Plasma Lipoproteins, Apolipoproteins, and Triglyceride Metabolism in Familial Hypertriglyceridemia

Anton F.H. Stalenhoef, Pierre N.M. Demacker, Jos A. Lutterman, and Albert van 't Laar

Several parameters of lipoprotein metabolism were examined in 38 men with primary hypertriglyceridemia (phenotype IV). Family investigation showed that 17 men had familial combined hyperlipidemia (FCH), seven had familial hypertriglyceridemia (FHT), and 14 had unclassified hypertriglyceridemia (UNC). In all three groups, plasma high density lipoprotein (HDL) cholesterol and the concentrations of apolipoprotein A-I and A-II were decreased, and apolipoprotein B was increased, each to the same extent. These results are compatible with an increased risk of cardiovascular disease in both FCH and FHT patients. The mean concentration of LDL cholesterol and the ratio of LDL to HDL cholesterol were significantly higher in FCH subjects, which could explain their increased risk. Postheparin lipoprotein lipase and hepatic lipase were the same in both groups. Determination of apolipoprotein C composition, which may modulate lipoprotein lipase activity, did not reveal any abnormalities in the different groups. In both FCH and FHT, the mean turnover rate of plasma triglycerides was almost twice normal, indicating that overproduction of plasma triglyceride plays an important role in both disorders. However, there was an overlap with normal controls, indicating impaired triglyceride removal in some subjects. The underlying mechanism of hypertriglyceridemia in FCH and FHT therefore seems to be heterogeneous. (Arteriosclerosis 6:387–394, July/August 1986)

Hypertriglyceridemia is one of the most common forms of hyperlipidemia and is frequently associated with premature atherosclerosis.¹ There is still disagreement as to the magnitude of the risk of elevated plasma triglycerides (TG) in the early development of atherosclerosis. Prospective population studies with multivariate analysis were used on high density lipoprotein (HDL) cholesterol (which is inversely correlated with coronary heart disease²) to show that plasma TG concentration is not an independent risk factor.³,⁴ In these studies, the risk was derived from secondary associations with atherosclerosis such as the negative correlation of plasma TG with HDL cholesterol. It has been established, however, that hypertriglyceridemia comprises a heterogeneous group of primary and secondary disorders. It seems important to recognize subgroups of subjects who have an increased risk and who may benefit by early treatment.

Two different familial forms of hypertriglyceridemia have been recognized: familial hypertriglyceridemia (FHT) in which the affected family members have an elevated plasma very low density lipoprotein (VLDL) concentration (lipoprotein phenotype IV), and familial combined hyperlipidemia (FCH) in which other lipoprotein phenotypes (IIa, IIb) may occur in the same family.⁵ The frequency of myocardial infarction is reportedly increased in families with FCH; subjects with elevated VLDL levels are at the same risk as subjects with elevated low density lipoproteins (LDL) levels, whereas the frequency of myocardial infarction in subjects with FHT has been shown to be similar to that of normolipidemic controls.⁶ Based on the original study by Goldstein et al.,⁵ however, this absence of increased risk for cardiovascular disease may not extend to all patients with FHT. Since no genetic marker has yet been detected for either FHT or FCH, investigation of rather large families is needed to establish the diagnosis in individual patients.

Kinetic studies have been performed only in a limited number of subjects after genetic classification,⁷⁻¹¹ and some authors have concluded that hypertriglyceridemia in FHT is caused by an overproduction of TG-enriched VLDL, whereas that of FCH is due to oversecretion of VLDL of normal composition.⁶,¹⁰ A higher ratio of VLDL-TG to VLDL-apo B and a larger size of the VLDL particles in FHT seemed to support this conclusion.¹² In all these studies, however, the group with FCH consisted of subjects with

³ From the Department of Medicine, Division of General Internal Medicine, St. Radboud University Hospital, Nijmegen, The Netherlands.

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⁵ Address for reprints: Anton Stalenhoef, M.D., Department of Medicine, St. Radboud University Hospital, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.

⁶ Received January 10, 1983; revision accepted February 10, 1986.
different lipoprotein phenotypes including Ia and IIb. Although the metabolic mechanism underlying these two disorders may be different, it is of interest to ascertain whether it is possible to discriminate Type IV subjects with FCH from those with FHT when comparing subjects with Type IV phenotype only. We therefore compared various metabolic characteristics including concentrations of plasma lipoproteins and apolipoproteins, lipolytic enzyme activities, and kinetics of plasma TG in a group of subjects with primary hypertriglyceridemia.

**Methods**

**Subjects**

We selected 38 male index patients on the basis of persistent hypertriglyceridemia and the existence of a large family. All subjects had phenotype IV defined as a plasma TG concentration greater than 2.00 mmol/liter without fasting chylomicronemia (over 40 years of age, TG > 2.20 mmol/liter) and a normal plasma LDL cholesterol concentration (< 95th percentile of normal for the same age group). These patients were originally referred to our clinic for various reasons such as hypertension, atherosclerosis, and hypertriglyceridemia. Patients with secondary causes of hypertriglyceridemia such as gross obesity (relative body weight > 140%), excessive alcohol consumption, or diabetes mellitus were excluded, as well as subjects with Type III hyperlipoproteinemia. The subjects showed no biochemical evidence for renal, thyroid, or liver disease. Drugs known to affect lipid metabolism were withheld for at least 2 months prior to this investigation, except for 8-blocking agents in 12 patients who used these drugs because of hypertension and angina pectoris (propranolol 80 to 160 mg daily, metoprolol 50 to 100 mg daily). Although it is known that some of these drugs produce small changes in serum lipids, this medication was not discontinued for ethical reasons. For at least 2 months prior to and during the investigation the patients ate an isocaloric diet containing approximately 45% of calories as carbohydrate, 40% as fat, and 15% as protein. Their body weights remained stable during this time.

**Study Protocol**

Fasting blood was sampled from 181 first-degree relatives (parents and siblings) for genetic classification. Children were not included because the full expression of FCH or FHT is not evident until the end of the second decade of life. Most relatives came to our department for blood sampling, but a few fasting blood samples were mailed to our laboratory. Cholesterol was determined in VLDL, LDL, and HDL in the majority of the normolipidemic relatives and in all relatives with elevated cholesterol levels. Patients were classified according to the strict criteria of Brunzell et al. as having FHT when at least two relatives had only hypertriglyceridemia (plasma TG > 2.00 mmol/liter), and if older than 40 years, > 2.20 mmol/liter. Patients were classified as having FCH when, besides hypertriglyceridemia, one or more relatives had hypercholesterolemia (LDL cholesterol above the 95th percentile of normal). The index patients were designated as having unclassified hypertriglyceridemia (UNC) when either one or no first-degree relatives showed evidence of hyperlipidemia or when too few lipoprotein analyses of relatives were available to identify the genetic basis.

**Procedures**

VLDL was separated by ultracentrifugation for 16 hours at 40,000 rpm as previously described. HDL was isolated after precipitation of LDL in the d > 1.006 g/ml fraction with heparin/MnCl. Cholesterol was determined with an enzymatic method, and TG, with a semiautomated colorimetric method. Apolipoprotein A-I, A-II, and B concentrations were determined by rocket immunoelectrophoresis in whole serum that had been frozen and stored. The coefficients of variation were 5.8% for apo A-I, 5.4% for apo A-II, and 7.9% for apo B (n = 17).

The Tris-urea soluble apoproteins of the VLDL fraction were semiquantitatively measured using isoelectric focusing according to the method of Weidman et al. which was slightly modified as described elsewhere. The composition of apo C and the ratio of apo C-II/C-III were determined. Lipoprotein lipase and hepatic lipase were mea-
sured 15 minutes after injection of 50 U of heparin/kg body weight with an immunochemical technique as previously described.20

Plasma TG turnover rate was assessed according to the method of Farquhar et al.21 as modified by Nikkilä and Kekki.22 After an overnight fast, 50 μCi 2-3H-glycerol (Radiochemical Centre, Amersham, England) was administered intravenously as a pulse injection. The plasma TG radioactivity and concentrations were determined in nine blood samples at 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, and 7 hours after the administration of the tracer. The subject remained fasting during that time. Plasma TG was extracted according to the method of Royer and Ko,23 using n-heptane instead of n-nonane. Fractionation of the lipoproteins was omitted for reasons discussed previously.22

The slope of the fall in specific activity of the endogenously labeled TG plotted with time on a semilogarithmic scale was determined by the method of least squares analysis, giving the fractional catabolic rate (FCR). Only monoexponential curves were accepted and a steady state in the concentration of plasma TG was required (a variation in plasma TG of less than 10%). The product of the fractional catabolic rate, the mean TG concentration during the experiment, and the plasma volume was required (a variation in plasma volume of less than 10%). The number in parentheses means the number of subjects using β-blockers.22

To convert values for cholesterol to milligrams per deciliter, multiply by 38.7; for triglycerides, multiply by 88.0.

Table 1. Clinical Data and Fasting Plasma Lipid Concentrations of the Different Groups of Men with Hypertriglyceridemia

<table>
<thead>
<tr>
<th>Genetic group</th>
<th>No. of subjects</th>
<th>Age (yrs)</th>
<th>Relative BW (%)</th>
<th>Vascular disease</th>
<th>Cholesterol (mmol/liter)</th>
<th>Triglycerides (mmol/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCH</td>
<td>17 (4)*</td>
<td>50 ± 10</td>
<td>117 ± 13</td>
<td>CHD 2</td>
<td>6.70 ± 1.16</td>
<td>4.52 ± 1.90</td>
</tr>
<tr>
<td>FHT</td>
<td>7 (3)*</td>
<td>49 ± 9</td>
<td>114 ± 6</td>
<td>PVD</td>
<td>6.11 ± 1.27</td>
<td>4.82 ± 1.47</td>
</tr>
<tr>
<td>UNC</td>
<td>14 (5)*</td>
<td>46 ± 9</td>
<td>112 ± 10</td>
<td>CHD PVD</td>
<td>6.32 ± 0.94</td>
<td>4.45 ± 1.76</td>
</tr>
</tbody>
</table>

Data are given as means ± SD with ranges in parentheses.

FCH = familial combined hyperlipidemia; FHT = familial hypertriglyceridemia; UNC = unclassified hypertriglyceridemia; CHD = coronary heart disease; PVD = peripheral vascular disease; BW = body weight.

Statistics

Statistical analysis was carried out by using Student's t test for unpaired data and Pearson's correlation coefficient. A p value less than 5% was considered significant. All results are presented as means ± SD.

Results

Plasma Lipoproteins and Apolipoproteins

The VLDL-TG and the VLDL, LDL, and HDL cholesterol concentrations are summarized in Table 2. The TG and cholesterol levels in the VLDL fraction were significantly higher by selection in the hypertriglyceridemic groups. LDL cholesterol concentrations in these groups of patients did not differ significantly from normal male controls. The mean LDL cholesterol concentration, however, was significantly lower in subjects with FHT compared with FCH (p < 0.05). The HDL cholesterol concentration was significantly lower in each of the three hypertriglyceridemic groups. Among the groups of patients there were no significant differences in the concentration of HDL cholesterol. The mean LDL/HDL cholesterol ratio in subjects with FCH and UNC was significantly higher than in normal controls, but not in subjects with FHT (Table 2). This ratio in subjects with FCH was significantly higher than in subjects with FHT. The HDL cholesterol concentration was inversely correlated with VLDL cholesterol concentration in the two genetic groups (FCH: r = -0.59, p < 0.01; FHT: r = -0.87, p < 0.05) and also with VLDL-TG (FCH: r = -0.58, p < 0.05; FHT: r = 0.95, p < 0.001). No significant correlations were found between VLDL-TG and LDL cholesterol in any group. The ratio of VLDL cholesterol to VLDL-TG, as an indirect estimate of the VLDL remnant concentration, was equal in the different groups and was not significantly different from the control group (Table 2).

The results of the measurements of the apoproteins A-I, A-II, and B in total plasma are summarized in Table 3. Apo A-I and A-II were significantly decreased and apo B, significantly increased, in each group. Among the hypertriglycerider-
Table 2. Plasma Lipoprotein Lipid Concentrations and Ratios In the Different Groups with Hypertriglyceridemia

<table>
<thead>
<tr>
<th>Genetic group</th>
<th>VLDL-chol (mmol/liter)</th>
<th>VLDL-TG (mmol/liter)</th>
<th>LDL-chol (mmol/liter)</th>
<th>HDL-chol (mmol/liter)</th>
<th>VLDL-chol/VLDL-TG</th>
<th>Total chol (mmol/liter)</th>
<th>LDL-chol (mmol/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCH (n = 17)</td>
<td>1.83 ± 0.64*</td>
<td>3.59 ± 1.58*</td>
<td>4.02 ± 0.58</td>
<td>0.86 ± 0.17*</td>
<td>0.53 ± 0.13</td>
<td>8.14 ± 2.43*</td>
<td>4.83 ± 1.11*</td>
</tr>
<tr>
<td>FHT (n = 7)</td>
<td>1.95 ± 0.45*</td>
<td>3.74 ± 1.35*</td>
<td>3.30 ± 1.11†</td>
<td>0.95 ± 0.33*</td>
<td>0.56 ± 0.14</td>
<td>6.87 ± 1.96†</td>
<td>3.61 ± 1.20†</td>
</tr>
<tr>
<td>UNC (n = 14)</td>
<td>2.03 ± 0.88*</td>
<td>3.56 ± 1.73*</td>
<td>3.48 ± 0.95</td>
<td>0.82 ± 0.12*</td>
<td>0.59 ± 0.13</td>
<td>7.84 ± 1.61*</td>
<td>4.31 ± 1.30*</td>
</tr>
<tr>
<td>Normal (n = 21)</td>
<td>0.43 ± 0.20</td>
<td>0.72 ± 0.27</td>
<td>3.72 ± 0.87</td>
<td>1.22 ± 0.22</td>
<td>0.62 ± 0.14</td>
<td>4.55 ± 1.20</td>
<td>3.17 ± 1.07</td>
</tr>
</tbody>
</table>

Values are mean ± so.  
FCH = familial combined hyperlipidemia; FHT = familial hypertriglyceridemia; UNC = unclassified hypertriglyceridemia; chol = cholesterol; TG = triglycerides.  
*p < 0.01 (or less) vs normal controls.  
†p < 0.01 vs FCH.  
To convert values for cholesterol to milligrams per deciliter, multiply by 38.7; for triglycerides, multiply by 88.0.

Table 3. Plasma Apolipoprotein A-I, A-II, and B Concentrations (mg/dl) and Ratios In the Different Groups with Hypertriglyceridemia

<table>
<thead>
<tr>
<th>Genetic group</th>
<th>Apo A-I</th>
<th>Apo A-II</th>
<th>Apo B</th>
<th>Apo A-I/A-II</th>
<th>Apo A-I/B</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCH (n = 13)</td>
<td>96.1 ± 24.6*</td>
<td>35.4 ± 5.5*</td>
<td>161.1 ± 45.1*</td>
<td>2.77 ± 0.63*</td>
<td>0.61 ± 0.17*</td>
</tr>
<tr>
<td>FHT (n = 7)</td>
<td>92.6 ± 38.1*</td>
<td>38.5 ± 6.7*</td>
<td>140.1 ± 41.9*</td>
<td>2.36 ± 0.70*</td>
<td>0.71 ± 0.44*</td>
</tr>
<tr>
<td>UNC (n = 11)</td>
<td>110.9 ± 21.3*</td>
<td>36.7 ± 5.1*</td>
<td>143.5 ± 58.7*</td>
<td>3.04 ± 0.54*</td>
<td>0.82 ± 0.38*</td>
</tr>
<tr>
<td>Normal (n = 11)</td>
<td>170.9 ± 21.1</td>
<td>48.3 ± 7.9</td>
<td>93.9 ± 30.7</td>
<td>3.59 ± 0.48</td>
<td>1.88 ± 0.74</td>
</tr>
</tbody>
</table>

Values are means ± sd.  
FCH = familial combined hyperlipidemia; FHT = familial hypertriglyceridemia; UNC = unclassified hypertriglyceridemia.  
*p < 0.05 (or less) vs controls.

Postheparin Lipolytic Activities

Table 4 summarizes the postheparin lipolytic activities.  
LPL and hepatic lipase activities were not significantly decreased in the different groups. Postheparin LPL activity was not significantly correlated with plasma TG concentration in the various groups (FCH: r = -0.25; FHT: r = 0.57; UNC: r = 0.13).

Table 4. Lipoprotein Lipase and Hepatic Lipase Activities in Postheparin Serum (50 U/kg) In the Different Groups with Hypertriglyceridemia

<table>
<thead>
<tr>
<th>Genetic group</th>
<th>Lipoprotein lipase</th>
<th>Hepatic lipase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(μmol FFA/m/hr)</td>
<td>(μmol FFA/m/hr)</td>
</tr>
<tr>
<td>FCH (n = 17)</td>
<td>6.3 ± 2.6</td>
<td>29.9 ± 12.2</td>
</tr>
<tr>
<td>FHT (n = 7)</td>
<td>7.2 ± 4.3</td>
<td>26.7 ± 13.0</td>
</tr>
<tr>
<td>UNC (n = 14)</td>
<td>7.9 ± 3.2</td>
<td>28.3 ± 10.8</td>
</tr>
<tr>
<td>Normal (n = 14)</td>
<td>8.0 ± 2.5</td>
<td>25.9 ± 9.1</td>
</tr>
</tbody>
</table>

Values are means ± sd.  
FCH = familial combined hyperlipidemia; FHT = familial hypertriglyceridemia; UNC = unclassified hypertriglyceridemia; FFA = free fatty acids.
UNC: \( r = -0.30 \); and normal controls: \( r = -0.28 \). LPL was not correlated with HDL cholesterol concentration in the various groups. There were also no correlations between LPL activity and the ratio of apo C-II to C-III in the various groups.

**Plasma Triglyceride Kinetics**

The results of the measurements of the plasma TG turnover rate are summarized in Table 5. The mean plasma TG turnover rate was increased in all the hypertriglyceridemic groups, but there was an overlap with the control group. Plasma TG turnover rate was positively correlated with plasma TG concentration in the subjects with FCH (\( r = 0.53, p < 0.05 \)) and normal controls (\( r = 0.72, p < 0.01 \)) but not in groups with FHT (\( r = 0.64, \text{ns} \)) and UNC (\( r = 0.40, \text{ns} \)). When the results of all groups were combined, the plasma TG turnover rate was significantly correlated with plasma TG concentration (\( n = 55, r = 0.65, p < 0.001 \)). This relationship is depicted in Figure 1; this figure also shows a wide range in turnover rates in the individual subjects within the various groups, both for FCH and FHT groups. The mean FCR was equally decreased in all groups with hypertriglyceridemia. In the hypertriglyceridemic groups, the FCR was inversely correlated with plasma TG concentration (FCH: \( r = -0.59, p < 0.01 \); FHT: \( r = 0.80, p < 0.05 \); UNC: \( r = -0.51, p < 0.05 \)). This correlation was not present in normal controls (\( r = -0.24, \text{ns} \)).

### Discussion

Several metabolic parameters of lipoprotein metabolism were studied in a group of patients with primary hypertriglyceridemia after genetic classification. We selected patients with the Type IV phenotype and looked for possible differences in an attempt to recognize the genetic form of hypertriglyceridemia in these subjects. The use of beta blockers had no effect on the metabolic variables (Table 6). One of the metabolic aspects in this study was the measurement of the TG turnover rate; the technique that we and others\(^8\) used to assess TG secretion rate has its limitations, as pointed out under Methods; the results may therefore not be accurate, but our data are consistent with a study\(^11\) in which VLDL-TG transport was investigated by multicompartamental analysis in normal controls and FCH subjects.

**Familial Combined Hyperlipidemia**

Hypertriglyceridemia in FCH seems to result in the majority of patients from an overproduction of VLDL particles. The underlying defect in this condition is supposed to be an increased hepatic production of VLDL-apo B with a secondary stimulation of VLDL-TG production. Three studies\(^6\) have been published in which the authors measured the production rate of VLDL-apo B with exogenously radiiodinated lipoproteins, and in these studies VLDL-apo B production averaged a twofold increase. In two of these studies,\(^6\) VLDL-TG production rate was also measured and found to be proportionally increased. The same twofold increase in VLDL-TG production in FCH was found by

![Figure 1. Relationship between plasma triglyceride (TG) turnover rate and plasma TG concentration in subjects with phenotype IV with familial combined hyperlipidemia (FCH), subjects with familial hypertriglyceridemia (FHT), subjects with unclassified hypertriglyceridemia (UNC), and normal controls as indicated. To convert values for triglycerides to milligrams per deciliter, multiply by 88.0.](http://atvb.ahajournals.org/ Downloaded from)

### Table 5. Plasma Triglyceride Turnover Rate, Fractional Catabolic Rate, and Plasma Triglyceride Concentration in Patients with Primary Hypertriglyceridemia

<table>
<thead>
<tr>
<th>Genetic group</th>
<th>TG turnover ((\mu\text{mol/kg-hr}))</th>
<th>FCR (hr(^{-1}))</th>
<th>Plasma TG (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCH ((n = 17))</td>
<td>18.0 ± 5.9(^*)</td>
<td>0.14 ± 0.05(^*)</td>
<td>3.72 ± 1.51(^*)</td>
</tr>
<tr>
<td>FHT ((n = 7))</td>
<td>17.2 ± 5.8(^*)</td>
<td>0.13 ± 0.03(^*)</td>
<td>3.72 ± 1.39(^*)</td>
</tr>
<tr>
<td>UNC ((n = 14))</td>
<td>17.7 ± 7.1(^*)</td>
<td>0.14 ± 0.06(^*)</td>
<td>3.62 ± 1.42(^*)</td>
</tr>
<tr>
<td>Normal ((n = 17))</td>
<td>9.9 ± 3.1</td>
<td>0.26 ± 0.06</td>
<td>1.09 ± 0.33</td>
</tr>
</tbody>
</table>

Results are presented as means ± sd. FCH = familial combined hyperlipidemia; FHT = familial hypertriglyceridemia; UNC = unclassified hypertriglyceridemia; TG = triglycerides; FCR = fractional catabolic rate.

Plasma TG values are the means of nine samples during the study period.

\(^*\)\( p < 0.001 \) vs controls.

To convert values for triglycerides to milligrams per deciliter, multiply by 88.0.
Table 6. Metabolic Variables of Hypertriglyceridemic Patients Who Used B-Blockers Compared with Patients Not on B-Blockers Irrespective of Genetic Classification

<table>
<thead>
<tr>
<th>Variable</th>
<th>B-blockers</th>
<th>No B-blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 12)</td>
<td>(n = 26)</td>
</tr>
<tr>
<td>Plasma chol (mmol/liter)</td>
<td>6.16 ± 1.16</td>
<td>8.59 ± 1.07</td>
</tr>
<tr>
<td>Plasma TG (mmol/liter)</td>
<td>4.49 ± 1.59</td>
<td>4.69 ± 1.91</td>
</tr>
<tr>
<td>VLDL-chol (mmol/liter)</td>
<td>1.84 ± 0.87</td>
<td>1.96 ± 0.76</td>
</tr>
<tr>
<td>VLDL-TG (mmol/liter)</td>
<td>3.57 ± 1.41</td>
<td>3.62 ± 1.65</td>
</tr>
<tr>
<td>LDL-chol (mmol/liter)</td>
<td>3.50 ± 0.80</td>
<td>3.77 ± 0.89</td>
</tr>
<tr>
<td>HDL-chol (mmol/liter)</td>
<td>0.83 ± 0.16</td>
<td>0.88 ± 0.21</td>
</tr>
<tr>
<td>Total chol/HDL-chol</td>
<td>7.42 ± 2.42</td>
<td>7.84 ± 1.94</td>
</tr>
<tr>
<td>VLDL-chol/VLDL-TG</td>
<td>0.52 ± 0.12</td>
<td>0.57 ± 0.13</td>
</tr>
<tr>
<td>LDL-chol/HDL-chol</td>
<td>4.30 ± 1.16</td>
<td>4.47 ± 1.31</td>
</tr>
<tr>
<td>TG turnover rate (μmol/kg/hr)</td>
<td>16.6 ± 5.1</td>
<td>18.3 ± 6.6</td>
</tr>
<tr>
<td>FCR (hr⁻¹)</td>
<td>0.13 ± 0.06</td>
<td>0.14 ± 0.05</td>
</tr>
<tr>
<td>Lipoprotein lipase (μmol FFA/ml-hr)</td>
<td>6.70 ± 2.91</td>
<td>7.25 ± 3.3</td>
</tr>
<tr>
<td>Hepatic lipase (μmol FFA/ml-hr)</td>
<td>29.3 ± 13.0</td>
<td>28.4 ± 11.2</td>
</tr>
<tr>
<td>Apo A-I (mg/dl)</td>
<td>101.0 ± 34.4*</td>
<td>99.7 ± 23.0†</td>
</tr>
<tr>
<td>Apo A-II (mg/dl)</td>
<td>34.8 ± 6.7*</td>
<td>35.8 ± 8.9†</td>
</tr>
<tr>
<td>Apo B (mg/dl)</td>
<td>155.6 ± 45.8*</td>
<td>153.3 ± 49.0†</td>
</tr>
</tbody>
</table>

*n = 10.  †n = 21.
chol = cholesterol; TG = triglycerides; FFA = free fatty acids.
To convert values for cholesterol to milligrams per deciliter, multiply by 38.7; for triglycerides, multiply by 88.0.

Although VLDL overproduction may play a major role in FCH, in this study (as well as in all other kinetic studies with VLDL-apo B and VLDL-TG production, that FCH is caused by an overproduction of VLDL of normal composition.8, 10

The removal of VLDL from the blood is dependent on the hydrolysis of their TG content by LPL as is evident from familial LPL deficiency.20, 21 However, subnormal activities of LPL as an explanation for a decreased TG removal in FCH subjects were not found in this study, nor in other studies of genetically defined subjects, either fasted or fed.11, 12 Furthermore, apo C-II, known as the specific activator of LPL,22 was normal as was the apo C-II/C-III ratio. Thus, plasma TG is not a simple function of LPL activity, as is evident from the poor correlations between LPL and plasma TG concentration, FCR, or TG turnover rate found in this study. The average percentage of conversion of VLDL-apo B to LDL-apo B has been found to be normal in FCH, varying from about 45% in the report by Janus et al.31 to 75% in that of Kissebah et al.10 One can therefore expect an increased production rate of LDL. An increased LDL-apo B synthesis as well as a direct LDL-apo B synthesis not derived from VLDL-apo B were indeed found with the kinetic models used by these same authors.31, 32 Janus et al.31 found no difference in VLDL-apo B FCR between FCH subjects with Type II phenotype and normal subjects, in contrast to the finding of Kissebah et al.32 Varying individual clearance capacities for LDL may again influence the concentrations of LDL and the phenotypic expression of FCH.

Of the risk factors investigated in our subjects with Type IV phenotype, LDL cholesterol was normal by selection; HDL cholesterol was decreased, as was the ratio of total cholesterol to HDL cholesterol and LDL cholesterol to HDL cholesterol; and the apo A-I and apo A-II concentrations were decreased, reflecting a decrease in the number of HDL particles. The ratio of apo A-I to apo A-II was also decreased. These findings agree with those from an earlier report on FCH12 and may indicate a relatively low concentration of the subfraction HDL2 of HDL34 which is considered to be the antiatherogenic fraction of HDL.34 The apo-proteins A-I, A-II, and B have been suggested as better discriminators for the risk of atherosclerosis than plasma lipids.35-38 In one report36 the apo A-I to B ratio discriminated best between cases of myocardial infarction and controls. These factors and possibly elevated LDL levels during other periods in life may account for the increased risk of premature atherosclerosis in Type IV FCH subjects.

Familial Hypertriglyceridemia

The underlying defect of FHT is less clear. This may due to the fact that FHT is probably heterogeneous, being more than just one disease, which would explain the conflicting reports on atherosclerosis5, 6 and risk and VLDL kinetics.7-10 The production rate of VLDL apo B was found to be normal in three subjects with FHT,9 mildly elevated in six subjects,8 and clearly elevated in two7 and eight10 subjects. These studies were performed with exogenously radioiodinated VLDL, with the exception of the study by Fisher et al.7 which used tritiated leucine as an endogenous marker of VLDL-apo B. The production rate of plasma TG averaged a twofold increase over the control values in our study, which is in accordance with an overproduction of VLDL-TG in FHT. On the other hand, some patients have TG transport rates below the upper limit of normal (Figure
1), consistent with a defective removal in those patients. The low FCR and positive correlation between the FCR and plasma TG concentration in FHT would support a role for a defective VLDL removal, but these findings may be influenced by an expanded pool size as discussed earlier. 

We could not demonstrate subnormal activities of LPL or hepatic lipase in our FHT subjects as an explanation for a possible defective lipolysis; the apo C-II/III ratio was also normal. Our findings on LPL are in agreement with the report of Goldberg et al.29 who found normal fasting and postprandial activities of this enzyme in five FHT subjects. In two other studies8,10 in which VLDL-TG production rate was measured in FHT, a disproportional increase to that of VLDL-apo B was found.8,10 Chemical composition of the VLDL fraction showed a relative enrichment of TG in these studies, and it was therefore concluded that the main feature of FHT is an overproduction of TG-enriched VLDL. The percentage of conversion of VLDL-apo B to LDL-apo B was decreased in the group of eight FHT subjects reported by Kisselbath et al.10 (48% vs 73%). However, this was found to be normal in the single subject reported by Janus et al.21 In FHT the VLDL particles tend to be larger than VLDL from normals.12 In has been shown29 that large VLDL particles of 30 to 150 nm in diameter are not appreciably converted to LDL.29 The reduced conversion of VLDL to LDL in FHT may reflect this size-dependent pathway. The relatively low LDL cholesterol concentration that we found in FHT subjects may also result from this reduced conversion.

HDL cholesterol concentrations, as well as the concentrations of apo A-I and apo A-II, were decreased in our FHT subjects. The ratio of apo A-I to apo A-II was also decreased. Brunzell et al.12 found a decreased cholesterol concentration in the HDL fraction at the expense of TG, whereas the apo A-I to A-II ratio was normal; this may again reflect the heterogeneity of this disorder. The total cholesterol to HDL cholesterol ratio was increased in our FHT subjects, although this was not the case for the more important LDL cholesterol to HDL cholesterol ratio. Taken together, our results and the literature indicate that the risk for atherosclerotic disease in FHT subjects is variable, probably as a result of heterogeneity; some patients are at increased risk, while others are not.

Subjects with UNC might have either FCH or FHT, if fully classified. The results from this group are comparable with those in FCH and FHT: an overproduction of plasma TG in general and a defective plasma TG removal in some patients (Figure 1).

Finally, when we compare the phenotype IV subjects with FCH and FHT in this study, there is a significant difference in the concentration of LDL cholesterol, which may be explained by the kinetic differences discussed above. During a later period of life, this difference may become accentuated and cause a phenotypic change to Type II. This could account for the higher risk in FCH compared to FHT, although in our study the risk appeared to be the same. From our work it is clear, however, that there is no genetic marker to distinguish between FCH and FHT in individual patients with phenotype IV. Sniderman et al.39 have suggested that an increased LDL-apo B concentration with normal LDL cholesterol levels (hyperapobetalipoproteinemia) might distinguish between the genetic groups. Further studies about the etiology of this condition and family investigations are needed to confirm this possibility.

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References


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A F Stalenhoef, P N Demacker, J A Lutterman and A van ‘t Laar

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