Marine Lipids and Atherosclerosis: A Review

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 A2, marine lipids serve as substrates for the weakly active thromboxane A2. 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.

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 1). 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 A2 and prostaglandin I2 (prostacyclin). Thromboxane A2 is produced in the platelets and promotes their aggregation and vasoconstriction. Prostacyclin, on the

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 docosahexaenoic 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.

From the Section of Cardiology, Rush-Presbyterian-St. Luke's Medical Center, Chicago.
This article won second prize in CVR&A's First Annual Manuscript Competition.
Address for reprints: Michael H. Davidson, MD, Rush-Presbyterian-St. Luke's Medical Center, 1753 West Congress Parkway, Chicago, I. 60612.
### TABLE I
**IMPORTANT DIETARY FATTY ACIDS**

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

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 A₂ with the formation of only small amounts of an apparently biologically inactive or weakly active thromboxane A₂, 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 studied ten Swedish men...
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.3 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.4 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.5 Additional studies have noted a modest reduction in serum viscosity.6 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.6–10

Aspirin also prolongs bleeding time, but it does so by inhibiting the enzyme cyclooxygenase, which converts arachidonic acid to thromboxane A2 and prostacyclin. The net result is a decrease of thromboxane A2 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.11 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, 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 B4 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 monounsaturated 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 docosahexaenoic 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 associates12 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-
the lipid-lowering effects of omega-3 fatty acids. In the mackerel diet group, there was a significant increase in HDL cholesterol level, a 30% to 60% reduction in triglyceride concentrations, 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 risk of coronary artery disease.

ANTIHYPERTENSIVE EFFECT

The antihypertensive effect of marine omega-3 fatty acids is also considered to be secondary to the change in prostaglandin derivatives, from the potent vasoconstrictor thromboxane A\(_2\) to the weakly active thromboxane A\(_1\). 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. Both diets were equivalent in calories and total polyunsaturated fat content. In the mackerel diet group, there was a significant 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. 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 aorto-
coronary bypass surgery. Antiplatelet agents such as aspirin and dipyridamole have been shown to
prolong vein graft patency. 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 har-
vested veins six weeks later in the cod liver oil group
compared with controls. This animal study sup-
ports the use of marine lipids to prevent graft failure
in patients who have undergone venous aortocoron-
ary or femoropopliteal bypass grafting. Intimal hy-
perplasia is believed to be a significant cause of
restenosis of coronary arteries following angio-
plasty. 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 coro-
mary artery disease has yet to be conclusively proven,
a retrospective study suggests that dietary fish con-
sumption may markedly reduce the risk of myocar-
dial infarction. 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 be-
 tween 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**

<table>
<thead>
<tr>
<th>CONTENT OF OMEGA-3 FATTY ACIDS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Fat (g)</td>
</tr>
<tr>
<td>Fish</td>
</tr>
<tr>
<td>Whitefish (lake)</td>
</tr>
<tr>
<td>Trout (brook)</td>
</tr>
<tr>
<td>Tuna (albacore)</td>
</tr>
<tr>
<td>Cod (atlantic)</td>
</tr>
<tr>
<td>Perch (white)</td>
</tr>
<tr>
<td>Salmon (pink)</td>
</tr>
<tr>
<td>Fish Oils</td>
</tr>
<tr>
<td>Cod liver oil</td>
</tr>
<tr>
<td>Salmon oil</td>
</tr>
<tr>
<td>Marine Lipid Concentrates</td>
</tr>
<tr>
<td>MaxEPA</td>
</tr>
<tr>
<td>Shaklee EPA</td>
</tr>
<tr>
<td>Res-q-1,000</td>
</tr>
</tbody>
</table>

* 100 g (3.5 oz), edible portion, raw.

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 lipo-
proteins and blood pressure and to prolong bleeding
time. Saynor and colleagues, using 20 capsules/d of
marine lipid concentrate, found a statistically signif-
ificant 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 com-
pleted in this institution compared the effects of
marine lipid concentrate with olive oil in a double-
blind, randomized fashion. 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 atheroscle-
rosis.

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 hyper-
tension. For patients who already have athero-
sclerotic coronary or peripheral artery disease, the
potential use of marine lipids to inhibit venous graft
closure or restenosis following coronary angi-
oplasty, alone, or in conjunction with other antiplate-
let agents, deserves further study. Regression of ath-
ersclerosis, once considered an impossibility, is a
REFERENCES


