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Effects of Omega-3 Fatty Acids on Markers of Inflammation in Patients with Chronic Kidney Disease: A Controversial Issue

Chun Hu^{1, #}, Ming Yang^{1, #}, Xuejing Zhu¹, Peng Gao¹, Shikun Yang^{1, 2}, Yachun Han¹, Xianghui Chen¹, Li Xiao¹, Shuguang Yuan¹, Fuyou Liu¹, Yashpal S. Kanwar³, and Lin Sun¹

¹Department of Nephrology, ^{2nd} Xiangya Hospital, Central South University, Changsha, Hunan, China

²Department of Nephrology, the third Xiangya Hospital, Central South University, Changsha, Hunan, China

³Department of Pathology, Northwestern University, Chicago, Illinois; Department of Medicine, Northwestern University, Chicago, Illinois

Abstract

Chronic kidney disease (CKD) is a global problem, which contributes to a significant morbidity and mortality in China. Concomitant inflammatory state further boosts the mortality due to cardiovascular events in patients with CKD undergoing dialysis. There is a general notion that Omega-3 fatty acid including, docosahexaenoic acids (DHA) and eicosapentaenoic (EPA) has certain health benefits perhaps via the regulation of inflammation. However, the anti-inflammatory effect of omega-3 fatty acids in patients with CKD is controversial. We analyzed the data of oral supplementation of omega-3 fatty acid in CKD patients by searching literature on database from inception to August 2016. The analysis included randomized controlled trials (RCTs) derived from multiple databases, and the effect of omega-3 fatty acids supplementation versus the control cohorts were compared. All of the data analysis was calculated by RevMan 5.2. A total of twelve RCTs involving 487 patients were included in the meta-analysis. Among them 254 patients received omega-3 fatty acid and 233 patients served as controls who received placebo. The meta-analysis revealed no statistical significance in serum levels of CRP (SMD, -0.20; 95% CI, -0.44 to 0.05; p=0.11), IL-6 (SMD, 0.00; 95% CI, -0.33 to 0.33; p=0.99) and TNF- α (SMD, 0.14; 95% CI, -0.17 to 0.44; p=0.38) between the omega-3 fatty acids supplementation group and control. This suggested that there is insufficient evidence to conclude the benefit of omega-3 fatty acids oral supplementation in reducing serum levels of CRP, IL-6 and TNF- α in patients with CKD.

Keywords

Omega-3 fatty acids; Chronic Kidney Disease; Dialysis; CRP; IL-6; TNF- α

Correspondence address: Lin Sun, MD, PhD, Department of Nephrology, Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, Tel: 86-731-5529-2064, sunlinnwu11@163.com.

[#]Both the authors contributed equally to this study.

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INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem. There is an increasing incidence and prevalence of kidney failure in CKD. Apparently, the uremic toxins in CKD patients induce inflammatory responses that are mediated by a variety of cytokines, chemokines and other inflammatory molecules. Consequentially, there is an enhanced oxidative stress and tissue injury. In such an inflammatory setting in patients with CKD and those undergoing dialyses may have a higher mortality due to precipitation of undesirable cardiovascular events (1–3). This chronic inflammatory state in patients on hemodialysis can be monitored by various serum biomarkers, such as, C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) (4). Thus, one can envisage that the modulation of inflammatory responses may serve an important target for the treatment of CKD (5), and efforts to prevent or attenuate inflammation would be an important step to delay the progression of CKD.

Omega-3 fatty acids (ω -3 fatty acid or n-3 fatty acid) are long-chain polyunsaturated fatty acids, which consist of α -linolenic acid (ALA, 18:3 n-3), eicosapentaenoic (EPA, 20:5 n-3) and docosahexaenoic acids (DHA, 22:6 n-3). ALA is present in vegetable oil like flaxseed, canola, olive oil, walnuts and so on, whereas EPA and DHA are found in abundance in marine oils and most fish, particularly oily ones such as tuna, salmon and trout etc (6). Omega-3 fatty acids are essential fatty acids since they are not synthesized in the body (7). There is increasing evidence that suggests omega-3 fatty acids participation in the regulation of inflammation and immune response by reducing the production monocyte pro-inflammatory cytokine, such as, interleukin-1 (IL-1), IL-6 and TNF- α (8). In addition, they can also reduce triglyceride (TG) levels (9, 10) and hence the cardiovascular risk (11, 12). In this regard, the American Heart Association (AHA) has issued guidelines for recommending daily supplementation of omega-3 fatty acids in patients with the potential to develop cardiovascular disease (13). Likewise, Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for Glomerulonephritis in 2012 (14) and the Japanese Clinical Practice Guides for IgA nephropathy (IgAN) in 2014 (15) recommended using omega-3 fatty acids in the treatment of these nephritides. In addition, the omega-3 fatty acids also reduce systemic inflammation by lowering the serum levels of TNF- α , IL-6 and CRP (16).

However, controversies have risen since recent studies have challenged the notion of anti-inflammatory effect of omega-3 fatty acids in patients with CKD. Most of the past studies indicate that patients with CKD have low omega-3 fatty acids levels, which expectedly result in an inflammatory co-morbid state (17). In support of this notion certain studies revealed that supplementation of omega-3 fatty acids decreases levels of inflammatory markers in hemodialysis patients (18, 19). However, other studies report no significant effect in lowering inflammation in CKD patients treated with omega-3 fatty acids supplementation (20, 21).

In this meta-analysis study, we report randomized controlled trial (RCT) while focusing on the changes in the serum concentrations of CRP, IL-6 and TNF- α following oral supplementation of omega-3 fatty acid in CKD patients, and evaluated whether or not omega-3 fatty acids improve the inflammatory state.

MATERIALS AND METHODS

Inclusion criteria

In this RCTs study we compared the effect of supplementation of omega-3 fatty acid, DHA and/or EPA, on markers of inflammation between experimental subjects and the controls receiving placebo. The experimental subjects included patients with CKD receiving renal dialysis and who were dialysis-independent. The outcomes parameters included measuring the levels of serum IL-6, TNF- α and CRP. The literature studies excluded were as follows: reviews, meeting summaries, case reports, and non-clinical research articles, non-randomized controlled trials, animal research data, incorrect or incomplete data that cannot be extracted, duplicate publications or poor quality data, and studies lacking inflammatory marker data.

Search strategy

We searched the literature in Pubmed, Embase, Cochrane Central Register of Controlled Trials (CCRCT) and China National Knowledge Infrastructure Database (CNKI) for clinical trials assessing the effects of omega-3 fatty acid on markers of inflammation in CKD patients from inception to August 2016. The following keywords were used: chronic renal failure (CRF), end stage renal disease (ESRD), chronic kidney disease (CKD), uremia, dialysis, hemodialysis (HD) or peritoneal dialysis; combined with omega-3 fatty acid, omega-3 polyunsaturated fatty acid, ω -3 fatty acid, n-3 fatty acid, n-3 polyunsaturated fatty acid, polyunsaturated fatty acids, fish oil, docosahexaenoic acid, eicosapentaenoic acid, DHA or EPA, and C-reactive protein, CRP, interleukin 6, IL-6, tumor necrosis factor alpha, TNF- α and inflammation. In addition, we also screened the references pertaining to the included studies with the aim to identify potential eligibility for RCTs.

Study selection

We included RCTs analyzing oral supplementation of omega-3 fatty acid that affects inflammation parameters in patients with CKD. Two investigators reviewed all the article titles and abstracts independently. The studies that were clearly irrelevant were excluded. For articles, full-text of the articles was examined and evaluated that seem to yield certain degree of certainty. The studies that failed to include inflammation markers were excluded. Study selection and exclusion process is shown in Figure 1.

Data extraction and management

The data extraction was collected independently by two investigators: first author's name, study design, publication year, sample size (treatment/control), sex ratio (men/female), measurements of IL-6, TNF- α and CRP levels, duration of follow-up, treatment group (dose of n-3 PUFAs), control group (placebo or other), and kidney disease status. At the same time, the mean with 95% confidence interval was used to calculate the mean $\pm$ standard deviation (SD) (22). The data were input to RevMan 5.2 by two investigators independently.

Study quality assessment

We used the Cochrane risk of bias guidelines (23) to assess the quality of studies, which included generation of random sequence, blinding of participants and personnel, blinding of outcome assessment, allocation concealment, incomplete outcome data as well as selective reporting, and other bias. For each study, according to the risk of bias guidelines, we designated as high risk of bias, low risk of bias or unclear risk of bias (Figure 2).

Statistical analysis

For continuous results, we used mean differences (MD) with 95% confidence interval (95% CI). Since the measurement unit is different in the included RCTs, the standardized mean difference (SMD) with corresponding 95% CI to calculate continuous variables was used. Assessment of statistical heterogeneity among trials by using χ^2 and I^2 statistics was employed (24). If heterogeneity didn't exist among studies, we applied fixed-effect model to calculate pooled effect size, otherwise a random-effect model was used. In addition, the outcomes were designated statistically significant when the p value <0.05.

RESULTS

Study selection

We identified records of 582 patients from Pubmed, Embase, Cochrane Central Register of Controlled Trials (CCRCT) and China National Knowledge Infrastructure Database (CNKI). Out of these 532 irrelevant studies were excluded because of duplication identified by surveying the article's title and abstract. We further excluded 38 studies after retrieving the full texts from the remaining 50 articles. The main reason was because of being non-RCTs or not inclusive of reporting inflammatory markers. Finally, 12 studies were eligible and thus included; the details of the retrieval processes are shown in Figure 1.

Characteristics of included studies and quality assessment

The characteristics of all the studies in this meta-analysis are shown in Table 1. These 12 studies included a total of 487 patients; among which 254 were treated with omega-3 fatty acid and a control group included 233 treated with placebo. These studies also provided the outcomes reflected in the levels of CRP (22, 25–33), IL-6 (25, 27, 28, 32–34) and TNF- α (27, 28, 34, 35). Among these, 4 studies included CKD patients who did not receive dialysis (22, 31, 34, 35). The treatment studies included oral supplementation of omega-3 fatty acid at doses of 0.8 – 6g/d for 2 – 6 months. Additionally, the risk assessments were included in these studies and they are listed in Figure 2.

Omega-3 fatty acids and CRP

Ten studies described the effect of omega-3 fatty acid supplementation on the serum CRP levels (22, 25–33). The pooled results of seven trials indicated that omega-3 fatty acids intake had no statistical difference in the levels of serum CRP (SMD, -0.20; 95% CI, -0.44 to 0.05; $p=0.11$; Figure 3), and there was no heterogeneity among these studies (heterogeneity $\chi^2=5.92$, $p=0.43$, $I^2=0\%$; Figure 3). In the study performed by Madsen, CRP changes were calculated as median with interquartile range. The results for the group

of omega-3 fatty acids supplementation and control groups were: (2.46 versus 1.47 mg/L; $p=0.06$) and (3.27 versus 3.14 mg/L; $p=0.12$), respectively (30). Overall, it indicated that the change of serum CRP level was not different among the two groups. In another study performed by Himmelfarb et al. where serum CRP data were expressed in the form of a histogram, and it also indicated no significant difference in the treatment and control group (32).

Omega-3 fatty acids and IL-6

Six studies were included pertaining to the changes in serum IL-6 levels (25, 27, 28, 32–34). Four articles were included in the pooled analysis, which suggested that serum IL-6 level were not significantly different in the group receiving omega-3 fatty acids supplementation compared with the controls (SMD, 0.00; 95% CI, -0.33 to 0.33; $p=0.99$; Figure 3). A low heterogeneity was detected in these studies (heterogeneity $\chi^2=4.58$, $P=0.21$, $I^2=34\%$; Figure 3). One study performed by Himmelfarb et al. was not included in pooled analysis since it reported serum IL-6 data as a histogram (32). However, in this study, IL-6 value was significantly reduced in the treatment group but it was not significantly different from the control group.

Omega-3 fatty acids and TNF- α

The effect of supplementation of omega-3 fatty acids on serum TNF- α level was also reported in four trials (27, 28, 34, 35). The pooled analysis suggested that TNF- α levels had no significant differences between the experiment and control groups (SMD, 0.14; 95% CI, -0.17 to 0.44; $p=0.38$; Figure 3). No heterogeneity in these studies was documented (heterogeneity $\chi^2=1.8$, $P=0.61$, $I^2=0\%$; Figure 3).

Omega-3 fatty acids affect serum IL-6, TNF- α and CRP levels in dialysis patients

We also evaluated the data of omega-3 fatty acids supplementation in dialysis patients and their effect on the serum levels of IL-6, TNF- α and CRP. The pooled analyses revealed that serum IL-6, TNF- α and CRP level were not significantly different in patients receiving omega-3 fatty acids versus the controls. The pooled respective results (Figure 4) pertaining to serum IL-6, TNF- α and CRP levels were: (SMD, 0.09; 95% CI, -0.28 to 0.47; $p=0.63$); (SMD, 0.09; 95% CI, -0.35 to 0.54; $p=0.68$) and (SMD, -0.23; 95% CI, -0.49 to 0.03; $p=0.09$).

Publication Bias

We used the funnel plots to evaluate the publication bias, as shown in Figure 5, the outcomes of serum IL-6, TNF- α and CRP were symmetric, suggesting that publication bias did not affect the result of our meta-analysis.

DISCUSSION

The meta-analysis data revealed no statistical differences in serum CRP levels between omega-3 fatty acids supplementation group and cohorts in CKD patients. Also, the serum levels of CRP and TNF- α were not statistically different between the dialysis patients receiving omega-3 fatty acids group and control group. Therefore, the current study

concluded that oral supplementation of omega-3 fatty acids did not have significant effect in reducing serum levels of IL-6, TNF- α and CRP in patients with CKD and/or those receiving dialysis. This would suggest that the omega-3 fatty acids do not exert obvious beneficial effect by reducing the inflammatory state in patients with CKD or dialysis.

Some of the recent literature reports suggest that micro-inflammation is a salient characteristic of patients with CKD in pre-dialysis or dialysis patients (36–38), which attributes to a relatively high cardiovascular risk in such patients (39, 40). Elevated levels of inflammatory mediators have a potential role in increasing oxidative stress and expression of advanced glycation end (AGE) products (41). It has been reported that the progression of CKD is related to low-grade inflammation, even in patients with moderate renal dysfunctions who may not be yet dialysis-dependent (43–45), suggesting that elevation of inflammatory mediators is associated with the development of chronic renal failure. While the data of certain other recent studies indicate that the lower levels of inflammation biomarkers may rather improve the survival of CKD patients (46–48). Therefore, modulation of micro-inflammation in patients with CKD may be of great clinical significance to delay the progression of CKD.

Some of the literature studies indicate that omega-3 fatty acids have beneficial effect in several inflammation-mediated diseases, such as, Crohn's disease (49), rheumatoid arthritis (50), IgAN (51) and various skin diseases (52). Also, some of the review articles (7, 10) mentioned the effects of omega-3 fatty acids supplementation in CKD patients who are dialysis-dependent as well as -independent. One of the problems seems to be the uremia-associated taste alterations in CKD patients undergoing hemodialysis, and as a result there would be inadequate supplementation of omega-3 fatty acids (53). Also, hemodialysis may directly affect omega-3 fatty acids bioavailability since these patients are under increased oxidative stress, and this will result in low levels of omega-3 fatty acids (54). Nevertheless, certain studies pertaining to endothelial biology and type 2 diabetes indicate beneficial effect of omega-3 fatty acids by modulation of inflammation (55–57). The mechanism by which omega-3 fatty acids exert their anti-inflammatory effect may be by possibly modulating AMP-activated protein kinase (AMPK) or cellular signaling mediated via silencing information regulator1 (SIRT1); the latter apparently leads to deacetylation of nuclear factor of kappaB (NF- κ B) and competitive inhibition of arachidonic acid that is involved in its conversion to pro-inflammatory intermediaries (58). In addition, the omega-3 fatty acids can alter the composition of cell membrane phospholipid fatty acid (59). Furthermore, Micallef et al. reported that omega-3 fatty acids are inversely related to CRP levels in healthy individuals (60), and they also reduce CRP and IL-6 levels in healthy older adults (61). Likewise, omega-3 fatty acids can decrease serum CRP concentrations in various chronic diseases (62) and patients with diabetic nephropathy (63). In addition, Tayyebi-Khosroshahi et al. also reported that omega-3 fatty acids significantly decrease the levels of TNF- α in hemodialysis patients (64). However, other studies indicated no significant effect on the inflammatory state in CKD patients with supplementation of omega-3 fatty acids (20, 21, 65). The present meta-analysis study indicate that there are no significant differences in serum IL-6, TNF- α and CRP levels between the untreated and patients treated with omega-3 fatty acid supplementation. This could be due to several variables, including the study duration, the number of studied patients, EPA/DHA ratios and dosage of omega-3 fatty acids

used, as well as the baseline levels of inflammation markers. In addition, the existing medical status or a given patient undergoing other treatments may be additional factors influencing the outcome (66). Another reason for the failure of omega-3 fatty acids supplementation to reduce inflammation in CKD/HD patients may due to the extent of inflammatory response which may too strong to be overcome by the anti-inflammatory effect of omega-3 fatty acids in CKD, especially those patients undergoing hemodialysis.

In terms of side effects of omega-3 fatty acids in CKD patients, there have been three trials reported in the literature (25, 34). The meta-analysis of these studies indicated no obvious alarming side effects related to omega-3 fatty acids supplementation. Our meta-analysis study also included a report by Saifullah et al. (30), which indicated minimal gastrointestinal disturbances in the group of patients taking fish oil. Also, none of the patients discontinued the omega-3 fatty acids supplementation due to these minor gastrointestinal side effects.

Finally, although meta-analysis was carefully performed in this study, there may be certain limitations. Primarily, this may be due to the trial size being relatively small. In this regard, a total of twelve RCTs involving 487 patients were included in this meta-analysis; with seven studies included in pooled analysis pertaining to the change in serum CRP levels, while four studies described the changes in serum levels of both IL-6 and TNF- α . Secondly, some of the included studies were not double-blinded. Thirdly, some of the results were described as median and range, while others in the form of histograms which could not be included in the meta-analysis. Finally, there was lack of long-term follow-up, and about the effect of omega-3 fatty acids supplementation in CKD patients on inflammatory markers.

CONCLUSION

Present meta-analysis indicates that there is insufficient evidence that provides a statistical significant benefit of omega-3 fatty acids supplementation on serum inflammation biomarkers, including CRP, TNF- α and IL-6 level in patients with CKD. Further large-scale and long-term clinical trials are needed to arrive at concrete conclusions.

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Figure 1.
Flow diagram of the literature selection and the exclusion process.

Figure 2.
Study quality assessment.

Figure 3.

Forest plot of studies comparing the role of omega-3 fatty acids supplementation versus placebo on serum inflammation markers in CKD patients.

Figure 4.
Forest plot of studies comparing the role of omega-3 fatty acids supplementation versus placebo on serum inflammation markers in dialysis patients.

Figure 5. Funnel plots with MD or SMD for studies comparing supplementation of omega-3 fatty acids with placebo for the effect of inflammation in CKD patients. MD: mean differences, SMD: standardized mean difference

Table 1

Characteristics of included studies

Stud(year)	Study design	No.patients	Gender (M/F)	Biomarkers	Duration (months)	Intervention	Treatment modality
Himmelfarb et al 2007[32]	RCT	T:31 C:32	T:23/8 C:17/15	IL-6 and CRP	2 months	T:(0.8g DHA)/day C: sunflower oil	hemodialysis
Saifullah et al 2007[30]	RCT	T:15 C:8	T:11/4 C:7/1	CRP	3 months	T: (1.3g ω 3FA)/day C: soybean/corn oil	hemodialysis
Madsen et al 2007[31]	RCT	T:22 C:24	T:13/9 C:17/7	CRP	2 months	T: (2.4g ω 3FA)/day C: olive oil	nondialysis
Bowden et al 2009[26]	RCT	T:18 C:15	T:11/7 C:8/7	CRP	6 months	T: (6g Fish oil)/day C: corn oil	hemodialysis
Mori et al 2009[22]	RCT	T:20 C:15	T:12/8 C:8/7	CRP	2 months	T: (4g ω 3FA)/day C: olive oil	nondialysis
Kooshki et al 2010[28]	RCT	T:17 C:17	T:10/7 C:11/6	CRP;TNF- α and IL6	2.5months	T:(1.24g EPA, 0.84g DHA)/day C: triglyceride oils	hemodialysis
Mat Daud et al 2012[29]	RCT	T:31 C:32	T:20/11 C:12/20	CRP	6 months	T: (1.8g EPA, 0.6g DHA)/TIW C: olive oil	hemodialysis
Deike et al 2012[34]	RCT	T:17 C:14	T:8/9 C:9/5	IL-6 and TNF- α	2 months	T: (2.4g Fish oil)/day C: safflower oil	nondialysis
Gharekhani et al 2014[27]	RCT	T:25 C:20	T:13/12 C:12/8	CRP, IL-6 and TNF- α	4 months	T: (1.08g EPA, 0.72g DHA)/day C: paraffin oil	hemodialysis
Hung et al 2014[25]	RCT	T:17 C:17	T:14/3 C:13/4	CRP and IL-6	3 months	T: (2.9g ω 3FA)/day C: placebo	hemodialysis
Mirhashemi et al 2016[35]	RCT	T:30 C:30	T:11/19 C:10/20	TNF- α	3 months	T: (1g ω 3FA)/day C: placebo	nondialysis

Stud(year)	Study design	No.patients	Gender (M/F)	Biomarkers	Duration (months)	Intervention	Treatment modality
Deger et al 2016[33]	RCT	T:11 C:9	T:9/2 C:8/1	CRP and IL-6	3 months	T: (2.9g ω3FA)/day C: placebo	hemodialysis

Note: T: omega-3 fatty acid group C: placebo group