**Very Low Density Lipoprotein Triglyceride Metabolism in Relatives of Hypertriglyceridemic Probands**

**Evidence for Genetic Control of Triglyceride Removal**

Timo Sane and Esko A. Nikkilä

The production and catabolism of very low density lipoprotein triglycerides (VLDL-TG) were determined in 11 index patients with primary hypertriglyceridemia and in their 70 first-degree relatives. In the probands the mean value for VLDL-TG production rate was twice normal, and the mean fractional catabolic rate (FCR) was reduced to 50% from normal. A similar kinetic pattern was also observed in most hypertriglyceridemic relatives. In the normotriglyceridemic relatives the mean values of both kinetic parameters were comparable to those of controls. No kinetic differences were observed between families with familial hypertriglyceridemia, familial combined hyperlipidemia, or genetically unclassified hypertriglyceridemia (all diagnosed by lipoprotein phenotypes). Thus, no explanation for the phenotypic differences between the two forms of familial hyperlipoproteinemia was found in plasma VLDL-TG metabolism. When the families were grouped according to the VLDL-TG production rate of the proband, there was no significant difference between the VLDL-TG production rates of relatives of “overproducer” probands and relatives of the probands with normal VLDL-TG production rate. In contrast, relatives of low FCR probands had significantly lower mean FCR than the relatives of probands with a normal FCR. This difference in FCR was present both in hypertriglyceridemic and normotriglyceridemic relatives. These results suggest that the catabolism (lipolysis) of VLDL-TG is under genetic control, whereas the VLDL-TG production rate is mainly related to obesity. It is likely that hypertriglyceridemia often develops on the basis of VLDL overproduction in individuals who have a genetically low VLDL triglyceride removal (lipolytic) capacity.


Human plasma endogenous triglycerides are transported mainly in very low density lipoprotein (VLDL) particles. These are synthesized in the liver and removed at extrahepatic tissues by the lipolytic action of endothelial lipoprotein lipase. The concentration of triglycerides in plasma is dependent on the number of circulating VLDL particles rather than on the triglyceride content of each individual VLDL particle. Hypertriglyceridemia develops either when production of VLDL is increased or when VLDL removal is impaired. Both mechanisms may, in fact, operate simultaneously, making it difficult to decide which is the basic abnormality primarily responsible for the rise in VLDL concentration. Primary hypertriglyceridemia is known to occur in families, suggesting that there are genetic defects in the synthesis or removal of VLDL. Two common forms of familial hypertriglyceridemia have been recognized: familial hypertriglyceridemia (FHTG) and familial combined hyperlipidemia, or familial multiple-type hyperlipoproteinemia (FCHL). In FHTG the affected family members have elevated plasma VLDL but normal or low LDL levels (phenotype IV or V), whereas in FCHL the affected individuals show a rise of VLDL (phenotype IV or V), LDL (phenotype IIa), or both (phenotype IIb). The basic genetic defect has not been identified in either of these disorders and, thus, there are, so far, no reliable markers to confirm the diagnosis in affected individuals. The composition of the VLDL particles may be somewhat different in the two conditions, but not different enough to serve as a specific diagnostic marker.

Attempts have been made to find abnormalities in lipoprotein lipid or apoprotein kinetics that would characterize the two genetic disorders. In both forms of familial hypertriglyceridemia, the probands showed an increased synthetic rate of VLDL triglycerides and VLDL apo B, suggesting the presence of an oversecretion of VLDL particles into plasma. In FHTG the VLDL triglyceride synthesis is relatively more increased than that of VLDL apo B, resulting in triglyceride enrichment of VLDL particles. Moreover, in FCHL the conversion of VLDL apo B to LDL apo B is increased, and, accordingly, there is an overproduction of LDL apo B. In addition, the fractional removal rates of VLDL triglycerides and VLDL apo B are often decreased in both conditions.

All previous studies on lipoprotein kinetics in the familial
hypertriglyceridemias have been made only in the probands; the family diagnosis was based on lipid screening of a variable number of first-degree relatives. Thus, we do not know whether there is any familial clustering of certain lipoprotein kinetic patterns or whether these are characteristic for either FHTG or FCHL. One recent study has shown that, in FCHL, the LDL apo B production rate is increased even without a rise in LDL concentration. This suggests that kinetic abnormalities might also be found in those family members who have normal VLDL or LDL concentrations. In the present study, we have assessed the VLDL triglyceride kinetics in both hypertriglyceridemic and normolipidemic first-degree relatives of hypertriglyceridemic probands.

### Methods

For this study, 11 index patients with primary hypertriglyceridemia were recruited from the patient files of the Helsinki University Central Hospital. In order to be eligible, the patients had to meet the following criteria: 1) fasting serum VLDL triglyceride concentration exceeding twice 132 mg/dl (representing the 90th percentile of healthy middle-aged subjects); 2) age less than 65 years; 3) no evidence of secondary hypertriglyceridemia as documented by a negative test for urinary protein and normal levels of blood glucose, serum creatinine, transaminases, T4, and TSH; 4) no history of excessive use of alcohol; 5) no use of drugs influencing serum lipid levels; 6) absence of incapacitating cerebrovascular, pulmonary, or heart disease and of morbid obesity (relative body weight (RBW) < 1.75 ideal body weight (IBW)); 7) presence of at least three, living, first-degree relatives willing to participate in the study.

The clinical data of the hypertriglyceridemic probands are shown in Table 1. The age of the probands ranged from 27 to 57 years (mean 45 years). Their RBW was between 1.16 and 1.69 with an average of 1.30. Five had RBW above 1.30, but apart from one patient, the obesity was of moderate degree. The massively obese proband (HK) lost 14 kg of weight but is still hypertriglyceridemic. Nine probands had at some time received hypolipidemic drugs, but these had been discontinued for at least 6 months before the study. Three of the probands (KN, TK, and HK) were survivors of previous myocardial infarction. Four probands (KN, TK, HK, and KM) were taking β-blocking agents but none was using a diuretic.

Six healthy males with VLDL triglyceride concentrations of less than 132 mg/dl volunteered as control probands. Their ages ranged from 31 to 50 years (mean 43 years) and their RBW, from 0.85 to 1.30 (mean 1.14). These probands were accepted only after examination of their first-degree relatives (n = 30) had shown that all had normal levels of VLDL triglycerides and LDL cholesterol (see below).

### Relatives

The 11 probands reported 98 living first-degree relatives (parents, siblings, or children). Of these, 11 were excluded from the study on the basis of age (less than 16 or more than 70 years old) or because they lived permanently abroad. All the remaining 87 relatives were contacted by letter or phone, and the purpose and design of the study were explained. All were invited to participate in the turnover study or, if this was not possible, to at least give a fasting blood sample for analysis of lipoproteins. A positive response was obtained from 85 relatives (98%); 70 of these came for the turnover measurement and the remaining 15 gave a blood sample. Among these, there were two parents, 66 siblings, and 17 adult children of the probands. There were 57 male and 28 female relatives between 16 and 61 years of age (mean 43 years). Their RBW ranged from 0.80 to 1.68 (mean 1.18) of IBW. Of the 85 relatives, 21 (25%) were obese (RBW > 1.30). Only a few of the examined relatives used hypolipidemic drugs or other medication that might influence lipid levels. One relative had mild, type II diabetes combined with elevated serum VLDL triglyceride level (type IV).

### Table 1. Clinical Characteristics of Index Patients at Screening

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>RBW (× IBW)</th>
<th>Total TG* (mg/dl)</th>
<th>VLDL TG* (mg/dl)</th>
<th>Total CHOL† (mg/dl)</th>
<th>LDL-CHOL† (mg/dl)</th>
<th>Phenotype</th>
<th>Family diagnosis</th>
<th>Coronary heart disease</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>HK</td>
<td>52 M</td>
<td>1.69</td>
<td>233</td>
<td>202</td>
<td>179</td>
<td>108</td>
<td>IV</td>
<td>FHTG</td>
<td>+</td>
<td>8-blocking agent</td>
<td></td>
</tr>
<tr>
<td>SV</td>
<td>42 F</td>
<td>1.26</td>
<td>2270</td>
<td>1601</td>
<td>549</td>
<td>57</td>
<td>V</td>
<td>FHTG</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>RK</td>
<td>40 M</td>
<td>1.33</td>
<td>398</td>
<td>319</td>
<td>196</td>
<td>127</td>
<td>IV</td>
<td>FHTG</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>KJ</td>
<td>43 M</td>
<td>1.16</td>
<td>458</td>
<td>344</td>
<td>222</td>
<td>108</td>
<td>V</td>
<td>FHTG</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>KN</td>
<td>57 M</td>
<td>1.34</td>
<td>266</td>
<td>217</td>
<td>255</td>
<td>178</td>
<td>IV</td>
<td>FCHL</td>
<td>+</td>
<td>8-blocking agent</td>
<td></td>
</tr>
<tr>
<td>TK</td>
<td>47 M</td>
<td>1.16</td>
<td>340</td>
<td>258</td>
<td>251</td>
<td>174</td>
<td>IV</td>
<td>FCHL</td>
<td>+</td>
<td>8-blocking agent</td>
<td></td>
</tr>
<tr>
<td>PA</td>
<td>47 M</td>
<td>1.34</td>
<td>372</td>
<td>290</td>
<td>298</td>
<td>190</td>
<td>IV</td>
<td>FCHL</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>PO</td>
<td>27 M</td>
<td>1.26</td>
<td>432</td>
<td>339</td>
<td>275</td>
<td>170</td>
<td>IV</td>
<td>FCHL</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>KS</td>
<td>48 M</td>
<td>1.31</td>
<td>447</td>
<td>342</td>
<td>280</td>
<td>165</td>
<td>IV</td>
<td>FCHL</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>RS</td>
<td>41 M</td>
<td>1.28</td>
<td>224</td>
<td>156</td>
<td>306</td>
<td>224</td>
<td>IIIB</td>
<td>GUC</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>KM</td>
<td>56 M</td>
<td>1.23</td>
<td>284</td>
<td>215</td>
<td>192</td>
<td>110</td>
<td>IV</td>
<td>GUC</td>
<td>—</td>
<td>8-blocking agent</td>
<td></td>
</tr>
</tbody>
</table>

RBW = relative body weight, IBW = ideal body weight, TG = triglyceride, CHOL = cholesterol, FHTG = familial hypertriglyceridemia, FCHL = familial combined hyperlipidemia, GUC = genetically unclassified hyperlipidemia.

*To convert mg/dl of triglycerides to molar units multiply by 0.011.
†To convert mg/dl of cholesterol to molar units multiply by 0.026.
Definitions of Hyperlipidemia and Familial Hyperlipidemia

The upper limits of "normal" used in this study were 132
mg/dl (1.50 mmol • l⁻¹) for VLDL triglycerides and 232 mg/dl
(6.00 mmol • l⁻¹) for LDL cholesterol. These reference values
were obtained from a large population survey (Mini-
Finland Study, unpublished observations) and represent-
ed the 90th percentile values of the Finnish adult
population. The family diagnosis was based on lipoprotein
lipid measurements at the first visit. Familial hypertriglyceri-
demia was diagnosed when at least three examined mem-
ers of the family (including the proband) had elevated
VLDL triglyceride levels but none had hyper-LDL-choles-
terolemia (phenotypes IV, V, or normal). Familial com-
bined hyperlipidemia was defined as a condition in which
at least three members of the family (including the pro-
band) had hyperlipoproteinemia and more than one lipoprotein
phenotype was present. In addition to a subject with
pure hypertriglyceridemia (type IV or V), the family
with FCHL had to include at least one member with elevat-
ed LDL cholesterol (type IIa or IIb) but without evidence of
xanthomatosus (thus excluding familial monogenic hyper-
cholesterolemia). Families with fewer than three hyper-
lipidemic members (i.e., only one affected relative in addi-
tion to the proband) were labeled as genetically uncategorized (GUC). By these criteria, the study families included four with FHTG, five with FCHL, and two with
GUC.

Study Protocol

After giving their consent, the subjects were advised to
follow their normal dietary and exercise habits until the
study. All hypolipidemic drugs were discontinued for a
minimum of 6 weeks before lipid analysis or turnover
study. Abstinence from alcohol was requested for the day
preceding the study. For each visit, the subjects were in-
structed to fast overnight for 12 hours. The study protocol
was accepted by the Ethical Committee of Helsinki Univer-
sity Central Hospital.

The blood samples were taken from the antecubital vein.
The serum was immediately separated by centrifugation
in the cold and stored at 4°C until analyzed. If the serum
appeared turbid, chylomicrons were separated by spinning
the sample for 30 minutes at 18 000 rpm in a Ti 50 rotor in a
Sorvall OTD 65 preparative ultracentrifuge. Thereafter,
the lipoproteins were separated by sequential ultracentrifuga-
tion for 24 hours at 40 000 rpm at solvent densities of 1.006
(VLDL) and 1.063 (LDL) g/ml. The bottom fraction of 1.063
g/ml run was taken to represent HDL. The serum and lipoprotein fractions were analyzed for total cholesterol
(Enzymatic assay kit no. 187313 from Boehringer Diag-
nostica, Mannheim GmbH, West Germany) and for tri-
glycerides (Enzymatic assay kit no. 297771 from Boehringer Diagnostica).

Measurement of VLDL Triglyceride Turnover Rate

The turnover rate of VLDL triglycerides was determined
by the endogenous 3H-glycerol labelling technique6, 17 by
using a single-pool analysis of the radioactivity disappear-
ance curves. At 8:00 A.M., the subjects received a bolus
injection of 150 μCi of 3H-2-glycerol (Radiochemical Cen-
tre, Amersham, England, specific activity 200 to 400 μCi/
μmol) diluted in sterile 10% ethanol-saline solution. Ve-
nous blood samples were taken from the opposite arm
through an indwelling catheter at 30-minute intervals up to
6 hours and at 1-hour intervals for an additional 4 hours.
The subjects abstained from the first 8 hours of the experiment
(until 4:00 P.M.) and then received a light, low fat dinner.
Chylomicrons were removed from the serum samples as
described above. Thereafter, VLDL was separated by ul-
tracentrifugation at a solvent density of 1.006 g/ml. The
surface layer containing the VLDL was separated by tube
slicing, and a 200-μl aliquot was taken for duplicate trigly-
ceride analysis. The rest of VLDL was extracted with chlo-
roform/methanol (2:1), the extract was washed, and the
phospholipids were removed from the organic phase by
absorption to silicic acid. The VLDL triglyceride radioactiv-
ity was then measured in an LKB Wallac RacBeta 1215
liquid scintillation counter by using a PPO toluene solution.
The specific activity of VLDL triglyceride was plotted on
semilog paper against time, and the monoexponential
slope of the curve was analyzed by a disc computer to
obtain the fractional removal rate. The absolute turnover
rate (equal to VLDL triglyceride synthetic or production rate) was then obtained from the formula:

\[ TR = k \times S \times PV \]

where k is the fractional removal rate, S is the steady-state
VLDL triglyceride concentration during the experiment
(mg/dl), and PV is the plasma volume assumed to be 4.5%
of body weight corrected according to the method of Alex-
der. 18 The turnover rate was expressed as the total turn-
over rate per hour and the turnover rate produced per hour
per kilogram of body weight.

It is well known that the transport of triglycerides in VLDL
is a complex process that is not exactly described by a
single-pool, kinetic model. 19, 20 A somewhat better esti-
mate of the true triglyceride flux through VLDL cascade is
obtained by multicompartamental analysis19 which also in-
cludes the slow turnover pool of VLDL triglycerides omitted
in the single-pool model. However, the turnover rates
obtained by the multicompartamental method are also ap-
proximations, since the analysis neglects the fact that tri-
glycerides with different (and unknown) specific activities
enter and leave the VLDL pool in exchange for cholesterol
esters derived from liver or from the circulating lipopro-
teins. 20, 21, 22 Moreover, the 48-hour sampling period need-
ed for the multicompartamental analysis requires special di-
etary arrangements18 that may influence the metabolism
of VLDL triglycerides. The laborious and relatively complex
experimental design used in the multicompartamental
method also makes it less well adapted for any large-scale
epidemiologic studies. This was the major reason why we
were forced to choose the "short" turnover method and the
single-pool analysis for the present study on a large popu-
lation of voluntary, healthy, working people.

In spite of the fact that the single-pool analysis method
gives only apparent turnover rates, the results may still be
useful. The validity of these estimates is supported by the
relatively high, significant correlation between the kinetic
parameters obtained for VLDL triglycerides from the single-pool vs. the multicompartmental analyses. The VLDL triglyceride turnover rates determined by the single-pool method show also a close correlation with corresponding VLDL apo B production rates over a wide range of VLDL concentration. Moreover, studies on the effects of different perturbations on triglyceride kinetics appear to give, in principle, equivalent results irrespective of whether a single-pool or a multicompartmental model has been used in the data analysis. In addition, the numerical values obtained by the two models for the VLDL triglyceride production and fractional catabolic rates (FCR) are similar.

**Statistical Methods**

The data analysis was performed with a Honeywell-Bull DPS-6 computer using the BMDP computer program (BMDP Statistical Software Incorporated, Los Angeles, California). The results are given as means ± SEM. The significance of the differences was assessed by a conventional Student's t test after the distributions were shown to be normal. Linear regression analysis was used for testing the correlations.

**Results**

**Proband**

The VLDL triglyceride kinetic data of the probands are shown in Table 2. The concentration of VLDL triglycerides at entry ranged from 156 to 1601 mg/dl (mean 389 mg/dl) and the concentration of VLDL triglyceride production rate when the upper limit of normal was set at 1000 mg•hr⁻¹ on the basis of the mean values of the lipoprotein lipids of the relatives. The VLDL triglyceride was increased (p<0.001) and the HDL cholesterol was reduced (p<0.001) in the relatives as compared to the values of the controls, whereas there was no significant difference between the LDL cholesterol levels of relatives and controls.

Table 2. Plasma VLDL Triglyceride Kinetic Parameters in Index Patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>Concentration at steady state (mg/dl)</th>
<th>Production rate (mg•hr⁻¹)</th>
<th>Fractional catabolic rate (pools•hr⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HK</td>
<td>186</td>
<td>1506</td>
<td>0.230</td>
</tr>
<tr>
<td>SV</td>
<td>1118</td>
<td>1031</td>
<td>0.036</td>
</tr>
<tr>
<td>RK</td>
<td>186</td>
<td>1024</td>
<td>0.201</td>
</tr>
<tr>
<td>KJ</td>
<td>466</td>
<td>1440</td>
<td>0.096</td>
</tr>
<tr>
<td>KN</td>
<td>178</td>
<td>1630</td>
<td>0.280</td>
</tr>
<tr>
<td>TK</td>
<td>136</td>
<td>801</td>
<td>0.207</td>
</tr>
<tr>
<td>PA</td>
<td>252</td>
<td>1128</td>
<td>0.143</td>
</tr>
<tr>
<td>PO</td>
<td>278</td>
<td>1446</td>
<td>0.156</td>
</tr>
<tr>
<td>KS</td>
<td>196</td>
<td>769</td>
<td>0.126</td>
</tr>
<tr>
<td>RS</td>
<td>139</td>
<td>1199</td>
<td>0.290</td>
</tr>
<tr>
<td>KM</td>
<td>275</td>
<td>919</td>
<td>0.100</td>
</tr>
<tr>
<td>Mean (SEM)</td>
<td>307 (82)‡</td>
<td>1172 (85)‡</td>
<td>0.169 (0.02)‡</td>
</tr>
<tr>
<td>Controls (range)</td>
<td>14 to 121</td>
<td>164 to 910</td>
<td>0.220 to 0.710</td>
</tr>
</tbody>
</table>

†p<0.01, ‡p<0.001 compared to controls.

The relationship between the VLDL triglyceride concentration and production rate in the probands is shown in Figure 1. It appears that, on this basis, the probands could be divided into two groups. The first group consisted of five subjects in whom the VLDL triglyceride concentration was close to the value predicted from the production rate. In all these patients, FCR was more than 0.200 pools•hr⁻¹ and the elevated VLDL triglyceride levels could be mainly accounted for by overproduction. The probands of the second group, on the other hand, had higher VLDL triglyceride levels than expected on the basis of their production rate, suggesting that lipolysis was defective in these patients. The FCR of these patients ranged from 0.036 to 0.156. However, the mechanism of hypertriglyceridemia in the probands did not bear any relationship to the family classification of the disorder (Figure 1).

**Relatives**

Serum lipoproteins were analyzed in 85 first-degree relatives, of whom 31 (36%) had hyperlipoproteinemia (increase of VLDL triglyceride, LDL cholesterol, or both). Of the affected relatives, five had phenotype IIA, five had type IIb, 19 had type IV, and two had type V. Table 3 shows the mean values of the lipoprotein lipids of the relatives. The VLDL triglyceride was increased (p<0.001) and the HDL cholesterol was reduced (p<0.001) in the relatives as compared to the values of the controls, whereas there was no significant difference between the LDL cholesterol levels of relatives and controls.

The VLDL triglyceride turnover kinetics were measured...
Figure 1. The relationship between VLDL triglyceride production rate and concentration in the probands. The dotted lines indicate the area in which all control subjects are included. A. VLDL triglyceride production rate expressed as absolute turnover rate. B. Turnover rate produced per kilogram of body weight. • = familial hypertriglyceridemia, ■ = familial combined hyperlipidemia, and ◦ = genetically unclassified hypertriglyceridemia.

Table 3. Plasma Lipoprotein Lipids of Relatives of Hypertriglyceridemic Probands and of Controls

<table>
<thead>
<tr>
<th></th>
<th>Relatives (n = 85)</th>
<th>Controls (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total triglycerides</td>
<td>187 ± 16f</td>
<td>118 ± 8.8</td>
</tr>
<tr>
<td>VLDL triglycerides</td>
<td>122 ± 13f</td>
<td>62 ± 7.0</td>
</tr>
<tr>
<td>LDL triglycerides</td>
<td>40 ± 1.8*</td>
<td>34 ± 2.6</td>
</tr>
<tr>
<td>HDL triglycerides</td>
<td>21 ± 0.9</td>
<td>21 ± 0.9</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>229 ± 5.8</td>
<td>244 ± 7.7</td>
</tr>
<tr>
<td>VLDL cholesterol</td>
<td>30 ± 3.0†</td>
<td>18 ± 2.3</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>155 ± 5.0</td>
<td>169 ± 7.4</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>44 ± 1.0‡</td>
<td>57 ± 1.9</td>
</tr>
</tbody>
</table>

Values are means ± SEM and are given in mg/dl. To convert mg/dl units to molar units, multiply by 0.011 for triglycerides and by 0.026 for cholesterol.

*p<0.05, †p<0.01, ‡p<0.001 compared to controls.

In 70 relatives. In 17 of these (24%), the VLDL triglyceride concentration was increased (>132 mg/dl) and in 16 it was in the upper normal range (88 to 132 mg/dl). As shown by Table 4, the hypertriglyceridemic relatives had a significantly greater VLDL triglyceride production rate and a lower FCR than the control subjects, whereas in the normotriglyceridemic relatives both rates were comparable to those of the controls. Of the 17 hypertriglyceridemic relatives, twelve had increased VLDL triglyceride production rate (>1000 mg·hr⁻¹) and ten showed impaired catabolism of VLDL triglycerides (FCR < 0.200 pools·hr⁻¹).

Tables 5 and 6 show the relatives' VLDL triglyceride production rates separated into two categories according to the production rates of the probands. The VLDL triglyceride production rate is expressed either as an absolute turnover rate (Table 5) or as a turnover rate produced per kilogram of body weight (Table 6). It is evident that the VLDL production status of the proband was not reflected in the relatives, irrespective of their VLDL triglyceride level.

Table 7 presents the relatives' VLDL triglyceride FCR data divided into two groups on the basis of whether the proband had normal or decreased FCR. Unlike the absent family association of the VLDL triglyceride production rate, the FCR revealed a familial pattern. Hypertriglyceridemic relatives of probands with reduced removal capacity of VLDL triglycerides (FCR < 0.200 pools·hr⁻¹) had significantly lower mean FCR than did the hypertriglyceridemic relatives of probands with normal FCR. This difference was present in normotriglyceridemic relatives with VLDL triglycerides in the upper normal range (NS, p<0.1, two-tailed t test) or in the range of less than 88 mg/dl (1 mmol/l). Of the relatives of probands with normal FCR, only 12% showed impaired removal of VLDL triglycerides, whereas 27% of the examined relatives of low FCR probands also had low FCR. Thus, a relative defect in the lipolysis of VLDL triglycerides appeared to be the trait that ran in families and accounted for the familial clustering of hypertriglyceridemia.

The steady-state, VLDL triglyceride concentrations were similar in the hypertriglyceridemic relatives of probands with low FCR and in those of probands with normal FCR (219 ± 30 vs. 201 ± 31 mg/dl, respectively). Interestingly, however, the VLDL cholesterol/triglyceride molar ratio was significantly greater in the relatives of removal-deficient probands than in relatives of probands with normal FCR (0.55 ± 0.05 vs. 0.41 ± 0.03, p<0.05). Also, the normotriglyceridemic relatives of the two groups had similar VLDL triglyceride concentrations (67 ± 5 vs. 72 ± 6 mg/dl), but, again, the VLDL cholesterol/triglyceride molar ratio was greater among relatives with a low FCR proband.
as compared to those with a normal FCR proband (0.62 ± 0.02 vs. 0.50 ± 0.02, p<0.01). These compositional differences in VLDL suggest that, in the presence of a moderate triglyceride removal defect, the VLDL remnant particles are accumulated into plasma to a greater extent than are the less hydrolyzed (secretory) VLDL.

**Kinetic Background of Hypertriglyceridemia in Individual Families**

The individual values of the VLDL triglyceride production rates in the 11 families are shown in Figure 2. In the whole material, there was a highly significant correlation between the VLDL triglyceride concentration and production rate (r = 0.51, p<0.001), indicating that the rate by which VLDL particles are secreted into plasma is an important determinant of the amount of circulating VLDL. The incidence of hypertriglyceridemia at VLDL triglyceride production rates of 1000, 1000 to 1500, and > 1500 mg hr⁻¹ was 12%, 74%, and 100%, respectively.

An overproduction of VLDL triglycerides (>1000 mg hr⁻¹) was observed in at least one member in 10 of the 11 families; the highest incidence was five of seven examined relatives (family HK). In six families, all hypertriglyceridemic subjects had greater VLDL triglyceride production rate than did their normotriglyceridemic relatives. In three families, three or more members had a VLDL triglyceride overproduction combined with a normal FCR (families HK, KN, and TK), suggesting that an abnormally high production rate was the predominant cause of hypertriglyceride-

### Table 4. Plasma VLDL Triglyceride Kinetic Data of Relatives and of Controls

<table>
<thead>
<tr>
<th>VLDL-TG</th>
<th>Hypertriglyceridemic relatives (n = 17)</th>
<th>Normotriglyceridemic relatives (n = 53)</th>
<th>Controls (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration at steady state (mg/dl)</td>
<td>208 ± 22‡</td>
<td>69 ± 4</td>
<td>50 ± 13</td>
</tr>
<tr>
<td>Production rate (mg hr⁻¹)</td>
<td>1189 ± 88‡</td>
<td>626 ± 38</td>
<td>460 ± 86</td>
</tr>
<tr>
<td>(mg hr⁻¹ kg⁻¹)</td>
<td>13.9 ± 0.8‡</td>
<td>8.71 ± 0.5</td>
<td>6.9 ± 1.3</td>
</tr>
<tr>
<td>Fractional catabolic rate (pools hr⁻¹)</td>
<td>0.197 ± 0.02*</td>
<td>0.354 ± 0.02</td>
<td>0.360 ± 0.08</td>
</tr>
</tbody>
</table>

Values are means ± SEM. *p<0.05, ‡p<0.001 compared to controls. VLDL-TG = very low density lipoprotein triglyceride.

### Table 5. VLDL Triglyceride Production Rates of Relatives in Relation to Those of Probands

<table>
<thead>
<tr>
<th>VLDL-TG production rate of probands</th>
<th>VLDL-TG production rate of relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL-TG &gt; 132 mg/dl</td>
<td>VLDL-TG 88 to 132 mg/dl</td>
</tr>
<tr>
<td>Increased (&gt;1000) (8)</td>
<td>1148 ± 108 (13)</td>
</tr>
<tr>
<td>Normal (&lt;1000) (3)</td>
<td>1321 ± 100 (4)</td>
</tr>
</tbody>
</table>

Values are given as mg hr⁻¹. Numbers in parentheses indicate the number of subjects in each group.

### Table 6. VLDL Triglyceride Production Rates of Relatives in Relation to Those of Probands

<table>
<thead>
<tr>
<th>VLDL-TG production rate of probands</th>
<th>VLDL-TG production rate of relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL-TG &gt; 132 mg/dl</td>
<td>VLDL-TG 88 to 132 mg/dl</td>
</tr>
<tr>
<td>Increased (&gt;12.5) (7)</td>
<td>14.05 ± 1.09 (12)</td>
</tr>
<tr>
<td>Normal (≤12.5) (4)</td>
<td>13.92 ± 1.14 (5)</td>
</tr>
</tbody>
</table>

Values are given as mg hr⁻¹ kg⁻¹. Numbers in parentheses indicate the number of subjects in each group.

### Table 7. Fractional Catabolic Rate of Relatives in Relation to Those of Probands

<table>
<thead>
<tr>
<th>FCR of relatives</th>
<th>FCR of probands</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCR of probands</td>
<td>VLDL-TG &gt; 132 mg/dl</td>
</tr>
<tr>
<td>Normal (&gt;0.200) (5)</td>
<td>0.227 ± 0.02 (10)</td>
</tr>
<tr>
<td>Decreased (&lt;0.200) (6)</td>
<td>0.154 ± 0.01† (7)</td>
</tr>
</tbody>
</table>

Values are given as pools hr⁻¹. *p<0.05, †p<0.01 for difference between relatives of the two groups. Numbers in parentheses indicate the number of subjects in each group. FCR = fractional catabolic rate.
Figure 2. VLDL triglyceride production rate in individual family members. The families are arranged in descending order by the mean value (bar) of production rate. The arrows indicate the probands. The family diagnosis is given in parentheses below the proband initials. FCHL = familial combined hyperlipidemia, FHTG = familial hypertriglyceridemia, and GUC = genetically unclassified hypertriglyceridemia. • = VLDL-TG > 132 mg/dl, ◦ = VLDL-TG 88 to 132 mg/dl, and ○ = VLDL-TG < 88 mg/dl.

Figure 3. VLDL triglyceride fractional catabolic rate (FCR) in individual family members. The families are arranged in descending order by the mean FCR value (bar). The horizontal line indicates the lower limit of the normal range. Symbols are the same as in Figure 2.

Figure 4. Distribution of relative body weight in individual family members. The families are arranged in descending order by the mean value (bar) of relative body weight. The arrows indicate the probands. The horizontal line discriminates obese and non-obese subjects. The family diagnosis is given in parentheses below the proband initials. FCHL = familial combined hyperlipidemia, FHTG = familial hypertriglyceridemia, and GUC = genetically unclassified hypertriglyceridemia. • = VLDL-TG production rate > 1000 mg·hr⁻¹, ◦ = VLDL-TG production rate < 1000 mg·hr⁻¹.
Table 8. Effect of Obesity on VLDL Triglyceride Kinetics in Examined Family Members (Probands Included)

<table>
<thead>
<tr>
<th>VLDL-TG concentration (mg/dl)</th>
<th>VLDL-TG production rate (mg/hr⁻¹)</th>
<th>VLDL-TG FCR (pools/hr⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL-TG</td>
<td>RBW&lt;1.30 (n = 57)</td>
<td>125 ± 21</td>
</tr>
<tr>
<td></td>
<td>RBW&gt;1.30 (n = 24)</td>
<td>149 ± 19</td>
</tr>
</tbody>
</table>

RBW = relative body weight, FCR = fractional catabolic rate. *p<0.05, †p<0.001 for the difference between the two groups.

Table 9. VLDL Triglyceride Kinetic Data Grouped according to Familial Diagnosis of Hyperlipoproteinemia (Probands Included)

<table>
<thead>
<tr>
<th>Family diagnosis</th>
<th>Concentration (mg/dl)</th>
<th>Production rate (mg/hr⁻¹)</th>
<th>FCR (pools/hr⁻¹)</th>
<th>Production rate (mg/hr⁻¹)</th>
<th>FCR (pools/hr⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FHTG</td>
<td>12 305 ± 79</td>
<td>1142 ± 75</td>
<td>13.8 ± 0.9</td>
<td>0.160 ± 0.02</td>
<td>557 ± 76</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8.0 ± 0.7</td>
</tr>
<tr>
<td>FCHL</td>
<td>3 215 ± 27</td>
<td>1262 ± 109</td>
<td>14.3 ± 1.0</td>
<td>0.207 ± 0.02</td>
<td>661 ± 36</td>
</tr>
<tr>
<td></td>
<td>30 73 ± 5</td>
<td>993 ± 85</td>
<td>13.4 ± 1.3</td>
<td>0.216 ± 0.05</td>
<td>590 ± 112</td>
</tr>
</tbody>
</table>

Values are means ± SEM. FHTG = familial hypertriglyceridemia, FCHL = familial combined hyperlipidemia, GUC = genetically unclassified families, FCR = fractional catabolic rate. *p<0.05 for difference from GUC.
of VLDL triglycerides was increased to a similar extent in patients (proband) with FCHL or FHTG. Even though the studies of both Chait et al.10,30 and Kissebah et al.11 suggested that probands with FHTG had a higher mean VLDL triglyceride production rate than the probands with FCHL, there was a considerable overlapping between the triglyceride turnover values of the two groups. Also, the ratio of VLDL triglyceride to apo B production rate does not sharply discriminate FHTG from FCHL or from simple obesity.10,11,28,29 It is possible, moreover, that the small differences in the relative rates of production of VLDL components may be secondary to the overall synthetic rate of VLDL particles, as suggested by the data of Poapst et al.1

On the other hand, it is important to realize that neither endogenous labelling of VLDL triglycerides nor incorporation of an exogenous label to circulating VLDL particles will give a reliable measure of the actual influx rate of nascent VLDL into the circulation.32,33 In addition, the composition and particle size distribution of VLDL, which may be characteristic for the two genetic forms of hypertriglyceridemia,8 may ultimately depend on the rate of production and the efficiency of removal of VLDL rather than on the nature of newly secreted nascent VLDL particles.

The results of the present study showed that the only kinetic variable that definitely followed a familial pattern was the FCR of VLDL triglycerides. The relatives of low FCR probands had significantly lower mean FCR than the respective relatives of probands with a normal FCR (> 0.200 pools.h⁻¹). What makes this finding particularly remarkable is the presence of the difference not only among the hypertriglyceridemic relatives, but also among the normotriglyceridemic relatives. Moreover, the incidence of low FCR was more common in family members of low FCR probands than among relatives of normal FCR probands. These results suggest that the removal of VLDL triglycerides is genetically controlled. The data do not, however, permit conclusions on the nature of the trait responsible for genetic regulation of the removal capacity. The most likely candidate is the functional (endothelial) lipoprotein lipase activity, but the composition and size of the substrate particles (VLDL and its remnants) may also influence the rate of the catabolism process.

In spite of its definite familial patterns, the FCR of VLDL triglycerides was not a specific marker for either FHTG or FCHL. In terms of applied kinetic model and family classification, the FCR did not segregate the families with FHTG, FCHL, or unclassified hypertriglyceridemia any better than did the VLDL triglyceride production rate. This failure to find any kinetic marker for the familial forms of hypertriglyceridemia suggests that the genetic defect is neither in the VLDL synthesis, in the composition of nascent VLDL particles, nor in the depolization process. It is possible that the difference between FHTG and FCHL is somewhere in the lipolytic cascade distal to the action of lipoprotein lipase, e.g., at the conversion of IDL to LDL.

References


23. Dunn FL, Grundy SM, Bilheimer DW, Havel RJ, Raskin P. Impaired catabolism of very low-density lipoprotein triglyceride in a family with primary hypertriglyceridemia. Metabolism 1985;34:316-324.


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