

Effect of Omega-3 Fatty acids Supplementation on Muscle Mass, Fat Mass, and Visceral Fat of Hemodialysis Patients; A Randomized Clinical Trial

Running Title: Omega-3 Supplementation and Hemodialysis

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ABSTRACT

Background: Several studies demonstrated the benefits of omega-3 fatty acids supplementation in chronic kidney disease (CKD) patients. The objective of this study was to investigate effect of omega-3 fatty acids supplementation in body composition, specifically on the lean body mass and fat mass in hemodialysis patients.

Methods: In this randomized, double-blind, placebo-controlled clinical trial, a total of 120 end-stage renal disease (ESRD) patients were randomly allocated into two groups. The intervention group has taken three grams of omega-3 fatty acids daily while the placebo group received three grams of medium chain triglycerides (MCT) as a placebo for a total of 2 months. The changes in in the body mass index (BMI) and body composition (fat mass, muscle, and visceral fat) were assessed at baseline and following the intervention.

Results: No significant difference was found in the mean of BMI, FAT, muscle, and visceral fat in the intervention group compared to the control group after the intervention. After two months of omega-3 fatty acid supplementation, the study found no statistically significant impact of omega-3 fatty acids supplementation on various indices of body composition. The effect of ω -3 supplementation in reducing visceral fat was close to significant ($P=0.08$).

Conclusion: This study suggests that there is currently inadequate evidence to support the effect of omega-3 fatty acid supplementation in improving anthropometric measurements in patients with CKD, except a partial effect on visceral fat. Further large-scale and long-term clinical trials are needed to confirm the present results.

Keywords: Omega-3 fatty acid, Muscle Mass, Fat Mass, Visceral Fat, Hemodialysis

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Introduction

Chronic kidney disease (CKD) which may progress to renal failure and lead to hemodialysis (HD) and renal transplant affects more than 10% of the general population worldwide (1, 2). Diabetes, hypertension, and glomerulonephritis are the major underlying pathophysiology of CKD in all high-income and middle-income countries (3). The complications of CKD include anemia, cardiovascular diseases and malnutrition and all of these complications are strongly associated with high rates of morbidity and mortality (4-6). Malnutrition, characterized by decreased physical performance, lower lean body mass and lower quality of life is common in HD patients (7-11). There are about 50-75% cases of malnutrition reported among the CKD patients at different stages of CKD (12, 13).

The malnutrition in HD patients is predominantly caused by low intake of dietary protein, physical inactivity, catabolic and inflammatory effects, metabolic acidosis, hormonal changes, and comorbid conditions (8, 14-19). Several epidemiological studies have consistently reported that greater muscle mass is associated with increased survival of CKD patients (5, 11, 20). However, an effective dietary practice to improve muscle mass in these patients is yet to be found. Omega-3 fatty acids demonstrated potential benefit in improving the body composition and anthropometric indices in patients with CKD (13, 21).

The benefits of omega-3 fatty acids supplements on inflammatory pathways in CKD patients were demonstrated (21-24). Omega-3 fatty acids provides a wider benefit to the vascular system by suppressing the pro-inflammatory mediators (22-25). Considering the possible association between inflammation and body composition in patients with CKD (26, 27), The aim of this clinical trial was to investigate the effect of omega-3 fatty acids supplements on the body composition, particularly increasing lean body mass along with the changes of fat body mass in hemodialysis patients.

Methods

Study design

This was a randomized, double-blind, placebo-controlled parallel clinical trial that includes 120 end-stage renal disease (ESRD) patients (60 patients in each group) treated with hemodialysis during April to September 2022 in the dialysis department of Caspian Dialysis Center, Rasht, Iran. Sample size was calculated using the Open EPI online software and $\alpha = 0.05$, power of 0.8, and allocation ratio of unexposed to exposed of 1:1.

The participants were randomly allocated by one of the researchers to either intervention or control groups using WinPepi 1.0 software (<http://www.brixtonhealth.com/pepi4windows.html>) which is a web-based program by random block method. This software generated a total of 20 random blocks with each block represented by 3 patients each on control and intervention (Figure 1). This study was a triple blind clinical trial which ensures that neither the patients, the researchers, nor the statistical analyst are aware of the study components.

The inclusion criteria were submission of a written consent to participate, age between 20 to 85 years, and KT/V in the standard range based on dialysis days in the standard range (1.2 for those who have 3 treatment sessions and 1.8 for 2 treatment sessions per week). Exclusion criteria were diagnosis of psychiatric disorders and mental retardation, having concomitant underlying diseases such as active inflammatory, infectious, pulmonary, cardiac, hemoglobinopathies, and coagulopathy disorders. Participants with malignant tumors, recent use of immunosuppressive drugs, chemotherapy or anticoagulant drugs such as warfarin and use of non-steroidal anti-inflammatory drugs and corticosteroids were excluded. The participants with incomplete medical documents, taking omega-3 fatty acid supplements during the last 3 months, history of peritoneal dialysis, undergone surgery in the last 6 months, pregnancy, and/or having adverse supplement effects including hypersensitivity reaction to omega-3 fatty acid supplements (n=5) and/or medium-chain triglyceride (MCT) oil, and hypersensitivity to fish or fish-derived products were also excluded. The exclusion criteria also included unwillingness to continue participating in the study, and failure to comply with the hemodialysis program. If the patients' conditions change, including the worsening of the disease, requiring hospitalization and surgery, the patients were excluded from the study according to the recommendation

of the center's physician, so that the treatment process would not be affected. Also, if a patient could not be followed up, he was excluded from the study.

Data collection

Data collection was performed on the following parameters: socio-economic status, past medical history (Hx), number of HD sessions/week, drug Hx, lab findings, urine output (OP), the nutritional supplements received by the patients, and physical examination including anthropometric indices. The demographic and clinical information of the participants were extracted from patients' records. The height and weight of the patients were determined using a tape meter and digital scale, respectively. Bio-impedance analyzer (BIA) (OMRON-BF511) was used to determine the percentages of body fat and muscle mass content.

The intervention

Three capsules of omega-3 fatty acids supplement including 3 grams of omega-3 fatty acids was given daily to the intervention group (each capsule contained about 230 mg eicosapentaenoic acid [EPA] and 150 mg docosahexaenoic acid [DHA] and 620 mg other omega-3 fatty acids) (Zahravi Pharmaceutical Co, Tabriz, Iran) were given orally daily for 2 months to the patients in the intervention group. The control group received three placebo capsules containing medium-chain triglyceride (MCT) (Zahravi Pharmaceutical Co, Tabriz, Iran). The participants were supplied with 21 capsules on a weekly basis. Both intervention and placebo consumptions were followed up with the patients through regular phone calls.

Statistical analysis

Descriptive statistics including mean $\pm$ standard deviation (for quantitative data) and percentage and number (for qualitative data) were used to describe the status of demographic, social, and anthropometric indicators of the participants. The Kolmogorov-Smirnov test was used to determine normal distribution. Independent samples T-test and Chi-square test methods were used to compare the quantitative and qualitative variables between the two groups at baseline, respectively. The general

linear model (GLM) repeated measure method was used to determine the effect of omega-3 fatty acid supplementation on anthropometric indices, and the confounding variables included age, sex, body mass index (BMI), smoking, diet, and underlying diseases including diabetes and hypertension were adjusted. In all calculations, SPSS version 20 software was used for all statistical analysis and a $P < 0.05$ was considered statistically significant.

Results

Finally, 115 patients with CKD with hemodialysis including 60 patients in the control group and 55 patients in the case group were included. The general characteristics of the participants are presented in Table 1. The intervention group was slightly older than the control group (61.2 ± 12.4 y vs. 55.3 ± 12.6 y, $P = 0.01$). The metabolic equivalent of task (MET) level in the intervention group (1174.08 ± 268.9 kcal/kg*h) was significantly ($P = 0.004$) lower than the control group (1315.25 ± 243.42 kcal/kg*h). The intervention and control groups had no significant difference in terms of weight, height, fat mass, muscle mass, body water content, body protein level, sleep duration, marital status, tobacco, use of alcohol, diabetes, hypertension, family history of diabetes, hypertension, CKD and heart disease.

A comparison of anthropometric parameters between the intervention group and control groups after the intervention is shown in Table 2. No significant difference was found for BMI (24.75 ± 3.80 vs. 25.01 ± 4.7 , $F = 0.99$), fat mass (27.82 ± 8.75 vs. 30.28 ± 9.4 , $F = 0.073$), muscle mass (47.12 ± 8.61 vs. 44.11 ± 9.24 , $F = 0.032$), and visceral fat mass (10.95 ± 4.24 vs. 10.02 ± 3.71 , $F = 0.072$) between the control and case groups after the intervention. Although, the effect of ω -3 supplementation on reduction of visceral fat mass was close to statistical significance ($P = 0.08$).

Discussion

The aim of this clinical trial was to investigate the effect of omega-3 fatty acids supplements on the body composition in hemodialysis patients. The results indicated no significant effect of omega-3 supplementation on the level of anthropometric indicators compared to the control group. However, the

effect of ω -3 supplementation in reducing visceral fat was close to significant. Sikorska-Wiśniewska et al. evaluated the status of serum level of ω -3 fatty acids in CKD patients treated with dialysis and the results showed that the patients have a relatively low serum level of ω -3 PUFA (28). Several studies reported the beneficial effects of omega-3 fatty acids in CKD patients with hemodialysis. For example, Roumeliotis et al. found that the multi-nutrient supplementation including vitamins E and C, statins, ω -3 PUFA, and N-acetylcysteine delayed the progression of cardiovascular diseases in end-stage renal disease patients (29). Regarding the effect of omega-3 fatty acids on body composition, Wong et al. assessed the association between the dietary ratios of ω -3 and ω -6 PUFAs and skeletal muscle mass (SMM) and appendicular skeletal muscle mass (ASM) in patients with diabetes undergoing hemodialysis (HD). Patients with adequate intake of ω -3 PUFAs had higher SMM and ASM. Also, a higher dietary ratio of ω -6/ ω -3 PUFAs was associated with reduced muscle mass in HD patients (30). In line with this study, several reports demonstrated no association between ω -3 PUFAs and clinical outcomes in patients with CKD. Poulia et al. assessed the effect of ω -3 PUFA on serum lipids and inflammation markers in chronic hemodialysis (HD) patients and no positive effects of ω -3 PUFA supplementation in HD patients were evident (31).

Although, in contrast with the present study that the effect of ω -3 supplementation had no significant effect on body composition compared to our control group, Sangouni et al. in a clinical trial reported that ω -3 PUFA supplementation for 12 weeks improves visceral adiposity index in diabetic patients with NAFLD (32). In addition, Mello et al. in an animal study diet-induced obesity model found that ω -3 PUFA polyunsaturated fatty acids have beneficial effects on visceral fat (33).

The underlying mechanism of the effect of omega-3 fatty acids in CKD is not yet clear. The known effects of omega-3 fatty acids supplementation among patients with CKD are largely restricted to vascular outcomes. For example, Lee et al. reported that ω -3 PUFA may inhibit vascular calcification (VC) (34). Few studies focused on the effect of ω -3 PUFA on body composition, fat mass, and fat-free mass. The results of this study showed that ω -3 PUFA supplement does not affect anthropometric indices. The effect of ω -3 supplementation on visceral fat had a trend toward statistical significance by

mitigate changes caused by the consumption of a dietary fat (33) or through altering epigenetic mechanisms, regulating adipokines such as adiponectin and leptin, modulating lipid metabolism, and alleviating adipose tissue inflammation (35).

However, the present study had some limitations. First, there was limited information on safety of high dosages of omega-3 fatty acid in CKD patients to form a concrete intervention. So, a low dose omega-3 (totally 3 grams of omega-3 fatty acids daily) was given to the intervention group. Second, our control group used MCT oil capsule and the result of MCT oil on body composition is not yet clear. Third, the duration of the intervention period was relatively short. Finally, further work includes investigating the association of visceral fat and physical performance in HD patients are required. Further longitudinal studies with larger sample size and considering these limitations are required to determine the association between dietary fatty acids with body weight and body composition in patients with CKD. If the effect of omega-3 fatty acids in improving body composition and visceral fat levels is proven, omega-3 fatty acids supplements can be used as safe recommendations to improve the conditions of CKD patients undergoing hemodialysis.

Conclusion

This study indicates that there is insufficient evidence that provides a statistically significant benefit of omega-3 fatty acids supplementation on anthropometric measurements including bodyweight, BMI, body composition, muscle mass and fat mass in patients with CKD. The effect of ω -3 supplementation in reducing visceral fat was relatively significant. Further large-scale and long-term clinical trials are needed to confirm the obtained results.

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) .

Competing interests

The authors declare no competing interests.

Data availability:

Data available upon on request of corresponding author.

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Authors' contributions

SAT, ZR, AT, ZS, SM, SSH, ZSA, AA, HSH and SD designed the study, involved in the data collection, analysis, and drafting of the manuscript. SD, PM, FM, BB, MKH and MGH were involved in the design of the study, analysis of the data, and critically reviewed the manuscript. All authors read and approved the final manuscript.

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Figure 1: Flowchart of the study protocol

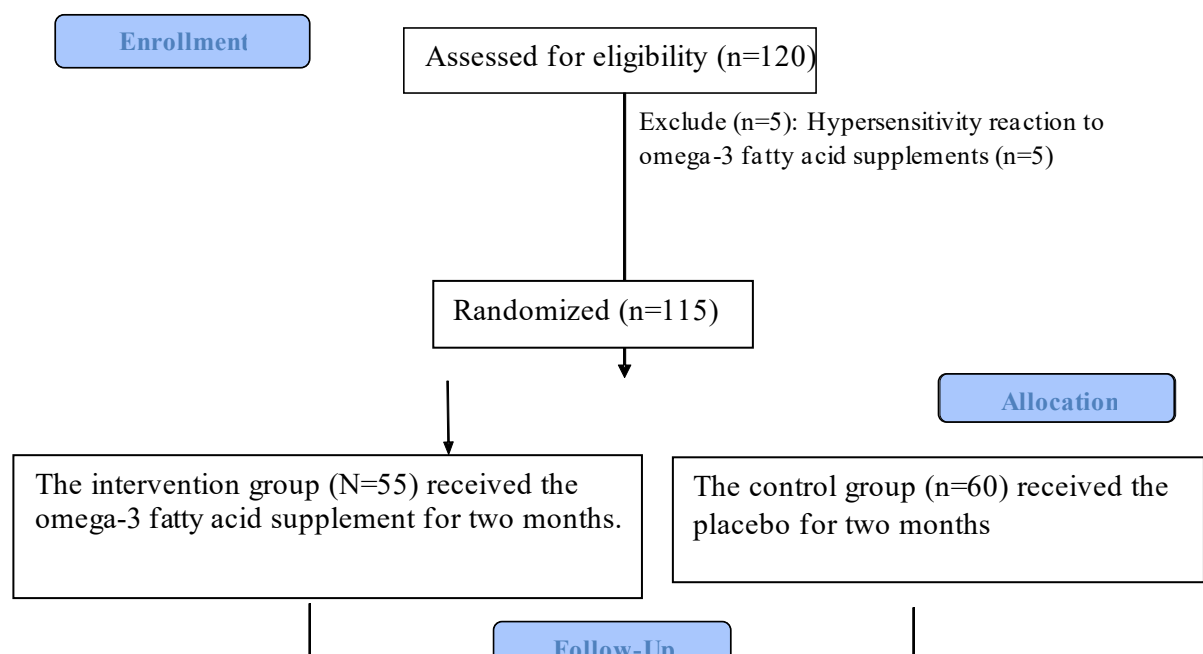


Table 1. The general characteristics of the participants at baseline(2)

	Intervention group	Control group	P
	N=55	N=60	
Age (y)	61.17±12.35	55.33±12.6	0.01
MET (kcal/kg*h)	1174.08±268.9	1315.25±243.42	0.004
Body water (kg)	48.80±5.94	48.5311±7.21	0.83
Body protein (kg)	17.42±3.78	18.07±5.13	0.44

Sleep duration (h)	7.99±2.51	7.95±2.52	0.95
Male, n (%)	30 (51.7)	37 (68.5)	0.08
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
Use Alcohol (y)	0 (0.0)	1 (1.8)	0.47
Family history of diabetes, n (%)	18 (41.9)	12 ((37.5)	0.64
Family history of hypertension, n (%)	8 (18.6)	9 (28.1)	0.15
Family history of heart disease, n (%)	9 (20.9)	4 (12.5)	0.81
Family history of CKD, n (%)	8 (18.6)	7 (21.9)	0.15
Weight (kg)	67.86±13.6	71.21±13.9	0.20
Height (cm)	164.28±9.32	167.18±9.01	0.09
Body Mass Index (kg/m ²)	25.6±4.26	25.45±3.83	0.46
Fat mass (kg)	31.57±9.59	29.41±8.02	0.48
Muscle mass (kg)	43.91±8.29	46.86±9.25	0.44
Visceral fat (kg)	10.16±3.49	11.08±4.46	0.16

CKD: Chronic kidney disease

Table 2: Comparison of biochemical 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*

Body Mass	25.6(4.26)	25.01(4.7)	25.45±3.83	24.75(3.80)	0.99	0.78
Index						
Fat mass	31.75(9.59)	30.28(9.4)	29.41(8.02)	27.82(8.75)	0.073	0.85
Muscle	43.91(8.29)	44.11(9.24)	46.86(9.25)	47.12(8.61)	0.032	0.78
mass						
Visceral fat	10.16(3.49)	10.02(3.71)	11.08(4.46)	10.95(4.24)	0.072	0.08

*Obtained using general linear model (GLM) repeated measure