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Mechanisms of Renoprotection Induced by Omega-3 Fatty Acids: Implications for Diabetic Nephropathy, Acute and Chronic Kidney Disease Management

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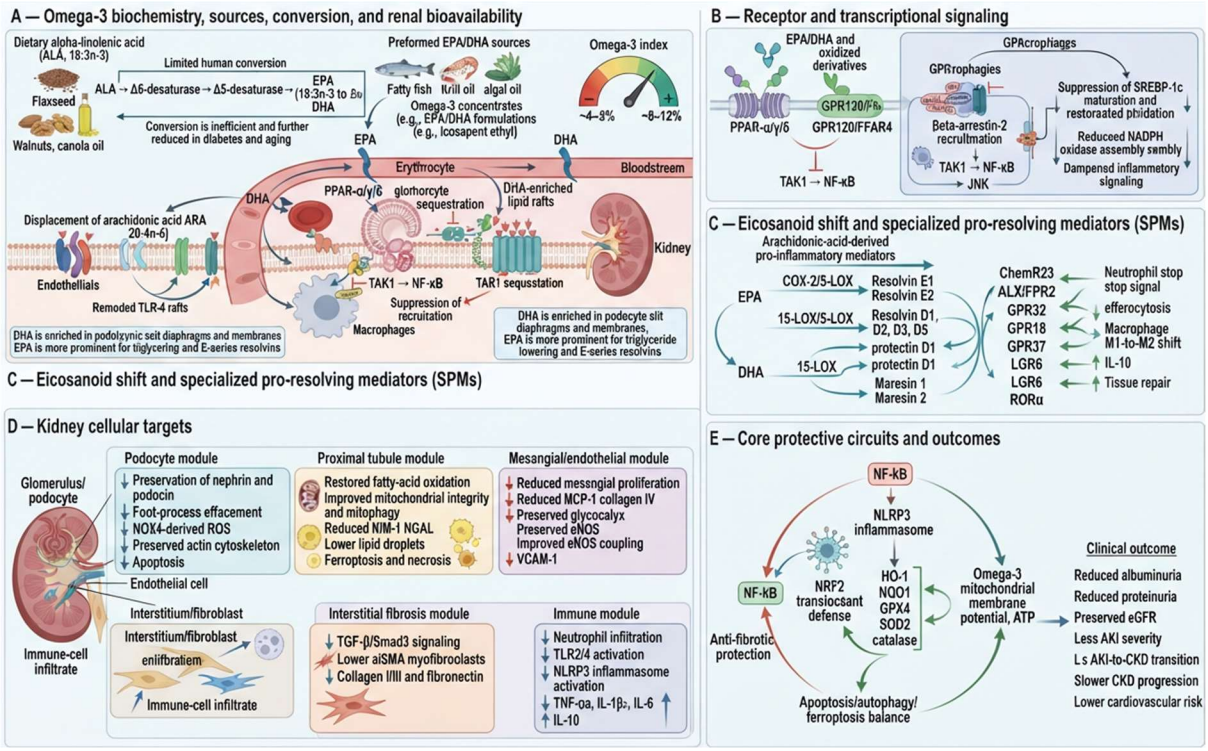

Graphical Abstract:

Mechanisms of renoprotection induced by omega-3 fatty acids: implications for diabetic nephropathy, acute kidney injury, and chronic kidney disease management. Dietary alpha-linolenic acid and preformed EPA/DHA sources contribute to systemic and renal omega-3 availability, membrane remodeling, and displacement of arachidonic acid-derived inflammatory lipid signaling. EPA- and DHA-derived metabolites generate specialized pro-resolving mediators, including E-series resolvins, D-series resolvins, protectins, and maresins, which act through defined GPCR pathways to suppress neutrophil recruitment, enhance efferocytosis, promote macrophage reprogramming, and support tissue repair. In the kidney, these actions preserve podocyte structure, improve proximal tubular mitochondrial and metabolic homeostasis, reduce mesangial and endothelial injury, and limit interstitial fibroblast activation and fibrosis. These effects converge on inhibition of NF-κB/NLRP3 signaling, activation of NRF2-dependent antioxidant defenses, preservation of mitochondrial function, and regulation of apoptosis, autophagy, and ferroptosis, thereby supporting improved renal and cardiometabolic outcomes across diabetic and non-diabetic kidney disease contexts

Abstract

Background:

Chronic kidney disease (CKD) affects >10% of adults worldwide, diabetic kidney disease (DKD) remains the leading cause of end-stage kidney disease, and acute kidney injury (AKI) complicates 10–15% of hospitalizations, often progressing to CKD. Persistent inflammation, oxidative stress, lipotoxicity, podocyte loss and tubulointerstitial fibrosis drive progression across aetiologies, yet current renin–angiotensin blockade, SGLT2 inhibitors and finerenone only partially attenuate risk. Omega-3 polyunsaturated fatty acids (n-3 PUFAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and their specialized pro-resolving mediators (SPMs) offer multitargeted, low-toxicity renoprotection.

Objective:
This narrative review explored cellular and molecular mechanisms of omega-3-induced renoprotection and evaluates implications for diabetic nephropathy, AKI and CKD management.

Methods:
A structured narrative search of PubMed/MEDLINE, Scopus and Web of Science (2000–2026) was performed for omega-3, EPA/DHA, resolvins, protectins, maresins, DKD, AKI, CKD, proteinuria, fibrosis and clinical trials. Mechanistic, preclinical and clinical studies, meta-analyses and guidelines were critically appraised.

Results:
EPA/DHA incorporate into renal membranes, activate GPR120, PPARs and NRF2, suppress NF-κB, TLRs and NLRP3 inflammasome, attenuate SREBP-1-driven lipotoxicity, stabilize podocytes, and inhibit TGF-β/Smad fibrosis, apoptosis and ferroptosis. DHA-derived resolvins D1/D2, protectin D1 and maresin 1, and EPA-derived resolvin E1 actively resolve neutrophil/macrophage inflammation, promote M2 polarization, enhance efferocytosis and heme oxygenase-1, and reduce albuminuria, glomerulosclerosis and AKI-to-CKD transition in rodents.

Conclusion:

Omega-3 fatty acids act as nutrient-derived resolution agonists with coherent mechanistic rationale for adjunctive renoprotection. Optimizing formulation (EPA+DHA vs. pure EPA), dose, Omega-3 Index targeting and SPM-based drugs, and testing in biomarker-enriched DKD/AKI trials, are priorities.

Keywords:

Omega-3 fatty acids; EPA; DHA; Resolvins; Diabetic nephropathy; Acute kidney injury; chronic kidney disease; Glomerulosclerosis

List of Abbreviations

Abbreviation	Full Term
AGE	Advanced Glycation End-Product
AKI	Acute Kidney Injury
ALA	Alpha-Linolenic Acid
ARA	Arachidonic Acid
CKD	Chronic Kidney Disease
COX	Cyclooxygenase
CVD	Cardiovascular Disease
DHA	Docosahexaenoic Acid
DKD	Diabetic Kidney Disease
DN	Diabetic Nephropathy
EPA	Eicosapentaenoic Acid
ESKD	End-Stage Kidney Disease
GBM	Glomerular Basement Membrane
GFR / eGFR	Glomerular Filtration Rate / Estimated GFR
GPR120 (FFAR4)	G-Protein-Coupled Receptor 120 (Free Fatty Acid Receptor 4)
HO-1	Heme Oxygenase-1
IL	Interleukin

IRI	Ischemia-Reperfusion Injury
LOX	Lipoxygenase
MaR	Maresin
MCP-1	Monocyte Chemoattractant Protein-1
NF-κB	Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells
NLRP3	NOD-Like Receptor Family Pyrin Domain Containing 3
NRF2	Nuclear Factor Erythroid 2–Related Factor 2
PD	Protectin
PPAR	Peroxisome Proliferator-Activated Receptor
PUFA	Polyunsaturated Fatty Acid
RAAS	Renin–Angiotensin–Aldosterone System
RCT	Randomized Controlled Trial
ROS	Reactive Oxygen Species
RvD / RvE	Resolvin D-series / Resolvin E-series
SGLT2	Sodium-Glucose Cotransporter-2
SPM	Specialized Pro-Resolving Mediator
SREBP-1	Sterol Regulatory Element-Binding Protein-1
TGF-β	Transforming Growth Factor-Beta
TLR	Toll-Like Receptor
TNF-α	Tumour Necrosis Factor-Alpha
UACR	Urine Albumin-to-Creatinine Ratio
UUO	Unilateral Ureteral Obstruction
VEGF	Vascular Endothelial Growth Factor

1. Introduction

Chronic kidney disease (CKD) affects more than 850 million people globally, causes 1.2 million deaths annually and is projected to become the fifth leading cause of death by 2040 [1]. Diabetic kidney disease (DKD), encompassing classic diabetic nephropathy (DN) with albuminuria and glomerulosclerosis plus increasingly recognized non-albuminuric phenotypes, develops in ~40% of patients with diabetes and accounts for ~50% of incident end-stage kidney disease (ESKD) [2]. Acute kidney injury (AKI) complicates 10–15% of hospital admissions and >50% of intensive-care stays, increases mortality 3–8-fold and initiates a high-risk AKI-to-CKD transition even after apparent recovery [3].

Across aetiologies, diabetes, hypertension, glomerulonephritis, ischemia-reperfusion injury (IRI) and nephrotoxins, a convergent pathobiology drives progression: unresolved innate immune activation, oxidative stress, endothelial dysfunction, podocyte depletion, tubular epithelial dedifferentiation, lipotoxicity and transforming growth factor-β (TGF-β)-driven interstitial fibrosis [1-3]. Renin–angiotensin–aldosterone system (RAAS) blockers, sodium-glucose cotransporter-2 (SGLT2) inhibitors and non-steroidal mineralocorticoid antagonists slow but do not halt progression, and many patients retain high residual inflammatory and cardiovascular risk [1,2].

Omega-3 polyunsaturated fatty acids (n-3 PUFAs), principally eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) from marine sources, are pleiotropic nutrient signals that modulate membrane biophysics, transcription, eicosanoid balance and, critically, active inflammation resolution [4]. Unlike conventional immunosuppressants that blunt host defence, EPA/DHA-derived specialized pro-resolving mediators (SPMs), E-series

and D-series resolvins, protectins and maresins, terminate neutrophil influx, enhance macrophage efferocytosis, repolarize macrophages toward reparative phenotypes and promote tissue regeneration without global immunosuppression [5,6]. Interest in renal applications is longstanding, from 1990s fish-oil trials in IgA nephropathy to contemporary DKD, AKI and dialysis studies, yet clinical uptake remains limited by heterogeneous trial results and incomplete mechanistic translation [2,4].

This narrative review provides an updated, cellular and molecular synthesis of omega-3-induced renoprotection and its practical implications for DN, AKI and CKD management. We examine (i) n-3 PUFA biochemistry and renal handling, (ii) cellular targets in glomerular and tubulointerstitial compartments, (iii) core molecular circuits (inflammation, redox, fibrosis, lipotoxicity, cell death, haemodynamics), (iv) SPM-specific pathways, (v) preclinical and clinical evidence by disease context, and (vi) dosing, safety and future directions.

2. Literature Search Strategy

A structured narrative search was conducted in PubMed/MEDLINE, Scopus and Web of Science from January 2000 to August 2026, supplemented by landmark pre-2000 trials. Search strings combined: (omega-3 OR EPA OR DHA OR fish oil OR icosapent ethyl) AND (kidney OR diabetic nephropathy OR diabetic kidney disease OR acute kidney injury OR chronic kidney disease OR proteinuria OR fibrosis OR resolvin OR protectin OR maresin). Priority was given to mechanistic reviews (2022–2026), rodent models with lipid-mediator profiling, randomized controlled trials (RCTs), systematic reviews/meta-analyses and KDIGO guidelines. Selection emphasized mechanistic coherence and clinical relevance; formal systematic appraisal with risk-of-bias scoring was beyond narrative scope.

3. Omega-3 Biochemistry, Metabolism and Renal Bioavailability

3.1. Structures, Sources and Conversion

Alpha-linolenic acid (ALA, 18:3n-3) from flaxseed, walnuts and canola is the essential precursor, but conversion via Δ6-desaturase, elongase and Δ5-desaturase to EPA (~5–10%) and especially DHA (<1–5%) is inefficient in humans, further impaired in diabetes and ageing [4,7]. Preformed EPA/DHA from fatty fish, krill, algal oil and concentrates (e.g., TAK-085, Omacor/Lovaza, icosapent ethyl) are therefore required for therapeutic tissue enrichment [4]. EPA and DHA differ functionally: EPA is a superior substrate for E-series resolvins and triglyceride lowering, while DHA dominates membrane phospholipids, lipid rafts, podocyte slit-diaphragm fluidity and D-series resolvins/protectins/maresins [5,7]. Notably, EPA-to-DHA conversion in diabetic kidney is limited by suppressed Δ6-desaturase, so EPA alone fails to raise renal DHA-docosaonoids, supporting combined EPA+DHA for renoprotection [7].

3.2. Membrane Incorporation and Transcriptional Regulation

Within weeks of supplementation (2–4 g/day), EPA/DHA replace arachidonic acid (ARA, 20:4n-6) in erythrocyte, glomerular, tubular and immune-cell membranes, increasing the Omega-3 Index (EPA+DHA in erythrocytes) from ~4–5% to 8–12%, the cardioprotective range [4]. This remodels lipid rafts, Toll-like receptor (TLR) clustering, ion channels and NADPH oxidase assembly, dampening pro-inflammatory signalling at its origin [7]. Intracellularly, EPA/DHA and their oxidized derivatives are natural ligands for peroxisome proliferator-activated receptors (PPAR-α/γ/δ), suppress sterol regulatory element-binding protein-1c (SREBP-1c) maturation and activate G-protein-coupled receptor 120 (GPR120/FFAR4), linking lipid sensing to anti-inflammatory and metabolic reprogramming [7-9]. GPR120 activation in macrophages recruits β-arrestin-2, sequesters TAB1 and inhibits TAK1 → NF-κB/JNK cascades, a pathway first defined in metabolic disease and now confirmed in renal macrophages [9].

3.3. Eicosanoid Shift and SPM Biosynthesis

Classically, EPA competes with ARA for cyclooxygenase (COX) and lipoxygenase (LOX), shifting from highly pro-inflammatory 2-series prostaglandins and 4-series leukotrienes toward less potent 3-series/5-series mediators [4]. The modern paradigm extends beyond competition to active resolution: EPA via aspirin-acetylated COX-2/5-LOX yields resolvin E1 (RvE1) and RvE2; DHA via 15-LOX/5-LOX yields resolvin D1 (RvD1), RvD2, RvD3, RvD5; via 15-LOX yields protectin D1 (PD1/neuroprotectin D1) and protectin DX; and via 12-LOX yields maresin 1 (MaR1) and MaR2 [5,6]. These SPMs act at picomolar–nanomolar concentrations through specific G-protein-coupled receptors, ALX/FPR2, GPR32, GPR18, ChemR23, LGR6, GPR37, to orchestrate resolution [6]. In diabetic and ischaemic kidneys, exogenous EPA+DHA markedly increase renal RvE, RvD and PD1, which inversely correlate with glomerulosclerosis scores, establishing SPMs as effectors, not mere markers, of renoprotection [7].

4. Cellular Targets of Renoprotection in the Kidney

4.1. Podocytes and Glomerular Filtration Barrier

Podocyte foot-process effacement, slit-diaphragm disruption (nephrin, podocin loss) and detachment are early, often irreversible steps in DN and focal segmental glomerulosclerosis [2]. Omega-3 supplementation in streptozotocin (STZ) diabetic rats reduced glomerular damage scores by ~70%, preserved podocyte pedicels, attenuated glomerular basement membrane (GBM) thickening and Bowman's space obliteration, and suppressed caspase-3 in glomerular and tubular compartments [10,11]. In vitro, DHA stabilizes podocyte actin cytoskeleton via PPAR-γ–synaptopodin, reduces advanced glycation end-product (AGE)-induced NADPH oxidase 4 (NOX4)–reactive oxygen species (ROS) and blocks transient receptor potential canonical 6-mediated calcium overload [10]. RvD1 directly protects podocytes from adriamycin injury, reducing apoptosis and cytoskeletal collapse [10].

4.2. Proximal Tubular Epithelial Cells

Proximal tubules, with high mitochondrial density and fatty-acid oxidation dependence, are vulnerable to ischaemia, proteinuria, glucotoxicity and ferroptosis [3]. EPA/DHA restore fatty-acid oxidation, reduce intracellular triglyceride droplets, enhance mitophagy and limit tubular atrophy [7,8]. In IRI and cisplatin AKI, RvD1, PD1 and MaR1 reduce tubular necrosis scores, kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL), and accelerate proliferative repair via epidermal growth factor receptor and hepatocyte growth factor signals [10].

4.3. Mesangial, Endothelial and Interstitial Cells

Mesangial expansion driven by high glucose, platelet-derived growth factor and TGF-β narrows capillaries in DN [2]. EPA inhibits mesangial proliferation, monocyte chemoattractant protein-1 (MCP-1) and collagen IV synthesis [7,12]. Glomerular endothelial glycocalyx loss and fenestral injury promote albuminuria; DHA preserves glycocalyx, increases endothelial nitric oxide synthase coupling and reduces vascular cell adhesion molecule-1 [7]. Interstitial fibroblasts/pericytes transdifferentiate into α-smooth muscle actin-positive myofibroblasts under TGF-β/Smad3; RvE1 via ChemR23–platelet-derived growth factor-BB and RvD1 via ALX/FPR2 suppress fibroblast proliferation, collagen I/III and fibronectin, limiting unilateral ureteral obstruction (UUO) and IRI fibrosis [10].

4.4. Resident and Infiltrating Immune Cells

Kidney-resident macrophages, dendritic cells and recruited neutrophils/monocytes dictate AKI severity and CKD progression [3,10]. SPMs inhibit neutrophil transendothelial migration and degranulation, block TLR2/4-mediated macrophage activation, enhance apoptotic-cell efferocytosis, increase interleukin-10 (IL-10) and shift macrophages from pro-inflammatory M1 (tumour necrosis factor-α [TNF-α], IL-1β, IL-6) to pro-resolving M2 (arginase-1, CD206, IL-10) [6,10]. T-regulatory cells are expanded by RvD1, while Th1/Th17 interferon-γ/IL-17 responses are restrained, relevant to lupus and IgA nephropathy [10,13].

5. Core Molecular Circuits of Omega-3 Renoprotection

5.1. NF-κB, TLR and NLRP3 Inflammasome Inhibition

Persistent NF-κB activation in podocytes, tubules and macrophages drives MCP-1, TNF-α, IL-6, intercellular adhesion molecule-1 and COX-2 in DN and AKI [2,3]. EPA/DHA inhibit IκB kinase-β phosphorylation, p65 nuclear translocation and histone acetylation at inflammatory promoters, partly via GPR120–β-arrestin-2–TAB1 and PPAR-γ trans repression [9,14,15]. TLR2/4 sensing of high-mobility group box 1, AGEs and endotoxin during IRI/sepsis is attenuated by DHA-enriched rafts and RvD1–ALX/FPR2, reducing MyD88–TRAF6 signaling [10,14]. Critically, n-3 PUFAs prevent NLRP3 inflammasome priming and assembly, caspase-1 cleavage and IL-1β/IL-18 maturation in kidney and macrophages, a mechanism demonstrated in metabolic and renal models and mediated by GPR120/GPR40, autophagy and reduced mitochondrial ROS [15,16]. Lipoxin A4 and RvD1 silence immediate-early response gene EGR-1 and TNF-α/TGF-β/NF-κB circuits in DKD, stabilizing a pro-resolving innate phenotype [10].

5.2. NRF2–antioxidant and Mitochondrial Defense

Hyperglycaemia, proteinuria and ischaemia generate mitochondrial superoxide, NOX4-derived ROS and lipid peroxides that oxidize proteins/DNA and trigger ferroptosis [2,3]. Low-micromolar DHA activates nuclear factor erythroid 2–related factor 2 (NRF2) nuclear translocation, upregulating heme oxygenase-1 (HO-1), NAD(P)H quinone dehydrogenase 1, glutathione peroxidase 4, superoxide dismutase 2 and catalase, while suppressing Kelch-like ECH-associated protein 1 [17,18]. PD1 amplifies renoprotective HO-1 in a 12/15-LOX–HO-1 feed-forward loop, increasing bilirubin/biliverdin and carbon monoxide that vasodilate and limit apoptosis [10,18]. MaR1 via LGR6–cAMP–superoxide dismutase 2 reduces mitochondrial ROS, albuminuria and cytokines in DKD [10]. Functionally, omega-3 restores pro-oxidant/antioxidant balance (malondialdehyde down, glutathione up), preserves mitochondrial membrane potential and ATP, and reduces ultrastructural cristae damage in diabetic tubules [11,17].

5.3. Anti-fibrotic TGF-β/Smad, MAPK and Wnt Blockade

Tubulointerstitial fibrosis predicts ESKD better than glomerular lesions [1]. TGF-β1–Smad2/3–connective tissue growth factor signalling, amplified by angiotensin II, AGEs and hypoxia, is the master fibrogenic program [1,2]. DHA/EPA suppress TGF-β1 transcription, Smad3 phosphorylation, Smad4 nuclear accumulation and microRNA-21, while preserving antifibrotic Smad7 and bone morphogenetic protein-7 [19,20]. RvD1, RvE1 and lipoxin A4 inhibit MAPK (ERK/p38), Akt and Smad crosstalk, reduce α-smooth muscle actin, collagen and fibronectin in UUO, adriamycin and diabetic models, and promote matrix metalloproteinase-mediated fibrotic matrix clearance by pro-resolving macrophages [10,19]. Wnt/β-catenin, Notch and Hedgehog profibrotic reactivation in injured tubules is also restrained by PPAR-γ agonism [20].

5.4. Lipotoxicity, SREBP-1 and PPAR Reprogramming

Ectopic renal triglyceride and cholesterol-ester accumulation, lipotoxicity, injures podocytes and tubules via diacylglycerol–protein kinase C, ceramide and endoplasmic-reticulum stress [2,8]. Diabetic kidneys upregulate SREBP-1c, fatty-acid synthase and acetyl-CoA carboxylase while downregulating PPAR-α–carnitine palmitoyltransferase-1α fatty-acid oxidation [8]. TAK-085 (EPA+DHA) attenuates albuminuria and renal dysfunction in db/db and SHRcp metabolic-syndrome rats with decreased SREBP-1 expression and renal triglycerides, increased DHA-docosaonoids and normalized ARA eicosanoids [7,11]. EPA inhibits SREBP-1 induction via liver X receptor antagonism and AMP-activated protein kinase, whereas DHA more potently activates PPAR-α/γ, restoring oxidation and adiponectin–AMP-activated protein kinase signalling [8,20]. This metabolic reprogramming complements glucose/lipid lowering and may explain greater benefit in hypertriglyceridaemic DKD [8].

5.5. Apoptosis, Autophagy and Ferroptosis Regulation

Podocyte and tubular apoptosis via BAX/BCL-2 imbalance, cytochrome c–caspase-9–caspase-3 and death receptors underlie cell dropout in DN and AKI [2,3,11]. Omega-3 markedly reduces caspase-3 immunoreactivity, terminal deoxynucleotidyl transferase dUTP nick-end labelling positivity and GBM/podocyte ultrastructural injury in STZ diabetes [11]. Autophagy, essential for podocyte homeostasis, is impaired in DKD (mTOR hyperactivation, LC3-II/p62 dysregulation); DHA restores autophagic flux via AMP-activated protein kinase–mTOR–unc-51-like kinase 1 and protects against high-glucose injury [21]. Ferroptosis, iron-dependent lipid-peroxide death via glutathione peroxidase 4 failure, is increasingly recognized in AKI, DKD and lupus nephritis; DHA/EPA, paradoxically peroxidizable substrates, upregulate glutathione peroxidase 4, ferroptosis suppressor protein 1 and NRF2–SLC7A11, reducing tubular ferroptosis in preclinical models, although dose and redox context matter [21,22]. RvD1–ALX/FPR2–GPR32 directly inhibits renal-cell apoptosis and NF-κB during IRI [10].

5.6. Haemodynamic, RAAS and Vascular Actions

Omega-3 modestly lowers blood pressure (~2–4/1–3 mmHg at ≥3 g/day), heart rate, arterial stiffness (pulse-wave velocity) and albuminuria-associated endothelial dysfunction, relevant because hypertension accelerates CKD [23,24]. Mechanisms include increased nitric oxide bioavailability, reduced thromboxane A2/angiotensin II vasoconstriction, antagonism of angiotensin II type 1 receptor signalling, improved baroreflex and reduced sympathetic tone [23]. EPA-derived 18-hydroxyeicosapentaenoic acid and RvE1 vasodilate afferent arterioles and reduce glomerular hypertension in rodents [10]. Triglyceride reduction (20–30% at 3–4 g/day) and remnant-lipoprotein lowering further decrease glomerular hyperfiltration and atherosclerotic renal-artery disease [24].

6. Specialized Pro-Resolving Mediators: Resolution Pharmacology in the Kidney

SPMs represent a conceptual advance: resolution is active, receptor-mediated and druggable, not passive decay of inflammation [5,6]. Key renal SPM circuits, extensively reviewed in AKI and CKD, include [6,10]: (i) RvE1 (EPA → 5-LOX/COX-2 → ChemR23 agonist/BLT1 antagonist): Inhibits neutrophil infiltration, dendritic-cell migration and fibroblast proliferation; in UUO, RvE1–ChemR23–platelet-derived growth factor-BB signalling reduces α-smooth muscle actin/collagen; in IRI, reduces cytokines and preserves function [10]. (II) RvD1/RvD2 (DHA → 15-LOX/5-LOX → ALX/FPR2, GPR32, GPR18): Attenuate tubular injury, apoptosis and NF-κB; expand T-regulatory cells; reduce interferon-γ/TNF-α/IL-6; repress interstitial fibrosis up to 72 h post-ischaemia; protect podocytes in adriamycin nephropathy with M1-to-M2 shift and reduced proteinuria/glomerulosclerosis [10,18]. (III) PD1/NPD1 (DHA → 15-LOX → GPR37, PPAR-γ): Inhibits neutrophil transmigration in murine kidney IRI, amplifies HO-1, enhances macrophage efferocytosis and M2 polarization, reduces TNF-α/IL-6/MCP-1 and increases IL-10 [10,18]. (IV)

MaR1/MaR2 (DHA → 12-LOX → LGR6, RORα): Via TLR4/MAPK/NF-κB → NRF2, reduces TNF-α/IL-6, increases IL-10/M2 and tissue regeneration; via LGR6–cAMP–superoxide dismutase 2 in DKD, reduces ROS, inflammation and albuminuria [10]. (V) Lipoxins (ARA → 15-LOX/5-LOX → ALX/FPR2): Although n-6-derived, aspirin-triggered lipoxin A4 is pro-resolving, reducing UUO collagen, TNF-α/interferon-γ, NF-κB/MAPK/Akt/Smad and increasing IL-10; silences EGR-1 in DKD with reduced mesangial expansion [10].

Importantly, SPMs increase pro-resolving IL-10 and efferocytosis without suppressing microbial killing at therapeutic doses, distinguishing resolution agonists from immunosuppressants, advantageous in infection-prone CKD/dialysis populations [6]. Stable SPM analogues (e.g., 15-epi-16-para-fluorophenoxy-lipoxin A4-methyl ester) protect in renal IRI and are templates for clinical development [10].

7. Diabetic Nephropathy and Diabetic Kidney Disease: From Mechanisms to Trials

7.1. Preclinical Coherence

Rodent type 1 (STZ) and type 2 (db/db, KKAy/Ta, SHRcp) models consistently show EPA/DHA (0.5–5% diet or 0.3–3 g/kg) reduce albuminuria 30–60%, glomerular hypertrophy/sclerosis, GBM thickening, podocyte loss, tubular vacuolation and interstitial fibrosis [7,11,25]. Katakura et al. demonstrated combined DHA+EPA (TAK-085), but not EPA alone, prevented renal failure in SHRcp rats, increasing renal protectin D1, RvD1/D2 and RvE with decreased triglycerides and normalized eicosanoids; glomerulosclerosis inversely correlated with DHA-docosaonoids [7]. STZ ultrastructural studies confirm preserved filtration slits, reduced hyaline casts and perivascular oedema, and restored antioxidant balance [11]. EPA ethyl ester improves KKAy/Ta DKD via SREBP-1 and PPAR-α, while DHA more potently raises SPMs, supporting combination therapy [7,8,25].

7.2. Clinical Signals and Heterogeneity

Human DKD trials are smaller and more heterogeneous than cardiovascular trials. Early RCTs (Rossing et al., 1996; Hamazaki et al.) in type 1/2 DN with 2–4 g/day fish oil for 6–12 months showed modest albuminuria and blood-pressure reductions without eGFR change [26,27]. EPA 1.8 g/day plus RAAS blockade in Japanese type 2 DKD reduced albuminuria and urinary podocyte markers versus RAAS alone [27]. A 3-month double-blind RCT in 100 predialysis CKD patients (3.7 g/day EPA+DHA vs. corn oil) found no significant albuminuria reduction (≥20% fall in 38% vs. 26%, p=0.27) but improved pulse-wave velocity and triglycerides [28]. Meta-analyses of proteinuria across CKD aetiologies report neutral overall effect (standardized mean difference ~−0.1, non-significant) with high heterogeneity (I^2 >60%), yet subgroup signals favour IgA nephropathy, higher baseline proteinuria (>1 g/day), EPA+DHA ≥3 g/day and ≥6-month duration [29,30]. Cardiovascular risk reduction with icosapent ethyl 4 g/day in REDUCE-IT (25% major adverse cardiovascular events reduction) and JELIS is directly relevant because CVD causes >50% of DKD mortality [31,32].

Interpretation must acknowledge: (i) background RAAS/SGLT2/finerenone attenuates incremental albuminuria effects; (ii) corn/olive-oil placebos are not inert; (iii) Omega-3 Index rarely targeted; and (iv) albuminuria is an imperfect surrogate for podocyte/fibrosis outcomes that SPMs may preferentially improve [29,30].

8. Acute Kidney Injury and AKI-to-CKD Transition

AKI, whether ischaemic, septic or nephrotoxic, involves neutrophil/macrophage influx, TLR/NLRP3 activation, tubular necrosis/ferroptosis and microvascular rarefaction; non-resolving inflammation drives AKI-to-CKD transition with atrophy and fibrosis [3,10]. Preclinically, n-3 PUFA-enriched diets improve survival after severe bilateral IRI (35 min), reduce creatinine/urea, tubular injury scores and KIM-1/NGAL, and attenuate 14-day AKI-to-CKD transition with less atrophy, collagen and α-smooth muscle actin [33]. Lipidomic profiling identifies active renal metabolites, 18-hydroxyeicosapentaenoic acid, RvE1, RvD1/D2, PD1 and 14S,21R-dihydroxy-DHA, that promote mesenchymal-stem-cell-mediated repair [10,33]. RvD1/RvD2/PD1 administered even post-ischaemia reduce neutrophil/macrophage accumulation, TLR-driven cytokines and chronic fibrosis, while MaR1 enhances efferocytosis and regeneration [10,18]. Lipoxin analogues similarly protect in IRI via cytokine/neutrophil modulation [10].

Clinically, perioperative fish-oil immunonutrition and ICU enteral EPA/DHA have shown reduced infection, ventilation days and possible AKI signals, but dedicated AKI-prevention RCTs (cardiac surgery, contrast, sepsis) are inconclusive and underpowered [3]. No guideline currently recommends omega-3 for AKI prevention/treatment, yet excellent safety supports testing SPM-enriched or intravenous n-3 emulsions in high-risk surgery/sepsis with MAKE (major adverse kidney events) endpoints [3,33].

9. Non-Diabetic CKD, Proteinuria, Dialysis and Cardiovascular Implications

9.1. IgA Nephropathy and Glomerulonephritis

The strongest renal RCT signal remains IgA nephropathy: Donadio et al. (Mayo, 1994, n=106, 12 g/day fish oil ≈1.9 g EPA+1.4 g DHA for 2 years) slowed eGFR decline and reduced ESKD/death (10% vs. 40% reaching 50% creatinine rise), with sustained benefit at 6.4 years [12]. A subsequent dose-comparison trial (2001) suggested low-dose EPA+DHA (2.9 g/day) was similarly effective with better tolerance [13]. KDIGO glomerular-disease guidance acknowledges fish oil as an option in persistent proteinuria despite optimized supportive care, particularly where immunosuppression is undesirable [12,13].

9.2. Proteinuria and CKD Progression

Beyond IgA, proteinuria meta-analyses (10–20 RCTs, n=500–1,000) show neutral overall effect but meaningful heterogeneity: EPA 1.8–3 g/day, DHA-containing formulas, baseline proteinuria >1 g/day and Asian cohorts' trend toward benefit [29,30]. Proposed explanations include variable RAAS co-therapy, short duration (<6 months), low dose (<2 g/day) and failure to enrich for high ARA/EPA ratio or low Omega-3 Index, a precision-nutrition gap [30].

9.3. Dialysis, Vascular Access and CVD

CKD/dialysis patients exhibit profound EPA/DHA deficiency, heightened sudden death and arteriovenous fistula/graft failure [1,24]. The FISH trial (n=567, 4 g/day fish oil vs. placebo) did not significantly improve graft patency at 12 months but reduced thrombosis, interventions and cardiovascular events in secondary analyses [34]. Observational cohorts link higher plasma n-3 PUFAs and Omega-3 Index ≥8% to lower all-cause/cardiovascular mortality in haemodialysis [24]. Svensson et al. and others reported reduced atherosclerosis progression, triglycerides and inflammation (C-reactive protein, IL-6) with n-3 supplementation in CKD [35]. Given CVD dominates CKD mortality and icosapent ethyl benefits persist across eGFR strata in REDUCE-IT, cardiovascular protection alone justifies considering omega-3 in hypertriglyceridaemic CKD [31].

10. Practical Implications for Kidney Disease Management

10.1. Who Might Benefit Most?

Synthesizing mechanisms and trials, priority candidates for adjunctive omega-3 (as part of, not replacement for, guideline therapy) include [2,12,24,28-30]:

10.2. Formulation, Dose and Monitoring

Evidence favours combined EPA+DHA 2–4 g/day (or icosapent ethyl 2–4 g/day where triglyceride/CVD indication dominates) for ≥6–12 months, with food to improve absorption [4,24,31]. DHA-inclusive formulas better raise renal docosaonoids; pure EPA (icosapent ethyl) has strongest CVD-outcome data [7,31]. Baseline and 3-month Omega-3 Index, triglycerides, UACR, eGFR, blood pressure and bleeding review are pragmatic monitors, targeting Index ≥8% [24]. Synergy with RAAS blockers (additive albuminuria/haemodynamic effects), SGLT2 inhibitors (complementary metabolic/anti-fibrotic) and statins (enhanced triglyceride control) is expected, without major pharmacokinetic interactions [2,24,36-39].

10.3. Safety, Interactions and Contraindications

At 2–4 g/day, omega-3 is well tolerated; common effects are fishy eructation, nausea and loose stools, minimized by enteric coating, freezing capsules and divided doses [36]. Bleeding time prolongation is modest; meta-analyses show no significant major-bleeding increase, even with antiplatelets/anticoagulants, but perioperative holding (3–7 days) is often practiced [36-40]. Atrial fibrillation risk is slightly increased with high-dose n-3 (hazard ratio ~1.2–1.35 in REDUCE-IT/STRENGTH), warranting rhythm review in elderly CKD [31]. Mercury/PCB contamination is negligible in molecularly distilled, IFOS-certified products; algal DHA offers a vegetarian, low-contaminant alternative [4]. KDIGO diabetes/CKD and AKI guidelines do not yet recommend routine omega-3 for renoprotection per se, but endorse CVD-risk management where n-3 may contribute [37,38,41-43].

11. Future Directions: From Fish Oil to Resolution Pharmacology

Key gaps include: (i) lack of adequately powered, biomarker-enriched renal-outcome trials with hard endpoints (≥40% eGFR decline, ESKD, MAKE); (ii) unclear EPA:DHA ratio, dose-response and duration for renal SPMs; (iii) limited human renal lipidomic; (iv) unknown interactions with SGLT2 inhibitors/finerenone/GLP-1 agonists; and (v) absence of approved SPM drugs [6,10,30,44].

Priorities for the next 5 years: (i) Precision trials: Enrich DKD/AKI cohorts by Omega-3 Index <6%, high soluble urokinase plasminogen activator receptor/TNF-receptor, APOL1 risk or hypertriglyceridaemia; test EPA+DHA 4 g/day vs. icosapent ethyl vs. placebo on UACR slope, eGFR decline and cardiac remodelling [24,29]. (ii) SPM therapeutics: Develop stable RvD1, RvE1, MaR1 and PD1 analogues, LGR6/ChemR23 agonists and 15-LOX modulators with oral/bioavailable formulations; explore low-dose aspirin to trigger 15-epi-lipoxins/resolvins [6,10]. (iii) Targeted delivery: Kidney-targeted nanoparticles, exosomal SPMs and GPR120-biased agonists to maximize renal exposure while minimizing systemic fish-oil burden [6]. (iv) Omics integration: Pair plasma/urine lipid-mediator panels (RvD1, PD1, MaR1, 18-HEPE) with proteomics to identify responders and titrate therapy [7,33]. (v) Implementation: Incorporate Omega-3 Index into CKD nutrition assessment and test Mediterranean/DASH-plus-n-3 dietary patterns for sustainable renoprotection [4,39-45].

Table 1. Preclinical and clinical evidence for the mechanisms of renoprotection induced by omega-3 polyunsaturated fatty acids (n-3 PUFAs; eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)): implications for diabetic nephropathy (DN), acute kidney injury (AKI) and chronic kidney disease (CKD) management. Evidence is hierarchically stratified from in vitro mechanism discovery in renal resident cells (Tier I), through disease-specific preclinical models of DN (Tier II), AKI (Tier III) and CKD progression/fibrosis (Tier IV), to randomized clinical trials in IgA nephropathy (Tier V), systematic reviews and meta-analyses in DN and CKD (Tier VI), AKI-prevention trials (Tier VII), and population-level cohort and human lipidomic evidence (Tier VIII). Mechanistically, EPA/DHA displace arachidonic-acid-derived pro-inflammatory eicosanoids and are enzymatically converted into specialized pro-resolving mediators (SPMs: resolvins, protectins, maresins) that engage ALX/FPR2-type receptors, suppress NF-κB/NLRP3/JAK2-STAT3/p38-MAPK-driven inflammation and oxidative stress, reinforce p62-Keap1-Nrf2 antioxidant defense, preserve podocyte and tubular epithelial integrity, and blunt TGF-β1-directed fibrogenesis.

Evidence domain / experimental model	Omega-3 intervention (source; dose; schedule)	Principal renal phenotype(s)	Molecular and signaling mechanism(s) (cellular and molecular targets)	Translational implication for DN / AKI / CKD management	Ref.
TIER I — IN VITRO CELLULAR AND MOLECULAR MECHANISMS (RENAL RESIDENT CELLS)					
Mouse glomerular mesangial cells under high-glucose (30 mmol/L) challenge (in vitro DN mimic)	Maresin 1 (MaR1, DHA-derived SPM); 10 nmol/L protective concentration	Mesangial cell injury mitigated; high-glucose-driven inflammation and early fibrogenic program suppressed	NLRP3 inflammasome blunted: NLRP3, caspase-1 and IL-1β↓ with procaspase-1/pro-IL-1β restored; ROS↓; TGF-β1↓ and fibronectin↓ (dose-dependent)	Interrupts the NLRP3-inflammation → TGF-β1/fibronectin-fibrosis axis central to DN glomerulosclerosis	[46]
Cultured podocytes (TNF-α challenge) with adriamycin-nephropathy in vivo validation	Resolvin D1 (RvD1, DHA-derived SPM); early-treatment window	Synaptopodin expression preserved; proteinuria, glomerulosclerosis and tubulointerstitial fibrosis attenuated (early, not late, treatment effective)	ALX/FPR2-dependent prevention of 14-3-3β acetylation, maintaining the 14-3-3β/synaptopodin complex; macrophage M1-to-M2 phenotypic shift	Direct podocyte-protective, anti-proteinuric mechanism operating beyond leukocyte-directed immunomodulation	[47]
TIER II — PRECLINICAL EVIDENCE: DIABETIC NEPHROPATHY					
Streptozotocin-nicotinamide-induced diabetic rats	Dietary fish oil (or flaxseed oil) supplementation, preventive	Renal oxidative stress, protein glycation and histological tubular injury reduced	Renal IL-6↓ and NF-κB p65↓; antioxidant defense gene expression restored; lipid peroxidation and glycation burden↓	Dietary n-3 PUFA restraint of the oxidative-glycemic-inflammatory triad that drives DN progression	[48]
Streptozotocin-diabetic mice subjected to renal ischemia-	Resolvin D1 (RvD1) administration	Heightened susceptibility to ischemic AKI in diabetes attenuated;	NF-κB signaling↓; renal cell apoptosis↓; diabetic patients with higher plasma RvD1	SPM insufficiency as a mechanism of AKI vulnerability in DKD; RvD1	[49]

reperfusion (AKI superimposed on diabetic kidney disease), with human plasma correlation		renal structural and functional damage↓	tolerated ischemic AKI better	replacement proposed as a targeted prevention strategy	
TIER III — PRECLINICAL EVIDENCE: ACUTE KIDNEY INJURY (ISCHEMIC, SEPTIC AND NEPHROTOXIC)					
Murine renal ischemia-reperfusion injury	D-series resolvins (RvD1–RvD3) and protectin D1; DHA infusion (5 µg/g body weight)	Postischemic serum creatinine↓; leukocyte influx↓; interstitial fibrosis↓, even when administration begins only after reperfusion	Endogenous DHA-to-SPM biosynthesis demonstrated in the postischemic kidney (LC-MS/MS lipidomics); TLR-mediated macrophage activation blocked	Proof of concept for resolution pharmacology: amplifying the endogenous resolution response, not merely suppressing inflammation, in AKI	[50]
Cecal ligation and puncture (CLP) septic AKI, rat	Fish oil, 4-day pretreatment (dexamethasone comparator)	Survival↑; serum creatinine, BUN, NGAL and KIM-1↓; oxidative injury and tubular apoptosis (TUNEL)↓	JAK2/STAT3 and p38-MAPK signaling inhibited; antioxidant capacity restored (SOD, GSH-Px↑; MDA↓); Bcl-2-family-mediated apoptosis suppressed	Systemic anti-inflammatory, antioxidant and anti-apoptotic preconditioning against sepsis-associated AKI	[51]
Cisplatin nephrotoxicity, mouse (single-dose AKI and repeated-dose chronic-fibrosis protocols)	EPA and DHA, alone or in combination; oral supplementation	Oxidative damage, inflammation and apoptosis mitigated, EPA+DHA combination superior to either alone; progression to chronic renal fibrosis after repeated cisplatin prevented	p62-Keap1-Nrf2 antioxidant transcription program activated; Nrf2-MDM2-p53-mediated apoptosis of tubular epithelial cells inhibited	Chemo-nephroprotection with rational EPA+DHA co-formulation; Nrf2 defined as the nodal renoprotective molecular switch	[52]
TIER IV — PRECLINICAL EVIDENCE: CKD PROGRESSION AND FIBROSIS (BALANCED APPRAISAL)					
Adenine-induced tubulointerstitial CKD, mouse (inflammatory-fibrotic model)	Fish oil supplementation	Renal IL-6, IL-1β and CXCL10↓; myofibroblast (α-SMA) and TGF-β markers↓; however, renal function and renal Klotho expression NOT restored	Selective suppression of inflammatory and fibrotic transcriptional markers without rescue of Klotho deficiency	Deliberate balanced appraisal: anti-inflammatory action alone is insufficient to reverse established CKD; supports early, adjunctive rather than rescue use	[53]
TIER V — CLINICAL EVIDENCE: IgA NEPHROPATHY RANDOMIZED TRIALS					

IgA nephropathy with persistent proteinuria; 2-year multicenter RCT (n = 106) with extended long-term follow-up	Fish oil 12 g/day (EPA+DHA) vs olive-oil placebo	≥50% serum creatinine rise in 6% (fish oil) vs 33% (placebo), P = 0.002; slower annual renal-function decline; benefit durable on multi-year follow-up	Putative: suppressed eicosanoid/cytokine-mediated glomerular injury; improved membrane fluidity, blood rheology and renal hemodynamics	Landmark clinical evidence that n-3 PUFAs retard progression of IgA nephropathy, the prototype immune-glomerular CKD	[54,55]
Severe IgA nephropathy; randomized high-dose vs low-dose comparison	High-dose vs low-dose omega-3 fatty acids	No additional renal protection from dose escalation; renal function generally stabilized in both arms	Dose-response plateau, consistent with saturation of n-3 substrate incorporation into membrane phospholipids and eicosanoid/SPM biosynthetic capacity	Dose-finding message: moderate-dose, long-term supplementation is the rational prescription; escalation offers no incremental benefit	[56]
TIER VI — CLINICAL EVIDENCE: DIABETIC NEPHROPATHY AND CKD (SYSTEMATIC REVIEWS AND META-ANALYSES)					
Meta-analysis of 17 clinical trials (n = 626) across IgA nephropathy, diabetic and lupus nephropathies	n-3 LCPUFA 0.7–5.1 g/day; median follow-up 9 months	Urine protein excretion reduced (Cohen's d = −0.19, P = 0.01; ≈190 mg/day reduction at 1 g/day baseline proteinuria); GFR decline slower but not significant	Anti-proteinuric effect convergent across glomerular diseases; functional (GFR) preservation unproven in small, heterogeneous trials	Quantitative anchor of n-3 renoprotection: proteinuria-centered benefit and a clearly defined evidence gap for hard renal endpoints	[57]
Meta-analysis of 10 RCTs (n = 344) in diabetic nephropathy	Omega-3 supplementation; benefit confined to interventions of ≥24 weeks	Proteinuria reduced in type 2 diabetes (SMD −0.29, P = 0.03) and in trials ≥24 weeks (SMD −0.30, P = 0.04); eGFR change not significant	Anti-proteinuric action requires sustained (≥6-month) exposure; neutral effects on HbA1c and LDL-cholesterol confirm metabolic safety	DN-specific, time-dependent anti-proteinuric benefit supporting adjunctive long-term supplementation	[58]
Meta-analysis of 9 RCTs (n = 444) in chronic kidney disease	Omega-3 supplementation as adjunctive therapy	Proteinuria↓ (SMD −0.31, P = 0.004); end-stage renal disease risk↓ (RR 0.49, 95% CI 0.24–0.99); creatinine clearance and eGFR unchanged	Anti-proteinuric and ESRD-risk signal across CKD etiologies; filtration markers stable within available trial durations	Outcome-level (ESRD) signal for omega-3 as adjunctive CKD therapy; trials underpowered for mortality	[59]
TIER VII — CLINICAL EVIDENCE: AKI PREVENTION (CONTRAST-INDUCED NEPHROPATHY)					
Patients undergoing elective percutaneous	Single 3750 mg omega-3 dose 12 h pre-procedure +	Post-PCI cystatin C rise significantly attenuated (P < 0.001); serum	Peri-procedural antioxidant/anti-inflammatory bioavailability within	Proof of concept for pharmacologic CIN prevention; single-bolus design limits	[60]

coronary intervention (n = 85, double-blind RCT)	hydration vs placebo	creatinine trend only (P = 0.08); CIN events rare	the contrast-injury time window	creatinine-based conclusions	
CKD patients (eGFR 30–60 mL/min/1.73 m²) undergoing elective PCI (n = 80, double-blind RCT)	Single 2500 mg omega-3 dose 12 h pre-procedure + hydration vs placebo	No significant effect on post-PCI serum creatinine or cystatin C; CIN 16.2% vs 9.3% (P = 0.50)	Single-bolus exposure insufficient to counteract contrast nephropathy in the highest-risk (CKD) stratum	Negative trial in the target population: dose, duration and timing optimization is mandatory before periprocedural omega-3 use	[61]
TIER VIII — POPULATION-LEVEL AND HUMAN MECHANISTIC (LIPIDOMIC) EVIDENCE					
Pooled analysis of 19 international cohorts (n = 25,570; median follow-up 11.3 years)	Circulating seafood-derived n-3 PUFAs (EPA, DPA, DHA) as objective exposure biomarkers	Incident CKD in 19.3% of participants; higher seafood n-3 PUFA levels associated with lower incident CKD (RR 0.92, 95% CI 0.86–0.98 per interquintile range, P = 0.009); consistent for ≥40% eGFR decline; plant-derived ALA null	Dose-response exposure-outcome gradient across general and high-risk populations, supporting (without proving) partial causality	Population-level kidney-protective signal for seafood n-3 PUFA intake; ≈8% lower incident-CKD risk per interquintile increment	[62]
Human serum lipidomics (LC-MS/MS oxylipin profiling) in IgA nephropathy patients receiving fish oil vs corn-oil placebo	Fish oil supplementation (clinical IgAN cohort)	Oxylipin profiles shifted with supplementation and tracked kidney functional alterations	In vivo confirmation of eicosanoid/oxylipin pathway engagement: the molecular interface through which n-3 PUFAs reprogram renal inflammation	Lipidomic biomarker platform to monitor target engagement and stratify therapeutic responders	[63]

INTEGRATIVE SYNTHESIS:

Multi-tier evidence convergence: omega-3 PUFAs operate as substrates of resolution pharmacology, reprogramming renal injury from persistent inflammation toward active resolution via specialized pro-resolving mediators (resolvins, protectins, maresins). The most consistent clinical signal is anti-proteinuric (landmark IgAN RCT plus meta-analyses across DN and CKD; approximately 190 mg/day urine-protein reduction at 1 g/day baseline proteinuria), accompanied by lower incident CKD at population level (RR 0.92 per interquintile range of seafood n-3 PUFA). By contrast, single-bolus periprocedural dosing, very-high-dose regimens and established fibrotic CKD yield no functional benefit, indicating that efficacy is contingent on sustained exposure, early disease stage and adequate dosing. This framework positions long-term n-3 PUFA supplementation, next-generation SPM analogues and lipidomic responder stratification as rational renoprotective strategies for diabetic nephropathy, AKI and CKD management.

Abbreviations:

α-SMA, alpha-smooth muscle actin; AKI, acute kidney injury; ALA, alpha-linolenic acid; ALX/FPR2, lipoxin A4/formyl peptide receptor 2; BUN, blood urea nitrogen; CKD, chronic kidney disease; CIN, contrast-induced nephropathy; CLP, cecal ligation and puncture; CXCL10, C-X-C motif chemokine 10; DHA, docosahexaenoic acid; DN, diabetic nephropathy; DPA, docosapentaenoic acid; DKD, diabetic kidney disease; EPA, eicosapentaenoic acid; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; FN, fibronectin; GFR, glomerular filtration rate; GSH-Px, glutathione peroxidase; IgAN, IgA nephropathy; IL, interleukin; JAK2/STAT3, Janus kinase 2/signal transducer and activator of transcription 3; KIM-1, kidney injury molecule-1; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LCPUFA, long-chain polyunsaturated fatty acid; MaR1, maresin 1; MDA, malondialdehyde; NGAL, neutrophil gelatinase-associated lipocalin; NF-κB, nuclear factor-kappa B; NLRP3, NLR family pyrin domain containing 3; Nrf2, nuclear factor erythroid 2-related factor 2; PCI, percutaneous coronary intervention; PD1, protectin D1; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; RvD1, resolvin D1; SCr, serum creatinine; SOD, superoxide dismutase; SPM, specialized pro-resolving mediator; STZ, streptozotocin; TGF-β1, transforming growth factor-beta 1; TNF-α, tumor necrosis factor-alpha; TLR, toll-like receptor.

Note (Evidence appraisal):

Evidence tiers follow the translational pipeline (in vitro mechanism → preclinical disease models → randomized trials and meta-analyses → population-level biomarker evidence). Both efficacy-positive and efficacy-neutral or negative studies (high-dose IgAN trial, single-bolus contrast-nephropathy trials, adenine-CKD model) were deliberately included to counteract positive-results publication bias. All entries derive from peer-reviewed sources with verifiable digital object identifiers (DOIs). No completed randomized trial of omega-3 PUFAs powered for dialysis or mortality endpoints in DN, AKI or CKD yet exists; ongoing trial networks are needed.

12. Conclusion

Omega-3 fatty acids exert coherent, multitargeted renoprotection spanning membranes, receptors (GPR120, PPARs), transcription (NF-κB, NRF2, SREBP-1), inflammasomes (NLRP3), mitochondria, autophagy/ferroptosis and, most distinctively, SPM-driven inflammation resolution. Preclinical DKD, AKI and fibrosis models demonstrate reduced albuminuria, podocyte/tubular injury and AKI-to-CKD transition with increased renal resolvins, protectins and maresins. Clinically, benefits are established for triglycerides, blood pressure, arterial stiffness and cardiovascular events, with modest/heterogeneous proteinuria effects and strongest signals in IgA nephropathy and hypertriglyceridaemic DKD. As safe, affordable adjuvants to RAAS/SGLT2/finerenone-based care, EPA+DHA, and imminently, SPM mimetics, merit rigorous, biomarker-guided trials to realize their full renoprotective potential.

Clinical Trial Number

Not applicable.

Conflict of Interest

The authors declare no competing interests that may have influenced in this manuscript.

Generative AI statement

The authors declare that Gen AI and large language models (LLMs) were used in this manuscript. Generative AI items like “QuillBot” and “DeepL” were used for structural editing and improve handwriting of the text. Also, the “NOAH AI” platform was used for some parts of figures illustrations.

Author Agreement

This paper is submitted with the agreement of all its co-authors and the author list has been approved by all authors.

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Author Contribution

We agree that the author list and order is correct and complete. We understand that any changes to the author list (additions, deletions, order changes) after submission will require a formal request to the editor signed by all authors. Order list include:

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