Therapeutic Use of Omega-3 Fatty Acids for Immune Disorders *In Search of the Ideal Omega-3 Supplement*

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Abstract

There has been continuing growth in the understanding of the role that omega-3 fatty acid supplements play in the support of immune function. The progress in both the basic science and clinical research surrounding the impact of various formulations of omega-3 fatty acid supplements on immune function has resulted in the recognition that the impact of these supplements is beyond that of the omega-3 fatty acids eicosapentaenoic acid (EPA) and docasahexaenoic acid (DHA) alone, and includes other fatty acids containing omega-3 derivatives termed *pro-resolving mediators*, along with vitamins A and D found naturally in some marine oils. The research on omega-3 oil supplements has also highlighted the importance that the supplement formulation be derived from a certified sustainable source, free of heavy metals and organic pollutants, minimally processed, and composed of the natural triglyceride form of the fatty acids for improved safety and effectiveness in providing immune support.

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More than 50 years ago, a landmark study was published that sent shockwaves through the cardiovascular research community, and it's still a source of controversy to this day. The year was 1971, the journal was *Lancet*, and the paper—authored by three Danish researchers who had spent years studying the native diet of one of the world's most remote cultures—was "Plasma Lipid and Lipoprotein Pattern in Greenlandic West-Coast Eskimos."[1] This indigenous population consumed the majority of their calories from fatty fish and mammals, yet routine and repeated testing of their serum lipids and lipoproteins indicated that these individuals carried a low risk to heart disease. Many people struggled with this data given that the prevailing belief at that time was that a high fat diet increased the risk profile to heart disease. The Greenlandic West-Coast Eskimos, it seemed, did not fit the narrative—and now we know why.

Omega-3 fatty acids from oily fish, which include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), as well as from plants, such as alpha-linolenic acid (ALA), have now been demonstrated to benefit cardiovascular health. Some of the most recent evidence includes a 2022 meta-analysis of clinical trials on omega-3 fatty acid supplementation, which stated the following: "Moderate evidence showed that the use of omega-3 fatty acids may reduce the risk of major cardiovascular events, myocardial infarction, and cardiovascular death." They continue: "Omega-3 fatty acids are relatively safe and in general do not increase gastrointestinal problems, bleeding-related disorders, or cancer, but attention needs to be paid to the risk of bleeding with prescription EPA ethyl ester formulations."[2]

A growing body of work also supports the role that omega-3 fatty acids have on immune function, as well as a subsequent reduction in vascular inflammation associated with the etiology of coronary heart diseases.[3] Of particular note is a recent study demonstrating that omega-3 fatty acid supplementation improves the TH1/TH2 ratio of lymphocytes and inflammation in individuals exposed to small airborne particulate matter associated with an increased risk to heart disease.[4]

Although EPA and DHA are the most familiar of the fatty acids, there is evidence that others may also may have a favorable impact on immune function and the reduction of inflammation in cardiovascular diseases. It has been reported that docosapentaenoic acid (DPA), which is found in reasonably high concentrations in some marine oils, serves as a precursor of vasculoprotective substances that have the ability to reduce immune-derived inflammation.[5] Additionally, eicosenoic acid (ESA), also found in certain marine oils, has been shown to have immune active function that is associated with the reduction of cardiovascular disease risk.[6,7]

Highly Purified vs Minimally Processed: What to Know About Omega-3 Supplements

Different types of fish have different types of fatty acid composition, and this fact directly impacts the omega-3 oils that are produced from a catch and ultimately rendered

into supplement products for the consumer marketplace. This is significant because when ingested, the fatty acids and other companion nutrients found in the omega-3 supplement are concentrated in different cell types in the body, therefore consumption of oils from different fish can result in variable clinical effects.[8] One key factor affecting fatty acid content and quality is the water temperature of the fish habitat. For instance, it has been found that cod liver oil derived from cold water Alaskan cod has a higher level of the beneficial eicosenoic acid (ESA) than cod liver oil derived from Atlantic cod (11% versus 5%), as well as a high level of omega-3 DPA (2%), which has been shown to have its own unique health benefits.

It has been assumed that the higher the concentration of EPA and DHA in the marine oil, the greater the efficacy of the omega-3 supplement. To control for this, many supplement producers rely on the use of chemically modified ester forms of EPA and DHA that can be concentrated through extensive fractional distillation. This is a process that results in the loss of many natural bioactive fatty acid-related constituents found in the original marine oil, some of which have their own immune-specific activities. It is now recognized that minimally processed marine oils from cold water regions of the world that retain the full portfolio of fatty acids can have a uniquely different influence on tissue levels of immune-active compounds than the highly purified EPA/DHA concentrates.[9]

Recent work at the National Institutes of Health has found that supplementation with a natural marine oil rich in eicosenoic acid (ESA) derived from Pacific saury, a cold water fish, improved plasma lipids in healthy humans, and decreased atherosclerosis in an animal model.[10,11] Other work has shown that supplementation with a marine oil in which the levels of ESA, EPA, and DHA were preserved resulted in improvement in metabolic syndrome in a diet-induced obesity animal model.[12]

The Role of Pro-Resolving Mediators in Specific Formulations of Omega-3 Fatty Acid Supplements

Awareness and understanding of another class of bioactive compounds found in minimally processed cold water marine oils is growing. Pro-Resolving Mediators (PRMs) are precursors to resolvins, protectins, lipoxins, and maresins, which are collectively known as Specialized Pro-Resolving Mediators (SPMs). Researcher Charles Serhan was credited with discovering this omega-3-derived class of compounds in 2004, and he famously described them as "brakes" on the inflammatory process.[13] Since this initial work, interest in this field has exploded, and today there are more than 1200 publications indexed, many of which demonstrate the clinical importance of SPMs.

What's important for both clinicians and consumers to understand is that bioactive Pro-Resolving Mediators, which much be present to metabolize Specialized Pro-Resolving Mediators, are lost in the industrialized processing of marine oils due to the application of high heat, as well as treatments such as bleaching and winterizing. This fact directly impacts the quality of dietary supplement concentrates of EPA and DHA, and although these products are widely available, there is a high degree of variability in terms of therapeutic potential. Clinical trials that include intervention with omega-3 fatty acid supplements can be affected by the composition of the formulations used, and the presence or absence of PRMs may account for differences observed in outcomes in these studies.

In 2020, the first study evaluating omega-3 fatty acid supplementation using a formulation that contained enhanced levels of specific Pro-Resolving Mediators in patients with peripheral artery disease was published.[14] Over a short intervention period, investigators found that a product enriched with 17-hydroxy-docosahexaenoic acid (17-HDPA) and 18-hydroxy-eicosapentaenoic acid (18-HEPE), both of which are PRMs, resulted in a significant increase in the plasma levels of several lipid mediator families associated with alteration in immune system function. The supplementation had a significant impact on immune cell number and function, with increased phagocytic activity of peripheral blood monocytes and neutrophils, and also reduced the expression of multiple proinflammatory markers. Evaluation of transcription profiling of monocyte-derived macrophages revealed a move towards a reparative phenotype that is associated with improved outcome in patients with peripheral artery disease.

Specialized Pro-Resolving Mediators are produced by enzymatic conversion in immune cells from the 17-HDPA and 18-HEPE proresolvin mediator precursors derived from two omega-3 fatty acids: docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). These mediators have been found to exert a potent impact on immune activation and assist in terminating an inflammatory process. In a recent randomized, double-blind, placebo-controlled study, it was found that healthy individuals taking an omega-3 fatty acid supplement enriched with 17-HDPA and 18-HEPE experienced an increase in levels of Specialized Pro-Resolving Mediators in their peripheral blood and reprogramming of the peripheral immune cells.[15] This finding indicates that a PRM-enriched formula may have a role in mediating the immune-directed actions of the supplement.

In a group of patients with chronic pain and a reduced quality of life, an observational trial showed that supplementation with a formula enriched with the 17-HDPA and 18-HEPE Pro-Resolving Mediators resulted in a reduction in chronic pain intensity, as well as better quality of life and improved mood.[16] Although this trial was not placebo-controlled, the findings do support the important role of PRMs in improving immune function in patients with chronic inflammation. Future trials of omega-3 formulations enriched in 17-HDHA and 18-HEPE are indicated and would be a welcome addition to the research base.

Omega-3 Supplements and Autoimmune Disorders

In 1985, important work was published by JM Kremer and his colleagues under the following title: "Effects of Manipulation of Dietary Fatty Acids on the Clinical Manifestations of Rheumatoid Arthritis."[17] They presented the results from a 12-week, double-blind, controlled study involving 20 patients with rheumatoid arthritis who followed a low saturated fat, high polyunsaturated fat diet. The experimental group received an omega-3 supplement containing 1.8 g of EPA. Compared to the placebo group, these individuals experienced reduced morning stiffness and a lower number of tender joints. This early work was groundbreaking, because it paved the way for many follow-up studies by groups around world interested in evaluating the impact of omega-3 supplements on arthritis and rheumatic disorders.

Kremer's group went on to undertake several other larger studies, including an evaluation of 66 patients with rheumatoid arthritis taking the potent non-steroidal anti-inflammatory drug, diclofenac. In this study, patients taking a high dose omega-3 supplement (a total of 5 grams of omega-3 oils daily, delivered in capsule form) had a statistically significant reduction in Interleukin 1 Beta, as well as a reduction in pain and joint swelling. A number of the patients were able to discontinue the use of the non-steroidal anti-inflammatory drug after supplementation with omega-3 oil.[18] Kremer later suggested that the body of clinical information from studies done around the world confirmed the impact of omega-3 supplementation on inflammatory and immune parameters across a range of rheumatic diseases.[19]

Impact of Marine Omega-3 Fatty Acid Supplements Containing Vitamin A and Vitamin D on Autoimmune Disorders

Autoimmune diseases represent a family of more than 80 different conditions that are characterized by immunological dysfunctions. Epidemiological data over the past three decades indicates a continued increase in the prevalence of these diseases. The specific etiology of autoimmune disease is not fully understood, but there is mounting evidence that lifestyle, diet, and environmental factors play a large role in their pathophysiology. Given the significant increase in autoimmune symptomatology and the lack of a proven pharmaceutical approach to their prevention, there is a need for both earlier prognosis and intervention to prevent later stage diagnosis, disability, and treatment. In 2003, Arbuckle et al. reported that autoantibodies are typically present many years before the diagnosis of systemic lupus erythematosus (SLE).[20] They found that the appearance of autoantibodies in SLE patients tends to follow a predictable path, with progressive accumulation of specific autoantibodies before the onset of SLE, while the patients are marginally symptomatic. From this study, it was recognized that this pre-autoimmune state was a period where preventive intervention could be administered if there was a well-established clinical approach to its remediation.

This work continues to this day. In the summer of 2022, an article published in *Frontiers in Immunology* reported that several environmental, lifestyle, and dietary factors are shared among individuals who go on to present with differing autoimmune diseases. The authors state: "A promising strategy for the prevention of autoimmune diseases might be to address these adverse life style factors by public health measures at the population level." [21]

According to recent data from researchers, global incidence of autoimmune disease is approximately 3 to 5%, and is particularly increasing in Westernized countries due to the shift from traditional dietary and agricultural patterns towards a highly processed and chemicalized diet. These dietary and environmental changes have impacted the intestinal microbiome, resulting in widespread chronic endotoxicity associated with increased intestinal mucosal permeability. This potentially alters the absorption and metabolism of immune-active nutrients such as vitamin A, vitamin D, and omega-3 fatty acids, increases possible exposure to antigenic substances, and results in alterations in immunometabolism and immune function.[22]

Vitamin A deficiency is known to impair innate immunity by reducing normal regeneration of mucosal barriers and diminishing the function of neutrophils, macrophages, and natural killer cells. Vitamin A is also required for adaptive immune system function and plays a role in the development of T helper and B-cells.[23]

Together, vitamin A and vitamin D regulate the complexity of the intestinal microbiome, mucosal barrier function, and the mucosal immune responses to ensure intestinal homeostasis.[24] It has been reported that a combination of vitamins A and D and omega-3 fatty acids at lower levels (as found in cod liver oil) has a synergistic impact on immune function that is comparable to using higher doses of the individual nutrients, thereby reducing the potential for adverse effects from high doses of the fat soluble vitamins.[25] This orchestration effect was demonstrated in a study on neuroinflammation and described by the investigators this way: "We show that vitamins A, D and omega-3 fatty acids (docosahexaenoic and eicosapentaenoic) at concentrations where they individually had little effect, significantly reduced the secretion of the inflammatory mediator, nitric oxide, when they were combined."[26]

These observations set the stage for the Vitamin D and Omega 3 Trial (VITAL), a nationwide, randomized, double blind, placebo-controlled trial with a two-by-two factorial design. This study was designed to evaluate whether a specific nutritional supplement intervention program could help prevent autoimmune disease in those who did not have a disease diagnosis at the initiation of the intervention. There were 25 871 participants, consisting of 12 786 men greater than 49 years of age and

13085 women greater than 54 years of age. The intervention consisted of a dietary supplement containing 2000 IU of vitamin D and 1000 mg of omega-3 fatty acids taken each day. Earlier studies had indicated that these nutrients might have beneficial influence on immune function in patients at risk to autoimmune diseases. Participants self-reported all incident autoimmune diseases from baseline to a median of 5.3 years of intervention; these diseases were confirmed by extensive medical record review. The primary endpoint of the study was incidence of autoimmune diseases, including rheumatoid arthritis, polymyalgia rheumatica, autoimmune thyroid disease, psoriasis, and all others within this diagnostic category. Vitamin D and omega-3 fatty acid supplementation for five years resulted in a reduction of all autoimmune disease incidence by 22%. The investigators of this trial concluded: "The clinical importance of this trial is high because these [nutrients] are well tolerated, non-toxic [nutritional] supplements, and other effective treatments to reduce the incidence of autoimmune diseases are lacking."[27]

This clinical trial is significant from several perspectives. First, it demonstrates the potential of preventing autoimmune disease with a targeted nutritional therapy. Second, it is of significant enough size to get the attention of those who claim there are no randomized, placebo-controlled clinical trials large enough to demonstrate the value of improving health outcomes with the use of nutritional supplementation. Third, it is an example of a successful collaborative, interdisciplinary clinical trial model that represents a systems biology approach to research. The VITAL trial was accomplished through the work of multiple divisions and teams at Brigham and Women's Hospital and Harvard Medical School.

The results of this study are not without precedent. For some time, it had been observed that infants who were supplemented with cod liver oil had much lower incidence of type 1 diabetes associated with autoimmune insulitis. Cod liver oil is known to have high levels of omega-3 fatty acids, vitamin A, and vitamin D, suggesting that these nutrients might have had a positive impact on preventing autoimmune type 1 diabetes. Vitamin A and vitamin D are known to work synergistically in support of both innate and adaptive immune function; of all vitamins, they have been found to have the greatest immune-modulating activity.[28]

In 2007, a retrospective study evaluating the effect of omega-3 fatty acid and vitamin D intake in islet autoimmunity in children at increased risk for type 1 diabetes was published in *The Journal of the American Medical Association*. From their preliminary observations of omega-3 fatty acid and vitamin D consumption in infants and their monitoring of future trials, the authors concluded: "If this [future] trial confirms this hypothesis, dietary supplementation with omega-3 fatty acids could become a mainstay for early intervention to safely prevent the development of type 1 diabetes." [29]

As of 2022, a 5-year field trial launched in 2019 is still underway to assess the relationship between vitamin D and omega-3 fatty acids among auto-antibody positive children who have not yet been diagnosed with type 1 diabetes.[30] Participants in this study are selected based upon prognostic criteria of being at risk to the development of type 1 diabetes. This includes individuals with a family history of type 1 diabetes or other autoimmune diseases, elevated HLA genotype, elevated serum high sensitivity C-reactive protein, low serum vitamin D levels (<40 ng/ml), and increased blood ratio of arachidonic acid to omega-3 fatty acid (>2:1). This is an example of a clinical trial that is evaluating methods of preventing pre-autoimmunity from transitioning to type 1 diabetes, using a specific intervention with vitamin D and omega-3 fatty acids.

The Ideal Omega-3 Supplement for Immune Support

From past research and evolving literature, there are a number of clinical takeaways about autoimmune disease and the ideal omega-3 supplement for immune support. Here is a summary:

1. Autoimmune diseases resulting from immune dysfunctions are rapidly increasing in prevalence.
2. Pre-clinical autoimmune disease is becoming recognized as a precursor to diagnosed autoimmune disease.
3. Pre-clinical autoimmune disease is associated with early-stage tissue-specific immune dysfunctions.
4. Diet, lifestyle, and environmental factors influence the production of autoimmune antibodies and early-stage immune dysfunction.
5. Omega-3 fatty acids, including EPA, DHA and DPA, have been found to rebalance immune function during the pre-autoimmunity stage.
6. The Pro-Resolving Mediators 17-HDHA and 18-HEPE, at total levels of not less than 30 mcg/g found in certain omega-3 fatty acid supplements, support the retraining of the immune system to resolve inflammation.
7. Vitamin A and vitamin D have a synergistic influence with omega-3 fatty acids in the reduction of inflammation associated with autoimmune disorders.
8. Cod liver oil that preserves the full spectrum of omega-3 fatty acids, Pro-Resolving Mediators (PRMs), and vitamins A and D, historically has been shown to have a positive impact on the immune dysfunction associated with pre-autoimmune conditions.

As we learn more about how to prognostically evaluate the early-stage immune dysfunctions associated with pre-autoimmune diseases, and about the role that specific nutritional and lifestyle therapies have on normalizing

immune function, the field of personalized preventive immunology will evolve. Presently, from the available research, it appears that the full spectrum of naturally occurring omega-3 fatty acids, in combination with Pro-Resolving Mediators and vitamins A and D, represent the bioactive ingredients in an ideal omega-3 formulation for the support of resolution of immune dysfunction. It is best that this omega-3 fatty acid supplement formulation be derived from a certified sustainable source, free of heavy metals and organic pollutants, minimally processed, and composed of the natural triglyceride form of the fatty acids for optimal immune support.

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