Editorial

Fish and coronary artery disease

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Does fish consumption protect against coronary heart disease? If so what are the mechanisms for such protection and how much fish (and of what types) would need to be consumed?

Atherosclerosis is apparently rare among Eskimos on a tradititioinal diet of seal, caribou, and fish but not among those on a western diet.1 Necropsy data showed that atherosclerosis was less severe in Canadian Eskimos2 than in white Canadians. From an analysis of hospital records Kromann and Green concluded that acute myocardial infarction was extremely rare amongst Eskimos from the West Coast of Greenland who still eat large amounts of seafood.3 The reliability of the mortality statistics for Eskimos may be questioned owing to a high mortality rate from accidents (for example through falling into holes in the ice) and a low necropsy rate. Cardiovascular mortality rates in Japanese fishermen, however, are reported to be lower than in Japanese farmers.4 Fish based diets provide more protein, less saturated fat, and a different type of polyunsaturated fat than the average western diet.

Sinclair subsisted for three months on food derived entirely from marine animals, notably seal.5 This resulted in considerable changes in haemostatic variables and serum lipids, especially in the fatty acid composition of the cholesterol esters and phospholipids. The most pronounced change was the replacement of polyunsaturated fatty acids of the 16 series, notably linoleic and its derivative, arachidonic acid, by those of the 18 series, notably eicosapentaenoic acid (20:5 18) and docosahexaenoic acid (22:6 18). The latter are the major polyunsaturates in marine animals whereas linoleic acid (18:2 18) and a linolenic acid (18:3 18) are the major ones in plant food.6 Eicosapentaenoic acid and docosahexaenoic acid can influence the metabolism of lipoproteins and eicosanoids (prostaglandins, thromboxanes, prostacyclins, and leukotrienes) in a way that might afford protection from coronary artery disease.

Dietary values

Before discussing the various studies that have investigated the effects of fish or fish oil consumption, it is necessary to relate these studies to the amounts of eicosapentaenoic acid and docosahexaenoic acid provided by these foodstuffs. The fat content of fish varies seasonally, geographically, and by species6 7 and is dependent on the marine food chain. White fish (cod, coley, plaice, haddock) contain about 1% fat by weight and oily fish (trout, salmon, mackerel, herring, pilchard, and sardine) contain 5–25% fat, depending upon when they are caught. In oily fish between 10% and 15% of the dietary energy is saturated fat compared with 1–2% in white fish. On an isocaloric basis oily fish provides about two to three times as much eicosapentaenoic acid and docosahexaenoic acid as white fish; 100 g of oily fish provides about 200 kcal (837 kJ), 1 g of eicosapentaenoic acid and 0.5–2 g of docosahexaenoic acid depending upon species; 100 g of white fish provides 96 kcal (402 kJ), 0.2 g eicosapentaenoic acid, and 0.3 g docosahexaenoic acid. A fish oil concentrate called MaxEPA (Seven Seas Health Care) has been used in some studies; 10 g provides 1.8 g eicosapentaenoic acid, 1.2 g docosahexaenoic acid, and 60 mg cholesterol.

Influence of the Eskimo diet on plasma lipoproteins

Greenland Eskimos have moderately low concentrations of low density lipoprotein (LDL) cholesterol.
terol, very low concentrations of low density lipoprotein (VLDL) triglycerides, and high concentrations of high density lipoprotein (HDL) cholesterol compared with Eskimos living on a western diet. The consumption of an Eskimo diet, mackerel (200 g/day) but not salmon, or fish oil supplements (20 g/day) slightly increased HDL cholesterol concentrations. Similar intakes considerably reduced triglyceride concentrations in both normal and hypertriglyceridaemic subjects by reducing the synthesis of both triglyceride and apoprotein B in VLDL. In vitro studies have shown that eicosapentaenoic acid and docosahexaenoic acid are reversible inhibitors of hepatic triglyceride synthesis.

Total plasma cholesterol concentrations are reduced by fish consumption but most of the reduction occurs in the VLDL fraction. Very high intakes of fish oil (90–120 g/day) do lower the concentration of both LDL cholesterol and LDL apoB by decreasing the rate of LDL synthesis. Such high intakes also prevent the rise in plasma cholesterol obtained with dietary cholesterol. At lower intakes (15 g/day), however, there is a tendency for LDL cholesterol and LDL apoB concentration to rise, particularly in patients with type V hyperlipoproteinaemia. A likely explanation is that a moderate intake of fish oil decreases hepatic triglyceride synthesis so that smaller than normal VLDL particles are secreted. These small particles are known to be more readily converted to LDL than the larger triglyceride rich ones. Thus on the one hand the reduction in VLDL synthesis by fish diets probably reduces the risk of atherosclerosis, whereas on the other the increase in LDL may be deleterious.

Antithrombotic and anti-inflammatory effects

Evidence is emerging that suggests that protection against atherosclerosis may be afforded by a mechanism that overrides the influence of plasma lipoproteins. For example, intimal hyperplasia of vein grafts in hypercholesterolaemic dogs was inhibited by feeding fish oil. A recent study showed that the development of coronary atherosclerosis in hyperlipidaemic pigs could be prevented by supplementing their diet with cod-liver oil. It was argued that protection was afforded by changes in eicosanoid metabolism. It has also been argued that dietary eicosapentaenoic acid and docosahexaenoic acid decrease the risk of arterial thrombosis and mitigate damage to the myocardium by reducing local inflammation and by maintaining collateral circulation.

Cyclo-oxygenase metabolites of arachidonic acid (20:4ω6), which have opposing effects in different locations, are believed to regulate platelet behaviour at the site of injury: thromboxane A2 produced by platelets causes platelet aggregation and vasconstriction; prostacycline PG12 produced by the vascular endothelium counteracts the effects of thromboxane A2. Coronary atherosclerosis decreases the capacity of the endothelium to produce prostacyclin so that the balance between thromboxane and prostacyclin is altered in a direction that increases the risk of coronary thrombosis. This view is supported by the observation that aspirin, which inhibits cyclo-oxygenase, halves the risk of myocardial infarction in patients with unstable angina.

Arachidonic acid is also converted to other important metabolites by platelets and neutrophils via the lipoxigenase pathway, which is not inhibited by aspirin. These metabolites, particularly leukotriene B4, are strongly chemotactic for leucocytes and may be responsible for the massive leucocyte migration into the myocardium that occurs in the vicinity of an experimental coronary occlusion. The ability of eicosapentaenoic acid to partially inhibit both cyclo-oxygenase and lipoxigenase pathways may explain why the infarct volume in dogs in which myocardial infarction was experimentally induced was lower in those treated with fish oil than in controls.

Dietary eicosapentaenoic acid and docosahexaenoic acid displace arachidonic acid from membrane phospholipids. They also decrease the conversion of linoleic acid to arachidonic acid. This incorporation of eicosapentaenoic acid into the erythrocyte membrane is accompanied by a reduction in whole blood viscosity and an increase in erythrocyte deformability—phemonena which are unrelated to eicosanoid production. In subjects given large amounts of fish or fish oil (usually in excess of 15 g/day), however, the capacity to produce thromboxane A2 and leukotriene B4 is also reduced, but the urinary excretion of prostacyclin PG12 metabolites is not decreased except in patients with atherosclerosis. Dietary eicosapentaenoic acid and docosahexaenoic acid decrease the formation of eicosanoids derived from arachidonic acid, probably by displacing arachidonic acid from precursor pools and by acting as competitive inhibitors of cyclo-oxygenase and lipoxigenase. Eskimos are liable to profuse nosebleeds and have extended template bleeding times; low platelet counts are also common. Reductions in platelet counts are occasionally seen with very high intakes of marine oil or fish oil. However, the regular consumption of oily fish (200 g/day) or fish oil supplements (20 g/day) prolongs template bleeding time.
after about three weeks of treatment without affecting the platelet count or the activity of clotting factors. Although there are similarities between the effects of consumption of oily fish and those obtained with aspirin, the reductions of thromboxane A2 production and platelet aggregation are modest compared with those brought about by small doses of aspirin. Furthermore, because aspirin potentiates the prolongation of bleeding time brought about by fish feeding it seems likely that a different mechanism is responsible especially as the urinary excretion of total prostaglandin metabolites is not significantly lower in Eskimos than in Danes.

Eicosanoids can be formed from eicosapentaenoic acid but they tend to be less active than those derived from arachidonic acid. For example, thromboxane A, and leukotriene B3 are less active but prostacyclin PGI is as active. Thromboxane B3 and leukotriene B4 have been detected after consumption of massive amounts of fish (400-800 g mackerel/day) or large amounts of fish oil (20-50 g/day). These observations support the hypothesis that eicosapentaenoic acid modulates the production of active eicosanoids.

**Potential hazards of high fish consumption**

Fish is a good source of selenium but is a poor source of vitamin E. Myocardial fibrosis occurred in domesticated animals fed on oily fish and in infants fed rancid cod-liver oil. This was caused by lipid peroxides. Precautions, therefore, need to be taken to guard against the formation of lipid peroxides, particularly in fish oil supplements, and to ensure an adequate intake of vitamin E. Mackerel, herring, and salmon gadoleic (20:1 ω11) and cetoleic (22:1 ω11) acids caused a transient myocardial lipoidosis when fed to experimental animals in large amounts. There is no evidence that these fish causes lipidosis in man, however. The salt content of many preserved fish (pickled herrings, kippers) is high, and this may have an undesirable effect on blood pressure. Pickled fish also contains high concentrations of tyramine and histamine and so should be avoided by patients treated with monoamine oxidase inhibitors. Excessive intakes of histamine in spoilt oily fish are believed to be the cause of scombroid toxicity. Fish are very susceptible to industrial pollution and are occasionally affected by naturally occurring toxins derived from the marine food chain.

**Conclusion**

It is necessary to eat large amounts of oily fish (> 200 g/day) or smaller amounts of fish oil (about 10 g MaxEPA/day) to affect plasma lipid concentrations and eicosanoid production. Generally, larger amounts of fish oil are needed to alter eicosanoid production than to lower plasma triglycerides. Consumption of α-linolenic acid, which is found in vegetable oils, does not have the same effects as dietary eicosapentaenoic acid and docosahexaenoic acid. A high intake of eicosapentaenoic acid and docosahexaenoic acid seems a plausible explanation for the low incidence of coronary artery disease among the Eskimos. Their extreme dietary practices are interesting because they shed light on the mechanisms leading to coronary artery disease; but it does not follow that such diets should be advocated for the general population.

Fish oil supplements have yet to be shown of value in the treatment of hypercholesterolaemia but they can be used to treat hypertriglyceridaemia. Multivariate analysis of several epidemiological studies suggests that plasma triglyceride concentrations are not an independent risk factor for coronary artery disease. None the less, there are several triglyceride bearing lipoprotein particles—chylomicrons, VLDL, and intermediate density lipoproteins (IDL)—and elevated plasma triglycerides may represent an increase in any of these particles. A raised concentration of plasma triglyceride caused by raised chylomicron concentration is not associated with an increased risk of atherosclerosis, whereas raised concentrations of plasma triglyceride associated with raised VLDL and IDL concentrations are, even when LDL concentrations are low. Several recent angiographic studies showed that high concentrations of plasma triglycerides associated with raised VLDL and IDL concentrations are, even when LDL concentrations are low. There is evidence that VLDLs are toxic to the vascular endothelium. Hypertriglyceridaemia is often accompanied by reduced concentrations of HDL cholesterol and a tendency to hypercoagulability. Since amelioration of hypertriglyceridaemia can both raise HDL cholesterol and reduce the level of certain clotting factors it is a potentially beneficial endeavour. This line of reasoning must, however, be tempered by the knowledge that moderate doses of fish oil not only reduce VLDL triglycerides but may also increase LDL concentrations at the same time. The overall assessment of risk will depend upon the size of these respective changes. Large quantities of fish oil seem free from this disadvantage but have the drawback of being too unpalatable for long term consumption.

There are reasons from believing that fish oil might be of benefit to patients with thrombogenic disorders, but the necessary clinical trials have yet to be
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be carried out. Fish oil does prolong bleeding time and the precise mechanism for this effect remains uncertain. It may well involve altered vascular reactivity rather than altered platelet behaviour, especially as a recent study showed that fish oil supplementation lowered blood pressure. 52 It should be borne in mind that fish oil may well potentiate the action of some drugs such as aspirin and ß blockers.

Formerly, fish was an important part of the British diet. It had the advantage of being available throughout the year. For religious reasons, it was eaten on Fridays and other fish days and almost daily during Lent. Lord Trenchard in his review of consumption patterns concluded that the decrease in fish consumption is one of the major changes in the British diet this century. 53 Cod-liver oil supplements were also widely used up until the 1950s. Fish contains several nutrients and foreign compounds that are scarce in other foods. For example, relatively small quantities of fish in the diet can contribute greatly to the total intake of retinol, vitamin D, taurine, and selenium. Consequently, fish might be providing some other yet to be identified protective factor. Selenium is a possible candidate, especially as selenium supplements prolong template bleeding time 54 and low serum selenium concentrations are associated with increased risk of coronary heart disease. 55

Kromhout et al recently claimed that eating fish once or twice weekly might reduce the risk of coronary heart disease. 56 In this prospective study a reduction in risk was found with an average daily intake of 30 g fish (two thirds white fish, one third oily), an amount that would provide far less eicosapentaenoic acid and docosahexaenoic acid than the minimum shown to influence either plasma lipid concentrations or eicosanoid production. This effect was independent of other known risk factors such as smoking, blood pressure, and plasma cholesterol concentration. The protective influence of fish consumption has been confirmed in one study in the United States 57 but not in studies in Hawaii 58 or Norway 59 where fish was consumed more frequently. In most cases the habitual diet of the subjects was assessed by a single 24 hour dietary recall. The assumption that one single dietary measurement is representative of an individual’s diet over the next twenty years is dubious especially as food consumption patterns are continually changing. The association between modest fish consumption and protection from coronary heart disease requires further confirmation and must be assessed in the light of total mortality statistics. It is also necessary to consider which foods were replaced by fish.

Despite these uncertainties it makes good sense to encourage people to eat more fish, but not fried or salted, in place of foods with a high content of saturated fat (such as cheese, meat products, and fatty meats). Such a change would also be in accord with the current dietary guidelines for the prevention of coronary heart disease. 50

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