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The Effect of Omega-3 Supplementation on Serum Inflammatory Factors in Hemodialysis Patients

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Background: The level of inflammatory factors such as tumor necrosis factor-alfa (TNF-α) and C-reactive protein (CRP) is increased in ESRD patients and is associated with incremental mortality in these patients. Omega-3 is known as a regulator of inflammatory system. The aim of this study is to evaluate the effect of omega-3 supplementation on TNF-α and CRP level in ESRD patients.
Methods: In this randomized _ controlled double-blind clinical trial, 54 ESRD patients were evaluated in two hemodialysis centers of Isfahan university hospitals. TNF-α and high specific-CRP (hs-CRP) were measured. In the experimental group, Patients were treated with Omega-3 capsules (1 gram capsules- Making factory Zahravi- containing Eicosapentanoic 180 mg and Dosahexanoic 120 mg) three capsules per day (3 g/day) and the control group received placebo capsules manufactured by the Zahravi with the same shape and size for 6 consecutive months.
Results: There were no differences in CRP and TNF-α levels in the beginning and the end of

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study between two groups (P > 0.05).
Conclusion: We conclude that using 3 g of omega-3 per day for 6 consecutive months caused no significant effect on serum levels of TNF-α and CRP in the heamodialysis population .Further studies with larger numbers of patients and longer duration of treatment are recommended.

Keywords: End stage renal disease; omega-3; inflammatory factors.

1. INTRODUCTION

Atherosclerotic disorders were considered the most important cause of death in end-stage renal disease (ESRD) patients [1,2]. Cardiovascular disorders are more common in ESRD patients and kidney transplant patients [3]. The known risk factors such as diabetes mellitus, hypertension, high cholesterol and smoking increases the relative risk of cardiovascular complications but new known risk factors such as high level of inflammatory factors, increase the risk of cardiovascular disease strongly in ESRD patients [4]. Renal failure and heamodialysis cause micro-inflammation, metabolic changes and oxidative stress [5]. CRP serum level, a known risk marker of cardiovascular disease (CVD), is elevated in many chronic renal failure patients and strongly predict hospitalization, mortality and malnutrition of CVD and plasma n-3 fatty acid levels was inversely related to CRP serum concentration [6,7]. Tumor necrosis factor alfa (TNF-α) is a known cytokine, that has adverse effects on different body tissues, and this effect was more common in ESRD patients[8,9]. oxidative stress is more common in dialysis patients due to blood contact with the dialysis membrane, dietary restriction to receive the antioxidant and high risk state of acute and chronic infections [10]. Omega-3 (n-3) fatty acids was known as an important modulatory factor in the immune system and inflammatory responses, and was effective in down progression of arteriosclerosis and vascular reactivity and known as a cell membrane function and gene expression regulator. Diet enriched with omega-3 and polyunsaturated fatty acids was associated with a decreased atherosclerotic disease and down incidence of CVD [11]. Over recent decades, evidences of the benefits of omega-3 fatty acid have been increased [12]. Recent studies have confirmed the benefits of omega-3 in reducing cardiovascular events [13,14]. it has been shown that omega-3 fatty acids can prevent atherosclerosis [15,16]. In various studies, the effect of anti-inflammatory and antioxidant supplements were investigated. For example it was shown that omega-3 can influence on reduction of inflammatory factors and tubulointerstitial fibrosis [17], or omega-3 can slowing down atherosclerosis in Heamo Dialysis (HD) patients [18], vitamin E can increase erythropoietin in ESRD patients [19] and has a good effect on systemic inflammation in men [20] and also vitamin E has an inverse association with serum CRP in women. omega-3 can regulate endothelial cell activation and inflammation by TNF-α [21]. Despite all these, the results about the effect of omega-3 on the levels of inflammatory markers are still unclear. A study on heart transplant recipients showed that there was an increase in TNF-α levels in the omega-3 group, but not in the placebo group [9]. In another study, there was a significant decrease in the levels of all inflammatory markers (TNF-α, IL-6, hs-CRP and ferritin) in ESRD patients in omega-3 group [22]. In the study of Madsen et al, there was no significant difference in hs-CRP levels between omega-3-treated and placebo groups [23].. This is probably due to the human race differences in response to omega-3 [24]. This study was conducted to evaluate the effect of omega-3 supplementation on inflammatory markers such as CRP and TNF-α in chronic heamodialysis patients.

2. METHODS

2.1 Participants

This double-blind randomized clinical trial was done by the grant of Isfahan University of medical sciences in the group of hemodialysis patients in Alzahra hospital and Noor-and-Ali asghar hospital (dependent to Isfahan University of medical sciences) with the clinical trial number of IRCT # IRCT201602012417N18 between May 2011 - December 2012. Inclusion criteria: Adult ESRD patients, the minimum age of 18 years, heamodialysis for at least 3 months, lack of using omega-3s in the last three months were consecutively included into the study. Exclusion criteria: patients with active malignancy or history of it, Steatorrhea (fatty stools) based on biographies, long-clotting test (PT) and (PTT) active or ongoing infection and need for anticoagulation. In this study, all patients were

visited by an internal ward resident. 62 patients fulfilled the inclusion criteria and were enrolled into the study and 8 patients were excluded during the study. All patients signed the informed consent at the beginning of the study and divided to 2 randomized groups. The study was approved by Isfahan University of Medical Sciences (Research project number: 293185).

2.2 Measurements

All patients were hemodialysis three times a week for four hours with Polysulfone membrane in proportion to body size, dialysis flow rate at least 300 And Potassium (k: 2). The patients were divided randomly to 2 experimental and control groups (27 patients in each group). Quantitative C-Reactive Protein (Q-CRP) and tumor necrosis factor alpha (TNF- α) serum levels were measured in patients in Isfahan University of Medical Sciences experimental physiology laboratory.

In the experimental group, Patients were treated with Omega-3 capsules (1 gram capsules-Making factory Zahravi- containing Eicosapentanoic 180 mg and Dosahexanoic 120 mg) three capsules per day (3 g/day) and the control group received placebo capsules were manufactured by the Zahravi with the same shape and size for 6 consecutive months. We told to patients If you forget to take the medication, use it as soon as recall and do not double the dose of drug. A form contains the profile of the patients was completed for each patient (demographic, treatment, side effects, comorbidities and laboratory results beginning and end of the study). The patients were visited monthly and side effects of the drug including nausea, diarrhea and dyspepsia and undesired drug smell were recorded. At the end of the study (after 6 months) Q-CRP and TNF- α levels were measured. The patients were followed-up for 6 months and were evaluated periodically for the appearance of complications as well as correct usage of the drug. Five patients discontinued the drug due to personal reasons and were excluded from the study. Other three patients were also excluded: one died and two underwent kidney transplantation. Thus, a total of 54 patients completed the study. For detection of TNF-α, we used ab ELISA kit of Human TNF-α, Lot: 41881009 and Ref: BMS225/4 manufactured by Austria Bender Med Systems. The results were reported as pg/ml. Hs-CRP was measured by immunoturbidometry, using a kit made by Iran Pars-Azmoon manufacture, the results were reported as mg/L.

2.3 Statistical Analysis

Data was analyzed using SPSS software version 20.0 (SPSS Inc., Chicago IL., USA). Normal distribution of quantitative data was checked with the Kolmogorov-Smirnov Test. Data is reported as mean ± standard deviation (SD) or number (%) for continuous and categorical data, respectively. Comparisons between before- and after-treatment measures were done with the Wilcoxon and mcnemar tests for continuous and categorical data, respectively. A two-tailed P value of < 0.05 was considered as statistically significant in all analyses.

3. RESULTS

62 patients met the inclusion criteria and were enrolled into the study. However, 8 patients excluded during study and 54 patients completed the study. Of the 54 patients, 36 were male (66.6%) and 18 were female (33.3%). The mean age of patients was 48.83 years (range: 18-63 years). The average duration on HD before the study was 43.1 months. Among the studied cases, 21.6% had diabetes mellitus (DM) and all had adequate control of their blood sugar levels.

In omega-3 group the mean hs-CRP level was 6.45 ± 4.86 mg/L before and 5.79 ± 4.42 mg/L after supplementation with omega-3 ($P = 0.441$) and the mean TNF-α level was 15.25±6.91 pg/ml before and 12.35 ± 6.02 pg/ml after supplementation with omega-3 ($P = 0.138$).

[Table 1] shows the comparison of the studied variables before and after supplementation with omega-3 fatty acids. There was no statistically significant difference in the levels of hs-CRP before and after supplementation with omega-3 fatty acids ($P >0.05$) also analysis showed that there was no statistically significant difference in the levels of TNF-α significantly ($P >0.05$).

Renal failure was due to hypertension (3.8%), hypertension concomitant with diabetes mellitus (9.6%), diabetes mellitus (50%) and other causes (consists of glomerulonephritis, tubulointerstitial injuries or other renal damages leading to ESRD) (36.6%). Systolic blood pressure were 141.15±20.79 mmHg in case group and 128.46±19.88 in control group which showed difference between groups using ANOVA test

Table 1. The comparison of studied variables before and after the supplementation

Groups	Variables	Before supplementation	After supplementation	P-value
Omega-3	TNF-α (pg/ml)	15.25 ± 6.91	12.35 ± 6.02	0.138
	hs-CRP (mg/L)	6.45 ± 4.86	5.79 ± 4.42	0.441
Placebo	TNF-α (pg/ml)	15.12± 6.85	15.31 ± 6.69	0.812
	hs-CRP (mg/L)	6.31 ± 4.77	6.42 ± 4.91	0.931

Table 2. Demographic data of patients in both groups

Groups	Number	Age	Sex
Omega-3	27	48.83 ±15.56	17 Male, 10 female
Placebo	27	49.34±14.36	19 male, 8 female
Total	54	49.08±14.96	36 male, 16 female

Table 3. The amount of blood's parameters in both group before and after treatment with Omega-3 supplementation and placebo consumption

	Before treatment		After treatment		P-value	
	Case	Control	Case	Control	Case	Control
Calcium	8.9±0.7	8.3±0.7	8.5±0.3	8.2±0.5	0.051	0.212
Phosphorus	4.5±1.9	4±1.3	4.8±1.1	4±0.6	0.413	0.922
Albumin	4±1	3.8±0.4	4±0.3	3.6±0.3	0.874	0.055
PTH	446.6±458.3	509.4±276.5	726.7±629.6	578.9±293.9	0.063	0.027
HDL	42.5±8.9	39.4±11.5	33.3±7.2	36.2±9	<0.001	0.259
LDL	81.4±21.7	68.7±22.7	84.1±38.6	73.9±19.8	0.726	0 .102
TG	111.9±53.6	120.5±73.1	107.3±68.4	110.3±91.8	0.67 8	0.424
Cholesterol	135.5±32.9	127.3±24.9	138.3±46.8	129±31 .4	0.775	0.714
KTV	1.2±0.2	1.2±0.2	1.2±0.2	2.6±5.1	0.793	0.359
BUN	60.6±18.7	53±15.5	61.3±14.2	51±11.4	0.843	0.903

(P-value=0.029) and we didn't assessed the effect of Omega-3 supplementation on blood pressure of each group. Individuals' body weight were 69.7±14.98 kg and 66.92±11.97 kg in case and control groups respectively; there was no significant differences between groups. (P-value=0.46).

4. DISCUSSION

Because the human body cannot synthesize omega-3 fatty acids in appreciable amounts, they are obtained from dietary sources (i.e., they are "essential" fatty acids) [24,25]. Recently, the American Heart Association established evidence-based recommendations for intake of omega-3 fatty acids [26].

Omega-3 fatty acids have anti-inflammatory effects. For example, the form of n-3-polyunsaturated fatty acids (PUFA)-rich fish oil reduces the symptoms in patients with severe inflammatory disease [27]. In our study, there was no significant reduce in TNF-α level after 6 months of omega-3 administration, n-3 PUFAS can reduce the production of inflammatory factors, such as interleukin-1 and interleukin-6 and TNF-α [28]. omega-3 fatty acids can decrease the expression of adhesive receptors involved in inflammatory interactions between leukocytes and endothelial cells[29]. It was shown that elevated levels of TNF-α are associated with muscle wasting, due to inhibition of myogenic differentiation pathway and increase in cell apoptosis [8]. CRP, as a known strong risk marker of CVD, and TNF-α are elevated in a large proportion of ESRD patients and it is believed that Omega-3 have cardioprotective effects, which may be due to its anti-inflammatory effects [30]. omega-3 intake for 2 years reduced the number of myocardial infarctions (MI) in ESRD patients [31,32]. Omega-3 fatty acids have an effective role in inflammatory pathways, arteriosclerosis and cardiovascular disease, cardiac dysrhythmias and lipid regulation [14,33]. It acts by decreasing leukocytosis, systemic inflammation and oxidative stress. omega-3 in post-MI patients is possibly due to decrease in triglyceride level as a risk factor for atherosclerosis [34,43]. There are many reasons for omega-3 deficiency in the dialysis patients: 1- foods containing omega-3

may be have unpleasant taste for these patients, 2- Seafood that enriched by omega-3 may be limited by social dietary habits,3- formal renal dietary recommendations that encourage fish consumption do not exist and use of the omega-3 fatty acid sources may be reduced due to kidney disease-related dietary potassium restriction [24,35]. In our study, hs-CRP level before and after supplementation with omega-3 fatty acid was not significant different ($P > 0.05$) that is comparable with the study of Madsen et al. [23]. Bowden et al. [36] demonstrated that omega-3 can lower CRP levels [36]. Another study showed that, low-dose omega-3 fatty acids had no effect on the plasma hs-CRP levels [37]. One study showed that only high doses of omega-3 given for a long time can reduced CRP [38]. Rasic-Milutinovic et al. [39] studied the effects of omega-3 fatty acid patients with CRF on maintenance of HD. There was a significant decrease in the levels of all inflammatory markers ($P = 0.01$ for TNF-α, $P = 0.001$ for IL-6, $P = 0.001$ for hs-CRP and$p = 0.01$ for ferritin). Madsen et al performed a randomized, double-blind, placebo-controlled study. They found a trend toward a reduction in hs-CRP in the n-3 PUFA group, but there was no significant difference in hs-CRP levels when both groups were compared [23]. omega-3 Supplementation can decrease TNF receptor p55 and CRP levels in patients with rheumatoid arthritis [40,41]. Holm et al measured levels of TNF-α and IL-10 in 45 heart transplant recipients before and after treatment with omega-3 fatty acids and placebo. In the omega-3 group–there was a rise in the TNF-α, and a decrease in IL-10 [9]. The most common adverse effects of fish oil supplements are a fishy after-taste and gastrointestinal complaints (e.g., nausea, dyspepsia) [24,28]. The risk for incremental bleeding times has been seen, primarily with >3 g/day fish oil, especially in patients who may be susceptible to increased bleeding (e.g., patients taking warfarin) [34,42,43].

In this study, noticeable omega-3 side-effects included nausea, diarrhea and unfavorable drug smell. There were no hemorrhagic and/or any severe side-effects in our patients. Overall the findings of this study and other studies suggest that the effects of omega-3 on inflammatory factors has been different and Further studies are needed to determine the exact role of omega-3 on blood levels of inflammatory markers. Racial differences, chronic diseases, use different drugs and probably many other factors are effective to determine the level of inflammatory factors that may be omega-3 cannot effects on these factors.

5. LIMITATIONS

The major limitation of this study was the short duration of administration of omega-3 in HD patients and the small number of study patients.

6. CONCLUSIONS

We conclude that the use of 3g of omega-3 per day for 6 consecutive months caused no significant decrease effect on serum levels of TNF-α and CRP in the heamodialysis population. Further studies with larger numbers of patients and longer duration of treatment are recommended. Evaluations of other factors such as comorbids, drugs, and groups Homogenization may be effective to determine omega-3 Various effects on inflammatory factors in ESRD patients.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by Regional ethics committee and research committee of the Isfahan University of Medical Sciences.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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