Definitions[7,8]

CRP: C-reactive protein is produced by the liver and present during episodes of acute inflammation. The most important role of CRP is its interaction with the complement system, one of the body's immunologic defense mechanisms. Elevated CRP levels are considered a strong cardiovascular risk factor.

Eicosanoids involved in inflammation and immune health: **PG, TX, LT**

Prostaglandins (PG): Prostaglandins are oxygenated unsaturated cyclic fatty acids, formed as cyclooxygenase metabolites, that perform a variety of hormone-like actions (as in controlling smooth muscle contraction and inflammation response).

Thromboxanes (TX): Thromboxanes are produced especially by platelets and cause constriction of vascular and bronchial smooth muscle. They also promote blood clotting.

Leukotrienes (LT): Leukotrines are any of a group of eicosanoids that are generated in basophils, mast cells, macrophages, and human lung tissue by lipoxygenase-catalyzed oxygenation; they participate in allergic responses.

Cytokines important to immune health: **IL-1, IL-6, TNF-α**

Interleukin-1 (IL-1): This interleukin is produced especially by monocytes and macrophages that regulate cell-mediated and humoral immune responses by activating lymphocytes. It also mediates other biological processes (such as the onset of fever) usually associated with infection and inflammation.

Interleukin-6 (IL-6): This interleukin is produced by various cells (such as macrophages, fibroblasts, T-cells, and tumor cells) and acts as a pyrogen, induces maturation of B-cells and growth of myeloma cells, activates and induces proliferation of T-cells, and stimulates synthesis of plasma proteins (as fibrinogen). Elevated IL-6 is a marker for the prediction of cardiovascular events.

Tumor necrosis factor (TNF-α): A protein produced chiefly by monocytes and macrophages in response especially to endotoxins. It mediates inflammation and induces the destruction of some tumor cells and the activation of white blood cells. Elevated TNF-α is a marker for the prediction of cardiovascular events.

Key fats:

NAME	NOMENCLATURE
DHA (docosahexaenoic acid)	22:6n-3
EPA (eicosapentaenoic acid)	20:5n-3
AA (arachidonic acid)	20:4n-6

References

1. Mori T, Beilin L. Omega-3 fatty acids and inflammation. *Curr Atheroscler Rep* 2004;6(6):461–467.
2. Robinson D, Xu L, *et al.* Suppression of autoimmune disease by dietary n-3 fatty acids. *J Lipid Res* 1993;34:1435–1444.
3. de Pablo M, Puertollano M, de Cienfuegos G. Biological and clinical significance of lipids as modulators of immune system functions. *Clin Diag Lab Immunol* 2002;9(5):945–950.
4. Simopoulos A. Omega-3 fatty acids in inflammation and autoimmune diseases. *J Am Coll Nutr* 2002;21(6):495–505.
5. James M, Gibson R, Cleland L. Dietary polyunsaturated fatty acids and inflammatory mediator production. *Am J Clin Nutr* 2000;71(1):343S–348S.
6. Trebble T, Wootton S, *et al.* Prostaglandin E2 production and T-cell function after fish-oil supplementation: Response to antioxidant cosupplementation. *Am J Clin Nutr* 2003;78(3):376–382.
7. Medline Plus. National Institute of Health, US National Library of Medicine. 2005. http://www.nlm.nih.gov/medlineplus/mplusdictionary.html. Accessed May 2, 2005.
8. Stipanuk M. *Biochemical and Physiological Aspects of Human Nutrition.* Philadelphia, PA: Saunders, 2000; 43–55.

THE ROLE OF FISH OIL SUPPLEMENTATION IN THE MANAGEMENT OF IMMUNE HEALTH

Gretchen Vannice, MS, RD

Fish oil provides eicosapentaenoic acid (EPA) and docosahesaenoic acid (DHA), two functional omega-3 fats that are essential to human nutrition. Although these essential fatty acids (EFAs) must be obtained through diet, most Americans under-consume them while at the same time over-consuming omega-6 fatty acids, which are more commonly found in the current diet. Omega-3 EFAs differ from omega-6 fatty acids, the other family of essential fats, in biological activity and dietary availability. In fact, over-consumption of omega-6 fatty acids in conjunction with under-consumption of omega-3 fatty acids has become a nutritional concern. In addition, the plant-based omega-3, alpha-linolenic acid (ALA) found in flax seeds, canola oil, and walnuts, is considered less potent, and human conversion to the more functional EPA is relatively inefficient[1].

Clinically proven data on the omega EFAs regarding immune health in humans, both innate and acquired, is a young area of research. The first report[2] directly linking marine-derived omega-3s and inflammation was published just over a decade ago (1993). Research involving fish oil is evolving rapidly now, and numerous clinical trials are underway.

Inflammatory and immune responses can be initiated by a number of bio-insults, including microbiological, immunological and toxic agents. In the early phases, interleukins and eicosanoids are secreted and become elevated. The interactions between immune and inflammatory cells are mediated by proteins called cytokines. Interleuken-1 (IL-1), Interleukin-6 (IL-6), and tumor necrosis factor (TNF-α) are important cytokines. Cytokine production is beneficial in response to infection, but excessive production can be problematic, and elevated levels of cytokines are implicated in the cause of the pathological responses that exist in inflammatory conditions.

EPA and DHA are directly associated with the modulation of immune and inflammatory response. EPA and DHA from fish oil are raw materials from which the body makes eicosanoids, which are short-lived, potent, locally acting, rapidly degraded cellular mediators that produce a broad range of biological affects on a multitude of tissues. Eicosanoid synthesis is dependent on the fatty acid composition of the membrane and limited by the availability of fatty acid precursors. Eicosanoids are synthesized as needed and are enzyme-competitive. Prostaglandins, thromboxanes, and leukotrienes are all eicosanoids.

Although our understanding of this whole process is only just beginning to evolve, there is an important role for adequate intake of omega-3 fats as essential dietary fats, and research is beginning to identify the mechanisms by which omega-3s support healthy modulation of inflammatory and immune responses. The modulation also depends on several factors such as the **type** and **amount** of dietary fatty acids and **duration** of supplementation[3].

In 2002, Simopoulos[4] published a historical and evidence-based review of the beneficial role of marine-derived omega-3 fatty acids in supporting immune health. She noted that the first evidence of this important role for omega-3s was observed in the low incidence of autoimmune and inflammatory conditions among Greenland Eskimos compared with gender- and age-matched Danes. Simopoulos also reviewed explanations of prostaglandin metabolism, including the enzymatic competition of omega-3 and omega-6 fats, and the impact of fish oil supplementation on prostaglandins and cytokines. She concluded that "many of the placebo-controlled trials of fish oil in chronic inflammatory diseases reveal significant benefit, including decreased disease activity and a lowered use of anti-inflammatory drugs." Human data was included in the review; and the mechanistic relationship between inflammation and atherosclerosis, obesity, major depression, rheumatoid arthritis, inflammatory bowel disease, asthma, and psoriasis was described.

In a more recent review[1] (2004), Mori and Beilin described the effect of EPA and DHA and eicosanoid metabolism with keen attention to its impact on inflammation. Citing experimental and clinical data, they demonstrated that omega-3 fatty acids from fish

What we know about fish oil supplementation and immune health:

Human clinical research[1,4,5] is showing that omega-3 EFAs consumed through fish oil supplementation:

- Measurably improve EPA levels in cellular membranes.
- Compete with and displace arachidonic acid (AA), an omega-6 precursor of the pro-inflammatory prostaglandin E_2 (PGE_2), in cellular membranes.
- Reduce cellular inflammation by increasing anti-inflammatory prostaglandin E_3 (PGE_3).
- Decrease circulating levels of pro-inflammatory cytokines, including tumor necrosis factor (TNF-α), Interleuken-1 (IL-1), and Interleukin-6 (IL-6).
- Reduce vasoconstrictive thromboxane levels TXA_2, also associated with high dietary intake of omega-6 fats, particularly AA.
- Appear to reduce C-reactive protein (CRP), a potent marker of inflammation.

oil have anti-inflammatory and immuno-modulatory effects, thus making them "potentially therapeutic agents for inflammatory and autoimmune disease." They also explored the relationship between cytokine metabolism and C-reactive protein, noting a mild direct impact of fish oil on CRP when it is combined with statin medications. (See our publication on fish oil and cardiovascular health, *Omega-3 Fatty Acids and Cardiovascular Health: An Evidence-Based Review*, for more detail). Mori and Beilin noted that the recently described F_2-isoprostanes are considered excellent biomarkers of in-vivo lipid peroxidative damage, and they cited studies reporting that F_2-isoprostanes fall when fish oil is in the diet. The beneficial role of EPA and DHA on endothelial function was also presented.

Fish oil supplementation has been shown to reduce disease severity and prolong survival in animal studies although the use of very high doses of supplementation has had some mixed results[3]. In a recently reported human clinical trial involving 16 healthy men[6], fish-oil supplementation (providing 300mg, 1gm then 2gm of combined EPA and DHA) decreased PGE_2 production and increased IFN-γ production and lymphocyte proliferation from baseline.

Proposed eicosanoid-independent mechanisms of marine-derived omega-3 fatty acids on immune response include[1,4]:

- Intracellular signaling pathways
- Transcription factor activity
- Cytokine production
- Adhesion molecule expression
- Alteration of gene expression
- Oxidative influences

Considerable clinical research is being done on the beneficial effects of a diet rich in marine-derived omega-3 essential fatty acids in other areas, including supporting cardiovascular health, eye and joint health, rheumatoid arthritis, triglyceridemia, diabetes, and metabolic syndrome. These human clinical trials consistently report no serious side effects.

Diets rich in marine-derived omega-3 fatty acids appear to induce[2,4,5,6]:

- Decreases in production of pro-inflammatory prostaglandin E_2 (PGE_2)
- Decreases in thromboxane A_2, a potent platelet aggregator and vasoconstrictor
- Decreases in leukotriene B_4 formation, an inflammation inducer
- Increases in leukotriene B_5, which displaces LTB_4
- Increases in thromboxane A_3, a weak platelet aggregator and weak vasoconstrictor
- Increases in prostacylcin I_3 without a decrease in PGI_2
- Increases in the anti-inflammatory prostaglandin E_3 (PGE_3)
- Inhibited production of pro-inflammatory cytokines IL-1 and TNF-α
- Inhibited production of IL-6, which is tightly correlated with serum CRP

About the author:

Gretchen Vannice, MS, RD, has a Master's degree in Nutrition Science and is a registered dietitian. A science-based nutrition writer and educator, she has worked in health care and the dietary supplement industry for 18 years.