

EPA/DHA and 'Silent Inflammation'

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'Silent Inflammation' – what is it?

Inflammation is a normal body response to injury or infection often resulting in swelling, heat, pain, or redness to the affected area for a very limited duration. On the other hand, 'silent inflammation' refers to a low-grade but constant inflammatory state in the body that is often due to dietary and other lifestyle factors. If such 'silent inflammation' persists and progresses, it can predispose people to a variety of chronic inflammatory conditions that affects morbidity (overall health and well-being) as well as increasing the risk of potentially threatening outcomes. 'Silent inflammation' is associated with sustained elevations of chemical mediators of inflammation known as pro-inflammatory biomarkers in the body that can have ongoing perturbing effects on various cells and tissues prior to the presentation of clinical symptoms and overt chronic disorders and disease.

Typically, certain chronic disorders have been long recognized as inflammatory diseases including rheumatoid arthritis, inflammatory bowel diseases (ulcerative colitis and Crohn's disease), psoriasis of the skin, certain cancers, and asthma to name a few. However, it is becoming increasingly apparent from numerous clinical studies that 'silent inflammation' is a risk factor for various stages of atherosclerosis and is associated with many cardiovascular risk

factors including the metabolic syndrome that precedes type 2 diabetes. As well, it is now considered that inflammatory factors and responses are involved in silent cerebral infarcts and clinical stroke events, stress-induced depression, and the pathogenesis of primary dementias and Alzheimer's disease.

What are the Chemical Mediators of Silent Inflammation?

Sustained inappropriate low-level inflammation is mediated by a whole variety of chemical mediators. The movement of cells known as monocytes/macrophages to the inflammatory sites is facilitated by so-called 'adhesion molecules' (including ICAM-1 and VCAM-1). These cells then produce pro-inflammatory mediators known as 'cytokines' (including various interleukins such as interleukin-6 and tumor necrosis factor). As well, these cells produce substantial amounts of a particular 'eicosanoid' known as PGE₂ (prostaglandin E₂) plus PGF_{2α}. PGE₂ has a broad range of pro-inflammatory effects including the enhancement of the production of cytokines. It is important to note that the omega-6 fatty acid known as arachidonic acid (AA) is the precursor (substrate) for the enzymatic synthesis of PGE₂ and PGF_{2α}. Dietary factors such as high intakes of omega-6 fatty acids and particularly the very low intakes of the marine/fish-based omega-3 fatty acids known as EPA (eicosapentaenoic acid) plus

DHA (docosahexaenoic acid) are responsible for the very high levels of AA in the cell membranes of monocytes/macrophages from people living in North America, Europe, Australia, elsewhere. This high level of residual cellular AA is directly linked to the elevated generation of PGE₂ and related pro-inflammatory chemical mediators.

Neutrophils (white blood cells) subsequently play a role in the inflammatory process by producing a potent pro-inflammatory eicosanoid known as leukotriene B₄ (LTB₄) by the enzyme-mediated conversion of AA to LTB₄. Other types of these '4-series' leukotrienes are formed in other cell types such as mast cells, basophils, and eosinophils. Again, higher intakes of dietary EPA plus DHA from fatty fish or via regular supplementation are known to consistently lower the levels of AA available for LTB₄ synthesis in neutrophils with a resulting reduction in the generation of this pro-inflammatory eicosanoid. It is also noteworthy that a number of pharmaceutical agents are becoming available which act as leukotriene antagonists (leukotriene receptor antagonists) such as their use as prophylactic anti-inflammatory therapy for asthma.

The aforementioned elevation of various chemical mediators in 'silent inflammation' is a common occurrence in a wide variety of inflammatory conditions and disorders.

Studies of Increased Intakes of EPA/DHA in Relation to Inflammatory Biomarkers in Humans

Epidemiological (population) studies have studied the association between increased intakes of omega-3 fatty acids and specifically EPA/DHA from fish/fish oils in relation to selected biomarkers of inflammation. For example, a cross-sectional study of 727 women from the Nurses' Health Study based at the Harvard School of Public Health revealed an inverse relationship between higher intakes of total omega-3 fatty acids and lower levels of selected biomarkers including interleukin-6 which they suggested to reflect lower levels of inflammation. Increasingly higher dietary intakes of EPA/DHA (combined) from the lowest 'quintile' (lowest 20 %) of 70 mg/person/day (median intake) up to the highest 'quintile' of 450 mg/person/day was associated with significantly lower circulating levels of ICAM-1 and VCAM-1. It is noted that EPA/DHA (combined) intakes in North America currently average 130-150 mg/person/day.

Very recently, a large study conducted jointly by Italian and American investigators on 1123 persons (aged 20-98 years) has been published which studied the relationship between blood plasma levels of polyunsaturated fatty acids (biomarker for dietary intakes) and circulating inflammatory factors. Interestingly, the sector of the population in the highest 'quartile' (upper 25 %) with respect to either EPA or DHA levels exhibited significantly lower levels of the pro-inflammatory cytokines in the form of interleukin-6 and tumour necrosis factor. These authors suggest that the low intakes of omega-3 fatty acids in older persons may contribute to their age-related trend towards a pro-inflammatory state.

Some but not all interventional studies conducted over short time intervals, in contrast to population studies, have exhibited that EPA/DHA supplementation can lower the levels of certain pro-inflammatory biomarkers. For example, EPA/DHA (combined) at intakes of 1100-2200 mg/day over a five-week period was found to decrease circulating levels of interleukin-6 in postmenopausal women on hormone-replacement therapy. Rupp and colleagues have suggested that higher daily intakes of EPA/DHA (combined) of 2-4 grams/day (2000-4000 mg/day) are needed for reducing pro-inflammatory eicosanoids and cytokines. Future studies of much longer duration than

generally conducted previously with varying doses of EPA/DHA (combined) will be of increasing interest in this regard.

Most human studies have used mixtures of EPA + DHA when demonstrating benefits in various chronic inflammatory disorders. Both omega-3 fatty acids can contribute to reducing inflammatory factors via somewhat different yet complementary mechanisms. Using sufficient amounts of EPA/DHA combined to reduce pro-inflammatory mediators, some animal studies using different ratios of EPA:DHA have indicated considerable anti-inflammatory activity with those ratios approaching a 2:1 ratio (EPA:DHA).

Recent findings on Mechanisms for Anti-Inflammatory Effects of EPA/DHA from Fish Oil

As mentioned above, increased intakes of EPA/DHA reduce cellular levels of AA with a resulting reduction in the formation of AA-derived eicosanoids along with a potential suppression in the levels of available pro-inflammatory cytokines. Other proposed mechanisms for the anti-inflammatory effects of EPA/DHA have included their involvement in modifying peroxisome proliferator activated receptors (PPAR α and PPAR β) that regulate gene transcription.

Very recently, Dr. Charles Serhan and colleagues from the Harvard Medical School have uncovered two new families of lipid mediators named 'resolvins' and 'protectins' which are formed from omega-3 polyunsaturated fatty acids. These compounds possess very potent anti-inflammatory activities including tissue protection and neuroprotective properties. EPA-derived mediators are referred to as resolvins of the E series (resolvin E1) and those formed from DHA are denoted as resolvins of the D series. While DHA is not converted to the non-inflammatory eicosanoids as for EPA, DHA is directly converted to resolvin D1 and protectin D1 that have anti-inflammatory properties. Increasing the generation of these bioactive molecules by dietary intakes of EPA/DHA can be expected to contribute to our understanding of the modes of action for EPA/DHA in attenuating low-level ('silent') inflammation as well as more advanced stages in relation to health and disease prevention/management.

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