Immunonutrition: the role of long chain omega-3 fatty acids

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Abstract
Dysregulation of the immune system is a key player in the development of several chronic illnesses and nutritional strategies using omega-3 to modulate immunity and inflammation is therefore of great interest to practitioners. Given the current shortfalls of omega-3 intake within the UK population, it is possible that there may be significant benefits to adding fish oil supplements to the diet. This addition is not only a safe and convenient method of meeting current recommended intakes, but also offers a method of meeting the required levels of omega-3 needed for an immunomodulatory effect.

Introduction
The immune system provides protection from an array of infectious agents whilst permitting tolerance to self-antigens and non-threatening agents such as food proteins and bacterial gut flora. The immune response divides into the innate and the acquired systems, which both involve a complexity of blood borne factors and different immune cells with different roles but which act together to create a highly regulated and well co-ordinated immune response. Fatty acids are known to influence immune function through a variety of mechanisms, of which changes in fatty acid composition of immune cell membranes and lipid rafts are examples. The effect of dietary fatty acid intake on immune function can be modulated by intake, offering the potential of a dietary management tool in its regulation.

Polyunsaturated fatty acids
The long-chain omega-6 and omega-3 polyunsaturated fatty acids not only comprise the framework of cell membranes ensuring fluidity and optimal cell function, but are also the precursors of ‘eicosanoids’ and ‘docosanoids’, hormonal substances involved in the regulation of inflammation, immunity, and platelet aggregation. Whilst the omega-6 family tend to give rise to pro-inflammatory products derived from arachidonic acid (AA), the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are synthesized endogenously or consumed through consumption of fish or fish oils, give rise to products that exert beneficial effects on the regulation of immunity, platelet aggregation, and inflammation. A high ratio of omega-6 to omega-3 has long been known to have significant effects on the development of a multitude of chronic conditions.

The role of polyunsaturated fatty acids in immunity and inflammation
The interactions between immune and inflammatory cells are mediated in part by several protein families including interleukins and cytokines. Interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor (TNF-alpha) are the most important products of monocytes and macrophages and the production of appropriate amounts is beneficial in response to infection, but inappropriate amounts or overproduction can be dangerous and are implicated in causing some of the pathological responses that occur in inflammatory conditions. Together they activate T and B lymphocytes and endothelial cells, induce fever and the synthesis of acute phase proteins by the liver as well as being involved in many other aspects of the acute phase response.

The phospholipid content of immune cells from individuals consuming a typical Western diet contain about 20% fatty acids as AA, about 2.5% as DHA and as little as 1% EPA. Because AA is the major fatty acid in immune cell membranes it is therefore the predominant eicosanoid producer giving rise to a series of inflammatory products such as prostaglandin E2 and leukotriene B4 and pro-inflammatory cytokines such as IL-1, IL-6 and TNF-alpha. The eicosanoids produced from AA therefore have direct roles in both inflammation and immunity. However, by increasing the membrane content of omega-3 fatty acids there is a changed pattern of production of eicosanoids, resolvins and cytokines, as well as changes in T cell reactivity and antigen presentation, all of which has a beneficial impact on both immunity and inflammation.

**Omega-3 as immunosuppressants**

Immune cell fatty acid composition can be modified through consumption of specific fatty acids, and incorporation of EPA and DHA is known to decrease the production of AA derived products indicating their use as adjuvant immunosuppressants in the treatment of various inflammatory diseases. Indeed, the increasing evidence that dietary fat can be directly correlated with inflammatory marker levels suggests that adjusting the amount of various dietary fats consumed could be a valuable mechanism to reduce inflammation. For example, both saturated fat and trans fats have been related to increased TNF-alpha levels, whereas omega-3 fatty acids lower inflammatory marker levels. In the UK, omega-3 intake is generally low with saturated fat intake higher than the recommended target. Indeed, total fat intake in the UK according to government guidelines, should average 35% of the total energy per day, with 13% from monounsaturated fat, not more than 2% trans-fat, 11% from saturated fatty acids and 6.5% of the total dietary energy intake from cis-PUFA. Genetic variations in genes encoding for delta-5 desaturase (FADS1) and delta-6 desaturase (FADS) have been shown to result in a decline in desaturase expression or activity as reflected in long-chain fatty acid levels. In addition, various dietary and lifestyle factors can impair synthesis including a high intake of saturated fat, trans-fat, alcohol and caffeine. The role of micronutrients is also significant. Zinc, magnesium, selenium, niacin, vitamin B6, folic acid, biotin, vitamin B12 and vitamin C are all necessary co-factors for elongase and desaturase enzymes and deficiency of these water soluble micronutrients can have significant effects on long chain fatty acid synthesis. Indeed it is estimated that less than 8% of alpha linolenic acid (ALA) is metabolised to EPA and only between 0.02% and 4% metabolised to DHA.

**Factors affecting n-3 intake from fish**

The flesh of oily fish is rich in EPA and DHA making a convenient source of preformed omega-3. However, the content of EPA and DHA in fish (and the ratio thereof) differs according to species, season, farmed or wild and type (white vs. oily). Because there are substantial variations in omega-3 content among fish species, factors such as palatability, frequency of consumption, cooking methods, availability of produce and socioeconomic status will all affect long-term trends of omega-3 intake, and whilst there may be lower within-subject variation in overall omega-3 intake, the between-subject variation is likely to be much higher. Fish consumption patterns vary greatly throughout Europe with cod generally the most commonly consumed. Modern changes in our diet and the current consensus that the UK is not an ‘oily fish-loving’ nation, means that many individuals run the risk of consuming insufficient amounts of the long-chain omega-3 fatty acids for optimal function of the cardiovascular, immune and inflammatory systems. The most recent government
recommendation for consumption is set at two portions of fish per week (a portion is approximately 140 g), of which at least one portion should be oil-rich to provide a daily amount of 450 mg EPA and DHA. However, the average intake of long-chain omega-3 fatty acids of the UK adult population is currently estimated to be 244 mg/day and for those individuals who consume no fish, intake can be as low as 46 mg daily. Direct dietary consumption of EPA and DHA, through fish oil supplements, may therefore be necessary to achieve not only the biological effects required for homeostasis but also as immunomodulators.

Omega-3, what dose?

Whilst there are known health benefits attributed to supplementing the diet with fish oils, it is becoming clearer that the dosages needed to exert biological changes within the body are much higher than levels typically consumed. For example, very high doses of omega-3 fatty acids (i.e., 8.0 g/day) have been shown to have both anti-inflammatory effects and to improve body composition in patients with heart failure. In relation to inflammatory bowel disease, one study of 5.36 g of fish oil decreased leukotriene B4 levels in ulcerative colitis, whereas 2.7 g of fish oil preparation reduced the rate of relapse in patients with Crohn’s disease in remission. The use of fish oil as an alternative treatment to nonsteroidal anti-inflammatory drugs (NSAIDs) in rheumatoid arthritis has also been widely investigated, although choice of supplement is of great importance when considering dose. For example, doses of cod liver oil at as much as 10 g are needed to provide the 2.2 g of omega-3 shown to reduce the daily NSAID requirement by more than a third in 39% of patients with rheumatoid arthritis. In processed fish oil supplements, DHA is predominantly localised at the sn-2 position of the triglyceride (TAG) whereas esterification of EPA at each site is more random. The positional distribution of fatty acids within triglycerides is significant as absorption into chylomicrons of the fatty acid in the sn-2 position is favoured over those of the sn-1 and sn-3. Because fish oil contains a mixture of TAG with various fatty acids, the concentration of EPA and DHA fatty acids is relatively low, certainly in comparison to oils containing EPA and DHA in ethyl-ester. Indeed, when comparing the EPA and DHA content of commonly available fish oil preparations, those that contain ethyl ester and free fatty acid show significantly higher levels of EPA (259–300 mg) and DHA (172–254 mg) per gram of oil in comparison to triglyceride oils where EPA ranges 80-250 mg, and DHA 78-56 mg per gram of oil. Indeed, very high concentrations of omega-3 in ethyl ester form have been shown to have a higher uptake than formulations containing lower concentrations. Furthermore the ratio of EPA to DHA within an oil may also be of relevance since unlike DHA, directly influences eicosanoid production by competitively inhibiting both incorporation of AA into cell membranes but also through the subsequent reduction of AA-derived inflammatory eicosanoids and through the direct increase in EPA-derived anti-inflammatory eicosanoids. It should, however, be advised that use of concentrated omega-3 oils also increase the risk of lipid peroxidation in plasma and tissues, and that supplementation with a variety of antioxidants is best to combat the possible effects of increased oxidative stress.

Conclusion

It is suggested that omega-3 fatty acids are required at generally high doses for demonstrable beneficial effects on immune function with around 2–8 g/day needed to reduce pro-inflammatory eicosanoids and cytokines. Whilst the benefits to increasing fish intake are becoming increasingly clearer, to achieve such a dose through fish consumption alone, the UK population needs to maintain a considerable increase in intake over that currently consumed. Unfortunately, this increase would also affect dietary exposure levels to chemical contaminants, with an increased risk of exceeding those levels currently considered to be safe (dioxins and dioxin-like PCBs are currently set at 2 pg WHO-TEQ/kg bw/day with limits for methyl mercury intake set at 0.23 mg/kg bw/day). Therefore, increasing fish intake may not be a viable option for the whole population. For example, pregnant and breastfeeding women, and women of child bearing age are advised against consuming more than two
portions weekly and advised to avoid eating larger living such as swordfish and marlin. The use of highly purified fish oils can therefore offer a safe alternative to fish consumption to achieve such amounts needed for optimal regulation of immunity and inflammation.

**References**


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