Omega-3 in Patients Undergoing Continuous Ambulatory Peritoneal Dialysis, Effects on Inflammatory Markers and Lipid Profile

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Introduction. CKD is one of the most prevalent entities associated with high morbidity and mortality. Most of the patients with renal diseases, particularly patients undergoing dialysis, suffer from cardiovascular disease and it is necessary to employ appropriate strategies to prevent and manage this complication. The aim of this study was to evaluate the anti-inflammatory effects of omega-3 in patients undergoing CAPD.

Methods. Nineteen CAPD patients with certain inclusion and exclusion criteria enrolled in this study. Omega-3 capsules with a dose of 1 g/d up to three months, were administrated. Some inflammatory markers such as ESR, CRP, HS-CRP, IL-6, MDA, and homocysteine were measured in three phases. In addition, lipid profile including triglyceride, cholesterol, LDL, and HDL were measured.

Results. Results of this study showed that CRP, HS-CRP, and homocysteine levels increased insignificantly ($P > .05$) whereas, MDA level was increased significantly ($P < .05$). ESR and IL-6 levels both decreased but did not show any statistically significance ($P > .05$). Results of lipid profile also suggested that none of the lipid levels changed significantly ($P > .05$).

Conclusion. It is necessary to design large trials in order to understand clear effects of omega-3 on inflammatory markers in PD patients. In addition, the results of this current pilot study should be interpreted with caution.

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INTRODUCTION

Nowadays, CKD is one of the most common diseases worldwide and its prevalence is increasing significantly. Based on the American National Health and Nutrition Examination Survey from 1988 to 1994, CKD prevalence was 10% and rapidly increased to 13.1% from 1999 to 2004.[1,2] Also, its prevalence in Iran is about 23.7%.[3] CKD patients are among the highest at risk groups for experiencing cardiovascular events. There are strong evidences, which demonstrated the inverse relationship between kidney function and cardiovascular risk.

Patients with CKD and end stage renal disease (ESRD) are at the risk of developing cardiovascular disease approximately 5 to 10 fold higher than age matched healthy controls.[4] Cardiovascular disease is also a major cause of mortality in CKD patients. It is documented that by every 10 mL/min/ 1.73m^2 reduction in glomerular filtration rate (GFR), the cardiovascular mortality risk would increase by 5%.[5] Cardiovascular diseases in CKD patients include ischemic heart disease, arterial vascular disease, arrhythmias, peripheral vascular disease, left ventricular dilation, and congestive heart failure.[6] Considering before-mentioned interpretations, it is imperative to overcome the cardiovascular problems in CKD patients by utilizing appropriate strategies. This requires a proper understanding of the pathogenic mechanisms. In these patients, inflammatory process and oxidative stress play essential roles in pathogenesis of cardiovascular disease.[7] Inflammation in CKD patients causes mortality from cardiovascular disease. Inflammation contributes to the development of vascular calcification and endothelial dysfunction. There are many inflammatory mediators in ESRD patients such as interleukin-6 (IL-6), C-reactive protein (CRP), homocysteine, and erythrocyte sedimentation rate (ESR).[8,9] Also, in ESRD patients, cytotoxins produce oxidative stress and finally free radical production and antioxidant defenses will be imbalanced.[10] Hence, these markers can predict the cardiovascular disease in patients with CKD. Among agents with anti-inflammatory and anti-oxidative characteristics, long-chain omega-3 polyunsaturated fatty acids have a well-known place. Many benefits have been reported from long-chain omega-3 polyunsaturated fatty acids such as protection against cardiovascular disease, improvement of lipid profile and inflammatory status.[11] Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DPA) are fatty acids present in oily fish and fish oil supplements. These fatty acids can inhibit many aspects of inflammatory process.[12] Long chain fatty acids affect inflammation by a variety of mechanisms. They change fatty acid composition pattern in cell membranes, which can modify membrane fluidity. In addition, they affect cell-signaling pathways leading to altered gene expression. In addition, these agents can change pattern of lipid mediator production.[13] The aim of this study was to evaluate the anti-inflammatory effects of omega-3 in patients undergoing CAPD.

MATERIALS AND METHODS

This study was an open-labeled, interventional, single group clinical trial accomplished in a well-known referral medical center for kidney diseases in Iran and Middle East. In this trial, 21 CAPD patients enrolled . The ethics committee of Shahid Beheshti University of Medical Sciences approved this study. The inclusion criteria were as follows: the ESRD patients[14] who were under continuous ambulatory peritoneal dialysis for at least three months, above 18 years old and providing written informed consent to participate in this study. In case of any one of patients met the following criteria he was excluded from the study: having history of malignancy, hypersensitivity to fish oil, coagulation disorders, taking anticoagulant medications, taking fibric acid derivatives, history of peritonitis in last six months, taking any antioxidant or anti-inflammatory medications, severe systemic or infectious diseases. All patients received Omega-3 capsules (120 mg DHA plus 180 mg EPA; Mix-Natural©, Exir Company, Iran) with a dose of 1000 mg/ d for three months. Baseline characteristics of patients including age, gender, concurrent diseases, habitual behaviors, and duration of dialysis were gathered through medical records. Medication history also had been reviewed in all patients. Inflammatory markers and oxidative stress levels including ESR, CRP, HS-CRP, malondialdehyde (MDA), and homocysteine were measured before starting the study and during it monthly. Lipid profile including triglyceride, cholesterol, low-density lipoproteins (LDL) and high-density lipoproteins (HDL) were measured subsequently. The patients were visited regularly regarding the occurrence of any side effects and regular use of medications. At the end of the study, the gathered data were entered into SPSS 23 (IBM, USA). The descriptive statistics presented and Kolmogorov-Smirnov test was used to determine the normal distribution. Consequently, the paired t test was used for parametric variables and Wilcoxon test used for non-parametric variables. For all the tests, the significance level was considered as 5% and results reported as mean ± standard division (SD). A post-hoc analysis to compute the achieved power also was performed by Gpower software (Erdfelder, Faul, & Buchner, 1996).

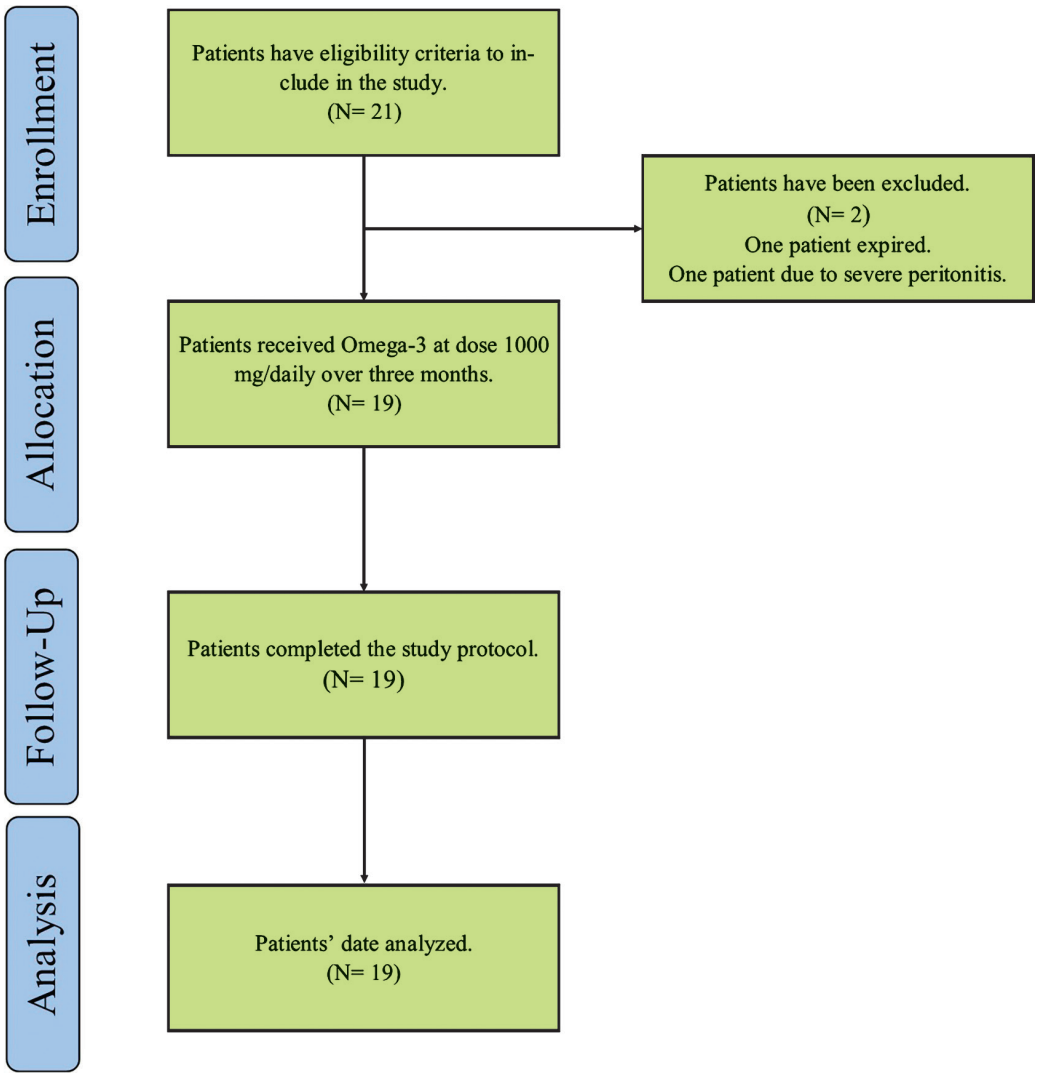
RESULTS

21 CAPD patients enrolled in the study and two patients (one case expired during study and another case presented severe peritonitis) were excluded. The Consort diagram of study is illustrated in Figure. Demographic information of patients showed that the mean age of participants was 54 ± 14 years (ranges from 24 to 81 years old). In addition, the sex ratio (male / female) of patients was 11:8. The most common concurrent comorbidities were hypertension (16 cases), diabetes (four cases), and hypothyroidism (two cases). None of the patients exhibited notable habitual behaviors. Mean duration of dialysis was 3.80 ± 2.71 years (ranges from 1 to 10 years). All patients were using conventional treatment regimen for CKD patients including statins and folic acid. All medication regimens were constant during the study. Summary of the demographic data is summarized in Table 1.

The inflammatory markers and oxidative stress indexes were measured in four steps including at

Table 1. The Demographic Features of Patients

Characteristic	Variables	Results
Age, year		54 ± 14
Gender		
	Male	11
	Female	8
Concurrent Diseases		
	Hypertension	16
	Diabetes	4
	Hypothyroidism	2
Duration of Dialysis, year		3.80 ± 2.71



It shows the consort diagram of current study.

baseline, after the first month, at the end of the second month and after third month. Dates of inflammatory markers and oxidative stress indexes measurements are also summarized in Table 2.

The mean ± SD of baseline ESR was 73.82 ± 12.38 mm/h and in the end of study decreased to 67.37 ± 16.26 mm/h, but this reduction was not statistically significant ($P > .05$). The mean ± SD of baseline CRP was 4.63 ± 2.60 mg/L which increased to 4.80 ± 3.71 mg/L, but still showed no statistically significant differences ($P > .05$). The mean ± SD of baseline HS-CRP was 5.64 ± 4.69 mg/L and increased to 5.76 ± 3.80 mg/dL, but this difference also was not significant ($P > .05$). The mean ± SD of baseline IL-6 was 17.76 ± 13.71 pg/mL and it decreased to 14.44 ± 9.45 pg/mL ($P > .05$). The mean ± SD of baseline MDA was 1.14 ± 0.70 µmol/L and increased to 2.05 ± 1.11 µmol/L, it is notable that these differences were statistically significant ($P < .05$). Another inflammatory index was homocysteine, the mean ± SD of baseline homocysteine was 22.33 ± 8.12 µmol/L and it increased to 25.16 ± 10.68 µmol/L ($P > .05$). Measurement of lipid profile also demonstrated that baseline Triglyceride was 128.81 ± 57.18 mg/dL that decreased to 110.94 ± 26.46 mg/dL ($P > .05$). The mean ± SD of baseline cholesterol was 162.79 ± 42.66 mg/dL and it decreased to 160.89 ± 47.98 mg/dL ($P > .05$). The mean ± SD of baseline LDL was 90.05 ± 27.02 mg/dL and it decreased to 84.84 ± 26.84 mg/dL ($P > .05$). The mean ± SD of baseline HDL was 43.37 ± 12.96 mg/dL and it decreased to 41.11 ± 10.75 mg/dL, but none of these changes reached to statistically significance ($P > .05$). The results of lipid profile are also presented in Table 3.

The post-hoc analysis also calculated the achieved power. The effect size was calculated equal to 0.52 according to IL-6 results and the achieved power reported as 0.72.

DISCUSSION

In this study, the therapeutic effects of omega-3 administration were evaluated in patients undergoing continuous ambulatory peritoneal dialysis. Morbidity and mortality from cardiovascular disease is significantly high in patients with ESRD undergoing continuous ambulatory peritoneal dialysis. Main causes for this excess risk include dyslipidemia, hyperhomocysteinemia, inflammation, oxidative stress, anemia, abdominal obesity, hypoalbuminemia, and disturbances of hemostatic system. In addition, uremia in peritoneal dialysis is another important risk factor for the development of cardiovascular disease.[15,16] The incidence of cardiovascular disease in patients undergoing dialysis is approximately 3 to 45 times higher.[17] Hence, treatment strategies should be

Table 2. The Results of Inflammatory Markers and Oxidative Indexes

Parameter	Baseline	1st Month	2nd Month	3rd Month	*P*
ESR, mm/h	73.82 ± 12.38	70.25 ± 7.93	79.83 ± 15.37	67.37 ± 16.26	> .05
CRP, mg/L	4.63 ± 2.60	5.25 ± 2.22	5.00 ± 2.74	4.80 ± 3.71	> .05
HS-CRP, mg/L	5.64 ± 4.69	9.70 ± 8.90	5.70 ± 3.67	5.76 ± 3.80	> .05
IL-6, pg/mL	17.76 ± 13.71	19.03 ± 6.55	21.43 ± 12.79	14.44 ± 9.45	> .05
MDA, µmol/L	1.14 ± 0.70	2.25 ± 0.65	2.25 ± 0.92	2.05 ± 1.11	< .05
Homocysteine, µmol/L	22.33 ± 8.12	21.25 ± 9.29	25.00 ± 10.46	25.16 ± 10.68	> .05

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; HS-CRP, highly sensitive C-reactive protein; IL-6, Interleukin 6; MDA, malondialdehyde.
The results are presented as mean ± SD.

Table 3. The Results of Lipid Profile Levels

Parameter	Baseline	1st Month	2nd Month	3rd Month	*P*
Triglyceride, mg/dL	128.81 ± 57.18	165.50 ± 47.98	96.50 ± 26.43	110.94 ± 26.46	> .05
Cholesterol, mg/dL	162.79 ± 42.66	168.00 ± 39.48	137.86 ± 41.10	160.89 ± 47.98	> .05
LDL, mg/dL	90.05 ± 27.02	80.05 ± 21.03	74.91 ± 25.77	84.84 ± 26.84	> .05
HDL, mg/dL	43.37 ± 12.96	47.00 ± 15.58	33.50 ± 5.79	41.11 ± 10.75	> .05

LDL, low-density lipoproteins; HDL, high-density lipoproteins
The results are presented as mean ± SD.
All the patients were screened closely to detect any adverse drug reactions. The remarkable adverse drug reactions were stomach cramps (9 cases), nausea (8 cases), constipation (5 cases) and headache (1 case).

considered for each of these risk factors suitably. In the review of literature, there are few studies regarding the effects of omega-3 administration in patients with kidney diseases. To the best of our knowledge, this is the first study in patients undergoing continuous ambulatory peritoneal dialysis, which assessed many inflammatory markers. Similar to our study, Naini AE *et al.* in 2015 studied the effects of omega-3 on inflammatory parameters in CAPD patients. They found that the administration of omega-3 (3 g/d, up to eight weeks) in 20 CAPD patients did not change inflammatory markers including CRP and IL-6.[18] In 2014, Gharekhani A *et al.* studied the effects of omega-3 (0.9 g/d, up to four months) on inflammatory markers in hemodialysis patients. They found among inflammatory markers, only serum ferritin level and IL-10 to IL-6 ratio showed significant changes. Similar to current results, the CRP levels were decreased in their study but this reduction was not significant. On the other hand, they found an insignificant reduction in IL-6 levels. They argued that low sample size was the main reason of obtained results.[19] There are other studies, which demonstrated significant reduction in inflammatory levels. Tayebi-Khosroshahi H *et al.* in 2013, evaluated the effects of omega-3 (3 g/d, up to two months) on serum homocysteine level in patients on hemodialysis. They found a significant reduction in homocysteine level. Hence, they introduced homocysteine as a predictor marker of cardiovascular disease in patients undergoing hemodialysis.[20] Rasmussen LE and *et al.* in 2010 also conducted a similar study and they found the content of omega-3 in serum phospholipids was inversely correlated with homocysteine levels and omega-3 (1.7 g/d, up to three months) administration did not reduce homocysteine level in ESRD patients.[21] The current results also suggested that homocysteine level did not change significantly in PD patients. Another important finding in the present study was a significant change in MDA levels. MDA is one of the most important byproducts of lipid peroxidation during oxidative stress. Hassan KS *et al.* in 2010 also found that omega-3 (3.4 g/d, up to eight weeks) administration in peritoneal dialysis patients lead to reduction of ESR, CRP, IL-6, TNF-α and malondialdehyde levels, but this pattern was not significant.[22] In comparison to Hassan KS study, current study had a larger sample size and longer follow up duration. In a randomized double-blind clinical trial which was done by Naini AE *et al.* in 2015, the effects of omega-3 (3 g/d, up to two months) was evaluated on blood pressure and serum lipids (triglyceride, cholesterol, LDL and HDL) in CAPD patients. Results of their study showed that omega-3 could reduce blood pressure significantly but had no significant effect on serum lipids. The results of the afore-mentioned study confirmed the results of current study. In the current study, triglyceride, cholesterol, LDL and HDL were decreased but this reduction was not significant. In another study by Kooshki *et al.* in 2011, the effects of omega-3 (2 g/d, up to 10 weeks) administration on lipid profiles was evaluated in hemodialysis patients. They found that omega-3 could reduce Triglyceride significantly, but not other parameters.[23] Taziki *et al.* in 2007, investigated the effect of low dose omega-3 (2 g/ d, up to three months) on lipid profile in hemodialysis patients. They found a significant increase in HDL level and significant decrease in Triglyceride level. In addition, LDL and cholesterol levels did not change significantly.[24] Khajehdehi P *et al.* in 2000 also studied the effects of omega-3 (1.5 g/d, up to two months) in hemodialysis patients. They found that omega-3 administration decreased HDL and Triglyceride levels, but LDL levels increased unfavorably.[25] Ando *et al.* in 1999, studied the effects of omega-3 (1.8 g/d, up to three months) in dialysis patients and showed that it can normalize the abnormalities of lipoprotein levels.[26] There are many studies in different populations regarding the omega-3 effects on lipid profile. The results of such studies are controversial and it may be due to several factors including the dose of omega-3, omega-3 sources, and type of intake dietary. In addition there are some confounding variables in current study which affect the inflammatory markers such as medication history. However, the medication history of included patients revealed that all of them was using medications with anti-inflammatory effects (statins, folic acid, etc.) All patients were using these agents due to their underlying diseases and effects of these medications couldn't be controlled due to ethical issues. Overall, omega-3 administration did not have significant effects on lipid profile levels. All CAPD patients included during study period, nevertheless, low

sample size was one of the important limitations of current study. Although the calculated power by post-hoc analysis revealed almost acceptable power, further studies with larger sample size are necessary. Also, it is suggested to extend the follow up duration to achieve comprehensive results.

CONCLUSION

The results of this study showed that administration of omega-3 did not change any inflammatory markers significantly, except MDA level. However, the results should be interpreted with caution, because in this study omega-3 was not administered with high dose. It seems that omega-3 is not probably able to change the inflammatory markers significantly. It is necessary to design large trials to understand the clear effects of omega-3 on inflammatory markers in PD patients.

CONFLICT OF INTERESTS DISCLOSURE

None.

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