Effects of Omega-3 Fatty Acid Supplementation on Serum Biomarkers, Inflammatory Agents, and Quality of Life of Patients on Hemodialysis

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Keywords. hemodialysis, cardiovascular disease, inflammatory markers, omega-3 polyunsaturated fatty acid

Introduction. Patients on long-term hemodialysis are at a higher risk of cardiovascular disease and premature mortality. It is generally believed that omega-3 supplementation can prevent cardiovascular events due to its anti-inflammatory and anti-atherosclerotic effects.
Materials and Methods. Fifty-two hemodialysis patients were divided into 2 groups to receive omega-3 and placebo for 6 six months. Serum biomarkers and inflammatory agents were measured in both groups before and after the intervention. Quality of life was also assessed before and after the trial using the Kidney Disease Quality of Life-Short Form questionnaire.
Results. Patients who received omega-3 showed an increase in serum calcium level ($P = .005$), a decrease in vascular cell adhesion molecule ($P = .04$), and an increase in the high-density lipoprotein cholesterol level ($P < .001$), while such changes were not documented in the control group. However, omega-3 administration did not have a significant effect on serum levels of albumin, low-density lipoprotein cholesterol, or triglyceride. Quality of life scores were improved after treatment with omega-3 in both scopes of general and kidney-specific assessment ($P = .37$ and $P = .20$, respectively), while no similar changes were seen in the control group.
Conclusions. Our data showed beneficial effects of omega-3 supplementation during chronic hemodialysis on inflammatory processes and also quality of life. We suggest administration of omega-3 in the hemodialysis community in a preventive manner for improvement of cardiovascular events and quality of life.

IJKD 2016;10:381-7
www.ijkd.org

Original Paper

INTRODUCTION

Patients with end-stage renal disease (ESRD) need renal replacement therapies, including hemodialysis, peritoneal dialysis, and kidney transplantation, in order to survive. These patients are more susceptible to cardiovascular disease (CVD), and about 50% of them die due to CVD complications as the leading cause of death.[1,2] This risk is not just limited to adults, but CVD is the prominent cause of death in ESRD children, too.[3] Statistical analysis showed that about one-third of hospital admissions in ESRD patients are due to CVD and half of them lead to death.[4]

There are several possible risk factors which could be related to the high incidence of CVD in ESRD patients including diabetes mellitus, hypertension, smoking, dyslipidemia, obesity, and factors related to uremia (increased body fluid volume, anemia,

secondary hyperparathyroidism, etc); however, there are also some recently recognized risk factors such as elevated homocysteine, inflammation, and oxidative stress.[5] Previous studies have shown that there is a significant role of inflammation in progression of coronary artery disease and atherosclerosis.[6] Atherosclerotic lesions are focal nonsymmetric thickened areas containing cells, connective tissue, lipid, and debris. Inflammatory mediators are released following plaques rupturing.[7]

Recent studies suggest that endothelial cell adhesion molecules such as intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM) are responsible for the formation of atherosclerotic lesions, and in ESRD patients, elevated level of these mediators are related to increased mortality rate and CVD complications.[8] On the other hand, quality of life of ESRD patients decrease in the background of inflammatory processes.[9] Overall, decreased quality of life in ESRD patients is related to chronicity of the disease and dialysis-dependent problems.[10]

It is believed that changes in the ratio of omega-3 fatty acid to omega-6 fatty acid would lead to changes in central nervous system function and cause depression, behavioral changes, and decreased life satisfaction.[11] Fish oil is a food supplementation containing 2 significant fatty acids of eicosapentanoic acid (EPA) and dosahexanoic acid (DHA) that have a significant role in central nervous system function, and it is widely used to promote population's quality of life and to decrease signs of depression.[11] It is also mentioned that because of its anti-inflammatory and anti-atherosclerotic role, omega-3 can improve patients' quality of life.[12] There is evidence showing the anti-inflammatory effect of omega-3 in the treatment of chronic obstructive pulmonary disease by reduction in quantity of inflammatory markers including leukotriene B4, tumor necrosis factor-α, and interleukin-8 levels.[13]

It is still a question for physicians that whether omega-3 can improve endothelial function and quality of life in ESRD patients on hemodialysis or not. In this clinical trial, we attempted to find an answer for this question.

MATERIALS AND METHODS

This randomized double-blinded controlled trial was done on hemodialysis patients at Alzahra Hospital and Noor-and-Ali Asghar Hospital, both affiliated to Isfahan University of Medical Sciences (Iranian Registry of Clinical Trials registry number, IRCT201309242417N13).

Fifty-two hemodialysis patients who met the following criteria were included into the study: hemodialysis for at least 3 months, age greater than 18 years, complete knowledge about the study and willingness for participation, and no omega-3 administration during past 3 months. Presence or history of malignancy, steatorrhea (according patient's history), anemia, prolonged prothrombin time or partial thromboplastin time, and anticoagulation therapy were considered as exclusion criteria. All of the participating patients were on hemodialysis 3 times in a week, each for 4 hours. Dialysis procedure characteristics and the dialysis membrane were the same for all of the patients.

The participants were divided into 2 groups, with 26 individuals in each group. The blood levels of ICAM and VCAM were measured in both groups before initiation of the intervention, using an Autoanalyzer BT 3000 machine in the physiology laboratory of the university. All of the patients' sera were collected before and after the intervention for the assessment of biomarkers such as calcium, phosphorus, albumin, parathyroid hormone, high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), triglyceride, cholesterol, and blood urea nitrogen. Analysis of serum biomarkers was done at Alzahra Medical Center's laboratory using automated machines. The Kidney Disease Quality of Life Short Form (KDQOL-SF) questionnaire was used for assessment of quality of life in both groups with a self-reporting manner of patients. The KDQOL-SF questionnaire has 74 questions of which 36 are specified for assessment of quality of life of patients with kidney damage. This questionnaire was validated into the Persian version for assessment of quality of life of patients on hemodialysis.[14]

Omega-3 capsules (1 g) manufactured by Zahravi Company (Tehran, Iran) were administered 3 times a day in the omega-3 group. Each capsule contained 180 mg of EPA and 120 mg of DHA. The control group received placebo with same appearance manufactured by same company in a similar pattern of consumption. Forgotten doses of drug were immediately taken by the participants after reminding and no one used double-dosage in a time.

The patients were observed closely by nephrologist in a routine monthly visit during the study. All of the patients were observed for 6 months for serum biomarkers assessment, measurement of blood pressure, and other signs and symptoms related to the disease, as well as medication complications such as nausea, vomiting, and hypertension. After 6 months of the trial, ICAM and VCAM were measured. The KDQOL-SF questionnaire was filled out by all twice: at the onset of the study and after 6 months.

The collected data were analyzed using the SPSS software (Statistical Package for the Social Sciences, version 20.0, SPSS Inc, Chicago, IL, USA). The paired test, independent *t* test, the analysis of covariance, and the Pearson correlation test were used to compare variables before and after the intervention. *P* values less than .05 were considered significant.

RESULTS

Fifty-two patients participated in the study, the age and sex distribution of whom was comparable between the two study groups (Table 1). All of patients received their routine medical care and no one died during the study period. There was no significant medical event or adverse drug reaction during the study. Kidney failure was due to hypertension (3.8%), hypertension concomitant with diabetes mellitus (9.6%), diabetes mellitus (50.0%), and other causes, consisting of glomerulonephritis, tubulointerstitial injuries, and other kidney damages (36.6%).

Baseline, mean systolic blood pressure was 141.15 ± 20.79 mm Hg in the omega-3 group and 128.46 ± 19.88 mm Hg in the control group (*P* = .03). We did not assessed the effect of omega-3 supplementation on blood pressure of each group. The mean body weight was 69.7 ± 15.0 kg and 66.9 ± 12.0 kg in the omega-3 and control groups, respectively (*P* = .46).

The mean score of the KDQOL-SF was 54.8 ± 14.6 and 56.2 ± 14.9 in the control and omega-3 groups, respectively at the beginning of the study (*P* = .74); however, there was a significant difference between the two groups at the end; the mean score was 54.0 ± 13.6 in the control group and 65.5 ± 16.3 in the omega-3 group (*P* = .009). There was a significant increase in the quality of life as indicated by the KDQOL-SF scores in the omega-3 group (*P* = .02), while the same effect was not seen in the control group (*P* = .70).

Table 1. Demographic data of patients in both groups

Characteristic	Omega-3 Group	Control Group	All
Participants	26	26	52
Mean age, y	57.76 ± 15.56	58.34 ± 14.36	58.05 ± 14.78
Sex			
Male	17	19	36
Female	9	7	16

Table 2. Blood Parameters and dialysis Adequacy in theOmega-3 and Control Groups*

Parameter	Omega-3 Group			Control Group		
	Before Intervention	After Intervention	*P*	Before Intervention	After Intervention	*P*
Serum calcium, mg/dL	8.9 ± 0.7	8.5 ± 0.3	.05	8.3 ± 0.7	8.2 ± 0.5	.21
Serum phosphorus, mg/dL	4.5 ± 1.9	4.8 ± 1.1	.41	4 ± 1.3	4 ± 0.6	.92
Serum albumin, g/L	4 ± 1	4 ± 0.3	.87	3.8 ± 0.4	3.6 ± 0.3	.06
Parathyroid hormone, pg/mL	446.6 ± 458.3	726.7 ± 629.6	.06	509.4 ± 276.5	578.9 ± 293.9	.03
HDLC, mg/dL	42.5 ± 8.9	33.3 ± 7.2	< .001	39.4 ± 11.5	36.2 ± 9	.26
LDLC, mg/dL	81.4 ± 21.7	84.1 ± 38.6	.73	68.7 ± 22.7	73.9 ± 19.8	.10
Triglyceride, mg/dL	111.9 ± 53.6	107.3 ± 68.4	.68	120.5 ± 73.1	110.3 ± 91.8	.42
Cholesterol, mg/dL	135.5 ± 32.9	138.3 ± 46.8	.78	127.3 ± 24.9	129 ± 31.4	.71
KT/V	1.2 ± 0.2	1.2 ± 0.2	.79	1.2 ± 0.2	2.6 ± 5.1	.36
Blood urea nitrogen, mg/dL	60.6 ± 18.7	61.3 ± 14.2	.84	53 ± 15.5	51 ± 11.4	.90
ICAM, U/mL	39.6 ± 21	32.1 ± 15.2	.18	44.3 ± 26.	46.1 ± 21.3	.57
VCAM, U/mL	34.1 ± 31.4	21.3 ± 12.9	.046	33.5 ± 24.3	32.27 ± 17.81	.76

*HDLC indicates high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; KT/V, dialysis adequacy; ICAM, intercellular adhesion molecule; and VCAM, vascular cell adhesion molecule.

Significant changes in serum levels of HDLC ($P < .001$) and VCAM ($P = .04$) were seen after the trial in the omega-3 group, but there were no significant changes in the measured parameters, except for parathyroid hormone ($P = .03$) in the control group (Table 2).

DISCUSSION

Inadequate intake of antioxidant nutrients, blood exposure to dialysis membranes, and presence of inflammation are factors responsible for higher oxidative stress in hemodialysis patients.[15] Much greater rate of mortality in ESRD patients on hemodialysis made the scientists to find pharmacological anti-inflammatory agents in order to ameliorate heart injuries in these patients,[16] and fish oil has been shown to have effects on decreasing cardiovascular mortality.[17] The United States Food and Drug Administration approved that omega-3 polyunsaturated fat (PUFA) can lower triglyceride in hypertriglyceridemia.[18] There are also some studies which show that there is a lowered risk of CVD in patients using omega-3 PUFA. Molecular studies revealed the gene downregulation of pro-atherogenic and pro-inflammatory genes in response to nutritional intake of omega-3.[19] Because of the abovementioned anti-inflammatory effects of omega-3, this agent is also effective in amelioration of diseases such as inflammatory bowel diseases, psoriasis, thyrotoxicosis, and bronchial asthma.[19-24] It is also shown that the risk of inflammation, atherosclerosis, neurological disorders, and hyperlipidemia are reduced by using omega-3 PUFA.[25-29]

Some studies considered omega-3 PUFA as a triglyceride- and lipid-lowering agent and also an antihypertensive agent; however, other possible mechanisms such as anti-atherosclerotic, anti-thrombotic, anti-arrhythmic, and anti-inflammatory effects are those with protective action of omega-3 PUFA.[26,30-35] Some anti-inflammatory mechanisms of action are mentioned for omega-3 PUFA such as changes in fatty acid composition of cell membrane and effects on production of peptide mediators of inflammation.[36]

Saifullah and coworkers found that fish oil administration (as much as suggested by the American Heart Association) is related to lower C-reaction protein and lowered triglyceride levels in long-term hemodialysis patients.[37] Tayyebi-Khosroshahi and colleagues found an antioxidative role of omega-3 fatty acid in hemodialysis patients.[15] Friedman and colleagues revealed that patients with chronic kidney disease in comparison with the healthy population consumed lower amounts of omega-3 as suggested by AHA.[38] He and colleagues found an inverse relationship between fish intake and CVD.[39] Svensson and associates did not find a significant protective effect of omega-3 PUFA in secondary prevention of mortality and cardiovascular events; however, they found a significant decrease in myocardial infarctions in high-risk patients who received omega-3 PUFA.[35] A research designed in urban American Midwest had interesting results associated with the topic that there was lowered omega-3 blood levels in hemodialysis patients, that is possibly related to consumption of inadequate amounts of omega-3 fatty acids due to restrictive renal diet and some socioeconomic problems for buying and eating fish.[38] Another study reported more suitable lipid profile and C-reaction protein level progression in hemodialysis patients on a combination of omega-3 and protein supplement in comparison with those hemodialysis patients on pure protein supplement.[40]

Previous studies on omega-3 supplementation in dialysis patients revealed no significant changes in serum albumin levels after treatment with omega-3 supplement,[12,41,42] and our data also support the hypothesis that omega-3 does not make changes in serum albumin level of ESRD patients on chronic hemodialysis. However, we found a direct relationship between omega-3 consumption and increased level of HDLC, which was supported by other studies.[43-47] Although there are several studies showing no change or even adverse effect of omega-3 supplementation on blood HDLC level.[42,48-57] Similar to a study by Fielder and coworkers,[57] our data did not reveal changes in serum LDLC levels after treatment with omega-3 and despite previous evidence, we did not have a significant difference in triglyceride levels of our patients after the intervention.[52,57-59]

Serum VCAM levels of our participants decreased in response to omega-3, but no similar changes was seen in the ICAM level. Caterina and associates found a similar result to ours and concluded that DHA, but not EPA, had a time- and dose-dependent role in decreasing the expression of

genes expressing VCAM. They also revealed that expression of e-selectin and ICAM are decreased after DHA administration in a concentration-dependent manner.[19] Researchers in another study used a combination of DHA and EPA and found effects on VCAM levels only.[60] In a randomized clinical trial, Kooshki and colleagues compared the effect of omega-3 versus placebo in 34 hemodialysis patients and showed a significant reduction in ICAM levels in their omega-3 group.[61] Nonetheless, we did not find similar decreases nor increases in the ICAM level after treatment with omega-3.

Quality of life was another parameter which we assessed in our patients in order to see whether omega-3 supplementation has beneficial effects on it or not. Our data revealed that omega-3 supplementation can improve quality of life of ESRD patients on chronic hemodialysis.

We used a combination of DHA and EPA in a small group of patients with a unique dose of consumption in all patients which can be a limitation of our study that we did not try different doses for assessment of dose-dependent manner of omega-3. Regarding some contradictory results in our data to previous studies, future studies with larger group of patients and molecular studies are needed in order to clarify omega-3's effects on hemodialysis patients. We also did not include patients' routine-used drug in the statistical analysis, some of which could make changes in inflammatory markers.

CONCLUSIONS

In summary, our data revealed improved quality of life of ESRD patients on chronic hemodialysis who had omega-3 supplementation in their daily dietary program. Improvements in HDLC level and decreased VCAM were also seen after treatment; however, no similar changes was seen in ICAM, triglyceride, albumin, and other blood biomarkers.

FININCIAL SUPPORT

This study was supported by a grant from Isfahan University of Medical Sciences.

CONFLICT OF INTEREST

None declared.

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Received January 2016
Revised April 2016
Accepted May 2016