Dietary Fish Oil Plus Lovastatin Decreases Both VLDL and LDL Apo B Production in Miniature Pigs

Murray W. Huff, Dawn E. Telford, and P. Hugh Barrett

Our previous apolipoprotein (apo) B kinetic studies of miniature pigs fed fish oil (Maxepa) demonstrated that very low density lipoprotein (VLDL) apo B concentrations were markedly reduced but that low density lipoprotein (LDL) concentrations were only modestly lowered because of a threefold increase in the conversion of VLDL apo B to LDL. In the present study, the effect of Maxepa plus lovastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, on apo B metabolism was assessed. Miniature pigs (n=6) were simultaneously injected with autologous 125I-VLDL and 125I-LDL after a diet of pig chow supplemented with 30 g/day of Maxepa and again after the addition of lovastatin, 30 mg/day. Kinetic data were analyzed by compartmental analysis with use of the CONSAM program. Compared with Maxepa alone, the addition of lovastatin reduced VLDL apo B concentrations by 21% (p<0.003) because of reduced VLDL apo B production (26%, p<0.005), as the fractional clearance rate was not affected. Conversion of VLDL apo B to LDL was reduced by 48% (p<0.005), and the direct removal of VLDL apo B from plasma was reduced by 25% (p<0.01). Maxepa plus lovastatin reduced LDL apo B concentrations by 44% (p<0.004). This was due to a 38% (p<0.002) decrease in LDL production, which was primarily derived from VLDL. The LDL apo B fractional catabolic rate was not significantly changed. Thus, a combination of Maxepa and lovastatin reduces both VLDL and LDL apo B concentrations, primarily by decreasing production rates. (Arteriosclerosis and Thrombosis 1992;12:902–910)

KEY WORDS • fish oils • Maxepa • lovastatin • very low density lipoproteins • low density lipoproteins • apolipoprotein B metabolism • cholesterol synthesis inhibition

Polyunsaturated fatty acids derived from marine oils, mainly ω-3 fatty acids, have been the subject of much interest because of their potential role in reducing the risk of atherosclerosis. Epidemiological studies indicate that populations consuming large amounts of ω-3 fatty acids have a low incidence of atherosclerotic disease. This correlation has been supported by several population surveys, even though the amounts of ω-3 fatty acids consumed that produced the observed biological effects were relatively small. In several animal models of atherosclerosis, dietary fish oil has been shown to prevent the disease, although this finding has not been universal. Although there are several potential mechanisms whereby these fatty acids may prevent the development of atherosclerosis, including diminished thrombogenicity and lower blood pressure, their effects on lipoprotein metabolism are likely to be at least partially responsible. Dietary fish oil almost invariably lowers plasma triglyceride concentrations; however, the effects of fish oil on plasma cholesterol have been inconsistent. In subjects with hyperlipidemia, including hypertriglyceridemia and familial combined hyperlipidemia, low density lipoprotein (LDL) cholesterol concentrations have been shown to increase in response to dietary fish oil supplements. It is not known whether the potential benefits of dietary fish oils outweigh the less favorable effect on LDL cholesterol.

The mechanism(s) by which ω-3 fatty acids lower plasma triglycerides has been shown to be due to a reduction in the synthesis and secretion of very low density lipoprotein (VLDL). However, the reasons for the paradoxical increases in LDL are less well understood despite a decreased concentration of LDL precursors. Several mechanisms have been proposed, which include the synthesis of VLDL particles that are preferentially converted to LDL, perhaps as a result of a reduced LDL receptor activity. Our apolipoprotein (apo) B kinetic studies of miniature pigs treated with dietary fish oil have provided support for both of these hypotheses. Comparing with corn oil supplements, fish oil significantly reduced VLDL concentrations, but the proportion of VLDL apo B converted to LDL was significantly increased. In addition, the fractional catabolic rate (FCR) of LDL apo B was reduced, suggesting reduced LDL receptor activity. However, despite these changes, LDL concentrations were modestly reduced...
Animals and Diets

Therefore, each animal acted as its own control. Each experiment was performed under the supervision of the Animal Care Committee of the University of Western Ontario.

In previous studies of miniature pigs, we demonstrated that lovastatin could significantly lower LDL concentrations, primarily by reducing LDL synthesis. Lovastatin was placed in gelatin capsules and to ensure sterility, the capsules were sterilized by addition of gentamicin sulfate (100 μg/ml) and checked for pyrogenicity and sterility. LDL contained <2% free iodine, 25–35% of the label was bound to the lipid, and 24–37% of the label was bound to apo B. LDL contained <1% free iodine, 25–30% of the label was bound to lipid, and 80–90% of the labeled protein was apo B. After a 16-hour fast, each animal received 20 μCi 125I–VLDL apo B and 15 μCi 125I–LDL apo B. After injection, blood samples (20 ml) were collected into tubes containing Na2 EDTA, allowed for ease of sample injection as well as blood sampling throughout each turnover study in restrained, unanesthetized animals.

Methods

Animals and Diets

Six miniature pigs, obtained from a local supplier (Hyde Park Farms, Hyde Park, Canada) and weighing between 22 and 30 kg, were used in the present experiments. After acclimatization for 1 week, animals were maintained on the experimental diet for 3 weeks before the lipoprotein turnover studies. One week prior to the first turnover study, an indwelling Silastic catheter (0.078 in. i.d.) was surgically implanted in an external jugular vein. Halothane was used as the anesthetic and ketamine as the preanesthetic. Catheters were held in place under the skin and externalized in the middle of the animal’s back. Three-way stopcocks were attached to the catheters, which were held to the animal with a foam pad, Elastoplast bandage, and elastic netting. The catheters, which were kept patent by filling with 7% Na2EDTA, allowed for ease of sample injection as well as blood sampling throughout each turnover study in unrestrained, unanesthetized animals. In most animals, catheter patency lasted for 2–3 weeks, and if required the surgical implantation of a catheter in the opposite external jugular vein was performed 1 week before the second turnover study. The experimental protocol was approved by the Animal Care Committee of the University of Western Ontario.

Six animals were studied in a crossover design in which each animal received a diet containing Maxepa, 30 g/day (R.P. Scherer, Windsor, Canada) for 3 weeks before a lipoprotein turnover study. Subsequently, in addition to Maxepa, the HMG-CoA reductase inhibitor lovastatin (Merck-Frosst, Montreal, Canada) at a dose of 1.2 mg/kg body wt/day (approximately 30 mg/day) was administered for a further 3 weeks. This dose was similar to that used in humans (40 mg b.i.d.) that resulted in maximal lowering of LDL cholesterol. Lovastatin was placed in gelatin capsules and to ensure ingestion was administered by hand before the daily feeding. A second turnover study was then carried out. Therefore, each animal acted as its own control. Each pig received 750 g/day Purina pig chow (Ralston Purina, Longueil, Canada), which contained 16% protein and 5% fat (wt/wt). The total dietary fat content was 9% (wt/wt) and provided 9.45 g/day ω-3 fatty acids (5.04 g/day eicosapentaenoic acid, 20:5; ω-3; 3.63 g/day docosahexaenoic acid, 22:6; ω-3), 3.54 g/day ω-6 fatty acids (3.48 g/day linoleic acid, 18:2; ω-6), and 110 mg/day cholesterol (contained in Maxepa oil). Maxepa, which contained 100 IU vitamin A/g, no vitamin D, and α-tocopherol (1 IU/g) as an antioxidant, was divided into aliquots in daily doses and stored under nitrogen in sealed vials at 4°C until just before feeding. Maxepa was then mixed with the chow, which was consumed within 1 hour. Although the dose of Maxepa used in this study (0.3 g/kg body wt) was 5–20% of that used in studies in rodents and similar to the dose used in previous studies in pigs and humans, it represents a dose that is two- to threefold higher than that used in the majority of human studies.

Lipoprotein Turnover Studies

Lipoprotein turnover studies were carried out essentially as described previously. Plasma (100–150 ml) was obtained after a 16-hour fast for isolation of VLDL (Sf 60–400) and LDL (Sf 0–12), which were subsequently radiolabeled with 125I and 123I, respectively. All labeled lipoproteins were autologous. Radiolabeling was performed by the iodine monochloride technique. Lipoproteins were sterilized by addition of gentamicin sulfate (100 μg/ml) and checked for pyrogenicity and sterility.

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Apo B was isolated from each lipoprotein fraction by isopropanol precipitation as described previously. Specific activities were calculated after counting the washed pellet and subsequent determination of its protein content by a modified Lowry procedure. The plasma concentration of apo B in each lipoprotein fraction was determined by subtracting the protein value of the first-precipitation supernatant from the total protein concentration. Apo B concentrations of the precipitated pellets were used only for specific activity calculations and not for plasma apo B concentrations because of the nonspecific losses of apo B that occur during delipidation and washing of the pellet.

Kinetic Analysis

The turnover data were analyzed with the multicompartamental modeling program CONSAM running on an 80386-based personal computer. Initially, plasma LDL apo B specific activity derived from reinjected 125I-LDL
A multicompartmental kinetic model was developed to analyze apolipoprotein (apo) B metabolism in very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), and low density lipoprotein (LDL). The VLDL fraction is described by three compartments, represented by circles 1, 2, and 5; IDL by two compartments (3 and 4); and LDL by a single compartment (10), which is connected to an extravascular exchange compartment (11). Arrows connecting the compartments describe paths by which material moves from one compartment to another. Double arrows identify sites of VLDL- and LDL—apo B input into the model.

was analyzed. The model chosen to describe the data is shown in Figure 1. This model, commonly referred to as Matthew’s analysis, is characterized by a plasma compartment, designated here as compartment 10, and an extravascular exchange compartment, compartment 11. Although this model assumes that LDL apo B is kinetically homogeneous, it is not possible to address the question of LDL heterogeneity without isolating LDL subfractions and/or collecting urine radioactivity data. 

FIGURE 1. Multicompartmental kinetic model used for analysis of apolipoprotein (apo) B metabolism in very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), and low density lipoprotein (LDL). The VLDL fraction is described by three compartments, represented by circles 1, 2, and 5; IDL by two compartments (3 and 4); and LDL by a single compartment (10), which is connected to an extravascular exchange compartment (11). Arrows connecting the compartments describe paths by which material moves from one compartment to another. Double arrows identify sites of VLDL— and LDL—apo B input into the model.
The addition of lovastatin to Maxepa significantly reduced VLDL apo B synthesis, with a 2-m column (SP 2230, liquid phase; Supelco, Toronto, Canada) on a Varian 6000 gas chromatograph. Lipoprotein protein was determined by the method of Markwell et al. Differences in lipid, apoprotein concentrations, and kinetic parameters during each treatment phase were compared by paired t test.

**Results**

Plasma and lipoprotein lipid concentration changes in response to the addition of lovastatin to the Maxepa diet are shown in Table 1. Total plasma and VLDL triglyceride concentrations were significantly reduced, by 16% (p<0.01) and 39% (p<0.005), respectively. Total plasma cholesterol was significantly reduced by 12% (p<0.05), and the concentrations of VLDL and LDL cholesterol decreased significantly by 30% (p<0.05) and 34% (p<0.02), respectively. The concentrations of HDL cholesterol were unaffected. Apo B concentrations were also significantly reduced by lovastatin plus Maxepa. VLDL and LDL apo B levels declined by 21% (p<0.003) and 44% (p<0.004), respectively.

Autologous radiolabeled VLDL and LDL were simultaneously injected into each pig after each treatment phase. The kinetic parameters estimated from the simultaneous analysis of all data using the model shown in Figure 1 are summarized in Tables 2 and 3. A fit of the model to the apo B specific radioactivity curves for 131I-VLDL, IDL, and LDL for one representative animal during both treatment phases is shown in Figure 2. The fit of the LDL section of the model to the 121I-LDL specific radioactivity data for the animal presented in Figure 2 is shown in Figure 3.

The addition of lovastatin to Maxepa significantly reduced the pool size of VLDL apo B by 20% (p<0.003) as shown in Table 2. This was primarily due to a significant reduction in the VLDL apo B production rate (26%, p<0.005), as the FCR was not altered. The reduced production rate of VLDL apo B resulted in a significant decrease in the amount of VLDL apo B converted to LDL (48%, p<0.002), as well as a significant decrease in the amount of VLDL apo B that leaves the plasma compartment without conversion to LDL (25%, p<0.006). The percentage of total VLDL apo B production (flux) through the LDL pool that was converted to LDL or that was removed directly did not change. The model allowed us to determine the production or flux of VLDL apo B converted to LDL directly (i.e., without being transported through the plasma IDL fraction) as well as the amount of VLDL apo B converted to LDL through the IDL fraction. The addition of lovastatin primarily lowered the former pathway by 67% (p<0.04, Table 2). The conversion of VLDL apo B to LDL via plasma IDL decreased by 28%; however, the difference was not statistically significant.

The kinetic parameters of LDL apo B metabolism are shown in Table 3. Lovastatin plus Maxepa significantly lowered the LDL apo B pool size by 44% (p<0.004). This was due primarily to a decrease in the LDL apo B production rate by 38% (p<0.002) because the FCR was not changed. The apparent direct synthesis of LDL, i.e., LDL that is not derived from the catabolism of plasma VLDL apo B, did not change.

A summary of the model parameters is shown in Table 4. The reduction in the VLDL apo B pool size is reflected in a significant 27% reduction in the size of M(5), the VLDL compartment that contains the majority of VLDL particles, the one that turns over most rapidly. Lovastatin plus Maxepa did not affect the sizes of the other two more slowly turning over VLDL pools. The plasma pool of LDL apo B, M(10), decreased significantly as described above. Lovastatin treatment did not affect the size of the extravascular exchange pool M(11). The fractional rate constant L(0.4) that describes the direct clearance of apo B from the LDL pool M(4) was significantly increased by 84% (p<0.05) by the combined treatment. Other fractional rate constants were not altered by lovastatin plus Maxepa treatment.

**Discussion**

The experiments reported in this article were designed to determine the effect on apo B kinetics of an HMG-CoA reductase inhibitor in miniature pigs given a diet rich in ω-3 fatty acids. The rationale for these experiments was based on the observation that dietary fish oil lowers VLDL triglycerides but has an inconsistent effect on LDL cholesterol, and in many studies, LDL cholesterol and LDL apo B have been shown to increase.15-19 Such unwanted biochemical side effects could outweigh the potentially useful hypotriglyceridemic effect of dietary fish oils. On the other hand, lovastatin has been shown in both animal and human studies to lower LDL cholesterol and LDL apo B.27-33

In previous apo B kinetic studies, we demonstrated that dietary ω-3 fatty acids (Maxepa) when compared with ω-6 fatty acids (corn oil) reduced VLDL apo B concentrations; however, the conversion of VLDL apo B to LDL was increased significantly.36
that this may be the mechanism whereby in some studies LDL concentrations did not fall with dietary fish oil, despite diminished concentrations of precursor lipoproteins. However, in our miniature pigs, despite this increased conversion, LDL apo B concentrations were reduced moderately because of the marked inhibition of the direct synthesis of LDL apo B. In other studies of miniature pigs, we showed that lovastatin treatment significantly lowered LDL apo B by reducing LDL production, primarily LDL direct synthesis.28 In the present study, we wanted to determine if lovastatin, given in addition to a diet containing Maxepa, would produce favorable changes in LDL apo B metabolism.

The major findings were that lovastatin plus Maxepa 1) reduced VLDL concentrations primarily by reducing the production of VLDL apo B, 2) increased the direct removal of VLDL apo B, and 3) reduced the concentrations of LDL apo B primarily by reducing LDL apo B production from VLDL catabolism.

The mechanisms by which ω-3 fatty acids lower plasma triglycerides have been shown to be related to the control of VLDL synthesis and secretion.20-22 Also, an increase in the FCR of VLDL has been observed.66 In the present study, the pigs treated with Maxepa alone had low plasma and VLDL triglycerides comparable with those reported previously.66 The further lowering of VLDL triglyceride and apo B by the addition of lovastatin was due to a reduced pool size of compartment 5 (Table 4). As defined by the model, compartment 5 represents the compartment containing most of the VLDL particles and is the most rapidly turning over VLDL compartment (Table 4). These findings are consistent with previous reports that in humans this drug reduces VLDL triglyceride27,42 and VLDL apo B 27 concentrations. In patients with combined hyperlipidemia42 and type III hyperlipidemia,43 lovastatin alone has been shown to reduce the synthesis of VLDL apo B. In our previous studies of miniature pigs, lovastatin alone lowered triglyceride concentrations by only a modest amount and had no consistent effect on VLDL apo B kinetics. The marked reduction in the production rate of VLDL apo B with the combination of lovastatin and Maxepa suggests that these two treatments may act synergistically in inhibiting VLDL apo B production by an as-yet-unknown mechanism. It is possible that Maxepa exerts its effects primarily on triglyceride synthesis,22,23 although some reports indicate that dietary fish oils also reduce hepatic cholesterol ester secretion.44 Lovastatin exerts its effect by inhibition of cholesterol biosynthesis, which may lower hepatic cholesterol esters. The combination of these two processes may limit the availability of core lipids destined for assembly and

### Table 2. Metabolic Parameters of VLDL Apo B in Miniature Pigs Treated With Maxepa and Maxepa Plus Lovastatin

<table>
<thead>
<tr>
<th>Animal/diet</th>
<th>Pool size* (mg/kg)</th>
<th>FCR† (hr⁻¹)</th>
<th>Total production (mg/kg·hr⁻¹)</th>
<th>Conversion to LDL directly from VLDL (%)</th>
<th>Conversion to LDL via IDL (%)</th>
<th>Direct removal (%)</th>
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<tr>
<td>M</td>
<td>0.339</td>
<td>10.20</td>
<td>3.50</td>
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<tr>
<td>M+L</td>
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<td>10.00</td>
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<td>0.036</td>
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<td>M</td>
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<td>M</td>
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<td>0.643</td>
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<td>p&lt;‡</td>
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<td>0.005</td>
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<td>0.05</td>
<td>0.034</td>
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VLDL, very low density lipoprotein; apo, apolipoprotein; FCR, fractional catabolic rate; LDL, low density lipoprotein; IDL, intermediate density lipoprotein; M, Maxepa; M+L, Maxepa plus lovastatin.

*Pool size, in milligrams per kilogram, refers to the plasma VLDL apo B concentration multiplied by 0.42 with the assumption that in the pig there are 42 ml of plasma per kilogram of body weight.

†FCR is determined by U(5)/VLDL pool size, where U(5) is the production rate of VLDL apo B.

‡Probability determined by paired t test.
secretion with VLDL. Further support for this hypothesis requires additional experimentation.

The mechanism(s) responsible for the increased conversion of VLDL apo B to LDL are not well understood. Explanations have included 1) the secretion of small, triglyceride-poor, apo B-rich particles that are preferentially converted to LDL and 2) a decrease in hepatic LDL receptor activity. Because hepatic LDL receptors are thought to mediate the hepatic uptake of VLDL remnants, lower LDL receptor activity may result in increased conversion of VLDL apo B to LDL. Evidence that fish oil affects hepatic LDL receptor activity is mixed. In rats, Roach et al showed that fish oil significantly reduced LDL receptor-mediated binding of LDL to hepatic membranes; however, Ventura et al demonstrated that fish oil increased hepatic LDL receptor-mediating LDL clearance in vivo. In our previous studies of pigs, the LDL fractional clearance rate (which in part reflects LDL receptor activity) was decreased by fish oil. In the present study, lovastatin plus Maxepa decreased the conversion of VLDL apo B to LDL by 48%, which may be related to an increase in LDL receptor activity and/or an increase in VLDL particle size. Although we did not assess the combined treatment for its influence on the size or relative composition of VLDL, in previous studies Maxepa or lovastatin alone produced no major alterations in VLDL composition. In addition, we have provided no clear evidence that LDL receptor activity was enhanced by the combination treatment. LDL FCR did not change (Table 3), and the FCRs reflecting the direct catabolism of apo B from the VLDL pools were not significantly altered. However, L(0,4), the fraction of the largest IDL pool cleared directly, increased significantly in all six animals, which may be related to an increased hepatic LDL receptor activity. The reasons why an increased LDL receptor activity would influence IDL clearance but not LDL clearance are not clear but may be related to subtle differences in particle composition as discussed below.

The reduced conversion of VLDL apo B to LDL appears to be related primarily to the reduced total VLDL apo B production, which results in both a reduced conversion to LDL as well as a reduced direct removal of VLDL. In both a reduced conversion to LDL as well as a reduced direct removal of VLDL. The finding that the percentage of total VLDL production converted to LDL or removed directly did not change suggests that no major alterations in VLDL composition or LDL receptor activity were responsible for the decreased conversion of apo B to LDL produced by Maxepa alone. The

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**Table 3. Metabolic Parameters of LDL Apo B in Miniature Pigs Treated With Maxepa and Maxepa Plus Lovastatin**

<table>
<thead>
<tr>
<th>Animal/diet</th>
<th>Pool size* (mg/kg)</th>
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<th>Total production (mg/kg·hr⁻¹)</th>
<th>Direct production‡ (mg/kg·hr⁻¹)</th>
<th>(%)</th>
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LDL, low density lipoprotein; apo, apolipoprotein; FCR, fractional catabolic rate; M, Maxepa; M+L, Maxepa plus lovastatin; NS, not significant.

*Pool size, in milligrams per kilogram, refers to the plasma LDL apo B concentration multiplied by 0.42, with the assumption that in the pig there are 42 ml of plasma per kilogram of body weight.
†FCR is the rate constant L(0,10) determined from the model.
‡Direct production (direct synthesis) is the production of apo B directly into compartment 10, U(10).
§Probability determined by paired t test.
reduced conversion of VLDL apo B to LDL occurred primarily as a result of a decrease in the flux of VLDL apo B converted directly to LDL. Although mean values for the flux of VLDL apo B converted to LDL after conversion to IDL were lower, the difference was not statistically significant (Table 2). It is possible that subtle differences in VLDL composition that are not detectable by common chemical techniques preferentially reduced the direct conversion of VLDL to LDL.

The addition of lovastatin to Maxepa reduced the LDL apo B pool size by 44% primarily by a reduction in LDL production, a result consistent with our previous studies of pigs given lovastatin alone. It is possible that the addition oflovastatin was not able to lower the direct synthesis of LDL any further. As mentioned above, lovastatin alone or in combination with Maxepa (this study) had little effect on LDL FCR. Theoretically, hepatic cholesterol synthesis inhibition would be expected to reduce hepatic cholesterol concentrations, thereby increasing the expression of LDL receptors, and thus lower LDL cholesterol by increasing the LDL FCR. A possible explanation for the lack of effect on LDL FCR is the synthesis of an LDL particle, during treatment with lovastatin, with an altered composition such that it interacts less efficiently with an enhanced LDL receptor. The net effect of this would be a lower or unchanged LDL FCR. Evidence for this effect of lovastatin in guinea pigs has been provided by Berglund et al. In addition, the lack of change in LDL FCR may be a function of the single plasma-pool analysis of the LDL apo B kinetic data. Others have shown that LDL in humans is kinetically heterogeneous. If lovastatin results in the preferential removal of a subtraction of LDL with a fast turnover rate, then the distribution of LDL particles may shift in favor of LDL particles that turn over more slowly. Such a shift may result in an LDL FCR that is unchanged, despite the reduced LDL apo B pool size.

FIGURE 2. Apolipoprotein (apo) B specific activity-time curves for very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), and low density lipoprotein (LDL) after injection of radiolabeled VLDL. Data points represent observed data, and lines are best-fit curves generated by the kinetic model. Results are for animal No. 1. Panel A was obtained during the Maxepa dietary period and panel B after addition of lovastatin.

for this difference is not readily apparent. In our studies with Maxepa alone, we demonstrated that LDL direct synthesis was significantly reduced. If it is possible that the addition of lovastatin was not able to lower the direct synthesis of LDL any further.

As mentioned above, lovastatin alone or in combination with Maxepa (this study) had little effect on LDL FCR. Theoretically, hepatic cholesterol synthesis inhibition would be expected to reduce hepatic cholesterol concentrations, thereby increasing the expression of LDL receptors, and thus lower LDL cholesterol by increasing the LDL FCR. A possible explanation for the lack of effect on LDL FCR is the synthesis of an LDL particle, during treatment with lovastatin, with an altered composition such that it interacts less efficiently with an enhanced LDL receptor. The net effect of this would be a lower or unchanged LDL FCR. Evidence for this effect of lovastatin in guinea pigs has been provided by Berglund et al. In addition, the lack of change in LDL FCR may be a function of the single plasma-pool analysis of the LDL apo B kinetic data. Others have shown that LDL in humans is kinetically heterogeneous. If lovastatin results in the preferential removal of a subtraction of LDL with a fast turnover rate, then the distribution of LDL particles may shift in favor of LDL particles that turn over more slowly. Such a shift may result in an LDL FCR that is unchanged, despite the reduced LDL apo B pool size.
The net effect of dietary fish oil on cardiovascular risk is complex. Whether the less favorable effect on the LDL cholesterol concentration induced by fish oil negates some of the benefit derived from the lowering of VLDL triglycerides and cholesterol is speculative. Plasma triglycerides and VLDL cholesterol have been increasingly recognized as risk factors for coronary atherosclerosis, whereas the risks associated with increased LDL cholesterol and apo B are well known. The results of this article indicate that a combination of dietary fish oil and the HMG-CoA reductase inhibitor lovastatin produces favorable changes in both the concentrations and the production rates of VLDL and LDL apo B in pigs. Patients with combined elevations of VLDL and LDL, who are at increased risk of atherosclerosis and in whom increased production of apo B is the primary abnormality, respond to dietary fish oil with significant decreases in VLDL concentrations but do experience elevations in LDL cholesterol and apo B. Patients with combined hyperlipidemia also respond to lovastatin, with reductions in LDL concentrations and apo B production rates. The findings in this article suggest that dietary fish oil together with lovastatin may provide a useful therapeutic combination.

Acknowledgments

We thank Martha Klinger and Charlotte McDonald for expert technical assistance and Allison Clift and David Grant for performing the surgery. The Maxepa was generously provided by Mike Ratko, R.P. Scherer Canada, Windsor, Canada, and theLovastatin was kindly donated by Dr. Alain Prat, Merck-Frosst Canada, Montreal, Canada.

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**FIGURE 3.** Apolipoprotein (apo) B specific activity–time curves for low density lipoprotein (LDL) after injection of radiolabeled LDL. Data points represent observed data, and lines are best-fit curves generated by the kinetic model. Results are for animal No. 1.


Dietary fish oil plus lovastatin decreases both VLDL and LDL apo B production in miniature pigs.

M W Huff, D E Telford and P H Barrett