Impaired Chylomicron Remnant Clearance in Familial Combined Hyperlipidemia

Manuel Castro Cabezas, Tjerk W.A. de Bruin, Hans Jansen, Luciènne A.W. Kock, Wouter Kortlandt, and D. Willem Erkelens

Postprandial chylomicron remnant clearance was studied in six patients with familial combined hyperlipidemia (FCH) and seven control subjects by using an oral retinyl palmitate (RP) fat-loading test. The chylomicron remnant clearance ($S_2<1,000$ fraction), expressed as the area under the RP curve (AUC-RP), was delayed in FCH subjects ($65.05\pm12.84$ hours$\times$[mg/L]) compared with control subjects ($25.1\pm5.4$ hours$\times$[mg/L]; $p=0.01$). Postprandial lipoprotein particle size and composition in the $S_f>1,000$ fraction were different between FCH and control subjects as analyzed by molecular-sieve chromatography. Fasting high density lipoprotein cholesterol was lower in FCH patients ($0.54\pm0.09$ mmol/L) than in control subjects ($0.89\pm0.05$ mmol/L; $p<0.01$). Mean plasma postheparin lipoprotein lipase and hepatic lipase activities were similar between FCH patients ($94\pm25$ and $427\pm57$ milliunits/mL, respectively) and control subjects ($126\pm16$ and $362\pm33$ milliunits/mL, respectively). In FCH, a 54% reduction ($p<0.05$) of plasma triglycerides to $2.63\pm0.41$ mmol/L by drug treatment resulted in an enhanced, but not normalized, clearance of chylomicron remnants ($39.4\pm6.0$ hours$\times$[mg/L]). Univariate regression analysis revealed that in FCH subjects the changes in fasting plasma apolipoprotein C-III concentrations after therapy were significantly associated with the changes in chylomicron remnant AUC-RP ($r=0.87; p=0.02$). Delayed elimination of atherogenic chylomicron remnants may contribute to the increased risk of premature atherosclerosis in FCH. (Arteriosclerosis and Thrombosis 1993;13:804-814)

KEY WORDS  • coronary heart disease  • triglycerides  • lipoprotein lipase  • hepatic lipase  • apolipoprotein B  • chylomicrons  • VLDL

Familial combined hyperlipidemia (FCH), the most common familial lipid disorder among survivors of premature myocardial infarction below the age of 60 years, was described as a new genetic entity in 1973. The prevalence of this autosomal dominant disorder is estimated to be 0.5% (one in 200 individuals). At least 10% of patients with coronary heart disease have FCH. FCH subjects may have a variable hyperlipidemic phenotype, and multiple-type hyperlipidemia in first-degree relatives (Fredrickson types IIa, IIb, IV, or V) is characteristic for FCH. Therefore, family studies are necessary to prove the presence of FCH in an individual patient. The cause of FCH is unknown, but overproduction of apolipoprotein (apo) B and very low density lipoproteins (VLDLs) has been demonstrated in combination with a relative triglyceride (TG) removal defect. The high incidence of premature atherosclerosis in FCH patients has been related to the observed lipoprotein abnormalities. However, neither elevated low density lipoprotein (LDL) concentrations nor decreased high density lipoprotein (HDL) levels are consistently found in all FCH patients. Increased production of VLDL and VLDL remnants in FCH patients may be important, since remnants are atherogenic particles that contribute to premature atherosclerosis. We studied postprandial lipoprotein metabolism in six patients with FCH and seven normolipidemic control subjects. Because postprandial chylomicron metabolism is known to depend on fasting plasma TGs, apo B, and HDL cholesterol, the FCH patients were studied both before and after lipid-lowering medication. We used the oral retinyl palmitate (RP) fat-loading test in separate studies of the elimination of chylomicrons and chylomicron remnants.

Methods

FCH Patients

The six male FCH patients (aged 30–66 years) were on a low-fat, low-cholesterol diet, comparable to the American Heart Association Phase I diet, and did not consume more than four alcoholic beverages per week. Patients were diagnosed as FCH when they had each of the following: 1) hyperlipidemia, defined as cholesterol and/or TG plasma concentrations $>6.5$ and $2.0$ mmol/L, respectively; 2) at least one first-degree relative with a different lipoprotein phenotype than the index patient; 3) an elevated fasting plasma concentration of apo B ($>0.9$ mmol/L)
After TG Reduction

Follow-up Study of FCH Patients After TG Reduction

On the day after the first oral fat load, the six FCH patients started lipid-lowering medication. The aim was to reduce plasma TG concentrations and to study the effects of reduced TG pool size on the postprandial elimination of chylomicrons and chylomicron remnants. At the time of the second oral fat load, one patient used simvastatin (10 mg daily) and gemfibrozil (600 mg b.i.d.), and the others used simvastatin as monotherapy (range, 10–40 mg once daily). All patients reached constant plasma TG and cholesterol levels within 8 g/L; and 4) at least one first-degree relative with an elevated plasma concentration of apo B and a history of premature myocardial infarction. Forty-three FCH relatives during 1 year demonstrated changing lipoprotein phenotypes, consistent with multiple-type hyperlipidemia.5

Causes of secondary hyperlipidemia were ruled out in all patients. Thyrotropin, insulin, and glucose levels did not differ from control subjects’ levels (data not shown). None of the patients used drugs that are known to affect lipid metabolism during the 4 weeks before the oral fat load. Type III hyperlipidemia was excluded in all FCH patients, and apo E phenotyping revealed no apo E2 homozygotes.17

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weeks, and the second oral fat load was performed subsequently.

**Normalipidemic Control Subjects**

The study protocol was approved by the Human Investigation Review Committee of the University Hospital Utrecht. Seven normalipidemic healthy male subjects (aged 28-49 years) were selected from volunteers. These control subjects had no diabetes; no hepatic, renal, thyroid, or cardiac dysfunction; and a negative family history. They consumed an average Dutch diet, which is characterized by an average daily intake of 105 g of fat.\textsuperscript{15}

**Oral RP Fat-Loading Test**

Cream was used as the fat source; this 40% (wt/vol) fat emulsion has a polyunsaturated:saturated ratio of 0.06 and contains 0.001% (wt/vol) cholesterol and 2.8% (wt/vol) carbohydrates. After a 12-hour overnight fast, the subjects ingested the fresh cream, to which 120,000 units aqueous RP had been added 18 hours before the meal. Tubes were protected against light by aluminum foil and centrifuged immediately for 15 minutes at 80°C at 4°C.

**Preparation of Chylomicron, Nonchylomicron, and HDL Fractions**

For separation of lipoproteins, plasma samples were subjected to a single ultracentrifugation step as previously described,\textsuperscript{10,15} according to the operational definition of chylomicrons of Grundy and Mok\textsuperscript{18} (S, > 1,000). The HDL fraction of all samples was prepared from 2 mL of the infranatant (S, < 1,000 fraction) by precipitating the apo B-containing lipoproteins as described.\textsuperscript{15} Aliquots were stored at -20°C until assayed.

**Analytical Methods**

TGs and cholesterol were measured in duplicate by commercial colorimetric assay (GPO-PAP, Boehringer Mannheim, No. 701912, and Monotest Cholesterol kit, Boehringer Mannheim, No. 237574, respectively).\textsuperscript{15} The quantitative assays of apo A-I and apo B have been described in detail.\textsuperscript{10-13} Plasma apo E was determined by commercial immunoturbidimetric assay (Daiichi Chemicals, Tokyo). Plasma apo C-III was measured by radial immunodiffusion using plates and apo C-III standards from Daiichi Chemicals. The diameter of the precipitation ring was measured by an investigator unaware of the specimens' identity. RP in plasma, chylomicrons, chylomicron remnants, and HDL fractions was determined by high-performance liquid chromatography as described.\textsuperscript{19-21} Postheparin plasma lipoprotein lipase (LPL) and hepatic lipase (HL) activities were determined by the release of free fatty acids from a \textsuperscript{14}C-labeled trioleyl emulsion, according to Huttunen et al.

### TABLE 2. Postprandial Chylomicron and Nonchylomicron Clearance

<table>
<thead>
<tr>
<th></th>
<th>AUC-RP (chylo)</th>
<th>AUC-RP (nonchylo)</th>
<th>AUC-TG (chylo)</th>
<th>AUC-TG (nonchylo)</th>
<th>AUC-TG (corrected)</th>
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<td>30.3</td>
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<td>23.0</td>
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<tr>
<td>±SEM</td>
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<td>5.4</td>
<td>0.7</td>
<td>3.5</td>
<td>1.60</td>
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<tr>
<td>(p)</td>
<td>0.05</td>
<td>0.01</td>
<td>0.04</td>
<td>0.008</td>
<td>NS</td>
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</table>

AUC-RP, area under the incremental retinyl palmitate curve; AUC-TG, area under the absolute triglyceride curve; chylo, chylomicron; nonchylo, nonchylomicron; FCH, familial combined hyperlipidemia; NS, not significant. Individual values of chylomicron and nonchylomicron fractions are expressed as AUC-RP in hours×(milligrams/liter) and AUC-TG in hours×(millimoles/liter) from 0 to 24 hours. Corrected AUC-TG was calculated by dividing the sum of chylomicron AUC-TG and nonchylomicron AUC-TG by the fasting plasma TG concentration.

Probability values were by unpaired \(t\) test (FCH vs. control subjects); AUC-TGs were logarithmically transformed.
FIGURE 2. Line graphs showing postprandial changes in retinyl palmitate (RP) in plasma (●), chylomicron (chylo) (○), and nonchylomicron (non-chylo) (●) fractions in six untreated familial combined hyperlipidemia (FCH) patients (left upper panel) and seven normolipidemic control subjects (left lower panel). The chylomicron (right upper panel) and nonchylomicron (right lower panel) RP concentrations of FCH and control subjects are also plotted. Values are expressed as mean±SEM.

as described. Lipolytic activity is expressed as nanomoles of free fatty acids per minute per milliliter of plasma. Apo E isoforms were determined by a single-dimension isoelectric focusing technique of VLDLs isolated by ultracentrifugation in a 40.3 Beckman rotor (40,000 rpm for 20 hours at 4°C). This method was validated in the laboratory of Dr. L.M. Havekes (Leiden, The Netherlands).

Analysis of Chylomicrons by Molecular-Sieve Chromatography, Sodium Dodecyl Sulfate Electrophoresis, and Immunoblotting

Two milliliters of chylomicron (S_r>1,000) fractions obtained before (t=0) and at 4 and 8 hours after ingestion of the cream was eluted on a 2.5×90-cm column of Sepharose 2B (Pharmacia, Uppsala, Sweden) to investigate the size and apolipoprotein composition of these TG-rich particles. The eluting buffer was 154 mmol/L NaCl, 1 mmol/L EDTA, pH 7.4, and 0.01% NaN_3, and the flow rate was 20 mL/hr. Absorbance at 280 nm was determined, and sodium dodecyl sulfate-polyacrylamide gradient gel electrophoresis (SDS-PAGE) of delipidated fractions was performed on 4–15% gels by using the PhastSystem configuration (Pharmacia). Gels were either silver stained according to the PhastSystem user manual or proteins were transferred to nitrocellulose. Apo B-100 and apo B-48 were detected by immunoblotting by using a specific polyclonal sheep anti-apo B antiserum, a biotinylated goat anti-sheep antiserum, and streptavidin-horseradish per-
Statistical Analysis

All values are expressed as mean±SEM. Postprandial 8-hour TG and 24-hour RP metabolism was estimated by calculating the incremental areas under the respective curves (AUC-TG and AUC-RP), with the fasting value as baseline or as absolute 24-hour AUC-TG (with zero as baseline). Pearson correlation coefficients were calculated by least-squares methods after logarithmic transformation of TG, apo C-III, and apo E. The changes in the postprandial apo B concentrations within each group were compared by analysis of variance with application of the Bonferroni correction; Fisher’s least significant difference test was used to determine the significant changes compared with baseline fasting values. Mean differences between groups were assessed by the unpaired *t* test and within groups by the paired *t* test.

Results

Subjects

FCH patients had significantly higher plasma concentrations of cholesterol, TGs, and apo B than normolipidemic control subjects. Baseline apo E and apo C-III were also significantly increased in FCH. Plasma HDL cholesterol (HDL-C) was lower in FCH patients than in the control subjects. The baseline postheparin plasma lipolytic activities were similar in both groups (Table 1).

Postprandial TG Metabolism

The fat meal was well tolerated by all subjects; none developed nausea or diarrhea. The TG response to the oral fat load in control subjects was characterized by a plasma TG peak at 4 hours and a return to baseline TG values at 7 hours (Figure 1). In control subjects, the incremental postprandial triglyceridemia (expressed as the area under the TG curve from 0 to 8 hours with
in FCH patients (untreated and control subjects).

**TABLE 5.** Lipids and Apolipoprotein B in Chylomicron Fractions (S,> 1,000) in the Fasting State and at the Chylomicron Triglyceride Peak

<table>
<thead>
<tr>
<th></th>
<th>Untreated FCH patients</th>
<th>Control subjects</th>
<th>p</th>
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<tbody>
<tr>
<td></td>
<td>(n=6)</td>
<td>(n=7)</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td></td>
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<tr>
<td>Fasting</td>
<td>0.30 (0.09)</td>
<td>0.06 (0.01)</td>
<td>0.05</td>
</tr>
<tr>
<td>Peak</td>
<td>0.35 (0.10)</td>
<td>0.14 (0.05)*</td>
<td>0.07</td>
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<tr>
<td>Triglycerides</td>
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<tr>
<td>Fasting</td>
<td>0.50 (0.20)</td>
<td>0.05 (0.01)</td>
<td>0.01</td>
</tr>
<tr>
<td>Peak</td>
<td>1.73 (0.60)*</td>
<td>0.65 (0.16)*</td>
<td>NS</td>
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<tr>
<td>Apo B</td>
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<tr>
<td>Fasting</td>
<td>0.04 (0.01)</td>
<td>0.02 (0.01)</td>
<td>NS</td>
</tr>
<tr>
<td>Peak</td>
<td>0.08 (0.01)*</td>
<td>0.03 (0.01)</td>
<td>NS</td>
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<tr>
<td>Chol/TG</td>
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<tr>
<td>Fasting</td>
<td>0.89 (0.27)</td>
<td>2.01 (0.75)</td>
<td>0.03</td>
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<tr>
<td>Peak</td>
<td>0.24 (0.03)*</td>
<td>0.23 (0.05)*</td>
<td>NS</td>
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<tr>
<td>Chol/apo B</td>
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<tr>
<td>Fasting</td>
<td>7.35 (1.39)</td>
<td>3.44 (0.58)</td>
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<tr>
<td>Peak</td>
<td>5.27 (0.87)</td>
<td>4.11 (0.72)</td>
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<td>TG/apo B</td>
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<tr>
<td>Fasting</td>
<td>10.7 (3.28)</td>
<td>3.30 (1.25)</td>
<td>0.02</td>
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<tr>
<td>Peak</td>
<td>22.2 (3.04)*</td>
<td>23.0 (5.14)*</td>
<td>NS</td>
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</tbody>
</table>

Fasting TG as baseline was lower in the plasma (4.5±1.3 hours×[mmol/L]), chylomicron (1.9±0.5 hours×[mmol/L]), and nonchylomicron fractions (1.6±0.8 hours×[mmol/L]), but not significantly different than in FCH patients (9.2±3.0 hours×[mmol/L], 5.4±2.4 hours×[mmol/L], and 2.3±1.3 hours×[mmol/L], respectively). Moreover, after correction for fasting plasma TG, the chylomicron and nonchylomicron triglyceride areas were identical in both untreated FCH and control subjects (Table 2). This finding is consistent with the well-known association between postprandial triglyceride response and fasting plasma TG.

In FCH patients, the TG response to the oral fat load showed an abnormal pattern. The maximal TG concentration in plasma was reached at 4 hours and remained increased until 6 hours after the fat meal. Furthermore, the increase in TG concentration in the nonchylomicron fraction did not follow the chylomicron TG curve, in contrast with normal control fractions. Plasma TG concentrations returned to baseline levels after 8.5±0.8 hours (not significant versus controls). An extended "overshoot" phase was observed among FCH patients that was characterized by plasma TG levels at 24 hours that were still below the initial concentrations. The ratio of absolute 24-hour AUC-TG to 24-hour AUC-RP was calculated in control and FCH subjects. The higher ratio in FCH subjects in the chylomicron (0.29±0.06) and nonchylomicron (1.76±0.43) fractions compared with control subjects (0.17±0.03 and 0.91±0.10, respectively) indicated the presence of TG-rich, RP-poor particles in FCH. These TG-rich, RP-poor particles in FCH presumably represented VLDLs.

Postprandial Chylomicron and Chylomicron Remnant Metabolism

In FCH patients, the course of the RP concentrations was abnormal. Maximal RP concentrations in the plasma (6–7 hours), chylomicron (6 hours), and nonchylomicron (7–8 hours) fractions were reached later than in control subjects (Figure 2). Moreover, in FCH patients the duration of the RP peak in each fraction was prolonged, resulting in higher AUC-RP values, especially in the nonchylomicron remnant fraction (65.1±12.8 hours×[mg/L]; control subjects, 25.1±5.4 hours×[mg/L]; Table 2).
Follow-up Study in FCH

Treatment of the six FCH patients resulted in lower fasting plasma TG, cholesterol, apo B, apo E, and apo C-III concentrations. Postheparin plasma LPL activity also increased after therapy ($p=0.05$). Compared with controls, however, plasma TG, cholesterol, apo B, and apo C-III levels remained significantly elevated in the treated patients. The reduction of plasma TG by 54% did not result in a statistically significant improvement in chylomicron and nonchylomicron AUC-TG (3.5±0.9 hours x [mmol/L] and 1.9±0.8 hours x [mmol/L], respectively) or RP metabolism in the chylomicron (28.6±11.6 hours x [mg/L]) and nonchylomicron (39.4±6.0 hours x [mg/L]) fractions (Table 3). Apolipoprotein markers of chylomicron remnant metabolism such as apo E and apo C-III improved but remained elevated.

Associations Between Chylomicron Metabolism, Lipids, and Apolipoproteins

Univariate analysis with the separate data of the FCH subjects before and after treatment demonstrated significant associations between chylomicron AUC-RP and fasting plasma concentrations of apo C-III, apo E, and triglycerides (Table 4). The nonchylomicron remnant AUC-RP demonstrated a trend with apo C-III ($r=0.62$, $p=0.1$) but not with other parameters. The delta plasma apo C-III, i.e., the difference in apo C-III concentrations before and after treatment, was strongly associated with the delta chylomicron AUC-RP ($r=0.98$, $p=0.0005$) and delta nonchylomicron AUC-RP ($r=0.87$, $p=0.02$) (Figure 3). Similar associations were found with delta plasma apo E. Delta plasma TG demonstrated a trend with only the delta chylomicron AUC but not with the nonchylomicron AUC (Figure 3). In control subjects, chylomicron AUC-RP was inversely associated with HDL-C concentrations ($r=-0.78$, $p=0.04$). Chylomicron remnant AUC-RP did not show significant correlations with any studied variable.

Postprandial Apo B Metabolism

In control subjects, apo B was significantly lower in postprandial plasma fractions from 10 to 14 hours compared with the initial values. In nonchylomicron fractions, lower apo B concentrations were seen at 6 hours and at 9–14 hours in comparison with initial concentrations. A rise in the apo B concentration in
chylomicron fractions, concomitant with the chylomicon TG peak, was seen at 3 hours after the fat load. In FCH patients, apo B in nonchylomicron fractions showed a similar pattern to that in the nonchylomicron apo B curve in controls (Figure 4).

**Size and Composition of S\textgreater{} 1,000 Fractions**

Fasting S\textgreater{} 1,000 fractions were cholesterol enriched (0.30±0.09 mmol/L) and TG enriched (0.50±0.20 mmol/L) in untreated FCH subjects compared with control subjects (0.06±0.01 and 0.05±0.01 mmol/L, respectively; Table 5). However, the S\textgreater{} 1,000 fractions were relatively more TG rich in FCH subjects, as demonstrated by the significantly increased TG:apo B ratio (10.7±3.28 mmol/g) compared with control subjects (3.30±1.25 mmol/g). The cholesterol content of peak postprandial S\textgreater{} 1,000 fractions in FCH patients was unchanged (0.35±0.10 mmol/L) compared with baseline values, in contrast to the significantly increased cholesterol concentration in postprandial S\textgreater{} 1,000 in control subjects (0.14±0.05 mmol/L). The TG content of the postprandial S\textgreater{} 1,000 fractions increased in both FCH and control subjects, resulting in a similar TG:apo B ratio in FCH (22.2±3.04 mmol/g) and control (23.0±5.14 mmol/g) subjects.

The characteristic absorbance patterns (280 nm) of fasting and 4-hour and 8-hour postprandial S\textgreater{} 1,000 fractions are shown in Figure 5 for an FCH subject with fasting hypertriglyceridemia (subject 5; panels A–C) and an FCH subject with lower fasting plasma TGs (subject 3; panels G–I) in comparison with a normolipidemic control subject (subject 7; panels D–F). In hypertriglyceridemic FCH, a peak at the void volume was followed by a “shoulder” in the fasting state that represented smaller chylomicrons (apo B-48) and VLDLs (apo B-100). Control and normotriglyceridemic FCH subjects showed no circulating chylomicrons in the fasting state, since no peak at the void volume was found. The chylomicron peak at 4 hours was less pronounced compared with that found in hypertriglyceridemic FCH subjects and had disappeared at 8 hours only in control subjects. No shoulder was found in any of the absorbance curves for control subjects, but some were found incidentally in FCH patients with normal plasma TG (Figure 5, panels G–I). The apolipoprotein composition of the particles recovered in the different fractions was studied by SDS-PAGE (Figure 5 inserts). A peak was also found between fractions 40 and 50 in the fasting state as well as postprandially both in patients and control subjects. In FCH patients these fractions always contained apo B-100, apo B-48, albumin, apo A-I, and apo C (data not shown). In control subjects the same apolipoproteins were found as in the FCH patients, although apo B-48 was only detected in the 4-hour sample.

**Discussion**

In the present study we found evidence of a delayed clearance of chylomicron remnants in FCH, and we demonstrated the presence of smaller-sized, TG-rich lipoproteins in S\textgreater{} 1,000 fractions after a short-term, oral fat load. The impairment of chylomicron remnant clearance was significantly associated with elevated TG and apo C-III plasma concentrations. The absolute magnitude of the postprandial triglyceridemia in FCH and normal subjects was also dependent on fasting plasma TG, as demonstrated by the lack of difference in chylomicron AUC-TG after correction for fasting plasma TG. In FCH subjects, plasma TG concentrations correlated with the chylomicron AUC-RP, and therefore they correlated inversely with chylomicron removal. It has been reported by many authors that the magnitude of the postprandial lipemia (the TG response) depends on the fasting plasma TG. Several mechanisms may be responsible for the relatively delayed chylomicron TG catabolism in FCH. Chylomicrons and VLDLs share a common, saturable pathway, mediated through LPL. Chylomicrons and VLDLs are converted by LPL to remnant particles that subsequently can be taken up by the liver, and the present findings provide further evidence for this mechanism. When the postprandial TG and RP curves in FCH subjects are compared, evidence for the delayed postprandial synthesis of TG-rich, RP-poor particles in S\textgreater{} 1,000 fractions was found. These (presumed) VLDL particles may compete with chylomicrons at the level of LPL.

Analysis of the S\textgreater{} 1,000 fractions revealed that in normolipidemic control subjects a population of postprandial apo B-48 and apo B-100 particles is produced that is relatively homogenous in size on Sepharose 2B chromatography. In contrast, in hypertriglyceridemic FCH subjects at 4 hours postprandially large variations in particle size were observed, with normal apo B-48 and apo B-100 particles and, in addition, a typical population of smaller TG-rich lipoproteins, which mainly consisted of apo B-100. Brunzell and coworkers previously reported on the abnormally small size of VLDLs in FCH in the fasting state. The present results extend that observation to the postprandial state, demonstrating particle heterogeneity in response to a fat load. The postprandially synthesized TG-rich, RP-poor particles in the S\textgreater{} 1,000 fractions, documented in the presently studied FCH subjects after the RP kinetics, have been found in the shoulder of the Sepharose 2B fractions from FCH subjects.

Delayed clearance of chylomicron remnants in FCH has not been described before. It has been well documented in familial dysbeta lipoproteinemia due to abnormal apo E ligand function, hyperapobetalipoproteinemia, and endogenous hypertriglyceridemia. It is generally accepted that chylomicron remnants are atherogenic in humans. The elimination of chylomicron remnants is predominantly dependent on apo E ligand function, the putative apo E receptor (LDL receptor–related protein), LPL protein binding, HL activity, and inhibitory factors like the apo C proteins. The apo B/E receptor may also bind remnant particles in humans, but it is not a necessary prerequisite for chylomicron remnant clearance. Dietary studies in normal humans have revealed that changes in plasma TG concentrations influence chylomicron remnant removal. This has been explained by the common lipolytic route for VLDLs and chylomicrons. The present findings support this mechanism, since a 54% reduction in plasma TG concentration in FCH subjects resulted in a 39% improvement of chylomicron remnant RP removal.
Interestingly, human apo C-III transgenic mice show severe hypertriglyceridemia with impaired removal of TG-rich lipoproteins such as VLDLs. The removal defect in this model was not at the level of LPL but apparently was caused by reduced uptake by HL receptors. This model was suggested to represent familial hypertriglyceridemia and not FCH, since apo C-III overexpression did not result in increased synthesis of apo B, the hallmark of FCH. In familial hypertriglyceridemia the basic defect is the production of a normal amount of hepatic apo B particles with increased TG content. It remains to be established whether TG and apo C-III, and particle number as measured by apo B, are related to delayed chylomicron remnant clearance in other disorders of human TG metabolism such as familial hypertriglyceridemia. The present study suggests that in FCH the overproduction of VLDL–apo B results in an increased number of circulating atherogenic particles that compete at the level of LPL. This mechanism results in reduced hepatic clearance of remnant particles, thereby promoting the process of premature atherosclerosis. The relation between apo C-III and remnant clearance in FCH remains unclear. Interestingly, approximately 50% of FCH families have a restriction site polymorphism (the X2 and/or S2 minor allele) in the chromosome 11 gene cluster apo A-I–C-III–A-IV, although this association was not confirmed in a recent report. The S2 allele of the apo C-III gene, however, has been associated with higher apo C-III plasma concentrations. In addition, elevated apo C-III concentrations have been associated with an increased risk for myocardial infarction in the Cholesterol-Lowering Atherosclerosis Study. The S2 minor allele of the apo C-III gene was significantly more frequent in subjects with atherosclerosis compared with control subjects. Four of the six presently studied FCH subjects have been analyzed, and three show the X2 allele (M. Castro Cabezas et al, unpublished observations).

In conclusion, in hypertriglyceridemic FCH subjects chylomicron remnant elimination is impaired. An abnormal population of postprandial TG-rich VLDLs contributed to the delayed elimination of chylomicron remnants in FCH, both by competition at the common lipolytic pathway and at the site of the hepatic chylomicron remnant removal.

Acknowledgments

The authors are grateful to the patients and their relatives for participating in this study. We thank M. van Linde-Sibben Trip, M. van Loon-Tanis, A.J. Zonneveld, and J.H.P.M. Vos- sen for their excellent technical assistance.

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Impaired chylomicron remnant clearance in familial combined hyperlipidemia.
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doi: 10.1161/01.ATV.13.6.804
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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