Fish oils and plasma lipid and lipoprotein metabolism in humans: a critical review

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Abstract  Epidemiological studies in Greenland Eskimos led to the hypothesis that marine oils rich in n-3 fatty acids (also referred to as omega (ω)-3 fatty acids) are hypolipidemic and ultimately antiatherogenic. Metabolically controlled trials in which large amounts of fish oil were fed to normal volunteers and hyperlipidemic patients showed that these fatty acids (FAs) are effective at lowering plasma cholesterol and triglyceride levels. Although more recent trials using smaller, more practical doses of fish oil supplements have confirmed the hypotriglyceridemic effect, they have shown little effect on total cholesterol levels; hypertriglyceridemic patients have even experienced increases in low density lipoprotein cholesterol (LDL-C) levels of 10-20% while taking n-3 FA supplements. Discrepancies among fish oil studies regarding the effects of n-3 FAs on LDL-C levels may be understood by noting that, in the majority of studies reporting reductions in LDL-C levels, saturated fat intake was lowered when switching from the control diet to the fish oil diet. When fish oil is fed and saturated fat intake is constant, LDL-C levels either do not change or may increase. Levels of high density lipoprotein cholesterol have been found to increase slightly (about 5-10%) with fish oil intake. Plasma apolipoprotein levels change in concert with their associated lipoprotein cholesterol levels. Although the decrease in triglyceride levels appears to result from an inhibition in hepatic triacylglyceride synthesis, the mechanisms leading to the increases in LDL and HDL have not been determined. Finally, fatty fish or linolenic acid may serve as alternative sources of long-chain n-3 FAs, but further studies will be needed to document their hypolipidemic and/or antiatherogenic effects. —Harris, W. S. Fish oils and plasma lipid and lipoprotein metabolism in humans: a critical review. J. Lipid Res. 1989. 30: 785-807.

Supplementary key words  docosahexaenoic acid • eicosapentaenoic acid • plasma lipids • lipoproteins • hyperlipoproteinemia

I. INTRODUCTION

The purpose of this report is to review the effects of the long-chain, n-3 fatty acids (also referred to as omega (ω)-3 fatty acids) found in fish oils on human plasma lipids and lipoproteins. Although there have been many studies conducted over the last several years examining this question, these studies have established only that n-3 fatty acids (FAs) lower plasma triglyceride levels. The effects of these agents on cholesterol and lipoprotein levels

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Abbreviations: VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; ω, cholesterol; FA, fatty acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; LCAT, lecithin:cholesterol acyltransferase; LPL, lipoprotein lipase; HTGL, hepatic triglyceride lipase; FCR, fractional catabolic rate.
have been variable and somewhat confusing. In some studies, low density lipoprotein (LDL) levels have fallen; in others they have increased. The same is true of high density lipoproteins (HDL). There is a need for a critical review to help clarify the reasons for these discordant results, and to provide a rationale for the use of fish oil in treating hyperlipidemia.

Fish oils are unique fats in the human diet because they are a rich source of n-3 FAs. This family of fatty acids is characterized by the presence of a double bond three carbon atoms away from the terminal methyl group. The major n-3 FAs found in fish oil are eicosapentaenoic acid (EPA, C20:5) and docosahexaenoic acid (DHA, C22:6). EPA serves as a substrate for cyclooxygenase and lipoxygenases, the enzymes that initiate the synthesis of prostaglandins, thromboxanes, prostacyclins, and leukotrienes (1, 2). Since all n-3 FAs (from linolenic acid, C18:3, to DHA) can be either elongated and desaturated or retroconverted to EPA (3-5), the basis for many of the biological effects of n-3 FAs (particularly their ability to inhibit platelet function (6)) may reside in their participation in these eicosanoid pathways. The reader is referred to several recent reviews (6-13) for a discussion of these aspects of the metabolism of n-3 FAs.

There exists a large body of data that strongly suggests that the highly unsaturated, n-3 FAs (EPA and DHA) are the active agents in fish oils. Although much of this evidence will be discussed below, some of the most important observations are as follows. 1) Pfeiffer et al. (14) showed that defatted fish flesh had no effect on cholesterol levels in rats, whereas the oil that was extracted from the flesh lowered cholesterol levels. 2) Imachi et al. (15) fed the saturated plus monounsaturated fraction of sardine oil to human volunteers and showed that the plasma lipid lowering effects resided in the latter, and not the former fraction. 3) There is very little effect of fish alone on human plasma lipoprotein levels (see Section VI); and 4) the effects of fish oils on lipid metabolism may be largely reproduced by feeding purified EPA (see Section III). Certainly, it is theoretically possible that a component of fish other than an n-3 FA could alter lipid metabolism, but until such evidence is forthcoming, the weight of the current evidence suggests that the n-3 FAs in fish oils are primarily responsible for influencing human lipid metabolism.

II. EPIDEMIOLOGICAL STUDIES

Epidemiological examinations of the health effects of n-3 FAs began with studies conducted in a coastal settlement of Greenland Eskimos in the 1970s. Dyerberg and Jorgensen (6) and Dyerberg (7) found that the intake of the long-chain, marine n-3 FAs was about 7 g/day among these people compared to less than 0.06 g/day in most western diets (16). This group of Eskimos (about 2,400 people) had an incidence of ischemic heart disease that was estimated to be about 8% of that seen in a comparable population in Denmark (17). More recent data set the Eskimo rate of incidence of ischemic heart disease at 20-30% of that seen in the Danish population (18).

Plasma lipid and lipoprotein levels were measured in a representative group of these Eskimos and compared to an age- and sex-matched group of Danes (6). The data for men, ages 41-50, were typical: cholesterol was 21% lower; triglyceride was 63% lower; very low density lipoprotein (VLDL) levels were 76% lower; and LDL levels were 12% lower in the Eskimos compared to the Danes. HDL levels were 50% higher in the Eskimos. Although similar changes in lipids and lipoproteins have been observed (except for the marked increases in HDL) by feeding fish oils in clinically controlled studies (see below), there are many differences between Eskimos and people in industrialized countries (i.e., exercise, cigarette use, genetic variables, alcohol use, etc.). Some of these factors may also contribute to the differences in heart attack rates.

Whether or not n-3 FAs are ever proven unequivocally to be responsible for the reduced rate of heart attacks in these Eskimos is, at this point, irrelevant. The hypothesis that the "Eskimo studies" generated has fueled the interest of scientists around the world in the potential hypolipemic and anti-atherogenic effects of n-3 FAs, and it is to the more well-controlled studies designed to test the hypothesis that we must now focus our attention.

III. FISH OILS AND PLASMA LIPID AND LIPOPROTEIN LEVELS

A. Clinical Studies

1. Description

Table 1 summarizes many of the studies (references 19-63) (excluding abstracts and symposia proceedings) published (or known by the author to be in press) by February 1988, in peer-reviewed, English language journals on the effects of fish oils on lipids and lipoproteins in human volunteers. Several studies (15, 64-70) from the 1950s and early 1960s have been omitted from Table 1 because they often lacked lipoprotein and/or triglyceride data, or they tested a variety of different oils in very few patients who occasionally had secondary hyperlipidemias. These studies were very important, however, because they helped show that the fatty acid composition of the dietary fat played a major role in determining the plasma cholesterol level.

Table 1 is divided into normalipidemics and patients with primary hyperlipidemia: isolated hypercholesterolemia (type IIa), combined hyperlipidemia (type IIb), and isolated hypertriglyceridemia (types IV and V). Type I
and type III patients have not been systematically examined. In most studies, age, sex, and plasma lipoprotein levels for individual patients were not given. Therefore, for the purposes of this review, mean plasma lipid levels of the group were used to roughly "phenotype" each study population into the various categories. Hypercholesterolemia was defined as an LDL cholesterol (LDL-C) of over 160 mg/dl, and hypertriglyceridemia as plasma triglyceride levels of over 200 mg/dl.

The amount of fish oil taken per day in each study, the intake of n-3 FAs, the study duration, the source of the n-3 FAs, and information about the control diets are given. In addition, the mean cholesterol, triglyceride, LDL-C, and HDL cholesterol (HDL-C) levels with and without n-3 FAs are given along with the calculated percentage change noted in that study. For each patient group, all of these parameters were averaged and weighted to give a per subject (not per study) mean value. This value is given at the end of the appropriate column for each patient group. It was necessary to weight the means because it would be inappropriate to give equal weight to all studies when some included many patients and others only a few. Thus, when determining overall means, larger studies were given more weight than smaller trials.

Since it is important to understand the weighting procedure used in Table 1, an example will be given using only two studies. How was the category "Change in Plasma Cholesterol" weighted so as to combine the results of Fehily et al. (24) and Bruckner et al. (23)? Since individual data were not given in either study, the following procedure was followed.

In the study Fehily et al. (24), dietary fish increased cholesterol by a mean of 1.4% in 118 subjects. Even though we were not given each person's percent change, we can at least determine what the total percent change for the group was by multiplying the mean change by 118. In this case, $1.4\% \times 118 = 165.2\%$ which was the sum of all the individual percentage changes. In the study of Bruckner et al. (23), 11 subjects had an average increase of 11.1%; $11.1\% \times 11 = 122.1\%$, the total percent change. When 165.2% and 122.1% are added together, and 118 and 11 are added together, the overall, total percentage increase was 287.3% for 129 subjects. Thus, the mean, per subject percent increase was 287.3%/129, or 2.2% which clearly gives greater weight to the study with the larger N. If this procedure was not followed and percent changes per STUDY were averaged, the mean change, for the example above, would have been (11.1% + 1.4%)/2, or 6.25% increase. That value would misrepresent the overall experience with fish oil in these two studies, allowing the smaller study to influence the overall mean change more than the larger.

Since some authors have reported the results of several different experiments in one publication, Table 1 lists each different experimental condition on a separate line.

Thus, the paper by Sanders and Roshana (40) is listed four times in the normolipidemic section because four different experiments were reported in one paper. This procedure was also followed when one group of patients was studied with various intakes of fish oil or with various oils. There are a total of 68 different experimental conditions reported in 45 separate publications. In order to keep Table 1 as simple as possible, the statistical evaluations of the lipid results from each study are not given; they may be found in the papers themselves.

As is clear from Table 1, there have been marked variations in the design of fish oil studies. Fish oil intakes have varied from as little as 1.6 g/day to over 100 g/day; n-3 FA intakes from 0.5 to 25 g/day, and studies lasted from 2 weeks to over 2 years. n-3 FAs were provided by whole fish, by fish liver oils, by fish oil concentrates, as fatty acid ethyl esters, and as purified EPA ethyl esters. Normal subjects and patients with various types of hyperlipidemia have been studied in trials differing in quality of design and in fat and cholesterol intake. Clearly, there is no typical fish oil study, and generalizations about the effects of fish oil based upon one or two studies may be inappropriate.

There were 61 experiments in which lipoprotein data (at least HDL-C) were given. (Studies not reporting lipoprotein data will have blanks in the LDL and HDL categories.) In 40 of these, LDL-C levels were calculated (noted in the table) using the values for total cholesterol, triglyceride, and HDL-C according to the Friedwald equation (64). Calculated LDL-C levels were considered reliable (and included in the calculations) only when the plasma triglyceride levels were less than 400 mg/dl (64). This restriction removed only one study (63) from the lipoprotein analysis.

2. Results

The effects of n-3 FAs on plasma lipid and lipoprotein levels for all trials are summarized in Fig. 1 according to lipoprotein disorder. Some of the confusion regarding the effects of fish oils can be understood from an examination of these data.

First, the normolipidemic subjects (who make up 596 of the 928 subjects studied overall) responded to n-3 FAs with essentially no change in total or LDL cholesterol, a 25% decrease in triglyceride levels, and a slight rise in HDL-C (+3%).

Although most of these trials were "before and after" designs (i.e., not placebo-controlled crossover), the overall results are similar to those seen in the more well-controlled studies giving relatively low doses of fish oil (<20 g/day) such as Sanders and Hochland (39), Zucker et al. (49), and Mortensen et al. (32). The only trial to provide purified EPA with no other dietary changes was that of Nagakawa et al. (33). They reported modest decreases in cholesterol and LDL levels, a marked decrease in triglycerides, and no change in HDL-C levels. More studies are...
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**Type IIa patients**

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**Table 1. Studies examining the effects of n-3 fatty acids on cholesterol.**

- **Design:** X, crossover design with total fat intake approximately equal on both phases. Control diet characteristics: B, fish oil diet was compared to baseline diet; S, baseline diet was clearly higher in saturated fat than the fish oil diet; P, baseline diet was clearly higher in polyunsaturated fat than the fish oil diet; F, fish oil diet had more (at least 60 mg) cholesterol than the control diet; C, control diet had more cholesterol.

- **M, MaxEPA; S, salmon oil; CLO, cod liver oil; FAEE, fatty acid ethyl esters; EPA-EE, EPA-ethyl esters; MACK, mackerel; HERR, herring; FF, fatty fish; MO, menhaden oil.**

- **LDL cholesterol determined after removal of VLDL by ultracentrifugation methods; all other LDL values were calculated.**

- **HDL given as 4.6 and 5.4 mg/dl in ref. 32. The author has assumed that this was a decimal error; LDL calculated based upon this assumption.**

- **In ref. 21, HDL-C may also be a typographical error.**

- **These values for LDL cannot be reliably estimated with triglycerides >400 mg/dl.**

- **Values not given; only percent changes.**

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| Percent Change | 0.03% | 3.4% |

Harris Fish oils and lipoprotein metabolism 789
and HDL-C rose by 5-776, and triglycerides decreased by
trials produced the same general results (49, 54, 56, 58).
38%. Again, the more well-controlled, low dose crossover
bined hyperlipidemia, total cholesterol levels were, again,
less, dietary n-3 FAs did not change total or LDL-C
lipoproteins were not reported in one of the three studies,
unaffected by fish oil supplementation, whereas LDL-C
longing platelet survival. In the 194 patients with com-
preliminary report, found that fish oil raised LDL-C
levels, lowered triglyceride levels, and slightly increased
HDL-C levels in these patients. Weiner et al. (71), in a
results must be viewed as very tentative. Neverthe-
1. Discussion
One of the objectives of this review is to address the
diversity of reported effects of fish oil on lipids and lipo-
needed with purified preparations of n-3 FAs in order to
factor out the effects of other components of fish oil.
Since only 37 type IIa subjects have been studied, and
lipoproteins were not reported in one of the three studies,
these results must be viewed as very tentative. Neverthe-
dietary n-3 FAs did not change total or LDL-C
levels, lowered triglyceride levels, and slightly increased
HDL-C levels in these patients. Weiner et al. (71), in a
preliminary report, found that fish oil raised LDL-C
levels in type IIa patients while, at the same time, pro-
longing platelet survival. In the 194 patients with com-
bined hyperlipidemia, total cholesterol levels were, again,
unaffected by fish oil supplementation, whereas LDL-C
and HDL-C rose by 5-7%, and triglycerides decreased by
38%. Again, the more well-controlled, low dose crossover
trials produced the same general results (49, 54, 56, 58).
Fish oils affected plasma lipids most noticeably in the
101 patients with isolated hypertriglyceridemia. Total cho-
sterol and triglyceride levels decreased (by 8 and 52%,
respectively), and LDL-C and HDL-C increased (by 30
and 10%, respectively). Since LDL-C and HDL-C levels
rose, it is obvious that the decrease in total cholesterol
resulted exclusively from a fall in VLDL-C levels. The
results from the type V patients contributed greatly to the
increase in LDL-C in this group. Mere typical responses
for the type IV subjects are 20% increases (56, 62).
3. Discussion
One of the objectives of this review is to address the
diversity of reported effects of fish oil on lipids and lipo-

\[ 
\begin{array}{|c|c|c|c|c|c|c|}
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\text{Ref.} & \text{First Author} & \text{N} & \text{Oil (g/day)} & \text{n-3 FA (g/day)} & \text{Source} & \text{Percent Change} \\
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\multicolumn{2}{|c|}{Type IIb patients} & & & & & \\
53 & Ahrens & 2 & X, P, F & 112 & 25 & MO & -14.4 \\
54 & Boberg & 27 & X, F & 10 & 3 & M & 0.0 \\
55 & Demke & 13 & X & 5 & 1.7 & M & 13.7 \\
56 & Harris & 7 & X & 12 & 5.4 & M-S & 94.9 \\
57 & Kahl & 16 & B, F & 8 & 1.8 & CFT & 43.7 \\
58 & Mehta & 8 & X, F & 18 & 5.4 & M & 10.0 \\
59 & Nestel & 1 & X, P & 75 & 23 & M & 9.0 \\
59 & Phillipson & 10 & X, F & 86 & 25 & M-S & 27.2 \\
59 & Phillipson & 4 & X, P & 86 & 25 & M-S & 13.3 \\
60 & Saynor & 92 & B, F & 20 & 6 & M-S & 9.3 \\
61 & Simons & 8 & X, F & 11 & 3.3 & M & 4.9 \\
62 & Zucker & 6 & X, F & 18 & 5.4 & M & 2.5 \\
194 & & & & & & & -2.0% \\
\multicolumn{2}{|c|}{Type IV/V patients} & & & & & \\
61 & Harris (type IV) & 8 & X, F & 18 & 5.4 & M & -5.1 \\
56 & Harris (type IV) & 11 & X & 12 & 5.4 & M-S & -1.3 \\
62 & Sanders (type IV) & 11 & X, P, F & 7 & 3.3 & M-S & -12.0 \\
51 & Simons (type IV) & 7 & X, F & 11 & 5.4 & M-S & -12.0 \\
44 & Sullivan (type IV) & 4 & X, F & 15 & 5.4 & M-S & -12.0 \\
63 & Singer (type IV/V) & 8 & X, F & 18 & 5.4 & M-S & -12.0 \\
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34 & Nestel (type V) & 23 & X, F & 15 & 5.4 & M-S & -12.0 \\
59 & Phillipson (type V) & 8 & X, F & 15 & 5.4 & M-S & -12.0 \\
59 & Phillipson (type V) & 8 & X, F & 15 & 5.4 & M-S & -12.0 \\
51 & Simons (type V) & 4 & X, F & 18 & 5.4 & M-S & -12.0 \\
101 & & & & & & & -7.8% \\
\hline
\end{array}
\]
proteins in human studies. Why does fish oil lower cholesterol in some studies and raise it in others? There are several factors to consider: the presence or absence of lipoprotein disorders, and the type of disorder, if present; the relationship between VLDL-C and total cholesterol levels; the type of fat in the control diet; the dose of fish oil given; and finally, the varying effects of EPA versus DHA. Each of these will be discussed separately.

Certainly, one of the most obvious factors involved in the variability in response is the type of patient being studied. As noted above, hypertriglyceridemic patients have had decreases in cholesterol levels while hypercholesterolemic and normal subjects generally have not. Secondly, it must be appreciated that the decrease in total cholesterol in the hypertriglyceridemics was entirely due to the marked fall in VLDL-C, not LDL-C levels (Fig. 1). The failure to take into account these two factors alone has contributed much to the confusion.

Another major source of variability in response stems from the failure to appreciate the role that control diets have played in the final outcome of each trial. Specifically, when the control diet contained more saturated fat than the fish oil diet, LDL levels were more likely to be lower on the fish oil diet. Unfortunately, the n-3 FAs were usually given credit for this effect and not the removal of saturated fat. This can be seen in two of the studies by Harris et al. (26, 27). In both cases, when the same patients were given diets rich in saturated fat, polyunsaturated fat, or fish oil, LDL-C levels were highest on the saturated fat diet and equivalent on the fish oil and polyunsaturated fat diets.

The studies in normolipidemic subjects also demonstrate this point. Those studies in which saturated fat was a variable have been separated from those in which saturated fat intake did not change. In Fig. 2, the effects of changing saturated fat intake on LDL-C levels are given. From this figure, it appears that in those studies in which saturated fat was held constant, LDL-C levels tended to rise (as did HDL-C levels). Studies in which saturated fat was lower during the fish oil diet reported reductions in LDL-C (and HDL-C) levels. About 30% of the subjects who consumed reduced amounts of saturated fat during the fish oil period experienced a decrease in LDL-C of greater than 10% (Fig. 3). Such a decrease in LDL-C was experienced by only about 6% of the subjects whose saturated fat intake did not change. Conversely, 38% of the subjects on constant saturated fat intakes had increases in LDL-C levels with fish oil supplementation as compared

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to only 3% of those with reduced saturated fat intakes. Clearly, there was a greater tendency among those with decreasing saturated fat intakes to have reductions in LDL-C levels than among those with constant intakes.

Among the studies in hyperlipidemia, in no case was saturated fat a variable, and in every case (but one (59)) LDL-C levels increased. The reasons for this one exception may be that this study treated patients with the highest saturated fat content of the control diet was higher than that of the fish oil diet (open bars). (Derived from Table 1; n = 320 and 276, respectively.)

Differences in dose may have caused different effects on lipoproteins; high doses of fish oil may have lowered LDL-C levels when low doses did not. There were eight “high dose” (>10 g of n-3 FAs/day) studies (26-28, 30, 31, 34, 35, 59) and 15 separate experimental conditions within those studies. In five situations saturated fat decreased from the control to the fish oil diet, and LDL-C levels clearly decreased every time. In nine of the other ten conditions, saturated fat intakes were constant and LDL-C levels either did not change or increased; the study of Phillipson et al. (59) again was the only exception to this rule. Since very high doses of fish oil may tend to crowd saturated fats out of the diet, LDL-C levels may decrease; but probably not because of the increased n-3 FA intake.

Finally, differences in response to fish oil may reflect different ratios of EPA and DHA in the preparations used as suggested by preliminary data from Childs, King, and Yamanaka (72). They reported that oils rich in DHA (tuna) lowered LDL-C, whereas oils rich in EPA (pollack) did not. Further examination of this possibility must await the availability of more purified preparations of the individual acids.

To summarize, the confusion surrounding the effects of fish oils on total and LDL-cholesterol levels has arisen primarily from failing to recognize that fish oils have different effects in different patient types and, secondly, that removing saturated fat from the diet will lower LDL-C levels regardless of the oil that replaces it. Variations in dose have played a relatively small role in the variability of response. Future studies should carefully select homogeneous patient populations and control the level of saturated fat in the diet.

Since fish oils may cause LDL-C levels to rise in hypertriglyceridemic patients, it is possible that fish oil consumption might raise cardiovascular risk in this group. For the type V patients, the rise in LDL-C may be immaterial since they have abnormally low LDL-C levels at the outset (51, 59). However, for the type IIb and IV patients, the increases in LDL-C may not be inconsequential since the levels in these patients frequently increased (see Table 1) into the borderline high or high risk categories (73). It would be prudent for these patients to have their LDL-C levels monitored by a physician while taking fish oil supplements. Nevertheless, one cannot conclude that the increase in LDL-C seen in these patients necessarily represents an increased risk for coronary heart disease (CHD) since fish oils appear to have many beneficial effects on other cardiovascular risk factors which may more than offset any potential, negative effects on LDL-C levels (see reviews 11 and 12). Certainly, more well-controlled, long-term trials utilizing practical intakes of fish oil in hyperlipidemic patients are needed.

**B. Phospholipid Levels**

Very little data exist on the effects of fish oils on plasma phospholipid levels. Ahrens et al. (53) reported that large
intakes of fish oil lowered phospholipid levels in two patients. The very long, although poorly controlled, studies of Nelson (74) found that patients who increased their fish intake had decreased levels of plasma cholesterol and phospholipid. This finding may simply reflect a reduction in saturated fat intake and may not be related to n-3 FAs. A preliminary trial in our laboratory in which five type IV patients were given 6 g of n-3 FAs per day for 4 weeks showed no effect of the treatment on total phosphatidylcholine levels (75).

**C. HDL and HDL Subfractions**

HDL-C levels usually rise with fish oil supplementation. Major decreases were noted only when high doses of fish oil were given (26, 28, 30, 35, 59). The majority of the placebo-controlled, crossover trials (Table 1) showed that fish oils increased HDL-C levels 5–10%, indicating that the n-3 FAs, and not the additional fat, were probably responsible.

The effects of n-3 FA supplementation on the two subfractions of HDL, HDL2, and HDL3, were reported in only a few trials (37, 46, 55, 56, 61, 62). In the first, hemodialysis patients with normal lipid profiles responded to 20 g of MaxEPA with an increase in HDL2 levels and no change in HDL3. However, there were no controls for fat intake in this study nor in the second which also reported increases in HDL2. When compared to vegetable oil controls, fish oil supplements produced no changes in HDL subfractions (56, 61, 62) or rise in HDL2 (55). When fish oil (22% of calories) was fed to African green monkeys, decreases in HDL-C and in intermediate-size HDL particles were noted (76). Polynsaturated vegetable oils had the opposite effect, raising the concentration of this HDL subfraction (77). Thus, in monkeys, n-3 FAs had different effects than n-6 FAs.

How these findings in monkeys apply to humans is difficult to evaluate. Similar decreases in HDL-C were noted when 29% of calories as fish oil were fed to humans (see above), but not when practical intakes (less than 5% of calories) were used (38–40, 45, 46, 48, 49, 52, 54–57). Thus, the cause and significance of this effect is not known, and no firm conclusions can be drawn as to the effects of fish oil on HDL subfractions in humans at this point.

**D. Apolipoproteins**

Relatively few investigators have examined the effects of fish oils on plasma apolipoprotein levels. When they were reported, they usually changed in concert with the cholesterol content of the corresponding density fraction. For example, in studies in which LDL-C levels increased by fish oil feeding (44, 55, 56, 61), apoB levels also increased. In trials reporting decreases in LDL-C (30, 34, 35, 59), apoB levels decreased.

ApoA-I levels were reported to decrease (relative levels on habitual diets) in healthy volunteers (35), but did not change in type IIb and V patients given high doses of fish oil (59). Plasma apoE levels were reported to fall in type V patients (59), probably reflecting a decrease in VLDL remnant levels. However, apoE levels did not change in type IIb patients given high doses of fish oil (59). As with HDL subfractions, much more work needs to be done to learn how fish oils affect plasma levels of apolipoproteins and their distribution among the plasma lipoproteins. Studies examining the influences of fish oil on Lp[a] levels would be most interesting.

**IV. FISH OILS AND PLASMA LIPID AND LIPOPROTEIN COMPOSITION**

**A. Fatty Acid Composition**

The consumption of fish oils rich in n-3 FAs consistently leads to increases in the levels of EPA and DHA in plasma lipids (22, 27–30, 41, 42, 47, 48, 53, 54, 61). However, these two FAs are not esterified into all lipid classes to the same extent. Triglycerides contain nearly equivalent levels of EPA and DHA, but cholesteryl esters become enriched with much more EPA than DHA (22, 29, 54). This selectivity occurs even though the plasma phospholipids, which are the major source of cholesteryl ester fatty acids, contain roughly equal amounts of EPA and DHA (22, 29, 54). The reasons for this selectivity are not known.

Because plasma phospholipids originate mainly from liver, their fatty acid composition may reflect tissue n-3 FA levels and thus, may serve as a marker to document n-3 FA intake. In a recent dose–response study in which 3 to 12 g of fish oil/day was given to hyperlipidemic patients for 6 months, increases in plasma phospholipid EPA levels clearly reflected intake levels (Fig. 4), whereas DHA levels were less discriminating (78). Several investigators have reported that the EPA content of cholesteryl esters shows a dose–response relationship to EPA intake (22, 41, 42, 43, 48). Since cholesteryl esters (unlike phospholipids) normally contain negligible amounts of n-3 FAs, this lipid class may also serve as a useful marker for n-3 FA intake.

**B. Lipoprotein Size**

The size distribution and chemical composition of VLDL and LDL have been reported by Sullivan et al. (44) in three normal subjects and in four type IV patients fed 15 g of MaxEPA (Seven Seas, Hull, England and R. P. Scherer Co. in Troy, MI) per day for 2 weeks. The distribution of light and heavy LDL particles, the percent apolipoprotein B, and the cholesterol to protein ratios were not different before and after fish oil in the type IV patients. However, the size distribution of VLDL changed...
had lower melting temperatures because of the increased amounts of n-3 FA cholesteryl esters (80). The reason for the decrease in LDL cholesteryl ester content may be explained by changes in the lecithin:cholesterol acyltransferase (LCAT) reaction. Parks, Rudel, and Bullock (81) in a recent report have suggested that HDL phospholipids rich in n-3 FAs are a poor substrate for LCAT. Thus, less cholesteryl ester may be synthesized during fish oil feeding leading to lower amounts of LDL-C. It is unlikely, however, that this also occurs in humans since fish oils do not generally affect the ratio of cholesterol to apolipoprotein B in LDL (35,44,56).

V. FISH OILS AND LIPOPROTEIN METABOLISM

A. Chylomicrons

Studies in which fish oil was fed to healthy volunteers have demonstrated that n-3 FAs are incorporated normally into chylomicrons (28, 82-84). Harris and Connor (85) reported that, in subjects consuming a diet rich in salmon oil, the postprandial rise in plasma triglyceride levels after an oral load of fish oil was blunted when compared to the rise observed when a control test meal was given during the control diet phase. Since this blunted response could have been caused by either inefficient fish oil digestion and absorption, slowed chylomicron formation, faster chylomicron removal, or a combination of these factors, further studies were conducted to examine the interaction of the fat in the background diet and the fat in the test meal. Those studies (28) revealed that the consumption of test meals containing 50 g of fish oil produced a normal rise in postprandial triglyceride levels when subjects were consuming their usual background diets (which contained no fish oil) (Fig. 5). However, when the background diets contained fish oil, the same oral load of fat (either fish oil or control fats) produced a significantly lower postprandial triglyceride increase. Thus, it appeared that chylomicron removal rates may have been enhanced, and/or fat absorption retarded by

<table>
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<th>TABLE 2. Effects of fish oil supplementation on lipoprotein chemical composition in five patients with type IV hyperlipidemia</th>
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*Patients took 6 g of n-3 FAs/day for 4 weeks.  
*, P < 0.05; **, P < 0.01.
Fish oils and lipoprotein metabolism

Thus, fish oils may reduce postprandial lipemia because of a reduced rate of lipolysis in the intestinal lumen.

These observations contrast with other in vivo observations in humans (noted above) in which a fish oil test meal caused a normal postprandial rise in plasma triglyceride levels when fed during a control background diet (28). Although the reasons for this apparent discrepancy are not known, the in vitro as well as the in situ studies may not have completely mimicked the in vivo situation in which a multitude of enzymes, cofactors, and gastrointestinal hormones all play a role in fat absorption.

The observed decrease in postprandial triglyceride levels during chronic fish oil feeding may have resulted from changes in the intraluminal digestive environment. In support of this, Nestel (35) observed that fish oil feeding blunted the expected rise in plasma cholesterol levels when large amounts of cholesterol were fed to human volunteers. It is possible that the n-3 FAs decreased cholesterol absorption as was observed by Chen et al. (88) in lymph-cannulated rats fed fish oil. These possibilities deserve further study.

2. Intracellular Chylomicron Formation

High tissue levels of n-3 FAs may affect the formation of the chylomicron particles in the enterocyte. Although this has not been directly investigated, the effects of n-3 FAs in hepatocytes have been studied. In the liver, these fatty acids are known to inhibit triglyceride synthesis and specifically the diacylglycerol acyltransferase (92) (see VLDL metabolism). Since triglyceride re-synthesis takes place in enterocytes during fat absorption (93), it is possible that this process is likewise inhibited by fish oil feeding. This would lead to a reduced rate of formation of chylomicrons secondary to sluggish triglyceride synthesis. As in the liver, this effect would only become evident after chronic treatment with fish oil, not after a single meal. This explanation fits with the data described above in which fat absorption was inhibited only when subjects were consuming fish oil-rich diets; both control fat and fish oil absorption were normal when fish oil was not in the background diet.

Can fish oil absorption be enhanced? n-3 FAs are absorbed more readily as free fatty acids than when esterified as triglycerides (90, 91). Emulsification may also enhance fish oil's absorption. Liu et al. (83) found that fish oil emulsified in an infant formula led to a higher plasma DHA level than the same amount of unemulsified oil given as a bolus to premature infants. In the absorption study described above (28), fish oil caused a normal rise in postprandial triglyceride levels when fed to normal volunteers eating their usual diets. The oil in these studies was blended in a liquid formula; it was not given as a bolus. Avarim, Brox, and Nordoy (84) reported that feed-
ing 100 g of cod liver oil to normal subjects did not raise postprandial plasma triglyceride levels as much as a saturated fat test meal containing cream did. This difference may have been due to the fact that the control fat was emulsified (in the cream) and the fish oil was not.

Preliminary studies in our laboratory with healthy volunteers, showed that chylomicron n-3 FAs levels were increased six times by giving fish oil (50 g) as a phospholipid emulsion as compared to the same amount of liquid fish oil (Fig. 6) (94). Thus, the physical form of the oil may alter its absorption rate. It should be noted that if emulsification enhances fish oil absorption, then hydrolysis of fish oil by pancreatic lipase may not be retarded since the emulsified triglyceride would still need to be hydrolyzed before absorption. Experiments using emulsified oil in control and fish oil-fed subjects would help determine whether chronic fish oil feeding affects intraluminal or post-absorptive processes.

3. Intravascular Chylomicron Catabolism

Decreased postprandial triglyceride levels with chronic fish oil feeding may result from an increased lipolytic rate and not from decreased absorption. There are several mechanisms by which this could occur. 1) Enhanced activity lipoprotein lipase (LPL) or hepatic triglyceride lipase (HTGL); or 2) facilitated interaction of chylomicrons with these enzymes because of higher n-3 FAs levels in the chylomicrons themselves, enrichment of the endothelial cell membranes with n-3 FAs, or reduced competition from VLDL.

As regards the first possibility, neither the activity of LPL nor of HTGL was found to be stimulated in fish oil-fed subjects when measured in vitro in postheparin plasma (43, 28). Enzyme activities were also not affected in chickens fed fish oil (95), and were even decreased in fish oil-fed rats (96). Herzberg and Rogerson (97) have suggested that while the activity of postheparin plasma LPL may not change, adipose tissue and/or muscle LPL may. The possibility that n-3 FAs in the chylomicron particles themselves somehow accelerate their clearance was investigated by Chen et al. who found that, both in vitro (98) and in vivo in rats (99), the presence of n-3 FAs in the chylomicrons did not affect the rate at which they were catabolized. Normal postprandial triglyceride levels in subjects given a fish oil test meal (28) also argue against enhanced removal of n-3 FA-containing particles.

Finally, chylomicrons may be able to interact with lipolytic enzymes more readily if competition from VLDL is reduced. It is well known that elevated plasma VLDL levels decrease the rate of chylomicron triglyceride removal (100-103). This presumably results from increased competition for LPL between these two particle types. Thus, the fish oil-induced reduction in postprandial lipemia may simply reflect a more rapid removal of chylomicron lipids because less VLDL is present to compete for removal mechanisms.

As attractive as this explanation may be, there is no difficulty with it. In the studies in which the blunted postprandial triglyceridemic effects were observed (28, 85), the mean plasma triglyceride levels during the control phases were about 80 mg/dl and during the fish oil phases, about 50 mg/dl. In order that the reduced-VLDL-competition mechanism could explain the reduced postprandial lipemia, one must assume that LPL was, to a significant extent, saturated at a triglyceride level of 80 mg/dl, and became less saturated at 50 mg/dl. Brunzell et al. (104) reported that the LPL does not appear to approach saturation until levels of 500 mg/dl are reached.

Several groups have studied the effects of fasting triglyceride levels on postprandial increases in triglyceride after a fatty meal (100-103). They have clearly shown that individuals who have high fasting triglycerides also have exaggerated postprandial triglyceridemic responses. Only Patsch et al. (102) confined their studies to normotriglyceridemic subjects. Although higher fasting triglyceride levels were weakly associated with higher postprandial triglyceride elevations (r = 0.45), the authors concluded that variations in postprandial lipemia were a function of differences in HDL2 levels; LPL saturation was not discussed. Thus, there is little evidence that fish oils accelerate chylomicron clearance and even less from which to conclude that the mechanism of this theoretical effect is via reduced competition from VLDL.

Preliminary findings that a prostaglandin inhibitor can reduce postprandial lipemia (105) suggest the intriguing
possibility that n-3 FAs may, via their participation in eicosanoid metabolism, influence postprandial lipid metabolism. Further studies are needed to examine the effects of fish oil supplements on postprandial lipoproteins and to determine whether chylomicron remnant levels are reduced. Since these particles have been implicated in the atherosclerotic process (106), reducing their levels by fish oil ingestion would be potentially beneficial and might help explain the reduced rate of coronary disease among fish eating populations.

B. Very Low Density Lipoproteins

1. Human Studies

Four studies in humans have examined the mechanism of the triglyceride-lowering effect of n-3 FAs (26, 34, 62, 107). They all provided evidence that fish oils reduce the rate of hepatic secretion of VLDL-triglyceride. Harris et al. (26) found that n-3 FAs prevented and rapidly reversed carbohydrate-induced hypertriglyceridemia in normolipidemic patients. Since carbohydrate feeding is known to stimulate triglyceride synthesis and VLDL secretion (108), this finding suggested that n-3 FAs inhibit hepatic triglyceride synthesis. Nestel et al. (34) examined the kinetics of VLDL apoB and triglyceride in patients consuming large amounts of fish oil. They found that synthetic rates for both components were reduced by more than 50%. They also reported that some of their patients appeared to have independent secretion of LDL particles (i.e., LDL that did not arise from VLDL) while on a high fish oil diet. This observation implied that the liver may secrete abnormally dense VLDL particles during fish oil feeding as Sullivan et al. (44) have also suggested. Connor (107) reported that high doses of fish oil inhibited VLDL triglyceride synthesis (Fig. 7), as did Sanders et al. (62) when smaller amounts of oil (15 ml/day) were fed. The effects of lower intakes of n-3 FAs on apoB synthesis and secretion have not been examined in humans.

In all three of the kinetic studies (34, 62, 107), there were tendencies (sometimes significant (107)) toward increased fractional catabolic rates (FCRs) during the fish oil period. Since fish oil feeding does not appear to stimulate lipolytic enzymes (see above), how can these increases in FCRs be explained? One must first appreciate that the FCR is calculated as the reciprocal of the residence time of the labeled material in the VLDL density range. This is determined from the slope of the VLDL radioactivity decay curve. Residence times may be shortened by at least two separate mechanisms: 1) an increase rate of particle catabolism (i.e., lipolytic rate), or 2) a decreased size (increased density) of the particle at entry into the VLDL density range. These abnormally dense particles would, even with an unchanged lipolytic rate, leave the VLDL density range more rapidly than normal VLDL by virtue of entering the pool at a smaller size. This would produce an increase in the FCR even though the lipolytic rate was not affected.

In the author's view, the latter mechanism is more plausible than the former because it is consistent with the data showing that VLDL from patients fed fish oil are smaller than normal (44), that triglyceride-poor VLDL is secreted from hepatocytes treated with n-3 FAs (see below), and that LDL may arise independently of VLDL catabolism in subjects fed fish oil (34). Studies examining the rate of removal of triglyceride-rich lipoproteins infused by vein in subjects on and off fish oil would help clarify these issues.

2. Potential Mechanisms

Several animal studies and in vitro investigations have documented the inhibition of hepatic triglyceride synthesis by n-3 FAs (92, 109-121) (Table 3). Triglyceride and apoB secretion from human hepatoma cells (HepG2) was reduced by prior incubation with n-3 FAs (109). Wong et al. (110) demonstrated that the reduction in triglyceride synthesis was accompanied by an increase in ketone production in perfused livers from rats fed fish oil. Induction of peroxisomal β-oxidation appeared to cause the increase in ketogenesis (111, 121). (Interestingly, the peroxisomal proliferation seen with fish oil is also seen with clofibrate, a drug which also lowers triglyceride levels (122). However, unlike clofibrate, fish oil does not reduce the activi-
ties of hepatic detoxifying enzymes (121) and thus, fish oil may be safer than the drug.

The enzymatic mechanisms by which n-3 FAs inhibit triglyceride synthesis have been examined by several investigators. Acutely, EPA and DHA were shown to be poor substrates for esterification to glycerol (112). Inhibition of the activity of diacylglycerol acyltransferase (92, 116) or phosphatidate phosphohydrolase (117) have been reported in rat hepatocytes treated with n-3 FAs. EPA has been shown to inhibit de novo FA synthesis (118, 120) and actually to reduce the amount of acetyl CoA carboxylase in rat livers (119). Clarke and Armstrong recently reported preliminary studies in which fish oil reduced the amount of hepatic m-RNA for the enzyme. Acyl-CoA:cholesterol acyltransferase is also inhibited by n-3 FAs in rat hepatocytes (124). Finally, n-3 FAs inhibit activity of delta-6 and delta-9 desaturases in rat liver leading to reduced synthesis of arachidonic acid from linoleic acid (114, 115). All of these effects fit well with the human kinetic data indicating that n-3 FAs inhibit VLDL triglyceride secretion.

C. Low Density Lipoproteins

1. Human Studies

Illingworth, Harris, and Connor (30) examined the effects of high doses of fish oil on LDL metabolism in normolipidemic humans. They reported that LDL-C levels and LDL apoB synthesis were reduced by feeding about 90 g of fish oil per day. This was taken as evidence for a reduction in VLDL apoB secretion rates since LDL apoB is derived from VLDL apoB in normolipidemic subjects (125). (However, as discussed previously, the decrease in saturated fat intake during the fish oil period may have contributed to the lower LDL levels and to the observed decrease in LDL synthetic rates.) There are no studies examining the effects of n-3 FA supplementation on LDL metabolism. Since LDL-C levels have been shown to increase with supplementation in hypertriglyceridemic patients, an examination of LDL kinetics in this setting would be most interesting.

2. Potential Mechanisms

How can one reconcile a reduced rate of synthesis of the precursor particle (VLDL) with an unchanged or increased level of the product (LDL)? Clearly either the LDL synthetic rate increased or the removal rate decreased (Fig. 8). Reciprocal changes in VLDL and LDL have been reported in hypertriglyceridemic patients treated with fibric acid derivatives (122, 126, 127) or after weight loss (128). In both of these cases, a decrease in the FCR was responsible for the rise of LDL-C levels (127, 128). Similarly, chickens fed n-3 FAs exhibited a decreased LDL FCR (95), and dogs fed fish oil tended to have reduced numbers of LDL receptors in their livers (129). Wong and Nestel (109) recently reported that LDL binding to HepG2 cells was inhibited by preincubation with linoleic acid (long known to lower LDL levels) also reduced LDL binding. In other studies, linoleic acid was reported to enhance LDL uptake and degradation in human peripheral blood mononuclear cells (130). Thus, there are contradictory findings in these different cell populations.

LDL-C levels increase primarily in patients with elevated VLDL levels and not in those with normal VLDL levels. If n-3 FAs reduced LDL receptor activity, they might be expected to do so in all subjects, not just in those with hypertriglyceridemia, and LDL-C levels might increase in all subjects. Thus, n-3 FAs probably do not interfere with receptor activity in humans, and the rise in LDL-C levels is likely to result from enhanced LDL synthesis from VLDL as suggested by Huff and Telford (131). Clearly the effects of n-3 FAs on LDL receptor activity will require further evaluation.

Although it might seem unlikely that an agent that so effectively lowers VLDL levels could raise LDL levels, one must realize that only certain VLDL particles are converted into LDL (Fig. 8). The liver appears to secrete both large (triglyceride-rich) VLDL particles and smaller VLDL particles (132). The smaller particles are approximately the size of the remnant particles arising from the LPL-mediated catabolism of the large particles. There
appear to be metabolic differences between these particles since the remnant particles are not converted into LDL as readily as the small VLDL are (132, 133). Remnant particles may be richer in apoE than small VLDL and thus more readily bound to hepatic apoB/E receptors and removed prior to conversion (by HTGL (134)) to LDL. In any event, fish oil feeding may selectively reduce the secretion of the smaller VLDL particles (which account for most of the plasma triglycerides) while, at the same time, increasing the output of the larger (pre-LDL) particles. Should this be the case, the LDL levels might increase despite an overall decrease in VLDL triglyceride mass. An alternative hypothesis from the studies of Gianturco et al. (135) would suggest that fish oil might produce VLDL particles which more effectively compete with LDL for receptor-mediated hepatic removal. Thus, LDL levels might increase because of increased competition for removal mechanisms. All of these potential pathways warrant investigation.

Finally, many of the fish oil studies have been done with cod liver oil, salmon oil, menhaden oil, or MaxEPA, all of which contain appreciable cholesterol and saturated fat. Thus, taking fish oil as a supplement to the diet could lead to an increased intake of saturated fat and cholesterol, and could thereby raise LDL levels. Although this potential mechanism also merits more investigation, a recent trial using a supplement of n-3 FA ethyl esters containing essentially no cholesterol or saturated fat still increased LDL-C and apoB levels in hypertriglyceridemic patients (Fig. 9) (56). Clearly, future studies will be needed to explain the effect of fish oils on LDL-C levels, and to assess the risks and benefits of fish oil supplementation in hyperlipidemic patients.

3. Atherogenicity of LDL

Is LDL as atherogenic in a patient taking fish oil as in those not doing so? While there are no direct data from which to answer this question, the reported reduction in atherosclerosis in swine fed fish oil (which occurred without lowering LDL-C) would suggest that maybe it is not (136). (It should be noted, however, that in studies in rats (137), nonhuman primates (138), and rabbits (139), fish oil-induced reductions in atherosclerosis were accompanied by reductions in plasma cholesterol levels.) Dehmer, Popma, and van den Berg (140) recently reported that fish oil supplements reduced the rate of restenosis following percutaneous, transluminal coronary angioplasty. Pertinent to this discussion was the observation that LDL-C levels tended to increase in the treated group.

In a recent report from Germany, LDL particles derived from subjects fed fish oil did not suppress prostacyclin synthesis in cultured endothelial cells as much as control LDL did (141). Monkeys fed fish oil incorporated large amounts of EPA into LDL cholesteryl esters which led to a marked disordering of the lipid core and a lowering of the LDL transition temperature (80). Greater fluidity of
Type IV Patients

Fig. 9. Plasma cholesterol (CHOL), triglyceride (TRIG), lipoprotein cholesterol (VLDL, LDL, HDL-C), and apolipoprotein B (ApoB) levels (mean ± SEM) in hypertriglyceridemic patients given 12 g of fish oil versus 12 g of safflower oil placebo for 6 weeks. Seven type IIb patients and 11 type IV patients were studied; open bars, placebo; dark bars, fish oil; *, P < 0.05; **, P < 0.01. Taken from Harris et al. (56).

the LDL core has been associated with reduced atherogenicity of the particle. These observations suggest that fish oil-induced changes in the LDL particle itself (or in the arterial milieu) may inhibit atherogenesis. Studies of the interaction between cells and LDL derived from subjects fed fish oil seem warranted.

D. High Density Lipoproteins

There have been no studies of HDL kinetics in humans fed n-3 FAs. Since HDL-C levels have tended to rise with fish oil supplementation (Fig. 1), such studies should be of interest. It is perhaps not surprising that fish oil treatment might increase HDL-C levels in view of the well-known inverse relationship between plasma triglyceride levels and HDL-C (142).

VI. FISH VERSUS FISH OIL SUPPLEMENTS

Kromhout, Bosschieter, and Coulnader (143) found that, over a 20-year period, heart attack rates were significantly lower in men reporting daily fish intakes of about 30 g compared to men reporting no fish intake. This same relationship was found in the Western Electric Study (144), but not in other similar (although shorter) studies (145, 146).

Was this effect the result of the n-3 FAs in the fish? The amount of fish reportedly consumed in the Kromhout trial would provide less than 1 g of n-3 FAs per week (roughly equivalent to one capsule of fish oil concentrate every other day). Since there are essentially no experimental data available on the effects of such low intakes over long periods of time, this question cannot be answered at present.

As noted in Table 1, several authors used fatty fish as their source of n-3 FAs. In most of these studies, fish was given instead of foods rich in saturated fats, control groups were not included, and study durations were short (less than 4 weeks). Among the studies of longer duration, Singer et al. (42) fed volunteers three tins of mackerel per week (about 1 g of n-3 FAs per day) for 8 months and found no statistically significant change in any lipid or lipoprotein parameter. Fehily et al. (24) studied 118 men who increased their intake of fatty fish by 10-fold to about 45 g/day for 3 months. Despite instructions to concomitantly decrease their meat and cheese intakes during the fish oil phase, no changes in total LDL or HDL cholesterol levels were noted, and triglycerides fell by only 6%.

Thus, although it appears prudent to recommend that patients substitute fish for other meats higher in saturated fat, there is little experimental evidence to show that this change alone will favorably affect plasma lipoprotein levels. Nevertheless, increased fish consumption may lead to long-term health benefits mediated via currently unknown mechanisms.

VII. LINOLENIC ACID VERSUS FISH OILS

It is well known that mammalian cells have the ability to synthesize EPA from linoleic acid (147). However, this transformation is quite slow, especially in people eating typical western diets rich in linoleic acid [18:2(n-6)] which competes for the same desaturase (148). Studies in humans comparing linseed oil (55% linoleic acid) to fish oils have found that the latter increase tissue EPA levels 10 times more efficiently (3). Sanders and Roshana (40) showed that 20 ml of fish oil lowered plasma lipids, whereas 20 ml of linseed oil did not. However, in these and other (149, 150) relatively short-term studies, there were small but significant increases in phospholipid EPA and DHA levels. Since the conversion on linolenic acid to
EPA is slow, long-term studies will be needed to examine the potential of linolenic acid to produce physiologically significant levels of EPA in man.

VIII. FISH OILS IN THE TREATMENT OF HYPERLIPIDEMIA

As is evident from the studies reviewed here, fish oils are most effective at lowering fasting plasma triglyceride levels. As a rule, n-3 FAs do not cause total cholesterol levels to change significantly, but HDL-C is generally raised 5-10%. LDL-C responds to fish oil feeding differently depending on the phenotype; the higher the triglyceride level, the greater the rise in LDL-C tends to be. It is this effect that complicates the picture when considering how fish oils may be used in clinical medicine. Is the decrease in VLDL-C and triglyceride levels worth the increase in HDL-C? In dealing with this question, it must be appreciated that changes in coronary heart disease (CHD) risk do not always follow changes in LDL-C levels (as noted in section V:C,3). All studies incriminating LDL as the atherogenic lipoprotein have been conducted in persons not taking significant amounts of EPA and DHA in their diet. Since these FAs may significantly alter other atherosclerotic risk factors (see reviews 11, 12), the disease process may not be enhanced by a 15-20% increase in LDL-C. At this point, it is not known how changes in lipoprotein levels influence CHD risk in persons with relatively large amounts of n-3 FAs in their tissues.

Since elevated triglyceride levels are not generally regarded as independent risk factors for CHD, why be concerned about them? There are several good reasons why VLDL in hypertriglyceridemic patients should be reduced. First, data from the Framingham Heart study has shown that 90% of hypertriglyceridemic individuals are, in fact, at increased risk for CHD; the exception being the 10% of patients with low total to HDL cholesterol ratios (151). In women over age 50, triglyceride levels are independently correlated with CHD risk and are even better predictors than LDL-C levels (152). Carlson, Bottiger, and Ahfeldt (153) in the Stockholm Prospective Study found that serum triglyceride levels were independent predictors of subsequent myocardial infarction in both sexes.

Gemfibrozil was recently shown to lower coronary risk in the Helsinki Heart Study (154). This drug lowered VLDL levels by 40%, raised HDL-C levels by 8%, and lowered LDL-C by only about 9%. Since gemfibrozil and fish oils appear to produce similar changes in VLDL and HDL, one might expect that n-3 FAs may be antiatherogenic as well.

Mechanisms to explain the relationship between elevated triglyceride levels and CHD risk have been proposed by Gianturco and associates (135, 155-158). VLDL from hypertriglyceridemic patients (HTG-VLDL) interacts with the LDL receptor much as LDL itself does. HTG-VLDL, but not normal VLDL, is toxic to cultured endothelial cells (157) and can convert murine peritoneal macrophages into foam cells in vitro (158). These effects appear to be mediated via apoE which assumes a unique conformation in HTG-VLDL (156). Thus HTG-VLDL can deposit cholesterol in tissues, is cytotoxic, and may be atherogenic.

The most obvious group of patients to benefit from fish oil supplementation would be those with extremely high triglyceride levels, the type V patients (59). Since these patients can be at high risk for acute pancreatitis, their triglyceride levels should be reduced as quickly as possible. Simons, Hickie, and Balasubramaniam (51) found that 4.6 g of n-3 FAs per day would lower triglycerides by 58% in type V patients. That intake could be achieved by consuming three capsules containing 500 mg of n-3 FAs per day. In the author's experience, fish oil supplements can substantially lower triglyceride levels within a few days to a week at most.

Fish oil has also been shown to lower triglyceride levels that are elevated secondary to other metabolic disorders (nephrotic syndrome, type II diabetes (37, 46, 159-162)) or as a side effect of drug treatments (163). Since LDL-C levels frequently increase in these settings, it would be prudent to carefully monitor lipoprotein levels.

Fish oils are potentially important agents in the treatment of hypertriglyceridemia. They are effective nutritional substances which are not known to have any serious side effects. There are currently no hypotriglyceridemic drugs that have a better risk:benefit ratio than n-3 FAs.

Finally, a case could be made for providing low levels of n-3 FAs (0.3 to 1 g (one or two capsules)/day) to any patient at increased risk for CHD, especially if that patient cannot or will not increase fish intake. This level of supplementation would provide as much n-3 FA as consuming three 100-g servings of salmon per week, and would surpass the n-3 FA intake associated with reduced coronary events in the study of Kromhout et al. (143). Although this low dose may have little, if any, measurable effect on plasma lipid levels, it may, in the long run, slow the progression of atherosclerosis, and the potential risk to the patient from this intake is essentially nil.

IX. SUMMARY AND CONCLUSIONS

Dietary n-3 FAs have a variety of effects on plasma lipids and lipoproteins. They lower plasma triglyceride levels in virtually all patients. Total and LDL cholesterol
levels are usually not affected unless compared to a diet richer in saturated fat, in which case they will decrease. HDL-C levels are often increased by 5-10%. Hypertriglyceridemic patients usually experience increases in LDL-C levels with fish oil supplementation. The impact of these changes on cardiovascular risk levels must be evaluated in light of the reported beneficial effects of n-3 FAs in platelet function, blood pressure, blood flow, inflammatory processes, atherosclerosis, etc. (9, 11, 12).

Atherosclerosis is a multi-factorial disease. Dietary fish oils may affect many risk factors which, taken together, may explain the lower death rate from myocardial infarction seen in fish-eating populations. Nevertheless, much work remains to be done before the apparent health benefits enjoyed by fish-eating populations can be attributed solely to n-3 FAs. Future research will be needed to define the amount and duration of n-3 FA supplementation required to produce beneficial effects, to explore the usefulness of linolenic acid as a source of EPA, to assess the safety of long-term fish oil consumption, to describe the mechanisms by which they function, and finally, to determine the role of these unique dietary lipids in the prevention and treatment of human disease.

ADDENDUM

While this manuscript was in review, three papers were published that merit special attention. Failor, Childs, and Bierman (164) reported on the effects of salmon oil (35% of calories) versus safflower oil and a control fat in normals and in patients with familial combined hyperlipidemia (FCHL). Their report nicely illustrates the effects of fish oil; triglyceride levels fell in all subjects. LDL-C levels were reduced in the normal subjects compared to the control (high saturated fat) diet, but they were not different from the LDL-C levels of subjects on a safflower oil diet. Fish oil raised the LDL-C levels in the FCHL patients in spite of the concomitant decrease in saturated fat.

The first reported case of a hypertriglyceridemic patient not responding to fish oil therapy was described by Stacpoole et al. (165). Kinetic studies showed that fish oil did not inhibit triglyceride synthesis in one of the two reported patients both of whom had lipodystrophic diabetes mellitus. In the other patient, triglyceride levels and synthetic rate fell with no increase in the VLDL-triglyceride FCR.

Finally, readers interested in a thorough discussion of n-3 FA absorption and transport are referred to a recent review of this topic by Nelson and Ackman (166).

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