Effect of Omega-3 Fatty Acid Supplementation in the Treatment of Uremic Pruritus among Dialytic Chronic Kidney Disease Patients: A Meta-analysis

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ABSTRACT

Background and Objectives. Pruritus is a common and disabling symptom affecting as much as 50-90% of chronic kidney disease (CKD) patients undergoing dialysis. The pruritus experienced by these patients is often resistant to common anti-pruritic agents and has an overall negative impact on quality of life. With its antioxidant property and anti-inflammatory effects, omega-3 fatty acids have been used to alleviate pruritus. The objective of this study is to assess the effect of omega-3 fatty acid supplementation in reducing the severity of pruritus among dialytic CKD patients.

Methods. Various electronic databases were searched from inception to August 2022. Randomized controlled trials comparing the effect of omega-3 fatty acids versus placebo on the pruritus scores were included. The studies were independently assessed by three reviewers. Revman version 5.4 was used to analyze the data extracted from the studies while heterogeneity was evaluated using Chi^2 and I^2.

Results. A total of four studies with a population of 166 patients were included in the meta-analysis. The results show an overall beneficial effect of omega-3 fatty acids with a standardized mean difference of -1.40 (CI -1.74 to -1.05, Z=7.95, *p* value <0.00001). With a Chi^2 of 2.91 (*p*=0.41) and I^2 of 0%, there was no significant heterogeneity observed in the pooled analysis.

Conclusion. Overall, the results of the meta-analysis support the finding that omega-3 fatty acid supplementation may have a beneficial effect on reducing the severity of pruritus among CKD patients on dialysis.

Keywords: omega-3 fatty acids, chronic kidney disease, pruritus

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INTRODUCTION

Chronic kidney disease (CKD) affects the lives of over 8-10% of the adult population worldwide. Patients who reach end-stage renal disease (ESRD) may eventually require renal replacement therapy in the form of dialysis or renal transplantation.[1] An estimated 50-90% of those on peritoneal and hemodialysis suffer from some degree of pruritus.[2] This condition is referred to as uremic pruritus or CKD-associated pruritus (CKD-aP) since it occurs even in the absence of overt signs of uremia.[3] Pruritus is typically a bothersome symptom and is among the most frequent causes of worry and disability among these patients.[4]

A primary lesion is typically absent in uremic pruritus. This feature helps differentiate it from other common

dermatologic causes of pruritus. However, secondary skin lesions such as excoriations, crusts, and ulcerations frequently develop as a result of vigorous scratching. Uremic pruritus is typically worse at night leading to altered sleep wake cycles, poor sleep quality, and chronic fatigue. The relentless itching seen in some patients has also been associated with anxiety and depression. Overall, uremic pruritus has been shown to have a negative impact on one's physical and mental well-being.[2]

The etiology of uremic pruritus has yet to be fully elucidated. Some proposed pathophysiologic mechanisms include allergic sensitization, proliferation of skin mast cells, and elevation of prostaglandin derivatives. Uremic pruritus has also been associated with secondary hyperparathyroidism, hypervitaminosis A, and divalent ion abnormalities. It may also be that this condition results from a combination of these different factors.[5]

Of particular interest is the association of uremic pruritus with essential fatty acids and metabolites derived from cyclooxygenase and lipoxygenase pathways.[6] Several studies observed a decrease in inflammatory markers with omega-3 fatty acid supplementation. In a meta-analysis, patients with gastric cancer who received omega-3 fatty acids were shown to have lower levels of IL-6 and TNF-alpha.[7] A similar trend was seen among diabetic patients where omega-3 supplementation resulted in lower concentrations of CRP compared to control.[8]

Because of its noted effects on inflammatory markers, it has been hypothesized that omega-3 fatty acids can alleviate uremic pruritus which is characterized as a pro-inflammatory state.[9] This study aims to give an updated summary of evidence on the effects of omega-3 fatty acids in the management of uremic pruritus.

OBJECTIVES

General Objective

To assess the effects of omega-3 fatty acid supplementation in the management of pruritus among dialytic chronic kidney disease patients.

Specific Objectives

1. To determine whether omega-3 fatty acid supplementation reduces severity of pruritus among dialytic chronic kidney disease patients using a standard scale.
2. To analyze the effects of omega-3 supplementation in CKD patients on hemodialysis versus peritoneal dialysis.

METHODS

This study was conducted based on the PRISMA-P (preferred items for systematic review and meta-analysis protocols) statement. GRADE framework was used to assess certainty of evidence. Electronic databases were searched from inception to August 2022.

Eligibility criteria

The articles selected in the study included randomized controlled trials conducted among CKD patients at least 18 years of age undergoing peritoneal or hemodialysis. All patients were treated with omega-3 fatty acids (fish oil) per orem versus placebo. The primary outcome evaluated is the severity of pruritus reported as a change in score based on a pruritus assessment scale.

Studies which were not RCTs including case reports, retrospective or prospective cohorts, and non-placebo-controlled trials were excluded. This review did not include studies published in another language with no formal English translation. The review excluded studies in which participants had pruritus prior to developing CKD and those with allergy to omega-3 fatty acids.

Electronic searches

A highly sensitive electronic search was used in identifying randomized controlled trials in the following databases with no restriction on time or language of publication: MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Scopus, ClinicalTrials.gov, World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal, and Google Scholar. The reference lists of all identified trials were searched for further information.

The search strategy combined the search terms "randomized", "omega-3", "fish oil", "pruritus", and "hemodialysis". The following search terms were used in the PUBMED search strategy: ((("random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR "random"[All Fields] OR "randomization"[All Fields] OR "randomized"[All Fields] OR "randomisation"[All Fields] OR "randomisations"[All Fields] OR "randomise"[All Fields] OR "randomised"[All Fields] OR "randomising"[All Fields] OR "randomizations"[All Fields] OR "randomize"[All Fields] OR "randomizes"[All Fields] OR "randomizing"[All Fields] OR "randomness"[All Fields] OR "randoms"[All Fields]) AND ("fatty acids, omega 3"[MeSH Terms] OR ("fatty"[All Fields] AND "acids"[All Fields] AND "omega 3"[All Fields]) OR "omega-3 fatty acids"[All Fields] OR "omega 3"[All Fields])) OR ("fish oils"[MeSH Terms] OR ("fish"[All Fields] AND "oils"[All Fields]) OR "fish oils"[All Fields] OR ("fish"[All Fields] AND "oil"[All Fields]) OR "fish oil"[All Fields])) AND ("pruritus"[MeSH Terms] OR "pruritus"[All Fields]) AND ("haemodialysis"[All Fields] OR "renal dialysis"[MeSH Terms] OR ("renal"[All Fields] AND "dialysis"[All Fields]) OR "renal dialysis"[All Fields] OR "hemodialysis"[All Fields]). A manual search using the same search terms was done on Google Scholar. A diagram illustrating the summary of our search strategy is shown in Figure 1.

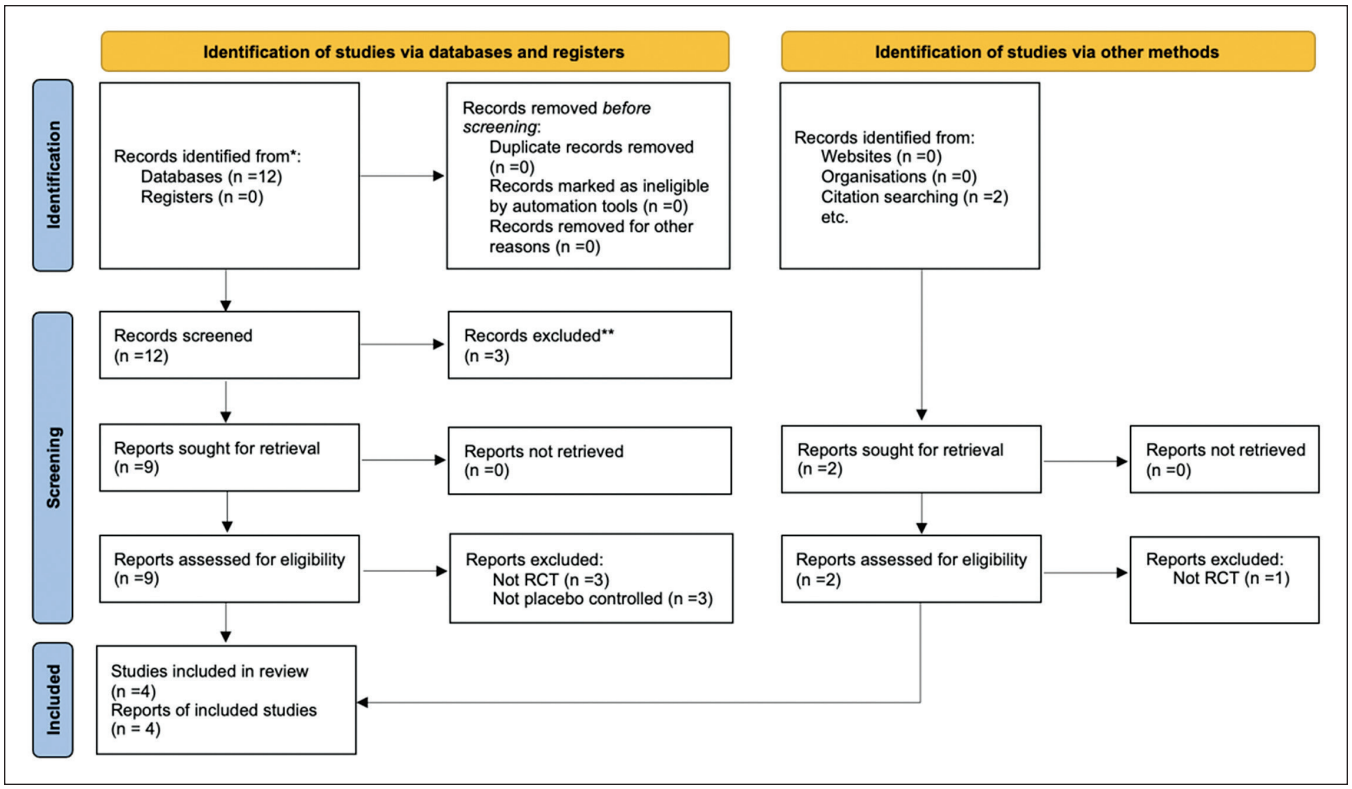

Figure 1. PRISMA flow chart (2020).

Selection of Studies

The studies were explored independently by three review authors. Selection was done through the use of an established inclusion and exclusion criteria. Differences were settled by discussing with a senior investigator and arriving at a consensus. Three reviewers independently assessed the methodological quality and suitability of each study for inclusion in the meta-analysis. Risk of bias was determined using the Cochrane risk-of-bias tool for randomized controlled trials based on the following domains: randomization, allocation concealment, blinding of participants, caregivers and outcome assessors, completeness of data, and outcome reporting. Each domain was rated with low, high, or unclear risk of bias through a discussion among the reviewers. Differences in individual assessment were resolved through consensus.

Data Synthesis/Analysis

Outcome measures were analyzed using the random effects model in RevMan 5.4 provided by the Cochrane Collaboration. The difference in the pre- and post-treatment pruritus scores were reported using standardized mean difference to account for the varying pruritus scales used in each study. Heterogeneity was assessed using chi-square with a p-value <0.10 representing significance. I^2 was used to quantify the degree of heterogeneity with a value >50% suggesting substantial heterogeneity.

RESULTS

Description of Studies

After searching electronic databases and reviewing citations of the individual studies, a total of 14 studies were identified. No duplicates were noted. Three non-relevant studies were excluded in the initial screening. A total of 11 articles were assessed for eligibility. On review of the full articles, four studies were not randomized controlled trials while three were not placebo controlled and were excluded from the study. A total of four studies were identified as eligible for inclusion in this review. Reference lists of the included articles were reviewed and no additional trials were identified. Characteristics of the included studies can be found in Appendix A.

Four randomized placebo-controlled trials involving a total of 166 participants met our inclusion criteria and were included in the study. All of these studies were conducted in Iran in a non-critical care setting. Lahiji included patients on peritoneal dialysis while the other three included patients on hemodialysis. Different scales were used to measure the pruritus scores which was our outcome of interest. Forouhari and Lahiji used a visual analog scale, Shayanpour used the standard 5D-questionnaire, while Ghanei used the Duo's pruritus score system.

Two of these studies, Lahiji and Forouhari, used a cross-over design. The review authors opted to include only data

from the first sequence where omega-3 and placebo were introduced to the experimental and control group prior to the cross-over. On review of these 2 studies, the succeeding sequence appeared to draw the same results – omega-3 supplementation demonstrated reduction on the mean pruritus score (VAS). No significant carry-over effects were detected on both studies.

The included studies also explored the effects of omega-3 on metabolic and inflammatory markers. Forouhari, Lahiji, and Ghanei all used 1 gram of omega-3 capsule containing 180mg of EPA and 120mg of DHA. The study by Shayanpour did not specify the actual EPA and DHA content of the 2-gram capsule used in the trial. The researchers attempted to request this data from the corresponding author but failed to receive any response.

Quality Assessment of Selected Studies

Quality assessment of the included studies was performed using the Cochrane risk of bias tool. A summary of the risk of bias is provided in Figure 2 with a graph provided in Figure 3. A summary of the quality of evidence using gradePRO can be found in Appendix B.

Overall, the included studies exhibit low risk of bias for most of the domains. All of the trials included in the study were randomized at level of treatment. However, only Shayanpour and Forouhari described the method of allocation. All studies are double blinded, with complete outcome data, and have low risk for reporting bias. Other than the domains mentioned, the adequacy of dialysis can be another potential source of bias as it can affect the degree of pruritus reported by the participants. Measures of dialysis adequacy were not clearly indicated except in the study of Ghanei where patients with KT/V index of less than 1.2 were excluded in the trial.

Effect of Intervention on Outcome of Interest

The mean values in Figure 4 represent the change in pruritus scores for the experimental and control group. A negative value signifies a reduction in the pruritus score while a positive value represents an increase. Standardized mean difference was selected as the measure of effect size to address the differences in the scales used in each study. Pooled analysis of the four studies assessing the effect of omega-3 fatty acid vs. placebo collectively favored the experimental group (omega-3 fatty acids) over placebo with a standardized mean difference of -1.40 (CI -1.74 to -1.05, Z= 7.95). A p value of <0.00001 suggests statistically significant reduction in the pruritus scores of participants given omega-3 fatty acids. With a Chi^2 of 2.91 (p=0.41) and I^2 of 0%, there was no significant heterogeneity observed in the pooled analysis.

A subgroup analysis of patients on hemodialysis was performed. This included three studies with a total population of 63. Pooled analysis showed a standardized mean difference of -1.25 (CI -1.63 to -0.86, Z= 6.36) with a p value of <0.00001. Heterogeneity in this subgroup was insignificant with a Chi^2 of 0.08 (p=0.96) and I^2 of 0%. A subgroup analysis could not be done for patients on peritoneal dialysis as only one study involved peritoneal dialysis (Figure 5).

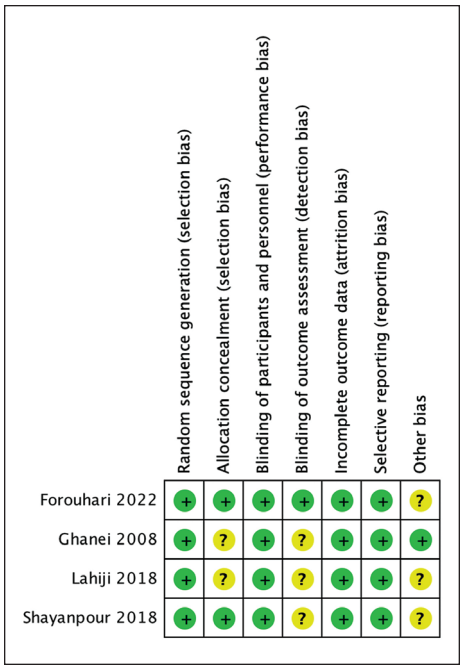

Figure 2. Summary of risk of bias.

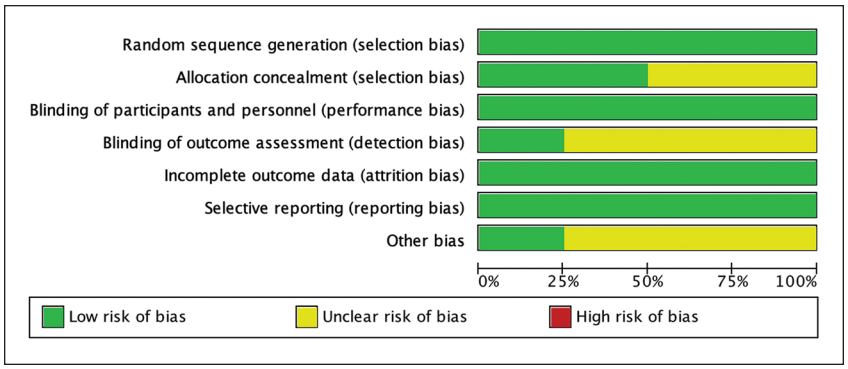

Figure 3. Risk of bias graph.

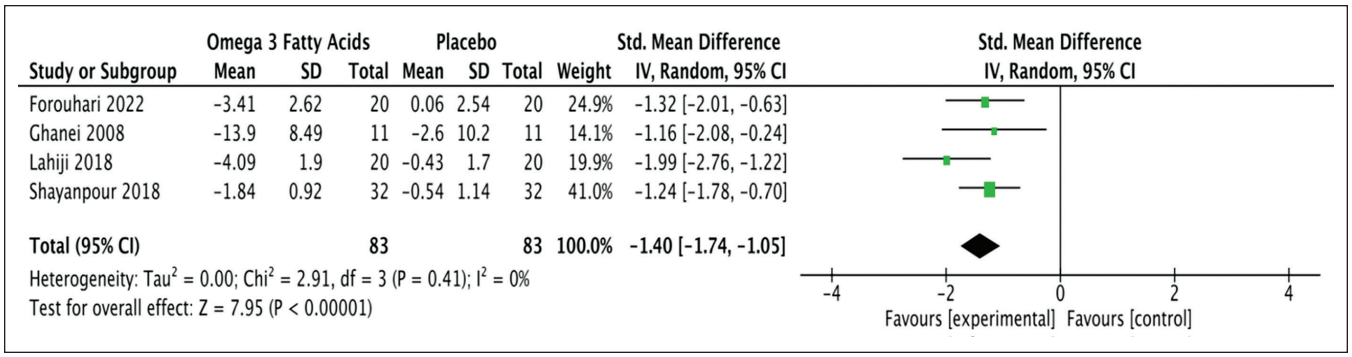

Figure 4. Forest plot showing omega 3 fatty acids vs. placebo.

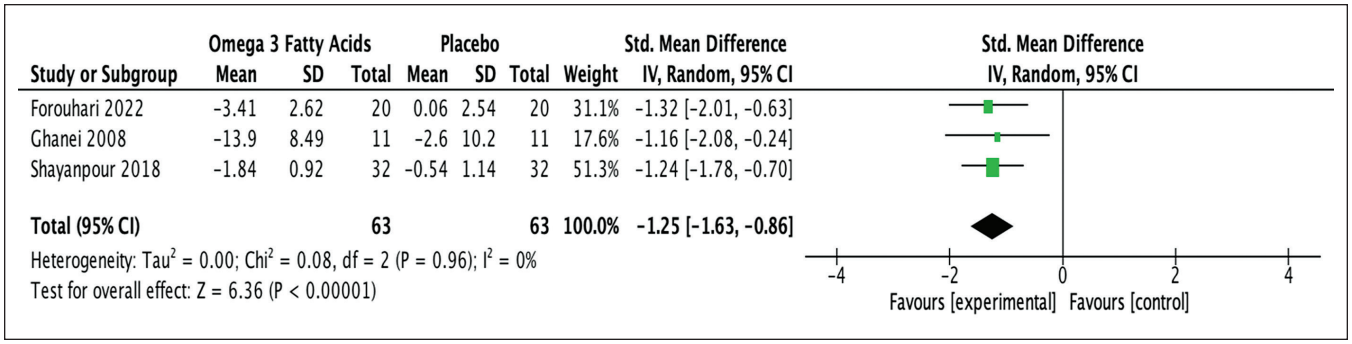

Figure 5. Forest plot showing subgroup of patients on hemodialysis.

DISCUSSION

Pruritus is among one of the multiple systemic manifestations of chronic kidney disease recognized to have a negative impact on one's quality of life. Four in every 10 dialytic patients experience at least moderate pruritus based on the Dialysis Outcomes and Practice Patterns Study.[10] Uremic pruritus has been associated with depression, poor sleep quality, and is considered an independent predictor of mortality.[11] Interestingly, Marthur et al. observed that a decrease of as little as 20% in pruritus scores was already sufficient to produce significant improvement in health-related quality of life.[12] The challenge is in the management of this unrelenting condition.

While there are no established clinical guidelines on the management of uremic pruritus, intensification of dialysis is often considered a cornerstone of therapy. A trial of pharmacologic treatment is recommended for persistent pruritus despite adequate dialysis.[11] A systematic review involving seven studies showed that the majority of patients with CKD associated pruritus were refractory to common anti-itch agents including topical emollients and anti-histamines.[13] This served as the impetus for the investigation of different agents for the treatment of CKD-aP.

In August 2021, the United States Food and Drug Administration (FDA) approved Difelikefalin (Korsuva) for the treatment of uremic pruritus making it the first drug approved for this particular condition. However, the drug is not widely available and is estimated to cost over $2000 per month of treatment.[14,15]

Omega-3 fatty acids have been widely investigated due to its anti-inflammatory properties which may alter the systemic inflammation and immune dysregulation central in the pathophysiology of uremic pruritus.[16] EPA and DHA reduce synthesis of key inflammatory products of the arachidonic acid pathway such as PGE2 and LTB4.[10] Commercially available fish oils are available in varying ratios of EPA and DHA. In the studies included, the majority were in 1-gram soft gel capsules containing 180 mg of EPA and 120 mg of DHA. This preparation is widely available in the Philippines.[17]

One of the included studies in the review investigated the effects of omega-3 on PGE2 levels. However, the results did not show any significant reduction in PGE2 levels in the intervention group. Similarly, there was no significant relationship between the change in PGE2 levels with pruritus scores.[10] This is inconsistent with previous studies where greater decrease in prostaglandin E2 levels were associated with better improvement in pruritus scores.[5]

Evaluation of pruritus can be challenging due to the absence of a uniform scale for comparison. Lahiji and Forouhari used VAS, Ghanei used the Detailed Duo pruritus score, while Shayanpour used the 5D itch scale. The VAS consists of a 10 cm vertical line graded from 0 (no pruritus)

to 10 (maximum intensity of pruritus). On the other hand, the Detailed Duo pruritus score system consists of four domains (extent of scratching, distribution range, frequency of attacks, and sleep disturbances) scored individually from 1 to 5.[18] The 5D itch scale, which used a scoring system qualifying itch in terms of duration, degree, direction, disability, and distribution, has been found to have good correlation with the visual analogue score.[19]

Since the studies were conducted using different scales, standardized mean difference was used as the outcome measure. However, in standardized mean difference, the results are reported in units of standard deviation rather than the units of the scales used in the studies. While the results show a statistically significant decrease in pruritus scores, it is difficult to translate these values to actual clinical benefit. Because of these limitations, the overall impact of omega-3 supplementation on the reduction of pruritus cannot be fully assessed.

CONCLUSION

The results of the meta-analysis support the finding that omega-3 fatty acid supplementation may have a beneficial effect on reducing the severity of pruritus among CKD patients on dialysis. However, further studies are warranted to examine the effect of omega-3 fatty acid supplementation on specific subgroups of patients with varying degrees of pruritus. An individualized approach is still recommended for its use.

Ethical Approval

The study does not involve any human participation and only analysed data from previously conducted studies. This was granted an exemption from ethics review by the University of the Philippines Manila Research Ethics Board with the code UPMREB 2020-764-EX.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

The investigators declare that they have no known competing interests or personal relationships that may influence the results of the study. To the authors' knowledge, there were no redundant publications during the conceptualization until completion of this paper.

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APPENDICES

Appendix A. Characteristics of Included Studies

Author, year	Study design	Sample Size (n)	Population	Intervention	Placebo	Outcome
Forouhari, et al. 2022	Double blind randomized controlled cross over trial	n=40	Patients >18 years old with HD duration of at least 3 months	1 g omega-3 capsules Each capsule: 180 mg EPA + 120 mg DHA	Yes	Intensity of pruritus using visual analogue scale
Shayanpour, et al. 2018	Double blind randomized controlled trial	n=64	Patients >18 years old with HD duration of at least 3 months	2 g omega-3 daily pre-lunch for 3 weeks	Yes	Intensity of pruritus using Standard 5D-questionnaire
Lahiji, et al. 2018	Crossover randomized clinical trial	n=40	Patients >18 years old, on CAPD for at least a month with pruritus of more than 8 weeks	Three capsules of 1 g omega-3 for 1 month. Each capsule: 180 mg EPA + 120 mg DHA	Yes	Intensity of pruritus using visual analogue scale
Ghanei, et al. 2012	Double blind randomized controlled trial	n=22	Patients 20-85 years old on maintenance dialysis 3x a week	1 g omega-3 capsules every 8 h for 20 days. Each capsule: 180 mg EPA + 120 mg DHA	Yes	Pruritus assessment using detailed pruritus score by Dr. Duo

Appendix B. GRADE Evidence Profile

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparison	Relative (95% CI)	Absolute (95% CI)		
Pruritus scores												
4	randomized trials	not serious	not serious	not serious	serious[a]	none	83	83	—	SMD 1.4 SD lower (1.74 lower to 1.05 lower)	⨁⨁⨁◯ MODERATE	CRITICAL

[a] *The individual studies utilized different scales in measuring pruritus*