

Effects of Dietary Fish Oil Consumption in Prevention of Human Diseases

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Abstract: Recently, the consumption of fish oils in the form of omega-3 polyunsaturated fatty acids and their positive health benefits has become a popular topic amongst health professionals and the public. The focus of this paper will be to look at the effects of the marine omega-3 (n-3) polyunsaturated fatty acids (PUFAs) EPA (Eicosapentaenoic acid / Icosapentaenoic acid) and DHA (Docosahexaenoic acid), to determine if their consumption is related to human health. To determine the scientific merit of this topic, a number of primary articles will be referenced to provide supporting evidence that the consumption of fish oils do indeed have a beneficial effect on health. Heart disease is a widespread health problem in modern society. Fish oil, rich in omega-3 fatty acids (DHA and EPA) has been proven in many clinical studies to benefit heart health. Studies have proven that omega-3 fatty acids improve brain function and that intake of fish oil and DHA is linked to a lowered risk of developing Alzheimer's disease. Fish oil has been found to protect against symptoms of hay fever, sinus infections, asthma, food allergies and allergic skin conditions such as hives and eczema. Fish oil improves the health of skin, nails and hair. EPA and DHA in fish oil reduce the amount of compounds causing inflammation. Fish oil has been proven to be beneficial in intestinal health. Fish oil has an anti-inflammatory effect in inflammatory bowel disease (Ulcerative colitis and Crohn's disease).

Key words: Fish oil • Human health • Prevent diseases

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 intake of saturated fat, trans fatty acids and arachidonic acid has been linked to the development of chronic disease, research shows omega-3 (n-3) fatty acids, (Table 1) specifically fish oils, are essential in the prevention and treatment of disease [1].

Biochemistry: Fish oils are mostly comprised of the essential fatty acids eicosapentaenoic acid (EPA, C20:5n-3) and docosahexaenoic acid (DHA, C22:6n-3), with lesser amounts of other fatty acids. EPA and DHA fall into a larger category of polyunsaturated fatty acids (PUFAs). Increasing the degree of unsaturation at a given carbon chain length increases the relative mobility and fluidity of the fatty acid, giving PUFAs physical properties not found in saturated fats, including increased

bioavailability.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 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, ALA is converted first to EPA and then to DHA. Both EPA and DHA are deemed conditionally essential, as the body can synthesize them from ALA; however, while consumption of ALA can lead to significant increases in tissue EPA, it does not necessarily do so for DHA.³ There are several circumstances where the requirement for DHA greatly exceeds the rate of synthesis, making supplementation necessary [2-4].

Scientific publications praising the merits of omega-3's have reached an astronomical figure. Most people today no longer know where to turn amid this wealth of information. In this article I will share with you some key facts which can provide you with a better understanding of the omega-3 fatty acids.

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Table 1: Omega 3 unsaturated fatty acids

Common name	Scientific name	Molecular name	Abbreviation
α - linolenic acid	9,12,15-octadecatrienoic acid	18:1 n-3	ALA
Eicosapentaenoic acid	5,8,11,14,17- eicosapentaenoic acid	20:5 n-3	EPA
Docosapentaenoic acid	7,10,13,16,19- docosapentaenoic acid	22:5 n-3	DPA
Docosahexaenoic acid	4,7,10,13,16,19- docosahexaenoic acid	22:6 n-3	DHA



Fig. 1: Salmon fish

Fish oils, due to their nature, are the most highly, overly refined and processed so-called “natural foods”. This article will not focus on the benefits of omega-3 fatty acids for that information can be found in a variety of publications. This article will address the question of, what is really natural about omega-3 fatty acids from fish oil and how to improve the bioavailability and where to find an all-natural whole food omega-3 fatty acid. EPA and DHA are mainly present in seafood (fish oil) and to a lesser degree in meat. However, meat is higher in omega-6 versus omega-3. The presence of omega-3 fatty acids in animals is a direct result of their plant diet. In fact, in the case of fish, it is the one-celled marine organisms like algae or plankton which synthesize EPA and DHA. Their consumption by crustaceans and fish permits an accumulation of omega-3 fatty acid in the tissue of predatory animals. As a general rule, the fattier a fish is (5% or more lipids) the higher its level of omega-3 fatty acids. Among them, salmon (Figure 1), herring, eel, mackerel, sardine and trout are good sources of omega-3 fatty acids. Certain crustaceans are also rich in omega-3’s including krill but they are also high in cholesterol and the cholesterol is only removed by the use of hexane. As an example, a 100 gram serving of Atlantic salmon provides about 1.2 grams of omega-3 fatty acids but several factors influence omega-3 content; geographic origin, species, diet and age. Interestingly, farmed Atlantic salmon is generally fattier than wild salmon and thus richer in EPA and DHA (+15% on average). Added to this is a difference in maturity between these two types of salmon. The slow growth of wild salmon increases the risks of absorption and storage of heavy metals in their tissues, unlike farm salmon which grow more quickly.

In spite of the disparities in sources of omega-3’s, it’s important to consume one serving of fish, preferably fatty fish, at least once weekly in order to cover in part the EPA and DHA requirements. For those who may not have the means or the desire to eat fish several times a week, can find a more reasonable solution by selecting Vectomega, a natural whole food omega-3 fatty acid supplement in the preferred form and ratio of EPA and DHA [5-8].

Some Facts about Treatment with Omega-3 Fatty Acids:

- Fish oil is currently the recommended source of omega-3. Flaxseed oil and perilla oil contain a different type of omega-3. Several cases of hypomania have occurred in people taking flaxseed oil, but the causes remain unclear.
- Omega-3s are usually added to whatever treatment you are already receiving, there is not yet enough experience to recommend using them alone in most cases. There are no known interactions with psychotropic drugs.
- Always discuss the use of any new medications, over-the-counter or otherwise, with your prescriber. Drug interaction risks and other dangers can be associated with any biological treatment.
- A starting dose of 5 grams of omega-3 per day is currently recommended. Calculate dosage based on the concentration of omega-3 fatty acids listed on the label of the fish oil supplement. This can be confusing due to the variety of different preparations. Focus on the omega-3 concentration in each capsule.
- The 2 main omega-3 fatty acids in fish oil are EPA and DHA. A high ratio of EPA to DHA is desirable in a fish oil capsule. Other desirable characteristics include small capsule size and high omega-3 concentration, which minimizes the number of capsules required per day.
- Dosage can be split between morning and night or taken all at night.
- Due to the volume of fish required to achieve the recommended daily dosage, it is not recommended that you use eating fish alone as a means of getting your Omega-3s.

- You may experience some fishy taste but treatment with fish oil does not make you smell like fish! Taking the supplements with orange juice can reduce the fishy taste.
- Do not pursue this treatment if you are taking any type of blood thinners, even high doses of aspirin, or any medications or substances that have the same blood thinning effect.
- Do not use cod liver or other fish liver oils to achieve high omega-3 doses, since it could result in vitamin A toxicity.
- The omega-3 fatty acids are not a panacea, but in many cases they do appear to be as effective as conventional medications [9, 10].

Some Additional Facts about Omega-3 Fatty Acids:

- Cold-water, oily fish are the main source of marine-derived omega-3 fatty acids.
- Farm-raised fish that are fed grain alone may contain little or no Omega-3s. Omega-3s come from algae that, in the marine food chain, are then eaten by krill which are in turn eaten by larger fish.
- Omega-3s have numerous health benefits in other areas, including heart, cholesterol, rheumatoid arthritis, & Crohn's Disease, to name a few. Again our thanks to Dr. Stoll for letting us share this information from his findings. A new web site has been launched by Dr. Stoll and other practitioners that contain information on where you can order a special Omega 3 formulation designed to maximize its efficacy [11].

Fish Consumption, Fish Oil, Omega-3 Fatty Acids and Cardiovascular Disease: Since the first AHA Science Advisory "Fish Consumption, Fish Oil, Lipids and Coronary Heart Disease," [12] important new findings, including evidence from randomized controlled trials (RCTs), have been reported about the beneficial effects of omega-3 (or n-3) fatty acids on cardiovascular disease (CVD) in patients with preexisting CVD as well as in healthy individuals [13]. New information about how omega-3 fatty acids affect cardiac function (including antiarrhythmic effects), hemodynamics (cardiac mechanics) and arterial endothelial function have helped clarify potential mechanisms of action. The present Statement will address distinctions between plant-derived (α -linolenic acid, C18:3n-3) and marine-derived (eicosapentaenoic acid, C20:5n-3 [EPA] and docosahexaenoic acid, C22: 6n-3 [DHA]) omega-3 fatty acids. (Unless otherwise noted, the term omega-3 fatty

acids will refer to the latter.) Evidence from epidemiological studies and RCTs will be reviewed and recommendations reflecting the current state of knowledge will be made with regard to both fish consumption and omega-3 fatty acid (plant- and marine-derived) supplementation. This will be done in the context of recent guidance issued by the US Environmental Protection Agency and the Food and Drug Administration (FDA) about the presence of environmental contaminants in certain species of fish [14].

Coronary Heart Disease: Fish consumption has been shown to be related to reduce sudden cardiac death. In a population-based, nested, case-control study, a strong negative relationship was reported between fish intake and risk for sudden death (ie, 5.5 g of omega-3 fatty acids per month, equivalent to two fatty fish meals per week, was associated with a 50% reduced risk of primary cardiac arrest [15]. In the US Physicians' Health Study, men who consumed fish at least once weekly had a relative risk of sudden death of 0.48 ($P=0.04$) versus men who consumed fish less than once per month [16]. A recent report from the Physicians' Health Study [17] reported an inverse relationship between blood levels of long-chain omega-3 fatty acids and risk of sudden death in men without a history of CVD. The relative risk of sudden death was significantly lower among men with levels in the third quartile (RR=0.28) and the fourth quartile (RR=0.19) compared with men whose blood levels were in the first quartile. Further evidence for a protective effect of omega-3 fatty acids comes from two recent studies by Landmark *et al.* [3,4] who reported that chronic intake of fish or fish oil was associated with a reduction in infarct size as estimated by the frequency of Q-wave infarcts and by peak creatine kinase and lactate dehydrogenase activities after MI. In contrast to all the studies demonstrating a beneficial association, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study found that estimated omega-3 fatty acid intake from fish was associated with a trend toward increased relative risk of coronary death after adjustment for trans, saturated and cis-monounsaturated fatty acids [18-20].

Triglycerides: The hypotriglyceridemic effects of omega-3 fatty acids from fish oils are well established. In a comprehensive review of human studies, Harris [21] reported that, 4g/d of omega-3 fatty acids from fish oil decreased serum triglyceride concentrations by 25% to 30%, with accompanying increases in LDL cholesterol of 5% to 10% and in HDL cholesterol of 1% to 3%. A dose-response relationship exists between omega-3 fatty

acid intake and triglyceride lowering [22]. Postprandial triglyceridemia is especially sensitive to chronic omega-3 fatty acid consumption, [23] with quite small intakes (<2g/d) producing significant reductions [24]. The plasma lipid and lipoprotein responses to fish oil are comparable in diabetic and nondiabetic subjects [25]. In addition, a recent meta-analysis of 26 trials of subjects with type 1 or type 2 diabetes mellitus reported no effects of fish oil on hemoglobin A_{1c} [26] although fasting blood glucose levels rose slightly in the latter group.

Fish oil can have a therapeutic role in the treatment of marked hypertriglyceridemia (>750 mg/dL). Effective doses of omega-3 fatty acids range from 3 to 5 g/d, which can only be obtained consistently by supplementation. At present, it seems that both EPA and DHA have triglyceride-lowering properties [27]. Patients taking >3 g of EPA+DHA from supplements should do so only under a physician's care because the FDA has noted that an intake in excess of this level could result in excessive bleeding in some individuals [28-31]. In contrast, cardioprotective intakes seem to be considerably lower (≈1 g/d), have almost no potential for adverse effects and can be achieved by diet.

Blood Pressure: Omega-3 fatty acids seem to have a small, dose-dependent, hypotensive effect, the extent of which seems to be dependent on the degree of hypertension [29]. In a meta-analysis, Morris *et al.* [11] found a significant reduction in blood pressure of -3.4/-2.0 mm Hg in studies with hypertensive subjects who consumed 5.6 g/d of omega-3 fatty acids. Likewise, Appel *et al.* [59] found that blood pressure was decreased -5.5/-3.5 mm Hg in trials of untreated hypertensives given >3 g/d of omega-3 fatty acids. DHA seems to be more effective than EPA in lowering blood pressure [32]. Still, in view of the high dose required to lower blood pressure and the proven efficacy of other nutritional factors and of antihypertensive medications, an increased intake of omega-3 fatty acids has a limited role in the management of hypertension.

Thrombosis and Hemostasis: Omega-3 fatty acids decrease platelet aggregation, [33] resulting in a modest prolongation of bleeding times [34]. Some evidence indicates that fish oil supplementation may enhance fibrinolysis [35]. Although omega-3 fatty acid intake has been negatively associated with levels of fibrinogen, Factor VIII and von Willebrand factor, [36] more recent evidence from the Coronary Artery Risk Development In young Adults (CARDIA) study found no significant associations between customary intakes of

fish (4 to 39 g/d) and omega-3 fatty acids (0.9 to 4.1 g/d) and these coagulation factors. [37-38] Marckmann *et al.* [17] also found no effect of omega-3 fatty acids (0.9 g/d) on levels of Factor VII, fibrinogen, endogenous fibrinolysis, β-thromboglobulin and von Willebrand factor. In contrast, a recent study reported that coronary patients taking 5.1 g/d of omega-3 fatty acids for 6 months experienced a reduction in von Willebrand factor (128% versus 147% for controls) and thrombomodulin (25 versus 33 ng/mL). [39] Although it seems clear that omega-3 fatty acids beneficially influence collagen-induced platelet aggregation (thereby affecting hemostasis), their effects on thrombosis remain unclear. There is little evidence to suggest that an intake <3 g/d of omega-3 fatty acids would cause clinically significant bleeding.

Arrhythmias: The possibility that omega-3 fatty acids (including α-linolenic acid) may reduce risk for sudden cardiac death is based on evidence from a prospective cohort study, [40] a case-control study, [41] and four prospective dietary intervention trials [42-44]. Proposed mechanisms to explain these observations center not on lipid or blood pressure lowering or on antithrombotic effects, but on a novel stabilizing effect of omega-3 fatty acids on the myocardium itself. Evidence for a direct effect of these fatty acids on the heart has come from several observations. First, increased heart rate variability in survivors of MI was associated with the consumption of one fish meal per week [46] or fish oil supplements (4.3 g/d of omega-3 fatty acids) [45]. Increases in this parameter predict a lower risk of mortality due to arrhythmic events in post-MI patients. EPA and DHA also have been shown to reduce resting heart rate and increase left ventricular filling capacity [47]. Animal experiments and cell culture studies have shown that fish oil has potent antiarrhythmic effects. For example, studies with rats and dogs [48] have shown that pretreatment with omega-3 fatty acids reduced damage to cardiac tissue and forestalled the development of ventricular dysrhythmias when heart attacks were induced. Similar observations were made in fish oil-fed cats that were protected from cerebral damage after stroke induction [49]. *In vitro* induction of tachyarrhythmias in cultured neonatal rat ventricular myocytes by various pharmacological agents (such as ouabain) can be prevented or abolished by the addition of omega-3 fatty acids to the culture medium (reviewed by Kang and Leaf [50]). This seems to be due to the ability of omega-3 fatty acids to prevent calcium overload by maintaining the activity of L-type calcium channels during periods of

stress and to increase the activity of cardiac microsomal $\text{Ca}^{2+}/\text{Mg}^{2+}$ -ATPase. In addition, omega-3 fatty acids (including α -linolenic acid) are potent inhibitors of voltage-gated sodium channels in cultured neonatal cardiac myocytes, which may contribute to the reduction in arrhythmia [51-52].

Other Biological Effects: Goode *et al.* [24] showed that acetylcholine-stimulated relaxation of small arteries taken from hypercholesterolemic patients was significantly improved after three months of supplementation with 3 g/d of EPA+DHA. Fish oil feeding has also been shown to improve endothelial function (reviewed by Chin and Dart) and to increase arterial compliance. These effects may be secondary to fish oil's ability to enhance nitric oxide production and may be the mechanism by which fish oil elicits a small hypotensive effect. Mechanisms to explain the antiatherogenic (inhibition of new plaque development) effect of omega-3 fatty acids have recently been proposed. For example, EPA and DHA seem to alter the metabolism of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), E-selectin and intercellular adhesion molecule-1 (ICAM-1). There is also *In vitro* evidence that DHA reduces endothelial expression of VCAM-1 and the expression of E-selectin, ICAM-1, interleukin (IL)-6 and IL-8 in stimulated cells. On the other hand, a study in male smokers with hyperlipidemia showed that six weeks of omega-3 fatty acid supplementation (4.8 g/d) increased soluble forms of E-selectin and VCAM-1. A subsequent study in coronary patients given supplemental omega-3 fatty acids (5.1 g/d for 6 months) found similar results. Fish oil also affects the metabolism of inflammatory mediators like the interleukins and tumor necrosis factor- α , molecules also believed to play a role in atherogenesis and plaque stability [53-54].

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 wide range of human cancers. 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. The dietary n-3/n-6 fatty acid ratio, rather than the quantity administered, appears to be the principal factor in the antitumor effect of n-3 PUFAs. An effective n-3/n-6 ratio appears to be in the range of 1.8-1.9. EPA and DHA supplementation, in the form of fish oil, has also been found to suppress both breast and colon cancer tumor growth and metastasis [55].

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 in Pakistanis, which was directly correlated to the decreased amount of fish eaten in North Pakistan.²⁰ It is also controversial at present whether infant formulas that contain only linoleic acid and alpha-linolenic acid are sufficient for brain development [56].

Depression: In several observational studies, low concentrations of n-3 PUFAs were predictive of impulsive behaviors and greater severity of depression. 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. 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 controls [57].

Diabetes: Rats that were 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. Similar studies found that 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. 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. The effect of fish oil on blood lipids should be evaluated in diabetics.

A randomized trial conducted on 41 type 1 diabetics found 15 grams 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 grams versus an average daily therapeutic dose of 5 grams [58].

Dosage: Clinical trials show dosages of 4g/day to be effective. Other literature suggests dosage ranges from 1-10 g/day. The maximum tolerated dose was found to be 0.3g/kg per day of fish oil capsules; thus, a 70-kg patient can tolerate up to 21 grams per day [59].

CONCLUSION

Heart disease is a widespread health problem in modern society. Fish oil, rich in omega-3 fatty acids (DHA and EPA) has been proven in many clinical studies to benefit heart health, also supported by the American Heart Association guidelines. Persons with mood disorders such as depression benefit from fish oil supplementation. Lack of omega-3 fatty acids and in particular DHA has been linked by researchers to depression. A new study of teenagers has found that fish oil and DHA consumption relates to lower hostility rates in teenagers. Hostility has been shown to predict the development and manifestation of heart disease. Studies have proven that omega-3 fatty acids improve brain function and that intake of fish oil and DHA is linked to a lowered risk of developing Alzheimer's disease. Studies suggest that fish oil and DHA may protect the nervous system. Studies learn that omega-3 fatty acid-intake by mothers during pregnancy may protect babies against the development of allergies. Fish oil has been found to protect against symptoms of hay fever, sinus infections, asthma, food allergies and allergic skin conditions such as hives and eczema. Skin disorders such as psoriasis have been shown to improve from fish oils. In the skin of persons with psoriasis the amount of compounds causing inflammation is many times greater than normal. Fish oil inhibits the production of these inflammatory compounds. Fish oil improves the health of skin, nails and hair. Fish oil supplements have been shown to benefit in rheumatoid arthritis (RA) and other inflammatory forms of arthritis, such as occurs in some persons with psoriasis and gout. EPA and DHA in fish oil reduce the amount of compounds causing inflammation. Diabetics suffering from non-insulin dependent diabetes or type II diabetes benefit from fish oil supplementation. Researches show that persons, who consume 5-10 percent of their dietary

energy consumption in the form of fish or fish oil, have less insulin resistance. The intake of fish oil has been proven to be beneficial for the body's immune function. Research has linked intake of fish oil to a lowered risk of breast cancer and prostate cancer. The consumption of fish oil lowers the risk for cardiovascular disease and osteoporosis in post-menopausal women. (Pre) Menstrual symptoms such as menstrual pain are often alleviated from the use of fish oil supplementation. Omega-3 fatty acids are converted into pain relieving substances (prostaglandins type-3) that control contractions of the uterus, which cause the cramping. Research has shown that consumption of fish oil is linked to lowered risk of age related macular degeneration, an eye condition which is the leading cause of severe visual loss in people over age 50. Fish oil has been proven to be beneficial in intestinal health. Fish oil has an anti-inflammatory effect in inflammatory bowel disease (Ulcerative colitis and Crohn's disease). We can conclude fish consumption can prevent most diseases in human. Human health is guaranteed with fishes regularly consumption in two to three times in week. Species fishes and cooking methods effect on seafood nutritional values and finally human health.

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