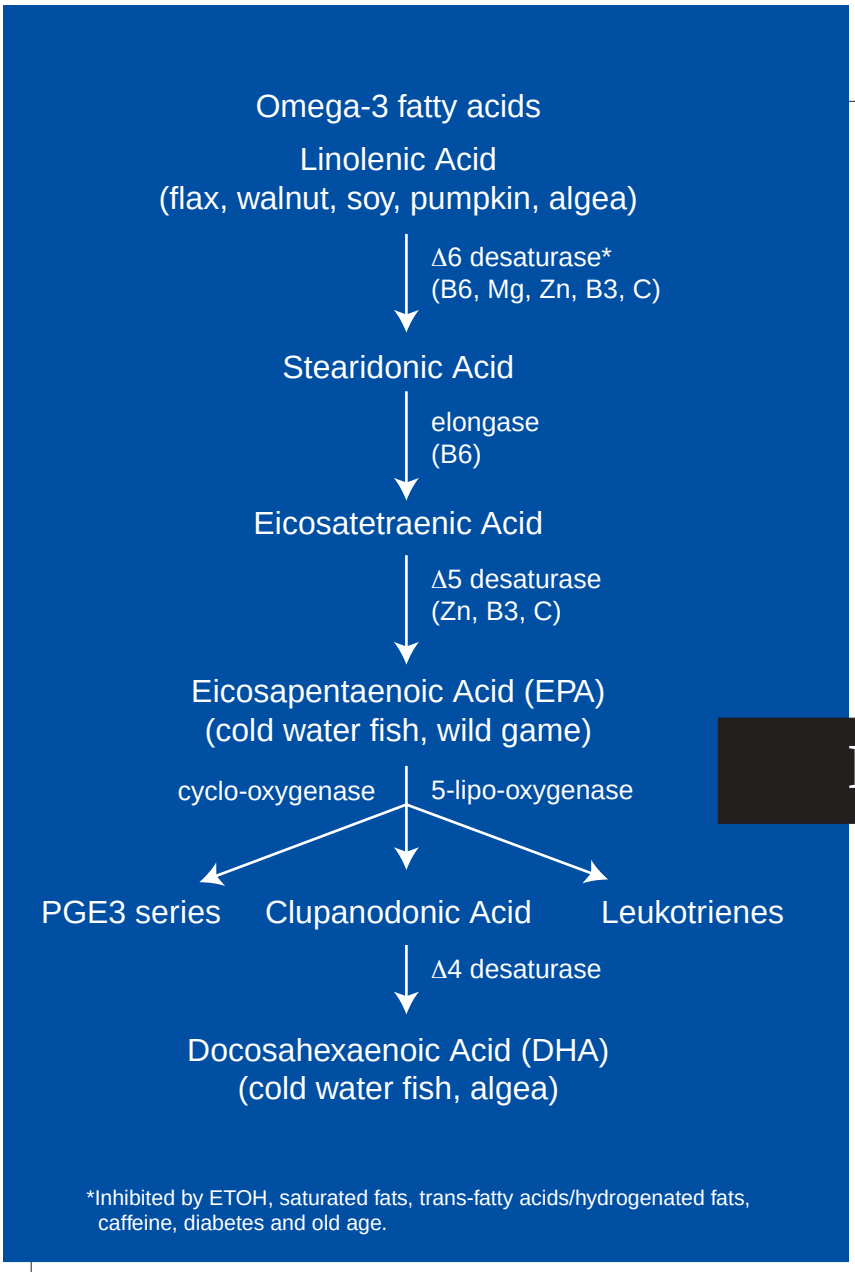

Monograph

Fish Oil

Introduction

Many well-recognized problems are associated with excessive intake of dietary fat, including obesity, insulin resistance, coronary heart disease, and some forms of cancer. While intakes of saturated, trans, and arachidonic fatty acids have been linked to the development of chronic disease, research shows omega-3 (n-3) fatty acids, specifically fish oils, are essential in the prevention and treatment of disease.

Biochemistry

Fish oils are comprised of the essential fatty acids eicosapentaenoic acid (EPA, C20:5n-3) and docosahexaenoic acid (DHA, C22:6n-3). Both EPA and DHA fall into an even larger category of polyunsaturated fatty acids (PUFAs). Compared to saturated fats, PUFAs are more readily used for energy when initially ingested. Increasing the degree of unsaturation at a given carbon chain length increases the relative mobility of stored fat, making PUFAs more bioavailable.[1] EPA and DHA come from the PUFA, alpha-linolenic acid (ALA) and are classified as omega-3 fatty acids. The nomenclature of an omega-3 fatty acid indicates that the first carbon-carbon double bond occurs at the third carbon atom from the methyl end of the molecule.[2] Through a series of enzymatic reactions, the 18:3 PUFA is converted first to EPA and then finally to DHA. Both EPA and DHA are deemed conditionally essential

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as the body can synthesize them from ALA. However, while consumption of ALA can lead to significant increases in tissue EPA, it does not do so for DHA.[3] There are several circumstances where the requirements for DHA greatly exceed the rate of synthesis, making supplementation necessary.

Mechanism of Action

EPA and DHA compete with arachidonic acid (AA) for the enzyme cyclo-oxygenase. EPA is converted by platelet cyclo-oxygenase to thromboxane A3 (TXA3), which is only a very weak vasoconstrictor, unlike thromboxane A2 (TXA2), which is formed by the action of cyclo-oxygenase on AA and is a strong vasoconstrictor. However, prostacyclin I3 (PGI3), formed from EPA in the endothelium, is as potent a vasodilator and inhibitor of platelet aggregation as is protacyclin I2 (PGI2) formed from AA. The net effect, therefore, of an increased dietary EPA:AA ratio is relative vasodilation and platelet aggregation inhibition.[2] EPA yields the 5-series of leukotrienes, which are only weakly chemotactic. A relative reduction in chemotaxis might be expected to be antiatherogenic. Fish oil decreases both very low density lipoproteins (VLDLs) and triglycerides due to inhibition of hepatic triglyceride synthesis. Because VLDL is a precursor to LDL, a reduction in LDL cholesterol is seen in some patients with hypertriglyceridemia; however, fish oil does not appear to lower plasma cholesterol in subjects with hypercholesterolemia.[4,5]

Clinical Indications

Arrhythmias

A series of animal studies by McLennan et al found that diets supplemented with tuna oil (n-3 PUFA) significantly reduced the incidence and severity of arrhythmias, preventing ventricular fibrillation during both coronary artery occlusion and reperfusion. These studies also found that severity of arrhythmias was significantly worsened by a diet supplemented with saturated fat.[6-8]

Coronary Heart Disease

The beneficial effects of fish oil on coronary heart disease (CHD) have been researched for more than two decades, particularly since the landmark study of Greenland Eskimos showed lower mortality rates from cardiovascular disease.[9] Fish oil has important metabolic effects, such as inhibiting platelet aggregation and lowering serum triglyceride levels, which could play a role in the prevention of CHD. A prospective study of European men found an inverse association between fatty fish consumption (but not lean or total fish consumption) and 20-year CHD mortality.[10] Fish oil has successfully been proven to reduce serum triglyceride levels in humans,[11] although the majority of studies have been conducted on men. More recently, a study has been conducted on the effects of n-3 fatty acid supplementation, specifically fish oil, on postmenopausal women either receiving or not receiving hormone replacement therapy (HRT). The fish oil supplement significantly reduced serum triglyceride concentrations by an average of 26 percent in both HRT-status groups, without affecting other lipid variables. The effect was estimated to decrease CHD risk by 27 percent in postmenopausal women.[12] A study by Thomas et al suggested fitness status, in addition to fish oil supplementation, may be an important factor in determining postprandial triglyceride levels. Sixty minutes of exercise, in addition to fish oil supplementation, decreased plasma triglyceride levels by 33 percent. It has been suggested that fish oil may inhibit lipoprotein lipase activity via its effect on insulin release.[13]

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Cancer

Epidemiological, experimental, and mechanistic data implicate n-6 PUFAs as stimulators and long chain n-3 PUFAs (specifically fish oil) as inhibitors of development and progression of a range of human cancers.[14,15] Studies have found the antitumor effect of EPA is mainly related to its suppression of cell proliferation. On the other hand, the effect of DHA appears to be related to its ability to induce apoptosis.[16,17] The dietary n-3/n-6 fatty acid ratio, rather than the quantity administered, appears to be the principle factor in the antitumor effect of n-3 PUFAs. An effective ratio appears to be in the range of 1.8-1.9.[16] EPA and DHA supplementation, in the form of fish oil, have also been found to suppress both breast and colon cancer tumor growth and metastasis.[18,19]

Cognitive Function

AA and DHA accrue rapidly in the prenatal human brain during the third trimester and the early postnatal period when the rate of brain growth is maximal and most vulnerable to nutritional deficiencies. Postnatal deficiencies of DHA have specifically been found to relate negatively to visual acuity, neurodevelopment, and behavior. In general, breast milk contains sufficient amounts of long chain PUFAs, including DHA, to meet these needs, assuming the maternal diet is adequate. A study examining breast milk and DHA content in Pakistani mothers versus Dutch mothers found significantly lower amounts of DHA which were directly correlated to the decreased amount of fish eaten in North Pakistan.[20] There is also controversy at present over whether or not the infant formulas that contain only linoleic acid and alpha-linolenic acid are sufficient for brain development.[21]

Depression

In several observational studies, low concentrations of n-3 PUFAs were predictive of impulsive behaviors and greater severity of depression.[22,23] Dopaminergic and serotonergic functions in the frontal cortex seem to be affected by the fatty acid composition of the diet. An n-3 deficiency may be related to catecholaminergic disturbances in depression.[24] Recently it was demonstrated that EPA, DHA, and total n-3 fatty acid levels are significantly lower in red blood cell membranes of depressed subjects compared to the control group.[25]

Diabetes

Rats fed diets high in fish oil and with a low n-6/n-3 PUFA ratio maintained normal insulin action. Diets high in saturated and mono-unsaturated fats led to profound insulin resistance in numerous tissues, as did diets high in omega-6 PUFAs.[1] Similar studies by Storlien et al found providing 5-10 percent of dietary energy from fish oil accelerated glucose uptake and maintenance of normal glucose metabolism, even at high levels of fat intake.[26] More importantly, the ability of fish oil to enhance the rate of glycogen storage allows skeletal muscle to increase its uptake of glucose, even under conditions where fatty acid oxidation is accelerated.[27] Fish oil enhances insulin secretion by incorporation of n-3 fatty acids into the plasma membrane to compete with AA production. This reduces the concentration of AA in the plasma membrane, decreasing the production of PGE2, which, in turn suppresses the production of cAMP, a well-known enhancer of glucose-induced insulin secretion. Consequently, fish oil enhances insulin secretion from β-cells, regulating blood sugar.[28] The effect of fish oil on blood lipids should be evaluated in diabetics. A randomized trial conducted on 41 type 1 diabetics found 15 g fish oil per day resulted in statistically significant elevations in LDL cholesterol.[29] It should be pointed out, however, that this study used a very high daily dose of fish oil – 15 g daily versus an average therapeutic dose of 5 g daily.

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Rheumatoid Arthritis

Clinical and biochemical studies have shown that fish oil, and to a lesser extent fish, can be used as a source of n-3 fatty acids in the treatment of rheumatoid arthritis. Studies found EPA and DHA reduced eicosanoid and proinflammatory cytokines. The synthesis of interleukin 1b decreased by 20 percent after a diet high in omega-3 fatty acids was consumed for two weeks and was decreased further at the end of four weeks. The synthesis of tumor necrosis factor-alpha decreased 40 percent after two weeks on the diet; at four weeks there was no significant change.[3]

Other Therapeutic Considerations

Studies also show fish oil to be effective in the treatment of acute respiratory distress syndrome, psoriasis, multiple sclerosis, and dysmenorrhea.[30-33]

Dosage

Clinical trials show dosages of 4g/day to be effective.[13] Other literature suggests dosage ranges from 1-10g/day. The maximum tolerated dose was found to be 0.3g/kg per day of fish oil capsules. This means a 70-kg patient can tolerate up to 21 one-gram capsules/day.[34]

Safety

Fish oil supplementation is generally safe and well tolerated. Few side effects have been reported. Studies to determine the maximum tolerated dose and dose-limiting toxicities of fish oil showed side effects included gastrointestinal complaints, mainly diarrhea.[34] Other areas of concern include heavy metal contamination found in fish, specifically mercury. In the general population, diet is the major source of mercury exposure, primarily through fish consumption.[35] Quality control of products is an essential part of safety. To ensure quality, fish oil extractions must be purified by a process that removes environmental toxins such as dioxins, PCBs, and heavy metals.

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