Potential Effects of Omega-3 Fatty Acids on Insulin Resistance and Lipid Profile in Maintenance Hemodialysis Patients

A Randomized Placebo-Controlled Trial

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Introduction. Insulin resistance (IR), a risk factor for cardiovascular disease and all-cause mortality, is prevalent among maintenance hemodialysis patients. Effects of omega-3 fatty acids on IR in hemodialysis patients have not been well understood. This study aimed to determine the effects of omega-3 fatty acids on IR and serum lipids of hemodialysis patients.

Materials and Methods. Fifty-four adult patients on hemodialysis were randomly assigned to receive either 1800 mg of omega-3 fatty acids or placebo daily for 4 months. Serum concentrations of glucose, triglyceride, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, C-reactive protein, insulin, leptin, and adiponectin were measured at baseline and after 4 months of the intervention. Insulin resistance was assessed using the homeostasis model assessment of insulin resistance and 2 adipokine-based measures of IR, including the leptin-adiponectin ratio and homeostasis model assessment corrected by adiponectin.

Results. Mean differences of serum C-reactive protein, insulin, leptin, and adiponectin concentrations did not show significant difference between the two groups following 4 months of intervention. Fasting serum glucose and low-density lipoprotein cholesterol were not significantly influenced by omega-3 supplementation, either. Serum triglyceride, total cholesterol, and high-density lipoprotein cholesterol levels significantly decreased in the omega-3 group ($P = .02$, $P = .03$, and $P < .001$, respectively). None of the indirect indexes of IR showed significant changes at the end of the study in either the omega-3 or placebo group.

Conclusions. Supplemental use of omega-3 fatty acids showed some beneficial effects on lipid profile of hemodialysis patients without any improvement in IR.

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INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death in patients on dialysis.[1] In addition to the traditional cardiovascular risk factors mentioned in the Framingham study, uremic state and dialysis-associated metabolic perturbations such as insulin resistance (IR), chronic inflammation, and enhanced oxidative stress burden contribute to advanced atherosclerosis yielding a life expectancy that is 25 to 30 years less than that in the healthy individuals.[2] Iinsulin resistance is highly prevalent among maintenance hemodialysis

patients and has been established as a major risk factor for the development of CVD and all-cause mortality among this patient population.[3,4] It occurs early in end-stage renal disease patients and is characterized by alteration in carbohydrate metabolism, hyperinsulinemia, dyslipidemia, and a pro-inflammatory state with altered serum concentrations of adipocytokines.[5]

There is a complex relationship between uremia and impaired glucose metabolism. Generally, abnormal glucose metabolism can be caused by impaired insulin secretion, impaired insulin sensitivity, or both.[6] It has been demonstrated that the predominant feature of abnormal glucose metabolism in hemodialysis patients is reduced insulin sensitivity, resulting from a postreceptor defect mainly in the skeletal muscle, named "uremic insulin resistance.[7]" Besides uremic toxins, other important factors contributing to the development of IR in end-stage renal disease patients may include chronic inflammation, altered adipocytokines (adiponectin, leptin, and resistin) metabolism, extravisceral fat mass, metabolic acidosis, vitamin D deficiency, oxidative stress, anemia, uncontrolled secondary hyperparathyroidism, and physical inactivity.[6] Given the strong association between IR and poor clinical outcomes, strategies directed towards prevention or improvement of IR might thus represent useful interventions for improved clinical outcomes in hemodialysis patients.

Fish oil, a rich source of long-chain omega-3 polyunsaturated fatty acids (omega-3 PUFA) has been cited in a large amount of literature for its benefits on quality of life,[8] depression,[9] cardiovascular protection, immune modulation, and lowering serum triglycerides.[10] Additional potential mechanisms responsible for cardiovascular protection my include decreased thrombotic tendency, lowering blood pressure, anti-arrhythmic effects, anti-inflammatory effects, improved vascular endothelial function, enhanced plaque stability, and improved insulin sensitivity.[11-13] While the mechanisms of therapeutic effects are complex, inhibition of the formation of eicosanoids from arachidonic acid largely contributes to their anti-inflammatory action.[14] Moreover, there exists evidence in favor of peroxisome proliferator-activated receptor γ (PPARγ)-like effects of omega 3-PUFA, yielding improved insulin sensitivity.[15] Positive as well as negative findings have been attained in the clinical investigations regarding the effects of omega-3 PUFA on IR.[16,8] However, effects of omega-3 PUFA on IR in hemodialysis patients have not yet been elucidated. We aimed to determine the potential effects of omega-3 PUFA on IR and serum lipids in maintenance hemodialysis patients.

MATERIALS AND METHODS

Patient Population

This randomized single-blinded placebo-controlled trial included 45 adult patients who had been on regular hemodialysis for at least 3 months. All patients received hemodialysis treatment for 4 hours, 3 times weekly, using a low-flux polysulfone hollow-fiber dialysis membrane and bicarbonate buffered dialysis solution. We excluded patients with malfunctioning hemodialysis vascular access, pregnancy, active inflammatory or infectious diseases, malignancy, chronic obstructive pulmonary disease, asthma, medical or surgical illness within 3 months of enrollment, thyroid disorders, psychiatric disorders, coagulopathies, warfarin therapy, malabsorption syndrome, consumption of fish oil during the past 3 months, allergy to fish or fish-derived products, and receiving corticosteroid, immunosuppressive, immunomodulator, or nonsteroidal anti-inflammatory therapy. The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran and was submitted to the Iranian Registry of Clinical Trial (ID number, IRCT201202203043N5). All pparticipants signed written informed consents forms.

Study Protocol

We used permuted-block randomization to randomize participants into the omega-3 or placebo group. All of the participants, care providers, and data monitors were unaware of the intervention assignment throughout the study. The omega-3 group received 1800 mg of omega-3 PUFA (6 soft-gel capsules, each containing 180 mg of eicosapentaenoic acid and 120 mg of docosahexaenoic acid) daily for 4 months, while the placebo group was treated with identically packaged soft-gel capsules of paraffin oil. Both the omega-3 and the matching placebo capsules were supplied by Zahravi Pharmaceutical Company, Tabriz, Iran. The participants were requested to

maintain their ongoing dietary and medications regimen, and physical activity throughout the study period. Patient compliance was ascertained by performing patient interview individually 3 times weekly and the pill counting practice. In addition, to reminders for adherence, all of the participants were visited monthly by a resident nephrologist during their routine hemodialysis treatment. Any alterations in drug regimens and reports of adverse effects were recorded during the study.

After a 10-hour overnight fasting, predialysis blood sample (10 mL) was taken from all the patients at the beginning and the end of the study. Sera were separated by centrifuging blood samples at 3000 g for 10 minutes at room temperature, and then frozen at -70°C for later biochemical analysis. The measured parameters included serum concentrations of glucose, triglyceride, total cholesterol, low-density lipoprotein cholesterol (LDLC), high-density lipoprotein cholesterol (HDLC), C-reactive protein (CRP), insulin, leptin, and adiponectin.

Measurements

Dialysis adequacy (KT/V) was measured for each patient from predialysis and immediate postdialysis blood urea nitrogen concentrations according to a formal single-compartment model of hemodialysis urea kinetics.

Serum glucose, total cholesterol, triglyceride, LDLC, and HDLC were measured by a routinely applied clinical biochemistry procedures using a conventional auto-analyzer (Autoanalyzer BT3000, Biotechnica, Italy). Serum CRP level was measured by a turbidimetric method (Autoanalyzer BT3000, Biotechnica, Italy). Serum adiponectin and leptin levels were measured by an enzyme-linked immunosorbent assay method using Mediagnost kits (Gesellschaft für Forschung und Herstellung von Diagnostika GmbH, Reutlingen, Germany). Serum insulin level was measured by an enzyme-linked immunosorbent assay method using DiaMetra kit (DiaMetra Co, Italy).

Insulin resistance was assessed by the homeostasis model assessment of insulin resistance (HOMA-IR) using fasting serum glucose and insulin concentrations, and according to the formula:

Insulin resistance = fasting plasma glucose (mg/dL) × fasting plasma insulin (μIU/mL)/405.

Two additional IR indexes determined were as follows:

HOMA-adiponectin = fasting plasma glucose (mg/dL) × fasting plasma insulin (μIU/mL)/405 × adiponectin (μg/mL)

Leptin-adiponectin ratio (LAR) = leptin (ng/mL)/adiponectin (μg/mL)

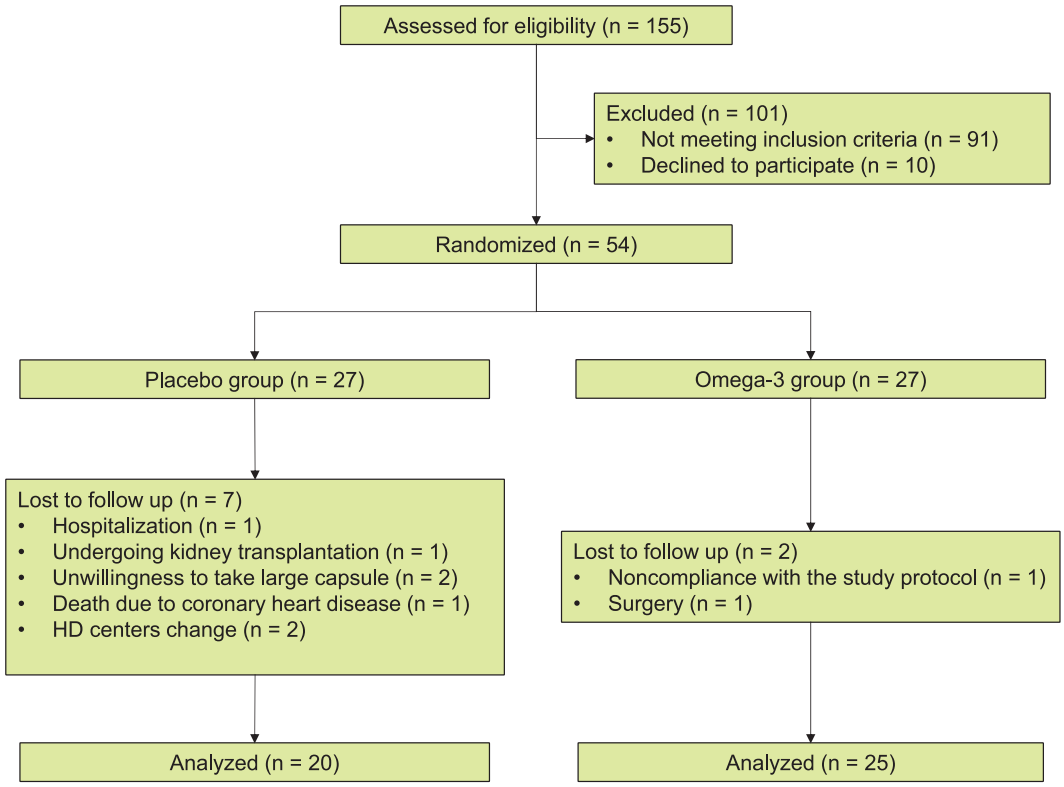
Statistical Analysis

Continuous data were expressed as mean ± standard deviation or median (interquartile range), as appropriate. Categorical data were presented as number and percentage. The normality of the distribution for continuous variables was assessed through the Shapiro-Wilk test. The Student *t* test was used to compare variables with a normal distribution, while Mann-Whitney U test or Wilcoxon signed ranks test was utilized to compare nonparametric continuous variables. Between-group comparison of categorical variables was performed using the chi-square test or the Fisher exact test. The statistical analyses were performed using the SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, IL, USA), and significance was defined as a *P* value less than .05.

RESULTS

The study process flowchart is depicted in the Figure. Of 155 patients screened for the study, 64 were eligible. Of those, 44 agreed to participate and signed written informed consent. There were 9 exclusions (7 in the placebo and 2 in the omega-3 group) after the randomization and during the therapy period; thus, 45 patients finished the study and their data were included in the final analysis.

The baseline demographic and clinical characteristics of the two groups are summarized in Table 1. As shown, there were no significant differences in the variables between the two groups. Notably, the two groups were matched regarding the concurrent medications with potential effects on lipid profile and IR (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and statins). None of the study patients was receiving fibric acid derivatives. As illustrated in Table 2, the mean differences of serum insulin, leptin, adiponectin, and were similar between the two groups following 4 months of the intervention period.



Patients' screening and randomization procedure

Fasting plasma glucose and LDLC were not significantly influenced by omega-3 supplement compared with the placebo group. Serum triglyceride levels were significantly reduced in the omega-3 supplemented group compared with the placebo group (P = .02). Serum total cholesterol significantly decreased in the omega-3 group (P = .03) and remained unchanged in the placebo group; however, the amount of reduction in the omega-3 group was not significant compared with the placebo group (P = .06). Serum levels of HDLC remained unchanged in the placebo group after 4 months, whereas its level showed a significant decrease in the omega-3 group (P = .001). Between-

Table 1. Demographic and Clinical Data of Participants at Baseline*

Characteristics	Participants Groups		*P*
	Placebo (n = 20)	Omega-3 (n = 25)	
Age, y	57.2 ± 15.19	56.8 ± 13.09	.90
Sex			.59
Female	8 (40)	12 (48)	
Male	12 (60)	13 (52)	
Months on dialysis	72.05 ± 60.51	59.88 ± 45.69	.45
Dialysis adequacy (KT/V)	1.27 ± 0.15	1.39 ± 0.22	.06
Cause of end-stage renal disease			.62
Diabetes	7 (35)	12 (48)	
Hypertension	8 (40)	9 (36)	
Other causes	5 (25)	4 (16)	
Concomitant medications with possible interaction			
Angiotensin-converting enzyme inhibitors	7 (35)	7 (28)	.61
Angiotensin receptor blocker	9 (45)	13 (52)	.64
Statin	7 (35)	8 (32)	.83

*Values are mean ± standard deviation for continuous variables and frequency (percentage) for categorical variables.

Table 2. Serum Concentrations of Insulin, Adipocytokines, C-Reactive Protein, and Cytokines in the Omega-3 and Placebo Groups*

Factor	Placebo (n = 20)			Omega-3 (n = 25)			*P* overall
	Baseline	Month 4	*P*	Baseline	Month 4	*P*	
C-reactive protein, mg/L							
Mean ± SD	7.73 ± 4.89	12.69 ± 14.02		9.24 ± 8.79	8.00 ± 6.78		.14
Median (IQR)	6.19 (4.79, 8.93)	6.26 (3.55, 18.81)	.25	6.23 (4.87, 10.26)	5.91 (3.25, 10.72)	.41	
Insulin, μIU/mL							
Mean ± SD	13.58 ± 11.69	9.54 ± 6.55		14.65 ± 11.86	12.62 ± 12.54		.55
Median (IQR)	11.70 (5.28, 18.63)	9.98 (4.55, 11.65)	.37	11.40 (5.40, 19.70)	10.30 (3.70, 15.60)	.21	
Leptin, ng/mL							
Mean ± SD	25.40 ± 28.61	20.66 ± 25.69		17.62 ± 19.70	25.05 ± 23.60		.11
Median (IQR)	14.40 (3.58, 39.73)	9.70 (3.43, 31.63)	.88	8.70 (2.70, 24.70)	14.90 (5.00, 42.60)	.17	
Adiponectin, μg/mL							
Mean ± SD	15.08 ± 14.37	27.49 ± 28.35		24.79 ± 23.62	27.64 ± 22.64		
Median (IQR)	7.27 (4.84, 21.28)	13.58 (2.65, 47.30)	.35	12.76 (2.53, 49.97)	23.44 (5.54, 46.97)	.70	.68

*SD indicates standard deviation and IQR, interquartile range.

group comparison of the HDLC level also showed a significant reduction in the omega-3 group compared with the placebo group ($P < .001$; Table 3).

None of the indirect indexes of IR showed significant changes at the end of the study in either the omega-3 supplemented group or the placebo group (Table 3).

During the study period, participants did not complain of any serious side effects with the issued soft-gel capsules leading to patient withdrawal. However, mild transient gastrointestinal complaints including fishy aftertaste, nausea, burping, and

Table 3. Metabolic Parameters and Peripheral Insulin Resistance Indexes in the Omega-3 and Placebo Groups*

Factor	Placebo (n = 20)			Omega-3 (n = 25)			*P* overall
	Baseline	Month 4	*P*	Baseline	Month 4	*P*	
FBG, mg/dL							
Mean ± SD	143.22 ± 112.69	124.17 ± 104.95		156 ± 109.35	121.60 ± 48.68		
Median (IQR)	105.50 (88.50, 140.50)	75.50 (69.25, 142.75)	.09	117.00 (77.25, 194.75)	114.50 (75, 152)	.07	.95
Triglyceride, mg/dL							
Mean ± SD	165.78 ± 92.20	169.06 ± 57.05	.85	169.10 ± 94.90	139.95 ± 66.63		.02
Median (IQR)	138.50 (83.25, 217)	172.00 (124, 202.50)		162.00 (87, 198)	135 (91, 149)	.15	
Cholesterol, mg/dL							
Mean ± SD	157.72 ± 35.64	161.50 ± 31.31	.64	167.38 ± 46.41	156.33 ± 57.92	.03	.06
Median (IQR)	150.50 (144.25, 169.25)	158.50 (134.25, 186.50)		161.00 (134, 198)	148 (118, 175)		
LDLC, mg/dL							
Mean ± SD	89.39 ± 32.05	84.72 ± 29.37		99 ± 46.34	79.95 ± 26.19		.60
Median (IQR)	95.00 (81.25, 107.50)	74.50 (63.25, 101.75)	.42	87.00 (74.50, 104.50)	79 (56.50, 99)	.07	
HDLC, mg/dL							
Mean ± SD	37.17 ± 15.60	42.94 ± 11.37		48.47 ± 18.52	33.58 ± 7.82		< .001
Median (IQR)	38.50 (22.75, 51.50)	42.00 (35.25, 50.75)	.16	42.00 (36, 54)	32 (30, 34)	.001	
HOMA-IR							
Mean ± SD	5.25 ± 6.32	2.81 ± 3.22		6.21 ± 5.88	4.37 ± 5.26		.88
Median (IQR)	3.69 (1.09, 6.35)	1.74 (0.99, 2.82)	.09	4.05 (0.92, 10.40)	2.96 (1.19, 4.69)	.11	
HOMA-AD							
Mean ± SD	0.827 ± 1.171	0.891 ± 1.680		2.053 ± 3.780	3.846 ± 11.349		
Median (IQR)	0.268 (0.11, 1.16)	0.14 (0.03, 0.75)	.37	0.19 (0.08, 1.48)	0.086 (0.06, 0.51)	.30	.63
LAR							
Mean ± SD	3.765 ± 5.037	6.027 ± 12.550		5.061 ± 8.507	4.687 ± 10.965		
Median (IQR)	1.41 (0.31, 4.81)	1.23 (0.23, 6.40)	.60	0.70 (0.16, 6.02)	1.23 (0.34, 2.22)	.64	.89

*FBG indicates fasting blood glucose; SD, standard deviation; IQR, interquartile range; HDLC, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-AD, homeostasis model assessment corrected by adiponectin; HOMA-IR, homeostatic model assessment for insulin resistance; and LAR, leptin to adiponectin ratio.

loose stool were the frequently reported side effects, which mostly occurred in omega-3 treated patients. Furthermore, adherence to omega-3 or placebo soft-gel capsules was good, since the count of returned soft-gel capsules was less than 10%.

DISCUSSION

To explain IR, several hypotheses have been proposed: first, excess generation of endogenous pro-inflammatory factors such as oxidative stress byproducts,[17] homocysteine,[18] and increased lipoprotein(a) levels,[19] and exogenous pro-inflammatory factors such as silent chronic infections by bowel bacteria,[20] infected vascular access prostheses, and intravenous iron therapy;[21] second, enhanced adipose tissue,[22] owing to extra caloric intake, resulting in a defective circle with elevated production of adipokines (leptin, resistin) and other pro-inflammatory factors such as tumor necrosis factor-α, interleukin-6, and nuclear factor kappa b.[23] These chemokines work as chemotactic mediators for macrophages and monocytes, thus causing continued IR.[24]

Cardiovascular benefits of omega-3 PUFA (namely, eicosapentaenoic acid and docosahexaenoic acid) have been widely reported in literature.[12,13] According to in vitro and in vivo findings, omega-3 PUFA may improve insulin sensitivity by PPARγ and PPARα stimulatory effects.[15] Human studies have yet generally failed to clearly indicate improved insulin sensitivity by omega-3 supplement[10]; however, our study was performed to determine potential effects of omega-3 PUFA on IR in hemodialysis patients.

According to the results, serum CRP did not decrease significantly by omega-3 supplement. It should be noted that results of the majority of the studies evaluating the effects of omega-3 PUFA on inflammatory markers in hemodialysis patients are inconclusive, largely due to diverse study design, supplement dosages, and study length. Saifullah and colleagues showed that daily administration of 1.3 g of omega-3 fatty acids for 12 weeks induced a significant reduction in serum CRP level of hemodialysis patients.[25] Bowden and colleagues treated hemodialysis patients with 1560 mg of omega-3 PUFA per day for 6 months, and found a significant decrease in serum CRP level.[26] Conversely, a recent study by Kooshki and colleagues failed to demonstrate any effects of omega-3 PUFA (2080 mg/d for 10 weeks) on serum CRP level in hemodialysis patients.[27] In addition, use of omega-3 PUFA for 4 months in our study caused no significant changes in the serum level of insulin, leptin, and adiponectin. A number of clinical studies have been conducted with omega-3 PUFA, using different supplement dosages, in diverse subgroups of patients including chronic kidney disease patients; however, none of them have yet been able to show clear effects of omega-3 PUFA on IR markers. Rasic-Milutinovic and colleagues demonstrated a significant reduction in fasting insulin level of hemodialysis patients after ingestion of 2.4 g omega-3 PUFA daily for eight weeks.[28] Spencer and colleagues performed a randomized placebo-controlled study to determine potential ameliorative effects of omega-3 PUFA on adipose tissue inflammation in non-diabetic obese patients with the metabolic syndrome and IR. After 12 weeks of intervention period with 4 g omega-3 PUFA, although adipose tissue inflammation reduced in the omega-3-treated subjects, no changes were observed in serum levels of adiponectin and leptin.[10] Similarly, in a recent study by Koh and colleagues, omega-3 treated IR subjects experienced no effects on plasma adiponectin level or IR.[29]

Adipose tissue, specifically visceral fat, functions as an active endocrine organ secreting adipocytokines and inflammatory mediators.[30,31] In hemodialysis patients, decreased renal clearance and altered secretory patterns of adipocytokines lead to the accumulation of these cytokines, playing a crucial role in the metabolic derangements and IR.[6] Adiponectin exerts insulin-sensitizing effects through the activation of AMP-activated protein kinase, which raises fatty acid oxidation and activates PPAR α.[32] In end-stage renal disease patients, the role of adiponectin in the prediction of poor outcomes has been contradictory and controversial,[33,34] and it has been presumed that greater levels of total or specific isoforms are reflective of either a counterbalance response to running injury or the presence of comorbidities.[6] Leptin mediates secretion of tumor necrosis factor-α and interleukin-6,[35] enhances formation and accumulation of reactive oxygen species,[36] and stimulates the synthesis of transforming growth factor-β.[37] Thus, the ability of leptin to advance cytokine signaling and growth factors might contribute to IR, endothelial dysfunction,

and atherosclerosis in hyperleptinemic conditions such as in end-stage renal disease.[38] Considering our results, the mean baseline concentrations of adiponectin in both groups, although being within the normal range (5 µg/mL to 30 µg/mL),[39] remained unchanged at the end of the study period. Although one of the main effects of omega-3 PUFA is the stimulation of adiponectin gene in adipose tissue, likely by working as ligands of PPARγ, omega-3 PUFA failed to increase adiponectin level significantly in our study. Reportedly, the extent of leptin accumulation is greater than that of adiponectin in advanced chronic kidney disease, leading to a high LAR in comparison with the general population;[40] However, neither serum leptin nor LAR changed significantly by omega-3 PUFA supplementation. It was possible that the dose of omega-3 PUFA, duration of supplementation, health status of the study patients, and presence of other uncontrolled conditions might contribute to these inconsistent results.

Given the strong correlation between the IR and clinical outcomes in advanced chronic kidney disease, its estimation requires accuracy and precision, particularly in chronic hemodialysis patients. Although hyperinsulinemic euglycemic clamp provides such accuracy in the sophisticated research setting and is considered the gold standard to measure insulin sensitivity, clamp studies are invasive, cumbersome, time-consuming, and expensive, and thus their use in epidemiological studies or large clinical trials is limited. Consequently, a number of indirect practical indices of IR have been developed, and included HOMA-IR, quantitative insulin sensitivity check index, McCauley index, fasting insulin resistance index, Matsuda index, Stumvoll index and two recently developed adipokine-based measures of IR: the LAR and HOMA-Adiponectin.[38,41] There exist limited studies comparing these measures of IR in hemodialysis patients. However, Hung and colleagues performed a study validating several practical, relatively new, and commonly used indirect indices of IR against the hyperinsulinemic euglycemic clamp method in hemodialysis patients.[38] Their results showed that two adipokine-based indices of IR, specifically HOMA-Adiponectin and LAR, were the best correlates of IR measured by hyperinsulinemic euglycemic clamp method. Moreover, HOMA-Adiponectin and LAR can potentially represent proper cardiovascular risk prediction in hemodialysis patients since adiponectin has been described as anti-atherogenic and leptin as atherogenic.[6] For the aforementioned reasons, we measured these two indirect indices of IR beside HOMA-IR. However, omega-3 PUFA supplementation in our study did not improve any of three indirect indices of IR. In a cross-sectional study on hemodialysis patients, Rasic-Milutinovic and colleagues observed a significant reduction in HOMA-IR by administration of 2.4 g omega-3 PUFA daily for eight weeks.[28] Conversely, a meta-analysis of other studies reported no marked impact of omega-3 PUFA on IR.[42] Also, in a recent study on IR subjects, administration of fish oil caused no effect on IR.[29] It seems that the dose and/or duration of omega-3 supplementation, studies' design, degree of IR, and differences in the sensitivity of the IR indices might have contributed to these inconclusive results.

In our study, omega-3 PUFA supplementation produced significant reduction in serum triglyceride level compared with the placebo group; however, LDLC and total cholesterol concentration were not influenced by the omega-3 PUFA. Kooshki and colleagues showed a significant decrease in serum triglyceride concentration in hemodialysis patients after supplementation with 2080 mg of omega-3 PUFA daily for 10 weeks, but LDLC and total cholesterol concentrations remained unchanged.[27] Lok and colleagues failed to illustrate positive effect of omega-3 supplement on lipid profile of hemodialysis patients while evaluating the effect of 2400 mg omega-3 PUFA given daily for 12 months on the patency of newly created synthetic arteriovenous grafts.[43] A recent meta-analysis of other studies by Zhu and colleagues concluded that fish oil decreases serum triglyceride and total cholesterol concentrations, and enhances HDLC levels, without affecting LDLC among hemodialysis patients.[44]

Unexpectedly and unfavorably, HDLC significantly decreased by omega-3 supplement compared with the placebo group in our study. Although the dose and even duration of omega-3 supplementation in our study was lower than those used in some previous studies, serum HDLC would be expected to increase or remain at least unchanged by omega-3 supplementation, what were observed in similar previous studies.[27,43,45] We were not able to provide any explanation for decreased serum HDLC by

omega-3 PUFA. Maybe, uncontrolled nutritional state or other undetermined conditions of patients might have contributed to this finding. Given that optimal daily dose and duration of omega-3 PUFA supplementation producing a lipid-altering effect (particularly on individual subclasses of HDLC) in dialysis patients are still not established, well-designed larger randomized trials are needed to answer these undetermined questions.

There were some limitations to our study, as follows: small sample size, shorter observation period, single center, lack of using different dosages of omega-3 supplement for different lengths, lack of measurement of the HDLC subclasses,[46] monitoring patient compliance with pill counting practice instead of in vivo measurement of omega-3 PUFA, and lack of careful monitoring of patients' dietary intake.

CONCLUSIONS

The present study showed some beneficial effects of omega-3 PUFA on lipid profile of hemodialysis patients. However, omega-3 supplement failed to improve IR during the study period. Based on available studies, further well-designed and larger trials are needed to determine utility of omega-3 PUFA in the improvement of IR and lipid profile in hemodialysis patients.

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CONFLICT OF INTEREST

None declared.

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