation with omega-3 fatty acids from fish oil diminishes the formation of pre-inflammatory cytokines in cell culture, animals and humans.[24,25] In the current study, which tested the same hypothesis in Iran, TNF-α concentration decreased significantly in the omega-3 fatty acid-supplemented group as compared to the control group. Moreover, the serum IL-2 levels in the treatment group decreased significantly in comparison to those in the control group. In line with our findings, it has been reported that dietary supplementation with fish oil, a rich source of EPA and DHA, decreases some interleukins and the production of TNF-α by leucocytes.[26] Moreover, the effects of EPA and DHA on the reduction of TNF-α levels and improved insulin resistance were reported to be quite noticeable in two studies.[27,28] EPA and DHA supplementation was found to drastically reduce IL-2 levels in both diabetic patients and controls.[29] In contrast with saturated fatty acids or AA, dietary EPA and DHA noticeably limit the secretion of IL-2 from lymphocytes of murine spleen.[30] In several other studies, EPA and DHA supplementation led to restrained releasing of cytokines such as TNF-α.[31-33]

However, our findings did not confirm the results of some researchers. For example, some studies reported that EPA and DHA have no influence on the plasma levels of IL-2 or TNF-α.[34,35] In Jellema et al's study, fish oil, which is less potent than omega-3 capsules, was used.[34] Klein-Platat et al's study was conducted on overweight teenagers, who are supposedly less vulnerable to inflammation and more responsive to anti-inflammatory agents such as omega-3 fatty acids.[35] Moreover, it has been reported that dietary supplementation with PUFAs has no clear effects on serum TNF-α concentration.[36] Schubert et al reported very small changes in TNF-α levels as a result of their study's smaller sample size (n = 30) and shorter intervention period (two weeks)[36] as compared to our study. Studies by Holm et al and Skuladottir et al found that omega-3 fatty acid supplementation increases the plasma levels of TNF-α.[37,38] The results of both studies differ from ours due to differences such as duration of supplementation and cell culture methods. In Holm et al's study, the supplementation period was 12 months, which is longer than that in our study. Skuladottir et al's study used *in vitro* cell culture setting, which differs from the method used in our study (*in vivo*).

As mentioned earlier, we did not observe any significant differences with regard to the initial or final CRP levels between the treatment and placebo groups. It has been proposed that there is no significant difference in terms of CRP levels between subjects receiving pure EPA and DHA or olive oil.[39] Similarly, one study found that consumption of fish oil did not affect the plasma levels of CRP among individuals who suffer from dyslipidaemia and obesity.[40] Another study reported that four weeks of omega-3 fatty acid supplementation can bring about a 93% decrease in the serum CRP levels of individuals with inflammatory diseases.[41] Our study, however, found no change in CRP levels due to intervention, whereas Wigmore et al's study reported a drop in CRP levels due to omega-3 fatty acid supplementation. This

difference could be attributed to the smaller sample size (n = 20) in their study.[41] A study by Fakhrzadeh et al found that omega-3 fatty acid-enriched eggs may significantly decrease the serum CRP level in healthy individuals.[42] The smaller sample size (n = 42) and difference in participant age from those in our study may explain the reason for the decreased CRP levels due to omega-3 fatty acid supplementation found in their study.[42]

In conclusion, based on this short-term study conducted on 84 diabetic patients, no definite conclusions can be drawn with regard to the effectiveness and safety of long-term omega-3 fatty acid administration. Thus, more studies are required in this area. In addition, the effects of omega-3 fatty acid supplements on other inflammatory biomarkers in diabetic patients should be further investigated. Our study found that short-term omega-3 fatty acid supplementation (3 g/day for eight weeks) may result in a decrease in the levels of serum biomarkers such as TNF-α and IL-2, which may in turn lead to alleviation of inflammatory symptoms in individuals suffering from type 2 diabetes mellitus. However, no effect on the CRP concentration was found with supplementation. It is recommended that diabetic patients take daily omega-3 fatty acid supplements.

ACKNOWLEDGEMENTS

This study was supported by a grant from the Vice-Chancellor for Research, Tehran University of Medical Sciences (Grant No. 9401). The authors sincerely thank the individuals who participated in the study and colleagues from the School of Public Health, Tehran University of Medical Sciences.

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