Latest Findings on Essential Fatty Acids and Cardiovascular Health

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Omega-3

The epidemiological studies by Bang and Dyer[1] in the mid 1970's of the Greenland Inuits established a low prevalence of age-adjusted mortality from myocardial infarction in that population as compared to Danes or North Americans. The striking difference between diets was the presence of 5 to 10 grams of the long-chain n-3 polyunsaturated fatty eicosapentaenoic acid (C20:5n-3) and docosahexaenoic acid (C22:6n-3) per day. Lower coronary heart disease has been established in at least three prospective epidemiological studies with men who ate at least some fish weekly as compared to men that ate none.[2] Men who consume 35 grams or more of fish daily compared with those who consumed none had a relative risk of death from CHD of 0.62 and a relative risk of nonsudden death from MI of 0.33.

Harris[3] has proposed that an omega-3 fatty acid biomarker, the omega-3 index (erythrocyte EPA+DHA), be considered at least a biomarker, if not a risk factor, for coronary heart disease, especially sudden cardiac death. The largest (11,000 plus patients) and most well- controlled study[4] with small intakes of omega-3 and CHD disease in high risk patients examined the randomized effects of one capsule of 850 mg (EPA+DHA) as compared to usual care. After following the patients for 3.5 years the patients that received the omega-3 capsule had a reduction of 20% risk of death and for sudden death by 45%.

The American Heart Association[5] acknowledges the beneficial effects of omega-3 fatty acids in those at high risk of—or who have—cardiovascular disease. Patients without documented coronary heart disease are recommended to eat a variety of fish at least twice a week. Patients with documented CHD are recommended to consume about one gram of EPA+DHA per day. The FDA ruled in 1997 [6] that intakes of up to 3 grams per day of marine omega-3 fatty acids are GRAS (generally recognized as safe) for the inclusion in the diet. The ruling included specific considerations of the reported effects of omega-3 fatty acids on glycemic control in diabetic patients, on bleeding tendencies, and on LDL cholesterol.

The enrichment of membrane phospholipids by omega-3 fatty acids influences the mechanisms by which many of the beneficial properties of omega-3 fatty acids are observed. Because of their highly unsaturated nature they alter membrane fluidity. The omega-3 fatty acids displace arachidonic acid (AA). Omega-3 fatty acids compete with AA for enzymes responsible the production of inflammatory mediators, such as eicosanoids and platelet-activating factor (PAF). Increasing the ratio of EPA to AA enhances the formation of prostaglandin E3 (PGE-3) which can block inflammation.

Intracellular omega-3 FA are able to serve as ligands for a number variety of nuclear receptors. Omega-3 FA are observed to alter the expression of genes responsible for production of TNF-alpha, interleukin-1 as well as modulating the expression of genes controlling both systemic and tissue-specific lipid homeostasis.[7] In addition, omega-3 fatty acids can regulate the activation of transcription factors including NF-kappa B. NF-kappa B induces many of the genes in response to inflammatory stimulation.

Inflammation plays a key role in coronary artery disease and other manifestations of atherosclerosi.[8] Immune cells dominate the early atherosclerotic lesions and their effector molecules accelerate the progression of the lesions. The infiltration and retention of LDL in the arterial intima initiate an inflammatory response in the artery wall. The balance between inflammatory and anti-inflammatory activities can control the progression of atherosclerosis. Omega-3 FA as modulators of the inflammatory process are natural agents that have also been reported to be beneficial for other inflammatory processes.

Maroon[9] treated 250 patients who had been seen by a neurosurgeon and were found to have nonsurgical neck or back pain with 1,200 mg per day of omega-3 FA. After taking the omega-3 FA for thirty days 59 per cent of the patients discontinued to take their prescription NSAID medications for pain. Sixty percent stated their overall pain was improved, and 60% stated that their joint pain had improved. Eighty percent stated they were satisfied with their improvement and 88% stated they would continue to take the omega-3 FA supplement. Maroon noted that "the literature reviewing rheumatoid and osteoarthritis, both chronic inflammatory conditions, consistently reports improvements in joint pain and function using omega-3 EFA."

The modern western diet which contains corn oil, sunflower oil and safflower oils supplies large amounts of linoleic acid (LA), omega-6 FA (C18:2n6). Vasquez[10] notes that two omega-6 fatty acids in particular, LA and arachidonic acid (AA) (C 20:4n6) should be reduced or eliminated from the diet to the extent possible. LA increases inflammation by several mechanisms, one of which is the activation of NK-kappa B. The increased omega-6/omega-3 ratio most likely contributes to an increased incidence of cardiovascular disease and inflammatory disorder.[11] The earlier hunter-gather diet provided an omega-6 to omega-3 ratio between 1:1 to 4:1. These ratios were maintained until the industrial revolution and are now estimated at between 16:1 and 20:1. In order to obtain a dietary fat intake that more closely resembles what our genomic code is based upon, a reduction of omega-6 oils and increase of omega-3 oils is necessary in the human diet. These dietary suggestions do not take into consideration the effects of trans fats, oxidized fats, and saturated fats that have occurred with industrial food supplies.

To obtain one gram of omega-3 FA per day from fish an individual would have to consume 2-3 ounces of salmon, sardines or mackerel per day or consume dietary supplements containing fish oil. A potential issue arises from the fact that some fish may be contain relatively high amounts of heavy metals, such as mercury and/or organic pollutants such as polychlorinated biphenyls and dioxins. Since July 2002, the FDA has tested over 3400 cans of tuna as well as 227 samples of various fish. Large carnivorous fish that are high in the food chain were found to have the highest levels of mercury. Swordfish may have 1 microgram of mercury per gram (1 ug/gm). Tuna was found to have an intermediate level of mercury (0.1-0.5 ug/gm).[12] The mean daily intake of mercury is 3.5 ug per day in the United States. Because of concerns of mercury contamination in the food supply, women of childbearing age are recommended by the FDA to eat no more than one or two portions of oily fish per week (about 0.4-0.8 g/day of omega-3 fats).[13]

In 1997, the US EPA recommended the value of 0.1 ug/ kg body weight per day as a lifetime safe daily intake of mercury (methyl mercury). For a 60 kg woman the EPA maximum safe dose of mercury per day would be 6 micrograms. This dose would have made the consumption of 7 ounces of canned tuna per week as

equaling or exceeding the EPA safe limits for mercury. The FDA has reviewed the data on mercury and proposed a reference dose of 0.5 ug/kg of body weight per day (NRC, 2000).[14]

To provide a diet of one gram omega-3 FA per day, supplementation with omega-3 fatty acid capsules becomes the only non-toxic remedy available. There are many sources of omega-3 FA in the market place. The food standards agency for the UK published[15] in 2005 the total mercury as measured in 100 samples of fish oil dietary supplements. The level of detection, minimal amount that can be measured, was reported as <0.0014 mg/kg. That level is the same as 1.4 mcg per gram. The consumption of six fish oil capsules could be acceptable by their own testing methods and could also result in a potential consumption of (6 x 1.4 ug) 8.2 ug of mercury from the fish oil capsules. The European guidelines for mercury are based upon the provisional tolerable weekly intakes set by the joint expert committee on food additives as set forth by the United Nations and World Health Organization. For mercury the European guidelines are 0.005 mg/kg body weight per day for which no more than two thirds should be from organic mercury (methyl mercury). For a 60 kg person a consumption of less than 20 ug per day of mercury from fish would be considered within their guidelines as safe.

Due to contaminates, fish such as tuna, swordfish or cod are recommended not to be consumed on a regular basis. Cod oil was the original sourcing for omega-3 FA capsules. Freezing the oil provided a rich fraction of omega-3 FA. Concerns over heavy metals, dioxins and PCBs (polychlorinated biphenyls) lead to methods of purification, such as clay and silica filtration, and reduced the contaminates in the oils. Refiners of fish oil now rely on sourcing fish that have lower levels of toxic exposure to produce omega-3 oils low in toxins. Harvesting of fish, such as Peruvian Achoveta and sardines off the north and south poles, combined with established refining methods allows the production of high purity fish oils. The high purity fish oils used in the manufacturing of high purity omega-3 FA will typically assay at less than 0.01 microgram mercury per gram oil (<10 ppb, parts per billion).

Because we can not synthesize omega-3 or omega-6 FA, they must be obtained from the diet and therefore are essential nutrients. Both omega-3 and omega-6 are structural components of all cell membranes. These fatty acids affect membrane properties such as fluidity, permeability and the activity of membrane bound enzymes. The adequate daily intake (AI) for adults of omega-3 FA (as EPA+DHA) is 0.65 gm. Found in flax seed, canola, soybeans, walnuts and dark green leaves, the omega-3 FA alpha-linolenic acid (LNA) (C18:3n-3) has a AI of 2.22 gm. LNA is a plant derived fatty acid and can be elongated to EPA and DHA by the enzymes delta-6-desaturase, elongase and delta-5-desaturase. The process of conversion of LNA to EPA and DHA requires essential vitamins (vitamin c, pyridoxine) and essential minerals (zinc, magnesium, iron). This process is inhibited by catecholamines (stress), thyroxine, glucagons, trans fats, saturated fatty acids, alcohol, smoking, elevated blood glucose and aging.[16, 17, 19] Functionally, the omega-3 FA EPA and DHA should be considered essential nutrients in many individuals. Siguel reports that essential fatty acid insufficiency (EFAI) is one of the most prevalent nutritional deficiencies, occurring in >10% of samples from the Framingham Offspring study. Siguel states "We believe that EFAI is associated with significant disease states and may underlie many of the chronic disease prevalent in Western societies. We have shown in patients with angiographically documented coronary artery disease that indicators of EFAI are highly predictive of coronary artery disease."[23]

Omega-6

The AI for the omega-6 FA linoleic acid (LA) (C18:2n-6) is 4.44 grams per day. The western industrialized countries rely on corn, safflower and soybean oils as sources of omega-6 FA. There is an overabundance of omega-6 FA in that food supply. Most American consumers obtain more than 15 grams of LA per day. To be fully utilized by the body, LA must be metabolized to a range of other substances.[18] The first step in this process requires the enzyme deta-6-desaturase and produces gamma linolenic acid (GLA). This enzymatic step is slow and rated "Limited", especially in humans.

GLA is present only in small amounts in the oils commonly used in the Western diet but is found in high amounts in the plant oils borage seed (23%), blackcurrant seed (18%) and evening primrose (9%). GLA is rapidly converted by the enzyme elongase to dihomo-gamma-linolenic acid (DGLA) (C 20:3n6). Increased dietary intakes of GLA or DGLA have been shown to increase prostaglandin E-1 (PGE-1) which suppresses PGE-2 production. PGE-2, produced from arachidonic acid (AA), is pro-inflammatory and suppresses T cell function. Both GLA and AA compete for the same cyclooxygenase enzyme. GLA down regulates the production of proinflammatory cytokines by competing with AA.

PGE-1 increases intracellular cyclic AMP and it is this increase in polymonuclear leukocyte cyclic AMP that reduces the release of lysosomal enzymes, reduces polymorphonuclear leukocyte chemotaxis, and reduces the margination and adherence of leucocytes to the blood vessels.[20] By a similar fashion, PGE-1 inhibits the inflammatory responses mediated by lymphocytes. PGE-1 is also a potent inhibitor of vascular smooth muscle cell proliferation[23] The interplay of these eicosanoids, PGE-1 and PGE-2, influences a wide range of physiological and pathological processes, including inflammation, immunity, hemostasis, blood pressure, and atherosclerosis. This balance is thought to be regulated by the complex interaction between DGLA, AA and EPA.[21]

The administration of GLA, which rapidly converts to DGLA, has been shown to reduce joint swelling and tenderness in patients with autoimmune diseases such as rheumatoid arthritis (RA). The dosage of GLA required for effectiveness is not well established. Studies using less than 500mg/day of GLA for periods of less than 6 months typically fail to show benefit in the treatment of RA. In a twenty four week trail, using 1.4 gm of GLA per day, Leventhal showed clinical improvement in RA patients. GLA reduced the number of tender joints by 36%, swollen joint count by 28%, whereas the placebo did not provide improvements.[24]

The reduced capacity to convert LA to GLA has been associated with a variety of other pathophysiological states including aging, diabetes, alcoholism, atopic dermatitis, premenstrual syndrome, cancer and cardiovascular disease.[25] The decline in delta-6-desaturase activity that occurs with aging is greater in women than in men.[26] DGLA also exerts its effects on cytokine activity independently of its effect on COX enzymes. DGLA is present in cells as a free fatty acid. DGLA has been shown to regulate gene function.[27] Das proposes[28] that a functional deficiency in delta-6-desaturase underlies the origins of the inflammation that leads to the initiation and progression of atherosclerosis. Provided adequate antioxidant status, increased levels of essential PUFA, GLA and DLGA are capable of suppressing inflammation and expression of various adhesion molecules on the surface of endothelial cells.

Combined Effects of Omega-3 and Omega-6

The enzyme elongase rapidly converts GLA rapidly converts DGLA. The enzyme delta-5-desaturase can convert DGLA to AA. *In vitro* and *in vivo* studies have shown that inflammatory cells such as neutrophils contain elongase but not the delta-5-desaturase activity. Because of this, dietary supplementation of GLA will increase only DGLA and not AA in cells such as neutrophils. Serum levels of AA maybe increased with dietary GLA. Since AA has been shown to enhance the formation of platlelet-aggregating endoperoxides and thromboxanes, platelet aggregation can be enhanced by dietary supplementation with GLA. EPA and DHA block the activity of delta-5-desaturase. The combination of EPA with GLA prevents the increase of serum AA. Barham[29] was able to show that an equal amount of EPA added to GLA prevented an increase of AA *in vivo*. The addition of EPA not did inhibit the conversion of GLA to DGLA in neutrophils.

Laidlaw and Holub[30] examined the effects of supplementation with fish oil n-3 fatty acid and GLA on circulating plasma lipid and fatty acid profiles in women. The objective of the study was to determine the effects of different levels of GLA supplementation together with a constant intake of EPA and DHA on the reduction of triglycerides (triacylglycerol) and fatty acid patterns of serum phospholipids. Four grams of EPA+DHA were supplied to thirty one healthy women who were assigned to one of four groups. The groups received,[1] no GLA,[2] one gram of GLA,[3] two grams of GLA or[4] four grams of GLA daily for 28 days. The group that received four grams of EPA+DHA and two grams of GLA had the largest mean reduction in non-HDL-cholesterol concentrations (14.4%). The DGLA increased only when the ratio of EPA+DHA to GLA was 4:2 or 4:4. The one gram, two gram and four gram GLA groups had decreases in LDL cholesterol and improved LDL:HDL ratios. Overall, the mixture of 4 grams EPA+DHA and 2 grams GLA (2:1 ratio) provided the greatest reduction, 43%, in the 10 year myocardial infarction risk as measured by the PROCAM program (which takes into account LDL, HDL, and triglyceride concentrations). The one gram GLA had a 33% reduction in risk and the four gram GLA group had a 24% reduction in risk.

Vitamin E Required with EFA Supplementation

PUFA supplementation increases the daily requirement for vitamin E. Concentrations of alpha tocopherol in plasma decrease significantly with fish oil supplementation. Kramer[31] observed a reduction of plasma alpha tocopheryl of 20% in patients supplemented with 7.5 grams EPA+DHA. In healthy elderly patients vitamin E supplementation has been found to increase immune responses such as lymphocyte proliferation.[32] The immuno-enhancing effect of vitamin E in the elderly has been shown to be dampened when it is consumed with fish oil. In subjects consuming 2.5 grams of EPA+DHA, 200 mg of vitamin E as dl-alpha tocopherol was able to increase plasma vitamin E levels by 25%.[33] Natural d-alpha tocopherol has a bioavailability of almost three times that of synthetic dl-alpha tocopheryl acetate.[36] An optimal dose of natural alpha tocopherol would be 67 units per 2.5 grams of EPA+DHA.

Vitamin E as a lipid soluble antioxidant inhibits the proliferation of smooth muscle cells, reduces platelet adhesion and aggregation and prevents monocyte-endothelial interactions. All of these actions are increased in the development of the atherosclerotic process. Clinical trails have demonstrated a linear decrease in oxidative stress markers in patients supplemented with vitamin E.[34] Plants produce eight different molecules with vitamin E activity [alpha, beta, delta and gamma tocopherols and the four corresponding tocotrienols]. Alpha tocopherol is the major form of vitamin E found in human tissues. Gamma tocopherol is the major form found in the US diet. Gamma tocopherol has been demonstrated to be a more powerful in trapping many reactive oxidative species and displays a broader anti-inflammatory profile than alpha tocopherol compared to alpha tocopherol, gamma tocopherol is a more potent inhibitor of COX activity, and is more effective for the inhibition of key mediators of inflammation such as TNF-alpha, nitric oxide an inflammatory eicosanoid production. Clinical evaluation of individuals suffering from coronary heart disease has shown decreased levels of gamma-tocopherol, but not to alpha-tocopherol.[35]

Omega-3, Omega-6 and Vitamin E

To obtain the optimal omega-3 index, supplementation with omega-3 FA is necessary. To obtain the optimal PUFA supplementation the addition of GLA with omega-3 FA is necessary. The 2:1 mixture of omega-3 to GLA has been shown to provide the greatest supplemental benefit to patients. The addition a high gamma tocopherol vitamin E to a 2:1 omega-3:GLA is necessary to insure healthy antioxidant status. Natural mixed tocopherols as found in many whole foods provide 20% alpha tocpherol, 60% gamma tocopherol and 24% delta tocopherol. The optimal dose of natural mixed tocopherols for 1.5 grams of EPA+DHA would contain 215 mg gamma, 86 mg dela and 50 IU of alpha tocopherol. All this factors must considered when choosing a supplement that contains omega-3, GLA and or vitamin E.

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