Omega-3 Polyunsaturated Fatty Acids and Coronary Heart Disease Prevention

William S. Harris, Ph.D.
Mid America Heart Institute at St. Luke's Hospital
Kansas City, Missouri 64111

Introduction

The interest in Omega-3 polyunsaturated fatty acids and coronary heart disease has arisen only over the course of the past 25 years. In the 1970s, Danish investigators studied heart disease rates in native peoples of Greenland and discovered significantly lower levels of acute myocardial infarction in Eskimos compared with age- and sex-matched Danes. On further investigation, Bang and Dyerberg concluded that the high level of Omega-3 fatty acids in their native diet may have accounted for the low rates of coronary heart disease (CHD). In studies of other populations such as the Japanese, higher fish intake has also been associated with lower rates of heart disease. In addition to replacing meat (with its saturated fatty acids and cholesterol), fish serves as the best source of long-chain ω3 fatty acids. By the mid 1980's, Omega 3 fatty acids became the focus of intense investigation.

Animal and clinical investigations into the functional effects, health impact, and metabolism of Omega-3 fatty acids have identified several promising uses of fish oil in disease prevention and treatment. Although their greatest impact may be in the arena of cardiovascular disease, a beneficial role for this class of fatty acids has clearly been implicated in several other systems. For example, it now appears that Omega-3 fatty acids are essential nutrients required in utero for proper development of nervous tissues. The Omega-3 fatty acid most clearly needed is docosahexaenoic acid (DHA; C22:6?3), the longest and most unsaturated of all known dietary fatty acids. It appears that consumption of the plant-derived precursor of DHA, α-linolenic acid (LNA; C18:??3), will provide enough DHA for term infants. However, pre-term infants may need direct delivery of DHA (and arachidonic acid; C20:??6) from the placenta for proper brain development. There is currently tremendous interest in fortifying infant formulas (especially preterm) with DHA, although important unanswered questions remain and are currently being addressed in clinical trials. Another area of intense omega 3 research is immunology. From rheumatoid arthritis, to psoriasis, IgA nephropathy and colitis many research groups are exploring the healing or preventive potential utility of this class of natural products. Another possible area in which the anti-inflammatory effects of Omega-3 fatty acids may be playing a major but still hidden role is in atherosclerosis.

Heart Disease

It is in the arena of heart disease prevention that omega 3 fatty acids were first discovered. Although Omega-3 fatty acids may play important roles in immune and inflammatory responses, their impact on platelet function and lipoprotein metabolism attracted most of the early attention. The recognition that eicosapentaenoic acid (EPA), the other major marine-derived Omega-3 fatty acid, was a substrate for cyclooxygenase, and that thromboxane A_3 was far less biologically active than its arachidonic acid-derived counterpart thromboxane A_2, helped explain the prolonged bleeding times in Greenland Eskimos. Subsequent research revealed that the other 3-series icosanoids derived from EPA (e.g., PGE_3, leukotriene B_5) also had reduced physiological activity relative to their 2-series siblings. It was these differences in metabolism between the EPA and AA derived metabolites that were likely to be the basis for not only the diminished thrombogenic vigor observed in subjects taking fish oils, but also for their anti-inflammatory properties. Thus, part of the anti-atherogenic mechanism of Omega-3 fatty acids is likely due to their impact on eicosanoid metabolism.

Lipoprotein metabolism was also affected by Omega-3 fatty acids, but apparently not via alterations in eicosanoid system. The effects of these fatty acids on serum triglyceride reductions (both fasting and postprandial) has been well-established. The mechanism of the triglyceride-lowering effect involves an inhibition of hepatic triglyceride synthesis and secretion with a possible effect on triglyceride clearance still being investigated. Total cholesterol levels usually do not change, whereas small increases in HDL-cholesterol have frequently been reported. Like the triglyceride-lowering fibrate drugs, LDL-cholesterol levels can rise with ω3 fatty acid treatment, particularly in subjects with significant hypertriglyceridemia; in other patients changes are uncommon. Non-lipid effects on CHD risk factors such as fibrinogen, blood viscosity or platelet aggregation may also explain some of the beneficial effects of fish oils on thrombosis and atherosclerosis. Finally,

Omega-3 fatty acids may also play a role in the reduction of blood pressure and thereby may reduce risk for CHD.

Animal Studies

In one of the first well-controlled animal trials in this area, Weiner et al. reported that pigs fed an atherogenic diet supplemented with 30 ml/d of cod liver oil for 8 months developed significantly less atherosclerosis than did the control animals. Of particular interest was the lack of association between LDL levels and atherosclerotic changes in the arteries of pigs given fish oil; in fact, the LDL-cholesterol concentrations were higher in the fish oil group. Davis et al. studied the effects of feeding coconut oil with two different doses of fish oil to Rhesus monkeys. In this study, feeding higher levels of fish oil depressed HDL levels. Nevertheless, there was a clear dose-response effect between fish oil intake and less arterial plaque. These observations suggest that Omega-3 fatty acids can improve the atherogenic millieu even in the face of adverse changes in serum lipids. Such adverse effects on serum lipoproteins are not observed in humans consuming "practical" levels (<4 g/d) of Omega-3 fatty acids.

Fish oil may play a role in preventing reperfusion injury to the heart and brain. In one study, rats were fed 12% of calories either as corn oil or as fish oil for a month; myocardial ischemia was induced by tying off the left main coronary artery for 15 minutes and then reperfusing for 6 hours. Among the rats fed fish oil, 76% survived the "heart attack" and 14% had ventricular tachycardia and fibrillation; among those fed corn oil, the percentages were 41% and 90%, respectively. Dog studies have shown that acute infusion of EPA and DHA can reverse ventricular fibrillation, strengthening the rationale for the use of these acids in preventing rhythm disorders.

Human Studies. There have been several epidemiological studies comparing CHD rates between fish eating and non-fish eating populations, and across the spectrum of fish consumption within populations. Although these studies have largely supported a cardioprotective effect of fish, the link to Omega-3 fatty acids has been more difficult to establish due to the low intake estimates characteristic of diet survey studies. These uncertainties have been addressed, however, in several prospective, randomized, intervention trials using either oily fish, or more recently, encapsulated fish oils or purified Omega-3 fatty acids.

Intervention Studies. The first study to prospectively explore the cardioprotective effect of Omega-3 fatty acids in a secondary prevention population was the Diet and Reinfarction Trial. Burr et al. studied 2,013 men who had survived a heart attack. Half were advised to eat oily fish twice a week or to take fish oil capsules, while the other half were advised only to eat a prudent diet. Survival over the subsequent 2 years was followed. The researchers used food diaries and blood EPA levels to confirm compliance. The group advised to consume oily fish showed a 29% reduction in overall, 2-year mortality compared with the control group. Interestingly, there were no significant differences between groups in total ischemic heart disease *events* because more subjects in the fish oil group experienced *nonfatal* myocardial infarctions while more subjects in the control group experienced *fatal* myocardial infarctions. These results pointed to a possible protective effect for Omega-3 fatty acids during ischemia and reperfusion.

Another prospective, randomized clinical trial using Omega-3 fatty acids was reported by Singh et al. Patients presenting with suspected myocardial infarctions (n=360) were randomized to placebo, fish oil (2 g of EPA+DHA per day) or mustard seed oil (containing 2.9 g of α-linolenic acid per day). After one year, CHD events were significantly reduced in both Omega-3 fatty acid groups. Von Schacky and colleagues recently reported a small but statistically significant reduction in angiographically-determined CHD progression in a study which provided 6 g of Omega-3 fatty acids for 3 months followed by 3 g/d for 21 months or placebo in 223 patients. There were 7 CV events in the control group and 2 in the Omega-3 group (p=0.10). In a study of the effects of Omega-3 fatty acids on coronary artery bypass graft patency, efficacy was highly correlated to serum omega 3 fatty acid levels, with those patients achieving the highest serum levels having an odds ratio for graft occlusion of 0.49 compared to those with the lowest increment in serum phospholipid Omega-3 fatty acid levels. This finding illustrates the perhaps obvious fact that differences in compliance and individual metabolism of omega 3 fatty acids may contribute to differences in clinical outcomes, and suggests that Omega-3 fatty acid levels in the blood be assessed in all outcome studies.

The most recent test of the effects of omega 3 fatty acids on CHD morbidity and mortality was the GISSI-Prevention trial. This study was conducted in Italy and included 11,324 patients with known CHD. In a factorial design, ¼ of the patients were assigned to take vitamin E (300 mg/d); another ¼ were given 850 mg of omega 3 fatty acids daily (one capsule of Omacor, Pronova Biocare, Oslo, Norway); another ¼ was given both and the final ¼ received neither. After 3.5 years of follow up, an intention-to-treat analysis revealed that total mortality in the patients given omega 3 fatty acids was 21% lower than in those patients not so treated, and the incidence of sudden cardiac death was reduced by 45%. Vitamin E showed a beneficial trend but it was not statistically significant. These results were achieved despite the fact that over 25% of patients reported that they stopped taking the capsules. The finding of the

GISSI-Prevention study provide strong support for the use of Omega-3 fatty acids in secondary prevention of acute coronary syndromes. The mechanisms by which Omega-3 fatty acids protect against cardiac death are not known with certainty, but may relate to their ability to prevent cellular damage during periods of ischemic stress.

In conclusion, the evidence for a protective role of omega 3 fatty acids in CHD is becoming clearer and firmer, especially for secondary prevention. Intakes of approximately 800-1,000 mg per day appear to be a prudent approach for the latter group of patients. The safety of intakes of up to 3,000 mg per day has been endorsed by the recent ruling of the FDA that this level of EPA+DHA (from menhaden oil) is generally recognized as safe (GRAS) for inclusion in the American food supply. Recommendations for primary prevention of CHD and for use in other conditions (inflammatory diseases, autoimmune conditions, cancer prevention, etc.) cannot yet be made as the requisite data to support such recommendations is not yet available.

Suggested Reading

Albert CM, Hennekens CH, O'Donnell CJ, Ajani UA, Carey VJ, Willett WC, Ruskin JN, Manson JE. Fish consumption and risk of sudden cardiac death. JAMA 1998;279:23-28.

Belluzzi A, Brignola C, Campieri M, Pera, A, Boschi S, Migloli, M. Effect of enteric-coated fish oil preparation on relapses in Crohn' disease. N Engl J Med 1996;334:1557-1560.

Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet 1989;2:757-761.

Connor WE, Connor SL. Diet, atherosclerosis, and fish oil. Adv Intern Med 1990;35:139-171.

Davis HR, Bridenstine RT, Vesselinovitch D, Wissler RW. Fish oil inhibits development of atherosclerosis in rhesus monkeys. Arteriosclerosis 1987;7:441-449.

Eritsland J, Arnesen H, Grønseth K, Fjeld NB, Abdelnoor M. Effect of dietary supplementation with n-3 fatty acids on coronary artery bypass graft patency. Am J Cardiol 1996;77:31-36.

GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: Results of the GISSI-Prevenzione trial. Lancet 1999;354:447-455.

Harris WS. n-3 fatty acids and lipoproteins: comparison of results from human and animal studies. Lipids 1996;31:243-252

Kremer JM. Effects of modulation of inflammatory and immune parameters in patients with rheumatic and inflammatory disease receiving dietary supplementation on n-3 and n-6 fatty acids. Lipids. 1996;31:S243-S247.

Kristensen SD, De Caterina R, Schmidt EB, Endres S. Fish oil and ischaemic heart disease. Br Heart J 1993;70:212-214.

Leaf A, Kang JX. Prevention of cardiac sudden death by n-3 fatty acids: a review of the evidence. J Intern Med 1996;240:5-12.

Schmidt EB, Dyerberg J. Omega-3 fatty acids: current status in cardiovascular medicine. Drugs 1994;47:405-424.

Singh RB, Niaz MA, Sharma JP, Kumar R, Rastogi V, Moshiri M. Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: the Indian Experiment of Infarct Survival-4. Cardiovasc Drugs Therap 1997;11:485-491.

Uauy R, Pierano P, Hoffman D, Mena P, Birch D, Birch E. Role of essential fatty acids in the function of the developing nervous system. Lipids 1996;31:S167-S176.

von Schacky C, Angerer P, Kothny W, Theisen K, Mudra H. The effect of dietary ω-3 fatty acids on coronary atherosclerosis. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1999;130:554-562.

Weiner BH, Ockene IS, Levine PH, et al. Inhibition of atherosclerosis by cod-liver oil in a hyperlipidemic swine model. N Engl J Med 1986;315:841-846.

Wu D, Meydaqni SN, Meydani M, Hayek MG, Huth P, Nicolosi RJ. Immunologic effects of marine and plant-derived n-3 polyunsaturated fatty acids in non-human primates. Am J Clin Nutr 1996;63:273-280.