EPA/DHA and 'Silent Inflammation'

What is 'Silent Inflammation'?

Inflammation is a normal body response to injury or infection, often resulting in swelling, heat, pain or redness in the affected area of a very limited duration. 'Silent inflammation', on the other hand, 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 affect their 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. Some of these biomarkers can be directly measured in the blood, providing valuable information about pathological events taking place in the body. They can also be used to measure the effect of therapeutic or dietary interventions.

Typically, certain chronic disorders have long been recognized as inflammatory diseases, including rheumatoid arthritis, inflammatory bowel diseases, psoriasis, certain cancers and asthma, to name just a few. However, it is becoming increasingly apparent from numerous clinical studies that 'silent inflammation' is a risk factor for atherosclerosis and is associated with many cardiovascular risk factors, including the metabolic syndrome in overweight and obese people that precedes type 2 diabetes. Moreover, inflammatory factors and responses are now believed to be involved in silent cerebral infarcts and clinical stroke events, stress-induced depression and the pathogenesis of Alzheimer's disease.

What are the Chemical Mediators of Silent Inflammation?

Sustained low-level inflammation is mediated by a whole variety of chemical mediators. White blood cells carry activators of inflammation. Some of them are known as 'cytokines'. In addition, these cells also produce substantial amounts of so called 'eicosanoids', which have a broad range of pro-inflammatory effects, including the enhancement of the production of cytokines. It is important to note that polyunsaturated fatty acids are substrate for the enzymatic synthesis of these eicosanoids. Dietary factors, such as high intakes of plant oils containing omega-6 fatty acids and, in particular, very low intakes of the marine -based omega-3 fatty acids known as EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid), are responsible for the very high production of eicosanoids in the cell membranes of white blood cells among people living in North America, Europe, Australia and elsewhere. Higher intakes of dietary EPA and DHA from fatty fish or via regular supplementation are known to consistently lower the levels of these chemical mediators of silent inflammation.

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

Epidemiological (population) studies have investigated the association between increased intakes of omega-3 fatty acids, and specifically EPA/DHA from fish/fish oils, and 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 these biomarkers, which it was suggested reflected lower levels of silent inflammation. Increasingly high dietary intakes of EPA/DHA were associated with significantly lower circulating levels of biomarkers of silent inflammation. It is noted that EPA/DHA intake in North America is currently very low due to the low intake of seafood.

A large study conducted jointly by Italian and American investigators on 1,123 persons (aged 20-98 years) was published very recently. It studied the relationship between blood plasma levels of polyunsaturated fatty acids and inflammatory biomarkers. Interestingly, people with the highest EPA or DHA levels exhibited significantly lower levels of these biomarkers. 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.

In contrast to population studies, some interventional studies conducted over short time intervals have shown that EPA/DHA supplementation can lower the levels of inflammatory biomarkers. For example, EPA/DHA at intakes of 1,100-2,200 mg/day over a five-week period was found to decrease biomarkers of silent inflammation in postmenopausal women on hormone-replacement therapy. Rupp and colleagues have suggested that higher daily intakes of EPA/DHA of 2-4 grams/day are required to reduce pro-inflammatory eicosanoids and cytokines.

The effects of EPA in particular on biomarkers of silent inflammation may be very different in the young and the elderly. Rees and collaborators in the UK studied the effects of some biomarkers on healthy young (18-42 years) and older (53-70 years) individuals given different doses of a high-EPA omega-3 concentrate (EPAX4510TG). The doses given for 12 weeks were 1.32, 2.7 or 4.05 g/day. Older subjects incorporated EPA into white blood cells better than younger subjects. This was reflected in lower immune response in the elderly at lower EPA doses compared with the younger subjects. The reason for these effects may be related to differences in diet betweens these two age groups. However, dietary survey data for adults in the UK do not suggest a big difference in the intake of polyunsaturated fatty acids. Another explanation may be that elderly people who have suffered from silent inflammation over a longer period of time may be more sensitive to treatment with EPA, which has anti-inflammatory effects.

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 marine-derived EPA:DHA have indicated considerable anti-inflammatory activity with those ratios approaching a 2:1 ratio (EPA:DHA).

Recent findings on the Mechanisms of Anti-Inflammatory Effects of Marine Omega-3 Fatty Acids

Increased intakes of marine omega-3 fatty acids reduce the production and effects of many biomarkers of inflammation. The effects may be mainly achieved by using EPA as substrate for the production of biological neutral eicosanoids. Other proposed mechanisms for the anti-inflammatory effects have included their involvement in modifying nuclear receptors that regulate gene transcription in cells. This effect seems to be mainly DHA dependent. The combination of EPA and DHA naturally occurring in fish therefore seems to be ideal.

Very recently, Dr Charles Serhan and colleagues from the Harvard Medical School have uncovered two new families of lipid mediators called 'resolvins'and 'protectins', which are formed from omega-3 polyunsaturated fatty acids. These compounds possess very potent anti-inflammatory properties that can further contribute to the anti-inflammatory effects of dietary EPA/DHA. EPA-derived mediators are referred to as resolvins of the E series and those formed from DHA are referred to as resolvins and protectins of the D series. 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 of 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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