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Omega-3 Fatty Acids in Rheumatic Diseases

A Critical Review

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Abstract: Many clinical trials of omega-3 fatty acids, supplied as fish oil supplements, have been carried out in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), lupus nephritis, and osteoarthritis (OA) over the past 3 decades. This review attempts to summarize the highlights of these studies to evaluate the clinical efficacy for omega-3 fatty acids to be added alongside existing treatment regimens. A total of 20 clinical trials have been carried out in RA, of which 16 exhibited significant improvements in multiple disease clinical outcomes. Nine clinical trials have been completed in SLE and lupus nephritis, of which 6 exhibited significant improvements in 1 or more clinical outcomes. A total of 4 clinical trials have been conducted in OA, of which 3 exhibited significant improvements in at least 1 clinical parameter. Multiple mechanisms for the clinical effects of omega-3 fatty acids have been implicated, including the modulation of eicosanoid synthesis toward a more anti-inflammatory profile and suppressed production of proinflammatory cytokines. Overall, fish oil supplements appear to be a safe and effective agent that could be added to the current treatment regimens in RA. Longer-term trials with larger patient cohort sizes are warranted to establish any long-term benefits of fish oil supplements in SLE, lupus nephritis, and OA.

Key Words: alternative medicine, DHA, eicosanoid, EPA, natural supplements, nutrition, osteoarthritis, rheumatoid arthritis, SLE, systemic lupus erythematosus

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Fish oil is rich in omega-3 fatty acids, which are part of a key family of polyunsaturated fatty acids (PUFAs). Both eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are important omega-3 fatty acids (n-3 PUFAs) that are primarily derived from marine-based sources.¹ Both EPA and DHA constitute an important component of cell membranes, influence membrane fluidity, and regulate membrane-receptor behavior.² In addition, n-3 PUFAs help regulate a large number of bodily functions including inflammation, blood pressure, blood clotting, and proper development and function of the nervous system.^{3,4}

The majority of Western diets (WDs) contain significantly higher levels of omega-6 than omega-3 fatty acids.^{5,6} The recommended dietary ratio of (omega-6):(omega-3) fatty acid intake has been suggested to be approximately 4:1⁵; however, the WD is typically associated with consumption in excess of a 15:1 ratio.⁵

In parallel, increased levels of n-6 PUFAs and decreased levels of n-3 PUFAs have been associated with elevated levels of proinflammatory eicosanoids, which can facilitate inflammatory and autoimmune diseases.⁷

The importance of dietary n-3 PUFAs was first brought to attention in an epidemiological study of Greenland Eskimos conducted in the 1980s.⁸ When compared with their age- and sex-matched Western European counterparts, the Eskimos had exceptionally low incidence rates of autoimmune and inflammatory diseases such as diabetes mellitus type 1, bronchial asthma, multiple sclerosis, and psoriasis. Further observational studies done with Greenland Eskimos^{9,10} suggested that consuming a diet high in n-3 PUFAs could lead to lower rates of chronic inflammatory diseases through alteration of eicosanoid precursors and modulation of other pathways.

Studies done in animals have shown a direct relationship between increased cellular levels of EPA and DHA and their ability to modulate proinflammatory mediators.^{11,12} Experimental studies in humans have corroborated these animal studies and have provided evidence that suggests increased dietary intake of n-3 PUFAs EPA and DHA play a role in anti-inflammatory function via alteration of the production of important proinflammatory eicosanoids prostaglandin E2 (PGE2), thromboxane B2, and leukotriene B4 (LTB4) toward a more anti-inflammatory profile.^{13,14} Clinical trials done in humans have shown that increased n-3 PUFAs have resulted in beneficial outcomes for coronary heart disease,¹⁵ obesity-related diseases,¹⁶ and rheumatic diseases.^{17–19} Previous meta-analyses or systemic reviews of fish oil in rheumatic diseases^{17–19} either concentrated on 1 particular rheumatic disease or focused on significantly fewer studies than this review. Examining multiple rheumatic diseases simultaneously offered the opportunity to better discriminate between possible n-3 PUFA mechanisms of action and comprehending differences in positive clinical outcomes. In this article, we review literature on the efficacy of the addition of fish oil supplementation alongside current treatment regimens on the following rheumatic diseases: rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), lupus nephritis, and osteoarthritis (OA).

METHODS

A computerized PubMed database search was conducted to retrieve articles for consideration utilizing the following search strategy: the MeSH terms (Fatty acids, Fish oils or Omega-3) AND (Rheumatoid arthritis or Lupus nephritis or Systemic lupus erythematosus or Osteoarthritis or Rheumatic diseases). The search identified 368 articles, of which 249 were on RA, 58 were on lupus nephritis or SLE, and 61 were on OA.

Criteria for Article Inclusion

The following a priori criteria were required for article inclusion: (1) randomized trial; (2) included control group consisting of at least a placebo or multiple n-3 PUFA dosage arms; (3) parallel or crossover design; (4) results for both placebo and treatment groups reported at baseline and follow-up; (5) quantifiable, daily

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oral dosage amount of EPA or DHA or both; and (6) published in full as a research article.

References of all retrieved articles were manually searched to obtain further relevant articles to ensure completeness. A total of 335 articles were excluded for not meeting all of the aforementioned criteria. Excluded articles were primarily studies on animals or nonhuman species, deficient in study design, or lacking daily oral dosage amounts of n-3 PUFAs. A separate search was conducted for other rheumatic diseases, such as Sjögren syndrome, which yielded 0 articles that met all criteria. From this process, a total of 33 articles were included in this review.

RESULTS

Impact of Fish Oil Supplementation on RA

At least 20 studies have been published on the role of fish oil supplementation in RA.^{20–39} All studies were double-blind and placebo controlled. Seventeen of these studies incorporated a parallel study design, whereas the remaining 3 studies utilized a crossover design,^{26,36,38} as summarized in Table 1. The average duration of fish oil intake ranged from 12 to 52 weeks. The amount of n-3 PUFAs, EPA and DHA, ingested ranged from 0.2 to 4.6 g EPA daily and 0.2 to 2.1 g DHA daily. The clinical outcomes that were measured in most studies included the following: duration of early morning stiffness (EMS), hand grip strength (GS), patient's global assessment (PatGA), physician's global assessment (PhyGA), Physician's Pain Index (PPI), Ritchie's Articular Index (RAI), swollen joint count (SJC), tender joint count (TJC), and joint pain intensity. Nonsteroidal anti-inflammatory drug (NSAID) use was also monitored as a possible outcome in 5 of the studies.^{21,23,29,30,33}

All but 1 of the studies²⁰ measured at least 1 clinical outcome. One study²⁰ solely measured oxidative stress biomarker levels. In 16 of the studies,^{21,22,24,26–29,31–39} dietary n-3 PUFA intake resulted in the improvement of at least 2 clinical measures, as listed in Table 1. Three studies reported no improvements in the clinical parameters associated with RA^{23,25,30}; however, in 2 of the studies,^{23,30} NSAID usage was significantly reduced in some patients. Furthermore, in 6 studies, at least 4 clinical outcomes improved (Table 1). The most common improved outcome for the fish oil group was a decrease in TJC, with 10 studies reporting favorable results. The second most common improved outcome was a decrease in the duration of EMS, with 8 studies reporting favorable results. Some additional notable improved outcomes included decrease in SJC in a total of 7 studies and improvement in PhyGA in 6. Nonsteroidal anti-inflammatory drug usage was reduced in all 5 of the studies where it was monitored.^{21,23,29,30,33}

In 3 of the 20 studies, at least 1 measured outcome demonstrated a favorable response in the control group.^{32,33,39} In the remaining 17 studies, no statistically significant changes were noted in the baseline outcomes of the control group.

Examination of Individual Studies

NSAID Reduction

Nonsteroidal anti-inflammatory drugs inhibit the cyclooxygenase (COX) pathway and act as potent anti-inflammatory agents; however, because of the possibility of adverse effects, they are of limited use.^{40,41} The 2 major COX pathways that have been discovered are the constitutively expressed COX-1 and the cytokine inducible COX-2. Evidence suggests that NSAID toxicity is caused by inhibition of the COX-1 pathway at the site of inflammation.^{42,43} In all 5 of the studies that monitored NSAID usage as an outcome,^{21,23,29,30,33} there was a reduction in NSAID intake

among certain patient groups during and after the trial. This suggests that n-3 PUFAs could act as an anti-inflammatory agent and be of potential use in curtailing inflammation in RA.

Geusens et al.²⁹ in 1994 conducted a study with 90 patients who were split in 3 different groups: “low dose,” which consumed 0.8 g EPA, 0.2 g DHA, and 3 g olive oil daily; “high dose,” which consumed 1.7 g EPA and 0.4 g DHA daily; and a “control,” which consumed 6 g of olive oil daily. The only group to exhibit statistically significant changes in outcomes was the high-dose group, in which clinical improvements in the following areas were observed: PatGA, PPI, and a significant reduction in NSAID usage. The use of olive oil as placebo in this study could have lessened the apparent effects of EPA/DHA, as olive oil itself may have anti-inflammatory properties. Of note, oleic acid, the main component of olive oil, may compete with arachidonic acid (AA) for incorporation into phospholipids.⁴⁴ In both Lau and colleagues³⁰ and Sköldstam and colleagues³³ studies, patients were also able to significantly lower NSAID use compared with the placebo group. In addition, Sköldstam et al. reported clinical improvements in 4 different clinical readouts: GS, PhyGA, RAI, and TJC.

In 2013, Park et al.²³ reported a study in which NSAID usage was significantly decreased in patients with a weight greater than 55 kg. The 16-week study incorporated 2 groups (n = 81); the fish oil group received 2.09 g of EPA and 1.165 g of DHA daily, and the placebo group received high-oleic-acid sunflower oil. As opposed to the other studies, fish oil supplementation did not result in improvement of clinical indicators of RA. Interpretation of this study has to factor in the fact that patients from both groups in this study also consumed an average of 60 g/d of fish as part of their diet. As n-3 PUFAs are primarily derived from marine-based sources,¹ there is a very high possibility that participants were already saturated with EPA and DHA, and as a result, no additional benefits were observed.

Rajaei et al.²¹ in 2015 conducted a 12-week study with 60 patients with a diagnosis of early-onset RA (<6 months) who were undergoing similar disease-modifying antirheumatic drug (DMARD) treatment. Patients were split into 2 groups: the omega-3 capsule group, who consumed 1.8 g EPA and 2.1 g DHA daily, and the placebo group. At the end of the study, significant clinical improvements in the following 7 areas were observed for the omega-3 group: morning stiffness, patient's global assessment, severity of pain, PhyGA, the number of swollen joints, the number of tender joints, and physical function. In addition, the omega-3 group was also able to reduce concomitant analgesic drug consumption (72% reduction vs. 8.33% in control). The results of this trial indicate that use of omega-3 supplements alongside the standard DMARD treatment can help manage the common symptoms of RA as defined by DAS28 (Disease Activity Score in 28 joints), in addition to lowering the need for analgesics.

Overall, these studies lend support to a potential link between fish oil supplementation and NSAID usage reduction, possibly due to n-3 PUFAs (EPA and DHA) serving an anti-inflammatory role.

Crossover Studies

Three of the studies reviewed incorporated a crossover study design.^{26,36,38} In 1987, Kremer et al.³⁸ reported significant clinical improvements, such as improved American Rheumatology Association class and PhyGA and decreased SJC and TJC and time to fatigue. Thirty-three patients with active RA were split into 2 groups; 1 group initially started with 2.7 g EPA and 1.8 g DHA daily for 14 weeks, whereas the other group simply took placebo. In addition to the clinical improvements, LTB4 values were discovered to be below baseline values in the group who ingested fish oil initially, for as long as 18 weeks after fish oil intake was stopped. This could have resulted in the continued clinical

TABLE 1. Impact of Omega-3 Supplementation on RA

Study	Study Design	No. of Patients	Study Duration, wk	Medications	Daily Omega-3 Supplement, g/d	Clinical Outcomes in Fish Oil Group ^a	Laboratory Outcomes in Fish Oil Group ^a
Vasiljevic et al., ²⁰ 2016	DB, PC	60	12	DMARD/NSAID continued	0.2 g EPA, 0.3 g DHA	N/A	↓ Oxidative stress (↑ TBARS, NO ₂ ⁻ , GSH, SOD; ↓ H ₂ O ₂) ↓ CRP, ESR, RF
Rajaei et al., ²¹ 2015	DB, PC	60	12	DMARD/NSAID continued	1.8 g EPA, 2.1 g DHA	↓ Disease activity (↑ PatGA, PhyGA; ↓ EMS, PPI, SJC, TJC). ↓ NSAID use	N/A
Proudman et al., ²² 2015	DB, PC	187	52	DMARD used/NSAID not allowed	Low: 0.4 g EPA + DHA; high: 5.5 g EPA + DHA	↓ Failure rate of triple DMARD therapy; ↓ time to ACR remission	N/A
Park et al., ²³ 2013	DB, PC	81	16	DMARD/NSAID continued	2.090 g EPA, 1.165 g DHA	— Disease activity (— EMS, PatGA, PhyGA); ↓ NSAID use in patients > 55 kg	↓ LTB4 in patients > 55 kg
Berbert et al., ²⁴ 2005	DB, PC	43	24	DMARD/NSAID continued	1.8 g EPA, 1.2 g DHA	↓ Disease activity (↑ GS; ↓ EMS, joint pain intensity, RAI)	— CRP, ESR; ↓ RF
Remans et al., ²⁵ 2004	DB, PC	55	16	DMARD/NSAID continued	1.4 g EPA, 0.211 g DHA	— TJC, SJC. No benefits reported	— CRP, ESR
Adam et al., ²⁶ 2003	DB, PC, CO	62	32	DMARD continued/NSAID reduction	30 mg/kg EPA + DHA ^b	↓ SJC, TJC	↓ Inflammatory markers (↓ C3, CRP, IgG, IgM, LTB4, PGE2, thromboxane B2) ↑ Monocyte lipids
Volker et al., ²⁷ 2000	DB, PC	50	15	DMARD/NSAID continued	40 mg/kg EPA + DHA ^c	↓ Disease activity (↑ PatGA, PhyGA; ↓ EMS, SJC, PPA)	↓ IL-1
Kremer et al., ²⁸ 1995	DB, PC	49	26 or 30	DMARD continued/NSAID stopped at week 18 or 22	4.6 g EPA, 2.0 g DHA	↓ Disease activity (↑ PatGA, PhyGA; ↓ EMS, PPA, TJC)	— ESR, RF
Geusens et al., ²⁹ 1994	DB, PC	60	52	DMARD varied/NSAID reduction	Low: 0.8 g EPA, 0.2 g DHA; high: 1.7 g EPA, 0.4 g DHA	↓ Disease activity (↑ PatGA, PhyGA; ↓ PPA); ↓ NSAID use in high-dose group	— ESR, RF
Lau et al., ³⁰ 1993	DB, PC	64	52	No DMARD/NSAID used	1.7 g EPA, 1.1 g DHA	↓ NSAID use	N/A
Kjeldsen-Kragh et al., ³¹ 1992	DB, PC	67	16	DMARD continued/NSAID varied between groups	3.8 g EPA, 2.0 g DHA	↓ Disease activity (↑ PatGA, PhyGA; ↓ EMS)	N/A
Nielsen et al., ³² 1992	DB, PC	51	12	DMARD/NSAID continued	2.0 g EPA, 1.2 g DHA	↓ EMS, TJC	↓ CRP
Sköldstam et al., ³³ 1992	DB, PC	43	24	DMARD continued/NSAID reduction	1.8 g EPA, 1.2 g DHA	↓ Disease activity (↑ PhyGA, GS; ↓ RAI, TJC); ↓ NSAID use	— CRP, ESR
Kremer et al., ³⁴ 1990	DB, PC	49	24	DMARD/NSAID continued	Low: 27 mg/kg EPA, 18 mg/kg DHA; high: 54 mg/kg EPA, 36 mg/kg DHA	↓ SJC, TJC	↓ LTB4, IL-1
Tulleken et al., ³⁵ 1990	DB, PC	27	12	DMARD/NSAID continued	2.0 g EPA, 1.3 g DHA	↓ RAI, SJC, joint pain index	— Vitamin E
Van der Tempel et al., ³⁶ 1990	DB, PC, CO	16	12	DMARD/NSAID continued	2.04 g EPA, 1.32 g DHA	↓ EMS, SJC	↓ LTB4, ↑ LTB5
Cleland et al., ³⁷ 1988	DB, PC	46	12	DMARD/NSAID continued	3.2 g EPA, 2.0 g DHA	↑ GS, ↑ TJC	↓ LTB4

Kremer et al., ³⁸ 1987	DB, PC, CO	33	14	DMARD/NSAID continued	2.7 g EPA, 1.8 g EPA	↓ Disease activity (↑ ARA class, PhyGA; ↓ SJC, TJC, TTF) ↓ EMS, TJC	↓ LTB4	N/A
Kremer et al., ³⁹ 1985	DB, PC	38	12	DMARD/NSAID continued	1.8 g EPA, 1.2 g DHA	↓ EMS, TJC		

^aAny particular outcome that was listed as a primary outcome (where indicated) was recorded in bold font.
^bCapsules contained 128.1 mg EPA and 95.8 mg DHA per gram of fish oil.
^cFish oil containing 60% n-3 fatty acids was supplemented at rate of 40 mg/kg body weight. Average amount was 1.3 g EPA, 1.0 g DHA.
 ↑↓ Indicates an increase or decrease in the value of the respective variable, —, no change occurred in the respective variable; ACR, American College of Rheumatology; ARA, American Rheumatology Association; C3, complement component 3; CO, crossover study; CRP, C-reactive protein levels; DB, double-blind; EMS, early morning stiffness; GS, hand grip strength; IgG, immunoglobulin G; IgM, immunoglobulin M; PC, placebo controlled; RE, rheumatoid factor; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substance; TBX2, thromboxane 2.

improvements that were observed in both groups after fish oil supplementation was stopped. This serves as a reminder that while conducting a crossover study, one must be careful to extend the washout (WO) period to allow the LTB4 levels and subsequent effects on the immune system to normalize.

Van der Tempel et al.³⁶ conducted a study incorporating a similar design as Kremer et al.³⁸ Sixteen patients with RA were split into 2 groups, with the first group receiving 2.04 g EPA and 1.32 g DHA daily for 12 weeks and the second group receiving a coconut oil placebo. After 12 weeks, both groups switched and took the opposite of what they initially received; there was no WO phase. Statistically significant improvements were observed for EMS and TJC. Leukotriene B4 levels were observed to decrease below baseline, and LTB5 exhibited a slight increase (from undetectable to slightly detectable). In addition, 4 to 8 weeks after fish oil discontinuation, LTB5 levels were undetectable again. In contrast, in the 1987 study by Kremer et al.,³⁸ levels of LTs were altered for up to 18 weeks.

In the final and most recent crossover study done by Adam et al.,²⁶ 68 patients with definitive RA were split into 2 groups. One group would remain on an anti-inflammatory diet (AID), providing an AA intake of less than 90 mg/d, and the other group would remain on a normal WD for the duration of the study. The placebo was 1 g of corn oil, and the fish oil supplementation was 30 mg fish oil (3.84 mg EPA and 0.843 mg DHA) per kilogram of body weight. After 12 weeks and an additional 8 weeks' WO period, both groups would cross over. There was an overall improvement in SJC and TJC, with the AID fish oil group improving the most. The greatest improvements were seen during months 6 to 8 for the AID group on fish oil supplementation. This time delay could be due to the slow accumulation of EPA into the cell membranes compared with n-6 PUFAs.⁴⁵ Although there was an increase in the EPA:AA ratio for the WD fish oil group, the EPA:AA ratio was significantly higher in the AID fish oil supplementation group. Because the WO phase was 8 weeks, this allowed biochemical levels to normalize for both groups and most likely had no effect on clinical outcomes.

Recent Studies

Proudman et al.²² conducted a 52-week study with 182 patients with early-onset RA (<12 months) who were also DMARD naive. The high-dose group received 5.5 g of EPA/DHA daily, while the control group received 400 mg EPA/DHA daily. The primary outcome measure was failure of triple DMARD therapy. Both groups received a "triple" regimen of DMARDs, which was adjustable based on an algorithm that was responsive to disease activity and tolerability/toxicity, which allowed for the extent of DMARD use to be an outcome measure. Fish oils were associated with benefits additional to those achieved by combination "treat to target" DMARDs with similar MTX use. Patients in the high-dose group had a significantly lower time to ACR remission compared with the control, in addition to reduced failure of triple DMARD treatment. There were no differences between groups in MTX dose, DAS28, or modified Health Assessment Questionnaire scores. The findings of this 52-week trial are significant: it has allowed long-term evaluation of fish oil usage adjunctive to contemporary early RA treatment regimens.

In 2016, Vasiljevic et al.²⁰ evaluated the oxidative status in patients with RA who used concentrated fish oil alone or concentrated fish oil in combination with evening primrose oil for a period of 12 weeks. Patients were divided into 3 groups: group 1 was the placebo, group 2 was given 0.2 g EPA and 0.3 g DHA daily, and group 3 was given 0.4 g EPA, 0.6 g DHA, and evening primrose oil capsules (1300 mg primrose oil, 0.949 mg linoleic acid, and 0.117 mg γ -linolenic acid) daily. After 3 months, the

results for group 2 revealed a significant increase in plasma levels of thiobarbituric acid reactive substances (TBARSs), NO_2^- , and glutathione (GSH) levels in erythrocytes, as well as a decrease in plasma hydrogen peroxide (H_2O_2) levels. For group 3, there was a significant increase in TBARS and NO_2^- , as well as increased activity of superoxide dismutase (SOD) and decreased levels of H_2O_2 . Increased oxidative burden has been well implicated in RA.⁴⁶ Increased reactive oxygen species have been associated with increased oxidative burden in autoimmune diseases, leading to neutrophil degranulation, which can release a plethora of harmful enzymes and peptides.⁴⁶ Several processes, such as TBARS, H_2O_2 , SOD, and GSH, have shown to protect the body from reactive oxygen species.⁴⁷ The results of this study indicate that intake of fish oil and evening primrose oil may be important to mitigate inflammation, disease activity, and biomarkers of oxidative stress through increased activities of antioxidant enzymes.

One study⁴⁸ utilized an alternate route of n-3 PUFA administration and was therefore excluded from the final study count. The 20-week study, in which n-3 PUFAs were intravenously infused into 23 patients, reported improvements in SJC and TJC for the n-3 PUFA group.

No adverse effects that could be attributable to fish oil supplementation were reported in any of these studies.

Impact of Fish Oil Supplementation on SLE

There have been at least 9 studies^{49–57} conducted on the effect of fish oil supplements on either SLE or lupus nephritis. Studies are placebo controlled and single,^{49,50} or double-blind,^{51–53} double-blind and crossover,^{54–56} or a WO study,⁵⁷ as summarized in Table 2. The number of subjects in each trial ranges from 12 to 85 patients, whereas the duration of fish oil supplementation ranged from 10 to 52 weeks. The amount of n-3 PUFA intake ranged from 0.54 to 3.60 g EPA and 0.30 to 2.25 g DHA per day. To quantitatively test outcomes, researchers assessed various serum and plasma components and used disease activity scales and scores. Some of the measured outcomes included the following: BILAG (British Isles Lupus Activity Group), SLAM-R score (Systemic Lupus Activity Measure—Revised), SLEDAI (Systemic Lupus Erythematosus Disease Activity Index), all 3 of which were used to measure overall disease activity; RAND SF-36 (Short-Form survey; a measure of overall patient well-being), flow-mediated dilation (measure of endothelial function), high-density lipoprotein (HDL), very-low-density lipoprotein (VLDL), total cholesterol levels, plasma interleukin (IL), erythrocyte sedimentation rate (ESR), and EPA and DHA levels.

Overall, 5 of the 7 SLE studies indicated that fish oil supplementation modified and improved disease activity.^{49,50,52,53,55} One of the studies⁵¹ reported no significant improvements. Another study⁵⁶ reported improved clinical parameters at the 3-month assessment time point; however, by trial conclusion at 6 months, the improvements retreated to baseline. One study,⁵⁴ focusing only on lupus nephritis patients, reported no significant improvements in disease activity. There was 1 study⁵⁷ that studied both nonnephritic SLE patients and lupus nephritis patients, reporting significant improvements in a number of measured serum and plasma markers.

Examination of Individual Studies

Lupus Nephritis Studies

Clark et al.^{54,57} conducted 2 different studies: the 1989 study⁵⁷ investigated the effect of n-3 PUFAs in patients with SLE and lupus nephritis, whereas the 1993 study⁵⁴ was focused solely on lupus nephritis. The 1989 study⁵⁷ exhibited a positive

dose-dependent relationship between dietary fish oil supplementation and measured clinical outcomes. All 12 patients underwent 2 different dose treatments: 1.08 g EPA and 0.72 g DHA daily for 5 weeks, a 5-week WO, followed by 3.24 g EPA and 2.16 g DHA daily for 5 weeks. Data show a significant dose-dependent incorporation of EPA and DHA in platelet membranes and reduction of mean blood viscosity. Mean red blood cell flexibility exhibited a nonsignificant dose-dependent increase. Based on measurements of neutrophil LTB4 release, blood viscosity, and lipid levels, fish oil supplementation favored a decrease in inflammatory microvascular disease in patients with lupus nephritis. On the other hand, the 1993 study⁵⁴ focusing solely on patients with lupus nephritis reported how fish oil supplementation only altered lipid levels but did not improve renal function. The treatment period lasted 2 years. Proteinuria, serum creatinine, and glomerular filtration rate levels, as well as mean SLEDAI scores, were unaffected. However, fish oil supplements lowered triglyceride levels and VLDL cholesterol significantly.

Other Fish Oil Studies in SLE

Five of the 7 SLE studies reported significant improvement in at least 1 measured parameter in those who consumed fish oil supplements,^{49,50,52,53,55} whereas 2 of the 7 studies^{51,56} reported no clinically significant improvements. Multiple studies used commonly adopted measures to determine disease activity or fatigue, including BILAG, SLAM-R, SLEDAI, and RAND SF-36.

Arriens et al.⁴⁹ evaluated treated patients using RAND SF-36, Fatigue Severity Scale (FSS), SLEDAI, and PhyGA. Fifty patients were given 2.25 g EPA and 2.25 g DHA per day for 6 months. SF-36 scores, in which patients self-report quality-of-life measures, showed an improvement trend, whereas PhyGA significantly improved in the fish oil group. However, FSS and SLEDAI scores in the fish oil group showed no improvement. For biomarker assessments, ESR was used as an indication of systemic inflammation, which significantly decreased in the fish oil group. From the cytokines assessed, serum IL-12 levels decreased, whereas serum IL-13 levels increased in the fish oil group.

On the other hand, another study⁵⁰ did report improvement in SLEDAI. Lozovoy and colleagues⁵⁰ study tested the effect of fish oil supplementation on adiponectin and leptin in an attempt to decrease the risk of cardiovascular disease (CVD) in SLE patients. The SLEDAI scores significantly decreased in patients on fish oil, accompanied by an increase in adiponectin levels and a decrease in leptin levels. Reduced levels of adiponectin and elevated leptin levels may be associated with CVD in SLE patients.⁵⁸

In 2013, Bello et al.⁵¹ conducted a 12-week study to determine the efficacy of n-3 PUFAs on endothelial function, disease activity, lipid profile, and inflammatory markers in SLE patients. At the conclusion of the study, no significant improvements were reported. However, 1 potential drawback of this study is its short duration. In contrast, Wright et al.,⁵² in a similarly designed study, reported significant improvements in disease activity at 12 weeks. In Wright and colleagues⁵² study, 60 patients with SLE were given 1.8 g EPA and 1.2 g DHA daily for 24 weeks to assess overall SLE disease activity and endothelial function. The fish oil group reported significant improvement in SLAM-R score, BILAG scores, and platelet 8-isoprostane levels.

In another 2 studies, fish oil was paired with copper or vitamin A and vitamin D supplements.^{53,55} Duffy and colleagues⁵³ study attempts to determine the effect of fish oil supplements with or without copper on disease activity in SLE patients. The SLAM-R scores significantly declined in patients taking fish oil compared with placebo, but no significant effect was noted in patients taking copper. Biomarker assessments were unaffected. In a study by Walton et al.,⁵⁵ patients on a low-fat, high-marine-oil diet

TABLE 2. Impact of Omega-3 Supplementation on SLE and Lupus Nephritis

Study	Study Design	Disease	No. of Patients	Study Duration, wk	Immunosuppressant Use ^b	Daily Omega-3 Supplement, g/d	Clinical Outcomes in Fish Oil Group ^a	Laboratory Outcomes in Fish Oil Group ^a
Arriens et al., ⁴⁹ 2015	SB, PC	SLE	50	24	Yes	2.25 g EPA, 2.25 g DHA	↓ Disease activity (↓ PhyGA, RAND SF-36). — FSS, SLEDAI	↓ Inflammatory markers (↑ serum IL-13; ↓ ESR, serum IL-12)
Lozovoy et al., ⁵⁰ 2015	SB, PC	SLE	62	16	Yes and antihypertensives	1.8 g EPA, 1.2 g DHA	↓ SLEDAI	↑ Plasma adiponectin; ↓ plasma leptin, triacylglycerol
Bello et al., ⁵¹ 2013	DB, PC	SLE	85	12	Yes	1.8 g EPA, 1.2 g DHA	— Disease activity (— SLEDAI)	— Endothelial function (— FMD) — Inflammatory markers (— IL-6, sICAM-1, sVCAM-1); ↑ LDL
Wright et al., ⁵² 2008	DB, PC	SLE	60	24	Yes	1.8 g EPA, 1.2 g DHA	↓ Disease activity (↓ SLAM-R, BILAG)	↓ Oxidative stress (↓ 8-isoprostane); ↑ endothelial function (↑ FMD)
Duffy et al., ⁵³ 2004	DB, PC	SLE	52	24	Yes	0.54 g EPA, 0.30 g DHA	↓ Disease activity (↓ SLAM-R)	— ESR, IgG, IgM, C3, C4
Clark et al., ⁵⁴ 1993	DB, CO	Lupus nephritis	21	52	Yes	2.7 g EPA, 1.7 g DHA	— Disease activity (— SLAM-R)	— Renal function (— GFR, proteinuria, Serum creatinine); ↓ triacylglycerol, VLDL
Walton et al., ⁵⁵ 1991	DB, CO	SLE	27	12	Yes	3.6 g EPA, 2.0 g DHA	N/A	↑ Red cell EPA levels
Westberg and Tarkowski, ⁵⁶ 1990	DB, CO	SLE	17	24	Yes	1.8 g EPA, 1.2 g DHA	— Disease activity (— SLEDAI)	— Renal function (— GFR)
Clark et al., ⁵⁷ 1989	WO study	SLE and lupus nephritis	12	10	Yes	1.08 g EPA, 0.72 g DHA initially, then 3.24 g EPA, 2.16 g DHA	N/A	↑ HDL, platelet EPA; ↓ LTB4, triglycerides, VLDL

^aAny particular outcome that was listed as a primary outcome (where indicated) was recorded in bold font.

^bImmunosuppressants include azathioprine, corticosteroids, cyclophosphamide, methotrexate, and NSAIDs.

↑ ↓ Indicates an increase or decrease in the value of the respective variable; BILAG, British Isles Lupus Activity Group; C3, complement component 3; CO, crossover study; DB, double-blind; FMD, flow-mediated dilation; GFR, glomerular filtration rate; IgG, immunoglobulin G; IgM, immunoglobulin M; LDL, low-density lipoprotein; PC, placebo controlled; sICAM, soluble intercellular adhesion molecule 1; sVCAM, soluble vascular cell adhesion molecule 1; SB, single-blind.

were tested. It is important to note that because of the low-fat diet, patients were directed to consume 1 vitamin supplement every day, which consisted of 4000 IU vitamin A and 400 IU vitamin D. To assess disease activity and patient health, researchers analyzed red blood cell content and established a set of criteria for each patient based on their individual clinical state. With the exception of 1 patient, all showed an increase in red blood cell EPA concentration. In addition, patients receiving the maximum fish oil dosage did significantly better than did those taking control capsules.

One study⁴⁹ reported occasional gastrointestinal discomfort and burping, whereas fish oil supplements were well tolerated in all the other studies.

The trials reviewed consist of several positive-outcome clinical trials that have been conducted on lupus patients that present some evidence of a short-term beneficial role of n-3 PUFA intake; however, the studies available for lupus are not yet sufficient to fully evaluate the efficacy of n-3 PUFA consumption in this cohort of patients. Lengthier trials, of up to a decade in length, with larger patient cohorts need to be conducted to establish any long-term benefits. A limiting aspect of many SLE studies is that multiple confounding factors such as medications in use, infections, and disease activity have not been properly controlled for.

Impact of Fish Oil Supplementation on OA

We reviewed a total of 4 studies in OA,⁵⁹⁻⁶² all of which included only patients experiencing active OA, as summarized in Table 3. With limited amount of trials conducted along with varying study design and implementation protocols, the effect of fish oil supplementation in OA is inconclusive. More well-designed trials need to be conducted to fully evaluate any potential benefits that fish oils may have in OA patients.

However, the trials presented report noteworthy results. There was a large range of trial durations, from 12 to 104 weeks, with the number of patients ranging from 81 to 202. Outcomes were measured in Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores,⁵⁹⁻⁶¹ visual analog scale scores,^{60,62} and NSAIDs/analgesics usage.^{61,62} Three studies⁶⁰⁻⁶² were double-blind and placebo controlled, and 1 study⁵⁹ was only double-blind. Three of the 4 trials resulted in decreased WOMAC scores,⁵⁹⁻⁶¹ along with partial pain improvement. One study⁶¹ reported decreased NSAID/analgesic usage. Another study⁶² reported no significant improvements.

No adverse effects attributable to fish oil supplementation were reported in any of these studies.

Overview of Mechanisms of Action

Omega-3 fatty acids modulate inflammation through a variety of mechanisms, with most associated through alteration of the PUFA composition of cell membranes. Changes in the PUFA composition of membranes can influence membrane receptors, inhibit the production of proinflammatory cytokines, and modify the synthesis of lipid mediators. Because both n-6 PUFAs (AA) and n-3 PUFAs (EPA/DHA) can constitute the cell membrane, levels of each respective PUFA can be modified through dietary intake.⁶³⁻⁷⁰ Eicosanoids, which include LTs, PGs, and thromboxanes, are primarily derived from AA and EPA and are crucial mediators and regulators of inflammation.⁶⁶ Arachidonic acid-derived eicosanoids tend to be proinflammatory, whereas EPA-derived eicosanoid products have anti-inflammatory roles.^{64,66-69} Thus, altering the PUFA composition of the cell membrane can lead to a modified production pattern of eicosanoid derivatives and inflammatory mediators and can ultimately influence the extent of the inflammatory response.⁶⁷

TABLE 3. Impact of Fish Oil Supplementation on OA

Study	Study Design	No. of Patients	Study Duration, wk	Antiarthritic Medication	Daily Omega-3 Supplement, g/d	Clinical Outcomes in Fish Oil Group ^a	Laboratory Outcomes in Fish Oil Group ^a
Hill et al., ⁵⁹ 2016	DB	202	104	NSAIDs and analgesics continued	High: 4.5 g/d omega-3; low: 0.45 g/d omega-3	↑ WOMAC function score; ↓ WOMAC pain score in low-dose group	— Cartilage volume, CRP
Gruenewald et al., ⁶⁰ 2009	DB, PC	177	26	Glucosamine sulfates required/no NSAIDs allowed	0.6 g omega-3, 1.5 g glucosamine sulfate daily	↓ WOMAC pain score; ↓ OA symptoms (↓ EMS, hip/knee pain, VAS scores)	— AP, CTX
Jacquet et al., ⁶¹ 2009	DB, PC	81	12	NSAIDs and analgesics continued	1.37 g/d omega-3, Vit. C 0.012 g/d, Vit. E 0.012 g/d	↓ Analgesic use, ↓ NSAID use, ↓ WOMAC pain, function, stiffness scores	N/A
Stammers et al., ⁶² 1992	DB, PC	86	24	NSAIDs	0.786 g EPA	— NSAID use (— joint pain, Inflammation, VAS)	↑ AP

^aAny particular outcome that was listed as a primary outcome (where indicated) was recorded in bold font.

↑ Indicates an increase or decrease in the value of the respective variable, —, no change occurred in the respective variable; AP, alkaline bone phosphatase; CRP, C-reactive protein levels; CTX, Beta crosslaps; DB, double-blind; PC, placebo controlled; VAS, visual analog scale.

Varied Eicosanoid Production Between Omega-3 and Omega-6 Fatty Acids

When diets are supplemented with fish oil, n-3 PUFAs begin to partially replace n-6 PUFAs as a substrate in the membrane composition of most cells.⁶³ Competition occurs between n-3 and n-6 PUFAs during PG and LT formation. Under normal circumstances, most inflammatory cells contain significantly higher amounts of AA compared with EPA, and AA becomes the primary substrate for eicosanoid production; however, this changes with fish oil consumption as EPA levels increase.⁶⁴ Arachidonic acid competes with EPA for the synthesis of PGs and LTs via the lipoxygenase and COX pathway.^{64,65} A study was done to examine the inflammatory potentials of LTB₄ (produced by AA) and that of LTB₅ (produced by EPA). LTB₅ was found to be from 10 to up to 100 times less potent as a neutrophil chemotactic agent compared with LTB₄ and thus a much weaker inflammatory agent.⁷⁰ Unfortunately, only a few of the studies in rheumatic diseases^{26,34,36–38,57} actually monitored these products, with all reporting a reduction in LTB₄ with fish oil supplementation.

Inhibition of Proinflammatory Cytokines Tumor Necrosis Factor and IL-1

Tumor necrosis factor (TNF) and IL-1 are key proinflammatory cytokines implicated in several inflammatory diseases.⁷¹ In studies conducted with animals, increasing the dietary intake of n-3 PUFAs via fish oil supplementation in mice resulted in the decrease in ex vivo synthesis of TNF and IL-1B by macrophages.^{12,72} Increased n-3 PUFA intake has also been implicated to suppress the ability of monocytes to synthesize IL-1 and TNF in healthy individuals via endotoxin-stimulated monocytes.^{71,73} Although fish oil supplementation has been shown to reduce the levels of these proinflammatory cytokines in other fields of study,⁷⁴ none of the trials described in rheumatic diseases have monitored these cytokines. Clearly, future studies should also examine the molecular mechanisms through which fish oil supplementation may be contributing to the modulation of inflammation in rheumatic diseases.

Additional Benefits of Omega-3 Fatty Acids

The protective effects of n-3 PUFAs extend outside rheumatic diseases. Increased consumption of n-3 PUFAs in CVD patients has been implicated in reduced serum triglyceride levels and improved HDL and low-density lipoprotein levels.⁷⁵ This mechanism could be implicated in a meta-analysis study,¹⁵ which found that n-3 PUFA intake can lead to a considerable reduction in mortality for patients with coronary heart disease. Since a strong association between the presence of coronary heart disease and increased inflammatory markers was established,⁷⁶ increasing n-3 PUFA intake could reduce the cardiovascular risk in rheumatic disease via decrease in serum lipid levels and reduction of shared inflammatory markers of both diseases.

In addition, n-3 PUFAs influence membrane fluidity and regulate membrane-receptor behavior.⁶³ Thus, increased n-3 PUFAs have been associated with maintaining optimal membrane fluidity and allowing for proper neurotransmitter signaling and binding.⁷⁷ This suggests a possible mechanism for a study in which n-3 PUFA supplementation resulted in improvements for patients with bipolar disorder, reducing the risk of relapse.⁷⁸ A meta-analysis also found n-3 PUFAs to have a positive effect on patients with major depressive disorder.⁷⁹

In general, increased n-3 PUFAs have shown to have a positive impact outside rheumatic diseases through a wide range of proposed mechanisms. Further studies need to be conducted

to establish a better understanding of the molecular mechanisms of action.

CONCLUSIONS

The majority of PUFAs consumed in the modern WD are n-6 PUFAs, drastically outranking n-3 PUFA intake. Ample evidence indicates that increased EPA/DHA levels can modify the production of eicosanoids, toward a more anti-inflammatory profile. This competition most likely occurs as both AA and EPA compete as substrates for the COX and lipoxygenase pathways for eicosanoid production. Given the importance of these pathways in rheumatic diseases, one would predict that EPA/DHA would be beneficial in various rheumatic diseases. Several positive-outcome clinical trials in RA present good evidence for the beneficial role of omega-3 fatty acid intake. In addition, there are several short-term positive-outcome clinical trials that have been conducted on lupus patients; however, lengthier trials, of up to a decade or more, with greater cohort size and control for multiple confounding factors need to be conducted to establish any long-term benefits. Conversely, the evidence is inconclusive on the role of fish oil supplementation in OA, with limited data and few published studies being available. Finally, few or no trials have been conducted in other rheumatic diseases. Longer-term trials are warranted to establish the long-term benefits of fish oil supplements in the different rheumatic diseases. Besides establishing the impact of fish oil supplementation on clinical activity indices, it would also be important to test the NSAID-sparing and steroid-sparing potential of fish oil supplements. Another open area for investigation is whether EPA and DHA may have differential impacts on the cardiovascular and neurological manifestations associated with rheumatic diseases, respectively. Finally, the molecular mechanism of action through which fish oil supplements may modulate autoimmune inflammation warrants further study.

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