Low Density Lipoprotein Kinetics in a Family Having Defective Low Density Lipoprotein Receptors in Which Hypercholesterolemia Is Suppressed

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Heterozygous familial hypercholesterolemia (FH) usually presents with severe elevations of low density lipoprotein (LDL) cholesterol. Recently, a family with FH was described in which several members heterozygous for a mutation in the LDL receptor gene had normal LDL cholesterol levels. Kinetic studies of LDL apolipoprotein B (apo B) were conducted to determine the metabolic differences between the normolipidemic and hypercholesterolemic FH heterozygotes in the family. Studies were performed in 14 family members including the proband (who has homozygous FH), four FH heterozygotes with high LDL levels, four FH subjects with normolipidemia, and five healthy relatives without FH. The proband had a very low fractional catabolic rate (FCR) for LDL (0.15 pool/day). All the FH and non-FH subjects studied, excluding the FH homozygote, had higher than expected FCRRs for LDL. The average FCRRs for LDL of hypercholesterolemic and normocholesterolemic subjects were not significantly different (0.39±0.06 versus 0.37±0.02 pool/day), and these values were 70–80% of those in unaffected relatives. Compared with hypercholesterolemic FH heterozygotes, normolipidemic heterozygotes had much lower input rates for LDL (17.1±author query macros2.6 versus 8.7±0.9 pools/day, respectively). These low input rates, together with the higher than usual FCRRs for LDL, are responsible for the normal concentrations of LDL cholesterol in some of the FH heterozygotes. The low input of LDL could be due to either a decreased secretion of apo B-containing lipoproteins or an enhanced clearance of LDL precursor lipoproteins. (Arteriosclerosis and Thrombosis 1991;11:578–585)

Familial hypercholesterolemia (FH) is an autosomal codominant disorder due to mutations in the gene that encodes the low density lipoprotein (LDL) receptor.1 FH homozygotes have two mutant LDL receptor genes and usually have a fourfold to sixfold increase in plasma LDL cholesterol. FH heterozygotes have one normal and one mutant LDL receptor gene that are associated with a twofold to threefold elevation in plasma LDL cholesterol concentrations. However, an occasional FH heterozygote has been described who has a normal LDL cholesterol level.2,3 Recently, Hobbs et al4 studied the family of an FH homozygote whose mother, an obligate FH heterozygote, was found to have a normal concentration of LDL cholesterol. Both defective alleles in the FH homozygote contained a missense mutation (Ser196—>Leu) in the fourth of seven cysteine-rich repeats comprising the ligand-binding domain of the LDL receptor.4 It is to this region of the protein that the LDL receptor binds either apolipoprotein B (apo B) of LDL or apo E of β-migrating very low density lipoprotein (β-VLDL).5 The substituted amino acid is part of a highly conserved, negatively charged triplet (Ser-Asp-Leu) that is important for ligand binding. The mutation results in an LDL receptor protein that is transported slowly out of the endoplasmic reticulum to the cell surface. The receptor protein that reaches the cell surface does not bind LDL apo B but can bind β-VLDL via apo E.

The mother of the proband (FH 848) has eight brothers and sisters. Seven of the nine-member sibship were heterozygous for a mutation in the LDL
Defective LDL Receptors Without Elevated LDL

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Figure 1. Pedigree of the P. family. Arrow shows the proband. Stars indicate those family members having the low density lipoprotein (LDL) -lowering allele, according to Hobbs et al. Those denoted by stippled areas underwent the LDL turnover test. Circles denote females; squares denote males. ND, not tested for LDL receptor defect (see Hobbs et al).

Methods

Family

Kinetic studies of LDL apo B were conducted in 14 members of the P. family (Figure 1). Family members demarcated by the shaded rectangles participated in the study. They included the proband with homozygous FH (III.23), four FH heterozygotes with hypercholesterolemia (II.6, II.7, II.11, and III.15), four FH heterozygotes with normcholesterolemia (II.4, II.14, III.21, and III.22), and five family members without FH (II.18, III.1, III.6, III.10, and III.18). The patient's clinical characteristics are summarized in Table 1; they have been presented previously. The kinetic studies were performed approximately 1 year after the study by Hobbs et al; ages given are those at the time of the turnover study. Each participant gave written informed consent to undergo lipoprotein kinetic studies that had been approved by the Institutional Review Board.

Experimental Design

Four weeks before the study, all hypolipidemic agents were discontinued. Participants were instructed to start a metabolic diet 2 weeks before entering the General Clinical Research Center (GCRC) of Parkland Memorial Hospital, Dallas, Tex., and to remain on the diet for the duration of the study. The study diet consisted of solid food in which 40% of total calories was fat (17% saturates, 18% monounsaturates, and 5% polyunsaturates), 45% was carbohydrate, 15% was protein, and daily cholesterol intake was 300–400 mg. The diet composition resembled a "typical" American diet such as used in our previous studies.

For the turnover studies, LDL was isolated and labeled with iodine-131. At the time of blood collection, all subjects were started on 400 mg KI daily to inhibit thyroidal uptake of radioactive iodine. The 131I-LDL was reinjected 5 days later, and the patients remained in the GCRC for a minimum of 48 hours to complete the first part of the LDL turnover study. The remainder of the turnover study was completed on an outpatient basis, that is, with daily blood sampling.

Lipids and Lipoproteins

Lipid and lipoprotein determinations were made on five samples taken on days 1, 3, 5, 8, and 12. Plasma total cholesterol and triglycerides were measured enzymatically. High density lipoprotein (HDL) cholesterol was determined after precipitation of apo B-containing lipoproteins with heparin–manganese. To measure the cholesterol content of VLDL-plus-intermediate density lipoprotein and LDL fractions, plasma was adjusted to a density of 1.019 g/ml, and lipoproteins of d<1.019 g/ml and d>1.019 g/ml were isolated by preparative ultracentrifugation. Cholesterol was measured in the two
ultracentrifugal fractions, and concentrations were corrected for losses during ultracentrifugation, assuming equal losses in both fractions. Recoveries averaged more than 95%. LDL cholesterol was estimated as the difference between $d=1.019$ g/ml infranatant cholesterol and HDL cholesterol.

**Kinetics of Low Density Lipoprotein Apolipoprotein B**

For isolation of LDL in adults, 200 ml plasma was obtained by plasmapheresis, and the red blood cells were returned to the patients. For the two children studied (III.22 and III.23), 20 ml autologous plasma was used. VLDL-plus-intermediate density lipoprotein and LDL were isolated from plasma by sequential ultracentrifugation.\(^\text{15}\) LDL was washed and concentrated by ultracentrifugation at its native density and dialyzed against 150 mM NaCl and 0.01% Na\(_2\) EDTA, pH 7.4. Approximately 5 mg LDL was radioiodinated by the iodine monochloride method.\(^\text{6,16,17}\) Excess free iodine was removed by dialysis. Thirty to 40 $\mu$Ci of tracer was injected intravenously into adults, and 10–20 $\mu$Ci was used for the children and adolescents.

Multiple blood samples were taken during the first 48 hours, and then samples were collected every 12 hours for the ensuing 2 days; from day 4 to day 14, one sample was collected each day. All samples were counted for radioactivity, and an isotope-decay curve was constructed. The fractional catabolic rate (FCR) for LDL was estimated by the two-pool model of Matthews.\(^\text{18}\) For all subjects except two, the FCR for LDL was estimated from sample points obtained during a 14-day period. The exceptions were two non-FH subjects (II.18 and III.18) who were unable to give daily blood samples after leaving the GCRC. Their FCRs for LDL were estimated as the fraction of radioactivity disappearing during the first 24 hours after injection; we\(^\text{19}\) reported recently that this value correlates highly with the FCR obtained by two-pool analysis.

The plasma volume was estimated by isotopic dilution of the injected dose of LDL at the 10-minute sample. The plasma pool of LDL apo B was determined as the concentration of LDL apo B times the plasma volume. LDL apo B concentrations were estimated as follows. The five samples obtained for lipoprotein cholesterol quantification were pooled, and the LDL ($d=1.019–1.063$ g/ml) was isolated by sequential ultracentrifugation. On the isolated LDL fraction, total protein (apo B) was measured by the Lowry procedure\(^\text{20,21}\) and total cholesterol by the enzymatic method.\(^\text{12}\) To determine the LDL apo B concentration, the ratio of apo B to cholesterol in isolated LDL was multiplied by the absolute LDL cholesterol concentration estimated separately on the same pool of whole plasma, as described above under “Lipids and Lipoproteins.” The pooled mean for LDL apo B concentration was taken as the concentration used to estimate the plasma pool of LDL apo B. The transport rate (input rate) for LDL apo B was estimated as the product of the plasma pool size of LDL apo B and the FCR.

**Data Analysis**

Analysis of kinetic data was performed with the Simulation Analysis and Modeling (SAAM)
TABLE 2. Clinical Characteristics

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Plasma lipids</th>
<th>Lipoprotein cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cholesterol</td>
<td>TG</td>
</tr>
<tr>
<td>FH subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homozygous FH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III.23</td>
<td>502±23</td>
<td>118±21</td>
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<tr>
<td>Heterozygous FH with hypercholesterolemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II.6</td>
<td>267±11</td>
<td>130±14</td>
</tr>
<tr>
<td>II.7</td>
<td>272±3</td>
<td>350±28</td>
</tr>
<tr>
<td>II.11</td>
<td>241±5</td>
<td>133±16</td>
</tr>
<tr>
<td>III.15</td>
<td>235±2</td>
<td>115±6</td>
</tr>
<tr>
<td>Mean±SEM</td>
<td>254±9</td>
<td>182±56</td>
</tr>
<tr>
<td>Heterozygous FH with normolipidemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II.14</td>
<td>150±13</td>
<td>105±17</td>
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<tr>
<td>II.4</td>
<td>206±3</td>
<td>139±13</td>
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<tr>
<td>III.22</td>
<td>165±2</td>
<td>130±12</td>
</tr>
<tr>
<td>III.21</td>
<td>162±7</td>
<td>62±5</td>
</tr>
<tr>
<td>Mean±SEM</td>
<td>171±12</td>
<td>109±17</td>
</tr>
<tr>
<td>Non-FH subjects</td>
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<td></td>
</tr>
<tr>
<td>II.18</td>
<td>175±9</td>
<td>207±15</td>
</tr>
<tr>
<td>III.18*</td>
<td>139±4</td>
<td>81±6</td>
</tr>
<tr>
<td>III.10*</td>
<td>165±2</td>
<td>62±4</td>
</tr>
<tr>
<td>III.1</td>
<td>188±3</td>
<td>132±26</td>
</tr>
<tr>
<td>III.6</td>
<td>144±7</td>
<td>148±31</td>
</tr>
<tr>
<td>Mean±SEM</td>
<td>162±9</td>
<td>126±26</td>
</tr>
</tbody>
</table>

Values are in mg/dl and are mean±SEM for five determinations.
TG, triglycerides; VLDL, very low density lipoprotein; IDL, intermediate density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; FH, familial hypercholesterolemia.
*Mean±SEM for three determinations during the first 3 days of turnover study only.

Results

Clinical data on the 14 subjects studied are given in Table 1. An effort was made to match by age and sex the non-FH family members with both the hypercholesterolemic and normocholesterolemic FH heterozygotes. The previously reported apo E phenotypes are provided. All study participants were above their desirable body weights (ranging from 110% to 171%). The plasma cholesterol and triglyceride levels, as well as the cholesterol concentrations of the different lipoprotein fractions, are given in Table 2. The FH homozygote, subject III.23, had severe hypercholesterolemia as expected. Four FH heterozygotes (II.6, II.7, II.11, and III.15) had LDL cholesterol levels greater than the 95th percentile, although they were lower than those generally seen in FH heterozygotes. Four other FH heterozygotes (II.14, II.4, III.22, and III.21) were normolipidemic. Triglyceride levels were moderately increased in subject II.7 but were normal in the other subjects. HDL cholesterol concentrations were relatively low in all members of the family studied. These low levels may have been related to obesity and a sedentary lifestyle for many of the patients. They apparently were not linked to FH because low HDL cholesterol levels were present in non-FH subjects as well.

Table 3 gives the results of the kinetic studies of LDL apo B turnover. Values are given for concentrations, FCRs, and total input rates for LDL apo B. Input rates were expressed as mg/kg-day and were normalized to desirable body weight (mg/kg DBW-day). For purposes of comparison, values for lipoprotein kinetics are presented for several groups previously studied in the laboratory (Table 4, References 25–28). Although these “historical controls” do not permit statistical comparison, they do provide reference values to give perspective. The FH homozygote (III.23) had a very low FCR for LDL apo B (0.15 pool/day) (Table 3). Both the hypercholesterolemic and normolipidemic FH heterozygotes had FCRs that were 70–80% of the non-FH family members. However, the non-FH family members had higher FCRs for LDL apo B than did previously studied normal men (Table 4). Consequently, even though the FH heterozygotes had FCRs that were reduced when compared with non-FH members, the FCRs were higher than those of previously studied FH heterozygotes (Table 4). In fact, the FCRs in current FH heterozygotes were similar to non-FH subjects of similar age studied previously.

The input rate for LDL apo B of the proband (Table 3) was much lower than has been previously...
TABLE 3. Low Density Lipoprotein Apolipoprotein B Kinetics

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Conc (mg/dl)</th>
<th>FCR (pool/day)</th>
<th>Total input rate (mg/kg-day)</th>
<th>Total input rate (mg/kg DBW-day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homozygous FH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III.23</td>
<td>202</td>
<td>0.15</td>
<td>12.6</td>
<td>13.9</td>
</tr>
<tr>
<td>Heterozygous FH with hypercholesterolemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II.6</td>
<td>128</td>
<td>0.29</td>
<td>12.6</td>
<td>18.7</td>
</tr>
<tr>
<td>II.7</td>
<td>117</td>
<td>0.54</td>
<td>24.4</td>
<td>29.9</td>
</tr>
<tr>
<td>II.11</td>
<td>111</td>
<td>0.41</td>
<td>16.6</td>
<td>21.9</td>
</tr>
<tr>
<td>III.15</td>
<td>120</td>
<td>0.33</td>
<td>14.6</td>
<td>20.1</td>
</tr>
<tr>
<td>Mean±SEM</td>
<td>119±4</td>
<td>0.39±0.06</td>
<td>17.1±2.6</td>
<td>22.7±5.0</td>
</tr>
<tr>
<td>Heterozygous FH with normolipidemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II.14</td>
<td>54</td>
<td>0.38</td>
<td>7.8</td>
<td>12.0</td>
</tr>
<tr>
<td>II.4</td>
<td>88</td>
<td>0.41</td>
<td>11.4</td>
<td>18.5</td>
</tr>
<tr>
<td>III.22</td>
<td>62</td>
<td>0.35</td>
<td>7.1</td>
<td>12.0</td>
</tr>
<tr>
<td>III.21</td>
<td>52</td>
<td>0.34</td>
<td>8.5</td>
<td>9.1</td>
</tr>
<tr>
<td>Mean±SEM</td>
<td>64±8</td>
<td>0.37±0.02</td>
<td>8.7±0.9</td>
<td>12.9±4.0</td>
</tr>
<tr>
<td>Non-FH subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II.18</td>
<td>63</td>
<td>0.58</td>
<td>13.6</td>
<td>17.4</td>
</tr>
<tr>
<td>II.18</td>
<td>58</td>
<td>0.37</td>
<td>7.5</td>
<td>10.4</td>
</tr>
<tr>
<td>II.10</td>
<td>75</td>
<td>0.51</td>
<td>16.7</td>
<td>19.9</td>
</tr>
<tr>
<td>II.1</td>
<td>68</td>
<td>0.55</td>
<td>13.8</td>
<td>18.1</td>
</tr>
<tr>
<td>II.6</td>
<td>70</td>
<td>0.42</td>
<td>8.9</td>
<td>15.2</td>
</tr>
<tr>
<td>Mean±SEM</td>
<td>67±3</td>
<td>0.49±0.01</td>
<td>12.1±1.7</td>
<td>16.2±3.6</td>
</tr>
</tbody>
</table>

Conc, concentration; FCR, fractional catabolic rate; DBW, desirable body weight; FH, familial hypercholesterolemia.

reported in FH homozygotes (Table 4). The current FH heterozygotes with hypercholesterolemia generally had higher input rates for LDL apo B than did the normolipidemic FH heterozygotes (Table 3). Since both groups tended to be overweight, transport rates, when normalized for desirable body weight, were higher than when expressed per kilogram of total body weight. This normalization provides for a better comparison of absolute input rates between groups (or individuals) with varying degrees of obesity. However, even after normalization to desirable body weight, the difference between the two groups of FH heterozygotes of this study persisted (Table 3).

Discussion

Recently, Hobbs et al described a family in which there was a bimodal distribution of LDL cholesterol concentrations in 18 FH heterozygotes; 12 of the heterozygotes had LDL cholesterol levels above the 95th percentile for age and sex, whereas six heterozygotes had levels well within the normal range. It was postulated that the FH heterozygotes had a normal LDL level due to the presence of a gene that lowers LDL cholesterol. Segregation analysis of the LDL-lowering trait in the pedigree was consistent with a single dominant gene effect. To better understand the unusual lipoprotein characteristics of this family,

TABLE 4. Lipoprotein Kinetics in Various Groups

<table>
<thead>
<tr>
<th>Group/ref No.</th>
<th>n</th>
<th>Age (yr)</th>
<th>Gender (M/F)</th>
<th>LDL chol (mg/dl)</th>
<th>Conc (mg/dl)</th>
<th>FCR (pool/day)</th>
<th>Input (mg/kg-day)</th>
<th>Input (mg/kg DBW-day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young adult men (normal)</td>
<td>19</td>
<td>25±0.5</td>
<td>19/0</td>
<td>108±7</td>
<td>70±4</td>
<td>0.36±0.02</td>
<td>10.1±0.5</td>
<td>10.3±0.5</td>
</tr>
<tr>
<td>Middle-aged men (normal)</td>
<td>14</td>
<td>56±2</td>
<td>14/0</td>
<td>143±9</td>
<td>101±5</td>
<td>0.30±0.01</td>
<td>13.5±0.07</td>
<td>14.7±0.08</td>
</tr>
<tr>
<td>Heterozygous FH (young adult)</td>
<td>5</td>
<td>28±2</td>
<td>1/4</td>
<td>222±9</td>
<td>123±9</td>
<td>0.28±0.02</td>
<td>13.7±2.0</td>
<td>13.8±2.0</td>
</tr>
<tr>
<td>Heterozygous FH (middle-aged)</td>
<td>22</td>
<td>44±9</td>
<td>17/5</td>
<td>281±3</td>
<td>168±9</td>
<td>0.22±0.01</td>
<td>16.5±1.3</td>
<td>16.2±1.4</td>
</tr>
<tr>
<td>Homozygous FH (&lt;20 yr)</td>
<td>10</td>
<td>8±1</td>
<td>2/8</td>
<td>675±63</td>
<td>409±42</td>
<td>0.15±0.01</td>
<td>27.3±3.0</td>
<td>28.1±3.0</td>
</tr>
</tbody>
</table>

All values except those for n and gender are mean±SEM.

Ref, reference; LDL, low density lipoprotein; chol, cholesterol; apo, apolipoprotein; conc, concentration; FCR, fractional catabolic rate; DBW, desirable body weight, according to 1959 Metropolitan Life Insurance Tables.
studies of kinetics of LDL apo B were performed in 14 family members. We found that the two groups of FH heterozygotes, those with an elevated LDL and those with a normal LDL level, had nearly identical FCRs but different input rates for LDL apo B.

The hypercholesterolemic FH heterozygotes in this family have a more moderate elevation of LDL cholesterol than is generally seen in FH heterozygotes. One reason could be that the mutant receptor is able to clear LDL in vivo. Prior studies with cultured skin fibroblasts from the homozygous proband revealed that LDL receptor mutation results in a protein that is transported slowly to the surface of cells and is unable to bind LDL.4 The LDL turnover study of the proband is consistent with the in vitro LDL cell-surface binding data. The proband had a markedly reduced FCR that was indistinguishable from previously studied FH homozygotes (Table 4). Therefore, the mutant LDL receptor protein is unable to bind LDL both in vitro and in vivo, and the lower LDL cholesterol levels of the FH heterozygotes in this family cannot be due to uptake of significant amounts of circulating LDL by the defective LDL receptor.

Of note, the non-FH family members had relatively high FCRs for LDL. Although the FH heterozygotes had FCRs that were only 70–80% of the non-FH family members, they had higher FCRs than have previously been observed in heterozygotes with classical FH (Table 4). The FCRs of the FH heterozygotes in this family were indistinguishable from those of normal subjects studied previously. The relatively high FCRs seen in all of the family members studied suggest that there is efficient removal of LDL via LDL receptors. The mechanisms for the increased availability of LDL receptors in these patients cannot be clearly delineated by our studies. Segregation analysis of the normal LDL receptor gene in this family has been previously performed and has demonstrated that the LDL-lowering effect was not due to changes in the normal LDL receptor gene or its promoter. Still, there may have been an alteration in the regulation of synthesis of the normal LDL receptor that resulted in an increased receptor production. Such an effect theoretically could have been due to a modification of cholesterol metabolism, leading to a lower hepatic content of cholesterol; this could stimulate the synthesis of the normal LDL receptor, thereby lowering LDL levels.

Alternatively, the FH heterozygotes could have a half-normal number of LDL receptors, as expected, but more of the receptors are available for removal of LDL because they are removing fewer other lipoproteins. This would happen if the number of lipoprotein particles entering the plasma compartment were reduced, or if there were enhanced direct removal of the lipoprotein precursors of LDL by a non-LDL receptor pathway (e.g., apo E receptors). Input rates for LDL apo B were normal to relatively high in the hypercholesterolemic FH subjects, and this observation speaks against an absolute decrease in hepatic secretion of apo B–containing lipoproteins in these subjects. However, we cannot rule out the possibility that newly secreted lipoproteins were removed at an increased rate by other pathways before conversion to LDL; this would free up more LDL receptors for clearance of LDL.

Why do some of the FH heterozygotes have normal LDL cholesterol levels? This could be due either to an accentuation of those mechanisms leading to moderate hypercholesterolemia in the other FH heterozygotes or to a cholesterol-lowering factor, as originally proposed by Hobbs et al.4 Segregation analysis in this family suggests that the LDL-lowering effect is mediated by a single dominant gene.4 There was no difference in the FCR for LDL between the FH heterozygotes with hypercholesterolemia and those with a normal LDL cholesterol level (Table 3); this finding apparently rules out the possibility of a greater availability of receptors for clearance of LDL in the normcholesterolemic FH heterozygotes. Instead, the FH heterozygotes with normal LDL cholesterol levels had a much lower input rate for LDL apo B did than their hypercholesterolemic counterparts. This was true even though most of the subjects were obese and might be expected to have relatively high input rates for LDL apo B.29-30 Of interest, the proband also had a strikingly low input rate for an FH homozygote. His LDL cholesterol levels were lower than are typical of FH homozygotes, despite his having an FCR that was markedly reduced. He probably has also inherited the cholesterol-lowering factor.

Several mechanisms may account for the relatively low input rates of LDL in the normcholesterolemic FH subjects. For example, they could have a decreased hepatic secretion of apo B–containing lipoproteins, as has been reported for hypobetalipoproteinemia.31 Hypobetalipoproteinemia can be due to mutations in the apo B gene that can interfere with the synthesis of apo B or result in the production of a functionally abnormal apo B protein.32–33 In both cases, the synthesis of apo B–containing lipoproteins is reduced. However, segregation analysis of the apo B gene in the P. family ruled out changes in the apo B gene as the factor responsible for the normal LDL levels in several FH subjects.4 Still, these subjects might have a regulatory defect for apo B synthesis that could reduce secretion of lipoproteins.34

Alternatively, the normcholesterolemic FH subjects could have enhanced clearance rates for newly secreted lipoproteins; this, too, would reduce input rates for LDL. One possibility is the overactivity of a receptor in the liver that recognizes apo E; if an overactive receptor of this type were present, fewer triglyceride-rich lipoproteins would pass through the lipolytic cascade, and input of LDL in turn would be reduced. To date, however, the definite existence of such a receptor remains to be proven. The ability of the mutant LDL receptor to bind apo E–containing particles might allow for removal of some triglyceride-rich lipoproteins, but this cannot explain low
inputs of LDL in normolipidemic heterozygotes compared with hypercholesterolemic subjects: The former must have a unique change in their lipoprotein metabolism that accounts for their lower levels. On the other hand, if the conversion of VLDL remnants to LDL were retarded in normocholesterolemic FH subjects, due to changes in apolipoprotein or lipid composition of remnants or to a decrease in hepatic lipase, then perhaps precursors to LDL could be cleared via the mutant LDL receptor. However, retardation of conversion of VLDL to LDL should raise triglyceride-rich lipoproteins in normocholesterolemic subjects, but this was not observed. Thus, while a variety of mechanisms or combination of mechanisms could underlie enhanced removal of LDL precursor lipoproteins in normocholesterolemic FH subjects, the current study failed to reveal their identity. Our findings, nonetheless, are consistent with this general mechanism.

In summary, this family is instructive for at least two reasons. First, the family as a whole had unusually high FCRs for LDL; this was true for both FH and non-FH subjects. The higher than usual FCRs for LDL in FH heterozygotes mitigated the severity of LDL elevation even in those with hypercholesterolemia. Whether the relatively high FCRs in this family are related to an increase in synthesis of normal LDL receptors or the freeing up of more LDL receptors because of changes in VLDL metabolism remains to be elucidated. Second, several obligate FH heterozygotes had normal levels of LDL cholesterol. These FH subjects had unusually low input rates for LDL apo B compared with those of other FH patients. Whether this LDL-lowering factor represents a reduced hepatic secretion of apo B-containing lipoproteins or enhanced clearance of triglyceride-rich lipoproteins could not be determined by these studies. The data nonetheless point to the importance of the metabolism of LDL precursor lipoproteins for determining concentrations of LDL cholesterol and indicate that changes in the metabolism of these lipoproteins apparently can lower LDL levels even in FH subjects.

Acknowledgments

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References

Defective LDL Receptors Without Elevated LDL

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KEY WORDS • low density lipoprotein receptors • lipoprotein kinetics • familial hypercholesterolemia • normocholesterolemia
Low density lipoprotein kinetics in a family having defective low density lipoprotein receptors in which hypercholesterolemia is suppressed.
G L Vega, H H Hobbs and S M Grundy