Effect of Omega-3 Supplementation on Serum Level of Homocysteine in Hemodialysis Patients

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Introduction. Patients with end-stage renal disease are at a high risk of adverse cardiovascular events. Elevated level of homocysteine is an important risk factor for cardiovascular morbidity and mortality in dialysis patients. There are some strategies for reduction of serum homocysteine level in these patients, including folate and vitamin supplementation. The aim of the present study was to evaluate the effect of omega-3 supplementation on serum homocysteine level in patients on hemodialysis.

Materials and Methods. In a randomized controlled trial, 100 hemodialysis patients were assigned into two groups to receive omega-3 (oral capsule, 3 g/d) or placebo for 2 months. Complete blood count, blood urea nitrogen, serum creatinine, serum lipids, and serum homocysteine levels were measured before the study and after 2 months at the end of study.

Results. Of 100 patients, 6 in each group were excluded, and 44 patients in each group completed the study. There were no significant differences regarding the age, sex, and the number of dialysis sessions per week between the two groups. No difference was observed between the two groups in the laboratory investigations at the end of the study, except for a significant reduction in serum homocysteine level in the omega-3 group as compared to the placebo group (P = .03).

Conclusions. Our study showed a significant reduction regulated by omega-3 supplementation in serum homocysteine level which is a cardiovascular risk factor among hemodialysis patients. Omega-3 can be considered as another homocysteine-reducing agent in this population.

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INTRODUCTION

Hemocycteine is a nonprotein amino acid and one of cycteine homologues that is not obtained from diet.[1] Instead, it is biosynthesized from methionine via a multistep process. Homocysteine can also be recycled into methionine by using N5-methyl tetrahydrofolate as the methyl donor and cobalamin (vitamin B12)-related enzymes. An elevated level of homocysteine occurs as a result of folic acid, pyridoxine, or cobalamin deficiencies; hereditary diseases such as homocycteinuria and methylene-tetrahydrofolate–reductase polymorphism genetic traits; long duration of exercise; and chronic consumption of alcohol.[2-4]

One of most powerful risk factors for cardiovascular disease is homocysteinemia. Homocysteinemia is one important risk factor for cardiovascular and cerebrovascular events in the general population of elderly men.[5] It has been shown that each 5 µmol/L increase in fasting or nonfasting homocysteine above

10 µmol/L is associated with highly increasing rates of cardiovascular and cerebrovascular events.[6-8] High levels of homocysteine are observed in patients on dialysis. These patients are most prone to cardiovascular events.[9,10] Between 1972 and 1996, about 17 studies published with respect to the correlation between end-stage renal disease (ESRD) in the predialysis phase and homocystinemia.[10] Dialysate losses of water soluble vitamins, including B vitamins, and restricted overall dietary intake patterns make it necessary to provide routine multivitamin supplementation to dialysis-dependent ESRD patients.[11] Also some evidence showed that uremia in ESRD population may result in increased hydrolysis of plasma pyridoxal phosphate, reducing the supply of coenzyme to peripheral tissues.[12,13]

Many studies suggest the beneficial effect of folate and vitamin B supplementations on decreasing homocysteine level in ESRD, as a protective factor for preventing cardiovascular and cerebrovascular accident.[14-16] Omega-3 fatty acids are "essential" fatty acids, because they are vital for normal metabolism and cannot be synthesized by the human body. More precisely, α-linolenic acid cannot be synthesized by the human body at all, and the other omega-3 fatty acids can only be synthesized from α-linolenic acid. The potential mechanism responsible for the observed homocysteine-lowering effect of omega-3 polyunsaturated fatty acids has not yet been fully elucidated. However, a possible mechanism is that omega-3 polyunsaturated fatty acid may modulates gene expression of enzymes that are involved in the formation and metabolism of plasma homocysteine by upregulation of cystathionine-γ-lyase activity and cystathionine-γ-lyase mRNA expression and downregulation of methylenetetrahydrofolate reductase, methionine synthetase, and betaine-homocysteine methyltransferase activity.[17-21]

Various studies investigated the efficacy of omega-3 fatty acids in controlling cardiovascular disease.[22-25] In 2010, it was reported that the content of docosahexaenoic acid in serum phospholipids was inversely correlated with plasma homocysteine levels, and supplementation with omega-3 polyunsaturated fatty acid would not reduce homocysteine levels in patients with ESRD.[26] However, in another study, the beneficial effect of omega-3 fatty acid in decreasing of triglycerides and a significant increase of high-density lipoprotein-cholesterol was reported.[27] In this study, we aimed to evaluate the role of omega-3 supplementation in reducing the level of homocysteine in the patients with ESRD on hemodialysis.

MATERIALS AND METHODS

One hundred ESRD patients who were on maintenance dialysis in hemodialysis centers of Tabriz University Hospitals were enrolled in this randomized clinical trial. These patients were divided into 2 groups randomly (50 patients as the case group and 50 as the control group). The exclusion criteria were being on dialysis less than 6 months, a history of active infectious or inflammatory disease, abnormalities documented by liver function tests or complete blood count, life expectancy less than 6 months, and a history of noncompliance with hemodialysis or medication regimens. The patients provided informed consent after the nature and intent of the study was been fully explained to them. The research protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences.

A random number was used to assign which block was chosen to randomize group selection. Of 50 patients in the omega-3 group, 6 patients were excluded from the study due to drug intolerance (3 patients), noncompliance (2 patients), and kidney transplantation (1 patient). Of 50 patients in the placebo group, 6 were excluded from study due to drug intolerance (2 patients), noncompliance (3 patients), and changing dialysis modality (1 patient). Considering a 95% power, and 95% confidence, the maximum sample size was calculated 44 in each group, based on omega-3 (standard deviation, 0.16 for placebo group and 0.09 for omega-3 group, and a deifrence equal to 0.1). Taking into account a dropout rate of 13%, we increased the sample size to 50 in each group, which at the end of the study, 44 participants were remained in the placebo and 44 in the omega-3 group.

Patients in the omega-3 group received 1 soft-gel pill of omega-3 (Zahravi Pharmaceutical Co, Tariz, Iran) with each meal (3 times per 24 hours) for 8 weeks. Participants in the placebo group were assigned to oral soft-gel pills (1 g each) of placebo (Zahravi Pharmaceutical Co, Tabriz, Iran), after each meal (3 times per 24 hours) for 8 weeks. Both groups were evaluated regarding the age, sex, duration of dialysis (month), the number of

dialysis sessions per week, and other medications.

Blood sample was taken from all patients for measurement of complete blood count, lipid profile, and serum levels of albumin, parathyroid hormone, iron, total iron binding capacity, serum ferritin, prothrombin time, international normalized ratio, and serum homocysteine levels before the start of the study and after 8 week at the end of the study. A single 5-mL venous blood sample for serum homocysteine detection was collected in the fasting state. The samples were centrifuged within 1 hour after collection and stored at -70°C. Serum homocysteine levels were measured using a biochemical method (Axis-Shield Diagnostic Ltd, Dundee, UK). In this method, oxidized homocysteine changes into cystationin by cystationin beta synthase and cystationin is converted to homocysteine ammoniac and pyrovat. Then pyrovat is converted to lactate by lactate dehydrogenase enzyme. Conversion of nicotinamide adenine dinucleotide, read by spectrophotometer in 340 nm wave, is correlated with homocysteine concentration.

All analyses were performed using the Minitab 15 (Minitab Inc, State College, PA, USA) and the SPSS software (Statistical Package for the Social Sciences, version 17.0, SPSS Inc, Chicago, Ill, USA). The results were expressed as mean ± standard error of mean. The normality of data was evaluated by the Q-Q test. For comparison of the two groups in two times, a nested-repeated measure model was used. *P* values of less than .05 were considered significant.

RESULTS

The mean age of the patients in the omega-3 group was 51.5 years (range, 19 to 84 years), and it was 48.6 years (range, 17 to 75 years) in the placebo group. The mean number of dialysis sessions per week was 2.56 in the omega-3 group and 2.43 in the placebo group (range, 2 to 3 per week). There were 32 men and 12 women in the omega-3 group and 31 men and 13 women in the placebo group. There were no significant differences between the two groups regarding age, sex, duration of dialysis, and the number of dialysis sessions per week (Table 1).

The laboratory findings in the two groups are summarized in Table 2. The mean serum homocysteine in the omega-3 group was 14.04 ± 1.11

Table 1. Baseline Characteristics of Hemodialysis Patients in the Omega-3 and Placebo Groups

Characteristic	Omega-3	Placebo
Mean age, y	51.50 (19 to 84)	48.60 (17 to 75)
Sex		
Male	32	31
Female	12	13
Mean dialysis per week	2.56	2.43

Table 2. Mean Values of Blood Laboratory Studies of Hemodialysis Patients Before and After the Study in the Omega-3 and Placebo Groups

	Omega-3		Placebo		
Parameter	Before Study	After Study	Before Study	After Study	*P**
Hemoglobin, g/dL	11.09 ± 0.23	11.31 ± 0.35	11.14 ± 0.39	11.09 ± 0.43	.52
Leukocyte, × 10^9/L	7132.43 ± 298.64	7086.49 ± 261.69	6470.97 ± 390.46	7217.74 ± 538.76	.13
Platelet, × 10^9/L	211.76 ± 11.57	214.58 ± 106.44	176.71 ± 129.91	168.335 ± 112.51	.96
Calcium, mg/dL	8.13 ± 0.35	8.63 ± 0.39	8.07 ± 0.21	8.50 ± 0.21	.13
Sodium, mEq/L	142.31 ± 0.64	142.55 ± 0.76	139.77 ± 0.81	138.07 ± 1.05	.77
Potassium, mEq/L	5.78 ± 0.14	5.62 ± 0.12	5.43 ± 0.11	5.26 ± 0.11	.49
Phosphorus, mg/dL	5.93 ± 0.27	5.31 ± 0.16	5.55 ± 0.24	5.65 ± 0.19	.59
Alkaline phosphatase, IU/L	455.66 ± 76.12	419.29 ± 57.68	305.28 ± 54.81	358.87 ± 41.35	.85
Intact parathyroid hormone, pg/mL	369.75 ± 60.10	391.05 ± 65.85	246.38 ± 43.19	288.76 ± 56.95	.32
Triglyceride, mg/dL	211.00 ± 26.19	204.78 ± 21.84	175.47 ± 20.37	171.23 ± 19.94	.88
Total cholesterol, mg/dl	180.58 ± 6.22	183.94 ± 8.11	152.83 ± 10.28	148.97 ± 6.39	.55
Low-density lipoprotein, mg/dL	99.77 ± 6.93	92.45 ± 8.78	79.50 ± 7.03	80.35 ± 10.45	.49
High-density lipoprotein, mg/dL	59.70 ± 17.72	45.26 ± 3.09	42.17 ± 5.19	41.88 ± 4.43	.31
International normalized ratio	1.05 ± 0.02	1.02 ± 0.01	1.00 ± 0.00	1.09 ± 0.04	.83
Prothrombin time, sec	29.00 ± 1.32	29.00 ± 0.87	30.33 ± 3.52	30.17 ± 3.53	.80
Total iron binding capacity, µg/dL	259.51 ± 9.80	270.81 ± 13.13	358.41 ± 15.30	367.92 ± 11.16	.53
Iron, µg/dL	69.96 ± 5.90	66.37 ± 3.85	62.31 ± 4.95	59.60 ± 4.44	.44

*Between Groups

Table 3. Pretest and Posttest Serum homocysteine Levels in Patients With End-Stage Renal Disease with and without Omega 3 Supplementation.

Study Group	Homocysteine, μmol/L		*P*
	Before Study	After Study	
Omega-3	14.04 ± 1.11	10.43 ± 0.66	.03
Placebo	11.27 ± 0.76	11.65 ± 0.52	.30

μmol/L before the study and 10.43 ± 0.66 μmol/L at the end of the study. In the placebo group, homocysteine level was 11.27 ± 0.76 μmol/L before the study and 11.65 ± 0.52 μmol/L at the end of the study. Accordingly, homocysteine level was significantly different between the two groups (P = .03) and omega-3 reduced the homocysteine by 3.61 units (P = .03; Table 3).

The differences between the omega-3 and the placebo groups were not significant for hemoglobin, leukocyte count, platelet count (between intervals); serum levels of calcium, sodium, potassium, phosphorus, alkaline phosphates, parathyroid hormone, triglycerides, total cholesterol, low- and high-density lipoprotein cholesterol, total iron binding capacity, and iron; and the international normalized ratio and prothrombin time.

DISCUSSION

Various studies have been performed for evaluation of the effects of omega-3 fatty acids, found in fish oil and serum level of homocysteine in different populations with different dosage and duration of omega-3 consumptions.[28-32] We studied the effect of omega-3 fatty acid on serum homocysteine level and other laboratory parameters of dialysis patients, taken as 3 g of capsules daily for 2 months. Similar studies are Zeman and colleagues' study on 24 diabetic patients who took 3.6 g of omega-3 daily for 3 months,[32] and Olszewski and McCully's study on 16 patients with normal lipid profile who took 6 g daily of omega-3 (fish oil),[30] and also Piolot and colleagues' study on the effect of 6 g omega-3 daily for 8 weeks on the level of homocysteine and lipid profiles of 16 individuals with normal lipid profiles.[31]

Fiedler and colleagues evaluated 11 hemodialysis patients taking 1.2 g of omega-3 along with 11.2 g of pectin daily for 12 weeks.[29] They showed limited positive effects on lipids without reduction of serum homocysteine level by short-term administration of omega-3 fatty acids in hemodialysis patients. The small number of patients in their study may affect the results. In contrast, our study was performed on more patients (44 dialysis patients) and showed significant impact of omega-3 supplementation on serum homocysteine level without any positive effect on lipids. Fiedler and colleagues concluded that only high doses of omega-3 fatty acids given for a longer time would influence inflammation and atherosclerosis.[29]

A systematic review of studies published until 2003 showed that omega-3 along with other polyunsaturated fatty acids and folic acid (3g to 6 g per day) can reduce the risk of intravascular clots.[28] Some studies have shown that long-term intake of omega-3 fatty acids increased bioavailability of platelets, reduced their activity (the ability of platelet aggregation), and also eliminated free radicals.[32] In an unpublished study, we could not find any impact of omega-3 on platelets count and activity.

In Ghaddar and colleagues' study on 60 chronic hemodialysis patients in Lebanon, the authors showed that omega-3, 3 g/d for 6 months, had no significant effect on hemoglobin levels and lipid profile of the patients.[33] However, in Taziki and colleagues' study on 16 hemodialysis patients, it was shown that daily consumption of 2 g of omega-3 fatty acid for 3 months significantly reduced triglyceride levels and increased the level of high-density lipoprotein cholesterol, but it did not change the total cholesterol and low-density lipoprotein cholesterol levels.[34] Svensson and colleagues studied 206 hemodialysis patients in 11 hospitals in Denmark in a double-blinded clinical trial.[35] They showed that daily taking of two 1.7-g capsules of omega-3 for 6 months could create a significant reduction in serum triglyceride levels without any clear effect on total cholesterol levels, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol.[35] Another study on 24 patients with diabetic dyslipidemia disorders showed that omega-3 in combination with nitrate statins reduced the level of homocysteine, triglycerides, and microalbuminuria.[32]

We found only 2 studies performed on the effects of omega-3 on homocysteine level in ESRD patients. Holdt and associates observed no effect of omega-3 on homocysteine levels of peritoneal dialysis patients participating in a 3-month clinical trial of omega-3 supplements (fish oil).[36] Beavers and colleagues did not report significant results,

either.[37] They carried out a 6-month study on the effect of omega-3 as fish oil on the level of homocysteine in 69 dialysis patients in Texas and could not find any significant correlation.[37]

Shojaei and colleagues demonstrated that the administration of 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors might elevate the homocysteine level.[38] In our study, platelet count, total cholesterol, alkaline phosphatase, serum sodium and potassium, and total iron binding capacity was significantly lower in the intervention group than the control group. Hemoglobin, leukocyte count, serum calcium and phosphorus, lipid profile (except for total cholesterol), prothrombin time, international normalized ratio, and total iron binding capacity had no significant change after the trial. Serum albumin was significantly different between groups and changed after the study. However, plasma level of homocysteine was significantly low only in the intervention group ($P = .03$). Also the results of effect of omega-3 on plasma level of homocysteine were significant. In contrast to Holdt and colleagues[36] and Beavers and colleagues,[37] we had matched groups because of randomization. Therefore, it appears changing diet-medicinal regime of dialysis patients in order to enhance omega-3 fatty acids intake may be helpful in reducing homocysteine levels. However, this conclusion should be considered with attention to the study limitations. The small number of patients in both groups and short course of therapy were factors that might have affected the results.

CONCLUSIONS

It seems that omega-3 supplementation is safe and cause significant reduction in serum homocysteine level as a cardiovascular risk factor. More studies on larger patient groups and longer duration are recommended.

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CONFLICT OF INTEREST

None declared.

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