

Fish oil supplementation in diabetic nephropathy prevents: inflammatory and oxidative stress target

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Abstract

Diabetic nephropathy is a major cause of progressive kidney disease and end-stage renal disease. The major treatment strategy for the prevention and cure of diabetic nephropathy development and progression is based on the management of blood glucose, blood pressure, lipids, oxidative stress, and inflammation. Fish oil is important for human health because of its high content of polyunsaturated fatty acids like omega-3. Inflammatory and oxidative stress pathways are potential targets of omega-3 fish oil for the development of diabetic nephropathy. Many studies have proven the activity of fish oil for both single and adjuvant therapy. However, not all experiments on animal models are effective in human research. This review provides thoughts on progress in research on a pre-clinical and clinical study of fish oil as a diabetic nephropathy therapy. According to a literature search, fish oil inhibits inflammation, specifically tumour necrosis factor- α , interleukin-1, interleukin-6, and nuclear factor- κ B. Several markers have an influence on oxidative stress, including glutathione, superoxide dismutase-1, catalase, glutathione peroxidase-1, glutathione reductase, and malondialdehyde. Several investigations have shown that research findings in experimental animals are not always the same as those in clinical trials. The main findings of this review were to identify the main causes of oxidative stress and inflammation from the use of fish oil in the prevention of diabetic nephropathy. Different results were found in several animal experiments and clinical tests, but they should be considered when treating diabetes. In the future, things like where the oil comes from and how good the fish oil is must also be considered carefully.

1. Introduction

Diabetic kidney disease or diabetic nephropathy (DN) is one of the main complications of diabetes mellitus (DM), characterized by oxidative stress, inflammatory response, thickening of basement membranes, fibrosis, necrosis, albuminuria, and renal dysfunction (Kishore *et al.*, 2020; Cao *et al.*, 2022). The number of cases of DM in the world with uncontrolled blood sugar levels causing complications is increasing, especially in the kidneys. Many studies have found that DN occurs in more than 40% of diabetic patients (Hu *et al.*, 2017; Lima *et al.*, 2022) and accounts for roughly 45% of new cases of end-stage renal disease (Domingueti *et al.*, 2016). Although the pathogenesis of DN is unknown, irregularities in glucose and lipid

metabolism are important to comprehend; chronic exposure of renal cells to glucose overload and lipids causes oxidative stress, inflammation, and intracellular hypoxia, eventually leading to interstitial fibrosis, glomerular hyperfiltration, and glomerulosclerosis, which later set the stage for DN (Adelusi *et al.*, 2020; Ayinde *et al.*, 2020; Chaudhuri *et al.*, 2022)

Controlling blood glucose levels and blocking the renin-angiotensin system are the major treatment approaches for treating or preventing the development and progression of DN (Ni *et al.*, 2019). Despite this, the disease incidence rate continues to rise due to poor effectiveness of treatments and a slew of severe side effects. Although currently available anti-diabetic

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medications such as biguanides and sulfonylureas are effective in controlling hyperglycemia, they are unable to entirely prevent the onset and progression of associated consequences (Gurumallu *et al.*, 2022). Because of the extremely long course and incurable character of diabetes, lifetime usage of anti-diabetic medicines is currently the global strategy to diabetes therapy (Huang *et al.*, 2020). Due to treatment-related financial pressures and medication side effects, the majority of patients do not adhere to these therapeutic measures (Zaccardi *et al.*, 2016).

The development of novel, effective, and safer therapeutic options that target glycemic management, oxidative stress inhibition, and inflammatory pathways involved in the evolution of DN has recently gotten a lot of attention (Ni *et al.*, 2019). As a result, new treatments with hypoglycemic, antioxidant, and anti-inflammatory properties may provide protection against DN (Abou-Hany *et al.*, 2018; Xu *et al.*, 2018). Fish oil contain omega-3 polyunsaturated fatty acids (n-3 PUFA) acts as an antioxidant supplement (Jiang *et al.*, 2019), and anti-inflammation (Crupi and Cuzzocrea, 2022; Sasongko *et al.*, 2019). Omega-3 polyunsaturated fatty acids have been demonstrated in clinical research to be beneficial in reducing inflammatory conditions in renal diseases (Keapai *et al.*, 2016; Méndez-Morales *et al.*, 2022) by competing with the enzymatic metabolism of arachidonic acid, which is transformed to pro-inflammatory eicosanoids such as prostaglandins, thromboxane, and leukotrienes, long chain n-3 PUFA regulate inflammatory pathways (Gebauer *et al.*, 2006). Unsaturated fatty acids, such as monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs), have been found to increase insulin sensitivity (Gao *et al.*, 2017). The beneficial effects of activity as anti-inflammatory and oxidative stress have demonstrated that omega 3 fatty acids can prevent kidney injury in cases of diabetes (Jangale *et al.*, 2016; Ghadge *et al.*, 2016; Rashidi *et al.*, 2020). Recent studies have proven the nephroprotective activity of fish oil containing n-3 PUFA for both monotherapy and adjuvant therapy. However, not all experiments on animal models are effective in human studies (Itsipoulos *et al.*, 2018). The novelty of this review is the discovery of major markers of oxidative stress and inflammation pathways in the application of fish oil for the prevention of DN. From these findings, the researchers were able to directly determine the target parameters without screening all markers in clinical or pre-clinical study.

The aim of this review was to provide an insight into advances in research on pre-clinical and clinical studies of fish oil as a therapy for DN. Furthermore, practical considerations regarding fish oil supplementation on

nephroprotective effects including fatty acid profile, dose, route of administration, duration of treatment, population, and markers, will be discussed.

2. Diabetic nephropathy

Diabetic nephropathy has a wide range of clinical and pathophysiologic manifestations. Hyperglycemia causes degenerative changes such as glomerular hyperfiltration, epithelial hypertrophy, and microalbuminuria, which is followed by glomerular basement membrane thickening, mesangial matrix buildup, and overt proteinuria, and lastly glomerulosclerosis and end-stage renal disease

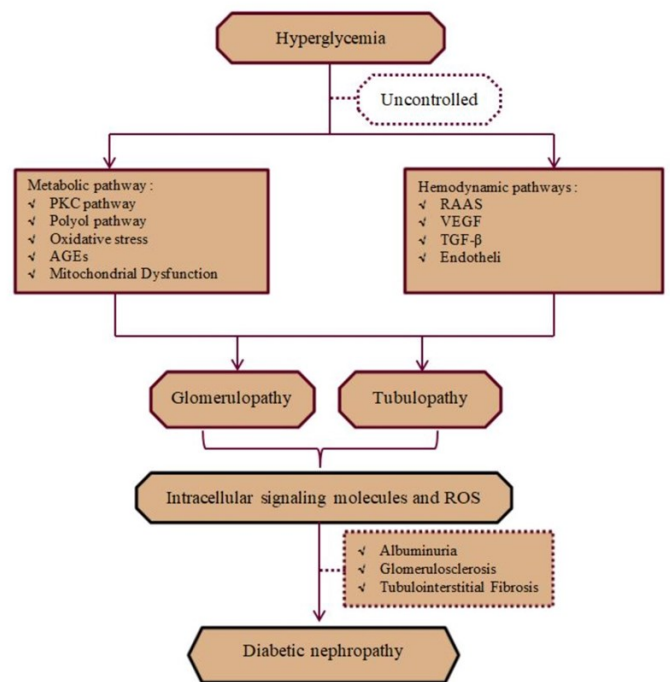


Figure 1. Metabolic pathways involved in the development of diabetic nephropathy. PKC: protein kinase C, AGEs: advanced glycation end products, RAAS: renin angiotensin aldosterone system, VEGF: vascular endothelial growth factor, ROS: reactive oxygen species, TGF- β : transforming growth factor-beta (Vinod, 2012)

(Mogensen *et al.*, 1983; Vinod, 2012). Increased oxidant species have been identified as the key unifying upstream event in a number of pathophysiological processes that underpin DN (Bohlouli *et al.*, 2021). Excessive production of reactive oxygen species (ROS) in diabetes individuals leads to oxidative stress and inflammation (Wang *et al.*, 2021). The pathogenesis of diabetic nephropathy is shown in Figure 1.

3. Oxidative stress

Hyperglycemia causes an increase in oxidative stress and the overproduction of reactive oxygen species (ROS) (Lima *et al.*, 2022). The latter ROS causes cell membrane lipid peroxidation, protein oxidation, renal

vasoconstriction, and DNA damage (Vinod, 2012). A high quantity of ROS can stimulate numerous molecular mechanisms and impair the activity of antioxidant enzymes, which can lead to illnesses like DN (Bohlouli *et al.*, 2021). Under normal conditions, ROS are important in processes such as cell signaling, aging, and degenerative diseases (Hajam *et al.*, 2022; Singh *et al.*, 2022). The kidney is especially vulnerable to damage from high blood glucose levels. The nephron (glomeruli and tubuli) is an insulin-independent organ, and the circulatory glucose concentration in the environment and the expression of glucose facilitators control the glucose flow to cells (Ravindran and Munusamy, 2022).

4. Inflammation

Inflammation is also linked to the development of DN. Multiple studies have found considerably higher circulating inflammatory mediators, as well as increased immune cell infiltration and levels of adhesion molecules and chemokines in the kidneys of DN animal models and humans, indicating that inflammation plays a role in the development of DN (Zheng and Zheng, 2016; Pérez-Morales *et al.*, 2019). Major production of inflammatory markers and an accumulation of inflammatory cells were identified in the renal tissue of patients with DN (Eisa *et al.*, 2021). As nephropathy progresses, these components' concentrations increase, and they've all been associated with increased albumin levels in the urine and clinical signs of glomerular and tubulointerstitial injury (Donate-Correa *et al.*, 2020). As a result, anti-inflammatory substances may have the ability to alleviate DN (Liao *et al.*, 2022).

5. Fish oil

Fish is one of the natural resources that contain essential fatty acids (FAs) for health (Sasongko *et al.*, 2018), and many studies have been carried out to be developed as drugs and supplements (Rizliya and Mendis, 2014; Sasongko *et al.*, 2021). Lipids in fish oil are mainly available as triacylglycerols (TAGs). Glycerol carbon atoms are counted with the stereochemical system, with the locations sn-1 and sn-3 outer, with the center position sn-2 (Alfio *et al.*, 2021). The lipid classes are different: saturated FAs (SFAs), monounsaturated FAs (MUFAs), and polyunsaturated FAs (PUFAs). Different types of FAs are found in lipids (PUFAs, containing more than one C-C double bond) and MUFAs (having one C-C double bond) (Zhang *et al.*, 2020). In general, the lipids of fish vary considerably according to their geographical location, kind of water, diet, season and ripe fish (Nurnadia *et al.*, 2011). Recent studies have shown the renoprotective benefits of a fish diet and supplementation with fish oil. Several studies

show that omega-3 FAs can reduce inflammation. They may do so by enhancing anti-inflammatory and antioxidant components or compounds in the body. The following Tables 1 and 2 summarize the general features of the studies covered.

All polyunsaturated fatty acids (PUFAs) may be synthesized by humans except two: linoleic acid (LA) and α -linolenic acid (ALA), which are considered essential fatty acids and must be obtained from dietary consumption. LA is a precursor to the omega-6 fatty acid, whereas ALA is a precursor to the omega-3 compounds (Mullin *et al.*, 2021). Omega-3 unsaturated fatty acids containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are reported to have various biological activities such as anti-inflammatory, cardiovascular, and metabolic diseases (Zhou *et al.*, 2021), (Sasongko *et al.*, 2018). In the stomach and throughout the body, omega-3 PUFAs have anti-inflammatory and immunoregulatory effects (Parian *et al.*, 2015). The cyclooxygenase (COX) pathway (specifically COX-2), which generates prostaglandin E-2, a pain and inflammation promoter, is downregulated by omega-3 fatty acids. This route often uses arachidonic acid (AA) as a substrate. EPA is a chemical homologue that varies from AA solely in the presence of the n3 double bond. It acts as a substitute substrate for COX and reduces the consumption of AA as a substrate for the COX enzyme. EPA also suppresses the 5-lipoxygenase pathway, which results in lower levels of proinflammatory leukotriene B4 in the body (Wild *et al.*, 2007). EPA and DHA are precursors for the synthesis of resolvins, which are generated to stop the neutrophil invasion, stimulate macrophage elimination of apoptotic cells, and promote tissue remodeling and homeostasis (Serhan *et al.*, 2004). Omega-6 fatty acids, such as LA, on the other hand, are more prone to proinflammatory activities (Ananthakrishnan *et al.*, 2013; Mullin and Limketkai, 2021). At various phases of inflammation, lipid mediators generated from omega-6 PUFA AA are implicated. Several lipid mediators, including the eicosanoids prostaglandins (PGs), thromboxanes (TXs), and leukotrienes (LTs), govern the onset of acute inflammation, modulating blood flow, endothelial permeability, polymorphonuclear neutrophil (PMN) chemotaxis, and blood clotting (Flower, 2006). The enzymes cyclooxygenase (COX) and lipoxygenase (LO) mediate the transformation of AA into a variety of pro-inflammatory mediators such as PGs, prostacyclin (PGI₂), TXA₂, and pro-inflammatory leukotrienes, commonly known as 4-series leukotrienes (Funk, 2001; Powell and Rokach, 2015). Omega-3 fatty acids have been shown to modulate gut immunity by reducing proinflammatory cytokines such as interleukin (IL)-1 and tumor necrosis factor (TNF)- α , as well as the peroxisome

Table 1. Clinical trials and meta-analyses of fish oil enriched omega-3 in diabetic nephropathy

Sample	Study Population	Methods	Duration	Dose	Clinical Outcomes in Inflammatory and/ or oxidative stress	Reference
Fish oil	32 overweight or obese patients (18 women and 14 men)	A pre-post pilot study in Brazil	8 weeks	Four times 2400 mg/day	↓ TNF α , ↓ IL-1 β , and ↓ IL-6	Souza <i>et al.</i> (2020)
Omega-3 PUFA soft gels containing 600 mg EPA and 300 DHA	61 patients (30 placebo - 31 interventions) in T2DM	Double-blind randomised placebo-controlled clinical trial in Iran	10 weeks	Three soft gels/day	↑ Ferric reducing ability of plasma (FRAP), induction antioxidant gene expression of NRF2, and ↓	Golpouir <i>et al.</i> (2020)
Omega-3 capsules	44 patients (22 placebo - 22 intervention) in T2DM with nonalcoholic fatty liver disease	Randomized double-blind clinical trial in Iran	12 weeks	Twice omega-3 capsules (1000 mg)/day	↑ IL-6	Orang <i>et al.</i> (2020)
Omega-3	1312 Inclusion criteria in T2DM patients	Double-blind randomised placebo-controlled clinical trial	5.3 years	One gram of Omega-3 FA daily (Omacor, 465 mg EPA + 375 mg DHA)	Not significant reduce concentrations of inflammatory biomarkers (IL-6, hsCRP or NT-proBNP)	Limonte <i>et al.</i> (2021)

Symbols ↑ or ↓ = significantly different compared with placebo group or before treatment (pretest)

proliferator-activated receptor/nuclear transcription factor kappa-beta (PPAR-/NF-kB), and improving epithelial barrier function and mucosal healing (Mullin *et al.*, 2021).

7. Fish oil in oxidative stress targets

Oxidative stress is an imbalance between endogenous antioxidant enzymes and free radicals (Lobo *et al.*, 2010). At the cellular level, DM causes renal mitochondrial injury and upregulates inducible nitric oxide synthase (iNOS), resulting in increased levels of ROS and reactive nitrogen species (RNS) due to lipid peroxidation and protein carbonylation (Taslimi and Gulçin, 2018; Gulçin, 2020; Stanton, 2021). ROS promotes inflammation by activating a variety of redox and inflammatory signaling pathways, including nuclear factor (NF)-kappa β (Mayyas *et al.*, 2019). Fish oil contains omega-3 PUFAs, which are antioxidants that influence lipid mediators and signaling pathways (Adkins and Kelley, 2010). Omega-3 PUFAs decrease oxidative stress in human and animal models by boosting antioxidant levels of superoxide dismutase (SOD) and glutathione (GSH) (Taneda *et al.*, 2010; Jangale *et al.*,

2016). GSH is an essential endogenous antioxidant for the detoxification of reactive oxygen species (ROS) and the maintenance of intracellular redox balance (Asgher *et al.*, 2017).

8. Conclusion

The main finding of this review is to identify the main makers of oxidative stress and inflammation from the use of fish oil in the prevention of DN. Different results were found in several animal experiments and clinical tests, but they should be taken into account when treating diabetes. In future tests, the source of the oil and the quality of the fish oil must be considered.

Conflict of interest

The authors declare no conflict of interest.

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Table 2. *In-vivo* study of fish oil enriched omega-3 in diabetic nephropathy

Sample	Animals	Duration	Dose	Inflammatory markers	Oxidative stress markers	Reference
Fish Oil	Wistar rats	35 days	10% w/w FO mixed with pellets	↓ mRNA expression of IL-6, and NF-κB	↓ TBARS, ↑ CAT, not significantly with SOD, mRNA expression of SOD-1, and GPx-1, and ↑ mRNA expression of CAT	Jangale <i>et al.</i> (2016)
Omega-3	Wistar rats	8 weeks	415 mg/kg/day, 5 times/week	↓ TNF-α, ↓ IL-1β, and ↓ IL-6	↑ GSH, ↑ SOD1, ↑ CAT, ↑ GPx1, ↑ GR, ↓ MDA, and ↓	El-Boshy <i>et al.</i> (2021)
Omega-3 fish oil (containing EPA 180 mg and DHA 120 mg)	Sprague-Dawley rats	4 weeks	Omega-3 fish oil (10% W/W diet)	n/a	↓ MDA	Eraky <i>et al.</i> (2018)
Fish Oil	Male LDLr ^{-/-} /ApoB ^{100/100} mice	8-11 weeks	Fish oil contains 44% EPA and 25% DHA mix with feed	↓ TNF-α, ↓ IL-1β, and iNOS gene expression	n/a	Perazza <i>et al.</i> (2021)
Ethyl eicosapentaenoate (EPA-E)	Male C57/BL6 mice	19 weeks	1000 mg/kg body weight/day of EPA-E	n/a	↓ MDA, ↓ mRNA expression of p47phox, Nox2, and Nox4 in renal	Yasuzawa <i>et al.</i> (2021)
Fish oil	Wistar rats	4 weeks	3000 mg/kg body weight/day	n/a	↓ MDA and ↑ CAT	Parveen <i>et al.</i> (2019)
Fish oil	Wistar rats	4 weeks	2.5% of fish oil supplements containing 16% EPA and 19%	n/a	↓ MDA	Vitlov Uljević <i>et al.</i> (2019)

Symbols ↑ or ↓ = significantly different compared with diabetic group.

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