



Fish Oil Supplements in Lupus - Weighing the Evidence



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Abstract

This review strives to examine the beneficial effects, or of lack thereof, of fish oil supplement use in systemic lupus erythematosus (SLE) patients. The majority of prospective studies reviewed in this article render support to fish oil supplement use in SLE patients, as evident by reduction in disease activity, inflammatory markers and increase in individual global well-being scores. The existing evidence also provides guidance with regards to future research.

Keywords: Lupus; Fish oil; Omega fish oil; Inflammation; Systemic lupus erythematosus; SLE; Western diet

Abbreviations: DHA: Docosahexaenoic Acid; DMARD: Disease Modifying Antirheumatic Drugs; EPA: Eicosapentaenoic Acid; HDL: High Density Lipoproteins; IL: Interleukin; LTB4: Leukotriene B4; NSAID: Nonsteroidal Anti-Inflammatory Drug; PhyGA: Physician's Global Assessment; SF-36: Short Form Survey (36 Items); SLAM-R: Systemic Lupus Activity Measurement - Revised; SLE: Systemic Lupus Erythematosus; VLDL: Very Low Density Lipoprotein; NS: Not Specified; ESR: Erythrocyte Sedimentation Rate; ↑: Enhanced/Increased; ↓: Reduced/ Decreased; ↔: No Change; NA: Not Applicable; HDL: High Density Lipoprotein; TG: Triglycerides; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; FSS: Fatigue Severity Scale; BILAG: British Isles Lupus Assessment Group; NA: Not Applicable; RBC: Red Blood Cell; Ω3-FA: Omega-3 Fatty Acids; Gm: Grams

Introduction

Fish oil nutritional supplement use was brought to relevance by an epidemiological study [1] conducted from 1950-1974 in Greenland Eskimos. Low incidence of chronic medical problems such as diabetes mellitus, bronchial asthma, multiple sclerosis and psoriasis in Eskimos in comparison to their age and gender matched Western European cohorts were attributed to omega-3 fatty acids. Greenland Eskimo diet predominantly comprises of fish; fish oil, in turn, is known to be a rich source of omega-3 fatty acids (n-3). Also known as eicosanoids, the omega-3 fatty acids are polyunsaturated fatty acids (n-3 PUFA), and chief among them are Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Both EPA and DHA tip the scales for anti-inflammatory eicosanoids over pro-inflammatory omega-6 fatty acids (n-6 PUFA). The latter group of polyunsaturated fatty acids (n-6 PUFA) comprise of immunoactive eicosanoids such as prostaglandin E2 (PGE2), thromboxane B2 (TXB2), and leukotriene B4 (LTB4) [2].

Animal studies established a causal relationship between EPA and DHA and their ability to promote anti-inflammatory

effects [3-5]. Subsequent clinical trials in humans confirmed the beneficial anti-inflammatory properties of the omega-3 fatty acids EPA and DHA in improving clinical outcomes in chronic medical illnesses such as coronary artery disease, obesity-related diseases and rheumatic diseases [6-10]. Rheumatic diseases, in particular, are widely recognized to have inflammatory pathophysiology at their core and thus represent ideal medical conditions to gauge clinical efficacy upon treatment with fish oil. In this review, we focus on available evidence in the literature with regards to clinical outcomes in systemic lupus erythematosus (SLE) patients treated with fish oil supplements [11-20]. SLE is one of the most common rheumatic diseases along with rheumatoid arthritis (RA) and osteoarthritis (OA), with prevalence rates ranging from 20 to 150 cases per 100,000 [21-23].

Impact of Fish Oil Supplementation in Systemic Lupus Erythematosus (SLE)

We have identified ten studies [11-20] that assessed the effects of fish oil supplementation on various clinical outcomes

mostly in systemic lupus erythematosus (SLE) and in some lupus nephritis cohorts. The available evidence is tabulated in Table 1 based on the study design. Seven out of these ten studies exclusively included patients with SLE, two of the three remaining studies included only patients with lupus nephritis, while one study included both patients with SLE and Lupus nephritis. The number of patients included in these prospective studies ranged from 6 to 85 and the study duration ranged from 10-52 weeks. In the treatment group, the patients received anywhere from 0.54-3.24grams of EPA and 0.30-2.25grams of DHA per day. Also, in all the trials both treatment and control groups simultaneously continued treatment with non-steroidal anti-inflammatory drugs (NSAID) and disease modifying anti rheumatologic drugs (DMARD), except in the Lozovoy et al. [12] study, where the patients were treated with NSAIDs and anti-hypertensive's. Outcomes were measured using a range of global subjective rating scales, including the Physicians Global Assessment (PhyGA), Short Form Survey-36 (SF-36), Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Fatigue Severity Scale (FSS), and Systemic Lupus

Activity Measurement- Revised (SLAM- R). Objective outcome measures included a host of biomarkers such as serum interleukin (IL) levels, erythrocyte sedimentation rate (ESR), lipid profiles, 8-isoprostane levels (an indicator of oxidative stress), red blood cell EPA concentration, etc.

Five of these studies [11,12,14,16,18] showed that patients in the treatment group that received daily omega-3 fatty acid supplementation with EPA and DHA benefitted with reduced disease activity, further corroborated by improvement in various biomarkers assayed, as outlined in Table 1. The study by Bello et al. [13], likely due to its shorter trial duration, failed to show any significant benefit in the treatment arm. In another SLE-only patient study [19], the initial benefits observed three months from baseline were not sustained at six months from baseline. Three of the studies reviewed in this article [15,17,20] included patients with lupus nephritis. Lupus nephritis patients who received fish oil supplementation exhibited a reduction in oxidative stress, increase in platelet EPA levels, reduction in pro-inflammatory cytokines such as LTB4 and a favorable lipid profile.

Table 1: Impact of Fish Oil Supplementation in Systemic Lupus Erythematosus (SLE) and Lupus Nephritis

Study Design	Ref	Patients (N)	Study Duration (Weeks)	Ω3-Fa/Day (Gm/Day)	Global Impression Scales in Treatment Group	Biomarkers in Treatment Group
Double blind, Placebo Controlled	13	85	12	1.8g EPA 1.2g DHA	↔ Disease activity	↔ Endothelial function, Lipid profile, Inflammatory markers
	14	60	24	1.8g EPA 1.2g DHA	↓Disease activity (SLAM-R & BILAG scores)	↓oxidative stress, platelet 8-isoprostane ↑endothelial function
	16	52	24	0.54g EPA 0.30g DHA	↓Disease activity (SLAM-R & BILAG scores)	↔ Biomarkers
Double blind, Cross-over	20	21	52	2.7g EPA 1.7g DHA	↔ Disease activity	↓TG and VLDL ↔Renal function
	18	27	12	3.6g EPA 2.0g DHA	NA	↑RBC EPA levels
	19	17	24	N.S	Initial benefits were not sustained	NA
Single blind, Placebo Controlled	11	50	24	2.25g EPA 2.25g DHA	Improved PhyGA and SF-36 ↔SLEDAI and FSS scores	↑Serum IL-13 ↓ESR, IL-12
Placebo Controlled	*12	62	16	1.8g EPA 1.2g DHA	↓Disease activity (SLEDAI scores)	↑Adiponectin levels ↓Leptin and TG levels
No Placebo, Not Blind	17	12	10	1.08g EPA 0.72g DHA	NA	↑Platelet EPA, HDL ↓LTB4, TG, VLDL
	15	6	12	1.8g EPA	NA	↓Oxidative stress ↔Lipid profile

Overview of Mechanism of Action

The fish oil supplements EPA and DHA modulate inflammatory pathways putatively via altering the levels of polyunsaturated fatty acids (PUFA) in the cell membranes. Although cell membranes contain both omega-6 fatty acids (n-6 PUFA) and omega-3 fatty acids (n-3 PUFA), if the ratio of n-3 PUFA to n-6 PUFA is not adequate, the arachnoid acid derivatives from n-6 PUFA have been documented to favor pro-inflammatory cytokine production [24-28]. Through experimental studies [29-33] it has been reported that cell membrane composition of omega-3 fatty acid (n-3 PUFA) can be increased by dietary intake of these fatty acids. Omega-3 fatty acids reinforce anti-inflammatory pathways via a host of mechanisms including alteration of membrane receptors and modifying the synthesis of lipid mediators, in addition to inhibiting production of pro-inflammatory cytokines such as Tumor Necrosis Factor (TNF) and Interleukin-1 (IL-1) [34].

Conclusion

Modern Western diet with high omega-6 fatty acid to omega-3 fatty acid ratio in excess of 15:1 over recommended ratios (2) have been shown to up regulate inflammatory pathways. This skewing can well promote a wide spectrum of chronic medical illnesses with inflammatory underpinnings, including the common rheumatic diseases. The preponderance of data in systemic lupus erythematosus (SLE) attests to the beneficial effects of fish oil supplements (omega-3 fatty acids) in moderating inflammatory pathways and improving clinical outcomes, with similar findings being noted in patients with lupus nephritis. However, the existing evidence also raises questions regarding the long-term benefits of fish oil supplement use. Further research is warranted to see if fish oil supplementation could reduce dependence on steroids, NSAID and other immunosuppressive agents that are invariably associated with side effects. Given that fish oil supplements are well tolerated by humans (except for rare gastrointestinal discomfort), studies are also warranted to establish the efficacy of long-term fish oil therapy over several years.

Conflict of Interest

All authors concur with the findings in this review. No financial support was received for this work, and none of the authors have any conflict of interest.

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