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Marine Lipids and Atherosclerosis: A Review

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Marine lipids rich in omega-3 fatty acids have been shown to beneficially modify plasma lipid concentrations and decrease platelet aggregation. The combined lipid-lowering and antithrombotic effects of marine omega-3 fatty acids make this natural food source an ideal intervention to potentially prevent and possibly regress atherosclerosis. The bleeding-time prolongation, reduction in platelet aggregation, and decrease in blood pressure with dietary omega-3 fatty acids are believed to be secondary to a change in prostaglandin substrates. Whereas vegetable omega-6 fatty acids serve as substrates for highly reactive thromboxane A_2, marine lipids serve as substrates for the weakly active thromboxane A_3. The net result is prostaglandin synthesis that favors less platelet aggregation and reduced vasoconstriction. The hypolipidemic effect of marine lipids, though of an uncertain mechanism, causes approximately a 10% reduction in total cholesterol and a 40% lowering of triglycerides and, unlike vegetable oils, does not lower HDL cholesterol. The recent development of a marine lipid concentrate allows practical omega-3 fatty acid supplementation for the majority of the adult population to be superimposed on the standard Western diet.

INTRODUCTION

The low incidence of coronary heart disease in Greenland Eskimos has stimulated considerable interest in fish consumption as a protective measure against the development of atherosclerosis. Compared with Western populations, the Eskimos have lower plasma-lipid levels, a decreased frequency of hypertension, and prolonged bleeding times—characteristics that were initially felt to be genetically determined.[1-3] It has recently been shown, however, that these characteristics are related to their diet, which consists of cold-water fish, seal, and whale meat; all three are high in the marine omega-3 series of polyunsaturated fats. The marine omega-3 series, eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA), was originally classified with the structurally similar vegetable oil omega-6 series of polyunsaturated fats; their differences in hypolipidemic activity and antithrombotic effect have only recently been recognized. This review will discuss the latest information regarding marine omega-3 fatty acids and the reasons that they are presently a focus of investigation into the prevention of coronary artery disease.

THEORY OF ATHEROSCLEROSIS

The prevailing "response to injury" hypothesis of atherosclerosis suggests that platelets contribute to lesion formation by releasing a potent growth factor, which stimulates the proliferation of arterial smooth-muscle cells that can subsequently accumulate lipid and become foam cells. Foam cells are also believed to be derived from monocytes. Monocytes can form fatty streaks, one of the earliest findings in the development of atherosclerosis. Like platelets, monocytes adhere to the arterial endothelium and release growth factors that stimulate smooth-muscle proliferation (Figure 1). Marine lipids may reduce the adherence of monocytes to the arterial wall, an effect of omega-3 fatty acids that has been recently shown to occur in neutrophils. Therefore, marine lipids may retard the development of atherosclerosis by both inhibiting platelet aggregation and, possibly, decreasing monocyte adherence to arterial endothelium.

INHIBITION OF PLATELET AGGREGATION

The prolonged bleeding time observed in subjects receiving increased amounts of dietary omega-3 fatty acids appears to result from changes in prostaglandin synthesis (Table I). The omega-6 series of polyunsaturated fats derived from vegetable oils (safflower, sunflower, soy bean, and corn oils) serve as substrates for the formation of two potent prostaglandins that modulate platelet aggregation, thromboxane A_2 and prostaglandin I_2 (prostacyclin). Thromboxane A_2 is produced in the platelets and promotes their aggregation and vasoconstriction. Prostacyclin, on the

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TABLE I
IMPORTANT DIETARY FATTY ACIDS

Name	Carbon Atoms	Saturation
Stearic acid	(18)	(Saturated)
Oleic acid	(18:1,9)	(Monosaturated)
Linoleic acid	(18:2,9,12)	(W6)
Alpha-linolenic acid	(18:3,9,12,15)	(W3)
Gamma-linolenic acid	(18:3,6,9,12)	(W6)
Arachidonic acid	(20:4,5,8,11,14)	(W6)
Eicosapentaenoic acid	(20:5,5,8,11,14,17)	(W3)

other hand, is synthesized in endothelial cells of arteries and veins, inhibits platelet aggregation, and is a vasodilator. The omega-3 fatty acids appear to compete favorably with omega-6 fatty acids, producing a combination of prostaglandins that retards platelet aggregation and promotes vasodilation. Omega-3 fatty acid consumption produces diminished amounts of proaggregatory thromboxane A_2 with the formation of only small amounts of an apparently biologically inactive or weakly active thromboxane A_3, whereas the prostacyclin effects are maintained or amplified (Figure 2). The net effects of these changes is a reduction in platelet aggregation and a prolongation of bleeding time.

The bleeding tendencies of the Greenland Eskimos were first noted in the 1930s, but prolongation of bleeding time in non-Eskimo subjects fed a high fish diet was not recognized until recently. Thorngren and Gustafson[4] studied ten Swedish men

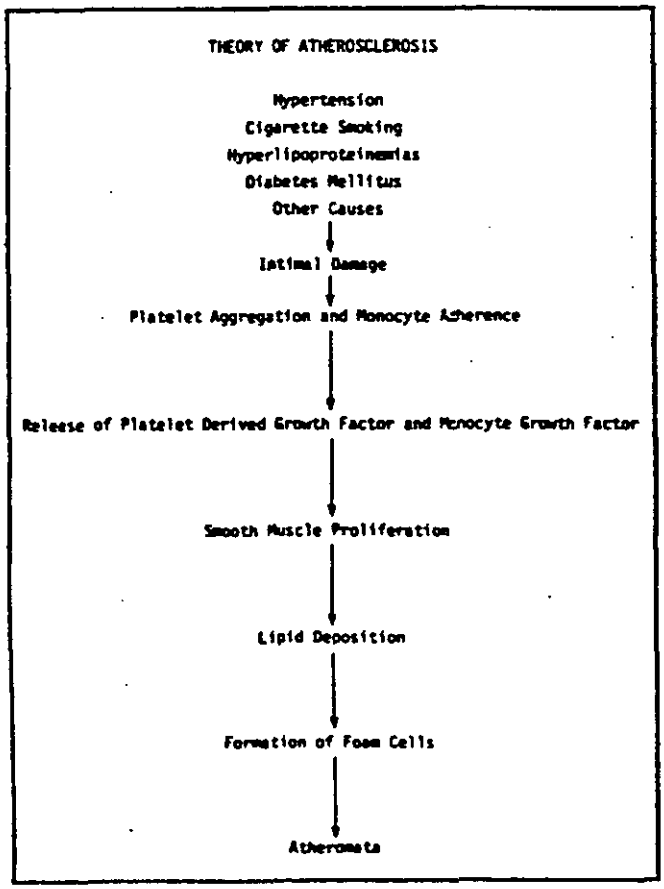

Figure 1. Sequence of events of the endothelial injury hypothesis of atherosclerosis.

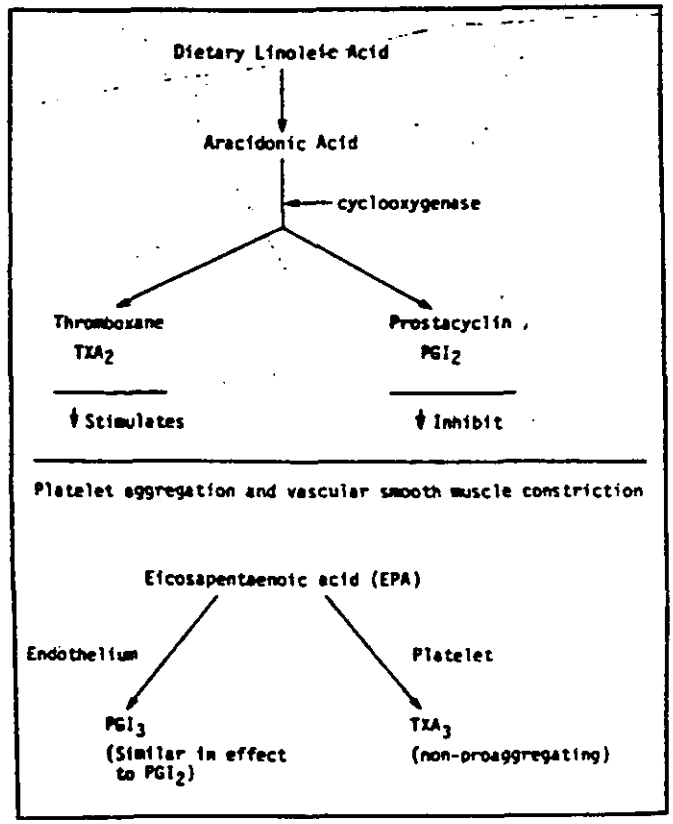

Figure 2. Prostaglandin production from the omega-6 linoleic acid compared with the omega-3 eicosapentaenoic acid.

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who were fed a diet that consisted mainly of mackerel and salmon, for a total of 2 to 3 g of EPA daily. After six weeks of this diet, there was a reduction in platelet aggregation to adenosine diphosphate, collagen, and epinephrine, as well as a prolongation of bleeding time. These results were also verified in healthy volunteers, using cod liver oil or marine lipid concentrate capsules as the source of EPA.[5] These studies also demonstrated an increase in platelet survival time, a 15% reduction in platelet count, a 75% decrease in platelet factor 4, and a 30% lowering of plasma thromboglobulin.[6] All of these additional effects contribute to an antithrombotic effect and bleeding-time prolongation. The thrombocytopenia appears to be transient, with the platelet count returning to baseline after three months of fish oil therapy.[7] Additional studies have noted a modest reduction in serum viscosity.[8] These same results have been achieved in patients with ischemic heart disease. The combined results of all these studies revealed a bleeding-time prolongation in the range of two to four minutes, a 25% to 50% increase.[8-10]

Aspirin also prolongs bleeding time, but it does so by inhibiting the enzyme cyclooxygenase, which converts arachidonic acid to thromboxane A_2 and prostacyclin. The net result is a decrease of thromboxane A_2 production by irreversibly inhibiting the cyclooxygenase present in platelet membranes and, at the same time, an only temporary inhibition of prostacyclin production by the vessel wall.

As might be predicted, the combination of aspirin and a high fish diet has been shown to prolong the bleeding time. The increase, however, exceeds the prolongation expected from adding the individual effects.[10] Among the explanations for this finding is the possibility that aspirin inhibition of cyclooxygenase may not fully block the conversion of omega-3 fatty acids to prostacyclin I_3 or that the bleeding-time prolongation cannot be fully explained by the altered balance of prostaglandin derivatives. Since the mechanisms of these effects of the fish diet and aspirin on hemostasis seem to differ, the combination of these two agents may provide an interesting preventive and therapeutic modality for atherosclerosis.

NEUTROPHIL AND MONOCYTE ENDOTHELIAL ADHERENCE

In a study in seven healthy subjects given a daily dose of EPA 3.2 g and DHA 2.2 g, using marine lipid concentrate, adherence of neutrophils to bovine endothelial cell monolayers pretreated with leukotriene B was inhibited completely, and the chemotactic response was also markedly reduced.[11] This study suggests that fish oil may have an anti-inflammatory response by inhibiting adherence and chemotaxis of white cells. These findings also have implications for effects on the development of atherosclerosis, which may be stimulated by monocyte adherence following endothelial damage, with subsequent release of a growth factor causing smooth-muscle proliferation and the formation of foam cells.

HYPOLIPIDEMIC EFFECT

Of the three classes of fatty acids, the saturated fatty acids (stearic, palmitic) have a potent hypercholesterolemic effect, the monosaturated fatty acids have a neutral or mild cholesterol-lowering effect, and the polyunsaturated fatty acids have a moderate hypocholesterolemic effect. The two classes of polyunsaturated fatty acids are the omega-6 vegetable oils, of which linoleic and arachidonic acids are most common, and the omega-3 marine oils, of which eicosapentaenoic and docosahexanoic acids are the most prominent. Alpha-linolenic acid (linseed oil) is also an omega-3 fatty acid, but studies have shown that humans are incapable of converting this fatty acid to EPA in sufficient quantities. Omega-3 fatty acids are not interconvertible, and both types can compete with each other for the enzyme cyclooxygenase for conversion to various prostaglandin derivatives. When the cholesterol-lowering ability of polyunsaturated fats was first noted, the difference in the lipid-lowering activity of these two series of fatty acids went unrecognized. With increased use of dietary polyunsaturated fatty acids, more information became available regarding the potentially harmful side effects of this class of fatty acids. Polyunsaturated fats of the omega-6 series were found to enhance cholesterol gallstone formation, decrease immune function, produce unstable lipid factors in cell membrane, and, although reducing low-density lipoprotein (LDL) cholesterol level, also lowered the beneficial high-density lipoprotein (HDL) cholesterol concentration. Although the safety of the omega-3 fatty acids is yet to be fully established, epidemiologic evidence suggests that populations such as the Eskimos, who consume a large quantity of the omega-3 series compounds daily, do not suffer from these possibly untoward effects.

The differences in lipid-lowering activity of acids of the omega-6 series and the omega-3 series were not recognized until Harris and associates[12] compared salmon oil with vegetable oil in healthy volunteers. This study demonstrated an equally significant fall in serum cholesterol level in both groups, but the salmon oil–diet group also experienced a marked reduction in triglyceride concentrations. Other studies have verified the significant lowering effect of omega-3 fatty acids on triglyceride-rich lipoproteins very-low-density lipoproteins [VLDL] and chylomicrons).[13,14] Although the triglyceride-lowering effect is present in healthy volunteers, the most marked reduction has been noted in type IV and type V hyperlipoproteinemias.[15]

The precise mechanism of lipid lowering by omega-3 polyunsaturated fats is not known. How-

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ever, studies indicate that inhibition of apoprotein B production rather than enhanced clearance is the probable mechanism of decreased VLDL plasma triglyceride concentrations. Several studies that have examined the lipid-lowering effects of omega-3 fatty acids have found a 10% to 20% reduction in total cholesterol level, a 30% to 60% reduction in triglyceride contents, and, unlike the omega-6 fatty acids, a 5% increase in HDL cholesterol level. The increased HDL cholesterol level appears to be a result of an increase in the HDL_2 fraction, believed to be the most protective compound against the development of coronary artery disease.[16]

ANTIHYPERTENSIVE EFFECT

The antihypertensive effect of marine omega-3 fatty acids is also believed to be secondary to the change in prostaglandin derivatives, from the potent vasoconstrictor thromboxane A_2 to the weakly active thromboxane A_3. However, a reduction in norepinephrine levels has been noted as well. In one study with ingestion of omega-3 fatty acids, 15 healthy volunteers were placed on a high EPA mackerel diet or a low EPA herring diet.[17] Both diets were equivalent in calories and total polyunsaturated fat content. In the mackerel diet group, there was a significant 10% reduction in both systolic and diastolic pressures, while the herring diet group did not display any significant change. In another study, eight healthy volunteers were given 40 mL/d of cod liver oil for 25 days.[5] At the end of the study period, there was a significant fall in both blood pressure and blood pressure response to norepinephrine. At present, there have been no studies on the effects of marine lipids on blood pressure response in hypertensive patients.

THE PREVENTION OF ATHEROSCLEROSIS

Although intimal hyperplasia and atherosclerosis are believed to be separate clinical entities, excessive platelet aggregation is presumed to contribute to both processes. Fibrous intimal hyperplasia is the

most common cause of late graft failure after aortocoronary bypass surgery.[18] Antiplatelet agents such as aspirin and dipyridamole have been shown to prolong vein graft patency.[19] In a group of mongrel dogs who underwent jugular vein grafting between femoral arteries and were also given cod liver oil supplementation and a high cholesterol diet, there was significantly less intimal hyperplasia in the harvested veins six weeks later in the cod liver oil group compared with controls.[20] This animal study supports the use of marine lipids to prevent graft failure in patients who have undergone venous aortocoronary or femoropopliteal bypass grafting. Intimal hyperplasia is believed to be a significant cause of restenosis of coronary arteries following angioplasty. The use of marine lipids to improve graft survival after venous bypass or to prevent restenosis after coronary angioplasty has yet to be explored.

Although the use of marine lipids to prevent coronary artery disease has yet to be conclusively proven, a retrospective study suggests that dietary fish consumption may markedly reduce the risk of myocardial infarction.[21] In the Netherlands, information about a group of 852 middle-age men was collected in 1960 by a careful dietary history. After 20 years of follow-up, 78 men had died of coronary disease. An inverse dose–response relation was observed between fish consumption in 1960 and death from coronary disease. The mortality from coronary heart disease was more than 50% lower among those who ate at least 30 g/d of fish as compared with those who did not eat fish. The conclusion of this study was that as little as two fish dishes per week may help prevent coronary artery disease (Table II).

TABLE II
CONTENT OF OMEGA-3 FATTY ACIDS*

	Total Fat (g)	EPA (g)	DHA (g)
Fish			
Whitefish (lake)	6.0	0.3	1.0
Trout (brook)	2.7	0.2	0.2
Tuna (albacore)	4.9	0.3	1.0
Cod (atlantic)	0.7	0.1	0.2
Perch (white)	2.5	0.2	0.1
Salmon (pink)	3.4	0.4	0.6
Fish Oils			
Cod liver oil	100	9.8	9.5
Salmon oil	100	8.0	11.1
Marine Lipid Concentrates			
MaxEPA	100	17.8	11.6
Shaklee EPA	100	28.0	8.0
Res-q-1,000	100	30.0	22.0

* 100 g (3.5 oz), edible portion, raw.
Derived from United States Department of Agriculture information.

MARINE LIPID CONCENTRATE

For most of the Western population, the Eskimo diet of fish, seal, and whale may be tolerable only for relatively brief periods of time. Cod liver oil contains high quantities of EPA and DHA. However, in order to ingest adequate amounts of these omega-3 fatty acids, vitamin A and D toxicity may occur. Recently, a commercial marine lipid concentrate has been developed that provides varying amounts of omega-3 fatty acids. There are three brands on the American market, MaxEPA, Shaklee EPA, and Res-q-1,000. Each of these brands provides about 300–500 mg EPA and DHA per capsule (Table II). Studies have shown that these capsules are an effective means of utilizing omega-3 fatty acids to lower plasma lipoproteins and blood pressure and to prolong bleeding time. Saynor and colleagues,[7] using 20 capsules/d of marine lipid concentrate, found a statistically significant reduction in total cholesterol and triglyceride levels, an increase in HDL cholesterol content, and a prolongation of bleeding time. The study also noted a marked reduction in nitrate use among patients with ischemic heart disease. This study was neither controlled nor randomized. A study recently completed in this institution compared the effects of marine lipid concentrate with olive oil in a double-blind, randomized fashion.[22] In the marine lipid concentrate group, there was a 13% reduction in total cholesterol compared with baseline or olive oil group, ($P < .025$), a 40% decrease in triglycerides ($P < .005$), a 5% increase in HDL (not significant), a 7% reduction in systolic blood pressure ($P < .005$), and an 8% decrease in diastolic blood pressure ($P < .01$). Compliance, as determined by capsule counting, was excellent, and neither group reported significant adverse reactions. Therefore, marine lipid concentrate capsules, which lack the toxicity of cod liver oil, can supply adequate amounts of omega-3 fatty acids to potentially retard atherosclerosis.

CONCLUSION

The combined hypolipidemic and antithrombotic effects of marine omega-3 fatty acids have evoked interest in these fatty acids as potential agents to retard atherosclerosis development. For patients with elevated serum cholesterol and triglyceride concentrations, marine lipids are an ideal means with which to lower these plasma lipoproteins. The blood pressure–reducing effect of omega-3 fatty acids has yet to be explored in patients with hypertension. For patients who already have atherosclerotic coronary or peripheral artery disease, the potential use of marine lipids to inhibit venous graft closure or restenosis following coronary angioplasty, alone, or in conjunction with other antiplatelet agents, deserves further study. Regression of atherosclerosis, once considered an impossibility, is a

process that may be a result of the unique combination of effects of marine omega-3 fatty acids.

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