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Review Article

Omega-3 Fatty Acids and Cardiovascular Disease: The Epidemiological Evidence

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Abstract

Epidemiological studies in the last 40 years suggest that omega-3 fatty acids derived from fish and fish oil decrease the risk of coronary heart disease, hypertension and stroke, and their complications. The beneficial effects of omega-3 fatty acids include effects on lipids, blood pressure, cardiac and vascular function, eicosanoids, coagulation, and immunological responses. However, not all population studies have shown that omega-3 fatty acids are associated with reduced rates of coronary mortality. Such studies suffer either from small numbers of subjects or the population already had a high intake of fish. When comparing the highest intake of fish to that of the lowest fish intake, the beneficial effects of omega-3 fatty acids have been shown. In population-based case-control studies, the patients consuming modest amounts of fish, the equivalent of one fatty fish meal per week, had a significant lower risk of primary cardiac arrest compared with those who did not eat fish at all. In case-control studies, the intake of eicosapentaenoic acid and docosahexaenoic acid as reflected in adipose tissue content is inversely associated with risk of myocardial infarction.

Key words: omega-3 fatty acids, eicosapentaenoic acid, docosahexaenoic acid, coronary heart disease, hypertension

Introduction

The majority of the studies on the epidemiological aspects of omega-3 fatty acids have been carried out on coronary heart disease. In the 1950s a number of studies involving animals and human beings indicated that ingestion of fish or fish oils had a hypolipidemic effect[1–7]. The hypocholesterolemic effect of fish and fatty acids of marine oils were observed by Nelson[2,3], Pfeifer et al.[4], Stansby[7], and Bierenbaum et al.[8] early on. Looking at the 1972 publication by Nelson, one might wonder why it took so long to appreciate these monumental research findings. Perhaps because Nelson's work was published in *Geriatrics*, it escaped the notice that it merited by experts in cardiology and lipid research. Dyerberg, in 1986[9], referring to Nelson's work, said, "In the 1950s, a Seattle cardiologist interested in nutrition decided to treat heart patients with a hypocholesterolemic diet that substituted fish for meat. Encouraged by reports of the cholesterol-lowering effect of fish oils[5,7] he advised his patients to consume fish as a main course three times a week[2]. These studies continued for 16 years and showed a fourfold greater incidence of fatal heart attacks in controls compared to the diet group. Although his study was not well received when first published, it was the first positive step supporting the view that fish in the diet held promise as a preventive dietary measure against coronary heart disease." However, because omega-6 fatty acids had been shown to be effective in lowering serum cholesterol[10,11], omega-3 fatty acids were not given the attention that was due to them. In fact, the health-related effects of omega-3 fatty acids did not become apparent to the scientific community until the epidemiological studies by Bang and Dyerberg in the 1970s[12–17]. Their work on cardiovascular disease and dietary fat intake among Greenland Eskimos clarified the important role of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Table 1[18] shows that the major difference in the dietary fat between Eskimos and Danes was in the higher intake of omega-3 fatty acids of marine origin and not in total fat.

Table 1 Dietary fats in Eskimo and Danish diets[a]

	Eskimos	Danes
Percent of total calories from fat	39%	42%
Percent of total fatty acids		
Saturated	23%	53%
Monounsaturated	58%	34%
Polyunsaturated	19%	13%
Polyunsaturated : Saturated (P : S) ratio	0.84	0.24
Grams per day		
Omega-3 fatty acids	14 g	3 g
Omega-6 fatty acids	5 g	10 g
Cholesterol	0.70 g	0.42 g

[a] Daily energy intake approximately 3,000 kcal.
Modified from Dyerberg[18].

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Coronary heart disease

Bang and Dyerberg studied 130 Eskimos in the Umanak district in the Northern part of West Greenland. The Eskimos had lower levels of serum cholesterol, ApoB lipoproteins, and triglycerides in comparison to the Eskimos living in Denmark whose lipid levels were comparable to those of the Danes, indicating that genetics was not the major factor that could account for this difference. Coronary heart disease and diabetes were rare among the Greenland Eskimos, whereas stroke and cirrhosis of the liver were more frequent. The Eskimos exhibited a prolonged bleeding time, easy bruisability, a decreased number of platelets, and platelet aggregation consistent with a decreased rate of coronary thrombosis. Bang and Dyerberg suggested that the high dietary intake of EPA and DHA, 6 and 7 g, respectively, and the low intake of linoleic acid of about 5 g/d, compared to 24 g/d in Western diets, were responsible for the lower cholesterol and triglyceride levels, the prolongation of bleeding time, and other aspects of health and disease states of the Greenland Eskimos, particularly their low death rate from cardiovascular disease.

Stimulated by the findings of Bang and Dyerberg, Hirai et al.[19] reported similar findings in Japanese fishing villagers. Hirai et al. compared dietary intake and plasma levels of EPA and arachidonic acid (AA) in a fishing village whose inhabitants consumed 250 g of fish daily, with those living in a farming village, who consumed 90 g of fish per day. The plasma EPA/AA ratio was higher in the fishing villagers. There was also a decrease in the aggregation of platelets in the fishing villagers, which Hirai et al. considered as an explanation for the relatively low incidence of cardiovascular disease in Japan.

In a subsequent more extensive study, Hirai et al.[20] demonstrated that fishing villagers had decreased platelet aggregation and decreased blood viscosity. The distribution of fatty acids (EPA and DHA) in their plasma and platelet membrane phospholipids was higher than in the farming villagers and Hirai et al. concluded, "The results of our epidemiological investigation in Japan strongly suggest that haemostatic function in man can be manipulated with dietary fish lipids (mainly with EPA) and that the ingestion of EPA rich fish diet could have a beneficial effect on thrombotic cardiovascular disorders by reducing platelet aggregability and whole blood viscosity."

In another study, Kagawa et al.[21] demonstrated that island inhabitants in Kohama had higher serum EPA concentrations than the inhabitants of mainland Japan, and significantly lower mortality rates from cardiovascular disease, cerebrovascular disease, and cerebral infarction.

The studies by Bang and Dyerberg reported between 1972 and 1980, Hirai et al. in 1980 and 1984, Kagawa in 1982, and a series of papers published in the *New England Journal of Medicine* in 1985 accompanied by an editorial[22–25] set the stage for the worldwide interest in the role of omega-3 fatty acids in health and disease. In 1985 Kromhout et al.[22] reported that as little as 30 g of lean fish per day lowered by 50% the mortality from coronary heart disease in a group of men living in Zutphen in The Netherlands. Again in 1985 Phillipson et al. presented data indicating that a high amount of fish oil (32 g/d) supplements in both normal volunteers and patients with hypertriglyceridemia lowered both serum cholesterol and triglyceride levels[23]. The paper by Lee et al.[24] emphasized the important role of omega-3 fatty acids as anti-inflammatory agents, and the editorial of Glomset[25] pointed to the important role of omega-3 fatty acids in coronary heart disease.

In 1985 Shekelle et al.[26] showed that "consumption of fish at entry was inversely associated in a graded manner with the 25-year risk of death from coronary heart disease and from all causes combined; it was not associated with death from other cardiovascular-renal diseases, from malignant neoplasms, or from other causes combined." Not all studies reported a decrease in coronary heart disease mortality rate. Curb and Reed[27] reported that their data from the Honolulu Heart Program revealed no significant difference in the incidence of total and fatal coronary heart disease between subjects on a high fish diet vs. those on a low fish diet. However, the total incidence of coronary heart disease was higher among the men who never ate fish than among those who did. In three other studies[28–30] fish oils did not lower mortality from coronary heart disease, probably due to a small number of subjects[28], a high intake of saturated fatty acids[29], or to changes due to cooking which led to increases in omega-6 fatty acids and loss of omega-3 fatty acids[30].

In addition, the studies of Burr et al.[31] and Dolecek and Grandits[32] provide further evidence on the beneficial role of omega-3 fatty acids in the prevention of coronary heart disease mortality. Burr carried out a controlled prospective dietary intervention trial in 2033 men who had recovered from myocardial infarction. Those who were advised to eat fish or take fish oil had a 29% reduction in 2-year all-cause mortality ($p<0.05$) compared with those who were not given this advice. Of interest is that those given advice to reduce fat and to increase the P : S ratio (polyunsaturates : saturates), and those given advice to increase fiber intake did not have any decrease in mortality. This is the first prospective dietary intervention trial for secondary prevention of coronary heart disease that demonstrated a decrease in total mortality without a decrease in coronary events, suggesting that a decrease in the rate from sudden death is most likely due to the prevention of cardiac arrhythmias by fish or fish oil.

Dolecek and Grandits[32] investigated the 24-h dietary-recall data in the usual-care group of the Multiple Risk Factor Intervention Trial (MRFIT). They distinguished between omega-3 and omega-6 fatty acid intake and their relationship to four mortality categories: coronary heart disease, total cardiovascular disease, all-cause mortality, and cancer. Significant inverse associations were found between coronary heart disease, cardiovascular disease, and all-cause mortality groups and intake of EPA and DHA. The benefit appeared to be in the highest intake quintile with a mean ingestion of about 664 mg/d of EPA and DHA. When compared with zero intake, mortality from coronary heart disease, cardiovascular disease, and all-cause mortality was 40, 41 and 24% lower, respectively.

In a population based control study, Siscovick et al.[33] assessed the dietary intake of EPA and DHA from seafood in the risk of primary cardiac arrest. All cases and controls were free of prior clinical heart disease, major comorbidity and use of fish oil supplements. Information on the dietary intake of omega-3 PUFA from seafood during the previous month was obtained from the spouses of the case patients and controls. Blood specimens were analyzed to determine fatty acid composition in red blood cell membranes. The data show that dietary intake of omega-3 PUFA from seafood is associated with a reduced risk of primary cardiac arrest compared with no fish intake. 5.5 g of omega-3 fatty acids per month or the equivalent of one fatty fish meal per week was associated with a 50% reduction in the risk of primary cardiac

Table 2 Ethnic differences in fatty acid concentrations in thrombocyte phospholipids and percentage of all deaths from cardiovascular disease[a]

	Europe and United States	Japan	Greenland Eskimos
Arachidonic acid (20 : 4ω6) (%)	26	21	8.3
Eicosapentaenoic acid (20 : 5ω3) (%)	0.5	1.6	8.0
Ratio of ω6 : ω3	50	12	1
Cardiovascular mortality (% of all deaths)	45	12	7

[a] Modified from Weber in Simopoulos[42].

arrest. A concentration of 5.0% omega-3 PUFA in red blood cell membrane phospholipids was associated with a 70% reduction in the risk of primary cardiac arrest.

Simon et al.[34] examined the relation between serum fatty acids and coronary heart disease (CHD) by conducting a nested case-control study of 94 men with incident CHD and 94 men without CHD who were enrolled in the usual care group of the Multiple Risk Factor Intervention Trial (MRFIT) between December 1973 and February 1976. The results are consistent with other evidence indicating that saturated fatty acids are directly correlated with CHD and that omega-3 PUFA are inversely correlated with CHD. Because these associations were present after adjustment for blood lipid levels, other mechanisms, such as a direct effect on blood clotting, may be involved.

The studies by de Lorgeril et al.[35–38], Singh et al.[39–40], and the GISSI study[41] have clearly shown that omega-3 fatty acids along with a Mediterranean type of diet decrease the risk of coronary heart disease in patients who already had one episode of myocardial infarction.

Populations with high consumption of fish, such as the Eskimos and Japanese, have lower rates of myocardial infarction (Table 2) and practically all epidemiological studies show that ingestion of omega-3 fatty acids is associated with a decrease in coronary heart disease mortality[42]. The mechanisms involved in the hypolipidemic, hypotensive, antiatherogenic, antithrombotic, and anti-inflammatory aspects of omega-3 fatty acids are summarized in Tables 3 and 4[43,44]. The effects of omega-3 fatty acids in decreasing the rate of restenosis noted in the majority of the studies are very encouraging and suggest that omega-3 fatty acids may prevent the development of atherosclerosis. Inconsistencies in some of the intervention trials are most likely due to differences in amount and source of omega-3 fatty acid, length of observation, disease state, and genetic differences in patients with various

Table 3 Functional effects of omega-3 fatty acids in the cardiovascular system

Decrease postprandial lipemia
Reduce platelet aggregation
Reduce blood pressure
Decrease whole blood viscosity
Reduce vascular intimal hyperplasia
Reduce vasospastic response to vasoconstrictors
Reduce cardiac arrhythmias
Reduce albumin leakage in type I diabetes mellitus
Increase bleeding time
Increase platelet survival
Increase vascular (arterial) compliance
Increase cardia beta-receptor function
Increase postischemic coronary blood flow

Adapted from Weber[43].

Table 4 Effects of fatty acids on factors involved in the pathophysiology of atherosclerosis and inflammation

Factor	Function	Effect of omega-3 Fatty acid
Arachidonic acid	Eicosanoid precursor; aggregates platelets; stimulates white blood cells	↓
Thromboxane	Platelet aggregation, vasoconstriction; increase of intracellular Ca^{++}	↓
Prostacyclin ($PGI_{2/3}$)	Prevent platelet aggregation; vasodilation; increase cAMP	↑
Leukotriene (LTB_4)	Neutrophil chemoattractant increase of intracellular Ca^{++}	↓
Tissue plasminogen activator	Increase endogenous fibrinolysis	↑
Fibrinogen	Blood clotting factor	↓
Red cell deformability	Decreases tendency to thrombosis and improves oxygen delivery to tissues	↑
Platelet activating factor (PAF)	Activates platelets and white blood cells	↓
Platelet-derived growth factor (PDGF)	Chemoattractant and mitogen for smooth muscles and macrophages	↓
Oxygen free radicals	Cellular damage; enhance LDL uptake via scavenger pathway; stimulate arachidonic acid metabolism	↓
Lipid hydroperoxides	Stimulate eicosanoid formation	↓
Interleukin 1 and tumor necrosis factor	Stimulate neutrophil O_2 free radical formation; stimulate lymphocyte proliferation; stimulate PAF; express intercellular adhesion molecule-1 on endothelial cells; inhibit plasminogen activator, thus, procoagulants	↓
Endothelial-derived relaxation factor (EDRF)	Reduces arterial vasoconstrictor response	↑
VLDL	Related to LDL, and HDL level	↓
HDL	Decreases the risk for coronary heart disease	↑
Lp(a)	Lipoprotein(a) is a genetically determined protein that has atherogenic and thrombogenic properties	↓
Triglycerides and Chylomicrons	Contribute to postprandial lipemia	↓

Modified from Weber and Leaf[44].

forms of hyperlipidemia.

Coronary heart disease is a multifactorial disorder due to many genetic and environmental factors and their interactions. Elevated serum cholesterol has been shown to be a risk factor for coronary heart disease. At the same time it is known that 50% of the serum cholesterol level is genetically determined, and that all the dyslipidemias described thus far are genetically determined. Patients who survive a myocardial infarction have one or more of four lipoprotein abnormalities: (1) increased LDL cholesterol concentrations; (2) decreased HDL cholesterol concentrations usually accompanied by increased triglyceride or VLDL concentrations; (3) increased concentration of chylomicron remnants and intermediate density lipoprotein (IDL); and (4) increased Lp(a). Omega-3 fatty acids lower triglycerides and chylomicrons, usually raise HDL, lower Lp(a), and have antithrombotic and antiatheromatous effects. Although omega-3 fatty acids alone will not lead to the universal eradication of coronary heart disease, as we begin to unravel the genetics of coronary heart disease and the mechanisms of atherogenesis, we should be able to identify individuals with genetic susceptibility who should modify their diet early in life. The provision of a low saturated fat diet, with increased amounts of omega-3 fatty acids and decreased amounts of omega-6 fatty acids in order to have an omega-6 : omega-3 ratio of 4 : 1 or less should be beneficial in the prevention of coronary heart disease[35–47].

Hypertension

The first studies on the effect of omega-3 fatty acids on blood pressure were reported in 1983 by two groups of investigators, Singer et al.[48] and Lorenz et al.[49]. They showed that adding mackerel to the diet of patients with mild hypertension lowered blood pressure. Most studies confirmed these findings in hypertensive patients and in normal subjects[50–55], although other studies did not[56,57]. Knapp and FitzGerald[53] evaluated the effects of omega-3 and omega-6 fatty acids in patients with essential hypertension, using different doses. High doses of fish oil, 50 ml of MaxEPA, reduced blood pressure in men with essential hypertension. In this group the formation of vasodilatory prostaglandins (PGI_2 and PGI_3) increased initially, but this effect was not sustained as blood pressure fell. The concentration of thromboxane A_2 metabolites fell, and thromboxane A_3 metabolites were detected in the groups receiving fish oil. As expected, omega-6 fatty acids, 50 ml given in the form of safflower oil, led to an increase of PGE_2 and tended to decrease with fish oil, although no PGE_3 metabolite was detected.

In another study Bonaa et al.[58] carried out a population-based intervention trial in which decreases of 6 mmHg in systolic and 3 mmHg in diastolic blood pressure occurred with fish oil supplementation. Of particular interest in this study is the observation that dietary supplementation with fish oil did not change mean blood pressure in the subjects who ate fish three or more times per week as part of their usual diet or in those who had a baseline concentration of plasma phospholipid omega-3 fatty acids >175.1 mg/l, suggesting that a relationship exists between plasma phospholipid omega-3 fatty acid concentration and blood pressure. Those subjects who habitually consumed more fish had a lower blood pressure at baseline. This finding suggests that supplementation with fish oils would be important from the primary prevention standpoint. Normal subjects given large doses of fish oil do not show any change in renal function[59], which is encouraging in terms of safety issues. Singer[51] used three cans of mackerel per week (equivalent to 1.2 g omega-3 fatty acids per day or 1.2×3=3.6 g of fish oil per day) for 8 months to lower blood pressure with good results and concluded that this amount of mackerel or equivalent amount of fish oil is considered acceptable for daily intake of the general population. The mechanisms by which omega-3 fatty acids exert their hypotensive effects have been investigated (Tables 3 and 4)[43,44]. Two research groups have shown that dietary EPA is converted to PGI_3 in humans without suppressing the formation of PGI_2 from AA[60,61]. Other mechanisms include effects of omega-3 fatty acids on renal function, a lowering of whole blood viscosity, and a reduction in vascular responsiveness to systemic vasoconstrictors[62]. The combination of propanolol and fish oil supplements potentiate their blood pressure lowering effects. In addition, the increase in plasma triglycerides that is often seen during antihypertensive therapy did not occur, indicating once again the importance of omega-3 fatty acids as adjuvants to drug therapy.

Bao et al. examined the potential effects of combining dietary fish rich in omega-3 fatty acids with a weight loss regimen in overweight hypertensive subjects, with ambulatory blood pressure levels as the primary end point[63]. Combining a daily fish meal with a weight-reducing regimen led to additive effects on ambulatory blood pressure and decreased heart rate. The effects were large, suggesting that cardiovascular risk and antihypertensive drug requirements are likely to be reduced substantially by combining dietary fish meals rich in omega-3 fatty acids with weight-loss regimens in overweight medication-treated hypertensives. The reduction in heart rate seen with dietary fish suggests a cardiac/autonomic component, as well as vascular effects, of increased consumption of omega-3 fatty acids from fish.

Conclusions and recommendations

The studies described above provide further support on the beneficial effects of omega-3 fatty acids in the prevention and management of cardiovascular disease. The effects of omega-3 fatty acids and the mechanisms involved are not operating in changing lipid levels. Most likely their effects are at the level of the vessel wall affecting blood clotting[34,64] or it is their antiarrhythmic effect[31,33,35,65]. Of further interest is the fact that effects of omega-3 fatty acids appear to occur within the first 4 months[35] whereas not such an effect was apparent in the Scandinavian Simvastatin Survival Study Group[66] or the Scottish trial[67] for six months to two years using simvastatin and pravastatin respectively. Furthermore, a recent study on the cost effectiveness of statins showed a great variation between different risk groups[68]. Dietary intervention with omega-3 fatty acids is cheaper and free of side effects. Clearly there is a need to carry out large randomized double blind controlled clinical trials to confirm the effects of omega-3 fatty acids in the prevention of sudden death, and decrease in total mortality.

Omega-3 fatty acids have been part of our diet since the beginning of time. They have been shown to be essential for normal growth and development[42]. For the primary prevention of cardiovascular disease the dose should be consistent with estimates derived from knowledge on the evolutionary aspects of diet, namely a ratio of omega-6 : omega-3 of 1[69,70]. Epidemiologic studies suggest that 1–2 fish meals per week or as little as 30–35 g/d

Table 5 Genetic determinants and environmental risk factors for coronary heart disease

Genetic determinants	Environmental risk factors
Family history of coronary heart disease at an early age	Smoking
Total serum cholesterol, LDL, and Apo B levels	Sedentary lifestyle (lack of aerobic exercise)
HDL cholesterol, Apo A-1, and Apo A-II levels	Diet
Apo A-IV-1/1	Excess energy intake
Apo E polymorphism	High saturated fat intake
Lipoprotein (a)	High *trans* fatty acids intake
LDL receptor activity	High ω-6 fatty acid intake
Thrombosis-coagulation parameters	Low ω-3 fatty acid intake
Triglyceride and VLDL concentrations	Psychosocial factors
RFLPs in DNA at the Apo A-I/Apo C-II and Apo B loci	Type A personality
Other DNA markers	Social class
Blood pressure	
Diabetes	
Obesity	
Insulin level and insulin response	
Heterozygosity for homocystinuria	

of fish throughout life decrease the risk of coronary heart disease relative to those who do not eat any fish[22,33]. Furthermore, in the study by von Schacky et al., patients with coronary artery disease who ingested approximately 1.5 g of omega-3 fatty acids per day for 2 years had less progression and more regression of coronary artery disease on coronary angiography than did comparable patients who ingested a placebo[71]. For the secondary prevention of coronary heart disease, 300 g of fatty fish providing 2.5 gms EPA from fish or fish oil/wk decreased the risk of sudden death by 29%[31]. The overall diet most definitely influences the dose of omega-3 fatty acids, since 2 g of 18 : 3ω3 added to a Mediterranean type diet decreased the rate of sudden death by 70% beginning at 4 months[35]. In the GISSI study, the dose of omega-3 fatty acids was 850–882 mg of EPA+DHA at a ratio of 2 : 1 in addition to a Mediterranean type diet. For the reduction of VPC the dose was 0.9 g of EPA and 1.5 g of DHA whereas for the prevention of occlusions following coronary by-pass grafting, the dose was 4 g/d of fish oil concentrate[41]. Although an RDA for omega-6 and omega-3 essential fatty acids does not exist, the Adequate Intake (AI) of omega-6 and omega-3 fatty acids has been determined[72]. Because dietary intake studies are inherently associated with large measurement error, the determination of tissue levels of fatty acids should be considered as the best alternative to dietary intake measurements[73]. Using adipose tissue fatty acid levels to determine the risk of myocardial infarction in a case-control study, Pedersen et al. showed that, "Intake of very long-chain n-3 fatty acids as reflected in adipose tissue content is inversely associated with risk of myocardial infarction. *Trans* fatty acids, linoleic and α-linolenic acid were intercorrelated and associated with increased risk. It is suggested that the increased risk may be connected to *trans* fatty acids or to some other factor associated with margarine consumption."[73].

Coronary heart disease is a multigenic and multifactorial disease. Table 5 lists a number of genetic and environmental factors that contribute to its development[74]. Double blind controlled clinical trials are the golden standard to demonstrate cause and effect relationship. In the planning of such trials, it is essential that the patients are stratified by genetic susceptibility, disease entity, as well as sex, age and severity of disease. The composition of the diet must remain constant throughout the intervention period, the ratios of saturated fat to unsaturated fat and the ratio of omega-6 : omega-3 must be taken into consideration[75]. *Trans* fatty acids should not comprise more than 2% of energy. The exact dose of omega-3 fatty acids and length of treatment prior to surgical procedures such as angioplasty appears to be a critical one. Judging from the beneficial effects of the study by Bairaiti et al.[76] it would appear that omega-3 fatty acid supplementation should be given at least 3 weeks prior to surgery. Many of the studies reported thus far were not controlled for many of the above factors. Common protocols need to be established, but modified according to prevailing genetic, dietary and other environmental factors. Further studies are needed on the role of omega-3 fatty acids in gene expression[77].

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