THE ROLE OF OMEGA-3 FATTY ACIDS IN CARDIAC PROTECTION: AN OVERVIEW

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1. ABSTRACT

There have been increasing research efforts in recent years to evaluate the role of various dietary supplements, such as antioxidant vitamins, L-arginine, glucan, isoflavones, soy estrogens, omega-3 fatty acids, etc., in cardiovascular health. Although there is not adequate evidence of the beneficial effects of many nutriceuticals on cardiac function, in the case of omega-3 fatty acids, the evidence has been more convincing.

Fish oil has historically been thought to be good for cardiovascular health; however, data have revealed a stronger cardioprotective role of fish oil in recent years.

Fish oil and specifically omega-3 fatty acids exhibit cardioprotective effects by mainly improving mortality in coronary artery disease patients. This is achieved through multiple mechanisms with the antiarrhythmic mechanism being the most prominent one. Effects on sodium and calcium channels and heart rate variability are well-accepted mechanisms of how omega-3 fatty acids exercise antiarrhythmic effects. In this review we will address some of the basic science and clinical data regarding omega-3 fatty acids and their direct cardiovascular protective role with details on the proposed mechanisms of this role. We will also address fish pollutants and their significance and finally, the current recommendations about using these fatty acids for cardiovascular protection.

2. INTRODUCTION

Atherosclerosis remains the single most common cause of death in the United States, other developed countries, and worldwide. It is also an increasing health problem in developing countries (1-5). There has been recent intense interest in identifying and modifying new risk factors and markers for atherogenesis, such as high sensitivity C-reactive protein (hs-CRP), homocysteine, fibrinogen, lipoprotein (a), apolipoprotein B, etc., in efforts to lessen the great impact of atherosclerosis on morbidity and mortality. Many dietary supplements have been studied to evaluate their effects on these risk markers, other known risk factors, and on endothelial function. The endothelium has been a major focus in recent years as being the primary site where atherogenesis and most vascular pathology occur.

The association between elevated serum cholesterol and the risk of coronary artery disease (CAD) is well documented in many studies (1, 5). Since the original work in the 1950's, it has been well documented that saturated fatty acids raise the level of low-density lipoprotein (LDL) and increase the risk of CAD, whereas unsaturated fatty acids have beneficial effects on coronary risk (6).

The role of diet in modifying atherogenesis by affecting lipoproteins and serum lipid levels has also been well established (3, 5). New findings about the role of certain dietary supplements in cardiovascular health have consistently emerged in the literature.

In this article we address one of the essential groups of unsaturated fatty acids, omega-3 fatty acids, and its role in cardiovascular protection.

3. OMEGA-3 FATTY ACIDS: BIOCHEMISTRY AND FUNCTION

Omega-3 fatty acids and omega-6 fatty acids represent two important groups of unsaturated fatty acids.

Omega-3 fatty acids and cardiac protection

Table 1. Physiological effects of arachidonic acid and eicosapentaenoic acid

Substance and physiological effects	Aarachidonic acid	Eicosapentaenoic acid
Thromboxane	Thromboxane A2	Thromboxane A3
• Vasoconstriction	++	-
• Platelet aggregation	++	-
Prostaglandin	Prostaglandin I2	Prostaglandin I3
• Vasodilatation	++	++
• Antithrombotic	++	++
Leukotriene	Leukotriene B4	Leukotriene B5
• Neutrophil chemotaxis	++	-

From references 7-11.   ++ = Strong effect.   – = No effect.

Table 2. Fish contents of omega-3 fatty acids among different species

Fish species	Average amount of omega 3 fatty acids "in grams" per one pound of fish	Average amount of fish "in pounds" per serving
Bass	1.5	1/3
Flounder	2.1	1/3
Haddock	0.9	1/3
Halibut	3.0	1/3
Herring	12.6	1/3 or one pan sized fish
Mackerel	11.1	1/3
Rainbow Trout	5.7	1/3 or one pan sized fish
Red Snapper	1.2	1/3
Salmon	8.4	1/3
Sardine	9.0	1/3
Shark	13.8	1/3
Swordfish	4.5	1/3
Tuna	6.0	1/3
Whitefish	3.8	1/2

From references 7, 13.

Omega-3 fatty acids are essential fatty acids that have three carbons between the last double bond and the omega terminal (methyl group). On the other hand, omega-6 fatty acids have six carbons between the double bond and the omega terminal. Both Omega-3 and Omega-6 fatty acids are polyunsaturated fatty acids (7) (Figure 1).

Omega-3 fatty acids include three important fatty acids: alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Omega-6 fatty acids include linoleic acid and arachidonic acid (AA) (7).

Both AA and EPA are eicosanoids precursors of cyclooxygenase and lipoxygenase pathways; hence, they produce substances, such as prostaglandins, leukotrienes, and thromboxanes, that lead to different physiological actions (7-11) (Table 1).

Omega-3 fatty acids are found in a variety of food sources. ALA is found in some leaves and plant or vegetable oils, especially flaxseed, canola, and soybean oils. Mammals consume linoleic acid and ALA from vegetable foods. Linoleic acid is the main source of AA. ALA consumed by mammals and fish could provide a small source of EPA and DHA, although most EPA and DHA come from direct consumption by mammals and fish, not from conversion of ALA. EPA and DHA are found in seafood and fish oil. Although fish are able to elongate and desaturate fatty acid chain molecules, the fact that fish contents of omega-3 fatty acids vary widely depending on the food available to fish indicates that fish, in the most part, do not produce DHA and EPA, but they consume these fatty acids from some marine single-celled organisms, algae, and fungi (8-11). Figure 1 summarizes omega fatty acids metabolism in plants, fish, and mammals (7-12). The oilier the fish, the more omega-3 fatty acids they contain. Salmon, Tuna, and Sardines are among the common oily fish (13). Table 2 shows fish contents of EPA/DHA among different species (7, 13). We must keep in mind that there is wide variation in these figures depending on types of fish in each species, types of fish food in wild vs. farm fish, salinity, season, and temperature. Also, how fish are harvested, processed, and prepared could change their contents of EPA/DHA (13).

Among other polyunsaturated fatty acids, omega fatty acids are generally beneficial to health. When talking about direct cardioprotective effects, however, only EPA and DHA (the long chain omega-3 fatty acids), as opposed to the ALA (the short chain omega-3 fatty acid), exhibit significant and direct cardiovascular protection (14-16). Although ALA is a precursor of EPA, and consequently DHA, it does not serve this purpose in humans. In fact, ingesting ALA does not raise EPA or DHA levels, but only serves as a calorie source (14-17).
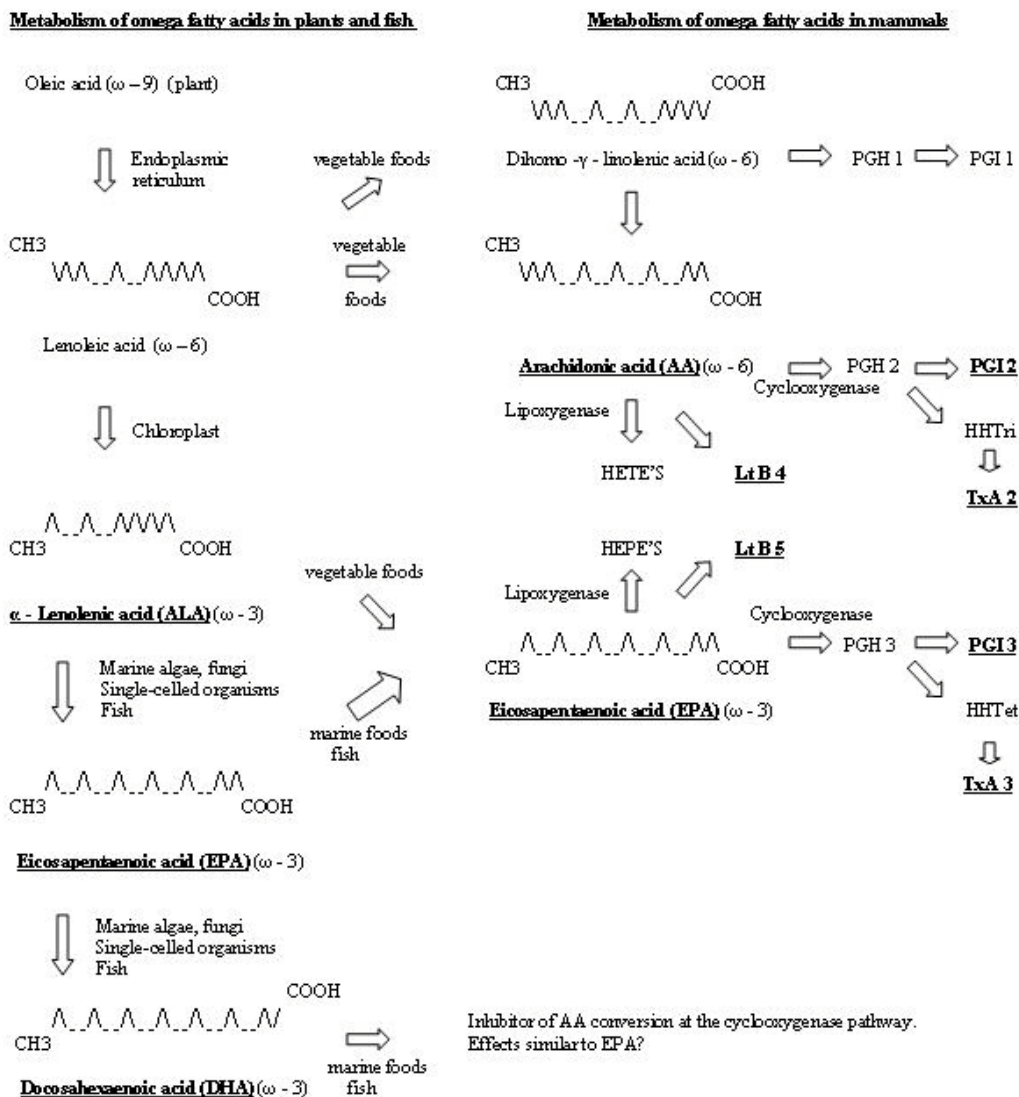
Figure 1. Depiction explaining metabolism of some omega fatty acids and their eicosanoid derivatives (from references 7-12). HETE = Hydroxyeicosatetraenoic acid. HEPE = Hydroxyeicosapentaenoic acid. HHTri = Hydroxyheptadecatrienoic acid. HHTet = Hydroxyheptadecatetraenoic acid. PG = Prostaglandin. Tx = Thromboxane. Lt = Leukotriene. -- = Double bond.

After EPA and DHA are ingested and absorbed by the intestines, they are combined with cellular phospholipids, esterified, and then released and oxygenated at target cells. EPA and DHA attenuate the physiological effects of AA by directly inhibiting the integration of AA into cell phospholipids and competing for shared receptors. Also, EPA mediators exhibit reduced effectiveness relative to AA mediators at target cell receptors (7, 18).

4. CLINICAL DATA

Several decades ago, polyunsaturated fatty acids, as opposed to saturated fat, were found to exhibit cholesterol-lowering effects according to many extensive studies (19, 20). Polyunsaturated fatty acids, or most commonly vegetable oils, are omega-6 fatty acids with linoleic acid and its metabolite AA being the most commonly ingested forms of these fatty acids. Mono-ethenoid acids, such as oleic acid, which are omega-9 fatty acids, were thought to be neutral on cholesterol level, but the cholesterol-lowering effect of these fatty acids was evident in later years (21). Several decades ago, when some types of fish oil and other omega-3 fatty acids, such as sunflower seed oil, were found to possess cholesterol-increasing effects, further exploration on the beneficial effects of fish oil was halted. However, further analysis of these old data and more recent studies stimulated more research about the effects of omega-3 fatty acids on lipids and cardiovascular health (22).

The link between fish oil and cardiac protection dates back to a study done on Greenland Eskimos in the 1970's by

Dyerberg and Bang. This study revealed that Greenland Eskimos had a low rate of CAD incidence despite consuming a high fat diet (23). This led to many similar observations that revealed a beneficial role for EPA and DHA in CAD (22, 24-28). Other observational studies followed; they consistently showed a protective role for EPA, DHA (14, 29), fish oil (15), and to a less extent, ALA (16, 30) in cardiac protection. Furthermore, some studies revealed that high blood levels of omega-3 fatty acids predicted a lower cardiac mortality even in patients with no known history of CAD (31).

More recently, randomized controlled trials have emerged to show a more direct and convincing evidence of the cardioprotective role of omega-3 fatty acids. The diet and re-infarction trial (DART) studied about 1000 British CAD patients who were offered two oily fish servings a week. They were followed for about two years and were compared to a similar group that was not offered a fish-oriented diet. The oily fish group showed reduced cardiac mortality by 29% compared to the control group. There was not a significant difference, however, in the frequency of ischemic cardiac events between the two groups (32).

The GISSI-prevention trial (33) showed similar results; about 2800 CAD patients were followed for 3.5 years. The study patients were given pill forms of purified DHA and EPA in equal amounts (a total of 850 mg). Compared to placebo, the study patients showed improvement in sudden cardiac death by 45% and in all cause-mortality by 20%. It was noted, however, that the EPA/DHA group did not have significantly less incidence of non-fatal myocardial infarction (MI) during the study period of 3.5 years (33). Another prospective randomized controlled trial involved 360 patients with suspected MI's. Patients were randomized to a total of two grams of EPA and DHA in the form of fish oil, 2.9 grams of ALA, or placebo. There was less cardiac mortality and less sudden cardiac death in the fish oil group compared to the ALA group or placebo after one year of follow up (12). A randomized controlled trial showed ALA not to be effective in cardiac protection (17). To date, there have been no randomized controlled trials showing that omega-3 fatty acids exhibit cardiac protection in patients with no known CAD (primary prevention).

5. MECHANISMS OF ACTION

Several mechanisms of action have been proposed. Among these mechanisms are reducing myocardial susceptibility to fatal arrhythmias, enhancing endothelial function, anti-inflammatory effects, platelet inhibition, improving blood pressure, and lowering lipid levels (34).

5.1. Antiarrhythmic mechanisms
About 250.000 people die every year in the United States from ventricular arrhythmias within an hour of acute MI. Accordingly, simple and cheap interventions to prevent these arrhythmias have a great impact on cardiovascular mortality and prove to be cost-effective from a public health standpoint (35). Yet, despite huge efforts and expenditures by pharmaceutical industry, there is no single safe and effective drug for treating or preventing fatal arrhythmias (12). The proposed antiarrhythmic mechanisms of omega-3 fatty acids were derived from the fact that myocardial ischemia leads to the release of EPA and DHA from myocardial cell membranes. Also, intravenous infusion of omega-3 fatty acids and omega-3 fatty acid-enriched foods prevented ischemia-induced ventricular fibrillation in laboratory dogs and rats respectively (35). The fact that DART and GISSI-prevention trials revealed no reduction in the incidence of non-fatal MI during study periods indicates that the main cardiac benefit of these fatty acids is prevention of sudden cardiac death owing to their antiarrhythmic effects. Studies suggested that EPA and DHA exert their antiarrhythmic effects by lowering myocardial susceptibility to arrhythmias as esterified fatty acids after being incorporated in myocardial cell membrane phospholipids (36). This is achieved according to the following proposed mechanisms:

5.1.1. Effects on sodium channels
Sodium channels are responsible for the fast-response action potentials that occur in atrial and ventricular myocardial and Purkinje's fiber cells (figure 2). By activating these channels, depolarization of the myocardial cell renders an action potential. Omega-3 fatty acids help shift inactivated sodium channels to more negative hyperpolarized ones. This seems to be the basic mechanism of the antiarrhythmic effects of these essential fatty acids on ischemic hearts, as the presence of a gradient of depolarization of myocardial cells in the ischemic cardiac tissue is the main mechanism of ischemia-induced ventricular arrhythmias. EPA and DHA alter the electrophysiology of the myocardial cell rendering it more electrically stable by binding to sodium channels' proteins at the myocardial cell membrane. This results in shortened action potentials, increased threshold for myocardial excitation, and prolonged refractory periods, thereby lowering the susceptibility for ventricular arrhythmias. These effects occur at the level of the myocardial cell membrane and may be related to activating protein kinase, which in turn blocks sodium channels and exercises physiological effects mimicking beta-blockers (12, 37-43).

5.1.2. Effects on calcium channels
Not all cardiac arrhythmias are caused by sodium channels dysfunction. Excessive levels of free calcium radicals could activate calcium channels and cause arrhythmogenic electrophysiologic myocardial changes resulting in fatal arrhythmias. Depolarization of resting potentials, increased automaticity and frequency of delayed after depolarization, and triggered activity are among the arrhythmogenic mechanisms of calcium. Clinical situations where hypercalcemia can trigger arrhythmias include, but not limited to, malignancy, hyperparathyroidism, and vitamin D or digitalis toxicity (41-46). Calcium channels are responsible for the slow-response action potentials that occur in the sinoatrial (SA) and the atrioventricular (AV) nodes (Figure 2). The cardiac myocyte has two types of calcium receptors:
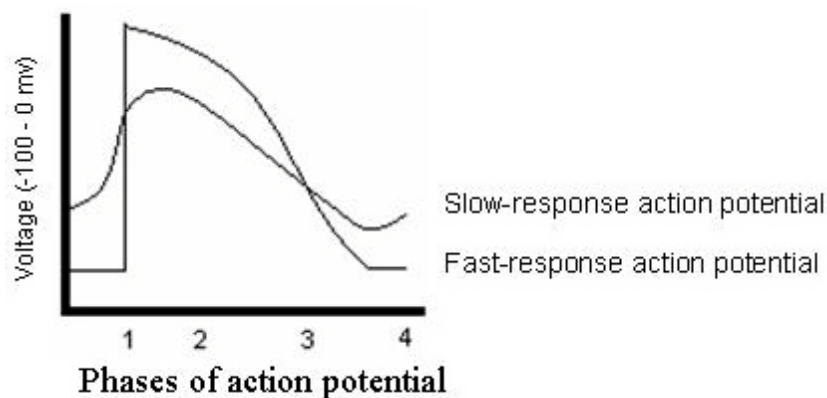
Figure 2. Depiction of the slow and fast-response action potentials with all the different phases (from references 43, 67-69). Note the difference between the two action potentials in regards to amplitude. Phase 0: Rapid or diastolic depolarization. It determines the amplitude of the action potential. Phase 1: Early repolarization. Phase 2: Plateau. Phase 3: Late repolarization. Phase 4: Diastolic depolarization or resting potential.

I. Dihydropyridine receptor (DHPR) with its subunit alpha-1 is the voltage-sensing receptor where many agonists and antagonists bind and exhibit their pharmacological effects on calcium influx at this calcium channel pore, which is part of the calcium channel complex (43-46).

II. Ryanodine receptor (RyR) is a calcium release channel that plays a crucial role in calcium homeostasis. RyR2 is the main isoform in cardiac muscle cells as opposed to RyR1 in skeletal muscle cells. Deficiency in RyR2 in mouse embryos led to early embryonic death due to abnormalities in heart tubes (43-46).

Animal studies revealed that the ischemic myocardium contains increased levels of an endogenous chemical mediator called lysophophatidylcholine (LPC). This agent is a cardiotoxic and proarrhythmic agent that accumulates during the early stage of myocardial ischemia and is associated with an increased level of free calcium ions at the level of the myocardial cell. Supplemental EPA/DHA prevented fatal arrhythmias in study animals that were injected LPC (41, 45).

The omega-3 fatty acids, EPA and DHA, have inhibitory effects on both L-type (dihydropyridine) and RyR2 calcium receptors leading to inhibition of calcium ion release from the sarcoplasmic reticulum in the myocardial cell. This reduces the duration and number of slow-response action potentials and prolongs the refractory phase of cardiac cell excitability. This mechanism seems to mimic the physiological effects of calcium channel blockers, yet delivers more potent antiarrhythmic effects (12, 37-46).

5.1.3. Effects on heart rate variability (HRV)

Heart rate variability, among other manifestations[1], is a measure of cardiovascular autonomic function and a strong predictor of cardiovascular events and sudden cardiac death (47). Increased parasympathetic tone resulting in an increase

in heart rate variability seems to protect the myocardium against ventricular arrhythmias. On the other hand, depressed heart rate variability is associated with poor short and long-term prognosis (48). In the setting of MI, HRV has an independent prognostic value that is unrelated to left ventricular function, and reperfusion therapies or interventions do not decrease this prognostic value (49, 50). Omega-3 fatty acids are known to increase parasympathetic tone and heart rate variability. Accordingly, they protect the myocardium against ventricular arrhythmias. Also, the main vagal neurotransmitter, acetylcholine, attenuates the release of tumor necrosis factor alpha (TNF-alpha) and interleukin-1 (IL-1) and probably enhances the production of anti-inflammatory cytokines. TNF-alpha has cardio and neurotoxic actions, whereas omega-3 fatty acids are potent cardio and neuroprotectors. The brain and the ischemic heart are rich in these fatty acids (48). Diabetes mellitus (DM) can lead to cardiac sympathetic dysfunction or the so-called cardiac autonomic neuropathy. Reduced heart rate variability in diabetes, as a manifestation of cardiac autonomic neuropathy, is associated with increased risk of myocardial ischemia and cardiac mortality (18). This positive effect of omega-3 fatty acids on HRV noted in observational trials indicates another mechanism of how omega-3 fatty acids lower myocardial susceptibility to arrhythmias (19, 51). This effect seems to be more prominent in diabetic patients since there is increased risk of cardiac autonomic dysfunction in diabetes. Further research is needed to confirm this observation and identify if diabetics benefit more from omega-3 fatty acids than non-diabetics (19, 51).

5.1.4. Competing with omega-6 fatty acids

Omega-3 fatty acids compete with omega-6 fatty acids at the level of the myocardial cell membrane and consequently reduce the levels of some types of leukotrienes, thromboxanes, and prostaglandins rendering less inflammatory and thrombotic effects that are responsible for acute cardiac events. Because

derivatives of AA, which is an omega-6 fatty acid, are more potent thrombotic and inflammatory substances than EPA/DHA's derivatives, omega-3 fatty acids exert anti-inflammatory and antithrombotic effects (37, 38).

5.2. Other mechanisms

Studies in humans have shown that supplemental EPA/DHA improves endothelial function, platelet inhibition, blood pressure, and lipid level (34, 52). There are only animal studies showing that omega-3 fatty acids lower myocardial susceptibility to fatal arrhythmias (39-41), although the significant reduction of sudden cardiac death in humans due to the use of omega-3 fatty acids in clinical trials is presumed to be related to reduction in fatal arrhythmias (12). Human trials on the favorable effects of EPA/DHA on endothelial function, platelet inhibition, blood pressure, and lipid level have utilized a much higher dosage of EPA and DHA than the dosage utilized in the randomized clinical trials that looked at mortality (34, 52). Accordingly, it seems that lowering myocardial susceptibility to fatal arrhythmias is the most reasonable mechanism of action that is translated into the significant clinical outcome.

Omega-3 fatty acids, especially EPA, attenuate cytokine mediated inflammatory response to endotoxins by inhibiting the production of TNF-alpha from macrophages (53). The anti-inflammatory effect is also mediated by inhibiting a leukocyte chemotactic factor, leukotriene B4, which is a product of AA through the lipoxygenase pathway (figure 1). *In vitro* studies on human umbilical vein endothelial cells revealed that supplemental omega-3 fatty acids disrupted the monocyte-endothelium interaction, which is an essential process of atherogenesis and endothelial dysfunction, by preventing adherance of monocytes to the activated endothelium (54).

The effects of omega-3 fatty acids, especially EPA, on platelet function are related to the inhibition of platelet production of thromboxane A2. An inhibitory effect on platelet activation, as reflected by a significant decrease of mean platelet volume (MPV) in blood samples treated with EPA/DHA, was seen in one study. Another study revealed that the antiplatelet effects of 10 grams of EPA/DHA are comparable to the effects of 100 mg of acetylsalicylic acid (ASA) (55, 56).

Although omega-3 fatty acids are not known to prevent hypertension in humans, animal and clinical data have revealed that they exhibit antihypertensive effects. This seems to be achieved through several proposed mechanisms: 1) Inhibition of angiotensin-converting enzyme (ACE) activity and reduction of angiotensin II production. 2) Improved endothelial nitric oxide (eNO) production. 3) Lowering transforming growth factor beta (TGF-beta) levels, which are noted to be elevated in patients with uncontrolled essential hypertension (57, 58). According to some animal studies, prenatal supplementation of omega-3 fatty acids, specifically DHA, improves blood pressure

control in adulthood. Since DHA was found in higher concentrations at synaptic membranes of the central nervous system (CNS) of these study mammals in the prenatal period, it was concluded that DHA exhibits its antihypertensive effects at CNS synaptic membranes (58). Dietary supplements of omega-3 fatty acids in the perinatal period have shown to lower the risk of essential hypertension in human adults (57).

The favorable effects of omega-3 fatty acids on lipids are mainly related to lowering triglyceride levels. Animal studies revealed a probable mechanism of action related to decreased diacylglycerol acyltransferase (DGAT) activity, which is responsible for triglyceride synthesis in the liver. EPA and probably DHA decrease triglyceride levels by increasing mitochondrial fatty acid oxidation, thereby decreasing the availability of fatty acids for triglyceride synthesis. There is some evidence that omega-3 fatty acids may preserve endothelial integrity against oxidative stress in hypertriglyceridemia. This observation was also noted, to a less extent, in normotriglyceridemia (59, 60).

6. FISH POLLUTANTS

Methylmercury (MeHg) is the most important pollutant in fish. MeHg may become concentrated in fish meat. Because it is water-soluble, it is not present in fish oil or fish oil capsules. Only certain species of fish, such as shellfish, shark, swordfish, and certain types of bass and mackerel, carry significant amounts of mercury. However, even these significant amounts do not seem to be significant enough to lead to a health concern. It is recommended, however, that pregnant or nursing women avoid these types of fish since fetuses and infants are more sensitive to mercury toxicity. Additionally, mercury tends to accumulate in fetuses. A Japanese study revealed that consumption of fish species known to contain more MeHg by pregnant women led to accumulation of mercury in fetal blood at higher concentrations than in maternal blood. The level of fetal blood mercury correlated well with the level of mercury that was bound to maternal red blood cells (RBC-Hg). Also, the level of fetal blood mercury correlated with the level of DHA in the fetal blood. Despite these data, there have been no reported adverse clinical outcomes due to ingestion of fish by pregnant or nursing women (61-63).

Other pollutants could be oil-soluble and might be present in very small amounts in some types of fish oil or fish oil capsules, such as cod liver oil, which is not frequently used in supplemental fish oil or commercial brands of fish oil capsules or liquid. These pollutants were not shown to be present in significant amounts to pose any health hazards (61-63).

7. CONCLUSION AND RECOMMENDATIONS

Based on the convincing clinical evidence that omega-3 fatty acids, specifically EPA and DHA, play a significant role in improving cardiac mortality in patients with CAD, American Heart Association

Table 3. Some of the common commercial brands of fish oil preparations and their contents of EPA/DHA

Brand	Milligrams of EPA/DHA in each capsule or teaspoon
Capsules (fish muscle oil)	------
EFA sense fish oil	180/120
HFS ultra 30/20 fish oil	300/200
K Max Alaska deep sea fish oil	180/120
Natrol omega-3	180/120
Nature made fish oil	216/144
Nature's bounty natural fish oil	180/120
Nature's way Max EPA fish oil	180/120
Omega-3 enteric coated	180/120
Rexall cholesterol-free fish oil	180/120
Spring Valley	216/144 or 180/120
Sundown fish oil	180/120
Walgreen fish oil concentrate	180/120
Capsules (fish liver oil)	------
GNC triple cod liver oil CLO	173/120
GNLD Salmon oil	540/360
Liquid (fish muscle oil)	------
GNC liquid Norwegian CLO	460/370
TwinLab emulsified Norwegian CLO	258/172
Liquid (fish liver oil)	------
Carlson Lab cod liver lemon	500/550

From references 13, 61

(AHA) recommends that patients with CAD consume a total of one gram of EPA and DHA in equal amounts daily. This should be achieved by taking purified forms of EPA and DHA since fish are inconsistent in the amount of EPA and DHA they contain (34). Table 3 includes some of the common commercial brands of fish oil preparations and their contents of EPA/DHA (13, 61).

The recommendations are less clear for people without CAD since the role for omega-3 fatty acids in primary prevention is not as evident as it is in secondary prevention. AHA, however, recommends that people without CAD eat oily fish twice a week or take 500 mg of purified form of EPA/DHA daily for primary prevention (34).

Finally, for patients with complex dyslipidemia, combination lipid-lowering drug therapy may be associated with an increased risk of significant side effects and higher drug costs. Recent evidence has shown that combining omega-3 fatty acids (EPA and DHA) with other lipid-lowering drugs, such as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, is free of significant side effects or drug interaction. Also, combining HMG-CoA with EPA/DHA enhances both the lipid lowering and the non-lipid lowering cardiovascular protective effects of both agents in high-risk patients with dyslipidemia, especially diabetics, patients with previous history of MI, and patients with metabolic syndrome [2] (64-66).

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[1] **Footnote:** Manifestations of cardiovascular autonomic dysfunction: 1) Heart rate variability or beat-to-beat variations: A difference between maximal and minimal heart rate of 10 beats/minute or less with the patient resting in the supine position and breathing slowly is considered abnormal. 2) Resting heart rate of

100/minute or higher is abnormal. 3) Orthostatic hemodynamic changes: A drop in systolic blood pressure of 30 mm/Hg within two minutes of standing from the supine position is abnormal. Bradycardia by beat 15 after standing from the supine position, and tachycardia by beat 30 are abnormal. 4) Diastolic blood pressure rise with exercise: Exercise is achieved by squeezing a dynamometer for 5 minutes to 30% of maximum. A rise of diastolic blood pressure over 16 mm/Hg is abnormal (47).

[2] **Footnote:** Metabolic syndrome is defined by having three or more of the following criteria: 1) Central obesity (a waistline of 40 inches or more for men and 35 inches or more for women). 2) A triglyceride level over 150 mg/dL. 3) A high-density lipoprotein level of less than 40 mg/dL for men or less than 50 mg/dL for women. 4) A fasting blood glucose level over 100 mg/dL (impaired fasting glucose). 5) A blood pressure of 130/85 mm/Hg or higher.The presence of metabolic syndrome significantly increases the risk of atherosclerosis and cardiovascular mortality. It is estimated that 20-30% of adult U.S. population has metabolic syndrome. The risk of the syndrome increases with age, reaching over 40% of people between 60 to 80 years of age (65, 66).

Abbreviations: AA: arachidonic acid, ACE: angiotensin-converting enzyme, AHA: American Heart Association, ALA: alpha-lenolenic acid, ASA: acetylsalicylic acid, AV: atrioventricular, CAD: coronary artery disease, CNS: central nervous system, DART: The diet and re-infarction trial, DGAT: diacylglycerol acyltransferase, DHA: docosahexaenoic acid, DHPR: Dihydropyridine receptor, DM: diabetes mellitus, eNO: endothelial nitric oxide, EPA: eicosapentaenoic acid, HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A, HRV: heart rate variability, hs-CRP: high sensitivity C-reactive protein, IL-1: interleukin-1, LDL: low-density lipoprotein, LPC: lysophophatidylcholine, MI: myocardial infarction, MPV: mean platelet volume, RyR: Ryanodine receptor, SA: sinoatrial, TGF-beta: transforming growth factor beta, TNF-alpha: tumor necrosis factor alpha.

Key Words: Fish oil, Omega-3 fatty acids, Oleic acid, Lenoleic acid, Alpha-lenolenic acid, Arachidonic acid, Eicosapentaenoic acid, Docosahexaenoic acid, Endothelium, Atherogenesis, Coronary artery disease, Diabetes mellitus, Thromboxane A3, Prostaglandin I3, Leukotriene B5, Leukotriene B4, Cardioprotective role, Antiarrhythmic effect, Sodium channels, Calcium channels, Slow and fast-response action potentials, Heart rate variability, Review

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