Fish Oil Supplementation Reduces $\beta$–Very Low Density Lipoprotein in Type III Dysbetalipoproteinemia

Jean Dallongeville, Lucie Boulet, Jean Davignon, and Suzanne Lussier-Cacan

$\beta$–Very low density lipoproteins ($\beta$-VLDLs) are atherogenic, cholesterol-rich chylomicron and VLDL remnants that accumulate in the plasma of type III dysbetalipoproteinemic subjects. To evaluate the effect of fish oil supplementation on plasma $\beta$-VLDL concentrations, we compared the lipid and lipoprotein responses in nine type III and nine type IV hyperlipidemic subjects. Each individual received 6 g/day $\omega$-3 fatty acids for 12 weeks. Before treatment, the mean total cholesterol, total triglyceride, VLDL triglyceride, low density lipoprotein (LDL) cholesterol, and high density lipoprotein (HDL) cholesterol levels were not different between groups. Conversely, VLDL cholesterol, intermediate density lipoprotein (IDL) cholesterol, and IDL triglycerides were higher in type III than in type IV subjects. Fish oil supplementation was associated with significantly lower levels of cholesterol (~50%), triglycerides (~50%), and apolipoprotein B (~50%) in the $d<1.006$ g/ml ultracentrifugation plasma fraction in both groups, compatible with a reduction in VLDL in type III and type IV subjects, and in $\beta$-VLDL in type III subjects. This finding was confirmed by analysis of the plasma zonal ultracentrifugation profile and the agarose gel electrophoretic pattern of lipoproteins, which showed a reduction in but not a disappearance of remnant particles, suggesting that not all $\beta$-VLDL had been cleared after treatment. The levels of IDL cholesterol and IDL triglycerides ($1.006<d<1.019$ g/ml) were not affected in either group. Initially low LDL cholesterol ($1.019<d<1.063$ g/ml) and HDL cholesterol levels rose significantly in both groups. In type III hyperlipidemics, all LDL cholesterol values remained below 120 mg/dl, whereas they were higher than 150 mg/dl after treatment in two individuals with type IV hyperlipidemia. In conclusion, our results demonstrate that fish oil supplementation is equally effective in lowering total triglycerides and triglycerides in the $d<1.006$ g/ml plasma fraction in type III and type IV hyperlipidemias. In addition, fish oils reduce chylomicron and VLDL remnant concentrations in type III dysbetalipoproteinemia. (Arteriosclerosis and Thrombosis 1991;11:864–871)

Type III dysbetalipoproteinemia is a lipid disorder characterized by the accumulation in plasma of cholesterol-rich very low density lipoproteins (VLDLs), that is, $\beta$-VLDL. These heterogeneous lipoproteins are made up of remnants of both hepatic and intestinal origin. Normally, remnants are rapidly cleared from the plasma through apolipoprotein (apo) E–mediated liver uptake and are detected only in postprandial plasma. Replacement of an arginine by a cysteine in position 158 of the 299-amino acid chain of apo E$^\epsilon$ is responsible for the defective binding of chylomicron and VLDL remnants to cell receptors in type III hyperlipidemic subjects. In vivo this phenomenon is associated with the slower plasma clearance of these particles. However, for $\beta$-VLDL to accumulate in the plasma of E2/2 subjects, other factors that may contribute to increased production or defective lipolysis of VLDL are necessary.

Endogenous hypertriglyceridemia (type IV) is a multifactorial disorder of lipid metabolism defined by elevated levels of VLDL. As in type III hyperlipidemia, VLDL accumulation in plasma of type IV subjects is due to the increased production and/or defective catabolism of VLDL. However, the apo E–mediated uptake of remnants is not altered in type IV, nor is there
an important remnant accumulation in plasma.\textsuperscript{11} Endogenous remnantidemia is commonly found in the families of type III hyperlipidemic probands, suggesting that it may contribute to the phenotypic expression of type III in E2/2 subjects.\textsuperscript{12}

The effects of \(\omega-3\) fatty acids extracted from fish oils on plasma lipoprotein metabolism have been recently reviewed.\textsuperscript{13} These appear to exert their primary influence on VLDL metabolism by inhibiting triglyceride and VLDL apo B production.\textsuperscript{14} Fish oils may also alter VLDL composition or structure in such a way that lipolysis of triglycerides is increased.\textsuperscript{15} The combined effect of decreased VLDL production and increased lipolysis may explain the reduced postprandial lipemia observed after ingestion of a fat load by normolipidemic individuals supplemented with \(\omega-3\) fatty acids.\textsuperscript{15,16} Therefore, we have hypothesized that \(\omega-3\) fatty acids reduce VLDL and chylomicron remnant concentrations in type III dysbetalipoproteinemia. To demonstrate this effect, the plasma lipid and lipoprotein response to fish oil supplementation of subjects with this disorder was studied and compared with that of subjects with type IV endogenous hypertriglyceridemia.

\section*{Methods}

\subsection*{Patients}

The study included nine subjects with type III dysbetalipoproteinemia and nine subjects with endogenous type IV hypertriglyceridemia. The study was approved by the institutional ethics committee, and informed consent was obtained from each participant. Type III hyperlipidemic subjects. These included eight men and one woman aged 40–65 years (mean±SD, 50±8.6 years). All subjects had triglyceride levels above 200 mg/dl, \(\beta\)-VLDL on agarose gel electrophoresis, and apo E phenotype E2/2 (arginine\textsuperscript{158}→cysteine).\textsuperscript{17} They had no secondary causes of hyperlipidemia such as diabetes, thyroid dysfunction, obesity (≥20% ideal body weight), or excessive alcohol intake (>30 g/day). Two subjects had no clinical signs of dysbetalipoproteinemia; the other seven had at least one or more of the following: arcus corneae, orange pigmentation of palmar creases, xanthoma eruptivum, xanthoma striata palmarum, or xanthoma tendinosum. Three subjects had peripheral vascular disease, and one had a history of coronary artery disease. Except for one subject who was taking indapamide and pindolol for hypertension, these subjects were not receiving any other drugs.

Type IV hyperlipidemic subjects. These included eight men and one woman aged 37–67 years (mean±SD, 45.5±11 years). All subjects had total triglyceride levels above 200 mg/dl, low density lipoprotein (LDL) apo B below 110 mg/dl, and apo E phenotype E3/3 (except for one subject with E4/3). Selection criteria also included the absence of secondary causes of hypertriglyceridemia such as mentioned previously. One subject had xanthelasma.

There was no concurrent medication except for one subject who was taking allopurinol for gout.

\subsection*{Control group}

A group of normolipidemic subjects was selected to determine control values. These were nine healthy normolipidemic subjects (five women and four men), aged 22–48 years (mean±SD, 30.8±6 years), who were members of our laboratory staff. All had the apo E3/3 phenotype except for one subject with E4/3. Three women were taking oral contraceptives, and one man was taking allopurinol for urolithiasis. Blood samples were drawn at 4-week intervals for plasma fatty acid and lipoprotein composition analysis.

\subsection*{Procedure}

This investigation was a comparative study of the effect of \(\omega-3\) fatty acids in type III and type IV hyperlipidemic subjects. All subjects received 6 g \(\omega-3\) fatty acids (56% eicosapentaenoic and 24% docosahexaenoic) in the form of 12 capsules of Promega daily (Parke-Davis, Scarborough, Canada) for 12 weeks. Blood samples were drawn one week before baseline (week −1), at baseline, and after 4 and 12 weeks of treatment. There were no statistically significant differences between the results obtained at week −1 and at baseline. To minimize extraneous alterations in plasma lipids, all subjects were placed on a diet low in cholesterol, saturated fat, concentrated sugars, and alcohol for at least 8 weeks before blood sampling. The patients' food intakes were evaluated by a dietitian 1 and 8 weeks before baseline and after 2 and 4 weeks of treatment. Body weight was kept constant during the 12 weeks of the experiment. Compliance was assessed at each visit by interview, questionnaire, and analysis of plasma phospholipid fatty acid composition by gas chromatography.\textsuperscript{18} Eicosapentaenoic and docosahexaenoic fatty acids rose from 0.9±0.7% to 4.7±3% and from 1.3±1.4% to 3.5±3%, respectively, in type III subjects and from 2.3±1% to 4.9±2% and from 1.1±0.8% to 3.2±1% in type IV subjects. Simultaneously, there were no significant changes in the fatty acid profile in normolipidemic subjects (1.4±1.4% to 1±1% and 0.2±0.4% to not detectable).

\subsection*{Plasma lipid and lipoprotein concentrations}

Plasma lipoproteins were separated under standard conditions by a combination of ultracentrifugation (at \(d=1.006\) and \(d=1.019\) g/ml) and heparin–manganese precipitation according to the Lipid Research Clinics protocol.\textsuperscript{19} Intermediate density lipoprotein (IDL) cholesterol and IDL triglyceride concentrations corresponded to the difference between measurements made on the \(d=1.006\) and \(d=1.019\) g/ml ultracentrifugation infranatants. LDL cholesterol concentrations were obtained after heparin–manganese precipitation of the \(d>1.019\) g/ml fraction for high density lipoprotein (HDL) measurement. HDL\textsubscript{2} and HDL\textsubscript{3} cholesterol were determined after precipitation of HDL\textsubscript{2} with dextran sulfate.\textsuperscript{20} Plasma lipid and lipoprotein cholesterol\textsuperscript{21} and triglyceride\textsuperscript{22} concentrations were measured enzymatically (Abbott Bichromatic Analyzer 100, Abbott Laboratories, Pasadena, Calif.).
Compositional analysis. Compositional analysis was performed on the $d<1.006 \text{ g/ml}$ plasma fraction separated by sequential ultracentrifugation ($1.5 \times 10^8 \text{ g \cdot min, 18 hours}$ at $d=1.006 \text{ g/ml}$. All fractions were dialyzed against a phosphate buffer, 0.01% EDTA (pH=7.4). Total cholesterol, free cholesterol, triglycerides, and phospholipids were determined enzymatically (Boehringer Mannheim, Mannheim, FRG). Cholesterol ester mass was calculated as (total cholesterol minus free cholesterol) times 1.68. Protein concentration was determined according to Lowry et al. with bovine serum albumin as the standard.

Zonal ultracentrifugation. Rate zonal ultracentrifugation of whole plasma was performed according to Patsch et al. by use of a Beckman Model L8-M ultracentrifuge (Beckman Instruments Inc., Palo Alto, Calif.) equipped with a Z-60 zonal rotor and an NaBr linear density gradient of 1.00-1.30 g/ml. The effluent was monitored continuously at 280 nm (model UA-5 absorbance monitor, Isco Inc., Lincoln, Neb.), and the density was measured with a Paar Model DMA-40 density meter (A. Paar KG, Graz, Austria).

Other measurements. Agarose gel electrophoresis was performed according to Noble with a Beckman electrophoresis kit. Briefly, five microliters of the $d<1.006 \text{ g/ml}$ plasma fraction was applied on a 0.5% agarose gel. Electrophoresis was performed for 1 hour in a barbital buffer (pH 8.6) at 100 V. Gels were stained in 0.07% Sudan black B and scanned with an optical densitometer (E-C Apparatus Corp., St. Petersburg, Fla.). The surface area under the curve was determined for $\beta$- and pre-$\beta$-VLDL by two independent observers (with <10% variation between the two measurements) using the CHROMATOCHART software (Interactive Microwave, Inc., State College, Pa.). The ratio of $\beta$- to pre-$\beta$-VLDL surface area was calculated and used as an estimate of the relative amount of $\beta$-VLDL. Apo B concentration was measured by electroimmunoassay in total plasma and in the $d>1.006 \text{ g/ml}$ plasma density fraction. The apo E phenotype was determined by isoelectric focusing of VLDL apolipoproteins.

Statistical Analysis

A two-way analysis of variance (hyperlipidemic group and treatment) with repeated measures on one factor (treatment) was performed, followed by a multiple comparison test. The level of significance was $p<0.05$.

Results

Fish oil supplementation was well tolerated by all patients. Although one third complained of gastric discomfort and fishy-smelling breath or taste, none of them had to interrupt the treatment.

Before treatment, type III subjects had cholesterol-enriched VLDL ($d<1.006 \text{ g/ml lipoproteins}$) as suggested by their higher VLDL cholesterol to triglyceride ratios ($p<0.0005$), higher levels of IDL cholesterol ($p<0.0005$), and higher IDL triglyceride levels ($p<0.05$) compared with those of type IV hyperlipidemic subjects, despite comparable levels of total and $d<1.006 \text{ g/ml}$ triglyceride concentrations. The differences were explained by $\beta$-VLDL accumulation in the type III plasma, which is illustrated in Figure 1 (baseline curve).

The plasma lipid and lipoprotein concentrations of type III and type IV hyperlipidemic subjects before and after 4 and 12 weeks of treatment with 6 g daily of $\omega-3$ fatty acids are presented in Tables 1 and 2. Fish oil supplementation caused a similar and significant reduction in total triglycerides, VLDL triglycerides, and VLDL cholesterol in both groups (probability values shown in tables). All subjects reduced their lipid concentrations in the $d<1.006 \text{ g/ml}$ plasma density fraction (Figure 2). However, cholesterol levels in the $d<1.006 \text{ g/ml}$ plasma fraction of type III subjects remained significantly higher than those of type IV subjects after treatment ($p<0.05$). IDL
TABLE 1. Plasma Lipid and Lipoprotein Concentrations in Nine Type III Dysbetalipoproteinemic Subjects Before and After ω-3 Fatty Acid Supplementation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>4 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chol</td>
<td>230±55</td>
<td>213±39</td>
<td>208±31</td>
</tr>
<tr>
<td>TG</td>
<td>459±149</td>
<td>176±55</td>
<td>207±56†</td>
</tr>
<tr>
<td>VLDL chol</td>
<td>90±45</td>
<td>36±12†</td>
<td>39±19†</td>
</tr>
<tr>
<td>VLDL TG</td>
<td>414±142</td>
<td>140±46†</td>
<td>174±61†</td>
</tr>
<tr>
<td>IDL chol</td>
<td>12±3</td>
<td>8±6</td>
<td>12±5</td>
</tr>
<tr>
<td>IDL TG</td>
<td>13±5</td>
<td>10±5</td>
<td>9±3*</td>
</tr>
<tr>
<td>LDL chol</td>
<td>97±25</td>
<td>135±27‡</td>
<td>122±28‡</td>
</tr>
<tr>
<td>HDL chol</td>
<td>30±7</td>
<td>34±8*</td>
<td>34±12*</td>
</tr>
<tr>
<td>HDL2 chol</td>
<td>6±2</td>
<td>8±6</td>
<td>7±5</td>
</tr>
<tr>
<td>HDL3 chol</td>
<td>25±6</td>
<td>26±4</td>
<td>27±8</td>
</tr>
<tr>
<td>VLDL apo B</td>
<td>81±39</td>
<td>24±10‡</td>
<td>26±15‡</td>
</tr>
<tr>
<td>VLDL chol/total TG</td>
<td>0.18±0.04</td>
<td>0.21±0.04</td>
<td>0.18±0.04</td>
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</table>

Values are expressed in mg/dl (mean±SD).

Chol, cholesterol; TG, triglycerides; VLDL, very low density lipoprotein; IDL, intermediate density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; apo, apolipoprotein.

*Significantly different from baseline: p<0.05, †p<0.005, ‡p<0.0005.

cholesterol and IDL triglyceride concentrations were found not to be statistically different after treatment in either group. During fish oil supplementation, significant increases in LDL (1.019<d<1.063 g/ml) and HDL cholesterol concentrations occurred in type III (p<0.05, p<0.05) and type IV (p<0.005, p<0.05) subjects (Tables 1 and 2). LDL cholesterol concentrations remained below 120 mg/dl in all type III

TABLE 2. Plasma Lipid and Lipoprotein Concentrations in Nine Type IV Hyperlipidemic Subjects Before and After ω-3 Fatty Acid Supplementation

<table>
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<td>HDL3 chol</td>
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<td>26±4</td>
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</tr>
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*Significantly different from baseline: p<0.05, †p<0.005, ‡p<0.0005.

FIGURE 2. Line plots showing changes as a function of time (weeks) in levels of plasma VLDL, IDL, LDL, and HDL cholesterol (all in mg/dl) in nine patients with type III and nine patients with type IV hyperlipidemias. VLDL, very low density lipoprotein; IDL, intermediate density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; -C, cholesterol.
peak of LDL. Fish oil supplementation induced a front extending from the initial effluent volume to density ranges corresponding to /J-VLDL and to a low hyperlipidemic profile was characterized by a massive changes were noted in the control subjects, who were significantly enriched in cholesterol after treatment relative to that of type IV subjects and controls. No changes were noted in the control subjects, who were following their usual diets.


density ranges (Figure 3). In type IV hyperlipidemic subjects, the decrease in the mass of large VLDL was accompanied by an increase in LDL mass and/or the appearance of small and dense VLDL (Figure 3, panels 3 and 4). There was no change in mean LDL density with treatment (from 1.148±0.004 to 1.115±0.004 g/ml).

**Discussion**

In this study we compared the effect of ω-3 fatty acids on plasma lipid levels in type III and type IV hyperlipidemias. Our findings demonstrate the hypotriglyceridemic properties of fish oil in type III and type IV subjects. In addition, we found that fish oil supplementation caused a significant reduction in the density of 1.006 g/ml plasma fraction triglyceride, cholesterol, and remnant concentrations in type III hyperlipidemic patients. These effects were associated with significant increases in plasma LDL and HDL cholesterol levels.

Although type III and type IV hyperlipidemias are distinguishable by specific abnormalities of lipoprotein profile and composition, they share common precipitating factors. Metabolic studies have demonstrated that both types of hyperlipidemias are associated with an increased production and a relatively defective catabolism of VLDL. In addition, the impairment in apo E-mediated uptake of VLDL and chylomicron remnants favors the accumulation of these atherogenic particles in type III hyperlipidemia. Low concentrations of LDL are also observed, suggesting defective synthesis and/or increased catabolism of LDL in type III hyperlipidemia. Previous work has demonstrated that fish oil supplementation reduces chylomicron concentrations in patients with type V hyperlipidemia and can improve the fat tolerance test in normolipidemic individuals. Our results allowed us to extend these observations to VLDL and chylomicron remnants in...
type III hyperlipidemia. Despite the absence of an accurate method to determine remnant concentrations, the following evidence indicates that a significant reduction in plasma remnant levels was achieved after fish oil supplementation: 1) Cholesterol and triglyceride concentrations in the $d<1.006$ g/ml plasma fraction were significantly reduced (~50%); 2) There was less material in the remnant density range, as demonstrated by rate zonal ultracentrifugation; 3) In most subjects the peak corresponding to β-VLDL tended to be lower relative to that of pre-β-VLDL on agarose gel electrophoresis; 4) the compositional analysis of $d<1.006$ g/ml lipoproteins revealed significantly lower cholesterol content after treatment.

Fish oils can reduce VLDL and chylomicron remnant concentrations by several mechanisms. First, they reduce triglyceride synthesis and VLDL production. Because VLDL and chylomicrons share the same lipolytic pathway, a significant decrease in VLDL mass may favor lipolysis of chylomicrons and therefore their uptake. Fish oils may also modify VLDL or chylomicron lipid compositions in such a way that they become a better substrate for lipoprotein lipase or liver receptor-mediated uptake, thereby increasing their catabolism. Finally, it has been shown in rats that fish oils can reduce cholesterol absorption. There is little evidence, however, that this happens physiologically in humans.

All type III subjects showed a considerable reduction in cholesterol levels in the $d<1.006$ g/ml plasma fraction (range, ~30% to ~70%). However, despite this decrease the VLDL cholesterol to triglyceride ratio and the VLDL cholesterol, IDL cholesterol, and IDL triglyceride concentrations remained significantly higher in type III than in type IV subjects, suggesting that fish oils did not remove all the remnants. This is consistent with the observation of a detectable (remaining) amount of β-VLDL on agarose gel electrophoresis after supplementation and agrees with results from an earlier report. The relative proportion of β- to pre-β-VLDL depends on
the equilibrium between the rates of VLDL and chylomicron production, on their ability to be lipolyzed, and finally on their uptake by the liver.\textsuperscript{36} Potentially, fish oils may alter any or all of these pathways, which may explain the heterogeneity of the response.

The increase in LDL cholesterol (1.019<d<1.063 g/ml) with fish oil supplementation was evident when LDLs were separated from IDL (1.006<d<1.019 g/ml) but was not statistically significant when the cholesterol value measured in the whole 1.006<d<1.063 g/ml fraction was used. In type III and IV hyperlipidemias, alterations of VLDL composition\textsuperscript{37} and/or defective interaction with lipoprotein lipase\textsuperscript{29} as well as LDL hypercatabolism\textsuperscript{30} have been observed, all of which may result in low LDL levels. The observed increase in LDL concentrations after fish oil treatment suggests a normalization of LDL metabolism\textsuperscript{37,30} and/or a direct secretion of LDL.\textsuperscript{14} Several possible mechanisms can account for this result. First, fish oils tend to normalize VLDL composition (Table 2), thereby potentially improving LDL formation.\textsuperscript{38} Second, apo E2 from hyperlipidemic and normolipidemic subjects presents an identical structural defect and the same low affinity for the LDL (B,E) receptor.\textsuperscript{39,40} It is possible that treatment with fish oils improves the receptor-binding affinity of apo E2-containing particles as a result of conformational changes secondary to lipid composition alterations.\textsuperscript{41} This could facilitate their uptake at the expense of LDL. Third, similar to those with type IV, type III hyperlipidemic subjects may produce small and dense VLDL particles\textsuperscript{42} after fish oil supplementation. These may not be detectable on rate zonal ultracentrifugation, as they were in type IV, due to the presence of remaining \( \beta \)-VLDL. We speculate that these denser VLDLs are a better substrate for LDL formation\textsuperscript{14,30} and/or a better competitor of plasma LDL for receptor binding. Finally, a reduction in LDL uptake by HepG2 cells\textsuperscript{43} and a reduction in rat liver LDL receptor activity\textsuperscript{44} have been described after dietary supplementation with \( \omega-3 \) fatty acid. This could also explain the higher LDL levels after treatment in hypertriglyceridemic subjects.

Similar to earlier reports,\textsuperscript{13,45} we observed higher HDL cholesterol levels after fish oil supplementation in type III and type IV subjects. This corresponded to a parallel and modest increase in both HDL\textsubscript{2} and HDL\textsubscript{3} subfractions.

In conclusion, our results demonstrate that treatment with \( \omega-3 \) fatty acids for 12 weeks causes an important reduction in the \( d<1.006 \) g/ml plasma fraction lipid concentrations in both type III and type IV hypertriglyceridemic subjects. This reduction also affects the atherogenic \( \beta \)-VLDL in type III hyperlipidemic patients. In our study, the reduction in VLDL was associated with a significant elevation of the abnormally low levels of plasma LDL in both type III and type IV subjects. Thus, in a few individuals treated with \( \omega-3 \) fatty acids the increase in LDL concentrations may attenuate the beneficial effect of VLDL and \( \beta \)-VLDL reduction. However, the influence exerted by fish oils on the atherogenic process results from the combination of its diverse effects on lipid metabolism, coagulation, platelet aggregation, and blood pressure. Further studies are clearly needed to evaluate the interaction of these pathways on overall cardiovascular risk.

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**KEY WORDS:** apolipoprotein E • lipoproteins • hyperlipidemia • fish oils • type III/type IV dyslipidemias • β-very low density lipoproteins
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J Dallongeville, L Boulet, J Davignon and S Lussier-Cacan