Advanced Pharmaceutical Bulletin

Adv Pharm Bull, 2016, 6(4), 509-514
doi: 10.15171/apb.2016.064
http://apb.tbzmed.ac.ir

TUOMS Publishing Group

Mini Review

Therapeutic Effects of Omega-3 Fatty Acids on Chronic Kidney Disease-Associated Pruritus: a Literature Review

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Article info

Article History:
Received: 24 July 2016
Revised: 20 September 2016
Accepted: 24 October 2016
ePublished: 22 December 2016

Keywords:
· Chronic Kidney Disease
· Omega-3 fatty acids
· Pruritus
· Supplement
· Uremia

Abstract

Uremic pruritus remains one of the most tormenting, frequent and potentially disabling problem in chronic kidney disease (CKD) patients. However, an area of substantial etiological interest with relation to uremic pruritus is the essential fatty acids deficiency. So we performed a literature review to elucidate the efficacy of omega-3 fatty acids on uremic pruritus. This review evaluated all of the studies published in English language, focusing on the clinical effects of omega-3 fatty acids on uremic pruritus. The literature review was conducted in December 2015 and carried out by searching Scopus, Medline, Cochrane central register of controlled trials, and Cochrane database of systematic reviews. The search terms were "kidney injury", "kidney failure", "chronic kidney disease", "end-stage renal disease", "dialysis", "hemodialysis", "peritoneal dialysis", "pruritus", "itch", "skin problems", "fish oil", "omega 3", "n-3 fatty acids", "polyunsaturated fatty acids", "docosahexaenoic acid", and "eicosapentaenoic acid". Four small studies investigating potential benefits of omega-3 fatty acids on symptoms of uremic pruritus were found. Among them, three small randomized controlled trials have shown a significant improvement in pruritus symptoms (evaluated by a standard questionnaire) in CKD patients who took omega-3 supplement compared to omega-6, omega-9, and placebo supplementation. Despite numerous limitations of the studies, it is worth noting that even minor reduction in itching symptoms may be clinically significant for CKD patients. Therefore, and considering multiple health benefits of omega-3 fatty acids in advanced CKD and negligible risk profile, omega-3 intake can wisely be applied to CKD patients with uremic pruritus.

Introduction

Uremic pruritus, more accurately named "chronic kidney disease-associated pruritus" (CKD-aP), remains one of the most tormenting, frequent and potentially disabling problem in patients with advanced or end-stage renal disease (ESRD).[1] It influences 15%-49% of pre-dialysis CKD patients and 50%-90% of those on dialysis including peritoneal dialysis and hemodialysis (HD).[2] Intensity and distribution of CKD-aP changed markedly over time. Itch intensity varies and seems to be cyclical in some patients; however, it does not completely resolve. Itching may range from sporadic disturbance to complete restlessness throughout the day- and night-time. Generally, the intensity of CKD-aP is worse during nighttime than during daytime. Pruritus in 25% of affected patients is most intense during or immediately after dialysis likely owing to hypersensitivity reactions against dialysis membranes.[3] Initially, skin appearance of affected patients remains frequently unchanged, similar to that of subjects without pruritus, which in most cases is dry and scaly. Contrary to dermatological itch, primary skin lesions are not seen in patients with CKD-aP. Nevertheless, linear crusts, excoriations with or without impetigo, papules, ulcerations, and less frequently prurigo nodularis may be observed as secondary skin lesions due to severe scratching.[4] Generalized pruritus is dominant complain in 25%-50% of patients, whereas in the remaining patients CKD-aP mainly affects back, face, and fistula arm, respectively.[3] Uremic pruritus has a substantial impact on quality of life, since it causes severe discomfort, anxiety, depression, and sleep disorders. Poor sleep quality causes chronic fatigue, and is associated with derangement of day and night rhythm and can also negatively affect mental and physical capacity.[5,6] Unfortunately, therapeutic options for CKD-aP are limited. Validity of most studies on this subject remains questionable because of poor documentation of the basics, of concomitant diseases and therapies taken, and of very small study population numbers. On the other hand, CKD-aP is often resistant to

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various conventional treatments. Indeed, numerous therapeutic modalities have been examined against pruritus. Non-pharmacologic measures for treatment of CKD-aP consist of regular, intensive, and efficient dialysis, use of non-complement-activating dialysis membrane, adopting dietary restrictions, acupuncture therapy, and ultraviolet B therapy. Pharmacological therapies that have been used comprise emollients and topical corticosteroids, capsaicin cream, endocannabinoid cream, tacrolimus ointment, antihistamines, gabapentin, naltrexone, nalfurafine, thalidomide, pentoxiphylline, activated charcoal, cholestyramine, epoetin, pizotyline, ketotifen, and nicergoline.[7-9]

The underlying mechanism(s) for CKD-aP have not yet been fully elucidated. However, an area of substantial etiological interest with relation to CKD-aP is the essential fatty acids and their metabolites derived from cyclooxygenase and lipoxygenase pathways including prostaglandins and leukotrienes, respectively.[10] ESRD patients are known to have abnormal fatty acid profiles and illustrate symptoms consistent with those associated with essential fatty acid deficiency such as pruritus, abnormal perspiration, delayed wound healing, susceptibility to infection, anemia, and augmented hemolysis.[11] Thus, it seems that supplemental use of essential fatty acids and their derivatives may offer multiple health benefits to ESRD patients, and positively affect cellular membrane structure and physiological features. Omega-3 fatty acids exert anti-inflammatory effects for many inflammatory disorders,[12,13] and oral supplementation with fish oil, high in omega-3 fatty acids, has been shown to be beneficial in the alleviation of the pruritus.[10,14] These prospects propose that dietary long chain omega-3 fatty acids may offer a therapeutic supplement for cutaneous inflammatory or itching disorders in CKD patients.

Thus, we aimed to perform a literature review in a comprehensive manner to elucidate potential clinical benefits of omega-3 fatty acids in the alleviation of the CKD-aP.

Literature Review

This review evaluated all of the prospective clinical studies published in English language, focusing on the clinical effects of omega-3 fatty acids on CKD-aP. The literature review was conducted in December 2015 and carried out by searching Scopus, Medline, Cochrane central register of controlled trials, and Cochrane database of systematic reviews. The search was done using key words related to chronic kidney disease (kidney injury, kidney failure, chronic renal failure, chronic kidney disease, end-stage renal disease, dialysis, hemodialysis, peritoneal dialysis), uremic pruritus (pruritus, itch, xerosis, skin problems, skin disorders), and omega-3 fatty acids (fish oil, omega 3, fatty acids, n-3 fatty acids, α-linolenic acid, polyunsaturated fatty acids, docosahexaenoic acid, eicosapentaenoic acid). We also reviewed reference list of each retrieved article for additional published studies.

Results

Body of Findings

Table 1 summarizes studies on the potential therapeutic effects of omega-3 fatty acids in the CKD-aP. In this section, we present fully the results of the published related studies in a chronological order.

In the study of Peck et al[15] on 25 HD patients, randomized into three equal groups, oral daily intake of 6 g omega-3 fatty acid esters for 8 weeks produced a greater decrease in the serum concentration of arachidonic acid and greater increase in prostaglandin E_2 (PGE_2) concentration than the equal supplemental dose of olive oil and safflower oil. Based on subjective assessment of severity and distribution of pruritus symptoms, patients receiving omega-3 fatty acids experienced greater relief of pruritus than those treated with olive oil or safflower oil. The authors explained that decreased arachidonic acid concentration together with increased PGE_2 concentration may reflect blockade of the lipoxygenase pathway by omega-3 fatty acids, and then pushing the metabolism of arachidonic acid to the cyclooxygenase pathway, resulting in less inflammatory products such as PGE_2 and improved pruritus symptoms. In this study it was also speculated that omega-3 supplement increases formation of the series-3 eicosanoids, which possess less inflammatory activity and may prevent formation of the series-2 eicosanoids. Begum et al[10] designed a prospective, randomized, double-blind, controlled study to compare the effects of supplementation with fish oil, rich in omega-3 fatty acids, with safflower oil, rich in omega-6 fatty acids, on lipoxygenase activity of stimulated polymorphonuclear leukocytes and symptoms of pruritus in HD patients. Twenty two subjects were randomized to receive either 6 fish oil capsules (728 mg omega-3 fatty acids in each capsule) or 6 safflower oil capsules (704 mg omega-6 fatty acids in each capsule) per day for 16 weeks. At the end of the study, analysis of the fatty acid composition of red blood cells phospholipids depicted that supplementation with fish oil significantly increased total omega-3 fatty acids and the ratio of total omega-3 to total omega-6 fatty acids compared to the safflower oil group. Production of leukotriene B_4 (LTB_4) by polymorphonuclear leukocytes decreased in both treatment groups, but higher reduction was seen in fish oil group. Despite the absence of a significant difference in the mean baseline pruritus score between two groups, the frequency of itching significantly decreased in fish oil group compared to the safflower oil group ($P < 0.05$) after 16 weeks. The overall pruritus score had a lower, though not statistically significant, value in the fish oil group compared to the safflower oil group. However, a decrease of 41.3% and 10.1% in the total pruritus symptoms respectively in the fish oil and safflower oil group might be considered clinically important finding although the changes did not reach statistical significance. The researchers considered the small sample size and low power of their study as limiting factors, led to a non-significant reduction in the pruritus score of fish oil group. Additionally, it was suggested that other inflammatory mediators (such as serotonin, histamine, proteases, platelet

activating factor, etc) may play a role in the clinical symptoms of pruritus, since the symptoms improved in a pattern which was not in parallel with the trend seen in the LTB_4 concentration. Also, other impressive factors on pruritus symptoms such as uremic toxins, hyperparathyroidism, and calcium-phosphate imbalance were not controlled in this study. The authors provided some reasons for their findings. First, there was 100% cross-reactivity between the assay antibodies against LTB_4 and LTB_5. Thus, it was not possible to detect an increased generation of LTB_5 if omega-3 fatty acids had sufficiently displaced omega-6 fatty acids in the membrane phospholipids. Second, it was predictable that the modification of biochemical parameters by omega-3 fatty acids might be too low to become significant in the presence of a background diet enriched with omega-6 fatty acids. Finally, in vitro measurement of leukotriene production by highly stimulated polymorphonuclear leukocytes may not reflect the restraining effects of fish oil on real lipoxygenase activity in vivo. Lastly, a clear relationship between the degree of decrease in LTB_4 concentration and improved pruritus symptoms was not established. A short-term, prospective and uncontrolled pilot study by Fiedler et al[16] investigated the effects of omega-3 fatty acid supplementation on serum concentrations of C-reactive protein (CRP), homocysteine, lipoproteins, complement factors, blood gas, peripheral oxygen saturation, blood pressure, heart rate variability, electrocardiography, shunt blood flow and recirculation, and itching symptoms in HD patients. Eleven non-diabetic HD patients with balanced lipid metabolism were treated with 1.2 g omega-3 fatty acids combined with 11.2 g pectin per day for 12 weeks. Unsatisfactorily, itching symptoms did not show any improvement during the study period. However, in a randomized, double-blind, placebo-controlled cross-over trial performed by Ghanei et al[17] on 22 HD patients, daily oral supplementation with 3 g fish oil (containing a total of 540 mg EPA and 360 mg DHA) for 20 days significantly mitigated uremic pruritus symptoms compared with the placebo group (65% reduction in the omega-3 *vs* 15% reduction in the placebo group, $P < 0.001$).

Interpretation

So far, several mechanisms have been postulated for the etiopathology underlying the development of CKD-aP, but none of them is conclusive. Uremic itch is believed to be the result of a complex contribution of numerous uremic and non-uremic factors. Known risk factors predisposing to uremic pruritus include male gender,[18] elevated serum levels of calcium, phosphorus, magnesium, urea, and β_2-microglobulin.[19,20] Other contributing factors comprise xerosis, anemia, high serum aluminum level, increased calcium × phosphate product, hypervitaminosis A, erythropoietin insufficiency, low albumin, low transferrin, elevated ferritin, secondary hyperparathyroidism, dialysis membrane material, inefficient dialysis, systemic inflammation, uremic neuropathy, allergic sensitization, elevated serum histamine level, intradermal mast cell proliferation.[21,22]

Most therapies directed at the possible underlying causes of uremic pruritus have demonstrated only limited success. For several times in the past, a new therapeutic option has been introduced to become beneficial, but immediately thereafter inconsistent results appeared. The main barrier to find effective therapeutic modalities is the poorly determined pathophysiological mechanisms of CKD-aP. Further, owing to the high clinical heterogeneity of CKD patients, systematically designed studies are difficult to undertake and thus sparse. However, accumulating evidence proposes that the fish oil-derived bioactive fatty acids, particularly EPA and DHA, provide a host of multiple health benefits for patients with advanced kidney disease.[23] Omega-3 polyunsaturated fatty acids (omega-3 PUFA) have been used as part of the human diet for many years.[24] The three main omega-3 PUFA, namely EPA, docosapentaenoic acid, and DHA are long chain (twenty or more carbons in length), polyunsaturated (two or more double bonds) in which one of double bonds exists in third carbon location from the methyl terminus ("n-3" or "omega-3"). Because endogenous production of omega-3 PUFA is extremely limited, humans obtain these fatty acids predominantly from dietary sources (i.e., they are considered "essential" fatty acids), most importantly from oily cold water fish.[25] Omega-3 PUFA supplementation have demonstrated promises in the general population in modulating multiple disease processes including the inflammatory and immune processes, the progression of arteriosclerosis and cardiovascular problems, cardiac arrhythmias, rheology, hypertension, and dyslipidemia.[23] However, despite the potential for various clinical benefits, omega-3 supplementation is neither used nor routinely recommended in the CKD population. Likely, this may be related partly to a general lack of awareness from the biochemical and clinical benefits of omega-3 supplementation.

Of course, clinical applications of omega-3 fatty acids have been investigated in a number of disease states that are directly relevant to patients with advanced CKD, and demonstrated a variety of protective physiological effects when used as dietary supplement. Disparate disease states obtaining clinical benefits from omega-3 supplementation included dyslipidemia, hypertension, IgA nephropathy, HD access thrombosis/stenosis, cardiovascular diseases, oxidative stress, immune response and inflammation, malnutrition, depression, and uremic pruritus.[23,25-27] Three randomized controlled trials have shown a significant improvement in pruritus symptoms in CKD patients who took omega-3 supplement compared to omega-6, omega-9, and placebo supplementation,[10,15,17] while a small pilot uncontrolled study failed to demonstrate beneficial effect of omega-3 supplement on symptoms of uremic pruritus.[16]

Challenges

Unfortunately, existing published studies suffer notable limitations including small sample size, modest follow-up, suboptimal study design, supraphysiologic omega-3 PUFA doses that may preclude consumption for extended periods, and lack of verification of compliance. By knowing the paucity of well-designed large-scale studies on the benefits of omega-3 PUFA in the uremic pruritus, nonetheless, any reduction in itching symptoms may be clinically important and significant for patients suffering with such a distressing and debilitating condition. On the other hand, other studies have documented marked improvement of pruritus symptoms and scaling in atopic patients treated with omega-3 supplements.[28,29] Consistently, the 2005 National Kidney Foundation Outcomes Quality Initiative Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients proposes further investigation on the use of omega-3 PUFA in CKD patients,[30] though no consumption guidelines on optimal daily intake of omega-3 fatty acids have so far been established. However, there are some barriers that preclude CKD patients from taking adequate amounts of fish-derived omega-3 PUFA. These include generally restraining renal diet, lack of formal renal dietary recommendations encouraging fish ingestion, uremic aversion to foodstuffs that are major sources of omega-3 fatty acids, and socioeconomic constraints to purchasing and consuming fish.[31]

Table 1. Summary of clinical studies on omega-3 supplements as a therapy in uremic pruritus

Authors,Year	Patients	Study Design	Treatment	Duration	Variable	Outcomes
Peck et al. 1996	25 HD	RCT	Random assignment to daily supplement of 6 g fatty acid esters of either olive oil, fish oil or safflower oil	8 w	Plasma fatty acid profile; prostaglandin E_2; pruritus symptoms assessed by a questionnaire [32]	Significant increase in plasma 20:5n-3 and 22:6n-3 by fish oil than olive oil or safflower oil, significant increase in 20:3n-9 by olive oil and insignificant increase in 18:2n-6 and 20:4n-6 by safflower oil; Greater increase in PEG_2 concentration by fish oil than the equal supplemental dose of olive oil and safflower oil; Greater relief of pruritus symptoms in fish oil group
Begum et al. 2004	22 HD (12 fish oil, 10 safflower oil)	RCT	Randomized to ingestion of either 6 fish oil capsules (728 mg omega-3 fatty acids in each capsule) or 6 safflower oil capsules (704 mg omega-6 fatty acids in each capsule) per day	16 w	Lipoxygenase activity of stimulated polymorphonuclear leukocytes; Pruritus symptoms assessed by a questionnaire [32]	Higher reduction of LTB_4 in fish oil group; Significant decrease in the frequency, but insignificant decrease in overall pruritus score in fish oil group
Fiedler et al. 2005	11 HD	A short-term, prospective and uncontrolled pilot study	1.2 g omega-3 fatty acids combined with 11.2 g pectin per day	12 w	Serum concentrations of CRP, homocysteine, lipoproteins, complement factors, blood gas, blood pressure, heart rate variability, electrocardiography, shunt blood flow and recirculation, peripheral oxygen saturation and itching symptoms assessed by a visual analog scale	No change in the studied parameters except for a significant increase in homocysteine and decrease in VLDL level
Ghanei et al. 2012	22 HD	RCT, Cross-over	Random assignment (alternation method) into omega-3-placebo or placebo-omega-3 group, and then daily consumption of 3 g of either fish oil (containing a total of 540 mg EPA and 360 mg DHA) or matching placebo	20 d	Uremic pruritus symptoms assessed by a questionnaire [32]	Significant decrease in the pruritus symptoms in the omega-3 compared with the placebo group

Abbreviations: CRP, C-reactive protein; d, day; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HD, hemodialysis; LTB_4, leukotriene B_4; RCT, randomized controlled trial, VLDL, very low density lipoprotein; w, week.
*Duo LJ. Electrical needle therapy of uremic pruritus. Nephron, 1987; 47:179-183.

Conclusion

Taken together, promising preliminary data on the benefits of omega-3 PUFA including relieving uremic pruritus make it an attractive treatment option that can be integrated into a CKD patient's diet. At least until more clear recommendations are available, the omega-3 PUFA intake guidelines released by American Heart Association (AHA) suggest rational intake goals (approximately 1g EPA + DHA per day) in advanced CKD. Fortunately, safety profile of omega-3 doses

recommended by AHA is excellent. Aside from minimal gastrointestinal side effects (e.g., nausea, stomach upset, eructation, fishy aftertaste), omega-3 consumption at these doses do not cause other serious adverse effects and thus can be considered safe in advanced CKD patients. However, further well-designed studies with greater number of patients and long-term follow-up need to be carried out to confirm this promising initial finding. In the meantime, and considering omega-3 PUFA's multiple health benefits in other areas relevant to CKD and negligible risk profile, the current AHA omega-3 intake guidelines can wisely be applied to CKD patients suffering from symptoms of uremic pruritus. Over time, the utility and optimal dosing of omega-3 PUFA in advanced CKD patients will be elucidated via randomized clinical trials.

Acknowledgments

The authors would like to express their special thanks of gratitude to Dr. Taher Entezari-Maleki for his cooperation and important intellectual comments on this manuscript.

Ethical Issues

Not applicable.

Conflict of Interest

The Authors report no declaration of interest.

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