



## **n-3 Fatty Acids and the Immune System in Autoimmunity**

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The beneficial effects of n-3 fatty acids in humans were extensively investigated in the last decade. These effects are already well established in the prevention and treatment of cardiovascular disorders [1]. n-3 Polyunsaturated fatty acids, mainly those contained in fish oils, retard coronary atherosclerosis [2] and significantly decrease cardiovascular mortality. Dietary supplement of n-3 fatty acids as fish oil, or as eicosapentanoic acid and docosahexanoic acid, has also been shown to decrease the incidence of inflammatory diseases in populations that consume high doses of these n-3 fatty acids [3]. However, the effects on the immune system are less conclusive and there are some conflicting reports. In this review we summarize the current understanding of the effects of n-3 fatty acids on the immune system.

### **Basic mechanism**

Mammals lack the enzymes to introduce double bonds at carbon atoms beyond C-9 in the fatty acid chain. Therefore, those essential fatty acids must be supplied in the diet. There are two principal families of polyunsaturated fatty acids: the n-3 and n-6 families. Linoleic acid is the precursor of n-6 and is the major component of plant oil and of fat in the western diet. The precursor of the n-3 family is alpha linoleic acid, found in green plants and some plant oils. In animal tissues linoleic acid is converted to arachidonic acid, the precursor of prostaglandins and leukotriens. The alpha-linoleic acid is converted in some animals into EPA and DHA.

The chemical composition of the cell membrane is affected by the relative amount of different dietary fatty acids; this change in structure translates into altered physical, chemical and biological properties. Consumption of fish oil rich in EPA and DHA leads to partial replacement of arachidonic acid in cell

membranes. Such a change can alter membrane fluidity, which could affect binding of cytokines or alter the cytokine effect on the cells [4]. Furthermore, n-3 and n-6 fatty acids compete for the same enzymes that metabolize them. The pro-inflammatory eicosanoids prostaglandin and leukotrien B4 are derived from the n-6 fatty acid, arachidonic acid. Metabolism of n-3 fatty acids results in thromboxane A3 and leukotrien B5, which are much less biologically active than their n-6 counterpart. Fish oil acts as a competitive inhibitor, causing a decrease in the synthesis of these pro-inflammatory mediators [5]. Competition between n-3 and n-6 also affects cell function in the immune system. These effects inhibit production of pro-inflammatory cytokines, including tumor necrosis factor-alpha, interleukins 1 and 6, and platelet-activating factor [6]. Fish oil also suppresses IL-2 production via downregulation of co-stimulatory molecules (like leukocyte function-associated antigen-1, intercellular adhesion molecule-1 and CD2) in T lymphocytes and accessory cells [4]. Fish oil also affects gene expression under various conditions; this effect is mediated by binding of n-3 fatty acids to regulatory transcription factors [7]. One possible mechanism includes interaction with peroxisome proliferator activated receptor-alpha, a transcription factor that downregulates inflammation via breakdown of leukotriens [8].

### **Animal studies**

In a few animal models of autoimmune diseases – such as systemic lupus erythematosus-like disease, experimental allergic encephalomyelitis (animal model for multiple sclerosis), and experimental uveitis – the supplementation of n-3 fatty acids was shown to have some beneficial effects on increasing survival and decreasing disease severity [9]. Attenuation of graft-versus-host and host-versus-graft reactions, and organ survival were

EPA = eicosapentanoic acid  
DHA = docosahexanoic acid

IL = interleukin

also observed. Fish oil supplementation improved survival of animals exposed to endotoxin, probably through downregulation of the immune response [6].

Dietary supplementation of PUFA in mice led to a reduction in the autocrine IL-2 activation pathway, reducing IL-12 P70 and interferon-gamma levels significantly [10,11]. Basically, dietary supplementation of n-3 fatty acids in animal models attenuates lymphocyte reactions and hence decreases T cell-dependent autoimmune activity. The mechanism of this attenuation is not entirely understood, and several mechanisms were suggested as an explanation. The decreased autoimmunity could be attributed to lower ability of antigen-presenting cells, such as dendritic cells and splenocytes, to present antigens [12]. This could be due, in part, to reduction of major histocompatibility complex class II expression in animals fed with n-3 fatty acids [13]. It was also shown that dietary n-3 fatty acids decrease the proliferative response of T cells to different mitogens (concanavalin A, phytohemagglutinin, etc.). This effect was accompanied by decreased IL-2 production from lymphocytes, a cytokine that stimulates T cell proliferation. Another affected cytokine is transforming growth factor-beta. This cytokine has a prominent inhibitory effect on T cell-mediated immunity, and was shown to have a pivotal role in active suppression [14]. In mice fed with n-6 fatty acids, higher TGF- $\beta$  mRNA expression was observed [15]. The effect of the n-3 fatty acids on macrophages was also observed, with decreased secretion of IL-1, IL-6 and TNF- $\alpha$ , which contributes to the inflammatory response. Most of the induced models of autoimmunity (via immunization) involve lymph nodes, the site of the initial T cell reaction to antigen. It was interesting to observe that adipose tissue around the lymph nodes selectively retains n-3 polyunsaturated fatty acids [14]. This observation can explain the beneficial effects in experimental allergic encephalomyelitis and experimental uveitis, which are induced models and are based upon active immunization, but not in the genetically based SLE-like disease where lymph nodes are not involved in the pathogenesis. Fish oil is generally well tolerated. Nonetheless, adverse effects in animals have been published, including delayed viral and bacterial clearance, reduced humoral response, and decreased delayed-type hypersensitivity. Concomitant vitamin E supplementation reversed the effects on T cell function [4].

## Human studies

Several studies and a recently published report from the U.S. Food and Drug Administration concluded that fish oil supplementation is safe [16,17]. Despite concern that increased intake may increase lipid peroxidation, recent human studies demonstrated that n-3 fatty acids reduced *in vivo* oxidant stress [18]. Although one study found increased incidence of tuberculosis

among native Alaskans, there are no other data to support that fish oil has any significant immunosuppressive effect in humans. Due to the encouraging therapeutic effects in animal models for human autoimmune diseases, dietary n-3 fatty acids were tested in normal volunteers, human autoimmune diseases, and immune-mediated disorders. Most of these studies examined the effect of n-3 fatty acids over 4–24 weeks. Kelley et al. [19], in a well-controlled study, assessed the effect of n-3 fatty acid supplement (DHA) on the immune response in healthy young men. The overall effect of 83 days was a reduction in the polymorphonuclear leukocyte cell count. All other measured parameters, including IL-2-producing cells, CD4/CD8 ratio, total immunoglobulin G and C3 were not altered with DHA consumption [19]. Several human studies examined the immune effects of n-3 fatty acid supplement on specific cell types. In another study, Kelley and co-workers [20] showed that DHA supplementation in healthy men reduced natural killer cell activity and suppressed production of several inflammatory cytokines without altering other B and T cell functions. High dose fish oil supplementation exerted anti-inflammatory effects on monocyte function without changing its phagocytic ability [21]. Recent studies examined the effects of short-term fish oil supplementation on monocyte expression of the major histocompatibility complex class II molecules, ICAM-1, and LFAA-1 in healthy volunteers. Monocytes were examined immediately after blood sampling and again after incubation with interferon-gamma. The intensity of expression of all the above-mentioned monocyte surface molecules was significantly reduced after fish oil supplementation, both before and after incubation with IFN- $\gamma$  [22]. High dose fish oil supplementation (3–4 g EPA daily) for a minimum of 4 weeks suppressed neutrophil leukotrien B4 synthesis and neutrophil chemotactic responsiveness to leukotrien B4 – apparently through a post-receptor mechanism [23]. Calder [15] recently reviewed the immunomodulatory effects of fish oil, and concluded that consumption of fish oil diminishes lymphocyte proliferation, T cell-mediated cytotoxicity, natural killer cell activity, macrophage-mediated cytotoxicity, and monocyte and neutrophil chemotaxis. Fish oil also suppresses major histocompatibility class II expression, antigen presentation, production of pro-inflammatory cytokines and adhesion molecule expression [15].

Human clinical trials in various disorders were conducted using different fish oil preparation, dosage and duration. Some of them are described below:

### Asthma

The cysteinyl leukotriens are produced by the sequential lipo-oxygenation of arachidonic acid. Leukotrien B4 is preferentially produced by neutrophils and is a powerful polymorphonuclear chemoattractant. Leukotrien C4, produced by mast cells, eosinophils and alveolar macrophages, is a potent constrictor.

PUFA = polyunsaturated fatty acids  
SLE = systemic lupus erythematosus

ICAM-1 = intercellular adhesion molecule-1  
LFAA-1 = leukocyte function-associated antigen-1

Drugs blocking leukotrien production and leukotrien receptor antagonists were shown to be effective in treating asthma. Therefore fish oil could, through reducing leukotrien production, affect both inflammation and constriction. However, epidemiologic and clinical studies in asthma have provided conflicting results on the importance of fish oil consumption in asthma. Previous studies have demonstrated a mild effect on cytokine production but failed to show a clinical effect on asthma severity [24]. Okamoto et al. [25] recently found that n-3 fatty acid supplementation in asthma patients for 4 weeks suppressed generation of leukotriens B4 and C4 by leukocytes, and significantly improved pulmonary function.

### **Inflammatory bowel disease**

In general, the composition of dietary fat affects immune responsiveness of the gut-associated lymphoid tissue. Specifically, n-3 fatty acids at high concentrations have a local and systemic suppressive effect on cell-mediated immunity via cytokine (including TNF- $\alpha$ ) release, through receptor affinity changes or interactions with intracellular signal transduction [26]. Several studies examined fish oil supplementation in patients with inflammatory bowel disease. Fish oil supplementation suppressed disease activity in patients with proctocolitis by reduction of IL-2 and leukotrien B4 production [27]. In another study, a diet rich in omega-3 fatty acids exerted some anti-inflammatory effects in patients with active ulcerative colitis, however the n-3 was clinically inferior to sulfasalazine [28]. There are contradictory results on maintenance of remission with fish oil in patients with inflammatory bowel disease. The n-3 fatty acids had only a mild and temporary effect on relapses of ulcerative colitis [29]. Similarly, omega-3 fatty acids showed no effect on extending the remission in Crohn's disease [30]. Yet, in another one-year double-blind placebo-controlled study, a novel enteric-coated fish oil preparation was moderately effective in maintaining remission in Crohn patients [31].

### **Rheumatoid arthritis**

Patients treated with n-3 fatty acids reported significant amelioration in morning stiffness and tender joints, yet all laboratory parameters were not found to be influenced by this treatment [reviewed in 32]. In contrast, Calder [15] observed that fish oil supplementation in rheumatoid arthritis patients does have some beneficial effect on biochemical or immunologic parameters (reduced IL-1 production by monocytes, and reduced leukotrien B4 levels).

### **Sepsis and catabolism**

Modulation of the inflammatory response via dietary manipulation constitutes the basis of immune nutrition. Several studies of critically ill patients suggested that a diet enriched with n-3 could be therapeutic. Gadek and colleagues [33], who studied n-3 supplementation in intensive care unit patients, reported that it could reduce neutrophil recruitment, improve gas exchange, shorten the period of mechanical ventilation and the length of

intensive care unit stay, and reduce the number of new organ failures. In another recent study [34], immune-enhancing enteral nutrition supplemented with arginine, mRNA, and omega-3 fatty acids from fish oil resulted in a significantly reduced mortality rate and infection rate in septic patients admitted to intensive care. Interestingly, n-3 PUFAs had a significant immunomodulating effect and seemed to prolong the survival of malnourished patients with generalized malignancy [35]. The mechanism involves inhibiting fat and protein catabolism, probably via reduction of cytokine production [36].

### **Renal disease**

Fish oil has shown a favorable effect on progression of kidney disorders, especially IgA nephropathy in some of the studies. Among the four published randomized clinical trials that tested the efficacy of fish oil treatment on IgA nephropathy, two reported beneficial effects on renal function while two showed no benefit [37]. Donadio et al. [38] reported that fish oil supplementation for 2 years preserved renal function in patients with IgA nephropathy and proteinuria. Long-term follow-up of these patients was recently extended to 6 years [39]. A significantly greater number of placebo-supplemented patients developed progression of renal failure or end-stage renal disease compared with those supplemented with fish oil. These authors observed that more fish oil-supplemented patients had stable renal function than non-supplemented ones.

## **Summary and Conclusions**

In short-term studies, both in animals and in humans, fish oil seems to exert anti-inflammatory effects. However, these effects may vanish during long-term treatment. There is a possibility that in autoimmune diseases, supplementation of dietary n-3 fatty acids might lead to a decrease in the number of autoreactive T cells via apoptosis, as demonstrated in (NZBXNZW) F1 lupus mice [40]. Thus, the "fade away" effect might be due to regrowth of pathogenic autoreactive cells. In animal models of autoimmune diseases, diets high in n-3 fatty acids from fish oil increase survival and reduce disease severity in spontaneous autoantibody-mediated disease, while n-6 linoleic acid-rich diets appear to increase disease severity.

The situation in human disease is probably more complex. Some of the discrepancy between studies can be attributed to methodologic problems. The effect of fish oil is dose, time and disease-dependent. Since the anti-inflammatory effects depend on the balance between n-3 and n-6 fatty acids, the relative proportion of EPA and DHA and possibly co-treatment with dietary vitamin E, the dose/effect ratio may vary between individuals. Furthermore, some animal studies demonstrating efficacy used very high doses that may be incompatible with human consumption. It seems that fish oil is only mildly effective in acute inflammation. In those chronic inflammatory

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IgA = immunoglobulin

disorders where it was found to be effective, several weeks are necessary to exhibit results. Yet, this mild anti-inflammatory effect, possibly through downregulation of pro-inflammatory cytokine production, leads to striking therapeutic improvement in critically ill patients. Fish oil supplementation seems advantageous especially in acute and chronic disorders where inappropriate activation of the immune system occurs. Fish oil has only a mild effect on active inflammation of diseases such as rheumatoid arthritis, SLE and Crohn's disease, but it could prevent relapse (in some of the studies). In diseases where the inflammation is mild, such as IgA nephropathy, fish oil may slow or even prevent disease progression. The above could explain the observation in some populations of a decreased incidence of inflammatory and autoimmune diseases [3], since the constant consumption of n-3 fatty acids could suppress any autoreactive (or hyper-reactive) T cells. However, if there is already an existing disease, increased consumption might not be beneficial over a long period. Therefore, the use of n-3 fatty acids can be recommended to the general healthy population, not only to prevent atherosclerosis but possibly also to reduce the risk of autoimmunity.

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