INPLASY

Effectiveness of Omega-3 Polyunsaturated Fatty Acids Supplementation for Reducing Uremic Pruritus: A Meta-Analysis of Randomized Controlled Trials

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ADMINISTRATIVE INFORMATION

Support - Self-funded.

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 7 November 2025 and was last updated on 7 November 2025.

INTRODUCTION

Review question / Objective The PICO (population, intervention, comparison, outcome) setting of the current meta-analysis was as follows: P: human participants; I: Omega-3 fatty acid supplementation; C: placebo; and O: changes in pruritus scores.
The following inclusion criteria of this meta-analysis were: (1) randomized controlled trials (RCTs) enrolling human participants with ESRD, (2) RCTs adapting quantitative outcome to measure the severity of uremic pruritus before and after omega-3 fatty acid supplementation, (3) placebo-controlled trials, and (4) trials with quantitative pruritus scores before and after intervention or trials with change of pruritus scores before and after intervention. Open-label studies were also included in this meta-analysis. The exclusion criteria of this meta-analysis were: (1) non-RCTs, (2) studies lacking a placebo-controlled group, (3) studies lacking quantitative measurements, (4) studies including participants overlapped with a previously published trial, and (5) studies as an extension of a previously published trial.

Rationale Uremic pruritus is a common and distressing symptom affecting patients with end-stage renal disease (1-3). Uremic pruritus impairs quality of life and causes sleep disturbance and emotional distress (4, 5). The prevalence of uremic pruritus increased as renal function worsened, from chronic kidney disease to end-stage renal disease (ESRD) (6). Current evidence suggests that uremic pruritus results from a complex interplay between xerosis, systemic in-flammation, and dysregulation of the endogenous opioid system (7). Clinically, uremic pruritus presents as persis-tent (6), symmetrical itching (8), frequently involving the back, arms, and legs (9), with few visible skin lesions aside from excoriations caused by scratching (9). Diagnosis requires excluding other dermatologic or systemic causes and assessing symptom severity, dialysis adequacy, and metabolic imbalances (10). Management involves a multimodal approach beginning with general skin

care, especially regular use of emollients for xerosis, and optimization of dialysis and correction of calcium-phosphate or parathyroid abnormalities (10). For refractory cases, systemic treatments such as gabapentin or pregabalin are effective neuromodulators, while newer κ-opioid receptor agonists, such as nalfurafine and difelikefalin, have shown strong evidence of benefit (9, 11, 12). Despite this management, pruritus may persist or recur. Alternative treatment for uremic pruritus includes gabapentin (13), acupuncture (14), phototherapy (15), herbal medicine (16), and omega-3 fatty acid supplementation (17-23).

Omega-3 fatty acids, a family of polyunsaturated fatty acids, are an essential nutrient (24). Structurally, the term "omega-3" describes that the position of the first double bond in the fatty acid chain is located at the third carbon atom from the methyl (omega) end of the molecule (25). There are three main types of omega-3 fatty acids, including alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) (24). ALA is rich in plant oils such as flaxseed, chia seed, and canola oil (26), whereas EPA and DHA are abundant in fish oil (27, 28). The terms DHA, EPA, omega-3, and fish oil are often used interchangeably. Omega-3 fatty acids have been widely used as dietary supplements because of their potential benefits for cardiovascular disease prevention (29) and brain health (29), reducing inflammation (30), and lowering triglyceride levels (24). The omega-3 fatty acids can also be used for uremic pruritus (31).

The definite mechanism by which omega-3 fatty acids alleviate uremic pruritus is not fully understood. Various mechanisms, including anti-inflammatory (30), immunomodulatory (32), peripheral neuropathy (8), and skin bar-rier (33), have been proposed. Systemic inflammation plays an important role in the pathogenesis of uremic pruritus. This argument is supported by evidence that elevated serum levels of cytokines and interleukins (IL), including IL-2, IL-6, IL-31, tumor necrosis factor alpha (TNF-α), and C-reactive protein, are found in patients with ESRD (10). In uremic pruritus, IL-6 and TNF-α recruit and activate immune cells in the skin (34), leading to the release of pruri-togenic substances and disruption of the epidermal barrier (7). Elevated serum IL-2 levels have been repeatedly observed in patients with uremic pruritus compared with those without pruritus (35), and increased IL-2 levels also suggest Th1 lymphocyte overactivity (6). One report that using the topical calcineurin inhibitor to suppress Th1 lymphocytes and IL-2 reduces the severity of uremic pruritus (36) suggests that IL-2 contributes to uremic pruritus. IL-31, a T-helper 2 (Th2)-associated cytokine directly linked to pruritus, binds to receptors expressed on cutaneous sensory neurons and keratinocytes, stimulating itch perception and inflammation (37). Finally, high CRP concentrations serve as a systemic marker of ongoing inflammation and correlate with itch severity in several clinical studies (38-40), suggesting that the inflammation contributes to the development of uremic pruritus. Collectively, these suggest inflammation plays an important role in uremic pruritus. Omega-3 fatty acids counteract.

Condition being studied Paitent with end-stage renal disease and uremic pruritus.

METHODS

Search strategy From PubMed, EMBASE, Cochrane Central, and Clinicaltrials.gov.

Participant or population human participants with ESRD.

Intervention Supplying omega-3 fatty acids.

Comparator Control placebo.

Study designs to be included Randomized control trials.

Eligibility criteria The inclusion criteria of this meta-analysis were: (1) randomized controlled trials (RCTs) enrolling human partici-pants with ESRD, (2) RCTs adapting quantitative outcome to measure the severity of uremic pruritus before and after omega-3 fatty acid supplementation, (3) placebo-controlled trials, and (4) trials with quantitative pruritus scores before and after intervention or trials with change of pruritus scores before and after intervention. Open-label studies were also included in this meta-analysis. published trial, and (5) studies as an extension of a previously published trial.

Information sources Electronic databases, contact with authors.

Main outcome(s) Omega-3 supplementation significantly reduced pruritus severity compared with pla-cebo.

Quality assessment / Risk of bias analysis The methodological quality of the studies enrolled for meta-analysis was evaluated using the Cochrane risk of bias tool for randomized trials (version 2, RoB 2, London, United Kingdom) (56). Bias of randomization process, deviations from intended interventions, missing outcome data, measurement

of the outcome, selection of the re-ported result, and overall bias were assessed as the Rob 2 assessment described (56). In the intervention adherence section of the RoB 2, two optional assessments, intention-to-treat analysis and per-protocol analysis, are available (56). In this work, a per-protocol analysis was selected for the meta-analysis.

Strategy of data synthesis The meta-analysis was conducted and plotted using Comprehensive Meta-Analysis software (version 3, Biostat, Englewood, NJ, United States) (80). In the Comprehensive Meta-Analysis software, meta-analysis was conducted using a random-effects model. A two-tailed p value of less than 0.05 was considered statistically significant. Hedg-es' g and 95% confidence intervals (CIs) were used to present the primary outcomes of the meta-analysis. Odds ra-tios and their associated 95% CIs were used to present secondary outcomes. I 2 statistics were used to examine the degree of heterogeneity across studies. I 2 with a value of 25, 50, and 75% was considered low, moderate, and high heterogeneity, respectively. Subgroup analysis, meta-regression, and funnel plots were processed and plotted using Comprehensive Meta-Analysis software. Sensitivity analysis using the one-study removal method was performed in Comprehensive Meta-Analysis.

Subgroup analysis Subgrouped by dialysis modality for patient with end-stage renal disease and dose of omega-3 fatty acids.

Sensitivity analysis Sensitivity analysis using the one-study removal method was performed in Comprehensive Meta-Analysis. Using one-study removal as.

Country(ies) involved Taiwan.

Keywords uremic pruritus, end-stage renal disease, omega-3 polyunsaturated fatty acids, eicosapentaenoic acid, docosahexaenoic acid.

Contributions of each author

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