



n-3 Fatty acids from fish and fish oil: panacea or nostrum?¹⁻³

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The steps in the development of important medical discoveries rest first on intuition and then on associations of a certain factor with a disease, followed by scientifically designed experiments. The history of the importance of the n-3 polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) illustrates this point beautifully. Early Arctic explorers commented on the rarity of coronary artery disease in Eskimos despite their consumption of a very-high-fat, high-cholesterol diet. This finding was indeed a paradox until it was resolved by 2 Danish scientists, Bang and Dyerberg (1). When these investigators looked at the coronary mortality statistics in Greenland Eskimos and in Danish persons living in Greenland but having a vastly different lifestyle, they found few deaths from coronary artery disease in Greenland Eskimos but many deaths in Danes. The answer to this riddle came from an analysis of the diet of the Eskimos compared with that of the Danes (1). The latter group ate a diet high in saturated fat and cholesterol from meat and dairy products similar to the diet eaten in the homeland of Denmark. The Eskimos, on the other hand, ate seal, whale, and fish, all of which are extremely rich in EPA and DHA. This was in contrast with the lower n-3 fatty acid content of the typical Danish diet. In the Greenland Eskimos also, the content of these same n-3 fatty acids in the blood was high (2), and the tendency of the blood to form thrombi was lessened because the n-3 fatty acids were taken up by the blood platelets (3).

The same situation prevails in present-day Eskimos, as illustrated by the study by Dewailly et al (4) in this issue of the Journal. The Nunavik Inuit of Quebec, despite some Westernization, still partly consume the diet of their ancestors, which is rich in fish and marine mammals. Mortality from coronary artery disease in the Inuit is 50% less than that in the Quebec province as a whole. The Inuit's high blood content of EPA and DHA reflects their consumption of these foods from the sea.

Why the n-3 fatty acids from fish and marine oils prevent coronary artery disease has now been delineated in hundreds of experiments in animals and tissue culture cells and in population and clinical trials (5). Of the nutritional modalities thought to prevent heart disease, the evidence for the efficacy of n-3 fatty acids is strong. This evidence may be best summarized in **Table 1** and by answering the following question: have other population studies and clinical trials shown that fish consumption is associated with a lowered incidence of coronary artery disease? Japanese, Dutch, and US studies indicate that deaths from coronary artery disease are reduced by $\geq 50\%$ by the consumption of 1-2 fish meals/wk (6-8). The most important finding is of a reduction in sudden death from ventricular fibrillation and tachycardia. About

300 000 such deaths occur in the United States each year. Direct clinical trials of fish and fish oil have also shown a striking reduction in sudden deaths (9, 10); these findings have great public health significance. Furthermore, animal studies and experiments in isolated myocytes showed that ventricular arrhythmias are inhibited by EPA, which affects sodium and calcium ion channels in the heart (11).

Thrombosis is a major complication of coronary atherosclerosis and leads to myocardial infarction. The n-3 fatty acids from fish oil have powerful antithrombotic actions. EPA inhibits the synthesis of thromboxane A₂ from arachidonic acid in platelets. Thromboxane A₂ causes platelet aggregation and vasoconstriction. By blocking thromboxane A₂ synthesis, fish oil ingestion by humans increases the bleeding time and decreases the number of platelets that stick to glass beads (12). In addition, administration of fish oil enhances the production of prostacyclin, a prostaglandin that produces vasodilation and less sticky platelets. In an in vivo baboon model, dietary fish oil prevented platelet deposition in a plastic vascular shunt (13). Injury to the intima of the carotid artery of the baboon invariably caused a marked proliferative and inflammatory lesion, greatly thickening the wall. When the animals were fed fish oil, this damage and intimal thickening were completely blocked.

The EPA and DHA contained in fish oil inhibit the development of atherosclerosis. There is evidence in both pigs and monkeys that dietary fish oil prevents atherosclerosis by actions other than the lowering of plasma cholesterol concentrations (14). These actions may be associated with the inhibition of monocyte migration into the plaque, with less cytokine and interleukin 1 α production, and with stimulation of the endothelial production of nitric oxide.

Dyerberg and Bang also found that the blood of Greenland Eskimos had lower triacylglycerol and cholesterol concentrations, particularly triacylglycerol, than the blood of Danes (2). Dewailly et al (4) found that n-3 fatty acids in the plasma phospholipids of Nunavik Inuit were positively associated with HDL-cholesterol concentrations and inversely associated with

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TABLE 1

Actions of n-3 fatty acids to prevent coronary heart disease and sudden death

- 1) Prevent cardiac arrhythmias (ventricular tachycardia and fibrillation)
- 2) Act as antithrombotic agents
- 3) Inhibit the growth of atherosclerotic plaques
- 4) Act as antiinflammatory agent (inhibit synthesis of cytokines and mitogens)
- 5) Stimulate endothelial-derived nitric oxide
- 6) Lower plasma concentration of triacylglycerol and VLDL cholesterol and increase plasma concentrations of HDL cholesterol


plasma triacylglycerol and the ratio of total to HDL cholesterol. These Inuit had higher n-3 fatty acid (EPA+DHA) concentrations in their plasma phospholipids proportional to the intakes of typical Eskimo marine foods. However, plasma total and LDL-cholesterol concentrations correlated positively with n-3 fatty acid concentrations. The divergent effects of n-3 fatty acids to reduce plasma triacylglycerol and elevate LDL may be explained by a dietary background high in cholesterol and saturated fat as well as in n-3 fatty acids. The 2 situations are completely compatible. In a feeding experiment by Nordoy et al (15), a diet high in n-3 fatty acids but also high in cholesterol and saturated fat decreased plasma triacylglycerol and VLDL and at the same time increased plasma LDL. The optimal diet would be one high in n-3 fatty acids and low in cholesterol and saturated fat, thus reducing both triacylglycerol and LDL concentrations in the plasma.

This pronounced effect of fish oil on hyperlipidemia is especially well documented by precise dietary studies in which a diet rich in salmon oil was fed and contrasted with a vegetable oil diet and a diet high in saturated fat (16). Fish oil lowers plasma triacylglycerol concentrations by inhibiting the synthesis of triacylglycerol and VLDL in the liver. Apolipoprotein B production is lower after consumption of fish oil than after consumption of vegetable oils such as safflower or olive oil. This mechanism of action is further substantiated by cultures of rabbit and rat hepatocytes in which EPA, for example, in contrast with oleic acid, inhibited triacylglycerol synthesis and stimulated the synthesis of membrane phospholipid.

Pronounced postprandial lipemia occurs after the absorption of fat from diets with high fat contents. Postprandial lipoproteins are known to be atherogenic. They are also thrombogenic because postprandial lipemia increases activated factor VII, a procoagulant. Pretreatment with fish oil greatly lessens postprandial lipemia (17), and this effect should be considered both anti-atherogenic and anti-thrombotic.

The emphasis on fish and fish oil for coronary prevention does not mean that vegetarians could not benefit from the consumption of n-3 fatty acids. The precursor to EPA and DHA in the n-3 fatty acid synthetic pathway is α -linolenic acid (18:3n-3), which is especially rich in certain vegetable oils such as canola, soy, flaxseed, and walnut oils. In the Lyon Heart Study, which emphasized linolenic acid consumption from canola margarine, blood EPA concentrations increased and the death rate from coronary artery disease was reduced by 70% with a concomitant

reduction in sudden death (18). A vegetarian diet, then, can still benefit from an increased n-3 fatty acid content.

In summary, n-3 fatty acids from fish and fish oil are natural food substances that prevent coronary artery disease and sudden death. Physicians should become acquainted with the powerful therapeutic potential of these fatty acids. n-3 Fatty acids have immense public health significance for the control of the current coronary epidemic. 

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