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Omega-3 polyunsaturated fatty acid supplementation in chronic kidney disease; effects on inflammation, proteinuria, and renal function – a narrative review study

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ABSTRACT

Chronic kidney disease (CKD) is a progressive disorder associated with high morbidity and mortality, primarily driven by cardiovascular complications and progression to end-stage renal disease (ESRD). Proteinuria and persistent low-grade inflammation are key mechanisms underlying disease progression. Omega-3 polyunsaturated fatty acids (PUFAs), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been investigated as adjunctive therapeutic agents due to their anti-inflammatory, antioxidant, and antifibrotic properties. This narrative review synthesizes evidence from the literature to evaluate the effectiveness of omega-3 PUFA supplementation on proteinuria, inflammatory markers, and renal function in patients with CKD. A structured literature search was conducted using relevant Medical Subject Headings (MeSH) and free-text terms, including observational studies, randomized controlled trials (RCTs), systematic reviews, and meta-analyses published in English. The findings indicated that omega-3 PUFA supplementation is associated with a modest but statistically significant reduction in proteinuria, particularly in patients with IgA nephropathy, along with a decreased risk of ESRD. However, its effects on estimated glomerular filtration rate (eGFR) and serum creatinine clearance are generally not significant. The anti-inflammatory effects remain inconclusive, as most pooled analyses do not show significant reductions in markers such as C-reactive protein (CRP), interleukin-6 (IL-6), or tumor necrosis factor-alpha (TNF- α), although some benefit has been observed in hemodialysis patients with elevated baseline inflammation. Experimental studies more consistently demonstrate antioxidant and antifibrotic effects. Overall, omega-3 PUFAs may serve as a supportive therapy in CKD management, particularly for reducing proteinuria and delaying disease progression, although further large-scale, well-designed clinical trials are necessary to confirm definitive clinical recommendations.

Implication for health policy/practice/research/medical education:

Omega-3 polyunsaturated fatty acids (PUFAs), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), may provide modest clinical benefits in chronic kidney disease (CKD) by reducing proteinuria, especially in IgA nephropathy, and lowering the risk of progression to end-stage renal disease (ESRD), although they show no significant improvement in estimated glomerular filtration rate (eGFR) or creatinine clearance. Their anti-inflammatory effects remain inconsistent, with most studies reporting no significant reductions in markers such as C-reactive protein (CRP), interleukin-6 (IL-6), or tumor necrosis factor-alpha (TNF- α), except for some benefit in hemodialysis patients with elevated baseline inflammation. Evidence from experimental models more consistently supports antioxidant and antifibrotic effects. Overall, omega-3 supplementation appears to be a potentially useful adjunct to standard CKD management, but its clinical efficacy requires confirmation through larger, well-designed trials.

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Introduction

Chronic kidney disease (CKD) is a major global public health burden affecting an estimated 10–15% of adults worldwide, and it remains a leading contributor to cardiovascular mortality and end-stage renal disease (1-3). Defined as a persistent abnormality in renal structure or function lasting more than three months, CKD arises from diverse etiologies including diabetes, hypertension, and glomerulonephritis (4). Despite advances in pharmacological management, most notably renin-angiotensin-aldosterone system (RAAS) blockade, a considerable proportion of patients progress toward kidney failure (5,6), underscoring the need for additional therapeutic strategies.

Proteinuria, the urinary excretion of protein beyond physiological thresholds, is both a marker and a mediator of kidney injury (7,8). Excessive urinary protein activates tubular inflammatory pathways, promotes tubulointerstitial fibrosis, and accelerates glomerulosclerosis, collectively hastening the decline in renal function (9-11). Alongside proteinuria, low-grade systemic inflammation, evidenced by elevated C-reactive protein (CRP), interleukin-6 (IL-6), or tumor necrosis factor- α (TNF- α), plays a central role in CKD pathophysiology and drives the disproportionate cardiovascular risk seen in this population (12).

Omega-3 polyunsaturated fatty acids (PUFAs), principally the marine-derived eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have long been recognized for cardiovascular benefits, including lipid-lowering, antithrombotic, and anti-inflammatory effects (13,14). Their potential relevance to CKD stems from these same properties, particularly the capacity to reduce proteinuria, limit renal inflammation, and slow disease progression (15). The clinical evidence now spans three decades of controlled trials, from early studies in pre-dialysis to large, rigorous investigations such as the vitamin D and omega-3 trial to prevent and treat diabetic kidney disease (VITAL-DKD) ancillary study (16,17). Yet findings remain heterogeneous. This review synthesizes evidence on three primary outcomes: proteinuria reduction, modulation of systemic inflammation, and preservation of renal function, while also discussing proposed mechanisms and factors that may explain variability in clinical responses.

Search Strategy

A structured search of the Scopus, Web of Science, DOAJ, and PubMed databases, as well as the Cochrane Library and Google Scholar search engine, was performed up to May 2026 using the following Boolean string: (“omega-3 fatty acids” OR “fish oil” OR “eicosapentaenoic acid” OR “docosahexaenoic acid” OR “polyunsaturated

fatty acids”) AND (“chronic kidney disease” OR “renal insufficiency” OR “nephropathy” AND (“proteinuria” OR “inflammation” OR “glomerular filtration rate” OR “renal function”). The following filters were applied: English language; human studies; publication types including observational studies, randomized controlled trials (RCT), systematic reviews, and meta-analyses. Articles were screened by title, abstract, and full text for relevance to proteinuria, renal function, and inflammatory outcomes.

Biochemical properties and mechanisms of action

Structural characteristics of omega-3 PUFAs

Omega-3 PUFAs are long-chain essential fatty acids that humans cannot synthesize and must obtain through diet or supplementation (18,19). Alpha-linolenic acid (ALA), found in plant sources such as flaxseed and walnuts, is a metabolic precursor; however, under normal conditions, its conversion to the biologically active forms EPA and DHA is less than 10% (20). Marine-derived EPA and DHA, abundant in fatty fish, including salmon, tuna, and mackerel, exert the most clinically relevant renal and anti-inflammatory effects (21).

Anti-inflammatory pathways

The central anti-inflammatory mechanism involves competitive inhibition of arachidonic acid (AA), the omega-6 fatty acid serving as primary substrate for pro-inflammatory eicosanoid synthesis (22). By displacing AA from cell membrane phospholipids and competing at cyclooxygenase (COX) active sites, EPA and DHA shift lipid mediator balance toward less inflammatory products (23). Additionally, EPA and DHA are precursors to specialized pro-resolving mediators (SPMs), including resolvins, protectins, and maresins, which actively promote inflammation resolution by shortening neutrophil lifespan, facilitating macrophage-mediated clearance of apoptotic cells, and reprogramming macrophages toward an anti-inflammatory phenotype; in the kidney, non-resolving inflammation is a recognized driver of chronic fibrosis and progressive renal failure; SPMs derived from EPA and DHA help mitigate these processes (24). At the molecular level, omega-3 PUFAs suppress nuclear factor- κ B (NF- κ B) signaling, a master regulator of pro-inflammatory cytokine transcription, and activate AMP-activated protein kinase (AMPK) and sirtuin-1 (SIRT1) pathways, collectively reducing IL-1, IL-6, and TNF- α production (12).

Renoprotective mechanisms

Beyond systemic anti-inflammatory effects, EPA and DHA exert specific renoprotective actions. In experimental models, omega-3 supplementation attenuated oxidative

stress, modulated TNF- α and malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GPx) activity (25). Transforming growth factor (TGF)- β suppression is particularly important, as this cytokine is the principal driver of renal fibrosis and epithelial-mesenchymal transition (EMT); both DHA and EPA reduce TGF- β -induced EMT in human proximal tubular (HK-2) cells through AMPK phosphorylation and autophagy flux enhancement (26). A recent study further identified EPA-derived metabolites, 18-hydroxyicosapentaenoic acid, 17,18-epoxyicosatetraenoic acid, and 17,18-dihydroxyicosatetraenoic acid, as novel antifibrotic compounds that attenuate the acute kidney injury-to-CKD transition (27). Omega-3 PUFAs also lower glomerular capillary pressure by modulating intrarenal prostaglandin synthesis, potentially reducing protein leakage across the filtration barrier (28). The EPA additionally inhibits the urate reabsorption transporter URAT1, offering a secondary benefit in hyperuricemic CKD patients (29).

Effects on proteinuria

Evidence from RCT studies

De Caterina et al provided foundational evidence in 1993 that n-3 PUFA supplementation reduced urinary protein excretion in patients with chronic glomerular disease, including membranous glomerulonephritis and focal glomerular sclerosis (30). This introduced the concept of dietary lipid modulation as a nephroprotective strategy. Subsequent trials focused predominantly on IgA nephropathy (IgAN); Donadio et al conducted a landmark controlled trial enrolling 106 IgAN patients randomized to fish oil (EPA 1.9 g/d + DHA 1.4 g/d) or placebo for up to 76.8 months; the fish oil group demonstrated significantly slower renal function decline and reduced proteinuria, particularly among high-risk patients, providing some of the most robust long-term evidence for the antiproteinuric effect of omega-3 PUFAs (31). A subsequent dose-comparison trial by the same group found no statistically significant difference in outcomes between high-dose (EPA 3.76 g + DHA 2.94 g/d) and low-dose (EPA 1.88 g + DHA 1.47 g/d) regimens in severe IgAN, suggesting that antiproteinuric efficacy may plateau above a certain threshold (32). Ferraro et al combined omega-3 supplementation with RAAS blockade in proteinuric IgAN and reported significantly greater proteinuria reduction compared to RAAS blockade alone, indicating a potential synergistic effect (33). In pediatric type 1 diabetes with diabetic nephropathy, a randomized controlled trial of omega-3 (1 g/d for 6 months) significantly reduced the urinary albumin-to-creatinine ratio (UACR) and kidney injury molecule-1 (KIM-1), alongside improvements in glycemic and lipid parameters (34). In contrast, the

double-blind, placebo-controlled trial by Mori et al in 100 adult CKD patients with albuminuria ≥ 30 mg/g creatinine found that 3,666 mg/d of EPA + DHA for 12 weeks did not achieve its primary endpoint of a $\geq 20\%$ reduction in urinary albumin excretion (16). These contrasting results highlight the sensitivity of the antiproteinuric response to disease etiology, baseline albuminuria severity, dose, and treatment duration.

Meta-analytic evidence

The 2017 meta-analysis by Hu et al pooled nine RCTs (444 patients with CKD) and demonstrated that omega-3 supplementation was associated with significantly lower proteinuria risk. No significant heterogeneity was detected across proteinuria trials; the same meta-analysis reported a 51% reduction in ESRD risk (RR: 0.49), suggesting that proteinuria reduction may translate into meaningful long-term renal protection (15). In contrast, a 2024 systematic review and meta-analysis by Fei et al, including nine studies and 347 participants, found a neutral overall effect on proteinuria under both fixed-effect and random-effects models, attributing the discrepancy with earlier analyses to high heterogeneity, diverse disease states, and variable dosing (7). Subgroup analyses from the Hu et al meta-analysis identified that antiproteinuric effects were most pronounced in IgAN patients, younger patients (mean age < 40 years), and studies with follow-up ≥ 24 months (15). Reinforcing these findings epidemiologically, a pooled analysis of 19 cohort studies comprising 25,570 participants found that participants with seafood-derived omega-3 PUFA levels in the highest quintile had a 13% lower risk of incident CKD compared to those in the lowest quintile (35).

Effects on inflammation

Systemic inflammatory markers

A meta-analysis by Hu et al analyzed 12 RCTs involving 487 CKD patients and found no statistically significant differences in serum CRP, IL-6, or TNF- α between supplemented and control groups; the investigators concluded that current evidence does not support the efficacy of oral omega-3 supplementation in reducing systemic inflammatory biomarkers in CKD (12). A 2024 meta-analysis by Fatima et al focusing specifically on hemodialysis patients found a statistically significant reduction in CRP with fish oil, particularly pronounced in patients with baseline CRP ≥ 5 mg/L; this subgroup-dependent effect implies that the anti-inflammatory action of omega-3 PUFAs may require a sufficient degree of pre-existing systemic inflammation to become clinically detectable (36). Supporting a more nuanced interpretation, a prospective trial in CKD stages 1–3 (2 g/d omega-3 for 6 months) found a significant reduction

in urinary monocyte chemotactic protein-1 (MCP-1) excretion without significant change in serum CRP or systemic MCP-1 concentrations; this localized renal anti-inflammatory effect, reflecting reduced tubular MCP-1 production, suggests that omega-3 PUFAs may exert meaningful kidney-specific anti-inflammatory actions not captured by systemic biomarker panels (37).

Oxidative stress

Oxidative stress, a hallmark of uremia, responds more consistently to omega-3 supplementation than traditional inflammatory markers. A clinical study in CKD patients with dyslipidemia found that omega-3 supplementation reduced thiobarbituric acid-reactive substances (TBARS) and triglyceride levels simultaneously (38).

Cardiovascular inflammatory risk

An eight-week non-randomized intervention study in hemodialysis patients supplemented with 2 g/d of omega-3 reported significant improvements in serum albumin and a reduction in the proportion of patients classified as cardiovascularly high-risk based on CRP strata, even in the absence of significant absolute changes in CRP (39). The cardioprotective effects of omega-3 PUFAs in CKD, spanning antithrombotic, antiarrhythmic, lipid-lowering, and vasodilatory properties, represent a clinically relevant dimension beyond direct renoprotection (40).

Effects on renal function

The eGFR and creatinine clearance

The most definitive measure of renal benefit is the trajectory of GFR decline. The meta-analysis by Hu et al found no statistically significant effect of omega-3 supplementation on eGFR or creatinine clearance rate across nine RCTs, with results consistent across most subgroup analyses (15). The VITAL-DKD ancillary study by de Boer et al, the largest and most methodologically rigorous trial, enrolled 1,312 adults with type 2 diabetes in a 2×2 factorial design testing vitamin D3 (2,000 IU/d) and omega-3 fatty acids (1 g/d) against placebo. Neither intervention significantly affected eGFR change over five years. The investigators concluded that supplementation has no role in primary prevention of CKD or slowing eGFR loss in the general population with type 2 diabetes; however, the relatively modest dose and the inclusion of patients without significant albuminuria may have limited the study's power to detect renal function benefits in higher-risk subgroups (25).

In contrast, the long-term dose-comparison RCT by Donadio et al in severe IgAN demonstrated that both high-dose and low-dose omega-3 regimens were associated with slower rates of serum creatinine increase, and patients in the lower baseline creatinine range experienced

significantly fewer ESRD events; these findings suggest that early intervention in patients with residual renal reserve may be a critical determinant of functional benefit (32).

ESRD risk

The most clinically significant finding in renal function data is the reduction in ESRD risk. The Hu et al meta-analysis reported a 51% reduction in relative ESRD risk, though this estimate rested on only three trials and should be interpreted cautiously (15). Earlier long-term trial data from the Mayo Nephrology Collaborative Group consistently supported a protective effect against renal failure in high-risk IgAN patients (31).

Disease-specific considerations

The renal function response is strongly influenced by the underlying nephropathy. In IgA nephropathy, the evidence for slowing functional decline is most consistent (31,32). In animal models of diabetic nephropathy, high omega-3 dietary intake significantly attenuated albuminuria (from 97.3 mg/day in diabetic controls to 8.3 mg/day in the omega-3 group), glomerulosclerosis, tubulointerstitial fibrosis, and renal expression of TGF- β , MCP-1, and IL-6 (41). Clinical results in human diabetic kidney disease have been less consistent, with the VITAL-DKD trial providing the most definitive negative result in this domain.⁹ In autosomal dominant polycystic kidney disease, EPA supplementation demonstrated no significant effect on renal function or kidney volume in the largest available RCT (42). These disease-specific patterns reflect distinct underlying mechanisms and underscore the importance of etiology-stratified trial design in future research.

Factors modifying clinical responses

The heterogeneity of findings across studies points to several important modifying variables. First, dose and chemical form matter: ethyl ester and triglyceride formulations differ in bioavailability, and the EPA-to-DHA ratio influences the downstream profile of lipid mediators (12). Doses in trials ranged from 1 g/d to 12 g/d, making cross-study comparisons unreliable (7, 15). Second, disease etiology is critical: antiproteinuric effects are strongest in IgAN and weakest in diabetic or non-specific CKD, likely because distinct immunological and fibrotic pathways operate in each condition. Third, treatment duration significantly affects outcomes; studies with follow-up ≥ 24 months most consistently demonstrate proteinuria reduction (15). Fourth, baseline characteristics, including degree of proteinuria, systemic inflammatory burden, and GFR at enrollment, predict responsiveness (7,36). Finally, concomitant RAAS blockade may amplify the antiproteinuric effect of omega-3 PUFAs (33).

Safety and tolerability

Omega-3 PUFA supplementation is generally well tolerated across CKD populations. The most commonly reported adverse effects are minor gastrointestinal disturbances such as nausea, belching, and fishy aftertaste, which rarely require discontinuation (12). At pharmacological doses (≥ 3 g/d), omega-3 PUFAs can prolong bleeding time through inhibition of platelet aggregation, a relevant consideration in dialysis patients; however, no clinically significant hemorrhagic events were reported in the reviewed trials (15). High-dose supplementation may rarely affect glycemic control in susceptible subgroups (43). The overall favorable safety profile makes omega-3 PUFAs a feasible adjunctive option in most CKD patients, provided attention is given to drug interactions, particularly with anticoagulants.

Conclusion

The current body of evidence establishes omega-3 PUFA supplementation as a biologically plausible and clinically promising adjunct in CKD management, particularly for reducing proteinuria and ESRD risk in IgA nephropathy. The mechanistic foundation—encompassing anti-inflammatory, antioxidant, antifibrotic, and antiproteinuric pathways—is well supported by both experimental and human data. Nevertheless, effects on direct GFR-based measures of renal function remain inconsistent, and the picture in diabetic kidney disease is particularly uncertain following the VITAL-DKD trial. Translating these findings into practice requires further research addressing optimal dosing and duration, ideal EPA/DHA ratios, patient selection criteria, and the potential additive benefit of combining omega-3 PUFAs with RAAS blockade or newer nephroprotective agents such as SGLT2 inhibitors. Large, multicenter RCTs with standardized outcome measures and adequate follow-up are needed before definitive guidelines can be issued. In the meantime, omega-3 PUFAs may be cautiously considered as part of a comprehensive nutritional strategy for proteinuric CKD patients, particularly those with IgA nephropathy or significant dyslipidemia.

Authors' contribution

Conceptualization: Mahdi Amirdosara and Farzaneh Futuhi.

Data curation: Mahdi Amirdosara

Investigation: Zahra Sahraei and Farzaneh Futuhi

Supervision: All authors.

Validation: Zahra Sahraei.

Visualization: Zahra Sahraei.

Writing—original draft: All authors.

Writing—review and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative artificial intelligence (AI) and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized AI (Perplexity.ai and Grammarly.com) to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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