Original Article

Effect of Omega-3 Fatty Acids Supplementation on Homocysteine Level in Patients Undergoing Continuous Ambulatory Peritoneal Dialysis

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ABSTRACT

Objective: One of the most common diseases with high morbidity and mortality rates is chronic kidney disease. Cardiovascular disease affects most patients with chronic kidney disorders, particularly patients undergoing dialysis; hence, appropriate prevention and management approaches are essential. This study aimed to evaluate the reduction of inflammatory biomarkers, especially homocysteine, by omega-3 fatty acids in peritoneal dialysis patients. **Methods:** This study enrolled 60 peritoneal dialysis patients who met specified inclusion and exclusion criteria and were randomized to intervention or placebo groups. Omega-3 capsules were given at a dose of 3 g/d for 8 weeks. Inflammatory markers, including high-sensitivity C-reactive protein (hs-CRP), homocysteine, albumin, and lipid profile measured before and after the study. **Findings:** Results of this trial revealed that the levels of homocysteine, hs-CRP, and albumin did not change significantly during the study. Analysis of lipid profiles before and after intervention showed omega-3 has no significant effect on the level of total cholesterol or low-density lipoprotein cholesterol; However, the level of triglyceride reduced remarkably ($P = 0.002$). In addition, serum levels of high-density lipoprotein cholesterol increased at the end of the study ($P < 0.001$). **Conclusion:** Omega-3 does not seem to be able to change the inflammatory markers significantly, particularly homocysteine. More extensive trials must be conducted to better understand the impact of omega-3 on inflammatory and nutritional markers, particularly in peritoneal dialysis patients.

KEYWORDS: *End-stage renal disease, homocysteine, omega-3 fatty acids, peritoneal dialysis*

INTRODUCTION

Cardiovascular diseases (CVDs) are being recognized as the primary reason for death in patients with end-stage renal diseases (ESRD).[1] According to the reports, the incidence of CVD in patients with chronic kidney disease (CKD) is estimated to be 25%–60%, which may be 5–10 times higher than in the age-matched healthy population.[2] Several risk factors increase the risk of CVD in CKD patients. In addition to traditional known modifiable risk factors, such as anemia, diabetes, hypertension, lipid disorders, and metabolic disorders, some studies suggest that the pathophysiology of CVD in these patients is also significantly influenced by other factors such as increased inflammation and oxidative stress, high levels of lipoprotein A, and hyperhomocysteinemia.[3]

Homocysteine is a sulfur-containing amino acid that cannot be obtained through diet. It is an intermediate product that is biosynthesized by methionine metabolism.[4] Homocysteine is an inflammatory mediator, and its abnormal increase in plasma, known as hyperhomocysteinemia, can be due to various causes, including folic acid and B Vitamins deficiency, genetic disorders, and chronic alcohol consumption.[5,6] Multiple studies have shown that elevated homocysteine levels adversely affect the endothelium, leading to cell damage,

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coagulation disorders, increased arterial stiffness and encouraging atherosclerosis, followed by increased cardiovascular events.[7-9] These findings are of particular concern because hyperhomocysteinemia occurs in almost all ESRD patients as renal function decreases.[10] Therefore, homocysteine-lowering interventions in ESRD patients can reduce cardiovascular events and lead to positive outcomes. However, the results of clinical trials to lower plasma homocysteine levels in ESRD patients are unclear and inconsistent.

One of the factors with homocysteine-lowering properties is long-chain omega-3 polyunsaturated fatty acids. Omega-3 fatty acids have cardiovascular protective properties by improving lipid profile and reducing inflammation and oxidative stress.[11] In addition, studies suggest that omega-3 supplementation may also reduce cardiovascular morbidity and mortality by lowering homocysteine levels.[12,13] Several trials have evaluated the homocysteine-lowering effectiveness of omega-3 supplements in ESRD patients. A double-blind clinical trial showed that omega-3 supplementation did not lower homocysteine levels in hemodialysis patients compared with controls.[14] However, the results of another study in 100 hemodialysis patients showed that omega-3 significantly reduced homocysteine levels.[15]

Different treatment strategies such as hemodialysis and peritoneal dialysis seem to cause other effects on various parameters, including homocysteine. Filiopoulos *et al*. showed that peritoneal dialysis patients had higher levels of homocysteine and erythrocyte sedimentation rate (ESR).[16] It also seems that the higher prevalence of increased body fat mass, hyperinsulinemia, and lipid profile disorder in peritoneal dialysis patients causes more cardiometabolic syndrome in these patients than in hemodialysis patients.[17] Nevertheless, studies on peritoneal dialysis patients are few. In a single-group trial, 19 patients undergoing continuous ambulatory peritoneal dialysis were treated with omega-3 supplements. The results showed little correlation between omega-3 fatty acids and inflammatory markers such as homocysteine levels. However, this study was a single-group trial, and the number of participants included was limited, so the results may be unreliable.[18]

Given the controversial reports in hemodialysis patients and the lack of robust clinical trials in peritoneal dialysis patients, in this study, we made an effort to assess how omega-3 supplementation affected patients receiving peritoneal dialysis in terms of their lipid profiles, homocysteine levels, and other inflammatory markers.

Methods

The current study was a randomized controlled clinical trial. Individuals over 18 years of age who underwent continuous ambulatory peritoneal dialysis for any reason in two teaching hospitals (Al-Zahra and Khorshid hospitals) affiliated with Isfahan University of Medical Sciences were evaluated. Exclusion criteria included a history of malignancy, known allergies to products containing omega-3, coagulation disorders and the use of anticoagulants, the use of any anti-inflammatory medicines or with antioxidant properties, and severe systemic or infectious diseases.

Isfahan University of Medical Sciences' local ethics committee authorized the presented work. All participants gave their consent in writing after being fully informed. The trial protocol was registered in the Iranian Registry of Clinical Trials (IRCT20160713028901N2).

After receiving written informed consent, the Blocked randomization method was used to assign patients to intervention and control groups randomly. Patients' demographic and clinical characteristics, including age, sex, body weight, current illness, past medical history, duration of dialysis, and concomitant medications, were recorded.

For the intervention group, omega-3 capsules provided by Zahravi Pharmaceutical Company, Tabriz, Iran (120 mg DHA plus 180 mg EPA) at a dose of 3000 mg per day, i.e., 1000 mg with each meal per day for 8 weeks was prescribed, and placebo was prescribed for the control group. A physician evaluated the patient's clinical symptoms during the treatment period. Before and at the end of the study, inflammatory and oxidative stress indexes, including high-sensitivity C-reactive protein (hs-CRP), homocysteine, lipid profiles including total cholesterol, triglyceride, low-density lipoprotein (LDL-C), and high-density lipoprotein (HDL-C) were measured. At the start and end of the trial, participants donate 12 ml of venous blood for analysis after fasting for 8–12 h.

Regular check-ups with patients were conducted to monitor adverse effects and medication usage. Patients were asked to inform their physician about regular medication use, such as what percentage of doses they may not take in a given period or how much they can follow the medication regimen.

All analyses were performed using SPSS software (Statistical Package for the Social Sciences, version 16.0, IBM company, Chicago, Illinois, United States). Paired samples test was used to compare the parameter changes within each group. Furthermore, to compare the changes in parameters between the two groups, the analysis of covariance was used. In each case, the proper nonparametric tests were applied if necessary (due to an

abnormal data distribution). A $P \leq 0.05$ was considered meaningful.

Results

Sixty-two patients who met the inclusion criteria and completed a written consent form were randomly allocated to one of two groups: intervention or control. Of these, we excluded 12 patients (five patients in the omega-3 group and seven patients in the placebo group) due to noncompliance, hospitalization, unwillingness to continue the study, and severe peritonitis. As a result, 25 participants in the intervention group and 27 participants in the placebo group completed the study, and their data were finally analyzed. Figure 1 illustrates the study protocol and patient screening during the study.

As shown in Table 1, the mean age of patients in the omega-3 and the placebo groups was 49.4 years (range 21–72) and 54.28 years (range 37–79), respectively. The sex ratio (male/female) in the omega-3 group was 17:8, and it was 16:9 in the placebo group.

Table 2 shows the hematological parameters measured in two groups before and after the intervention. As can be seen, the concentration of triglycerides in the omega-3 group decreased significantly ($P = 0.002$), while these changes in the placebo group were insignificant. Therefore, omega-3 caused a meaningful reduction in triglyceride concentration.

During the study, the serum concentration of HDL-C in the omega-3 group increased significantly ($P < 0.001$), but this change in the placebo group was negligible. As a result, omega-3 supplementation significantly increased HDL-C compared with placebo.

During the study, there was no significant difference in homocysteine levels between the two groups. In addition, the study showed no significant changes in serum levels of hs-CRP, albumin, LDL-C, or total cholesterol.

Table 1: Demographic information of peritoneal dialysis patients in omega-3 and placebo groups

Characteristics	Omega-3	Placebo
Mean age (years)	49.4 (21-72)	54.28 (37-79)
Sex, *n* (%)		
Male	17 (68)	16 (64)
Female	8 (32)	9 (36)
Mean BMI	24.4	24.15

BMI=Body mass index

Discussion

This study investigated the impact of omega-3 supplementation on patients undergoing peritoneal dialysis. The findings of this trial indicate that omega-3 supplementation does not significantly affect the level of homocysteine and other inflammatory markers, including hs-CRP and albumin. However, it can reduce triglyceride levels and increase HDL-C serum concentration in these patients.

Patients with ESRD who receive peritoneal dialysis have much higher morbidity and mortality due to CVD. Disturbances in the hemostatic system and dyslipidemia are major contributors to this increased risk of CVD. Other significant risk factors include inflammation, hyperhomocysteinemia, oxidative stress, anemia, and uremia.[19] Patients on dialysis have a 3–45-fold risk of CVD.[20] As a result, treatment approaches for each

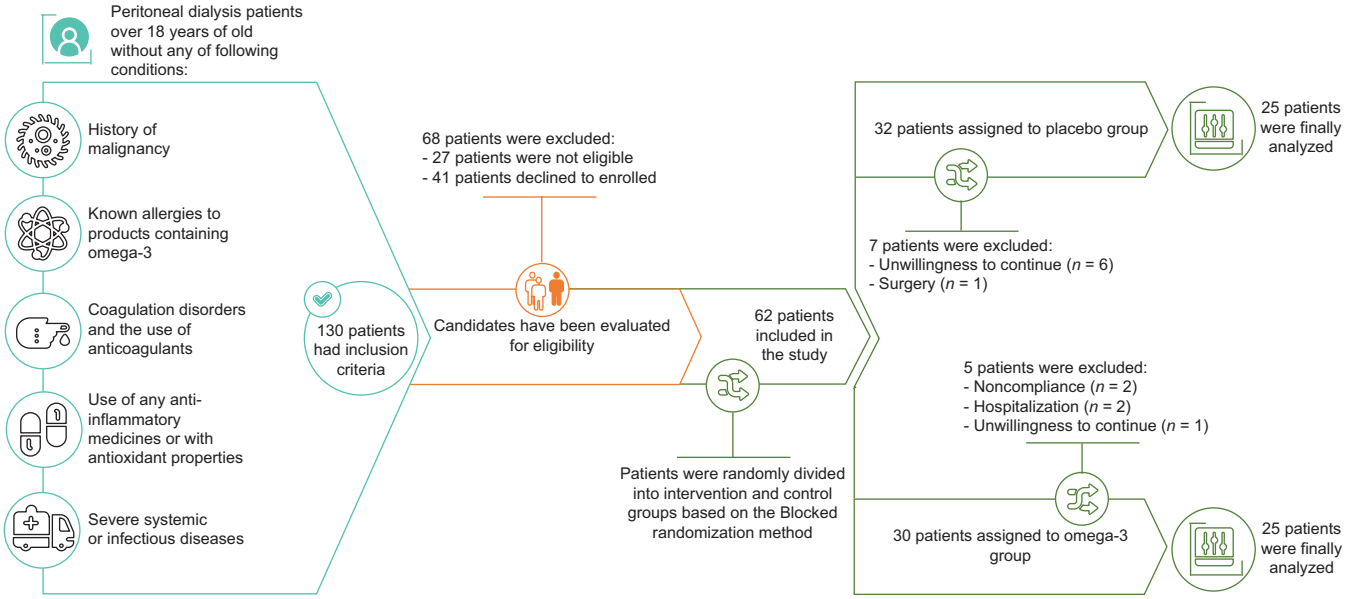

Figure 1: Study protocol, patient selection and randomization

Table 2: Mean values of homocysteine, lipid profiles, and inflammatory markers in placebo and omega-3 groups before and after study

Parameter	Omega-3		Placebo		*P*
	Before study	After study	Before study	After study	
Homocysteine (μmol/L)	21.17±10.23	18.82±8.64	21.59±10.52	21.42±9.07	0.144
hs-CRP (mg/L)	0.45±0.89	0.31±0.43	0.43±0.80	0.61±0.83	0.057
Triglyceride (mg/dL)	180.56±107.32	145±64.39	177.12±98.79	169.28±77.41	0.002
Cholesterol (mg/dL)	180.52±54.14	173.96±46.36	180.52±55.25	185.24±53.82	0.082
LDL-C (mg/dL)	100.72±36.71	98.16±38.87	103.84±37.25	105.68±39.35	0.446
HDL-C (mg/dL)	40.72±8.26	46.56±6.61	42.28±6.61	42.96±6.51	0.000
Albumin (g/dL)	3.58±0.46	3.73±0.36	3.61±0.39	3.6±0.39	0.409

The results are illustrated as mean±SD. SD=Standard deviation, hs-CRP=High sensitive C-reactive protein, LDL-C=Low-density lipoproteins cholesterol, HDL-C=High-density lipoproteins cholesterol

of these risk factors should be carefully addressed. After receiving the omega-3 treatment in this trial, the serum homocysteine concentration did not significantly decrease. This result was consistent with the findings of a few earlier studies on ESRD patients. Peritoneal dialysis patients may benefit from omega-3 supplementation, but the evidence is limited. Similar to our research, in a single-group open-label clinical trial, the effectiveness of omega-3 on homocysteine and inflammatory markers in peritoneal dialysis patients was investigated. Twenty-one patients received omega-3 capsules 1 g/day for 3 months. The findings reveal that inflammatory markers such as CRP, hs-CRP, and homocysteine were not significantly affected by omega-3 supplementation. They suggested that the small number of participants was the primary cause of the findings.[18] In 2013, Tayebi-Khosroshahi *et al*. reported that the levels of homocysteine in 44 hemodialysis patients decreased significantly after treatment with omega-3 fatty acids (3 g/day for up to 2 months). As a result, homocysteine was introduced as a prognostic biomarker of CVD in this group of patients.[15] On the other hand, similar to our findings, the homocysteine-lowering benefits of omega-3 fatty acids were not seen in any of the other clinical trials. Omega-3 (1.7 g/day for 6 months) had no significant impact on the homocysteine levels of 206 hemodialysis patients who had verified CVD. A similar study indicated that taking omega-3 supplements at a dose of 6 g/day for up to 6 months had no impact on the homocysteine levels of 69 ESRD patients.[14] In addition, Xu *et al*. investigated the efficacy of omega-3 on lipid profile and inflammation in ESRD patients. They analyzed the data from a total of 20 RCTs involving 1461 participants. This analysis showed that omega-3 supplementation could reduce triglycerides, LDL-C cholesterol, and CRP while not affecting other inflammation markers, including homocysteine.[21]

In this study, supplementation with omega-3 fatty caused a significant decrease in serum triglyceride levels. This result was in line with most prior studies.[22-25] The beneficial effect of omega-3 fatty acid supplementation on oxidative stress and cardiometabolic outcomes in CKD patients was assessed using a systematic review and meta-analysis. The findings showed that taking supplements of omega-3 lowers the levels of total cholesterol, triglyceride, and malondialdehyde. Results, however,[26] indicate that taking omega-3 has no appreciable impact on HDL-C, LDL-C, or blood pressure. The fact that CKD is a very heterogeneous disease should be highlighted. Patients with CKD, immunoglobulin A nephropathy, and hemodialysis are generally described as CKD patients; however, due to significant variability, present results should be interpreted with caution. Dietary intake, *de novo* biosynthesis, and lipid catabolism influence triglyceride levels in the human body. Omega-3 prevents the synthesis of triglycerides and fatty acids from scratch by inhibiting the transcription of sterol regulatory element-binding protein genes. In addition, by controlling the activation of the proliferator-activated receptor gene, omega-3 enhances the clearance of triglyceride-rich lipoproteins and stimulates the oxidation of fatty acids as well as the catabolism of triglycerides in adipose and muscle tissues. The overall result is a shift away from the storage of triglyceride toward oxidation as the source of metabolic fuel.[26,27]

The 8-week treatment of omega-3 supplements in our study did not change the total serum cholesterol and LDL-C levels significantly. Earlier research has demonstrated that omega-3 fatty acids had no effect on total cholesterol and LDL-C, which is consistent with our findings.[22,23,25] In addition, a recent systematic review revealed that the serum level of LDL-C in CKD patients was not changed significantly by the administration of omega-3. However, the findings showed that patients with CKD who take omega-3s have significantly lower total cholesterol levels.[28] Many studies have shown that omega-3 positively affects lowering the

total cholesterol and LDL-C concentrations.[24,29] There could be numerous explanations for these seemingly contradictory findings, including differences in the lipid profile of patients, duration of the study, and daily dose of omega-3 supplementation. Because most patients in our trial had normal serum total cholesterol and LDL-C levels before the study, we did not anticipate that taking an omega-3 supplement would affect these levels.

Our study's results are consistent with those of other earlier research in that taking supplements of omega-3 fatty acids can increase HDL-C levels.[22,23,29-31] On the other hand, some researchers suggest that taking supplements of omega-3 had no impact on serum HDL-C.[25,32,33] The baseline serum HDL-C and triglyceride levels may be to reason for these contradictory results. Research has shown that HDL-C levels increase when triglycerides in the blood are reduced.[34] Fazelian *et al*. showed that HDL-C levels in CKD patients are unaffected by omega-3 supplementation. However, a subgroup analysis of the duration of the treatment revealed that omega-3 had a significant impact on HDL-C levels when given for longer than 10 weeks.[28] This conclusion contradicts the findings of Zhu *et al*.[35] which discovered that individuals on dialysis who took omega-3 reported a significant increase in HDL-C levels after treatment. According to Eslick *et al*.'s study, consuming fish oil may slightly increase HDL-C levels.[36] In 2016, a study was carried out on 16 hemodialysis patients. Results showed that consuming 2 g/day of omega-3 fatty acid for 3 months can cause a significant decrease in triglyceride levels and increase HDL-C levels. However, total cholesterol or LDL-C levels did not change after the end of the study.[15] In 2000, Khajehdehi.[29] investigated how omega-3 fatty acids affected hemodialysis patients at a dosage of 1.5 g/day for up to 2 months. When individuals take omega-3 supplements, their HDL-C and triglyceride levels decrease, but their LDL-C levels increase, which is not desirable.

Another of the biomarkers of functional status, serum albumin, did not alter in the intervention group compared to the placebo, which is consistent with prior findings.[37,38] Gharekhani *et al*.[39] reported that omega-3 increased the serum level of albumin compared to the control group. However, other studies fail to show the beneficial effect of omega-3 on serum albumin. Perunicic-Pecovic *et al*.,[30] administering 2400 mg/day of omega-3 capsule for 2 months increased the serum level of albumin significantly in patients receiving chronic hemodialysis. Vernaglione *et al*. observed a similar result after giving 2,100 mg of omega-3 supplement to patients undergoing chronic hemodialysis for 4 months, finding no change in their serum albumin levels.[40] A placebo-controlled, double-blinded clinical trial was conducted. They analyze the effect of a liquid form of protein supplement (containing 18 g protein) together with four omega-3 capsules after each dialysis session on inflammatory and nutritional indices in hemodialysis patients. Indices of nutrition, such as serum albumin levels, body mass index, and malnutrition-inflammation score, did not significantly change in maintenance hemodialysis patients.[41] In CKD patients, serum albumin levels decrease due to a reduction in protein intake and proliferation in the inflammatory response. According to some research, serum albumin is more likely to be a disease marker rather than a nutritional indicator.[42]

According to the literature, it seems that omega-3 fatty acids may have a significant impact on human health, in part by regulating inflammatory responses. Epidemiologic, experimental, and clinical research evidence suggests that omega-3 may help treat several inflammatory disorders, including CVD. Reduction in the levels of inflammatory markers such as hs-CRP, lipoprotein-associated phospholipase 2, and oxidized LDL-C are linked to these effects.[40,43-46] However, the results of our study did not show any significant effect of omega-3 on hs-CRP levels. The serum level of the CRP rises in response to injury, surgery, trauma, infection, and inflammation. According to research, chronic low-level inflammation significantly impacts atherosclerosis, which is usually associated with CVD. The hs-CRP test helps determine a person's risk of developing CVD because it accurately monitors low levels of CRP, which helps identify low but chronic levels of inflammation. Compared to other acute-phase reactants, hs-CRP offers higher assay accuracy, reliability, availability, and the presence of standards for adequate calibration, making it the analyte of choice for assessing cardiovascular risk.[47] According to a meta-analysis, there were no statistically meaningful differences in serum CRP levels between the CKD patient cohorts and the omega-3 fatty acid supplementation group. They would suggest that the omega-3 fatty acids do not appear to have a positive impact by lowering inflammation in CKD patients.[48] In 2015, Taheri, *et al*.[49] conducted a study to investigate the effects of omega-3, specifically on Interleukin-6 and CRP levels in peritoneal dialysis patients. Similarly, omega-3 supplementation did not affect the aforementioned inflammatory markers after 8 weeks.[49]

Despite the lack of significance in our investigation into the role of omega-3 supplements in lowering homocysteine levels and reducing inflammation in peritoneal dialysis patients, our trial had several

advantages. It was a placebo-controlled study, and no severe adverse effects led to patient exclusion. Furthermore, more interactions with patients help to improve their compliance. We do, however, acknowledge significant limitations that should be taken into account when interpreting the findings. Our study appeared to be shorter in length than other prior studies. Furthermore, we employed the traditional "pill counting" method to track patient compliance, which may be less accurate. Even though none of the patients complained that the omega-3 capsules smelled "fishy," it did not present in the placebo capsules, which could have impacted the trial participants' ability to remain blind. Finally, although the dietary intake of patients can be a potential confounder to our intervention, we did not consider it.

In conclusion, our research findings showed that patients undergoing peritoneal dialysis tolerated omega-3 supplementation well. The treatment for 2 months was beneficial in reducing triglyceride levels and increasing HDL-C levels. The study's outcomes also indicated that omega-3 supplements did not significantly alter any inflammatory markers, including homocysteine levels. The inflammatory markers do not seem to be substantially affected by omega-3. More extensive studies are needed to determine the effect of omega-3 on homocysteine and cardiovascular outcomes, particularly in peritoneal dialysis patients.

Authors' contribution

S. Badri, S. Vahdat, S. Seirafian, and M. Pourfarzam developed the idea of research and criticized the findings. T. Gholipur recruited and followed the patients. All authors contributed in manuscript preparation and revision.

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Conflicts of interest

There are no conflicts of interest.

References

1. Cho SM, Jeon JY, Yoo TH, Lee HY, Lee YH, Kim HC. Ideal cardiovascular health duration and risk of chronic kidney disease and cardiovascular disease. Heart 2022;108:523-8.
2. Klinger M, Madziarska K. Mortality predictor pattern in hemodialysis and peritoneal dialysis in diabetic patients. Adv Clin Exp Med 2019;28:133-5.
3. Harmankaya O, Akalin N, Akay H, Okuturlar Y, Erturk K, Kaptanogullari H, *et al.* Comparison of risk factors for cardiovascular disease in hemodialysis and peritoneal dialysis patients. Clinics (Sao Paulo) 2015;70:601-5.
4. Koklesova L, Mazurakova A, Samec M, Biringer K, Samuel SM, Büsselberg D, *et al.* Homocysteine metabolism as the target for predictive medical approach, disease prevention, prognosis, and treatments tailored to the person. EPMA J 2021;12:477-505.
5. Miller JW, Nadeau MR, Smith D, Selhub J. Vitamin B-6 deficiency versus folate deficiency: Comparison of responses to methionine loading in rats. Am J Clin Nutr 1994;59:1033-9.
6. Bleich S, Carl M, Bayerlein K, Reulbach U, Biermann T, Hillemacher T, *et al.* Evidence of increased homocysteine levels in alcoholism: The Franconian Alcoholism Research Studies (FARS). Alcohol Clin Exp Res 2005;29:334-6.
7. Capelli I, Cianciolo G, Gasperoni L, Zappulo F, Tondolo F, Cappuccilli M, *et al.* Folic acid and vitamin B12 administration in CKD, why not? Nutrients 2019;11:383.
8. Mullick AE, Zaid UB, Athanassious CN, Lentz SR, Rutledge JC, Symons JD. Hyperhomocysteinemia increases arterial permeability and stiffness in mice. Am J Physiol Regul Integr Comp Physiol 2006;291:R1349-54.
9. Takamitsu Y, Nakanishi T. Association of endothelial dysfunction with sulfur amino acid metabolism in chronic renal failure. Am J Kidney Dis 2001;38:S95-9.
10. Suliman ME, Stenvinkel P, Bárány P, Rashid Qureshi A, Lindholm B. Hyperhomocysteinemia, malnutrition, and inflammation in ESRD patients. Semin Nephrol 2006;26:14-9.
11. Badri S, Vahdat S, Seirafian S, Pourfarzam M, Gholipur-Shahraki T, Ataei S. Homocysteine-Lowering interventions in chronic kidney disease. J Res Pharm Pract 2021;10:114-24.
12. Galan P, Kesse-Guyot E, Czernichow S, Briancon S, Blacher J, Hercberg S, *et al.* Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: A randomised placebo controlled trial. BMJ 2010;341:c6273.
13. Schunck WH, Konkel A, Fischer R, Weylandt KH. Therapeutic potential of omega-3 fatty acid-derived epoxyeicosanoids in cardiovascular and inflammatory diseases. Pharmacol Ther 2018;183:177-204.
14. Beavers KM, Beavers DP, Bowden RG, Wilson RL, Gentile M. Omega-3 fatty acid supplementation and total homocysteine levels in end-stage renal disease patients. Nephrology (Carlton) 2008;13:284-8.
15. Tayebi-Khosroshahi H, Dehgan R, Habibi Asl B, Safaian A, Panahi F, Estakhri R, *et al.* Effect of omega-3 supplementation on serum level of homocysteine in hemodialysis patients. Iran J Kidney Dis 2013;7:479-84.
16. Filiopoulos V, Hadjiyannakos D, Takouli L, Metaxaki P, Sideris V, Vlassopoulos D. Inflammation and oxidative stress in end-stage renal disease patients treated with hemodialysis or peritoneal dialysis. Int J Artif Organs 2009;32:872-82.
17. Li Y, Zhang L, Gu Y, Hao C, Zhu T. Insulin resistance as a predictor of cardiovascular disease in patients on peritoneal dialysis. Perit Dial Int 2013;33:411-8.
18. Ziaie S, Polroudi Moghaddam M, Samadian F, Sistanizad M, Afzal G, Saffaei A, *et al.* Omega-3 in patients undergoing continuous ambulatory peritoneal dialysis, effects on inflammatory markers and lipid profile. Iran J Kidney Dis 2020;14:126-32.
19. Li J, Huang N, Zhong Z, Joe P, Wang D, Ai Z, *et al.* Risk factors and outcomes of cardiovascular disease readmission within the first year after dialysis in peritoneal dialysis patients. Ren Fail 2021;43:159-67.
20. Giray B, Kan E, Bali M, Hincal F, Basaran N. The effect of vitamin E supplementation on antioxidant enzyme activities and lipid peroxidation levels in hemodialysis patients. Clin Chim Acta 2003;338:91-8.
21. Xu T, Sun Y, Sun W, Yao L, Sun L, Liu L, *et al.* Effect of omega-3 fatty acid supplementation on serum lipids and vascular inflammation in patients with end-stage renal disease:

A meta-analysis. Sci Rep 2016;6:39346.
22. Taziki O, Lessan-Pezeshki M, Akha O, Vasheghani F. The effect of low dose omega-3 on plasma lipids in hemodialysis patients. Saudi J Kidney Dis Transpl 2007;18:571-6.
23. Svensson M, Christensen JH, Sølling J, Schmidt EB. The effect of n-3 fatty acids on plasma lipids and lipoproteins and blood pressure in patients with CRF. Am J Kidney Dis 2004;44:77-83.
24. Fiedler R, Mall M, Wand C, Osten B. Short-term administration of omega-3 fatty acids in hemodialysis patients with balanced lipid metabolism. J Ren Nutr 2005;15:253-6.
25. Svensson M, Schmidt EB, Jørgensen KA, Christensen JH. The effect of n-3 fatty acids on lipids and lipoproteins in patients treated with chronic haemodialysis: A randomized placebo-controlled intervention study. Nephrol Dial Transplant 2008;23:2918-24.
26. Liu QK. Triglyceride-lowering and anti-inflammatory mechanisms of omega-3 polyunsaturated fatty acids for atherosclerotic cardiovascular risk reduction. J Clin Lipidol 2021;15:556-68.
27. Jump DB, Botolin D, Wang Y, Xu J, Christian B, Demeure O. Fatty acid regulation of hepatic gene transcription. J Nutr 2005;135:2503-6.
28. Fazelian S, Moradi F, Agah S, Hoseini A, Heydari H, Morvaridzadeh M, *et al.* Effect of omega-3 fatty acids supplementation on cardio-metabolic and oxidative stress parameters in patients with chronic kidney disease: A systematic review and meta-analysis. BMC Nephrol 2021;22:160.
29. Khajehdehi P. Lipid-lowering effect of polyunsaturated fatty acids in hemodialysis patients. J Ren Nutr 2000;10:191-5.
30. Perunicic-Pekovic GB, Rasic ZR, Pljesa SI, Sobajic SS, Djuricic I, Maletic R, *et al.* Effect of n-3 fatty acids on nutritional status and inflammatory markers in haemodialysis patients. Nephrology (Carlton) 2007;12:331-6.
31. Rolf N, Tenschert W, Lison AE. Results of a long-term administration of omega-3 fatty acids in haemodialysis patients with dyslipoproteinaemia. Nephrol Dial Transplant 1990;5:797-801.
32. Donnelly SM, Ali MA, Churchill DN. Effect of n-3 fatty acids from fish oil on hemostasis, blood pressure, and lipid profile of dialysis patients. J Am Soc Nephrol 1992;2:1634-9.
33. Bonanome A, Biasia F, De Luca M, Munaretto G, Biffanti S, Pradella M, *et al.* n-3 fatty acids do not enhance LDL susceptibility to oxidation in hypertriacylglycerolemic hemodialyzed subjects. Am J Clin Nutr 1996;63:261-6.
34. Miller M, Langenberg P, Havas S. Impact of lowering triglycerides on raising HDL-C in hypertriglyceridemic and non-hypertriglyceridemic subjects. Int J Cardiol 2007;119:192-5.
35. Zhu W, Dong C, Du H, Zhang H, Chen J, Hu X, *et al.* Effects of fish oil on serum lipid profile in dialysis patients: A systematic review and meta-analysis of randomized controlled trials. Lipids Health Dis 2014;13:127.
36. Eslick GD, Howe PR, Smith C, Priest R, Bensoussan A. Benefits of fish oil supplementation in hyperlipidemia: A systematic review and meta-analysis. Int J Cardiol 2009;136:4-16.
37. Valle Flores JA, Fariño Cortéz JE, Mayner Tresol GA, Perozo Romero J, Blasco Carlos M, Nestares T. Oral supplementation with omega-3 fatty acids and inflammation markers in patients with chronic kidney disease in hemodialysis. Appl Physiol Nutr Metab 2020;45:805-11.
38. Sarav M, Friedman AN. Use of Intradialytic parenteral nutrition in patients undergoing hemodialysis. Nutr Clin Pract 2018;33:767-71.
39. Gharekhani A, Khatami MR, Dashti-Khavidaki S, Razeghi E, Abdollahi A, Hashemi-Nazari SS, *et al.* Potential effects of omega-3 fatty acids on anemia and inflammatory markers in maintenance hemodialysis patients. Daru 2014;22:11.
40. Vernaglione L, Cristofano C, Chimienti S. Omega-3 polyunsaturated fatty acids and proxies of cardiovascular disease in hemodialysis: A prospective cohort study. J Nephrol 2008;21:99-105.
41. Daud ZA, Tubie B, Adams J, Quainton T, Osia R, Tubie S, *et al.* Effects of protein and omega-3 supplementation, provided during regular dialysis sessions, on nutritional and inflammatory indices in hemodialysis patients. Vasc Health Risk Manag 2012;8:187-95.
42. Donadio C, Tognotti D, Donadio E. Albumin modification and fragmentation in renal disease. Clin Chim Acta 2012;413:391-5.
43. Maki KC, Bays HE, Dicklin MR, Johnson SL, Shabbout M. Effects of prescription omega-3-acid ethyl esters, coadministered with atorvastatin, on circulating levels of lipoprotein particles, apolipoprotein CIII, and lipoprotein-associated phospholipase A2 mass in men and women with mixed dyslipidemia. J Clin Lipidol 2011;5:483-92.
44. Orringer CE, Jacobson TA, Maki KC. National lipid association scientific statement on the use of icosapent ethyl in statin-treated patients with elevated triglycerides and high or very-high ASCVD risk. J Clin Lipidol 2019;13:860-72.
45. Davidson MH, Maki KC, Bays H, Carter R, Ballantyne CM. Effects of prescription omega-3-acid ethyl esters on lipoprotein particle concentrations, apolipoproteins AI and CIII, and lipoprotein-associated phospholipase A(2) mass in statin-treated subjects with hypertriglyceridemia. J Clin Lipidol 2009;3:332-40.
46. Miller M, Ballantyne CM, Bays HE, Granowitz C, Doyle RT Jr., Juliano RA, *et al.* Effects of icosapent ethyl (Eicosapentaenoic Acid Ethyl Ester) on atherogenic lipid/lipoprotein, apolipoprotein, and inflammatory parameters in patients with elevated high-sensitivity C-reactive protein (from the ANCHOR study). Am J Cardiol 2019;124:696-701.
47. Alfaddagh A, Martin SS, Leucker TM, Michos ED, Blaha MJ, Lowenstein CJ, *et al.* Inflammation and cardiovascular disease: From mechanisms to therapeutics. Am J Prev Cardiol 2020;4:100130.
48. Hu C, Yang M, Zhu X, Gao P, Yang S, Han Y, *et al.* Effects of omega-3 fatty acids on markers of inflammation in patients with chronic kidney disease: A controversial issue. Ther Apher Dial 2018;22:124-32.
49. Taheri S, Keyvandarian N, Moeinzadeh F, Mortazavi M, Naini AE. The effect of omega-3 fatty acid supplementation on oxidative stress in continuous ambulatory peritoneal dialysis patients. Adv Biomed Res 2014;3:143.