Identifying and Treating Severe Familial Hypercholesterolemia
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Lipid metabolism in familial hypercholesterolemia

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Disclosures

- Honoraria for Speakers Bureau (Pharma)
  AstraZeneca, Sanofi, Pfizer

- Advisory Boards: Sanofi, Aegerion, AstraZeneca

- Research Funding: Pfizer
Cholesterol Importance

- A stabilizing component of cell membranes
- A precursor of bile salts
- A precursor of steroid hormones
- A cholesterol precursor is converted to cholecalciferol (vit. D)
Cholesterol Balance

Synthesis
Mainly in the liver, endocrine organs, muscle and skin

Absorption
From the diet and excretion into bile

Of the cholesterol absorbed in the intestines: 25% is from dietary sources (exogenous)
75% is from biliary sources undergoing enterohepatic circulation (endogenous).

Biosynthesis of cholesterol

In the cytosol + ER

**Precursor - acetyl CoA from:**

1. The β-oxidation of fatty acids
2. The oxidation of ketogenic amino acids
3. The pyruvate dehydrogenase reaction

**The reducing agent - NADPH**

- from PPP

**Energy for synthesis**

- hydrolysis of CoA and ATP
HMG CoA Reductase (More Than Cholesterol Synthesis)

Acetyl CoA → HMG CoA Reductase → HMG CoA → Mevalonate

Mevalonate → Isopentenyl adenine (transfer RNA)

Mevalonate → Farnesyl Pyrophosphate → Dolichols

Farnesyl Pyrophosphate → Cholesterol

Farnesyl Pyrophosphate → Prenylation of signalling peptides (ras, rho, etc.)

Inhibition of other key products of mevalonate may relate to nonlipid effects & rare side effects of statins.
NORMAL CHOLESTEROL ABSORPTION

Diet
400 mg/day

Oil phase
Luminal cholesterol

Bile salts
Unabsorbed cholesterol

Diet
1,300 mg/day

Oil phase
Luminal cholesterol

Bile salts
Unabsorbed cholesterol

Diet
17,400 mg/day

Bile salts

Duodenal/jejunal
enterocyte

Cholesterol transporter
850 mg/day

Chylomicron

Lymph
Chylomicron

Liver
Lipoproteins

**Function:**
- Lipid transport (cholesterol, cholesterol esters, triacylglycerols, phospholipids)

**Structure:**
- A nucleus: triacylglycerols, cholesterol esters
- A shell: phospholipids, apoproteins, cholesterol

A nucleus: triacylglycerols, cholesterol esters
A shell: phospholipids, apoproteins, cholesterol
Composition of lipoproteins

Chylomicron
- 84% Triacylglycerols
- 7% Cholesterol
- 7% Phospholipids
- 2% Proteins
100-1000nm

VLDL
- 54% Triacylglycerols
- 9% Cholesterol
- 18% Phospholipids
- 19% Proteins
30-90nm

LDL
- 45% Triacylglycerols
- 21% Cholesterol
- 22% Phospholipids
- 11% Proteins
20-75nm

HDL
- 50% Triacylglycerols
- 24% Cholesterol
- 22% Phospholipids
- 4% Proteins
5-12nm
## Apoproteins

**Major function:**

- structure, solubility, activation of enzyme, ligands for receptors

<table>
<thead>
<tr>
<th>Apoprotein</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apo A-I</td>
<td>activates LCAT, structural component of HDL</td>
</tr>
<tr>
<td>Apo B-48</td>
<td>Assembly and secretion of chylomicrons</td>
</tr>
<tr>
<td>Apo B-100</td>
<td>VLDL assembly and secretion; structural protein of VLDL, IDL and LDL; ligand for LDL receptor</td>
</tr>
<tr>
<td>Apo C-II</td>
<td>Activator of lipoprotein lipase (LPL)</td>
</tr>
<tr>
<td>Apo E</td>
<td>ligand to LDL receptor; ligand to Apo E receptor</td>
</tr>
</tbody>
</table>
Lipoproteins - metabolism

- Dietary lipids
  - Receptor-mediated endocytosis
  - Chylomicrons
    - HDL
    - Fat
  - Liver
    - Cholesterol
    - Fats
    - LDL
    - IDL
    - VLDL
  - Muscle
    - Free fatty acids
  - Adipose tissue
    - Free fatty acids
- Endogenous lipids
  - Cholesterol return
  - Extrahepatic tissues
    - Cholesterol
    - Fatty acids
  - Exchange of lipids and apoproteins

1. Lipoprotein lipase
2. Lecithin-cholesterol acyltransferase (LCAT)
Metabolism of VLDL, IDL and LDL
Receptor-Mediated Endocytosis of Lipoproteins

- LDL receptor are located at coated pits, which also contain clathrin
- Vesicles fuse with lysosome where cholesterol esters are hydrolyzed into cholesterol & re-esterified by ACAT
- This avoids damaging effects of high concentrations of free cholesterol on membrane
LDL Receptor (apoB-E receptor)

Regulates cholesterol synthesis and plasma cholesterol levels

LDL-_Receptors

LDL

LDL

Endosome

Lysosome

HMG-CoA reductase

SREBP

Cholesterol

Amino acids

Cholesteryl ester (storage)

ACAT
Modification of LDL

- **Derivatization:**
  - Aldehydes
  - Glucosylation
  - eg. diabetes

- **Oxidation:**
  - Degradation of Apo B-100 by reactive oxygen species

**LDL**

- Apo B-100

**Derivatized LDL**

**Oxidized LDL**
The Scavenger Receptor:
Clearance of modified LDL by macrophages

Macrophage

Scavenger receptor (SR-A1)

Oxidized LDL

Macrophage Foam Cell

Lipid droplets

Fatty streaks
Elevated LDL: Increased residence time in plasma
Increased modification/oxidation of LDL

LDL and Atherosclerosis
Fitting the pieces together

Monocyte

Endothelial cells

oxLDL (stimulates cytokine secretion)

Cytokines

Artery wall

oxLDL

Macrophage foam cell

Smooth muscle cell proliferation
laboratory tests in FH

• Secondary hypercholesterolemia causes
• Genetic diagnosis
• LDL Receptor activity
• PCSK9 levels
• Lp(a) levels
<table>
<thead>
<tr>
<th>Affected lipids</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Total cholesterol and LDL-C</td>
<td>• Hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>• Nephrosis</td>
</tr>
<tr>
<td></td>
<td>• Dysgammaglobulinemia (systemic lupus erythematosus, multiple myeloma)</td>
</tr>
<tr>
<td></td>
<td>• Progestin(^a) or anabolic steroid treatment</td>
</tr>
<tr>
<td></td>
<td>• Cholostatic diseases of the liver due to abnormal lipoproteins, as in primary biliary cirrhosis</td>
</tr>
<tr>
<td></td>
<td>• Protease inhibitors for treatment of HIV infection(^b)</td>
</tr>
</tbody>
</table>
PCSK9 Levels Are Elevated in FH

Raal F et al. J Am Heart Assoc 2013;2:e000028
Plasma levels of PCSK9 and phenotypic variability in familial hypercholesterolemia

**TABLE 1. Characteristics of the untreated study participants**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>FH Low</th>
<th>FH High</th>
<th>Control vs. FH Low</th>
<th>Control vs. FH High</th>
<th>FH Low vs. FH High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males [number (%)]</td>
<td>54 (48)</td>
<td>37 (39)</td>
<td>25 (40)</td>
<td>0.20</td>
<td>0.36</td>
<td>0.84</td>
</tr>
<tr>
<td>Age (years)</td>
<td>40.7 ± 8.1</td>
<td>36.7 ± 8.4</td>
<td>33.9 ± 8.6</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.054</td>
</tr>
<tr>
<td>Hypertension [number (%)]</td>
<td>10 (9)</td>
<td>5 (5)</td>
<td>4 (7)</td>
<td>0.33</td>
<td>0.63</td>
<td>0.72</td>
</tr>
<tr>
<td>Diabetes [number (%)]</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>—</td>
<td>0.17</td>
<td>0.21</td>
</tr>
<tr>
<td>Current smoker [number (%)]</td>
<td>23 (21)</td>
<td>16 (17)</td>
<td>18 (30)</td>
<td>0.52</td>
<td>0.19</td>
<td>0.066</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.6 ± 4.1</td>
<td>25.6 ± 5.3</td>
<td>24.3 ± 4.8</td>
<td>0.95</td>
<td>0.098</td>
<td>0.097</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>128 ± 15</td>
<td>124 ± 13</td>
<td>122 ± 14</td>
<td>0.038</td>
<td>0.014</td>
<td>0.54</td>
</tr>
<tr>
<td>Lipid profile (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At genetic FH test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pLDL (IQR)</td>
<td>40 (19–65)</td>
<td>45 (20–63)</td>
<td>97 (95–98)</td>
<td>0.89</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At study visit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>5.3 ± 1.1</td>
<td>5.4 ± 1.1</td>
<td>7.1 ± 1.2</td>
<td>0.24</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C</td>
<td><strong>3.3 ± 0.9</strong></td>
<td><strong>3.5 ± 1.0</strong></td>
<td><strong>5.3 ± 1.1</strong></td>
<td><strong>0.11</strong></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.5 ± 0.4</td>
<td>1.5 ± 0.4</td>
<td>1.4 ± 0.4</td>
<td>0.65</td>
<td>0.83</td>
<td>0.55</td>
</tr>
<tr>
<td>Triglycerides (IQR)</td>
<td>0.9 (0.6–1.4)</td>
<td>0.7 (0.5–1.1)</td>
<td>0.7 (0.5–1.1)</td>
<td>0.024</td>
<td>0.012</td>
<td>0.69</td>
</tr>
<tr>
<td>Mean cIMT (SE) (mm)</td>
<td>0.63 ± 0.008</td>
<td>0.62 ± 0.009</td>
<td>0.67 ± 0.013</td>
<td>0.38</td>
<td>0.009</td>
<td>0.001</td>
</tr>
</tbody>
</table>
LDL-C Levels Correlate With Residual LDLR Activity

\[ r = -0.655 \]
\[ P = 0.0003 \]

N=32 HoFH

Penn HoFH Cohort:  
LDLR Negative Subjects Have a More Severe Phenotype

<table>
<thead>
<tr>
<th></th>
<th>LDLR negative (n=18)</th>
<th>LDLR defective (n=16)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median (range)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr) at visit 1</td>
<td>11.5 (3.3 - 29)</td>
<td>28.1 (3.3 - 44.6)</td>
<td>0.008</td>
</tr>
<tr>
<td>Age at 1st xanthomas</td>
<td>2.0 (0.25 - 4)</td>
<td>7.0 (1 - 15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (yr) at FH dx</td>
<td>3.0 (0.5 - 7)</td>
<td>8.0 (2 - 17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC (mg/dl) at dx</td>
<td>895 (602-1260)</td>
<td>686 (519-900)</td>
<td>0.002</td>
</tr>
<tr>
<td>Age (yr) at start of Rx</td>
<td>5.0 (1.2 - 10)</td>
<td>16.0 (2 - 31)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age (yr) at CAD</td>
<td>12.5 (6 - 16)</td>
<td>22.0 (16 - 37)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Lipid profile at visit 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>618 (238)</td>
<td>453 (162)</td>
<td>0.025</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>535 (214)</td>
<td>393 (159)</td>
<td>0.040</td>
</tr>
<tr>
<td>Apo B (mg/dl)</td>
<td>388 (142)</td>
<td>293 (92)</td>
<td>0.032</td>
</tr>
</tbody>
</table>

Kolansky DM, Am J Cardiol 2008; 102:14-38-43
Lipoprotein (a)

- An LDL + apolipoprotein a

- Different lengths of apo a (kringles) caused by a variable number of kringle IV repeats

- More kringles = lower Lp(a) levels

- Hepatic synthesis

- Lp(a) plasma concentrations are highly heritable and mainly controlled by the apolipoprotein(a) gene [LPA] located on chromosome 6q26-27.

LIPOPROTEIN (a):
mechanisms of atherogenesis

Homology with plasminogen (= impaired fibrinolysis)

Binds to macrophages → foam cell formation

Binds to platelets (inhibition or stimulation?)

Deposition of cholesterol into plaques?
Box 7  Individuals who should be considered for lipoprotein(a) screening

<table>
<thead>
<tr>
<th>Individuals with:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Premature CVD</td>
</tr>
<tr>
<td>• Familial hypercholesterolaemia</td>
</tr>
<tr>
<td>• A family history of premature CVD and/or elevated Lp(a)</td>
</tr>
<tr>
<td>• Recurrent CVD despite optimal lipid-lowering treatment</td>
</tr>
<tr>
<td>• ≥5% 10-year risk of fatal CVD according to SCORE</td>
</tr>
</tbody>
</table>
LIPOPROTEIN (a) MEASUREMENT

- Quantitative Lp(a) measurements
  - rocket immunoelectrophoresis
  - rate and endpoint nephelometry
  - turbidimetry
  - radio-immuno assays
  - enzyme immuno assays (ELISA)
  - dissociation-enhanced lanthanide fluorescent immunoassay (DELFIA)