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Effect of animal versus plant omega-3 polyunsaturated fatty acids on serum level of fetuin-A in patients with chronic renal failure; a randomized double-blinded parallel clinical trial

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ABSTRACT

Introduction: Low levels of fetuin-A in patients with chronic kidney disease (CKD) are associated with arterial stiffness, vascular calcification and cardiovascular mortality.
Objectives: The aim of the present study was to investigate and compare the effect of omega-3 supplements with plant (flaxseed) and animal origins on fetuin-A levels in patients with chronic renal failure.
Patients and Methods: In the present clinical trial, 90 patients with chronic renal failure (chronic kidney disease) were randomly divided into three groups. The first group received two grams of omega-3 tablets per day of animal origin (fish oil), the second group received 2 g of omega-3 tablets per day of plant origin (flaxseed oil), and the third group received one placebo per day as the control group. The duration of the drug treatment was 90 days. Before and after the intervention, blood levels of fetuin-A, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C) and triglyceride (TG) were determined. Data were analyzed by SPSS statistical software.
Results: Before and after the intervention, LDL-C and HDL-C levels were not significantly different in the study groups. In the animal origin omega-3 group, the levels of triglycerides and cholesterol decreased significantly after the intervention compared to before the intervention (P=0.004), however they did not change significantly in the plant origin omega-3 and control groups. Before and after the intervention, fetuin-A and ESR levels were not significantly different in the study groups. The frequency of positive CRP results in the animal and plant origin omega-3 groups was 20% and 24% respectively before intervention and 4% and 24% after intervention respectively, indicating a decrease in the levels of CRP in the animal origin omega-3 group.
Conclusion: Animal origin omega-3 is more effective in reducing serum lipids and CRP than plant-origin omega-3. Omega-3 supplements of plant or animal origin have been more effective in men than in women.
Trial Registration: The present study was registered in the Iranian Registry of Clinical Trials (identifier: IRCT20180820040839N1; https://www.irct.ir/trial/33581, ethical code: IR.SKUMS.REC.1396.94).

Original

Implication for health policy/practice/research/medical education:
In a randomized double-blinded parallel clinical trial on 90 patients with chronic kidney disease, we found animal origin omega-3 is more effective in reducing serum lipids and C-reactive protein than plant-origin omega-3.

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Introduction

Mortality from cardiovascular diseases in patients with chronic kidney disease (CKD) is 9% per annum, which is 30 times higher than that in the general population and even 10 to 20 times higher in patients with CKD following the age homogenization (1). In general, CKD patients are prone to ischemic heart diseases, heart failure, atherosclerosis, calcification, heart valves insufficiency and stenosis, and left ventricular structural and functional disorders (2). Calcification is an almost pervasive pathological process in patients with kidney disease and is the most common and perhaps clinically the most important problem in these patients (3).

In addition to dialysis and age, a number of risk factors for calcification have been identified, including diabetes mellitus, hypercalcemia, and hyperphosphatemia, doses of phosphorus chelators containing calcium, intact parathyroid hormone, increased levels of fibrinogen and serum C-reactive protein (CRP) and decreased levels of albumin, dyslipidemia, and hyperhomocysteinemia (4). The link between CRP and cardiovascular events is very strong in CKD patients and remains independent even after adjustment of a number of risk factors (5). It has been reported that blood lipids exacerbate calcification. Out of the body, low-density lipoprotein cholesterol (LDL-C) and several other lipid oxidation products increase the calcification of smooth vascular muscle cells (6).

Fetuin-A is a Hermans Schmidt alpha-2 glycoprotein that is made in the liver and plays an important role in bone formation (7). The anti-inflammatory effects of fetuin have been identified in several articles and it has been shown that fetuin-A is associated with decreased inflammatory response and increased life expectancy (8). It has also been said that low levels of fetuin-A as a negative acute phase protein have a strong association with the CRP inflammatory marker (9). There is ample evidence that shows fetuin-A plays a protective role against vascular calcification in dialysis patients (9). In fact, the deficiency of this protein is associated with increased mortality due to cardiovascular problems and atherosclerosis in these patients, which is the most common cause of death in them (10).

Omega-3 fatty acids are a family of unsaturated fatty acids whose first double-bond is between the third and fourth carbon in the carbon chain. Omega-3 fatty acids are essential for regulating some of the activities of the human body, but they are not made in the human body. Omega-3s are made up of three fatty acids; alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). ALA is found in walnuts, chia seeds, some beans, vegetables, soybean oil, canola oil, flaxseed/linseed, and olive oil. The other two fatty acids, EPA and DHA, are found in fish such as salmon, fish oil, and also in fish supplements (11). In patients with CKD, serum levels of omega-3 fatty acids are significantly lower than in the general population, which is possibly due to lower omega-3 intake in their diet, inflammation, malabsorption, metabolic changes, and loss of omega-3s during the dialysis process (12). Lack of omega-3 fatty acids in CKD patients is independently associated with an increased risk of cardiovascular diseases (13). Therefore, omega-3 supplements and dietary modification are a promising strategy for improving cardiovascular health in CKD patients (12). In non-dialysis CKD patients, omega-3 fatty acids are associated with lowering of blood pressure and inflammation, improving endothelial function, improving the fluidity of red blood cell membranes, and reducing the risk of end-stage renal disease (11). Apart from their preventive effects against vascular calcification and cardiovascular diseases, omega-3 fatty acids activate vitamin D, increase serum fetuin-A, and improve fetuin-A reserves in the erythrocyte membrane of CKD patients (14).

Objectives

Considering that flaxseed is a rich source of omega-3 of plant origin and unlike animal omega-3s is not contaminated with heavy metals and costs less to produce, the present study was designed to investigate and compare the effect of these two forms of omega-3s on the serum fetuin-A levels in patients with chronic renal failure.

Patients and Methods

Study design

In this randomized double-blinded parallel clinical trial, 90 chronic renal failure patients referring to Shahrekord clinic entered to the study. Inclusion criteria included being over 18 years old, having glomerular filtration rate between 15 and 60 cc/min, not consuming antioxidants and other supplements, not participating in other clinical trials, and not using anti-inflammatory drugs. Exclusion criteria included being sensitive to omega-3 products and being affected by infectious and inflammatory diseases. Patients were randomly divided into three groups of 30 people. In this study, all eligible patients were assigned to three groups using random sequence extraction from the computer (via www.randomization.com) and simple randomization. The resulting random numbers, i.e. the allocation of patients to groups, was concealed using sealed envelopes. In each group, patients were divided into three groups in terms of glomerular filtration rate, i.e. 15 to 30 cc/min, 30 to 45 cc/min, and 45 to 60 cc/min, based on which the three groups were matched. The first group received 2 grams omega-3 tablet per day of animal origin (fish oil), the second group received 2 grams omega-3 tablet per day of plant origin (flaxseed oil), and the third group received one placebo per day as the control group. The duration of medication was 90 days in all patients. Before and after the study, the blood levels of fetuin-A, CRP, erythrocyte sedimentation rate (ESR), LDL-C, high-density lipoprotein (HDL-C) and triglyceride (TG) were measured and recorded in a checklist. Patients from 1 to 90 divided randomly into three groups that every group had 30 members, then patients and data analyzer were blinded.

Ethical issues

The research conducted in accordance with the tenets of the Declaration of Helsinki. The institutional ethical committee at Shahrekord University of Medical Sciences accepted all study protocols (#IR.SKUMS.REC.1396.94). Accordingly, written informed consent was taken from all participants before any intervention. This study was part of internal medicine residential thesis of Elham Khodadustan at this university. The trial protocol was registered in the Iranian Registry of Clinical Trials (identifier: IRCT20180820040839N1; https://www.irct.ir/trial/33581).

Statistical analysis

Quantitative data were shown by mean and standard deviation, and qualitative data by number and percentage. Normality of studied variables was assessed by Kolmogorov-Smirnov test and histogram plot. One-way analysis of variance (ANOVA) was used to detect between group differences at baseline. To determine the effects of the intervention on biomarkers and antioxidant capacity, we used multivariate analysis of covariance (MANCOVA). P values < 0.05 were considered statistically significant. Additionally, intention to treat (ITT) approach was used for loss to follow up individuals. Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 18 (SPSS Inc., Chicago, IL, USA).

Results

In the present study, 90 chronic renal failure patients were enrolled in the study, however six individuals withdrew from the study in the first days due to drug intolerance. After 1-2 months, 4 people were excluded from the study due to gastrointestinal and dyspepsia problems, as well as 5 individuals due to infectious and inflammatory diseases, one patient due to intracranial hemorrhage and hospitalization in the ICU, and three participants due to uremic syndrome and the need for dialysis excluded from the study. Finally, 71 people took the drug regularly for 90 days (Figure 1). Accordingly 71 patients were divided into in three groups of 25 ones receiving animal omega-3, 25 ones receiving plant omega-3 (flaxseed oil), and 21 ones receiving placebo (Figure 1). The frequencies of females in the animal omega-3, plant omega-3, and placebo groups were 11%, 28%, and 39.4%, respectively, and the frequencies of males were 46%, 72%, and 60.6%, respectively. Additionally the groups did not differ significantly in terms of gender distribution (P = 0.337). The mean ages in animal omega-3, plant omega-3, and placebo groups were 60.92 ± 11.3 years old, 57.48 ± 9.87 years old, and 60.52 ± 10.40 years old, respectively, which did not differ significantly (P = 0.471). The results of the

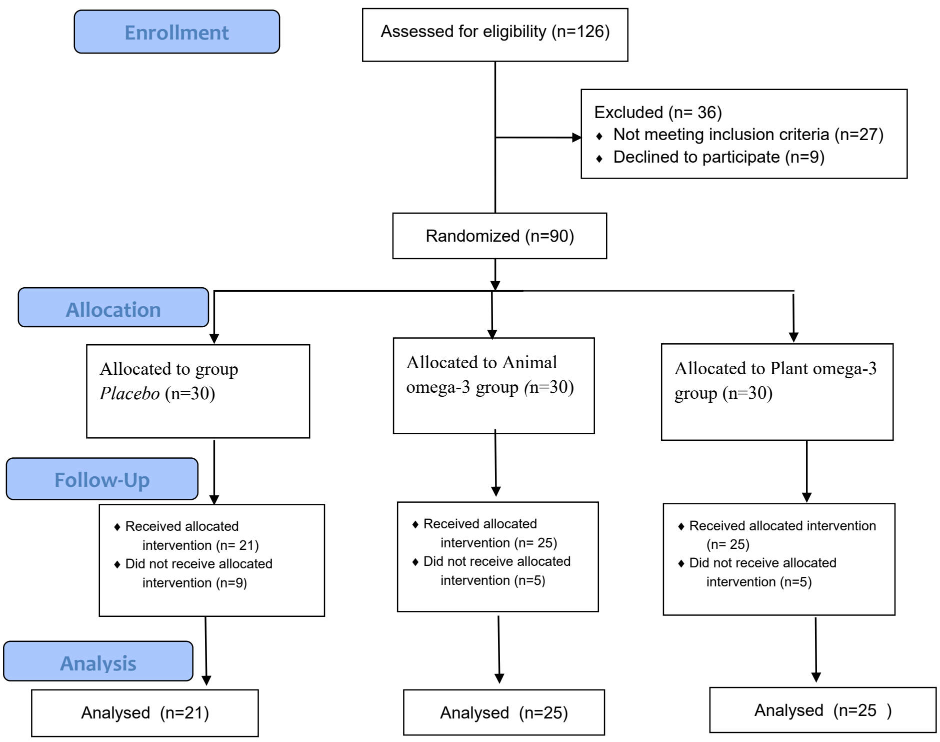

Figure 1. CONSORT flow diagram of study design.

Kolmogorov-Smirnov test showed that the distribution of data on height, weight, body mass index (BMI), plasma triglycerides, cholesterol, LDL-C, and HDL-C was normal, however it was not like the data of fetuin-A and ESR. According to the results of analysis of variance, the studied groups did not have a significant difference in weight, height, and BMI (Table 1).

According to the analysis of variance test, the levels of triglycerides, cholesterol, LDL-C, and HDL-C had no significant difference in the studied groups before the intervention ($P>0.05$, Table 2). Additionally, after the intervention, there was also no statistically significant difference in terms of triglycerides, cholesterol, and LDL-C and also HDL-C levels between the studied groups ($P>0.05$). According to the paired t test, in the animal omega-3 group, triglycerides and cholesterol levels decreased significantly after the intervention compared to before the intervention ($P=0.004$). In the plant omega-3 and control groups, the levels of triglycerides, cholesterol, LDL-C, and HDL-C did not differ significantly after the intervention compared to before of intervention ($P>0.05$).

Comparison of fetuin-A and ESR levels in the studied groups before and after the intervention is shown in Table 3. Before the intervention, the levels of fetuin-A and ESR had no significant difference in the studied groups using Kruskal-Wallis test ($P>0.05$). Likewise, after the intervention, there was no statistically significant difference in terms of fetuin-A and ESR levels between the studied groups ($P>0.05$). According to the paired t test, in the animal omega-3, plant omega-3, and placebo groups, the levels of fetuin-A and ESR did not differ significantly after the intervention compared to before the intervention ($P>0.05$).

The comparison of the frequency of CRP results in the studied groups before and after the intervention is shown in Table 4. Using the chi-squared test, the frequency of CRP results before the intervention did not differ significantly in the studied groups ($P>0.05$). Similarly, after the intervention, no statistically significant difference in the frequency of CRP results between the studied groups was detected ($P>0.05$). Before the intervention, five people (20%) from the animal omega-3 group and six people (24%) from the plant omega-3 group had a positive CRP result. After the intervention, one person (4%) from the animal omega-3 group and six people (24%) from the plant omega-3 group had a positive result.

The results of the covariance analysis test showed that none of the plant-derived or animal-derived omega-3s had a significant effect on the women participating in the present study (MANCOVA, Wilks' lambda $P>0.05$). However, these interventions were effective on male participants (MANCOVA, Wilks' lambda, $P=0.011$).

According to the data in Table 5, the use of animal and plant origin omega-3s in men reduced the serum levels of cholesterol, CRP, and fetuin-A and increased HDL-C serum levels while it did not have such an effect on women.

Table 1. Baseline comparison of mean and standard deviation of weight, height, and BMI in the studied groups

Group	Weight (kg)	Height (cm)	BMI (kg/m²)
Group 1	80.4±11.1	169.3±9.1	28.02±4.08
Group 2	74.9±14.0	167.2±10.8	26.54±3.7
Group 3	77.9±10.6	166.2±10.1	28.1±3.6
P value (between group differences)*	0.756	0.985	0.469

* Obtained from ANOVA.

Discussion

In the present study, we aimed to determine and compare the effect of omega-3 supplements with plant (flaxseed) and animal origins on the level of fetuin-A in patients

Table 2. Comparison of mean and standard deviation of serum lipids in the studied groups before and after the intervention

Variable	Level	Groups: Animal omega-3 Mean ± SD	Groups: Plant omega-3 Mean ± SD	Groups: Placebo Mean ± SD	P value
Triglycerides (mg/dL)	Before the intervention	178.680±	142.5±57.1	150.1±69.7	0.165
	After the intervention	145±58.5	144.4±85.5	136.8±58.6	0.907
	P value	0.004*	0.860	0.219	-
Cholesterol (mg/dL)	Before the intervention	157.3±46.2	148.6±34.5	148.9±42.2	0.706
	After the intervention	147±36.6	152.1±38.9	141.4±27.8	0.636
	P value	0.024*	0.596	0.379	-
LDL-C (mg/dL)	Before the intervention	82.68±25.7	81.9±30.4	80.6±33.3	0.978
	After the intervention	79.2±27.7	84.2±34.1	77.6±31.5	0.752
	P value	0.349	0.887	0.678	-
HDL-C (mg/dL)	Before the intervention	39.3±10.1	37.76±10.1	37.7±8.2	0.788
	After the intervention	38.6±9.5	37.72±8.7	37±7.86	0.809
	P value	0.553	0.976	0.641	-

* Indicates a significant difference at the level of $P<0.05$.

Table 3. Comparison of mean and standard deviation of fetuin-A and ESR in the studied groups before and after the intervention

Variable	Level		Groups			*P* value
			Animal omega-3	Plant omega-3	Placebo	
Fetuin-A (mg/L)	Before the intervention	Mean ± SD	1058.7±449.2	1118.8 ± 757.8	867.8 ± 263.4	0.106
		Median	972.7	875.3	785.7	
	After the intervention	Mean ± SD	1046.7 ± 689.4	1053.5 ± 608.3	963.2 ± 581.6	0.722
		Median	893.5	846.7	787	
	P value		0.619	0.527	0.821	-
ESR (mm/h)	Before the intervention	Mean ± SD	17.1 ± 18	24.1 ± 21.7	24.8 ± 20.4	0.206
		Median	9	19	24	
	After the intervention	Mean ± SD	19.5±18	21.9 ± 19.6	21.4 ± 16.6	0.907
		Median	14	20	20	
	P value		0.367	0.119	0.219	-

Table 4. Comparison of the frequency of CRP results in the studied groups before and after the intervention

Groups	Before the intervention					After the intervention			
	Negative	Trace	+1	+2	+3	Negative	Trace	+1	+2
Animal omega-3	20	0	4	1	0	24	1	0	0
Plant omega-3	19	1	2	2	1	19	2	2	2
Placebo	17	4	0	0	0	19	1	0	1
P value	0.906*					0.091*			

*According to the size of the data, the statistical test was based on negative and positive classification.

Table 5. Comparison of variables between males and females

Gender	Variable	Placebo group	Animal omega-3 group	Plant omega-3 group	*P* value
Male	TG (mg/dL)	10.27±23.9	-20.93±20.14	-17.71±19.48	0.276
	TC (mg/dL)	0.45±23.5	-16.32±24.96	-12.20±26.95	0.045
	LDL-C (mg/dL)	-0.14±23.5	-4.23±25	-5.33±30.04	0.665
	HDL-C (mg/dL)	0.05±24.5	10.55±29.1	13.55±28.9	0.036
	CRP (mg/L)	0.35±12.1	-16.14±18.18	-12.33±10.3	0.01
	Fetuin-A (mg/L)	10.86±23.5	-68.12±23.5	-24.13±18.23	0.038
Female	TG (mg/dL)	12.24±13.9	-10.63±18.14	-20.11±17.45	0.173
	TC (mg/dL)	0.32±23.5	-10.20±14.56	-12.45±22.43	0.133
	LDL-C (mg/dL)	0.11±24.6	-3.23±12.1	-5.03±25.04	0.298
	HDL-C (mg/dL)	-0.10±24.5	8.55±24.1	10.35±28.9	0.235
	CRP (mg/L)	0.15±10.1	-14.14±15.18	-13.43±12.3	0.467
	Fetuin-A (mg/L)	9.64±23.5	-18.12±13.5	-25.43±20.23	0.698

[a] Numbers are the percentage of change in each of the variables.

Note: Result of MANCOVA, Wilks' lambda test indicated significant effects of interventions on men (P=0.011) and non-significant effects of interventions on women (P>0.05).

with chronic renal failure. In our study, 71 patients were divided into three groups of 25 animal omega-3, 25 plant omega-3 (flaxseed oil), and 21-individual placebo. According to the results, before and after the intervention, the levels of triglycerides, cholesterol, LDL-C, HDL-C, fetuin-A, ESR, and CRP were not significantly different in the studied groups. In the animal omega-3 group, triglycerides and cholesterol levels decreased significantly after the intervention compared to before the intervention, however no significant changes were observed in the plant omega-3 and control groups. In the animal omega-3 group, the levels of triglycerides and cholesterol decreased by 33.6 and 10.3 mg/dL, respectively, while they did not significantly change in the plant omega-3 group. These results show that the use of animal omega-3s has a better effect on reducing triglycerides and cholesterol levels than plant omega-3s.

Similar results were obtained in a comparative study by Hodson et al in 2018. In this study, 303 healthy female volunteers were treated with fish oil and flaxseed oil for 14 days and then serum lipid levels were determined. After 14 days, serum triglycerides levels decreased significantly in fish oil group, while in flaxseed oil group, no significant change was observed in triglycerides levels (15). In a meta-analysis and systematic review study by Balk et al, the effectiveness of animal omega-3 (fish oil) and plant omega-3 in lowering serum lipids were evaluated. In 21 evaluated studies, fish oil significantly changed the levels of triglycerides, LDL-C, and HDL-C. The highest changes were observed in high doses of fish oil and in people with higher serum lipid levels, and the highest change was in serum triglycerides. Studies have not shown a significant reduction in serum lipids following the use of plant oils (16).

The effectiveness of fish oil in reducing serum lipids in CKD patients has been shown in a number of studies. In a study by Ateya et al in 2017, 49 hemodialysis children who were treated with one gram of omega-3 capsules (fish oil) per day for 16 weeks. The results showed that in hemodialysis children, omega-3 significantly reduced serum cholesterol (17). In a study on 80 patients with CKD in 2010, Bouzidi et al reported that daily intake of 2 grams of fish oil omega-3 for 90 days was associated with a significant reduction in serum triglycerides levels in the first, second, and third months as well as a significant reduction in serum cholesterol in the third month, with no significant change in LDL-C and HDL-C levels, which are consistent with the present results (18). Additionally, Donnelly et al evaluated the effectiveness of fish oil omega-3 in comparison with placebo (olive oil) and reported a significant decrease in serum triglycerides levels following fish oil consumption (19). Studies have also shown that serum levels of poly unsaturated fatty acids (PUFAs) such as EPA, and DHA are significantly reduced in CKD patients (13) and there is a significant and inverse relationship between serum triglycerides levels with EPA and DHA content (20).

Our study showed, after the intervention by fish oil, the frequency of positive result of CRP decreased, which indicates the effectiveness of fish oil in reducing CRP. However, before and after the intervention, no significant difference was observed between the frequency of CRP results in the placebo group and plant omega-3. In a study by Saifullah et al in 2007, the intake of fish oil omega-3 supplement of 1.3 g/d for 12 weeks was associated with a significant decrease in serum CRP of hemodialysis patients (21). A study of the elderly found that consuming 720 g of high-fat fish and 15 milliliters of fish oil per week was associated with a significant reduction in serum CRP after 12 weeks (22). In a systematic review and meta-analysis study by Balk et al in 2006, it was reported that fish oil intake had no significant effect on serum CRP in four studies (16).

In CKD patients, various inflammatory processes lead to lipid disorders (increased saturated fatty acids and decreased levels of supersaturated fatty acids (PUFA)) and also exacerbate inflammation and cause atherosclerosis (19). In addition, in CKD patients, the metabolism of arachidonic acid changes from cyclooxygenase to lipoxygenase, which is associated with the production of more inflammatory mediators. High levels of EPA and DHA can stop the production of arachidonic acid from the lipoxygenase pathway and activate the cyclooxygenase pathway, which ultimately leads to the production of prostaglandin E2 that has less inflammatory activity than leukotriene B4 (23). Activation of the peroxisome proliferator-activated receptor alpha (PPARA) may also be another mechanism involved in reducing the expression of inflammatory markers following omega-3 supplementation (24). The anti-inflammatory effects of omega-3 fatty acids in fish oil have been shown in a number of animal studies (25) as well as in human studies (19,21).

In our study, fish oil did not significantly change the levels of serum fetuin-A in CKD patients. So far, the effectiveness of fish oil on serum fetuin-A has been investigated in a study by An et al in 2012. In this study, 47 hemodialysis patients were treated with fish oil for 6 months at a rate of 3 g/d. The final results showed that fish oil significantly increased serum fetuin-A and improved fetuin-A reserves in erythrocyte membranes (14).

The reason for the discrepancy between the present results and the findings of An et al can be due to the differences in populations assessed in terms of various factors such as age, body mass index, dialysis, disease duration, as well as omega-3 consumption duration and its quality used in terms of APA and DHA content. It is recommended that in future studies with a larger sample size, the effectiveness of animal omega-3s on fetuin-A be reassessed.

According to the results of our study, flaxseed oil did not have a significant effect on inflammatory parameters and serum lipids in CKD patients. In the present study, unlike the above studies, flaxseed oil did not significantly change the levels of CRP and serum lipids. The reason for this difference could be due to the lower dose of flaxseed oil in the present study (2 g daily) compared to the above studies (6 g daily). In a study by Lemos et al in 2012, 160 hemodialysis patients were treated with 2 g of flaxseed oil or placebo per day for 120 days. The results of this study showed that consumption of flaxseed oil reduces CRP and inflammation in hemodialysis patients (26). The reason for the difference between the present results and the findings of Lemos et al can be due to the shorter course of treatment in the present study (90 days) compared to the above-mentioned study (120 days) (26). A meta-analysis study by Ren et al in 2016 evaluated the studies conducted on the effectiveness of flaxseed products in reducing CRP. The results showed that flaxseed products were not effective in reducing CRP levels. Significant inconsistencies were observed in most studies. Regression analysis showed that BMI is an important source of heterogeneity (P-interaction = 0.032), hence a significant decrease in CRP levels of 0.83 mg/dL (95% confidence interval from -1.34 to -0.31, P = 0.002) was observed in people with BMI greater than 30 kg/m^2. The researchers concluded that there was insufficient evidence for the effectiveness of flaxseed products (oils and lignans) in reducing CRP in blood, although there was evidence showing that flaxseed products were effective in reducing the CRP of obese people (27). In a systematic review and meta-analysis study in 2019, Ursoniu et al stated that flaxseed products did not have a significant effect on reducing CRP in 16 studies including 1256 individuals (28).

The studies conducted by Ursoniu et al in 2016 were evaluated in a meta-analysis study regarding the effectiveness of flaxseed supplements in lowering blood pressure. When the studies were reviewed according to the type of supplement and the duration of the intervention, the best effectiveness was observed in the intervention period of more than 12 weeks. In addition, flaxseed powder has been shown to significantly reduce blood pressure, but the oil and its extract have no significant effect. The researchers have attributed the different efficacy of flaxseed supplements, including powder, oil, and extract, to their differences in fiber content, viscosity, and effect on bile acids metabolism (29). Increased intraluminal viscosity after consumption of flaxseed has been shown to limit the absorption of bile acids, which increases the hepatic synthesis of bile acids and can limit the formation of micelles, thereby reducing fat absorption (30).

Conclusion

According to the study results, fish oil treatment did not significantly change the levels of LDL-C, HDL-C, fetuin-A, and ESR, however it significantly reduced triglycerides and cholesterol levels. Flaxseed oil had no significant effect on serum lipid levels and inflammatory factors. The frequency of positive CRP results in the animal and plant omega-3 groups was 20% and 24% before intervention and 4% and 24% after intervention, which indicates a decrease in positive results in the animal omega-3 group compared to the plant one. The use of omega-3s of animal and plant origins has been shown to reduce serum cholesterol, CRP, and fetuin-A levels in men and increase serum HDL-C levels. However, it did not have such an effect on women.

Limitations of the study

This study was conducted on a limited number of patients. We suggest further studies on this subject.

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Authors' contribution

EKH, TJ, AHD and LM were the principal investigators of the study. AHD, TJ, and LM were included in preparing the concept and design. MK, AM and MRM revised the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that Barij Essence Company had no role in the design and conduct of the study; collection of the data, and analysis aof the data. The authors had no financial and other relationships with Barij Essence Company.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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