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Original Article

Does Omega-3 supplementation decrease carotid intima-media thickening in hemodialysis patients?

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ABSTRACT

Objective: A randomized, double-blind, placebo-controlled clinical trial was performed to assess the effect of omega-3 supplementation (3 g/day) on atherosclerosis progression by measuring carotid intima-media thickness (cIMT) in hemodialysis (HD) patients.
Methods: A total of 54 HD patients were randomized into two groups: Intervention group (n = 27), in which patients were given 3 g/day omega-3 for 6 months and placebo group (n = 27), in which patients received placebo using the same administration protocol. All patients underwent a carotid artery ultrasound scan to measure cIMT at baseline and at 6 months.
Findings: cIMT decreased significantly in omega-3 group (0.79 ± 0.21 mm at baseline vs. 0.65 ± 0.18 mm at 6 months, $P < 0.001$). On the other hand, a nonsignificant increase in cIMT was seen in placebo group (0.75 ± 0.17 mm at baseline vs. 0.79 ± 0.17 mm at 6 months, $P = 0.12$). Moreover, cIMT was statistically significantly different between omega-3 and placebo groups at 6 months ($P < 0.001$). After 6 months, a statistically significant increase was observed in high-density lipoprotein level in omega-3 group compared to placebo group ($P = 0.03$). Urea reduction ratio was also statistically significantly higher in omega-3 than placebo group at 6 months ($P = 0.03$). No significant difference was observed in terms of other variables between the two groups.
Conclusion: These data suggested that omega-3 supplementation plays a protective role in the progression of atherosclerosis in HD patients.

Keywords: Cardiovascular disease; carotid intima-media thickness; hemodialysis; Omega-3

INTRODUCTION

Cardiovascular disease (CVD) is the main cause of mortality in end-stage renal disease (ESRD) patients. Mortality of CVD in these patients is 10–20 times higher than general population.[1-3] Some traditional risk factors[4-6] and some factors which are related to ESRD patients contribute to the high incidence of CVD among these patients.[7-9] Accelerated atherosclerosis is the most important reason of dialysis patients' mortality and morbidity, although volume overload and left ventricular hypertrophy are also among the important factors related to cardiovascular mortality.[10]

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Carotid artery intima-media thickness (cIMT) measurement by ultrasound is a well-established index of atherosclerosis which predicts CVD in general population. Some studies have also reported that cIMT is associated with cardiovascular mortality in hemodialysis (HD) patients.[11,12]

Cardioprotective effects of fish oil and omega-3 polyunsaturated fatty acids have been proved. It has been suggested that omega-3 fatty acids decrease CVD through affecting lipid profiles, arrhythmias, inflammation, endothelial function, and platelet activity.[13,14] Some studies also investigated the relationship between omega-3 and CVD in HD patients, but their results are controversial. A study by Vernaglione *et al*. showed that blood pressure was the only factor which was influenced by omega-3 supplementation in patients on long-term HD.[15] Conversely, some studies have indicated that serum omega-3 fatty acids reduce CVD risk and its mortality in HD patients independently.[16,17]

The aim of the present study was to assess omega-3 supplementation role on cIMT as an important index of CVD in ESRD patients who receive HD.

METHODS

This was a double-blind, placebo-controlled, randomized clinical trial carried out on HD patients who were attending Al-Zahra and Noor-and-Ali-Asghar hospitals affiliated with Isfahan University of Medical Sciences (IUMS), Isfahan, Iran. Patients more than 18 years of age who had received HD for at least 3 months and had not consumed omega-3 fatty acids during the past 3 months were included in the study. Exclusion criteria were the presence of malignancy or ongoing chemotherapy, steatorrhea history, prolonged prothrombin time or partial thromboplastin time, anticoagulation therapy, shifting to peritoneal dialysis, and kidney transplantation during the study. A total of 60 patients were enrolled in the study, in which 8 of them were excluded from the study. Research Ethics Committee of IUMS approved (Research project number: 292281) the study, and all patients signed a written informed consent form.

Three omega-3 capsules (1 g) (Zahravi Company, Tabriz, Iran) were administered for intervention group per day. Each omega-3 capsule contains 180 mg eicosapentaenoic acid (EPA) and 120 mg docosahexaenoic acid (DHA). Placebo group received an equal amount of placebo capsules (3 capsules/day) which were produced by the same company. Both patients and doctors were blinded to treatments.

All patients received HD as we have described before.[18] Blood samples were collected on the day of ultrasonography. Serum levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, total cholesterol, triglycerides (TGs), albumin (Alb), calcium (Ca), and phosphate (P) were measured using autoanalyzer (BT 3000). Systolic and diastolic blood pressures were also measured by an internal medicine resident. Serum parathyroid hormone (PTH) level was measured by a gamma counter.

An expert neurologist blinded to treatments assessed cIMT using an ultrasound machine (ATL Ultramark 9) with 5–7 MHz probes before and after the intervention in both groups. Atherosclerosis was considered cIMT >1.2 mm. Two echogenic bright lines in the vessel wall were considered as intima and media lines. The distance between the main edges of the first line to the main edge of the second line of distal common carotid arteries was considered cIMT. All the patients managed for 6 months, and their vital signs, laboratory data, and drug complications such as nausea, vomiting, and hypertension were assessed. cIMT were re-evaluated for omega-3 and placebo groups by the same nephrologist.

All statistical analyses were done using Statistical Package for Social Sciences software (version 15.0, SPSS, Inc., Chicago, IL, USA). Quantitative data were expressed as mean ± standard deviation whereas qualitative data were presented by percentages. Normality of quantitative data was evaluated using Kolmogorov–Smirnov test and Q-Q plot; non-normal data were subjected to logarithmic transformation. Paired-sample *t*-test was used to compare means before and after intervention of different variables in omega-3 and placebo groups. Means of the study variables after intervention between omega-3 and placebo groups were compared using analysis of covariance, considering the baseline values as covariate. A two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Of the sixty patients enrolled in the study, 52 fulfilled the inclusion criteria. All participants were randomized to omega-3 ($n = 26$) or placebo ($n = 26$) group and completed the study. There was no previous or current history of transient ischemic attacks or strokes in our patients. As shown in Table 1, there were no significant differences between omega-3 and placebo groups in terms of demographic and clinical characteristics except for mean blood pressure which was significantly lower in placebo group than omega-3 group ($P = 0.03$) [Table 1].

cIMT decreased significantly in omega-3 group at 6 months (0.79 ± 0.21 vs. 0.65 ± 0.18, $P < 0.001$). However, a nonsignificant increase in cIMT was observed in placebo group (0.75 ± 0.17 mm at baseline vs. 0.79 ± 0.17 mm at 6 months, $P = 0.12$) [Table 2]. Moreover, there was a significant difference in cIMT between omega-3 and placebo groups at 6 months ($P < 0.001$). HDL level increased significantly among HD patients after omega-3 intervention (33.34 ± 7.29 vs. 42.5 ± 8.98, $P < 0.001$). At 6 months, there was a significant difference on HDL level in omega-3 in comparison to placebo group ($P = 0.03$). No significant change was seen in total cholesterol, LDL, and TG level in omega-3 or placebo group. Urea reduction ratio (URR) changes were not significant in omega-3 and placebo groups after 6 months; however, URR was significantly higher in omega-3 group when compared to placebo group ($P = 0.03$). Our findings also showed that PTH increased significantly both in placebo ($P = 0.02$) and omega-3 groups ($P < 0.001$). However, there were no significant differences between the two groups at 6 months on PTH ($P = 0.73$). Serum phosphorus increased significantly after omega-3 intervention in HD patients ($P = 0.005$) while there were no significant differences between placebo and omega-3 groups after 6 months ($P = 0.27$). Plasma Alb decreased significantly in placebo group ($P = 0.04$); however, no significant changes were observed in omega-3 group ($P = 0.78$). In addition, a nonsignificant difference was seen in plasma Alb level between omega-3 and placebo groups at 6 months ($P = 0.06$).

Table 1: General characteristics of patients in omega-3 and placebo groups

Variables (unit)	Groups		*P*
	Omega-3	Placebo	
Male (%)	65.4	73.1	0.54
Age (years)	57.76±15.56	58.34±14.26	0.59
Weight (kg)	69.70±14.98	66.92±11.97	0.46
Cardiovascular disease (%)	38.5	46.2	0.57
Mean BP (mmHg)	141.15±20.79	128.46±19.88	0.03
Underlying diseases			0.54
Hypertension (%)	3.8	3.8	
Diabetes (%)	42.3	57.7	
Hypertension+diabetes (%)	7.7	11.5	

Data are presented as mean±SD or percent of the participants. SD=Standard deviation, BP=Blood pressure

DISCUSSION

CVD morbidity and mortality among dialysis patients are greatly higher than normal population, and half of all deaths among these patients are related to CVD.[3,19,20] Increased cIMT is an important predictor of cardiovascular mortality in ESRD patients.[12,21] Previous studies have reported that low levels of plasma omega-3 are related with a high incidence of CVD in normal population.[22,23] In the current study,

Table 2: Comparison of clinical variables at baseline and at 6 months between omega-3 and placebo groups

Variable	Placebo		P_1	Omega-3		P_1	P_2
	Preintervention	Postintervention		Preintervention	Postintervention		
Intima-media thickness (mm)	0.75±0.17	0.79±0.17	0.12	0.79±0.21	0.65±0.18	<0.001	<0.001
	0.81 (1.12-0.51)	0.82 (1.12-0.51)		0.81 (1.2-0.46)	0.68 (0.94-0.4)		
URR (mg/dL)	0.63±0.09	0.62±0.12	0.9	0.65±0.08	0.66±0.09	0.62	0.03
	0.62 (0.8-0.46)	0.65 (0.81-0.36)		0.66 (0.76-0.45)	0.64 (0.94-0.54)		
LDL cholesterol (mg/dL)	68.77±22.78	73.91±19.84	0.1	81.42±21.75	84.15±38.61	0.72	0.15
	63 (127-14)	70 (130-40)		84 (116-28)	70 (176-45)		
HDL cholesterol (mg/dL)	37.6±7.01	36.23±9.03	0.57	33.34±7.29	42.5±8.98	<0.001	0.03
	38 (85-25)	38 (58-20)		38.5 (59-28)	33.5 (55-19)		
Total cholesterol (mg/dL)	127.38±24.96	79.03±31.43	0.71	135.57±32.9	138.34±46.86	0.67	0.18
	130 (187-90)	129 (185-79)		133.5 (191-71)	123.5 (248-79)		
Triglyceride (mg/dL)	120.53±73.19	110.34±91.81	0.42	111.96±53.65	107.38±68.49	0.77	0.46
	93.5 (312-30)	81 (431-25)		110.5 (249-46)	77.5 (292-39)		
Parathyroid hormone (pg/ml)	509.46±276.59	578.92±293.94	0.02	446.46±458.3	726.7±629.65	<0.001	0.73
	504.5 (890-80)	630 (926-89)		328.5 (1663-53)	582 (1900-93.9)		
Albumin (g/dL)	3.84±0.43	3.69±0.39	0.04	4±1.04	4.06±0.36	0.78	0.06
	3.90 (4.50-2.60)	3.70 (4.30-2.70)		3.85 (9-3.50)	4.05 (5.10-3.50)		
Calcium (mg/dL)	8.39±0.67	8.21±0.56	0.21	8.91±0.78	8.56±0.35	0.43	0.24
	8.55 (9.50-6.50)	8.35 (9.40-6.60)		9 (10.20-7.20)	8.60 (9.20-8)		
Phosphorus (mg/dL)	4.03±1.32	4.06±0.66	0.92	4.58±1.9	4.8±1.12	0.005	0.27
	3.80 (9.10-2.40)	4.10 (5.20-2.80)		4.55 (7.90-2)	4.95 (7.10-3.10)		

Data are presented as mean±SD and median (range) for each variable. P_1=Resulted from within-group analysis based on paired samples *t*-test, P_2=Resulted from between-group analysis based on ANCOVA; adjustment was made for baseline values and SBP. SD=Standard deviation, URR=Urea reduction ratio, LDL=Low-density lipoprotein, HDL=High-density lipoprotein, ANCOVA=Analysis of covariance, SBP=Systolic blood pressure

we assessed the role of omega-3 supplementation on cIMT in HD patients.

Few studies have reported that CVD risk factors are reduced after fish oil supplementation in HD patients.[24-26] However, we could not find any study evaluated atherosclerosis progress in HD patients after omega-3 supplementation by cIMT. The results of the current study showed that HD patients' treatment with 3 g of omega-3 for 6 months improved cIMT. There was also a significant difference between omega-3 and placebo groups at 6 months in terms of cIMT.

The results of the present study showed that PTH increased in both placebo and omega-3 groups significantly at 6 months, although changes between omega-3 and placebo groups were not significant. The changes in PTH level have been resulted from phosphorus retention and low levels of calcium as others suggested.[27,28]

A 6-month treatment with omega-3 increased HDL levels in HD patients significantly. We also found a significant difference between omega-3 and placebo groups at the end of the study. Khajehdehi showed a significant increase in HDL level after supplementation with 1.5 g of omega-3.[29] Treatment of CRF patients with 2.4 g of omega-3 also increased HDL in a study which was done by Svensson *et al.*[30]

TG did not decrease significantly after omega-3 supplementation among HD patients in the current study. This is in accordance to a study which was done by Christensen *et al*. Treatment of 24 HD patients with 3.2 g/day of omega-3 had no significant effect on serum TG.[31] In contrast, TG has decreased significantly in studies which have administered lower doses of omega-3.[29,31] We assume that the effect of omega-3 on TG among HD patients is dose dependent. It explains why the administration of 3 g/day had no impact on TG level in HD patients. In addition, it has been indicated that higher baseline levels of TG is associated with its greater serum decline after omega-3 supplementation.[32] No effect of omega-3 was observed on LDL and total cholesterol which is in direction to other studies.[31,33]

After 6 months of intervention, there was a significant difference on URR between placebo and omega-3 groups. There is an association between URR and clinical outcome;[34] thus, it seems that HD patients' treatment with omega-3 improves HD adequacy in ESRD patients.

A number of studies have investigated the association between hypoalbuminemia and cardiac disease in ESRD patients.[35-37] The exact mechanism of hypoalbuminemia in HD patients has not been detected; however, it is possibly a result of inflammation rather than protein malnutrition.[36,38] Alb level decreased significantly in placebo group while no significant difference was seen in omega-3 group. Furthermore, plasma Alb was not significantly different between the two groups at 6 months.

In the present study, we showed that omega-3 supplementation improves cIMT in HD patients. Thus, omega-3 administration in these patients as a part of primary prevention strategy reduces atherosclerosis.

AUTHORS' CONTRIBUTION

All authors contributed in conducting the study concept and design, acquisition of data, analysis and interpretation of data. Mortazavi M, Kajbaf MH and Amani Tirani S contributed in drafting of the manuscript, revising the draft, and approval of the final version of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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