Low density lipoprotein metabolism in the normal to moderately elevated range of plasma cholesterol: comparisons with familial hypercholesterolemia

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Abstract Low density lipoprotein (LDL) metabolism was investigated using a pulse injection of $^{125}$I-labeled LDL in 20 subjects who did not have familial hypercholesterolemia (FH) (plasma cholesterol 160–297 mg/dl) and in 9 subjects who did have heterozygous FH (plasma cholesterol 273–501 mg/dl). Subjects were also injected with $^{131}$I-labeled LDL chemically modified with cyclohexanedione. This technique permitted a calculation of the amount of apoLDL removed via receptor-mediated and receptor-independent pathways. In subjects without FH, 40% (range 25–49%) of LDL was cleared via receptor-mediated pathways and in subjects with FH this figure was 22% (range 5–33%). In nonfamilial hypercholesterolemia there was clear evidence of defective removal of LDL via receptor-independent pathways in association with some overproduction of apoLDL. In heterozygous FH there was evidence of defective removal of LDL via receptor-mediated pathways, while some subjects also showed evidence of overproduction of apoLDL. It is suggested that LDL catabolism via receptor-independent pathways plays a major role in regulating plasma cholesterol levels in the normal to moderately elevated range.

METHODS

Subjects The studies were performed in 29 subjects whose clinical data are recorded in Table 1. The diagnosis of FH in the heterozygous form was an arbitrary one based on an LDL cholesterol level in excess of 220 mg/dl, plus the presence of at least two of the following three characteristics: xanthomatous disease, similarly affected first degree relatives, and premature coronary heart disease under the age of 35 years. Subjects without FH...
exhibited a range of LDL cholesterol levels, but had none of the additional characteristics used to define FH.

None of the 29 subjects exhibited disease affecting renal, hepatic, or endocrine systems. Some of the hypercholesterolemic subjects had previously used drugs affecting lipid metabolism, but not in the 2 to 3 months prior to study.

Studies were conducted on an outpatient basis and subjects were instructed to continue their existing diets. Vegetarian subjects had been consuming a lacto-ovo-vegetarian diet, most of the hypercholesterolemic subjects had been consuming a diet restricted in cholesterol and saturated fat, while the remaining subjects were consuming a typical Australian ad lib diet. Nutrient intake was assessed by 24-hr recall to confirm the dietary status (12). Research protocols were approved by Ethics and Research Committees at St. Vincent’s Hospital and the University of New South Wales, and each subject gave informed consent prior to participation.

**Preparation and chemical modification of labeled LDL**

Sixty ml of blood was collected in EDTA (0.1% w/v) from each subject. LDL (1.019 < d < 1.055 g/ml) was isolated by preparative ultracentrifugation and purified by re-centrifugation at d 1.055 g/ml. The LDL was dialyzed against 0.15 M NaCl-0.01% EDTA, pH 7.4 (4°C), and then divided into two aliquots that were

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**TABLE 1. Clinical data**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>Weight</th>
<th>Total Cholesterol</th>
<th>VLDL</th>
<th>LDL</th>
<th>HDL</th>
<th>Triglycerides</th>
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<tr>
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<tr>
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<td>75 ± 20</td>
<td>197 ± 26</td>
<td>12 ± 8</td>
<td>139 ± 24</td>
<td>47 ± 9</td>
<td>177 ± 59</td>
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<tr>
<td>Mean ± S.D. #2</td>
<td>58 ± 9</td>
<td>67 ± 17</td>
<td>269 ± 23(\text{a})</td>
<td>14 ± 11</td>
<td>201 ± 21(\text{b})</td>
<td>54 ± 14</td>
<td>197 ± 79</td>
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Subjects with familial hypercholesterolemia

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>Weight</th>
<th>Total Cholesterol</th>
<th>VLDL</th>
<th>LDL</th>
<th>HDL</th>
<th>Triglycerides</th>
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<td>69</td>
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<td>382</td>
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<td>T.B.</td>
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<td>273</td>
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<td>M</td>
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<tr>
<td>Mean ± S.D.</td>
<td>52 ± 12</td>
<td>66 ± 9</td>
<td>381 ± 89&lt;sup&gt;\text{a,b}&lt;/sup&gt;</td>
<td>21 ± 19</td>
<td>320 ± 90&lt;sup&gt;\text{a}&lt;/sup&gt;</td>
<td>40 ± 6&lt;sup&gt;\text{c}&lt;/sup&gt;</td>
<td>239 ± 79&lt;sup&gt;\text{b}&lt;/sup&gt;</td>
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</tbody>
</table>

<sup>a</sup> The first 12 subjects were nonvegetarians and the last 8 were vegetarians. These 20 subjects were arbitrarily classified into those with LDL cholesterol < 180 mg/dl (Mean #1, n = 13) and those with LDL cholesterol ≥ 180 mg/dl (Mean #2, n = 7).

<sup>b</sup> Significantly different from Mean #1 (P < 0.05 or less).

<sup>c</sup> Significantly different from Mean #2 (P < 0.02 or less).
labeled with Na$^{125}$I or Na$^{131}$I (Radiochemical Centre, Amersham) using a modification of the iodine monochloride method (1). Labeled lipoproteins were then dialyzed exhaustively against the above-mentioned buffer. The efficiency of iodination was 15–40%, the degree of lipid labeling was 2–6% (chloroform-methanol 2:1 extraction), and the amount of label precipitable by trichloroacetic acid was >97%. $^{131}$I-labeled LDL (3 mg) was modified with 1,2-cyclohexanedione (CHD) as previously described (10). $^{125}$I-labeled LDL was similarly treated at 35°C for 2 hr in sodium borate buffer (0.2 M, pH 8.1) but CHD was not added. The samples were then exhaustively dialyzed against 0.15 M NaCl–0.01% EDTA, pH 7.4. A small aliquot was checked for radiochemical purity and CHD modification using agarose gel electrophoresis and autoradiography. Each labeled LDL migrated as a single band, while CHD-modified LDL migrated with substantially increased anodic mobility, as previously demonstrated (4). Each sample was then sterilized by membrane filtration (0.22 µm filter, Millipore Corp.), a small aliquot was reserved for dosimetry, and approximately 25 µCi of each tracer (0.5–1.0 mg protein) was made ready for re-injection into the donor.

**Lipoprotein turnover studies**

For 3 days prior to re-injection and for the duration of the investigation each subject consumed 180 mg/day of KI to prevent thyroidal uptake of radiiodide. Five days after initial sampling, the donor was re-injected with each label sequentially through a running intravenous line kept open with 0.9% saline. Blood samples were then collected at 5 min (for estimation of plasma volume by isotope dilution) and thereafter daily for 12–14 days. The plasma decay curve for each tracer could be resolved into two exponentials and kinetic parameters were calculated according to Matthews (13), as described previously (5). The parameters derived from $^{125}$I-labeled LDL related to overall LDL metabolism, and those derived from $^{131}$I-labeled LDL were assumed to relate to LDL metabolism via receptor-independent pathways. Receptor-mediated metabolism was calculated as the difference between total and receptor-independent turnover, as demonstrated by Shepherd et al. (4).

**Other measurements and statistical methods**

The concentration of apoLDL for the duration of a turnover study was obtained as follows. Two plasma pools representing the first and second halves of each study period were created by drawing a small aliquot from each daily sample; total radioactivities in these samples were assessed; LDL (1.019 < d < 1.055 g/ml) was isolated in the preparative ultracentrifuge and its specific radioactivity was measured by counting and by Lowry assay using a standard of bovine serum albumin (14); apoLDL concentration was then calculated from specific radioactivity and total radioactivity in plasma. Standard diagnostic separations of lipoprotein classes were performed according to previously published methods (15). Plasma cholesterol and triglyceride concentrations were measured on the Technicon Autoanalyzer (Methods N-24a and N-78, respectively). Data was analyzed using the Statistical Package for the Social Sciences (16). The means of various samples were compared using t-test for independent samples (two-tailed distribution), while correlation analysis examined only the linear Pearson correlation.

**RESULTS**

**Subjects without familial hypercholesterolemia**

This was a diverse group of subjects with plasma cholesterol concentrations extending from 160 to 297 mg/dl, the lower cholesterol levels generally belonging to the vegetarian subjects (Table 1). To overcome some of this heterogeneity, these subjects were arbitrarily subgrouped into those with LDL cholesterol levels above and below 180 mg/dl (‘hypercholesterolemic’, $n = 13$ and ‘normals’, $n = 7$). Mean (±S.D.) plasma cholesterol levels were respectively 269 ± 23 and 197 ± 26 mg/dl ($P < 0.001$), while LDL cholesterol levels were respectively 201 ± 21 and 139 ± 24 mg/dl ($P < 0.001$). Plasma triglyceride and VLDL cholesterol concentrations did not differ significantly between the two subgroups (Table 1).

The kinetic parameters of LDL metabolism are summarized in Table 2. The rate of clearance of LDL was 38–42% slower in the presence of CHD-modification, indicating that a minimum 40% of LDL was cleared in vivo via specific receptors.

The relationships between apoLDL concentration and overall LDL catabolism are presented in Fig. 1. The concentration of apoLDL was negatively correlated with its fractional catabolic rate (FCR) ($r = -0.49$, $P < 0.02$) and positively correlated with its absolute catabolic rate (ACR) ($r = 0.50$, $P < 0.02$). There was a significantly lower FCR in hypercholesterolemic subjects versus normals (0.264 ± 0.023/day versus 0.308 ± 0.040, $P < 0.02$). ACR tended to be higher in hypercholesterolemic subjects compared to normals, but this difference was not statistically significant.

The relationships between apoLDL concentration and catabolism of LDL via receptor-mediated and receptor-independent pathways are presented in Fig. 2. The concentration of apoLDL was negatively correlated with FCR via receptor-independent pathways ($r$
ship with FCR via receptor-mediated pathways. These subgroup via receptor-mediated pathways.

tor-independent pathways (0.153 normal subjects by a significantly lower FCR via recep-

findings were supported in hypercholesterolemic versus

mal subjects tended to have higher ACR via receptor-

though the latter failed to reach statistical significance

(\(P = 0.192\)).

with ACR via receptor-mediated pathways.

Subjects with familial hypercholesterolemia

Mean

Mean

\(\text{J.R.} \) 2942 143 0.208 0.156 0.052 12.7 9.5 3.2

\(\text{L.C.} \) 2032 238 0.172 0.160 0.012 16.3 15.2 1.1

\(\text{T.B.} \) 2344 157 0.277 0.186 0.091 16.4 11.0 5.4

\(\text{M.E.} \) 2580 208 0.162 0.134 0.028 12.4 10.3 2.2

\(\text{M.H.} \) 2027 116 0.257 0.172 0.085 10.2 6.9 3.4

\(\text{D.I.} \) 2843 164 0.234 0.178 0.056 13.6 10.4 3.3

\(\text{R.W.} \) 2038 207 0.189 0.142 0.047 12.1 9.1 3.0

\(\text{J.C.} \) 1942 180 0.178 0.141 0.037 10.4 8.2 2.2

\(\text{S.D.} \) 2377 154 0.183 0.178 0.005 9.2 9.0 0.3

Mean ± S.D. 174± 38ced \(0.207 \pm 0.040ced \) 0.161 ± 0.019ed \(0.046 \pm 0.029ced \) 12.6 ± 2.5e 9.9 ± 2.3ed 2.7 ± 1.5d

a These subjects did not receive CHD-modified LDL.

b See footnote a Table 1.

c Significantly different from Mean #1 (\(P < 0.05\) or less).

d Significantly different from Mean #2 (\(P < 0.01\) or less).

Nonvegetarian subjects consumed more cholesterol than vegetarians (345 ± 252 mg/day versus 119 ± 57, \(P < 0.05\)). Mean FCR of apoLDL in nonvegetarians was significantly lower than in vegetarians (0.277 ± 0.029/ day versus 0.317 ± 0.043, \(P < 0.02\)). This decrease in FCR of apoLDL was due to a decrease in FCR via receptor-independent pathways (0.158 ± 0.023/day versus 0.201 ± 0.026, \(P < 0.002\)).

Subjects with familial hypercholesterolemia

Subjects with FH were of similar age and body mass index to subjects without FH. They had significantly higher total and LDL cholesterol levels (Table 1). The
average nutrient intakes of both groups were broadly similar (188 ± 72 mg/day of cholesterol in FH versus 260 ± 228 in non-FH; 38 ± 8% of energy from fat in FH versus 34 ± 11 in non-FH; 30 ± 6 Kcal/kg per day in FH versus 30 ± 8 in non-FH).

The kinetic parameters of LDL metabolism in subjects with FH are presented in Table 2. The FCR of apoLDL was significantly lower in FH compared with normals (0.207 ± 0.040/day versus 0.308 ± 0.040, P < 0.001), due to a removal defect principally confined to receptor-mediated pathways (see Fig. 3.) Mean ACR in FH was slightly higher than in normals (12.6 ± 2.5 mg/kg per day versus 10.4 ± 2.3, P < 0.05), but did not differ significantly from that in hypercholesterolemia not due to FH. ACR in FH via receptor-independent pathways was significantly higher and ACR in FH via receptor-mediated pathways tended to be lower than in either normal subjects or in those with hypercholesterolemia not due to FH (see Table 2 and Fig. 4).

In subjects with FH, apoLDL concentration was negatively correlated with total FCR (r = -0.69, P < 0.02) and with FCR via receptor-mediated pathways (r = -0.59, P < 0.05). AopLDL concentration was not significantly correlated with ACR.
Fig. 2. The relationships between receptor-mediated and receptor-independent catabolism and apoLDL concentration in subjects without FH. Receptor-independent catabolism was derived from $^{131}$I-labeled LDL metabolism and receptor-mediated catabolism from the difference between $^{125}$I-labeled LDL and $^{131}$I-labeled LDL metabolism.

**DISCUSSION**

In many respects the subjects without FH represent a grouping of diverse metabolic variables, including diet, physical activity, genetic and other environmental factors. This was likely to complicate interpretation of any observed relationships between LDL concentration and its metabolism. However, the extremes of diet experienced in the present study were accepted in the hope of highlighting any subtle metabolic relationship that might have remained concealed in subjects consuming more homogeneous diets. Although the data have been analyzed for a continuum of LDL protein concentration from the normal to moderately elevated
Fig. 3. Parameters of fractional LDL catabolism in subjects with FH and without FH ('non FH'). Horizontal bars represent mean values.

range, it has also proved useful to examine the data in an independent manner by subdividing the subjects above and below an arbitrary LDL cholesterol concentration. Fortuitously, the hypercholesterolemic and normal subgroups have similar levels of plasma triglycerides and other lipoprotein classes and this has removed the potentially confounding influence of variations in the transport of triglyceride-rich lipoproteins.

Our findings clearly suggest that in subjects without FH, moderate hypercholesterolemia is due to a defect in LDL removal mechanisms. Somewhat weaker evidence has been obtained to suggest that these subjects may also have above-normal production rates of apoLDL (equivalent to ACR in the metabolic steady state). In a recent investigation, where diet was the same in all subjects, Kesaniemi and Grundy (17) found that moderate hypercholesterolemia was clearly associated with overproduction of apoLDL, yet these patients failed to manifest a removal defect. This contrast with our own results is possibly due to differences in case selection and diet, and suggests that moderate hypercholesterolemia not due to FH may be associated with a combination of defective catabolism and overproduction of apoLDL, or with overproduction alone.

Our results confirm the previous observation that a chemical modification of functional arginyl residues in apoLDL leads to slower clearance of LDL from plasma in vivo (4). Two assumptions have been made in interpreting the results: i) modified LDL is removed only via receptor-independent pathways, and ii) modified LDL is catabolized at the same rate as native LDL via receptor-independent pathways. It is possible that some CHD-modified LDL is still removed via specific receptors, but this is very difficult to evaluate. Hence, the proportion of LDL removed via receptor-mediated pathways must be regarded as a minimum estimate. Recent data from Slater, Packard, and Shepherd (18) further support the use of CHD-modified LDL as a suitable marker for the study of receptor-independent catabolism in vivo. Based on the above-mentioned assumptions, our calculations show that in normal subjects (mean plasma cholesterol 197 mg/dl) a minimum of 37% of LDL is removed via receptor-mediated pathways. This is in good agreement with a figure of 33% observed by Shepherd et al. (4). In subjects with heterozygous FH (mean plasma cholesterol 381 mg/dl), LDL removal via receptor-mediated pathways was reduced to a minimum mean value of 22%. In all of our subjects examined, the major portion of LDL is removed from plasma via receptor-independent pathways.

The use of modified LDL in the current investigation has provided new information on LDL metabolism in subjects with nonfamilial hypercholesterolemia. In subjects without FH, LDL levels appear to be regulated in part by the FCR of apoLDL (Fig. 1). This regulation, in turn, appears to be related to the amount of apoLDL removed via receptor-independent pathways (Fig. 2). There is little relationship between receptor-mediated removal of LDL and its concentration in these subjects, which is in contrast to the situation in FH. The present observations suggest, for the first time, that a removal defect for LDL via receptor-independent pathways is an important contributing factor in nonfamilial hypercholesterolemia, in association with some overproduction of apoLDL. Although some hypercholesterolemic patients may manifest overproduction of apoLDL as the sole metabolic lesion (17), subjects in the present study manifest clearer evidence of a removal defect. We have not noted a pronounced overproduction of apoLDL and it is suggested that the removal defect via receptor-independent pathways could be the dominant lesion in these cases.

Although much is known about the properties of LDL receptors, the mechanisms involved in receptor-independent pathways are unclear. The reticuloendothelial system may well play an important role (19). Our findings in vegetarians do suggest that a diet high in cholesterol is associated with a significant reduction in

Fig. 4. Parameters of absolute LDL catabolism in subjects with FH and without FH ('non FH'). Horizontal bars represent mean values.
LDL removal via the receptor-independent pathways. However, the design of the present study precludes any precise measurement of the relationship between diet and LDL metabolism. Other studies have shown that vegetarianism may influence both LDL production and remeasurement of the relationship between diet and LDL metabolism. Other studies have shown that vegetarianism may influence both LDL production and removal (1–5). There is, however, controversy as to whether heterozygous subjects for FH overproduce LDL or not. In the present study only two subjects out of nine had undisputed evidence of overproduction of apoLDL (Fig. 4). These observations suggest that defective removal and overproduction of apoLDL can be independent phenomena, as in the non-familial subjects.

We acknowledge the excellent technical assistance of Mr. J. Ruys and the secretarial assistance of Mrs. A. Reeves. We also acknowledge the technical assistance and cooperation extended by the staff at the Sydney Adventist Hospital. This work was supported by a grant from the National Health and Medical Research Council of Australia.

Manuscript received 8 June 1982 and in revised form 5 October 1982.

REFERENCES