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REVIEW ARTICLE

The Use of Fish Oil Supplements in Clinical Practice: A Review

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ABSTRACT

Increasing dietary consumption of fish high in omega-3 (n-3) fatty acids is well established as a way to improve numerous health outcomes. The prevention of both primary and secondary cardiovascular events, as well as intervention for such unrelated outcomes as depression and rheumatoid arthritis are now linked with n-3 fatty acid intake. Increasing fish consumption is neither an exact science, nor without risk of consuming toxins of various kinds. The advent of highly purified fish oil supplements, now widely available, has allowed very high levels of n-3 fatty acid consumption for both preventative and therapeutic clinical use. This review will focus on the data concerning fish consumption, fish oil supplements and their fatty acids as it pertains to clinical outcomes, with an emphasis on cardiovascular health.

BACKGROUND

In the early 1970s, it was observed that high levels of fat intake in the form of long-chain omega-3 fatty acids in Greenland Eskimo populations resulted in fewer cardiovascular events than Western populations who ingested less total dietary fat.[1] In fact, these studies and others prompted the scrutiny of fatty acids based upon whether they were omega-3 (n-3), omega-6 (n-6) or omega-9 (n-9). Fatty acids in the n-3 and n-6 families are considered essential to humans because our metabolism is unable to de-saturate (make a double-bond) between carbons-3 and 4 (n-3) or between carbons 6 and 7 (n-6); counting from the omega or last carbon (See Figure 1 for basic fatty acid information). Typical Western diets provide much in the way of polyunsaturated fatty acids from vegetable sources, which supply high levels of n-6 fatty acids. Data from numerous epidemiological studies have suggested that lowering one's ratio of n-6/n-3 in the range of 3:1 to 6:1 (typical American diet may be as high as 20:1) will have great health benefits.[2] The creation of trans-fatty acids through food processing and cooking further complicates the issues both metabolically and epidemiologically.

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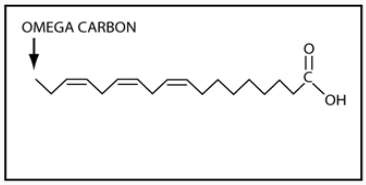
N-3 FATTY ACIDS

Alpha-linolenic acid (ALA) is an n-3 essential fatty acid found primarily in certain seeds and green leafy vegetables. Flaxseeds are one of the richest sources of ALA. Converting this 18 carbon fatty acid to the 20 and 22 carbon fatty acids found primarily in fish oils requires several steps of elongation and de-saturation (see Fig. 1), reported to be a very inefficient process in adults, suggesting that direct consumption is more reliable.[3,4] And while some data suggests that ALA may help prevent secondary cardiovascular events,[5] most of the focus on n-3 fatty acid research is with consumption of eicosapentanoic acid (EPA) and docosahexanoic acid (DHA) from fish and fish oil supplements. In humans, the retroconversion between ingested DHA to plasma EPA seems to be higher than the conversion of EPA to DHA.[107,110]

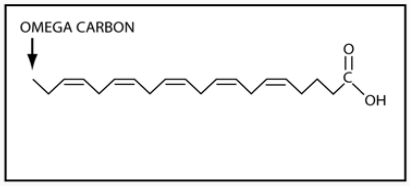
Figure 1:

OMEGA-3 FATTY ACIDS

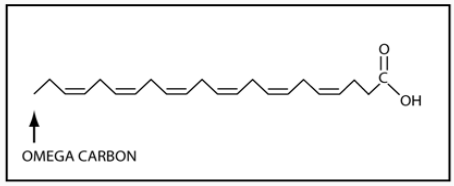
STRUCTURES



Alpha-Linolenic Acid (ALA) 18:3 n-3



Eicosapentanoic Acid (EPA) 20:5 n-3



Docosahexaenoic Acid (DHA) 22:6 n-3

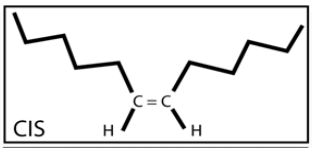
NAMING FATTY ACIDS

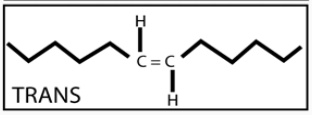
Common Name	Shorthand
Oleic	18 : 1 n-9
Linoleic	18 : 2 n-6

Number of Carbons

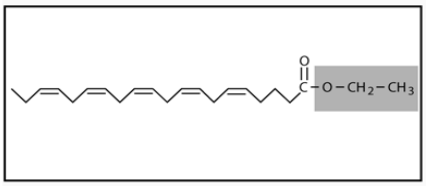
Number of Double Bonds

Location of First Double Bond

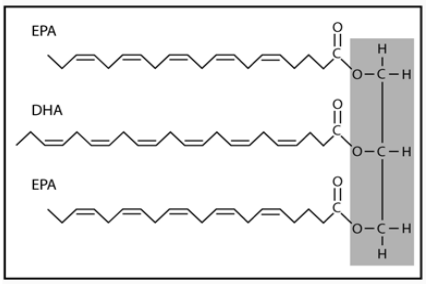




An unsaturated fatty acid double bond is normally in the cis conformation (both hydrogens on the same side). This gives the molecule a bend or kink at each double bond. These bends increase the fluidity or mobility of the fatty acid. When these molecules are heated, exposed to damaging light or oxygen; or partially hydrogenated, trans bonds form. These cause fluid oils to become more rigid (margarine). These new molecules are difficult for the body's enzymes to metabolize. There are significant levels of research looking into the connection between the increased dietary intake of trans-fatty acids and the increased incidence of chronic illnesses.



EPA Ethyl Ester



Triglyceride

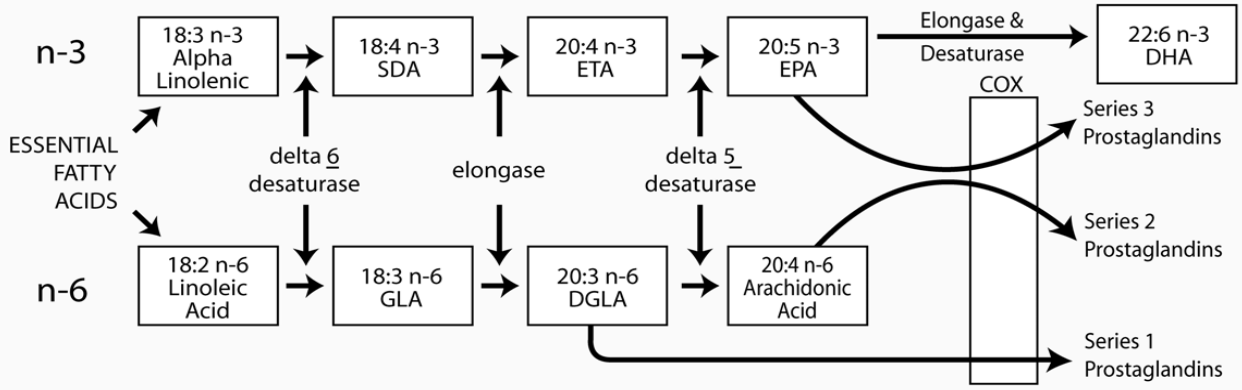
Typical Fatty Acid Profile of Various Oils & Cooked Fish

(Oils: % of total fat | Fish: mg/3 oz serving)

	Saturated			Mono-unsaturated		Polyunsaturated			
	4:0-14:0	16:0	18:0	18:1 n-9 Oleic	Other MUF A	18:2 n-6 LA	18:3 n-3 LNA	20:5 n-3 EPA	22:6 n-3 DHA
Butter	22	26	12	25		2.2	1.4		
Olive Oil	-	11	2.2	72.5		7.9	0.6		
Corn Oil	-	10.9	1.8	24.2		58	0.7		
Canola Oil	-	4	1.8	56.1		20.3	9.3		
Coconut Oil	58.7	8.2	2.8	5.8		1.8	0		
Flax Seed Oil	-	5.5	4.5	18		15	55		
Anchovy, canned	364	1127	357	2501	648	308	14	649	1098
Catfish, farmed	95	1113	271	3177	338	875	70	42	109
Cod	3	72	13	55	34	7	3	88	147
Fish sticks, frozen	59	1588	1006	4241	60	2327	146	73	109
Haddock	9	96	36	73	55	10	3	65	138
Halibut	61	231	54	394	424	32	71	77	318
Mackerel	503	1169	218	1022	3935	125	96	428	594
Orange Roughy	6	11	6	305	207	8	2	2	-
Salmon, wild	150	689	231	1427	821	187	321	349	1215
Salmon, canned	41	1148	115	908	642	49	49	718	685
Sardine, canned	163	844	292	1823	1466	3012	423	402	433
Trout, wild	173	780	225	780	617	245	159	398	442
Tuna, canned	70	503	100	440	225	47	60	198	535

* Data from USDA Nutrient Data Laboratory website (http:// www.nal.usda.gov/fnic/foodcomp) Accessed January 8th, 2005

n-3 and n-6 FATTY ACIDS COMPETE FOR ENZYMES DURING METABOLISM



SDA - Stearidonic Acid, ETA - Eicosatetraenoic acid, DGLA - Dihomogammalinolenic Acid, COX - Cyclooxygenase

CARDIOVASCULAR USES

Primary Cardiovascular Event Prevention

Numerous reviews have summarized the cardiovascular benefits of fish and fish oil consumption.[6,7,8,9,10] The data concerning primary prevention, however, is less straightforward than the data relating to secondary prevention. In several large cohort studies, the relative risk for CHD and sudden death is reduced with increased fish consumption in men and women,[11,12,13,22,27] while others showed no statistical differences based on fish consumption.[14,15] Plasma EPA and DHA levels measured upon initiation of the Physicians' Health Study did not relate inversely with incidence of myocardial infarction,[16] however in this same group both fish consumption, based on dietary questionnaire, and blood n-3 levels were statistically related to reduced risk of sudden cardiac death.[17,18] In this cohort of 20,551 men, the multivariate relative risk for sudden cardiac death in those consuming 1 fish meal per week was 0.48, compared with men who consumed fish less than once per month.[17] The adjusted relative risk in the 4th quartile of red cell n-3 levels was 0.19.[18]

The Honolulu Heart Program, following Japanese-Americans living in Hawaii, found that the relative risk for CHD mortality was cut in half for heavy smokers (>30 cig/day) if they consumed greater than 2 fish meals per week.[19] Siscovick[20] reported that in a population-based case-control study in King County, WA that both dietary intake of seafood containing n-3 fatty acids and red blood cell membrane n-3 fatty acid concentrations were inversely related to primary cardiac arrest. Both of these associations were dose-related. Among the Nurses' Health Study cohort, fatty fish intake was associated with a reduced risk of thrombotic stroke, while there was no increased risk for hemorrhagic strokes in women.[183] A similar large cohort in the Physicians' Health Follow-up study found the same lowered risk of stroke with fish consumption in men.[184] The American Heart Association recommends that patients without documented coronary heart disease (CHD) eat a variety of (preferably fatty) fish at least twice a week, including oils and foods rich in alpha-linolenic acid (flaxseed, canola and soybean oils; flaxseed and walnuts).[9,21]

Secondary Cardiovascular Event Prevention

One of the first studies to assess the secondary prevention potential of n-3 fatty acids from fish was the diet and reinfarction trial (DART).[23] The men randomized to receive advice to increase fatty fish consumption (others were advised to increase fiber or reduce fat intake) after recovery from MI, had a 29% reduction in 2-year all cause mortality. Unfortunately, like many lifestyle changes, this advice was difficult to maintain over many decades and both compliance and benefits seem to have been diminished after a decade.[24]

The largest secondary prevention trial to date is the GISSI-prevention trial.[25] In this study, over 11,000 patients (surviving a recent MI) were randomized to receive 1 g/day n-3 fatty acids (capsules containing a minimum of 850 mg EPA and DHA as ethyl esters), 300 mg of vitamin E (acetyl *d,l*-alpha tocopherol), both or placebo. Most of these patients were concomitantly on cardiovascular pharmaceuticals of various kinds, as well as advised about diet and lifestyle changes. Total (RR=0.59) and cardiovascular mortality (RR=0.66) were significantly reduced in the fish oil group as early as 3 and 4 months into the study, respectively. The most dramatic reduction was in sudden deaths, for which relative risks of 0.37 (after 9 months) and 0.55 (42 months) were reported.[26] Among the lipids measured, only triglyceride levels showed significant improvements. In all, there are over 20 randomized, placebo-controlled trials of dietary n-3 fatty acid from fish in CHD patients. A meta-analysis[28] of these trials shows a 3-year average reduction of all cause mortality of 16% and death from MI of 24%. The American Heart Association recommends that patients with documented CHD consume about 1 g of EPA+DHA per day, preferably from fatty fish; EPA+DHA supplements could be considered in consultation with a physician.[9,21]

Anti-arrhythmic Effects of Fish Oils

Both primary and secondary prevention studies showed that n-3 fatty acid intake was profoundly better at preventing sudden deaths than reducing the incidence of non-fatal MI. Over 50% of the deaths attributed to CHD are sudden deaths (within 1 hour) caused by sustained ventricular arrhythmias. These data suggested that n-3 fatty acids may have anti-arrhythmic effects which initially do not lower the incidence of MI, but prevent many of these events from becoming fatal.[10] This anti-arrhythmic effect has been reported in several animal and cell culture models.[29-33] It is fairly well established that the incorporation of EPA and especially DHA within the plasma membrane of electrically excitable cardiac tissue changes membrane fluidity and modulates the actions of ion channels to prevent the destabilization that permits arrhythmias and ventricular tachycardia.[34-37]

One small pilot study was conducted with 10 patients who had implanted cardioverter defibrillators and repeated episodes of documented, sustained ventricular tachycardia.[38] Compared with baseline, after these patients were infused with n-3 fatty acids, sustained ventricular tachycardia was non-inducible in 5 of the 7 (3 of the 10 patients who ate significantly more dietary fish were non-inducible at baseline). More research, including controlled trials, needs to be done using oral doses of fish oil preparations and clinical outcomes. Leaf et al.[10] recommend that those with a family or personal history of CHD should supplement their diets with 600 mg of EPA plus DHA, and higher, 1 to 2 grams, if there is also a family history of sudden cardiac death.

Reducing Triglycerides

Elevated triglycerides (TG), both fasting and postprandial, are directly related to the progression of atherosclerosis and are considered independent risk factors for CHD,

especially in women.[39,40] Long-chain n-3 fatty acids from fish like EPA and DHA have shown consistent TG lowering effects in both animals and humans.[42] A meta-analysis of 65 published reports showed TG reduction averaging 25% was typical with fish oil consumption (mean dose 4 g/day EPA + DHA) in both normolipidemic and hypertriacylglycerolemic subjects.[41] These data also show a dose-response relationship between fish oil intake and triglyceride lowering as well as a slight rise in LDL cholesterol (5-10%) and a smaller elevation in HDL cholesterol (1-3%).

Post-prandial (after a fatty meal) plasma TG levels may even be more correlated to atherosclerotic progression than fasting TG levels.[43] Chronic intake of n-3 fatty acids from fish has been shown to reduce post-prandial plasma TG levels.[44] A recent study showed that exercise when combined with fish oils was additive in post-prandial TG lowering.[45] Ten healthy recreationally-active subjects in a cross-over design were tested for changes in fasting and post-prandial (after 1,000 calorie shake- 99% fat after 12-hour fast) TG levels after 5 weeks of fish oil supplementation (4 g/day in 8 capsules of 300 mg EPA and 200 mg DHA each) or exercise (60% VO_2max on treadmill for 1 hour), both or neither (control). When exercise was added to fish oil supplementation, the peak plasma TG levels went from 38% reduction (fish oil vs. control) to 50% reduction (fish oil + exercise vs. control). Total area under the TG curve was reduced from 27% to 42% respectively. While both EPA and DHA seem to have triglyceride lowering benefits, DHA may have a more favorable effect. The American Heart Association recommends that under a physician's care, patients who need to lower triglycerides should consume 2 to 4 grams of EPA+DHA per day provided as capsules.[9,21]

Other Cardiovascular Risk Factors

In general, fish oil supplements have a favorable, but small effect on HDL cholesterol levels (1-5%). Combined with the more widely observed TG lowering, this (this what?) improves the important TG:HDL ratio. A small study (n=14) was conducted in patients with familial combined hyperlipidemia, noted for their increased cardiovascular risk due to elevated atherogenic lipoproteins and decreased protective lipoproteins.[57] In a cross-over design, patients were given either 4 g/day of a concentrated fish oil preparation in capsules (Omacor- 44%EPA, 36% DHA as ethyl esters) or placebo (corn oil) for eight weeks. As expected, TG levels were lowered significantly (378 to 210), while HDL cholesterol rose a non-statistical 8%. The relative increase in HDL_2, a more cardioprotective lipid subfraction, was statistically significant. LDL, but not total cholesterol, was significantly increased in the fish oil group. In one group of hyperlipidemic patients, DHA (4 g/day) had a more significant (29%) increase in HDL_2 levels than equivalent levels of EPA.[106] Other clinical trials have also reported that DHA has a slightly more favorable effect on lipid profiles (TG lowering, TG:HDL ratio and lipoprotein fractioning),[107] and post-prandial lipid margination.[108]

It is not uncommon to see elevations in plasma LDL cholesterol after fish oil intake, especially in individuals with elevated triglyceride levels. Since total cholesterol usually remains unchanged in these subjects and it is known that most of the increase is due to an increased shift from VLDL to LDL, the clinical significance of this elevation in plasma LDL cholesterol is not yet known, but LDL subfraction analysis suggests that it is the larger, less-dense (and less atherogenic) LDL fraction which is raised and not the smaller (more atherogenic) LDL particles.[46,186,187] One report suggested a potential down-regulation of LDL receptors to account for part of this phenomenon.[47]

In a group of patients (n=64) with chronic renal failure, assigned to either 2.4 g/day fish oil (4 capsules- 3:2 EPA:DHA) or olive oil for 8 weeks; those receiving fish oil had statistically lower TG (21%), higher HDL cholesterol (8%) and no change in total or LDL cholesterol. A small, non-statistical, drop in Lp(a) was seen in these patients but Lp(a) is very rarely measured in other studies and similar drops were not reported in those studies where it was measured. Also, little effect is reported in lowering high sensitivity C-reactive protein (hsCRP), a marker of inflammation and an independent risk factor for cardiovascular disease.[48,49]

Metabolic Syndrome and Diabetes

Metabolic syndrome is a disorder characterized by insulin resistance, high triglycerides, high LDL and low HDL cholesterol, hypertension and central adiposity. An increasingly prevalent condition considered "pre-diabetic," individuals with metabolic syndrome are also at an increased risk of cardiovascular disease even before a diabetes diagnosis.[51,52] In both sucrose and fructose-induced animal models of metabolic syndrome, EPA and DHA from fish oils were able to prevent the onset or diminish several parameters (hypertension, adiposity, dyslipidemias) associated with the syndrome.[53,54] One animal study concluded that insulin-sensitive GLUT4 activity is enhanced in adipocytes (not myocytes) to account for the fish oil's improvement of insulin sensitivity in these animals.[55] While many of the subjects in the TG lowering trials mentioned previously would likely be categorized as having metabolic syndrome, a trial looking at either the prevention or treatment of individuals by this diagnosis as an end-point has apparently not been performed. In one study of overweight treated hypertensive patients (n=69), likely to be deemed as having metabolic syndrome if lipids were reported, combining fatty fish consumption (dietary) with weight-loss had an additive effect on ambulatory blood pressure and decreased heart rate.[56]

Like those with metabolic syndrome, type 2 diabetic patients are characterized with various lipid disorders, insulin resistance and increased risk for CHD. A cohort

within the Nurses' Health study (n=5103) who were free of CHD but with diagnosed type 2 diabetes were evaluated for CHD risk, relative to n-3 intake from fish.[58] After adjusting for age and other cardiovascular risk factors, the RRs for CHD were 0.70 (1 to 3 fish meals per month), 0.65 (2 to 4 times per week) and 0.38 (>5 times per week). Fish consumption in this cohort was more protective against CHD by quintile than it was when looking at all the women in the Nurses' Health Study,[27] implying that n-3 fatty acid supplementation in diabetic patients may prove even more beneficial than in the general population. Consumption of fish is associated with a significantly reduced progression of coronary artery atherosclerosis in women (a higher correlation in diabetic women) with coronary artery disease. Generally, fish and fish oil supplements reduce triglyceride levels and improve HDL levels but seem to have no clinically significant affect on fasting glucose, fasting insulin, HbA_{1c}, or glucose tolerance tests in diabetic subjects.[59-61]

In one study, fish *protein* consumption was associated with a significantly lower risk of microalbuminuria in a nested case-control study of 1150 type 1 diabetic patients,[62] although this lowered risk was also reported in a small group (n=16) of type 1 and 2 diabetic patients consuming only concentrated EPA (1.8 g/day).[63] Several animal models have suggested a role for fish oil in general, and DHA specifically, for increasing nerve conduction velocity in diabetic neuropathy. Collectively, these data suggest that diabetic patients should consume 1 to 2 grams per day of n-3 fatty acid from fish, balanced between EPA and DHA.

Hypertension

There is a dose-dependent inverse relationship between n-3 fatty acid intake and blood pressure in hypertensive patients, but little effect is noted in normotensive or borderline hypertensives. A meta-analysis of 31 placebo-controlled trials found an average -0.66/-0.35 mm Hg drop in systolic/diastolic blood pressure per gram of n-3 fatty acid consumed in hypertensive patients.[67] Many of these trials used doses in excess of 5 grams per day and were associated with gastrointestinal complaints. Another meta-analysis reported an average reduction of 5.5/3.5 mm Hg in hypertensive patients given at least 3 g/day of n-3 fatty acids. Fish oil consumption (~3.6 g/day from diet) had an additive effect when combined with weight loss in overweight hypertensives (-6.0/-3.0 fish alone, -5.5/-2.2 weight loss alone, -13.0/-9.3 mm Hg combined).[56] The authors conclude that given the magnitude of the BP reduction with the fish/weight loss combination, withdrawal of antihypertensive therapy may have been possible.

DHA and EPA have been tested separately for their hypertensive activities. Mori et al. has reported that 4 g/day of DHA, but not EPA, reduces ambulatory blood pressure and has favorable effects on arterial compliance.[104,105]

Additional Cardiovascular Mechanisms[77]

Discussing the various potential biological mechanisms in detail is beyond the scope of this review. For the sake of those interested in pursuing this avenue, however, a list of reported potential mechanisms attributed to n-3 fatty acids and several references are included below.

- Anti-inflammatory[68-73]
- Arterial compliance[74,75,76]
- NO- induced endothelial relaxation[78,79]
- Reduced asymmetric dimethyl arginine (ADMA)[80,81]
- Reducing atherogenic adhesion molecules[82,83,84]
- Anti-thrombogenic[85,86,87]
- Stabilizing atherosclerotic plaques[88]
- Peroxisome proliferator-activated receptors (PPAR) regulation[89,90]

NON-CARDIOVASCULAR USES

Anti-inflammatory- Rheumatic Diseases[115,116]

The well-known pathways which covert the 20 carbon n-6 fatty acid arachidonic acid into pro-inflammatory cytokines is often termed the arachidonic acid cascade. Key enzymes in the formation of pro-inflammatory prostaglandins and leukotrienes are the cyclooxygenase (COX) and lipoxygenase (LOX) enzymes. Inhibition of these enzymes is one of the most popular anti-inflammatory mechanisms in the pharmaceutical trade. Since the substrate for each of these enzymes is a 20 carbon fatty acid, eicosapentanoic acid (EPA) is capable of both competing for the use of the enzyme as well as forming eicosanoids which function to counteract the activity of eicosanoids derived from arachidonic acid.[127] These mechanisms have led to the proposal that increasing n-3 (especially EPA from fish) and lowering n-6 fatty acid intake would have a favorable benefit on the overall inflammatory burden, particularly in individuals with chronic conditions such as rheumatoid arthritis.[117,118]

Omega-3 fatty acids from fish oil have been studied extensively in patients with rheumatoid arthritis.[119] Meta-analysis data suggest a modest improvement in tender joints and morning stiffness with the addition of fish oil supplementation.[120] Dosing and fish oil content vary widely in different clinical trials. The most significant benefits seem to require at least 3 grams/day, although benefits were seen in some trials with 2.6 grams/day,[121] 30 mg/kg/day[122] and 40 mg/kg/day.[123] Significantly more benefit is seen when patients who use fish oil supplements are also consuming a low arachidonic acid, anti-inflammatory diet.[122]

The role of fish oils has also been explored in patients with inflammatory bowel diseases such as ulcerative colitis and Crohn's disease. Reviews of the various clinical trials have shown that doses as high as 4.5 and 5.4 grams per day have limited benefit on preventing relapses, but often

reduce the dependence on steroid therapy and dramatically reduce inflammatory markers.[124] A specially prepared enteric-coated, free fatty acid preparation (1.8 g/day EPA, 0.9 g/day DHA) was able to significantly reduce the level of relapse compared to placebo in a group of Crohn's disease patients (n=78).[125] Another group recently reported that stimulated T-cells and monocytes taken from Crohn's disease patients supplemented with fish oil (1.6 g/day EPA, 1.08 g/day DHA- non-enteric coated) and an antioxidant blend (Vit. A, C, E, selenium, manganese) produced lower interferon-gamma and PGE_2, compared to placebo.[126] In general, these data suggest that individuals with inflammatory bowel conditions may be benefited by increasing fish oil intake equivalent to 2.5-5 grams per day.

Depression and Other Mood Disorders

Long chain n-3 fatty acids are important components of membranes within neurological organs and tissues. They affect membrane fluidity and excitability, influence synaptic function, and perhaps serotonin and dopamine metabolism.[128,145] In several epidemiological studies, fish consumption is related to decreased risk of depression, especially in women.[129,130,131] Although not all cohort studies proved statistically significant,[132,133] a recent case-controlled study (China) reported that low red blood cell EPA levels are associated with increased risk for attempting suicide.[139] Previous reports suggest there is a link between violent suicides and seasonal intake of EPA.[140]

Several clinical trials have used n-3 fatty acids to treat depression and related disorders.[141] Most of the studies to date have used a preparation of pure EPA (EE form). Peet et al.[142] reported that 1 gram (but not 2 grams) of EPA improved depression scores in patients (n=17 each group) with ongoing medicated depression. However, Nemets et al.[143] reported that similar patients (n=20) receiving 2 grams per day of a comparable preparation had highly significant reduction in Hamilton depression scale scores (mean 12.4 point reduction vs. 1.6 for placebo). This same group attempted to use this preparation at the same dose to treat medicated patients with obsessive compulsive disorder (OCD) without success.[144] Pure DHA (2 g/day) had only a small, non-statistical benefit in patients with major depression. Bipolar patients given high doses of fish oil (6.2 g EPA/3.2 g DHA) had a significantly longer period before relapse than similar patients taking olive oil.[147] Physicians treating patients with depression or related disorders should consider measuring patient serum fatty acid levels and including fish oil supplements (particularly EPA) at 1-2 grams per day.

Maternal and Infant Care

Maternal fatty acid levels, especially DHA levels steadily drop in late pregnancy,[135] increasing risk for post-partum depression.[136,137] A meta-analysis of 41 studies showed that lower fish consumption and breast milk DHA content were associated with increased risk for post-partum depression.[134] Low doses of DHA (200 mg/day -algae-derived) given post-delivery, however, were unable to significantly lower symptoms of post-partum depression.[138]

The role of n-3 fatty acids in maternal gestation and parturition, as well as offspring development has been reviewed elsewhere.[148] Generally, women with higher n-6 to n-3 intake have a higher likelihood to deliver prematurely. This phenomenon is thought to be related to changes in eicosanoid production (prostaglandins, leukotrienes) which take place prior to parturition. Epidemiological studies suggest that gestation is generally longer in women with higher intake of n-3 fatty acids from fish in some cohorts,[149,150] but not in others.[151,152,153] High n-6 to n-3 fatty ratios also correlate to an increased risk for preeclampsia.[154,155] Intervention trials, during high risk pregnancies have shown some improvement in prolonging gestation (2.7 g/day n-3),[156,157] but not in pregnancy related hypertension.[157-160]

Rapid growth in the brain occurs during the last trimester of pregnancy and the first several postnatal months. The need for maternal DHA is critical during these months since fetal and newborn fatty acid metabolism is inadequate to provide proper levels of DHA for brain development. Several reports suggest that maternal supplementation of fish oils or DHA alone during the third trimester and while breast-feeding can improve cognitive development in newborns,[161] improve sleep patterns (a measure of brain development),[162] and even increase IQ scores at age 4.[163] Maternal fish oil supplementation (3.7 g/day n-3, 56% DHA) in atopic women (offspring considered at high risk for allergic diseases) significantly increased breast milk levels of the protective Immunoglobulin A (IgA) and CD14.[164] Children born from these mothers have reduced levels of allergic related cytokines and allergen-specific immune responses.[165,166,167,168] Children at high risk for atopic diseases had reduced allergy-related cough at age 3 if they were supplemented with fish oil (500 mg of tuna oil/d- 185 mg n-3) from 6 months to 3 years.[169] Eating high levels of n-3 fatty acids directly from fish is contraindicated in young children and pregnant women due to the potential for ingesting mercury and other toxins. Fish oil supplements, virtually free of these toxins,[170,171] are safer and allow for specific dosing regimens. Many liquid as well as capsule preparations can be used which provide varying levels of DHA, some of which are specially prepared and flavored for children.

Ocular and Cognitive Health

As a specialized portion of the nervous system, the retina has one of the highest levels of long-chain fatty acids in the human body; especially concentrated is the level of DHA.[172,173] Infant visual acuity is diminished in n-3 deficiency. Children supplemented with DHA (115 mg/day) from 6 months to 1 year of age had significantly better improved visual acuity than similar control children.[174] The long-term visual benefits for infant supplementation is not

yet known. In adults, fish and DHA intake (determined by food questionnaire) reduces the risk for age-related macular degeneration.[175,176] Preventative or intervention trials in patients with or at risk for macular degeneration have not been published.

The relationship between DHA and retinitis pigmentosa (RP) is currently being investigated. RP patients have lower levels of DHA,[177] partly due to reduced activity of the enzyme delta-5-desaturase.[178] Despite this relationship, trials attempting to slow the progression of RP with supplementation of DHA have been unsuccessful,[179,180] although chronic vitamin A users who added 1200 mg/d of DHA had some slowing in progression after 2 years.[181]

Increased dietary intake of fish and DHA (but not EPA) is correlated (cohort of 815) with a decreased risk of Alzheimer's disease.[182] Whether this correlation will prove to be of preventative or therapeutic benefit is yet to be determined. Studies also suggest that DHA is protective against dendritic cell damage in a mouse model of Alzheimer's disease.[185]

Fish Oil- The Product

Recommendations to increase fish consumption are not always straightforward. Some fish have high levels of EPA and DHA; others do not (see chart figure 1). How the fish is prepared also has a significant affect on whether these long-chain fatty acids will be beneficial. In a population-based cohort study, dietary fish consumption was correlated with increased plasma n-3 levels and reduced risk of cardiovascular death in individuals consuming tuna or other similar fish (broiled or baked), but neither was associated with fried fish or fish sandwiches (fish burgers).[91] The same group reported similar differences for reducing the risk of atrial fibrillations in these different populations based on type of fish consumed.[92] The susceptibility to loss or modification of EPA and DHA has been reported in various cooking processes, especially deep-frying.[93] The additional potential hazard of consuming environmental toxins such as methyl mercury and other heavy metals or pesticides like DDT, DDE or PCBs is a concern for many. The Environmental Protection Agency warns those most at risk (pregnant women, nursing mothers and their infants and young children) to limit fish intake to avoid potentially dangerous mercury levels.[94] Several advantages of fish oil supplements directly address these concerns. Levels of EPA and DHA are consistently dosed in capsule or liquid products. Levels of heavy metals and pesticides can be dramatically reduced, often below detectible limits, when using fish oil supplements in lieu of consuming more fish.[170,171] Fish oil is inherently more susceptible to oxidation, requiring that most products contain additional fat-soluble antioxidants such as natural vitamin E, fat soluble ascorbates or other natural antioxidants to protect them from becoming rancid under normal storage conditions.

Commercial fish oil is a by-product of the fish meal industry. It is typically a blend of many different fish species including mackerel, anchovies, sardines, tuna, salmon and others. The raw oil from these fish is then purified and concentrated by removing (hydrolyzing) the individual fatty acids from the fish triglycerides so the various fatty acids can be separated and concentrated. This process allows for the separation of contaminant toxins, proteins (which may increase allergenicity and burping), and other non n-3 fatty acids. These concentrated fatty acids remain as free fatty acids (FFA) before they are stabilized by esterification to ethanol (ethyl esters, EE) or further esterified back to a glycerol backbone to create a re-esterified triglyceride (rTG). Both EE and rTG forms of varying concentration (30-70% EPA+DHA) are used in the dietary supplement industry throughout the United States.

Few studies have looked at differences between fish oil supplements provided as EE or rTG. One study reported that plasma EPA and DHA levels were higher when equivalent levels of these fatty acids were consumed directly from salmon than from fish oil supplements provided as ethyl esters.[95] Whether the ethyl ester form diminished or some fish component enhanced bioavailability is not known. Several studies have shown that plasma bioavailability of the EE form is less than 50% of that from the rTG form.[96,97,98] Other studies, however, show no difference in bioavailability between these two forms.[99,100] All of these studies were uncontrolled and involved very few subjects. Dyerberg et al.[114] completed a study involving 72 subjects, comparing the bioavailability of EPA and DHA from natural fish triglycerides, EE, rTG, cod liver oil and FFA. They found that compared to natural fish TG (100% standard), the bioavailability of EPA and DHA combined was highest from the re-esterified TG (124%) and lowest from EE (73%). The EPA and DHA incorporated into phospholipids was 62% and 290% greater when consumed as rTG rather than EE. At this time there are no trials comparing the potential differences in the EE and rTG forms as it pertains to clinical outcomes (triacylglyeride lowering, hypertension, etc.); many reports don't specify the forms used. Since data suggests that individuals are likely to absorb the rTG form better, and lipase and biological incorporation of the EE is diminished,[99,101] clinical trials should be done to assess whether the rTG form may have better clinical outcomes, or require lower doses for equivalent results. Consistent results at a lower dose would help increase compliance and reduce both side-effects and cost.

As with any dietary supplement, choosing a high-quality fish oil product is important. The Council for Responsible Nutrition (CRN), along with many of the leading fish oil manufacturers in the world, published a monograph in 2002 outlining various quality aspects which the industry should use to regulate fish oil products.[102] This monograph stipulates upper limits for mercury and other

heavy metals, pesticide levels and oxidation levels such as peroxide and anisidine values. These guidelines have been adopted by the United States Pharmacopoeia (USP) for their current n-3 fatty acid from fish oil monograph.[103] Additionally, some companies monitor the production from catch to finished product in order to provide kosher products to the market.

Side-effects and Contraindications

High-dose fish oil supplementation is extremely well tolerated in nearly all individuals. The most common side-effect is a fishy aftertaste or "burping" associated with high doses. When products are consumed with meals and carbonated beverages are avoided, this unpleasant feature is dramatically reduced. The complete purification of the fatty acids from fish proteins virtually eliminates the potential for allergic components in the fish oil supplements. Because fish oil is prone to oxidation, consuming high doses without additional antioxidant protection (from diet or supplemental sources) may increase vulnerability to lipid peroxidation, especially in warm and sunny climates. While the in vivo consequences of this vulnerability are still being debated, antioxidant supplementation should be recommended for every individual consuming high amounts (3 grams or more) of fish oil daily. These high doses can be consumed directly from bottles for those wanting to avoid gelatin capsules due to concerns about consuming non-fish animals in general or bovine-derived products specifically.

The most frequent contraindication concern is the combination of high dose fish oil with pharmaceutical drugs that affect blood clotting (coumadin, aspirin, etc.), used by many cardiovascular patients. A group of 250 patients who had undergone coronary artery bypass surgery were given 4 g/day of fish oil concentrate and either aspirin (300 mg/d) or warfarin therapy.[111] Compared to patients not receiving fish oil, these patients had no increase in bleeding time. Another report showed no change in INR when 6 g/day of fish oil was given to patients on chronic warfarin therapy.[112] However, one case report has been published of a woman (67 years old on coumadin, 1.5 years at 1.5 mg/day) who had an increased INR (2.8 to 4.3) in the month she doubled her fish oil supplement from 1 to 2 g/day.[113] These data suggest that the concern for bleeding times is generally not an issue, but INR should be checked in patients on both warfarin and fish oil therapies.

CONCLUSION

Epidemiological evidence is quite clear in demonstrating numerous health benefits in consuming long-chain polyunsaturated n-3 fatty acid from fish, especially as a ratio to n-6 fatty acids derived from vegetable oils. Even an "Omega-3 Index" of RBC EPA and DHA levels is being proposed as a routine laboratory test for measuring cardiovascular risk.[109] In the past decade, the clinical use of fish oil supplements has greatly increased, as has the data supporting their use. While dietary and lifestyle changes are ideal ways to modify a number of cardiovascular risk factors, many individuals with personal or family history of cardiovascular disease cannot safely consume high levels of n-3 fatty acids from fish alone, or do not maintain the dietary habit.[24] Since fish oil supplements have been shown to have beneficial effects on nearly every risk factor for cardiovascular disease, and so many individuals are currently at risk, the recommendation to use these supplements in clinical practice is encouraged. There are few patients who would not realize some benefit by increasing their fatty fish consumption or adding fish oil supplements to their daily routine. Patients with previous CHD, hypertriglyceridemia, hypertension, type II diabetes or metabolic syndrome should be taking at least 2 g/day of n-3 fatty acids from fish oil daily via supplements. Pregnant women should be encouraged to consume fish oil supplements to increase n-3 fatty acids, particularly DHA throughout the second half of pregnancy and while breast-feeding.

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