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# OMEGA-3 FATTY ACIDS AND RHEUMATOID ARTHRITIS: MECHANISMS AND CLINICAL EVIDENCE

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**ABSTRACT**

**Introduction and Purpose:** Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by joint inflammation and systemic manifestations. Omega-3 fatty acids, particularly EPA and DHA, have been suggested to modulate inflammatory processes and immune responses. This review aims to summarize current evidence on the role of omega-3 fatty acids in the pathophysiology and clinical management of RA.
**Material and Methods:** A literature search was conducted using PubMed to identify original studies, randomized controlled trials, meta-analyses, and reviews examining the effects of omega-3 supplementation on RA. Key outcomes included disease activity, inflammatory markers, pain, morning stiffness, and use of nonsteroidal anti-inflammatory drugs.
**Results and Conclusion:** Omega-3 fatty acids demonstrate anti-inflammatory properties through modulation of cytokine production, competition with omega-6 fatty acids in eicosanoid pathways, and generation of pro-resolving lipid mediators. Clinical studies indicate that supplementation may reduce morning stiffness, pain, and NSAID requirements in RA patients, although heterogeneity in doses, sources, and study duration limits generalizability. Omega-3 fatty acids represent a promising adjunctive therapy for RA, but further standardized clinical trials are warranted.

**KEYWORDS**

Omega-3 Fatty Acids, Rheumatoid Arthritis, EPA, DHA, Inflammation, Supplementation

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## Introduction:

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease associated with a substantial health and social burden. Analyses from the Global Burden of Disease study indicate a steady increase in the number of patients and a persistent impact on disability, making RA one of the major challenges in modern rheumatology. Recent estimates suggest approximately one million new cases annually and about 18 million people living with the disease worldwide, with a predominance among women (1). These data highlight the importance of secondary prevention and treatment optimization at the population level.

The pathogenesis of RA is complex, involving a sustained cytokine-driven inflammatory process (notably TNF-α, IL-1, and IL-6), activation of T and B lymphocytes, pannus formation, and progressive destruction of cartilage and bone (2, 3). In recent years, growing attention has been directed towards nutrition as a modifiable environmental factor that may influence the course of inflammatory diseases. In this context, long-chain omega-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) are of particular interest. By competing with omega-6 fatty acids in the eicosanoid pathway and serving as precursors of specialized pro-resolving mediators (SPMs), such as resolvins, protectins, and maresins, omega-3s can modulate immune responses and promote the physiological resolution of inflammation (4-6).

Clinical evidence suggests that omega-3 supplementation may reduce disease activity and the need for non-steroidal anti-inflammatory drugs (NSAIDs) in patients with RA. Meta-analyses have reported reductions in pain, morning stiffness, and NSAID consumption, with the most consistent benefits observed at doses exceeding 2–3 g/day of EPA+DHA and supplementation periods of at least three months (7-9).More recent systematic reviews and meta-analyses support these findings, although they also emphasize the heterogeneity of available studies, including variations in dosages, sources, treatment duration, and concomitant use of disease-modifying antirheumatic drugs (DMARDs) (7-9).

The aim of this review is to provide a comprehensive synthesis of the role of omega-3 fatty acids in the context of chronic inflammation using RA as a model. We will discuss biochemical mechanisms, clinical evidence, and practical implications, as well as the limitations of current research. Furthermore, studies investigating the effects of omega-3 fatty acids on inflammatory markers in non-RA populations will be considered, as they provide additional insights into the systemic anti-inflammatory potential of these compounds (10).

**Pathophysiology of Rheumatoid Arthritis:**

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent inflammation of the synovial joints, leading to cartilage degradation, bone erosion, and functional disability (2). The pathogenesis of RA involves a complex interplay between genetic predisposition, environmental factors, and dysregulated immune responses (11).

**1. Genetic and Environmental Factors**

Genetic factors play a significant role in RA susceptibility. Specific human leukocyte antigen (HLA) alleles, particularly HLA-DRB1, are strongly associated with an increased risk of developing RA (11). Environmental triggers such as smoking, infections, and hormonal changes can interact with genetic predispositions to initiate and propagate the disease process (3).

**2. Immune System Dysregulation**

RA is characterized by the activation of both the innate and adaptive immune systems. The synovial tissue becomes infiltrated with various immune cells, including T lymphocytes, B lymphocytes, macrophages, and dendritic cells (2, 11). These cells produce pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), which perpetuate the inflammatory cascade and contribute to joint damage (3, 12).

**3. Synovial Inflammation and Pannus Formation**

Persistent inflammation leads to hyperplasia of the synovial lining and formation of pannus—a mass of inflamed tissue that invades and destroys adjacent cartilage and bone (11). This destructive process is mediated by matrix metalloproteinases (MMPs) and receptor activator of nuclear factor-kappa B ligand (RANKL), promoting osteoclastogenesis and bone resorption (12).

**4. Systemic Manifestations**

RA extends beyond the joints, producing systemic effects including cardiovascular disease, osteoporosis, and interstitial lung disease (2, 3). Chronic inflammation contributes to endothelial dysfunction and accelerated atherosclerosis, increasing the risk of cardiovascular events in RA patients (3).

**Omega-3 Fatty Acids- General Characteristics:**

Omega-3 polyunsaturated fatty acids (PUFAs) are essential components of the human diet and play an important role in maintaining normal physiological functions. They are characterized by a double bond at the third carbon from the methyl end of the molecule. The main omega-3 fatty acids relevant for human health are alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). ALA is primarily found in plant-based foods such as flaxseeds, chia seeds, walnuts, and some vegetable oils. It can be converted into EPA and DHA in the human body, but this process is inefficient, with less than 10% of ALA converted into EPA and only a very small proportion into DHA (13, 14). By contrast, EPA and DHA are present in fish and marine oils, where they are readily absorbed and directly used by the body (15, 16).

The bioavailability and effectiveness of omega-3 fatty acids depend strongly on the dietary source. EPA and DHA from oily fish such as salmon, mackerel, or sardines are incorporated into cell membranes much more efficiently than ALA from plants (15). For individuals who do not consume fish, algal oils represent an alternative vegetarian source of DHA (17). These fatty acids are important structural components of cell membranes, where they influence fluidity, signaling pathways, and the function of membrane proteins (16).

A particularly important role of omega-3 fatty acids is their impact on the immune system and inflammation. EPA and DHA compete with arachidonic acid (an omega-6 fatty acid) for enzymatic pathways, leading to the production of eicosanoids and other lipid mediators that are generally less pro-inflammatory (18). In addition, they are precursors of specialized pro-resolving mediators, such as resolvins and protectins, which actively contribute to the resolution of inflammation (19). Through these mechanisms, omega-3 fatty acids can reduce the production of inflammatory cytokines and modulate the activity of immune cells, including T lymphocytes and macrophages (16, 19).

Clinical studies and epidemiological observations support these effects. Populations with high fish consumption, such as the Inuit in Greenland, have been shown to have lower rates of cardiovascular and inflammatory diseases compared to Western populations (15). More recent studies confirm that higher dietary intake of EPA and DHA is associated with reduced markers of systemic inflammation and may help in the management of chronic diseases such as rheumatoid arthritis and inflammatory bowel disease (16, 18).

**Mechanisms of Omega-3 Action In Inflammation:**

**1. Competition with Omega-6 in the Eicosanoid Pathway**

Omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) share the same enzymatic pathways for the production of eicosanoids, including prostaglandins, leukotrienes, and thromboxanes. Omega-6-derived eicosanoids, primarily from arachidonic acid, generally have pro-inflammatory properties, promoting leukocyte chemotaxis, vasodilation, and increased vascular permeability. In contrast, eicosanoids derived from omega-3 fatty acids, particularly EPA, tend to have weaker inflammatory activity or even anti-inflammatory effects (4, 20).

The ratio of dietary omega-6 to omega-3 PUFAs is critical in modulating the inflammatory response. A high omega-6/omega-3 ratio, typical in Western diets, favors the production of pro-inflammatory mediators, which can exacerbate chronic inflammatory diseases such as rheumatoid arthritis (RA). Conversely, increasing omega-3 intake shifts the balance toward the generation of less inflammatory or pro-resolving mediators, potentially reducing joint inflammation and systemic inflammatory markers (20, 21).

Furthermore, omega-3 PUFAs can compete with arachidonic acid for cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, reducing the synthesis of pro-inflammatory prostaglandins (e.g., PGE2) and leukotrienes (e.g., LTB4). This enzymatic competition is a central mechanism by which omega-3 fatty acids exert anti-inflammatory effects at the cellular level (4).

**2. Production of Resolvins, Maresins, and Protectins**

EPA and DHA, the long-chain omega-3 fatty acids, are precursors to specialized pro-resolving mediators (SPMs) such as resolvins, protectins, and maresins. These mediators actively terminate inflammation and promote tissue repair [3, 4]. For instance, resolvins reduce neutrophil infiltration into inflamed tissues and enhance macrophage-mediated clearance of apoptotic cells, a process known as efferocytosis (21).

Maresins, produced predominantly by macrophages, not only limit neutrophil accumulation but also stimulate tissue regeneration and anti-inflammatory signaling pathways. Protectins, synthesized mainly in neural and immune tissues, provide protection against tissue damage by reducing pro-inflammatory cytokine production and oxidative stress (22).

Clinical and preclinical studies indicate that supplementation with omega-3 PUFAs increases circulating levels of SPMs, which correlates with reduced inflammatory markers and improved clinical outcomes in patients with chronic inflammatory diseases, including RA (23, 24).

**3. Inhibition of Pro-inflammatory Cytokines (TNF-α, IL-1, IL-6)**

Omega-3 fatty acids modulate the expression and secretion of key pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-6, which are central mediators in RA pathogenesis (23). This effect is mediated partly through inhibition of nuclear factor-kappa B (NF-κB), a transcription factor that regulates many genes involved in inflammation (23, 24).

By downregulating cytokine production, omega-3 fatty acids reduce synovial inflammation, cartilage degradation, and systemic inflammatory responses. In vitro studies demonstrate that exposure of macrophages and T lymphocytes to EPA and DHA decreases TNF-α and IL-6 release, highlighting the immunomodulatory properties of these fatty acids (5, 24).

Furthermore, omega-3 fatty acids may modulate inflammasome activity, reducing IL-1β activation, and thereby dampening the inflammatory cascade that contributes to joint damage (5).

**4. Effects on T Lymphocytes and Macrophages**

Omega-3 fatty acids affect both adaptive and innate immune cells. In T lymphocytes, they reduce the production of inflammatory cytokines such as IL-2, TNF-α, and interferon-gamma (IFN-γ), leading to decreased proliferation of effector T cells (24).

In macrophages, omega-3 PUFAs promote polarization towards the M2 phenotype, which is associated with anti-inflammatory functions and tissue repair. This polarization enhances the resolution of inflammation, increases efferocytosis, and reduces oxidative stress in inflamed tissues (5, 23).

Moreover, omega-3 fatty acids can modify cell membrane composition, influencing receptor signaling, lipid raft formation, and membrane fluidity, which further modulates immune cell activation and cytokine production (23).

The cumulative effects on T lymphocytes and macrophages, combined with the regulation of eicosanoid pathways and SPM production, explain the broad anti-inflammatory potential of omega-3 fatty acids and their therapeutic relevance in conditions like RA (23).

**Omega-3 Fatty Acids in Rheumatois Arthritis- Clinical Studies:**

Over the last several decades, extensive clinical research has explored the role of long-chain omega-3 polyunsaturated fatty acids (PUFAs), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), as adjunctive therapy in rheumatoid arthritis (RA). These compounds have drawn attention due to their known anti-inflammatory mechanisms, favorable safety profiles, and potential to enhance conventional treatment regimens.

Randomized controlled trials (RCTs) provide the core clinical evidence. One of the earliest and most influential, Kremer et al. (1995), administered ~3.5 g/day of EPA + DHA via fish oil in RA patients who discontinued non-steroidal anti-inflammatory drugs (NSAIDs). Over 12 weeks, significant reductions were observed in tender joint counts, the duration of morning stiffness, and levels of interleukin-1β, indicating both symptomatic and biochemical improvements (25). Similarly, Kjeldsen-Kragh et al. (1992) demonstrated that combining fish oil with naproxen for 16 weeks yielded better outcomes in morning stiffness and physician global assessment compared to naproxen alone, suggesting that omega-3 supplementation may enhance conventional NSAID therapy (26). More recently, Rajaei et al. (2015) conducted a double-blind RCT involving 60 RA patients on disease-modifying antirheumatic drugs (DMARDs). After 12 weeks of omega-3 supplementation, significant reductions were noted in tender and swollen joint counts and analgesic usage, reinforcing the potential additive benefits of omega-3s alongside DMARDs (27).

Complementing the RCTs, several meta-analyses and systematic reviews have aggregated and analyzed pooled data to clarify the overall efficacy of omega-3 supplementation in RA. In their 2012 meta-analysis, Lee et al. reviewed ten RCTs involving 183 RA patients and found that omega-3 supplementation (≥2.7 g/day for at least three months) significantly reduced NSAID consumption (standardized mean difference [SMD] –0.518; 95% CI –0.915 to –0.121; $p = 0.011$), although reductions in tender joint count, swollen joint count, morning stiffness, and physical function did not reach statistical significance (8). Earlier, Goldberg and Katz (2007) conducted a meta-analysis of 17 RCTs and identified significant reductions in patient-reported joint pain (SMD –0.26), morning stiffness (SMD –0.43), tender joint count (SMD –0.29), and NSAID use (SMD –0.40), although physician-rated assessments did not yield significant improvements (28).

A particularly comprehensive systematic review by Gioxari et al. (2018) incorporating 20 RCTs with 717 subjects revealed significant reductions in leukotriene B4 (SMD –0.440; 95% CI –0.676 to –0.205; $p < 0.001$) and blood triacylglycerols (SMD –0.316; 95% CI –0.561 to –0.070; $p = 0.012$), signaling both anti-inflammatory and metabolic effects of omega-3 supplementation in RA (7). A more recent meta-analysis by Wang et al. (2024), involving 18 RCTs and 1, 018 RA patients, documented robust increases in EPA (SMD 0.74; 95% CI 0.46–1.01; $p < 0.001$) and DHA (SMD 0.62; 95% CI 0.35–0.89; $p < 0.001$), along with a reduced omega-6:omega-3 ratio (SMD –1.06; 95% CI –1.39 to –0.73; $p < 0.001$). These biochemical shifts were complemented by a significant decrease in tender joint count (SMD –0.59; 95% CI –0.79 to –0.39; $p < 0.001$), although markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and DAS28 showed nonsignificant changes (29). Furthermore, Gkiouras et al. (2024), after reviewing 23 placebo-controlled RCTs, found modest reductions in pain (SMD –0.16), tender joint count (SMD –0.20), swollen joint count (SMD –0.10), and NSAID use (SMD –0.22), albeit with low to very low evidence quality (30).

Collectively, these RCTs and meta-analyses highlight several consistent clinical effects: modest yet meaningful reductions in morning stiffness and joint pain, decreased reliance on NSAIDs, and improvements in inflammatory mediators and lipid profiles. Notably, symptomatic relief often emerges after several weeks to months of supplementation, particularly at higher doses (≥2.7 g/day) using marine-derived omega-3s (4, 8).

Nevertheless, the current evidence has significant limitations. Doses, formulations (fish oil vs. capsules), and supplementation durations vary widely—from months to over a year—complicating comparisons. The majority of studies are relatively small and underpowered, often lacking long-term outcomes such as radiographic progression or cardiovascular health. Moreover, inconsistent results in objective disease activity scores, like DAS28, along with control groups receiving oils that may possess anti-inflammatory properties (e.g., olive oil), raise concerns of bias (28). Safety profiles are generally positive, with only mild gastrointestinal symptoms reported; high doses may marginally increase bleeding tendencies, especially in anticoagulated individuals (31).

**Conclusions**

In summary, omega-3 polyunsaturated fatty acids (PUFAs), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), demonstrate anti-inflammatory properties that can positively influence disease activity in rheumatoid arthritis (RA). Clinical studies, including randomized controlled trials and meta-analyses, indicate that omega-3 supplementation may reduce morning stiffness, joint tenderness, and the need for nonsteroidal anti-inflammatory drugs (NSAIDs).

While the evidence is promising, the clinical benefits are generally modest, and variations in study design, dosage, supplementation duration, and omega-3 sources limit the ability to draw definitive conclusions. Omega-3 PUFAs should therefore be considered as a complementary therapy alongside standard RA treatments rather than a replacement for conventional disease-modifying medications.

Future research is needed to establish optimal dosing regimens, evaluate long-term efficacy and safety, and better understand the mechanistic pathways by which omega-3 fatty acids modulate inflammation in RA. Overall, omega-3 supplementation represents a low-risk, potentially beneficial adjunctive therapy that can support the management of RA symptoms and improve patient quality of life.

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