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The effects of omega-3 fatty acids supplementation on hemoglobin, hematocrit, and platelet levels of patients with ESRD condition undergoing dialysis

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ABSTRACT

Background: Concomitant inflammation may boost the cardiovascular complications in end-stage renal disease (ESRD) patients undergoing hemodialysis (HD). Omega-3 fatty acids may have certain health benefits in HD patients. The aim of this study was to investigate the effects of omega-3 fatty acids supplementation on hematocrit (HCT), hemoglobin (HB) level and platelet (PLT) counts of HD patients.

Methods: A randomized controlled trial was conducted on HD patients at a private dialysis center in Rasht, Iran. Three omega-3 fatty acid supplement capsules (3 g/d) were administered daily for two months to patients in the intervention group (n = 55). The control group (n = 60) were given three placebo capsules containing medium chain triglyceride (MCT) oil, similar to the supplemental dose of the intervention group at the same period. Three parameters of HCT, HB and PLT were measured at baseline and after the intervention.

Results: The PLT count decreased in the intervention group compared to the control group (173.38 ± 74.76 vs. 227.68 ± 86.58 $10^3/mm^3$, F = 4.83, P = 0.03). No significant change was found on the levels of HCT and HB parameters between the two groups after the intervention.

Conclusion: Omega-3 supplementation in HD patients may decrease the risk of forming blood clots in the blood vessels. Further studies are warranted.

1. Introduction

Chronic kidney disease (CKD) is a major public health issue with a rise in global incidence [1–4]. Kidney disease has been ranked as the 12th leading cause of death, accounting for 1.1 million deaths worldwide, according to the 2015 Global Burden of Disease Study [1]. The

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prevalence of end stage renal disease (ESRD) is 242 per million in global population and is increasing by about 8% annually [2]. A 31.7% increase in the global CKD mortality rate has been observed over the past 10 years [1].

Patients with CKD, particularly those with ESRD, have a higher risk of protein-energy wasting (PEW) as a result of insufficient intake, higher catabolism, inflammation, and uremic toxins, which are common states of metabolic dysfunctions [5,6]. PEW has a higher prevalence in patients with CKD stages 4 and 5(50–75%) and is linked to higher mortality and morbidity that leads to worsening of the quality of life [7]. Furthermore, cardiovascular diseases (CVDs) is recognized as one of PEW-related conditions and the most life-threatening factor in ESRD patients [8,9]. CVDs are the most common cause of death for patients undergoing HD [10]. Chronic inflammation has a key role in higher CVDs incidence among HD patients. Inflammatory markers, such as C-reactive protein (CRP) and interloukin-6 (IL-6) are increased in HD patients, implying an underlying inflammation, which could in turn increase the incidence of CVDs in this population [11].

Recent studies demonstrated the beneficial effects of omega-3 fatty acids in HD patients, with most focusing on markers of CVDs and nutrition [12–16]. Patients with high stages of CKD are reported to have lower n-3 poly unsaturated fatty acids (PUFA) levels in the blood than the general population, possibly due to lower dietary intake of n-3 PUFA, in addition to the metabolic changes, inflammation, malabsorption and loss of n-3 PUFAs during dialysis [17,18]. Studies have shown that omega-3 fatty acids may control inflammation by reducing pro-inflammatory eicosanoids, chemokines and other inflammatory mediators [19–22]. Patients with ESRD on chronic hemodialysis, who daily received 2 g of omega-3(containing 360 mg eicosapentaenoic acid or EPA and 240 mg docosahexaenoic acid or DHA) for 3 months had lower serum levels of IL-6 and CRP [23]. Moreover, patients with CKD who daily received one capsule of omega 3 including 1000 mg n3-PUFAs containing 330 mg of EPA, 220 mg of DHA, and 100 mg of other acids such as alpha-linolenic acid (ALA) for six months had lower urinary excretion of monocyte chemoattractant protein-1(MCP-1) has a vital role in reducing inflammation [24].

High doses of omega-3 fatty acids (6.5 g) at the initiation of HD for a period of 3 years resulted in significant reduction in triglyceride (TG) levels and lower risk of fatal CVD events compared to the control group [25]. Lower doses of omega-3 supplementation in HD patients also resulted in significant positive effects with respect to inflammatory status and lipidemic profile. More specifically, patients receiving omega-3 fatty acids presented improved lipidemic profiles, lower incidence rates of myocardial infarction, and more stable atherogenic plaques, although no difference was found in deaths from CVD [26]. On the other hand, CKD is one of independent risk factors for venous thromboembolic (VTE) [24] and omega-3 supplementation may protect the blood vessels against VTE [23].

Low amounts of omega-3 fatty acids cause a reduction in composition of erythrocyte membrane phospholipids in HD patients that may lead to a higher risk of inflammation and CVDs [13]. However, Some studies reported that Omega-3 supplementation in hemodialysis patients produced a slight attenuation in systemic inflammation without any remarkable effects on CVDs markers [27]. Given the controversial reports on the effects of omega-3 fatty acids in hemodialysis patients and considering that the effect of omega-3 fatty acids on some blood indices related to CVDs has not been sufficiently investigated. Therefore, considering that most of the studies on the effects of omega-3 fatty acids in HD patients have focused on inflammatory markers and the available studies on the effect of omega-3 supplementation on biochemical factors are very limited [12–16], this study aimed to investigate the effects of omega-3 fatty acids on hemoglobin, hematocrit, and platelet levels in hemodialysis patients.

2. Methods

2.1. Study design and participants

A randomized controlled trial was conducted on patients with ESRD treated with hemodialysis in 2023 at a private dialysis center of Rasht, Iran. Hemodialysis was carried out 3 days a week, with each session lasting around 4 h. A randomized block sampling method and the WinPepi program were used to assign the participants to the intervention and control groups. Finally, 16 blocks were used and, in each block, 3 persons were assigned in the control group and 3 persons were assigned in the intervention group in a random sequence. Two intervention and control groups were randomized via the web using https://www.randomizer.org. Both groups were matched in terms of age and sex. It's a triple blind randomized trial which ensures that neither the patient, the researcher, nor the statistical analyst are aware of the study components (Fig. 1).

Inclusion criteria were completing written consent form, age over 20 years, having stage 5 CKD, no more than 6 month from CKD diagnosis, standard KT/V, no consumption of omega-3 fatty acid supplement during the last 3 months before starting the study, no history of peritoneal dialysis, no surgery in the previous six months, no history of hypersensitivity response to omega-3 fatty acid supplementation and/or medium chain triglycerides (MCTs) oil, no history of allergy to fish and fish products, and not to be pregnant. Exclusion criteria were refusal to continue the participation in the study, diagnosis of psychiatric conditions and mental retardation, have underlying diseases such as active inflammatory, infection, pulmonary, cardiac, hemoglobinopathies and coagulopathy which may interfere with the research process, malignant tumors diagnosis, recent use of immunosuppressant, chemotherapeutic or anticoagulant drugs such as warfarin and the use of nonsteroidal anti-inflammatory medications, corticosteroids, incomplete medical documents, non-compliance with omega-3 supplementation program, not adhering to the hemodialysis schedule, the need for hospitalization and surgery.

Data on the demographic and socioeconomic status, medical information such as medical history, dialysis data, drug history, and nutritional supplements were collected from the patient's file. The patient's height and weight were measured using a bio-impedance analyzer (BIA) scale (OMRON-BF511).

2.2. The intervention

Three omega-3 fatty acid supplement capsules (Mega Nut Co., Australia) were administered daily for two months to patients in the intervention group. The control group were given three placebo capsules containing MCT oil (Mega Nut Co., Australia), similar to the supplemental dose of the intervention group over the same period. In order to prevent supplement abuse and follow the process properly, the supplements were given to patients as 21 capsule packs per week. The use of the supplements was monitored weekly by one of the researchers face to face or by phone call.

2.3. Biochemical measurements

10 cc of blood was collected from all the participants at baseline and after two months of the intervention. The serum was separated and used to assess the serum levels of HB, HCT, and PLT using Cell Counter Sysmex; Model KX21 N.

2.4. Statistical analysis

The Kolmogorov-Smirnov test was used to determine the normal distribution of data. T-test and Chi-squared test were used to compare the quantitative and qualitative data between two groups, respectively. The general linear model repeated measures test was used to determine

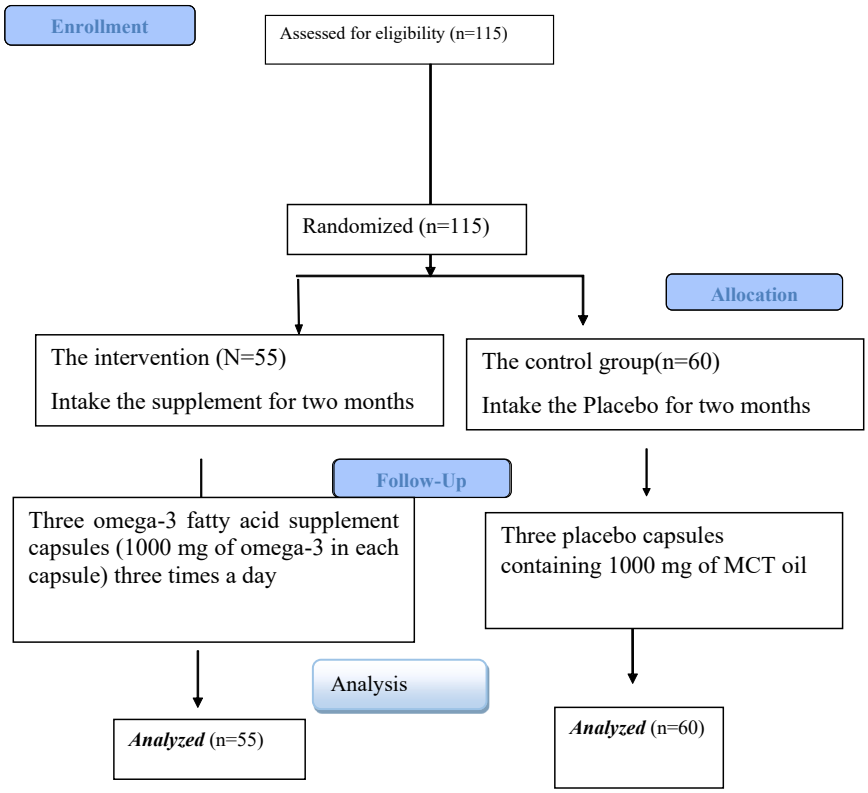

Fig. 1. The diagram of study.

the effect of omega-3 fatty acids supplementation on hematologic indices after adjusting the confounding variables including age, sex, body mass index (BMI), smoking, dietary intake, and underlying diseases. A P value < 0.05 was considered to be statistically significant. SPSS version 20 were used for all statistical analysis.

3. Results

There was no significant difference in terms of age, sex, weight, height, the amount of sleep, marriage status, diabetes, hypertension, metabolic disorder, heart disease, using tobacco, alcohol drinking, HB, HCT, and PLT between the groups after intervention (Table 1).

As presented in Table 2, PLT levels was decreased in the intervention group (196.82 ± 75.66 vs. 173.38 ± 74.76 $10^3/mm^3$) and increased in the control group (207.55 ± 86.61 vs. 227.68 ± 86.58 $10^3/mm^3$) after the intervention ($P < 0.05$). No significant difference was found regarding the levels of HCT and HB between the groups after the intervention.

Table 1
The general characteristics of the participants.

	Intervention group N = 55	Control group N = 60	P
Age (y)	61.17 ± 12.35	55.33 ± 12.6	0.14
Weight (kg)	67.87 ± 13.64	71.21 ± 14.0	0.204
Height (cm)	164.28 ± 9.32	167.19 ± 9.02	0.094
Sex			
Females	28 (48.3%)	17 (31.5%)	0.084
Male, n (%)	30 (51.7)	37 (68.5)	0.08
Amount of sleep (h)	8.0 ± 2.51	7.96 ± 2.52	0.951
Married, n (%)	53 (94.6)	48 (92.3)	0.71
Diabetes, n (%)	26 (43.3)	26 (47.3)	0.71
Hypertension n (%)	48 (81.4)	41 (74.5)	0.49
Metabolic disorder n (%)	3 (5.0)	3 (5.5)	1.00
Heart Disease n (%)	16 (26.7)	14 (25.5)	1.00
Tobacco (y)	4 (6.7)	8 (14.5)	0.23
Drink Alcohol (y)	0 (0.0)	1 (1.8)	0.47
HB (g/dL)	11.0 ± 1.54	11.46 ± 1.42	0.100
HCT (%)	34.96 ± 4.78	36.4 ± 4.50	0.118
PLT ($10^3/mm^3$)	196.82 ± 75.66	207.55 ± 86.61	0.577

4. Discussion

In the present study, three parameters of HCT, HB and PLT were investigated in two intervention and control groups in HD patients. The PLT level significantly increased in the control group and decreased in the intervention group. Based on this research a similar study showed that high doses of omega-3 fatty acids (6.5 g) at the start of HD for a 3-year period resulted in a significant reduction in the risk of fatal CVD compared to the control group [25]. However, most studies that showed

Table 2
Comparison of hematological parameters between the intervention group and control group after the intervention.

Factor	Intervention group mean (SE)		Control group mean (SE)		Group*Time[a]	
	Baseline	After	Baseline	After	F	P
HB	11(1.54)	11 (2.14)	11.46 (1.42)	11.37 (2.44)	0.012	0.91
HCT	34.96 (4.78)	34.77 (6.07)	36.4(4.5)	36.61 (9.37)	0.043	0.83
PLT	196.82 (75.66)	173.38 (74.76)	207.55 (86.61)	227.68 (86.58)	4.83	0.03

[a] Repeated measure ANOVA.

the beneficial effects of omega-3 fatty acids in HD patients focused on inflammatory markers [12–16].

Regarding the effect of omega-3 supplementation on PLT level, McEwen et al. reported that a 4-week supplementation of omega-3 PUFAs (640 mg/day) in patients with CVD and healthy controls lowered PLT in healthy participants but not in CVD patients. The authors highlighted the necessity to use higher doses of omega-3 PUFAs in for the correction of PLT serum levels. Furthermore, Li et al. reported that a supplementation of EPA as high as 6 g/day may reduce platelet adhesion [28].

Another study reported that omega-3 supplementation in hemodialysis patients slightly reduced systemic inflammation without any significant effect on nutritional markers [27]. Lower doses of omega-3 supplementation in HD patients also had significant positive effects regarding hematologic indices and patients receiving omega-3 fatty acids showed an improved lipid profile, a lower incidence rate of myocardial infarction, and more stable atherogenic plaques, although no difference in CVDs mortality was found [28]. It is possible that only high doses of omega-3 fatty acids can reduce the risk of CKD-related mortality. Considering the controversial reports about the effects of omega-3 fatty acids in hemodialysis patients, we need more studies to find out the exact mechanism.

Omega-3 and omega-6 PUFAs are components of phospholipids, which are constituents of cell membranes. Due to the catalytic action of phospholipase A2 (PLA2), these fatty acids are released from the membrane and become precursors of eicosanoids, such as prostaglandins, thromboxanes, leukotrienes or lipoxins, with a plethora of biological effects [29]. Linoleic acid (LA) is an important member of the omega-6 PUFAs and the precursor of arachidonic acid (AA) which is characterized by pro-inflammatory properties. By contrast, ALA is a major fatty acid from the omega-3 group and is a precursor of EPA, which is a substrate for DHA. These fatty acids are characterized by anti-inflammatory properties [29–31]. The metabolic pathway of AA by cyclooxygenase (COX) results in the development of eicosanoids. The synthesis of pro-aggregatory thromboxane A2 (TXA2) from LA takes place in blood PLT. In addition, prostacyclin I2 (PGI2) is produced by LA in the endothelium with an antagonistic effect on platelet activity. On the other hand, omega-3 fatty acids may have a significant effect in the reduction of platelet aggregation [32]. In cardiovascular disease, abnormal clotting occurs that can result in heart attacks or stroke. Blood vessels injured by smoking, cholesterol, or high blood pressure develop cholesterol-rich plaques and these plaques can rupture and cause the platelets to form a clot [33]. Thromboxane A3 (TXA3) synthesized by ALA in platelets exhibits only slight pro-aggregatory activity. Furthermore, prostaglandin I3 (PGI3) produced in the endothelium possesses anti-aggregatory properties [29,34]. The balance between pro-inflammatory and anti-inflammatory factors and improved levels CVDs markers of may be achieved by higher intake of omega-3 fatty acids.

Our study had some limitations. Although the sample size was acceptable, the results need to be confirmed in larger studies. Other limitations of this study were the short duration of the study and low dose of omega-3 fatty acid supplementation. Also, we only focused on HB, HCT, and PLT in the present study and other hematologic parameters were not analyzed as some of them are linked with the inflammatory process such as WBC, polymorphonuclear Neutrophils (PMN), lymphocytes (Ly), monocytes, and erythrocyte sedimentation rate (ESR). Future studies with a longer period of time, higher doses of omega-3 fatty acids, and measuring different types of hematologic indices would give a clearer picture of the effects of omega-3 fatty acid against CVDs.

5. Conclusion

Omega-3 fatty acids may lower the risk of CVDs by improvement the levels of PLT. If the results obtained in the present study are proven in future studies considering the clinical consequences, it is possible to recommend the supplementation with omega-3 fatty acids as a therapeutic strategy to prevent cardiovascular complications caused by kidney failure. More studies are warranted to confirm this result and to discover the exact mechanism.

Ethics approval and consent to participate

This study was approved by the ethical committee of the cancer research center, Guilan University of Medical Sciences (code: IR.GUMS.REC.1401.307).

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CRediT authorship contribution statement

Zahra Mahmoudi: Data curation. **Zahra Roumi:** Data curation. **Seyed Ali Askarpour:** Formal analysis. **Zahra Mousavi:** Conceptualization. **Hanieh Shafaei:** Data curation. **Neda Valisoltani:** Data curation. **Mahsa Shapouri:** Software. **Seyed Reza Mirshafaei:** Data curation. **Pouya Mirzaee:** Data curation. **Khadijeh Abbasi Mobarakeh:** Formal analysis. **Elahe Taghavi Sufiani:** Data curation. **Zeinab Motiee Bijarpasi:** Formal analysis. **Zeynab Motiei:** Conceptualization. **Masoud Khosravi:** Conceptualization. **Saeid Doaei:** Data curation, Formal analysis. **Maryam Gholamalizadeh:** Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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