Are fish oils beneficial in the prevention and treatment of coronary artery disease?1,2

Sonja L Connor and William E Connor

ABSTRACT The n−3 fatty acids of fish and fish oil have great potential for the prevention and treatment of patients with coronary artery disease. Unlike many of the pharmaceutical agents used in patients with coronary artery disease that have just a single mechanism of action, the eicosapentaenoic and docosahexaenoic acids of fish oil have multifaceted actions. One of their most important effects is the prevention of arrhythmias, with documentation derived from experiments in cultured myocytes, experiments in animals, epidemiologic correlations, and clinical trials. Especially important is the ability of these n−3 fatty acids to inhibit ventricular fibrillation and consequent cardiac arrest. Eicosapentaenoic acid has several antithrombotic actions, particularly in inhibiting the synthesis of thromboxane A2, the prostaglandin that causes platelet aggregation and vasocostriction. Fish oil retards the growth of the atherosclerotic plaque by inhibiting both cellular growth factors and the migration of monocytes. The n−3 fatty acids promote the synthesis of the beneficial nitric oxide in the endothelium. Experiments in humans indicate a profound hypolipidemic effect of fish oil, especially lowering of plasma triacylglycerol. Both very-low-density lipoprotein production and apolipoprotein B synthesis are inhibited by fish oil. Finally, fish oil has a mild blood pressure−lowering effect in both normal and mildly hypertensive individuals. These composite effects suggest a prominent therapeutic role for fish oil in the prevention and treatment of coronary artery disease. Am J Clin Nutr 1997;66(suppl):1020S−31S.

INTRODUCTION

The development of coronary artery disease can be depicted as a three-stage process. First, lipid-rich atherosclerotic plaques grow with the proliferation of smooth muscle cells and the infiltration of monocytes and macrophages from the blood. In the second stage the coronary artery disease becomes clinically manifest because the plaque grows to obstruct blood flow; in the third stage, the endothelial lining ulcerates and the resulting thrombus leads to myocardial infarction. The n−3 fatty acids from fish and fish oil can inhibit the growth of atherosclerotic plaques, checking the tendency to thrombosis and protecting the damaged myocardium from a fatal arrhythmia.

Fish and fish oils contain the very-long-chain and highly polyunsaturated n−3 fatty acids, which are derived from phytoplankton, the base of the food chain in the oceans, lakes, and rivers (1). Phytoplankton synthesize the n−3 fatty acids eicosapentaenoic acid (20:5n−3; EPA) and docosahexaenoic acid (22:6n−3; DHA), which are subsequently incorporated into fish, shellfish, and sea mammals. These fatty acids have profound biological and biochemical effects in the body. Despite a wealth of scientific information [a recent review listed > 120 references about cardiovascular effects alone (2)], clinical interest in n−3 fatty acids has not been high in the United States although considerable attention is paid to their use in Europe and Japan. This review will focus on the considerable and underrated therapeutic benefits of the n−3 fatty acids.

In the 1950s it was discovered that polyunsaturated vegetable oils containing the n−6 fatty acid linoleic acid (18:2n−6) had a pronounced plasma cholesterol-lowering effect, yet the mechanism of this action has remained obscure (1). In those early days, it was noted that fish oil, which was also polyunsaturated, had a similar hypcholesterolemic effect. No mention was made of the fact that fish oil contained very-long-chain n−3 fatty acids (DHA and EPA) and that these might act differently from the n−6 fatty acids of vegetable oils. These early data about fish oil lay fallow until the pioneering observations of Bang and Dyerberg (3) focused special attention on EPA and DHA in marine oils. They observed a lower coronary mortality of Greenland Eskimos whose diet was especially rich in marine oils compared with Danish people eating a diet high in saturated fat (4). Later it was found that not only were these n−3 fatty acids cholesterol lowering, but they also had a profound plasma triacylglycerol-lowering effect, especially in hypertriglyceridemic patients (5−7). More than a decade of research in humans, animals, profused organs, and tissue cultures has firmly documented the mechanisms of the hypolipidemic actions of these n−3 fatty acids from fish and, furthermore, has shown that these fatty acids have many other beneficial effects in cardiovascular disease.

This review focuses on seven different areas of research, which will help to answer the question about the potential benefits of n−3 fatty acids from fish oil: 1) antiarrhythmic actions, 2) thrombosis, 3) experimental animal studies to inhibit the growth of atherosclerotic plaques, 4) lipid and lipoprotein disorders, 5) diabetes mellitus, 6) hypertension, and 7) clinical trials and epidemiologic observations on coronary disease prevention.

1 From the Division of Endocrinology, Diabetes and Clinical Nutrition, Department of Medicine, Oregon Health Sciences University, Portland.
2 Address reprint requests to WE Connor, Division of Endocrinology, Diabetes and Clinical Nutrition, Department of Medicine, Oregon Health Sciences University, Portland, OR 97201-3098. E-mail: connors@ohsu.edu.

ANTIARRHYTHMIC ACTIONS

Sudden death from ventricular arrhythmia is a much dreaded complication in patients with coronary artery disease. Several experimental studies have addressed this problem with the use of n-3 fatty acids from fish oil. McLennan et al (8) used coronary artery ligation in rats to produce an in vivo model of ventricular fibrillation and myocardial infarction. They found that the number of ventricular ectopic beats and duration of tachycardia or fibrillation increased when rats were fed sheep kidney fat (a saturated fat) compared with tuna fish oil, a rich source of n-3 fatty acids. The rats fed tuna fish oil had a significantly reduced incidence and severity of arrhythmias. In another study, ventricular fibrillation was prevented by fish oil during both the occlusion of the coronary artery and during reperfusion (9).

In other experiments, Hallaq et al (10) used isolated neonatal cardiac myocytes (from hearts of 1-d-old rats) as a model for the study of cardiac arrhythmogenic factors as modified by n-3 fatty acids. They incubated isolated myocytes (for 3-5 d) in a culture medium enriched with arachidonic acid or EPA. The arachidonic acid–enriched myocytes developed toxic cytosolic calcium concentrations on exposure to ouabain, whereas in EPA-enriched myocytes physiologic calcium concentrations were preserved. An increase of EPA in the membrane phospholipids was shown with a small reduction in arachidonic acid in myocytes fed EPA. A second study by the same researchers further indicated the mechanism of action of the fish oil fatty acids in preventing the arrhythmias of these isolated myocytes (11). It was found that n-3 fatty acids prevented a calcium-depleted state in the myocytes caused by the L-type calcium channel blocker nifedipine. The protective effects of the n-3 fatty acids appeared to result from their modulatory effects on nifedipine-sensitive L-type calcium channels. These studies indicated a definite beneficial effect of dietary n-3 fatty acids on the heart: the prevention of cardiac arrhythmias in animals.

More recently, fatty fish consumption was shown to prevent cardiac arrest from ventricular fibrillation in coronary patients. This is the cause of death in most patients with coronary artery disease and accounts for the 20-30% of persons whose first indication of coronary disease is cardiac arrest. A recently published study from the University of Washington compared the effects of eating fish with the incidence of cardiac arrest (12). There was a 50% reduction in the risk of cardiac arrest in people who consumed at least one fatty fish meal per week. A typical fatty fish would be salmon. Other fatty fish include sardines, mackerel, and Chilean sea bass. Even those who consumed fish that are less fatty such as tuna also benefited because all fish and shellfish contain the beneficial n-3 fatty acids.

This protection against cardiac arrest was due to the n-3 fatty acids EPA and DHA. The benefits of eating fish were measured biochemically in the fatty acids of the red blood cells. If the red blood cells had a relatively low amount of the n-3 fatty acids, 3.3% of total fatty acids, there was a much greater risk of cardiac arrest than in those individuals whose red blood cell n-3 fatty acids were ≥ 5% of the total fatty acids. In other words, there was a 70% reduction in the risk of cardiac arrest in those persons with the higher red blood cell n-3 fatty acid content.

This information is particularly valuable because it fits in nicely with the study conducted several years ago by Burr et al (13) in Wales, in which men who were advised to eat fatty fish or to consume some fish oil capsules had a 29% reduction in total deaths, and, in particular, deaths from coronary artery disease. Thus, the evidence becomes stronger and stronger that even some fish and n-3 fatty acid consumption on a consistent basis (at least one serving a week) will prevent many deaths from coronary artery disease.

THROMBOSIS

n-3 Fatty acids invariably have an antithrombotic effect, particularly a diminution in thromboxane A₂, which produces platelet aggregation and vasoconstriction (1, 14). Platelet reactivity and adhesion are considerably reduced after fish oil ingestion (15). There are also reductions of plasminogen activator inhibitor 1, fibrinogen, and t-plasminogen activator, and increases in platelet survival and bleeding time with n-3 fatty acid consumption (2). Enhanced fibrinolysis has also been observed. Perhaps even more significant is the finding from a study in baboons that n-3 fatty acids eliminate both vascular thrombus formation and vascular lesions after vascular injury (16). Fish oil blocked thrombus formation at sites of surgical carotid endarterectomy in the treated baboons.

The function of the endothelium, important in both thrombosis and atherosclerosis, is affected by n-3 fatty acids (14). The production of prostacyclin is enhanced and endothelial-derived relaxation factor or nitric oxide, which is depressed in atherosclerotic disease, is greatly increased by the n-3 fatty acids of fish oil (17-19).

EXPERIMENTAL ATHEROSCLEROSIS AND FISH OIL

When menhaden oil was incorporated into atherogenic diets fed to rhesus monkeys, aortic plaques were fewer and their cholesterol content much less (20). Because plasma lipid concentrations were roughly similar in control groups, the inhibition of atherosclerosis must have involved other mechanisms operative in the vessel wall itself. Carotid atherosclerosis was likewise inhibited. Pigs fed an atherogenic diet had much less coronary atherosclerosis when also given cod liver oil containing n-3 fatty acids (21). There is good evidence that DHA and EPA in the diet from fish oil are incorporated into even advanced human atherosclerotic plaques (22). They are present in gruel plaques as components of cholesterol esters and phospholipids. The incorporation of EPA and DHA from plasma lipoproteins is detectable within 1 wk of fish oil feeding. Perhaps the inhibition of atherosclerosis occurs because EPA and DHA inhibit cellular growth in the arterial wall (23). Atherosclerosis cannot develop even after injury and the influx of low-density-lipoprotein (LDL) cholesterol and cholesterol ester unless there is also a cellular reaction. The two important cells in atherosclerosis are smooth muscle cells and macrophages. Because of the suppression of cellular growth factors by n-3 fatty acids, proliferation of smooth muscle cells is inhibited (24). Likewise, macrophage infiltration into the vessel wall is lessened by n-3 fatty acids (20). Even the initial lesion of atherosclerosis—the fatty streak—develops less under the influence of dietary n-3 fatty acids.
EFFECTS ON PLASMA LIPIDS AND LIPOPROTEINS

A major effect of dietary n-3 fatty acids from fish oil is on plasma concentrations of lipids and lipoproteins (6). The science in this area is clear: n-3 fatty acids lower plasma very-low-density lipoprotein (VLDL) and triacylglycerol concentrations through depression of synthesis of triacylglycerol in the liver. n-3 Fatty acids also suppress postprandial lipemia, the chylomicron remnants of which are considered atherogenic. Effects on LDL and high-density lipoprotein (HDL) have been variable. HDL either increases or does not change. Like the drug gemfibrozil, n-3 fatty acids may cause an increase in LDL as they lower the plasma triacylglycerol concentration in some hyperlipidemic states such as familial combined hyperlipidemia.

Theoretically, as has been shown in one experiment described later, the ideal nutritional program to reduce plasma lipid and lipoprotein concentrations maximally would be a diet very low in cholesterol and saturated fat, which would upregulate the LDL receptor and reduce LDL plasma concentrations, and a diet containing fish oil, which would suppress VLDL production and lower plasma triacylglycerol concentrations.

Effects of fish oil in normal subjects

As other reviews have summarized, the n-3 fatty acids of fish have a great effect on plasma lipids and lipoproteins even in normal subjects (1, 6). The principal action is on plasma triacylglycerol and VLDL concentrations. This hypolipidemic action is well illustrated in a study of 12 healthy adults (6 men and 6 women) who were given three different diets fed in random order for 4 wk each: a saturated control diet, a salmon diet containing considerable amounts of n-3 fatty acids, and a vegetable oil diet high in n-6 fatty acids (25). Both the salmon diet and the vegetable oil diet decreased plasma cholesterol similarly, from 4.9 to 4.2 mmol/L (188 to 162 mg/dL). Both diets reduced LDL, from 3.3 to 2.8 mmol/L (128 to 108 mg/dL). HDL-cholesterol concentrations were not changed by the salmon diet. The salmon diet decreased VLDL-cholesterol concentrations; changes in plasma triacylglycerol were most striking, however, decreasing from 0.9 to 0.6 mmol/L (76 to 50 mg/dL). The polyunsaturated vegetable oils did not lower VLDL or triacylglycerol concentrations.

Studies in hyperlipidemic patients

Because of the hypolipidemic effect of n-3 fatty acids in normal subjects, it seemed reasonable to test the effects of these fatty acids in hyperlipidemic patients (7). The two groups of hyperlipidemic patients selected for this study were characterized by hypertriglyceridemia, because previous studies showed that decreases in plasma triacylglycerol and VLDL appear to be a unique effect of n-3 fatty acids from fish oil.

Twenty hypertriglyceridemic patients volunteered for the study (8 men and 12 women). Ten of the patients had elevated concentrations of both VLDL and LDL consistent with the type II-b phenotype. Their mean plasma lipid concentrations at time of entry were 8.8 mmol/L (337 mg/dL) for cholesterol and 4.0 mmol/L (355 mg/dL) for triacylglycerol. Clinically, many of these patients had familial combined hyperlipidemia, a disorder characterized by a strong disposition to the development of coronary artery disease and by overproduction of lipoproteins, particularly VLDL. The other 10 patients had apparent type V hyperlipidemia, characterized by increased chylomicrons and greatly increased VLDL concentrations in the fasting state. Their mean plasma lipid concentrations at entry were 13.4 mmol/L (514 mg/dL) for cholesterol and 32.5 mmol/L (2874 mg/dL) for triacylglycerol. Four of the type V patients had concomitant, non-insulin-dependent diabetes mellitus and two had adult-onset, insulin-dependent diabetes mellitus. Their insulin doses and diabetic control remained constant throughout the study despite the salmon oil.

The type V phenotype is characterized by both overproduction of VLDL and impaired clearance of the remnants of chylomicron and VLDL metabolism. Clinically, type V patients have chylomicronemia syndrome, characterized by episodes of abdominal pain from enlargement of abdominal viscer (hepatomegaly and splenomegaly) and by episodes of acute pancreatitis. These patients also suffer from eruptive xanthomata, neuropathy, and lipemia retinalis. Although LDL concentrations are low in type V patients, the presence of the atherogenic remnant particles predisposes these patients to the development of atherosclerotic complications, including coronary artery disease.

Special care was taken to make certain that the patients were in steady state conditions before entry. Steady state was defined as constant body weight and diet and the absence of any residual hypolipidemic drug effect. Most of the patients had not been receiving any hypolipidemic drugs just before the study. In patients previously given drugs, these were discontinued and plasma lipid concentrations monitored until predrug concentrations were attained.

Two different control diets were used for the two groups of hypertriglyceridemic patients, depending on the phenotype of hyperlipidemia. Patients with type II-b hyperlipidemia received their usual low-cholesterol (100 mg/d), low-fat (20-30% of total energy) diet. Subsequent dietary periods for type II-b patients consisted of a fish oil diet for 4 wk, followed in some patients by a 4-wk period of a diet high in a vegetable oil containing a predominance of n-6 fatty acids. Both of these diets were balanced for cholesterol content (~250 mg/d) and contained 30% of energy as fat. The diets in all periods were euergetic, such that the subjects neither gained nor lost weight.

For patients with type V hyperlipidemia, the control diet consisted of a very-low-fat diet (5%) to lower plasma triacylglycerol concentrations maximally. The next dietary interval contained fish oil at 20% or 30% of total energy. Finally, a polyunsaturated vegetable oil diet was also provided, which contained 20-30% of energy as fat and 200-300 mg cholesterol/d. Both the fish oil and the vegetable oil diets were initially used cautiously in the type V patients to minimize the risk of hepatosplenomegaly, abdominal pain, and acute pancreatitis.

The salmon oil diet provided ~20 g n-3 fatty acids/d for a 10 878-KJ (2600-kcal) intake, with 30% of total energy as fat. On the other hand, the vegetable oil diet provided ~47 g linoleic acid, an n-6 polyunsaturated fatty acid. Thus, the fish oil diets actually provided 43-64% less total polyunsaturated fatty acids gram for gram than did the vegetable oil diet.

The fish oil diet decreased plasma LDL-cholesterol concentrations in the type II-b patients by 0.7 mmol/L (26 mg/dL). Of individual lipoprotein cholesterol changes, the decline of VLDL cholesterol was most striking; but LDL and HDL cho-
lesterol also decreased. Plasma triacylglycerol changes were even greater than the cholesterol changes with the fish oil diet, decreasing from 8.7 to 3.1 mmol/L (334 to 118 mg/dL). This occurred largely because of the change in VLDL triacylglycerol, which was lowered from 2.4 to 0.6 mmol/L (216 to 55 mg/dL).

The highly polyunsaturated vegetable oil diet had much less effect on VLDL cholesterol and triacylglycerol. LDL values were similar; in contrast, HDL cholesterol was higher after the vegetable oil diet. Plasma apolipoprotein (apo) changes reflected the lipoprotein lipid changes. In the type II-b patients, there were significant reductions in apo B and C-III concentrations in the fish oil period, which paralleled the declines in LDL and VLDL concentrations.

In the type V patients, effects of the fish oil diet were even more striking (Figure 1 and Figure 2). With consumption of the very-low-fat control diet, initial plasma lipid concentrations in these patients declined considerably but still remained greatly elevated. Many of these patients still had milky-appearing plasma, with chylomicrons present in the fasting state. The first change to occur in these patients after the fish oil diet was the virtual disappearance of fasting chylomicronemia, which had been present in five of the patients. During the fish oil diet period, total plasma triacylglycerol decreased from a control value of 15.3 to 3.2 mmol/L (1353 to 281 mg/dL), a drop of 79% (Figure 1). VLDL triacylglycerol decreased similarly, from 12.3 to 1.9 mmol/L (1087 to 167 mg/dL). Plasma cholesterol concentrations declined into the normal range after the fish oil diet, from 9.7 to 5.4 mmol/L (373 to 207 mg/dL) (Figure 2). Most of this total plasma cholesterol decrease occurred as the result of marked changes in the amount of VLDL cholesterol, which decreased from 7.0 to 1.8 mmol/L (270 to 70 mg/dL). Of interest was the 48% concomitant rise of LDL cholesterol, from the low value of 2.2 to 3.3 mmol/L (84 to 125 mg/dL). Apo concentrations changed to reflect the altered lipoprotein lipid concentrations. Apo A-I concentrations did not change, whereas apo B, C-III, and E all decreased significantly.

When the n-6-rich vegetable oil replaced the fish oil in the diets of eight type V patients, all patients had increases in plasma triacylglycerol concentrations within 3 to 4 d. After 10 to 14 d of the vegetable oil feeding, mean plasma triacylglycerol values rose 198% and VLDL triacylglycerol increased from 1.9 to 6.2 mmol/L (171 to 550 mg/dL). Plasma cholesterol also increased, from 5.1 to 6.9 mmol/L (195 to 264 mg/dL). LDL-cholesterol concentrations, on the contrary, were reduced 28% by the vegetable oil diet: another indication that the metabolic abnormality of the type V phenotype was worsening. Because of enhanced hypertriglyceridemia and the risk of development of abdominal pain typical of this type V disorder, the vegetable oil feeding period was discontinued prematurely in all type V patients.

Implications of the fish oil studies in hypertriglyceridemic patients

In the 20 hypertriglyceridemic patients (7), fish oil incorporated in the diet led to an even more profound hypolipidemic effect than had been observed in normal subjects. Plasma triacylglycerol concentrations decreased in each of the 20 pa-
tients, a 79% decrease in the type V patients and a 64% decrease in the type II-b patients; plasma cholesterol concentrations decreased 45% and 27%, respectively. In the 12 normal subjects previously investigated (25), decreases were less for plasma triacylglycerol (38%) and much less for plasma cholesterol (14%). Apparently, the greater the hypertriglyceridemia, the greater the reductions brought about by dietary fish oil in plasma lipids, especially VLDL.

These results may have considerable therapeutic importance for patients with severe and moderate hypertriglyceridemia. The only dietary treatment to date for severely hypertriglyceridermic type V patients has been the very severe and therapeutically difficult restriction of dietary fat to between 5% and 10% of total energy in an effort to approach normal plasma triacylglycerol concentrations. Most Americans find this possible to do on a short-term basis, but difficult in the long term because they are accustomed to eating higher quantities of fat, i.e., ~34% of total energy. Hitherto, all fatty foods have been contraindicated in type V hyperlipidemia. The findings of this study suggest that some fatty, and even high-cholesterol, foods (e.g., fish or even shellfish) containing marine n-3 fatty acids are appropriate for ingestion and may produce further triacylglycerol lowering over and above that resulting from a very-low-fat diet.

Other studies in familial combined hyperlipidemia and in type IV hyperlipidemia have shown increases in LDL and apo B while plasma VLDL and triacylglycerol values were declining (6, 26, 27). Such LDL increases have also occurred in type IV patients given the drug gemfibrozil. Perhaps this is an expected physiologic action when hypertriglyceridemia is being corrected. Should the LDL concentrations become abnormally high after either drugs or fish oil, then further therapy of the LDL specifically is warranted (i.e., bile acid binding resins or lovastatin). Fish oil has also produced plasma cholesterol and triacylglycerol lowering in type III patients and in familial hypercholesterolemia (28).

Reduction of postprandial lipemia after fatty meals

It has been observed that fish oils markedly decrease the usual chylomicronemia that follows fatty meals (29, 30). In other words, fat tolerance is greatly improved (Figure 3). This improvement could result from diminished absorption, slower synthesis, slower entry of chylomicrons into the circulation, or, alternatively, more rapid removal of the chylomicrons that do appear in the circulation. There is no evidence for diminished absorption and fat balance studies have not shown increased fat excretion in stools after dietary periods enriched with fish oil. Whether reduced chylomicron production or enhanced removal of chylomicrons is responsible has not yet been completely clarified. Fish oil feeding produces small VLDL particle size in animals. Smaller VLDL has enhanced catabolism. Perhaps, after a background diet of fish oil, chylomicrons are smaller in size and hence more rapidly catabolized with a much flatter fat tolerance curve.

Mechanism of the hypolipidemic effects of fish oil

How n-3 fatty acids exert their effects to decrease concentrations of plasma triacylglycerol and cholesterol has been tested in humans in two different sets of experiments: 1) the inhibition by fish oil of the usual hypertriglyceridemia that inevitably results when a high-carbohydrate diet is suddenly fed to humans, and 2) the effects of fish oil on apo B, VLDL, and LDL production rates and turnovers. Studies in animals and cultured hepatocytes will be described later.

Fish oil and the inhibition of carbohydrate-induced hypertriglyceridemia

The well-known phenomenon of carbohydrate-induced hypertriglyceridemia is a physiologic response. In this model, VLDL triacylglycerol synthesis is stimulated as the dietary carbohydrate intake abruptly increases. The increased VLDL synthesis leads to hypertriglyceridemia, which may persist for many weeks. If n-3 fatty acids do inhibit VLDL synthesis, then the usual carbohydrate-induced hypertriglyceridemia should not occur when fish oil is incorporated into the high-carbohydrate diet.

Seven mildly hypertriglyceridemic but otherwise healthy subjects (aged 22–54 y) were fed three different experimental diets (31). Each was composed of a liquid formula plus three bran muffins per day to supply fiber. The baseline diet contained 45% of energy from carbohydrate. The two high-carbohydrate diets (control and fish) contained 15%, 10%, and 75% of energy as fat, protein, and carbohydrate, respectively. In the baseline and high-carbohydrate control diets, a blend of peanut oil and cocoa butter provided the fat, which was replaced by fish oil (in the form of a commercially available marine lipid concentrate) in the high-carbohydrate fish oil diet. The total amount of fish oil consumed per day was 50 g (in a 12 552-kJ, or 3000-kcal, diet), equivalent to ~48.8 mL (3.3 tablespoons) oil. This amount provided 8.5 g EPA and 5.5 g DHA.

The three experimental diets were fed in three different sequences in a clinical research center (Figure 4). In the first sequence, the high-carbohydrate control diet preceded the high-carbohydrate fish oil diet (Figure 4A). In the second sequence, the high-carbohydrate diet was given for 20 instead of 10 d to show that the hypertriglyceridemia did not spontaneously resolve after the first 10 d. It was then followed by the
FISH OILS AND CORONARY ARTERY DISEASE

The line be removed

(#{149} -

1.8

0

0)

(69

103

an

doubled

from

the

control, 

apo

C-Ill

triglyceride-

baseline

cholesterol

concentrations;

apo A-I and E concentrations did not change. The high-carbohydrate fish oil diet decreased apo A-I and apo C-III concentrations; apo B and E concentrations did not change.

The incorporation of corn oil in place of fish oil into the high-carbohydrate regimen failed to prevent the induced hypertriglyceridemia. For the three subjects who participated in this study, triacylglycerol concentrations were as follows: baseline, 1.1 ± 0.3 mmol/L (93 ± 23 mg/dL); high-carbohydrate control, 2.2 ± 0.7 mmol/L (196 ± 58 mg/dL); high-carbohydrate fish oil diet (Figure 4B). In the third sequence, the fish oil was fed first with the high-carbohydrate diet for 25 d and then removed to permit the effects of the high-carbohydrate diet to be manifest for the next 15 d (Figure 4C). Three subjects were studied with the first sequence, and two subjects each were studied with the second and third sequences.

In all seven subjects, the high-carbohydrate control diet increased plasma triacylglycerol concentrations over the baseline diet from 1.2 to 2.2 mmol/L (from 105 to 194 mg/dL) (31). The magnitude of the carbohydrate-induced hypertriglyceridemia correlated significantly with each individual’s baseline triacylglycerol concentration. The rise in plasma triacylglycerol concentration was complete by day 5 and resulted almost entirely from an increase in the VLDL triacylglycerol fraction, which more than doubled during the control diet: from 0.8 to 1.8 mmol/L (69 to 156 mg/dL) (Figure 5). Although the total plasma cholesterol concentration did not change, VLDL-cholesterol concentrations approximately doubled: from 0.5 to 0.9 mmol/L (18 to 34 mg/dL), and HDL cholesterol was reduced: from 1.3 to 1.1 mmol/L (49 to 41 mg/dL).

When the fat of the high-carbohydrate control diet was replaced isoenergetically with fish oil, the elevated plasma triacylglycerol concentration was reduced from 2.2 to 0.9 mmol/L (from 194 to 75 mg/dL), a decrease of 61%. This decrease usually occurred within 3 d. Once again, changes in VLDL triacylglycerol concentrations were largely responsible for this effect [from 1.8 to 0.4 mmol/L (156 to 34 mg/dL)]. Total cholesterol concentrations decreased insignificantly during the high-carbohydrate fish oil diet [from 4.5 to 4.0 mmol/L (172 to 153 mg/dL)], primarily because of the drop in VLDL-cholesterol concentrations [from 0.9 to 0.3 mmol/L (34 to 12 mg/dL)].

The hypertriglyceridemia persisted even when the period of carbohydrate induction was prolonged from 10 to 20 d and did not significantly decrease until fish oil was incorporated into the diet (Figure 4B). When the high-carbohydrate fish oil diet followed the baseline diet, the plasma triacylglycerol concentration did not rise, but the concentration increased when the high-carbohydrate control diet followed the high-carbohydrate fish oil diet (Figure 4C). The high-carbohydrate control diet decreased concentrations of apo B and increased apo C-III concentrations; apo A-I and E concentrations did not change. The high-carbohydrate fish oil diet decreased apo A-I and apo C-III concentrations; apo B and E concentrations did not change.

FIGURE 4. The effects of the baseline (●) and the control (○ - ○) and fish oil (□ - □) diets on plasma triacylglycerol concentrations. Shown are the reversal of carbohydrate-induced hypertriglyceridemia by dietary fish oil (A, n = 3), the persistence of the hypertriglyceridemia (throughout 20 d) and the subsequent reversal by fish oil (B, n = 2), and the prevention of carbohydrate-induced hypertriglyceridemia by fish oil (C, n = 2). CHO, carbohydrate. Adapted from reference 31.

FIGURE 5. Effects of high-carbohydrate control and fish oil diets on plasma VLDL triacylglycerol concentrations in seven subjects. Adapted from reference 31.
drate corn oil, 2.4 ± 1.0 mmol/L (215 ± 90 mg/dL); and high-carbohydrate fish oil, 1.0 ± 0.1 (86 ± 10 mg/dL).

In this study, dietary fish oil not only prevented but also rapidly reversed the dietary carbohydrate-induced elevations in plasma triacylglycerol and VLDL concentrations, whereas the n-6-rich corn oil had no effect. Because the primary difference between corn oil and the commercial fish oil preparation is the type of polyunsaturated fatty acids present (corn oil: 57% 18:2n-6; the commercially available fish oil preparation: 32% n-3 fatty acids), the difference in effect was due to the n-3 fatty acids in the fish oil (ie, EPA and DHA). This finding implies a probable inhibitory effect of n-3 fatty acids on hepatic VLDL production. 

Fish oil and the synthesis and turnover of apo B, VLDL, and LDL

The hypothesis that n-3 fatty acids probably reduce VLDL concentrations by inhibiting VLDL synthesis was further supported by studies designed to elucidate further mechanisms of the hypotriglyceridemic effect of n-3 fatty acids. Dietary fish oil probably affected either the synthesis or the removal of VLDL. The rates of flux and turnover of VLDL triacylglycerol were measured after injection of [3H]glycerol into persons studied under two dietary protocols, one containing fish oil and the other containing fats typical of the US diet (32). This technique permits the calculation of both synthesis and removal rates of VLDL.

Ten male subjects were selected on the basis of having a wide range of fasting plasma triacylglycerol concentrations, from 0.4 to 47.2 mmol/L (34 to 4180 mg/dL), so that the hypothesis about the mechanism of action of dietary fish oils could be tested in subjects with greatly different pool sizes of plasma triacylglycerol. Liquid formula diets containing 15–20% fat, 65–75% carbohydrate, and 10–15% protein were fed during both the control and the fish oil dietary periods. The two diets differed only in the type of fat they contained. In the control diet, a blend of cocoa butter and peanut oil (1:2) was incorporated into the formulas. The fish oil diet containing the commercial preparation was taken in three divided doses daily and was not mixed into the formulas. The principal difference between the two diets was the higher content of linoleic acid (18:2n-6) in the control diet and the presence of n-3 fatty acids in the fish oil diet. The former diet contained virtually no n-3 fatty acids, whereas the latter provided ∼17 g/d of these highly polyunsaturated fatty acids.

The experimental diets were consumed for a period of 3–5 wk before the actual VLDL turnover procedure was conducted. This time was needed for plasma triacylglycerol concentrations to stabilize, particularly in subjects whose triacylglycerol concentrations were above normal. Seven subjects consumed the control diet first, followed by the fish oil diet; in the remaining three subjects, the order was reversed. The order in which the diets were administered did not affect the results.

The isoenergetic substitution of fish oil for the control vegetable fat produced the expected significant reductions in the total and lipoprotein lipid concentrations in all 10 subjects. Total cholesterol concentrations for all 10 subjects fell from 5.1 to 3.7 mmol/L (from 195 to 144 mg/dL), a reduction of 22%. Decreases in VLDL concentrations accounted for most of the drop in plasma cholesterol [from 2.2 to 0.6 mmol/L (83 to 21 mg/dL)]. LDL-cholesterol concentrations did not change significantly, whereas HDL-cholesterol concentrations fell from 0.8 to 0.6 mmol/L (from 31 to 24 mg/dL). All of these changes were evident in both the normal and the hypertriglyceridemic groups.

After the administration of [3H]glycerol and its incorporation into the triacylglycerol of VLDL, the decay curves were analyzed by computer models, so that VLDL synthesis and turnover could be calculated. Typical turnover curves for one subject after the control and fish oil diets are displayed in Figure 6. The incorporation of n-3 fatty acids into the diet caused a 72% decrease in the VLDL triacylglycerol pool size (from 11.4 to 3.2 g, P < 0.025). The decreased pool size was associated with a 45% reduction in the VLDL triacylglycerol synthetic rate (23 to 12.6 mg · h⁻¹ · IBW⁻¹, where IBW is ideal body weight; P < 0.005) and a 45% decrease in the residence time of VLDL triacylglycerol in the plasma (5.8 to 3.2 h, P < 0.005). The reciprocal of the residence time is the fractional catabolic rate, which was increased by 65% (0.23 to 0.38 h⁻¹, P < 0.005). There was a significant rise in the ratio of cholesterol to triacylglycerol in VLDL during the fish oil interval (0.18 to 0.25, P < 0.05). Finally, the ratio of the fast to the slow synthetic pathways did not change with fish oil feeding. The same trends were seen in both normal and hypertriglyceridemic patients. Similar results were also found through use of a slightly different dietary plan and with the labeling of VLDL apo B with 125I (33). There was a striking reduction of VLDL synthesis and enhanced turnover.

Direct evidence that the hepatic synthesis of triacylglycerol and VLDL is suppressed by n-3 fatty acids from fish oil was supplied by three in vitro studies of perfused rat liver and of liver cells from rats and rabbits in primary culture (34–36). In all of these studies triacylglycerol synthesis was reduced. In one, enhanced ketone body production resulted; in the others there was a diversion of n-3 fatty acids from triacylglycerol synthesis into phospholipid synthesis as illustrated in one study (36). When one adds the net results of the human and animal studies together, the evidence is strong that suppression of VLDL and triacylglycerol synthesis is a primary mechanism of
the hypolipidemic effects of n-3 fatty acids, along with an increased fractional catabolic rate of VLDL.

**Fish oil and LDL turnover**

Radiolabeled LDL turnover studies have been carried out in normal subjects given fish oil. It was shown that there was decreased synthesis of LDL and a tendency for an increased fractional catabolic rate (37). Ventura et al (38) showed enhancement of LDL receptor activity after the administration of fish oil in the rat. This result fits well with the increased fractional catabolic rate observed in normal human subjects. It seems clear that n-3 fatty acids from fish oil affect all of the major lipoproteins with the exception of HDL.

**Synergistic action of n-3 fatty acids with a diet low in saturated fats**

How do the n-3 fatty acids from fish fit into the context of the generally recommended diets to prevent coronary artery disease? Such diets are low in saturated fat and lower plasma cholesterol and LDL (39). These diets up-regulate the LDL receptor, which promotes the removal of LDL from the plasma. The n-3 fatty acids, as was previously emphasized, depress the synthesis of VLDL triacylglycerol. The data in Table 1 emphasize this twofold action of low dietary saturated fat and high dietary n-3 fatty acids (40). Note that plasma cholesterol declined 28% and plasma triacylglycerol decreased 32% from a diet combining both features: low in saturated fat and high in n-3 fatty acids. LDL was reduced 30% and VLDL triacylglycerol 47%.

**Summary and conclusions: fish oil effects on plasma lipids and lipoproteins**

The n-3 fatty acids from fish oil and fish have a remarkable effect on the synthesis and clearance of triacylglycerol-rich lipoproteins, especially VLDL and chylomicrons. Even LDL synthesis and clearance are affected. Because of these significant effects on lipoprotein synthesis and clearance, beneficial effects of fish oil have been shown in a variety of hyperlipidemic states, especially those conditions with hypertriglyceridemia and chylomicronemia. Therapeutic implications for fish oil are especially positive in type V, type IV, and type III hyperlipidemia. Recent data indicate a similar effectiveness in hypertriglyceridemic diabetic patients without an effect on glucose homeostasis as will be discussed later.

Difficulty in interpreting the effects of fish oil in various hyperlipidemic patients has occurred because of vastly different experimental conditions. In some studies, fish oil was simply added as a supplement to the usual diet in doses of 6-8 g/d. In the control period a placebo oil such as olive or safflower oil was not always used. In other studies, there was the customary diet plus the use of an appropriate placebo oil. Furthermore, various kinds of fish oil have been used, some containing a considerable amount of cholesterol and saturated fat. Newer fish oils have much less saturated fatty acids and have higher concentrations of n-3 fatty acids as well as a low cholesterol content.

Some conclusions have emerged from the wide variety of studies, most of which were not metabolically controlled. Fish oil is most effective when administered at 6% to 30% of total energy and when the diet is metabolically controlled. In studies with these conditions, LDL lowering usually occurred as well as profound VLDL and triacylglycerol lowering in normal subjects and in a wide variety of hyperlipidemic states. In our experience, this lowering of plasma cholesterol concentrations occurs in patients with types V, II-a, II-b, III, and IV hyperlipidemia, with the most dramatic results occurring in the type V patients who do not tolerate any other kind of dietary fat (6, 7, 41). In the literature and in our experience, HDL concentrations are not greatly affected by fish oil. Clearly the use of fish oil in hyperlipidemia must be individualized as to both use and dosage. Lower doses of fish oil (8-15 g/d) in particular lower plasma triacylglycerol concentrations.

Why plasma LDL and apo B concentrations have at times increased after fish oil when at the same time plasma VLDL and triacylglycerol concentrations decreased is a most challenging question and may relate to fundamental aspects of VLDL-LDL metabolism. Normally, LDL is derived from two sources: conversion from VLDL and direct synthesis from the liver. The catabolism of VLDL is likewise in two directions through intermediate-density lipoprotein (IDL). IDL may be removed by the apo E receptor in the liver or converted to LDL. The experiments of Huff and Telford (42) suggest why in some instances fish oil might increase LDL turnover studies in miniature pigs revealed that fish oil feeding increased the proportion of VLDL being converted to LDL. Apparently, the n-3 fatty acids of fish oil produce a smaller VLDL particle, which is more likely to be converted to LDL. In this pig study, LDL concentrations, however, did not increase because the direct synthesis of LDL was reduced more by fish oil than the

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>High-saturated-fat diet (18% of energy)</th>
<th>Low-saturated-fat diet (5% of energy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>With n-3 fatty acids</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>6.1 ± 1.0 (236)</td>
<td>5.9 ± 1.2 (227)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>4.2 ± 1.0 (161)</td>
<td>4.4 ± 1.2 (170)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.6 ± 0.4 (60)</td>
<td>1.4 ± 0.4 (55)</td>
</tr>
<tr>
<td>Triglycerol</td>
<td>1.4 ± 0.8 (127)</td>
<td>0.8 ± 0.4 (74)</td>
</tr>
<tr>
<td>VLDL triglycerol</td>
<td>0.9 ± 0.6 (77)</td>
<td>0.4 ± 0.3 (35)</td>
</tr>
</tbody>
</table>

1 *x ± SD. n = 6. Interaction of amount of fat with n-3 fatty acids was not significant (two-way ANOVA). Adapted from reference 40.

2,3 Significantly different from dietary periods without n-3 fatty acids (two-way ANOVA): *P < 0.01, **P < 0.001.

4,5 Significantly different from high-saturated-fat diet with and without n-3 fatty acids (two-way ANOVA): *P < 0.05, **P < 0.01.
increase in LDL from VLDL. These pig studies await confirmation in humans. They do explain why LDL may increase in some humans fed fish oil: more VLDL is converted to LDL and direct LDL synthesis does not decrease, thus adding up to more LDL. LDL turnover studies have shown decreased production of LDL in normal humans given large amounts of salmon oil compared with vegetable oil (37). In this study, plasma LDL decreased after n-3 fatty acids.

**FISH OIL IN DIABETIC PATIENTS**

In diabetic patients there is enhanced risk for vascular disease, so that the use of fish oil might be particularly desirable if glucose control is not disturbed. The literature is controversial regarding effects of n-3 fatty acids in diabetic patients (43, 44). For patients with insulin-dependent diabetes there is universal agreement that glucose control is not hampered and that there are beneficial effects of n-3 fatty acids on plasma lipids and lipoproteins. For patients with non-insulin-dependent (adult onset) diabetes, the results are somewhat conflicting, possibly because such patients are very susceptible to the energy load imposed. In most studies, plasma triacylglycerol and VLDL concentrations declined, but some studies showed a deterioration in glucose homeostasis. This literature was reviewed by Heine (43). Most of the above studies were short term and in some energy control was somewhat distorted by the administration of energy-dense fish oil without a suitable placebo. The addition of fish oil to the usual diet will be hyperenergetic, thereby disturbing glucose control. When attention is paid to the energy content of the supplement, there are beneficial effects on plasma triacylglycerol and VLDL without a disturbance of glucose homeostasis as illustrated below.

These problems and objections were considered in the experimental design of a study in 16 subjects with non-insulin-dependent diabetes who were randomly assigned to a double-blind, placebo-control, crossover study (45). The subjects of the study were overweight and most were receiving hypoglycemic agents. There was a 3-mo baseline stabilization period during which subjects were given a euergetic, low-fat, high-complex-carbohydrate diet with 30% of energy from fat and 55% from carbohydrate. This was followed by two 6-mo intervention periods in which subjects continued on the same diet and received a supplement of 15 g/d of either olive oil or fish oil. The fish oil contained 6 g n-3 fatty acids/d. The endpoints of the study were plasma lipid and lipoprotein concentrations and glucose homeostasis. Plasma triacylglycerol concentrations were much lower with the fish oil preparation than with olive oil (2.9 compared with 5.1 mmol/L (260 compared with 449 mg/dL)). VLDL cholesterol was lower and VLDL triacylglycerol as well. Total plasma cholesterol was unchanged. There was a significant increase in LDL cholesterol, as was mentioned previously, when hypertriglyceridemic individuals were given fish oil, from 3.0 to 3.8 mmol/L (117 to 145 mg/dL). HDL cholesterol did not change. These results were not unexpected.

There were no effects of the 6-mo period of olive oil administration on glucose homeostasis. Body weights were also unchanged. Fasting glucose concentrations were 9.6 and 9.9 mmol/L (172 and 178 mg/dL) with the olive oil and fish oil diets, respectively. There were no differences in hemoglobin A1C or 24-h urinary glucose excretion, plasma C-peptide, or 24-h urinary C-peptide.

In view of the extremely high mortality from coronary artery disease in patients with non-insulin-dependent diabetes, this action of fish oil is of interest because diabetic control did not deteriorate and there were significantly beneficial plasma lipid and lipoprotein effects. The other actions of the n-3 fatty acids from fish oil in inhibiting the development of atherosclerosis, in preventing thromboxane A2 formation, in increasing endothelial-derived relaxing factor, and in inhibiting platelet-derived growth factor are additional reasons for postulating a therapeutic benefit of fish oil in diabetic patients (44).

**HYPERTENSION**

Eleven studies have shown a mild decrease in systolic blood pressure and at times a decrease in diastolic blood pressure, particularly when subjects are in an upright position, with consumption of n-3 fatty acids. This has occurred especially in subjects with mild hypertension (2, 46, 47). The suggested mechanism is an attenuation in the responses of forearm vascular resistance and blood flow to angiotensin, i.e., less vascular reactivity. Because decreases in both systolic and diastolic pressures are not great even in the best studies (4.6 and 3.0 mm Hg, respectively) (47), fish oil cannot be regarded as a single treatment modality for hypertension. However, when used for other purposes, the mild blood pressure-lowering effect of n-3 fatty acids is an added benefit.

**POPULATION STUDIES AND CLINICAL TRIALS**

The epidemiologic data on and clinical trials of n-3 fatty acids and coronary disease are extensive and go back to the initial observations of Bang and Dyerberg (4), who found much less coronary artery disease in Greenland Eskimos than in Danes. They deduced by means of extensive studies that it was the n-3 fatty acid content of the Eskimo diet that inhibited the atherosclerotic disease, despite the fact that the Eskimo diet was a high-cholesterol, high-fat diet (3). The dietary fat, instead of being pathogenic, was protective because it was derived from the seas (eg, from fish and seal) and contained n-3 fatty acids. Furthermore, the pathology of atherosclerosis in Alaskan natives was found to be much less than atherosclerosis found in whites living in Alaska (48).

Several studies correlating fish consumption (providing n-3 fatty acids) and mortality from coronary artery disease have been carried out (2). In Dutch men the mortality from coronary artery disease was > 50% lower among those who consumed ≥ 30 g fish/d than among those who did not eat fish (49). In the Multiple Risk Factor Intervention Trial, n-3 fatty acid consumption correlated inversely with all-cause and coronary mortality (50). Even in the Harvard Health Professionals Follow-up Study of 51,529 men the consumption of one to three servings of fish per week was associated with a lower incidence of coronary artery disease (51).

This information was buttressed by a randomized controlled clinical trial in 2333 men who had recovered from myocardial infarction and who were then asked to increase their intake of fatty fish or fish oil (13). There was a 29% reduction in 2-y all-cause mortality in subjects advised to eat fatty fish and also...
TABLE 2
Fat and n–3 fatty acid content of fish and shellfish

<table>
<thead>
<tr>
<th>Fish (100 g edible portion, raw)</th>
<th>Fat</th>
<th>n–3 Fatty acids^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>undetermined</td>
<td>g</td>
<td></td>
</tr>
<tr>
<td>Anchovy, European</td>
<td>4.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Bass, striped</td>
<td>2.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Bluefish</td>
<td>6.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Carp</td>
<td>5.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Catfish, channel</td>
<td>4.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Cod</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atlantic</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Pacific</td>
<td>0.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Flounder, unspecified</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Haddock</td>
<td>0.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Halibut, Pacific</td>
<td>2.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Herring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atlantic</td>
<td>9.0</td>
<td>1.6</td>
</tr>
<tr>
<td>Pacific</td>
<td>13.9</td>
<td>1.7</td>
</tr>
<tr>
<td>Mackerel, Atlantic</td>
<td>13.9</td>
<td>2.5</td>
</tr>
<tr>
<td>Mullet, unspecified</td>
<td>4.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Ocean perch</td>
<td>1.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Pike, Walleye</td>
<td>1.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Pompano, Florida</td>
<td>9.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Sablefish</td>
<td>15.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Salmon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atlantic</td>
<td>5.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Chinook</td>
<td>10.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Pink</td>
<td>3.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Sockeye</td>
<td>8.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Sardines, in sardine oil^3</td>
<td>15.5</td>
<td>3.3</td>
</tr>
<tr>
<td>Shark</td>
<td>1.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Snapper, red</td>
<td>1.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Sole</td>
<td>1.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Sturgeon</td>
<td>3.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Swordfish</td>
<td>2.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Trout</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brook</td>
<td>2.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Lake</td>
<td>9.7</td>
<td>1.6</td>
</tr>
<tr>
<td>Rainbow</td>
<td>3.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Tuna</td>
<td>2.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Crustaceans</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alaska King</td>
<td>0.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Dungeness</td>
<td>1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Crayfish, unspecified</td>
<td>1.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Lobster, northern</td>
<td>0.9</td>
<td>0.2</td>
</tr>
<tr>
<td>Shrimp, unspecified</td>
<td>1.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Mollusks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abalone, New Zealand</td>
<td>1.0</td>
<td>Trace</td>
</tr>
<tr>
<td>Clam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hardshell</td>
<td>0.6</td>
<td>Trace</td>
</tr>
<tr>
<td>Littleneck</td>
<td>0.8</td>
<td>Trace</td>
</tr>
<tr>
<td>Mussel, blue</td>
<td>2.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Octopus, common</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Oyster, Pacific</td>
<td>2.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Scallop, unspecified</td>
<td>0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Squid, unspecified</td>
<td>1.1</td>
<td>0.3</td>
</tr>
</tbody>
</table>

^1 From reference 52.
^3 Analysis by the Lipid-Atherosclerosis Research Laboratory, Portland, OR.

FISH OILS AND CORONARY ARTERY DISEASE

This was the first intervention trial in which all-cause mortality was reduced in a coronary intervention program. One likely reason for the reduction in coronary mortality was the decrease in cardiac arrest as documented recently by another study (12). Men who ate fatty fish at least once per week had a 50% reduction in cardiac arrest, which probably resulted from the antiarrhythmic action of the n–3 fatty acids.

RECOMMENDATIONS

The intake of n–3 fatty acids from fish should be increased to prevent coronary artery disease. This recommendation could best be met in the form of two to three fish meals per week in the context of a low-fat diet. The diet should be reduced in fat content to 20% of total energy whereas carbohydrate and fiber intakes should be high. Cholesterol intake should be limited to 100 mg/d. The fat content and n–3 fatty acid content of a wide variety of fish and shellfish are listed in Table 2 (39, 52). All fish and shellfish contain n–3 fatty acids. The lower the fat content, the higher the percentage of n–3 fatty acids that are present in a given fish or shellfish. Fish, of course, could be substituted for meat in the diet. The goal of this recommendation is to produce an increased content of the n–3 fatty acids EPA and DHA in the blood and tissues of the body. This will occur if there is regular consumption of ≥ 200–300 g fish and shellfish/wk.

There are excellent markers for documenting the chronic intake of fish and shellfish should this be desired. These markers include the measurement of n–3 fatty acids in the plasma, which would reflect a more immediate intake; measurement of n–3 fatty acids in red blood cells, which, because of the greater half-life of these cells, would reflect intake over a longer period of time; and biopsies of the adipose tissue, whose fatty acids would reflect intake over many months and years (53).

For the intensive treatment of various forms of hyperlipidemia as well as the production of an antithrombotic state, fish oils need to be used in addition to the consumption of fish. The dose of fish oil might well be from 6 to 15 g/d, titrated according to the endpoint desired. For people who are unable to consume fish or shellfish, the use of fish oil would be advisable. For primary prevention, 2–3 g/d is desirable. Higher doses, as noted above, should be used for secondary prevention and the attainment of discrete endpoints of plasma lipid and lipoprotein concentrations and platelet function.

In conclusion, n–3 fatty acids from fish and fish oil greatly inhibit the atherosclerotic process and coronary thrombosis by many actions and should be considered as an important therapeutic modality in patients with coronary artery disease and to prevent coronary disease in highly susceptible people.

REFERENCES


