Pathophysiology of Lipid Disorders

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CHD in the United States

- CHD is the single largest killer of men and women
- 12 million have history of MI and/or angina
- Each year 1.1 million people have MI
  - 370,000 die of MI
  - 250,000 die within 1 hr
- By age 60, every 5th man and 17th woman develops CHD (1986 Framingham data)
- 1999 estimated direct and indirect costs of heart disease are $99.8 billion
- 53.3 million adults have elevated LDL-C and warrant intervention (1994 NHANES data)
  - 22.3 million qualify for drug therapy
  - 5.5 million actually receive drug therapy


Development of Atherosclerotic Plaques

Unoccluded Coronary Artery
Fibrous Lesion with Necrotic Core

Occluded Coronary Artery

Filtration theory of atherogenesis

PLASMA -- VESSEL -- FILTRATE

Normal lipid

Hyperlipemia

Hyperlipemic

Normal lipid

Thickened intima

Normal lipid

Impact of Diabetes on Cardiovascular Mortality

* Risk factors analyzed were: smoking, dyslipidemia and hypertension

Diabetes Care 12:573-579, 1989
**Lipoprotein Lipid Composition**

<table>
<thead>
<tr>
<th>Density</th>
<th>Cholesterol</th>
<th>Triglyceride</th>
<th>Phospholipid</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHY 0.98</td>
<td>5%</td>
<td>90%</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>VLDL &lt;1.006</td>
<td>13%</td>
<td>65%</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>IDL/LDL 1.006-1.063</td>
<td>43%</td>
<td>10%</td>
<td>22%</td>
<td>25%</td>
</tr>
<tr>
<td>HDL 1.063-1.210</td>
<td>18%</td>
<td>2%</td>
<td>30%</td>
<td>50%</td>
</tr>
</tbody>
</table>

**Apolipoproteins**

- Protein components of lipoprotein
- Functions include: serve as membrane stabilizers, cofactors for enzyme activation, interact with receptors to promote lipid metabolism
- Four major classes: A, B, C, and E

**Classification & Location of Major Apolipoproteins**

  - HDL, Chylomicron
- Apo A-IV
  - Chylomicron
- Apo B_{48}
  - Chylomicron
- Apo B_{100}
  - VLDL, LDL
- Apo A-I, A-II, C-III
  - Chylomicron, VLDL
- Apo C-I, C-II, C-III
  - Chylomicron, VLDL
- Apo E
  - Chylomicron, VLDL

**Apolipoproteins**

<table>
<thead>
<tr>
<th>Apolipoprotein</th>
<th>MW (KDa)</th>
<th>Lipoproteins</th>
<th>Metabolic Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apo B_{100}</td>
<td>540,000</td>
<td>VLDL, IDL, LDL</td>
<td>Essential structural protein Ligand for LDL receptor</td>
</tr>
<tr>
<td>Apo B_{48}</td>
<td>250,000</td>
<td>chylomicron</td>
<td>Essential structural protein Ligand for LDL receptor</td>
</tr>
<tr>
<td>Apo C-I, C-II, C-III</td>
<td>8-12,000</td>
<td>VLDL, IDL, HDL, chylomicron</td>
<td>C-I inhibits remnant uptake, C-II activate LPL, C-III inhibits LPL and remnant uptake</td>
</tr>
<tr>
<td>Apo E</td>
<td>34,000</td>
<td>VLDL, LDL, HDL</td>
<td>Ligand for LDL and LRP receptors</td>
</tr>
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**Apolipoproteins**

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<th>Metabolic Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apo A-I</td>
<td>28</td>
<td>HDL, chylomicron</td>
<td>Structural component of HDL, LCAT activator</td>
</tr>
<tr>
<td>Apo A-II</td>
<td>17</td>
<td>HDL, chylomicron</td>
<td>Unknown</td>
</tr>
<tr>
<td>Apo A-IV</td>
<td>40</td>
<td>HDL, chylomicron</td>
<td>Unknown, but strong Association with hiTG</td>
</tr>
<tr>
<td>Apo (a)</td>
<td>400-800</td>
<td>Lp(a)</td>
<td>Competitive inhibitor of plasminogen</td>
</tr>
</tbody>
</table>
Transport of Intestinal Cholesterol

Clinical signs of severe hypertriglyceridemia

Eruptive xanthomas

Lipemia Retinalis
Structure Differences Between Apo E Alleles

Apo E (E3) COOH
1 299
(E4) 112 Cys → Arg
(E2) 158 Arg → Cys
Receptor binding domain

Tuberous Xanthomas
Common Causes of Hypertriglyceridemia

- Caloric excess/obesity
- Insulin resistance
- Diabetes mellitus
- High dietary simple carbohydrates
- Alcohol
- Estrogen therapy
- Lipoprotein lipase mutations
Substrate Driving Forces for the Assembly and Secretion of apoB-Lipoproteins

Mechanisms Relating Insulin Resistance and Dyslipidemia

- Fat Cells
  - Insulin
  - ↑↑ TG
  - ↑↑ Apo B
  - ↑↑ VLDL

Liver
- Insulin
- IR
- ↑↑ FFA
- ↑↑ VLDL

Hypertriglyceridemia: A risk factor for atherosclerosis

- VLDL can enter the artery wall
- Associated with increased factor VII, fibrinogen, and PAI-1
- Associated with other lipid abnormalities

- VLDL
- TG
- ApoB
- VLDL
- Lipogenesis
- FFA
- Plasma FFA
- VLDL
- and Chylo Remnant FFA
Production of HDL by Liver and Intestine

HDL Metabolism and Reverse Cholesterol Transport

Causes of low HDL cholesterol
- Hypertriglyceridemia
- Obesity
- Insulin resistance
- Anabolic steroids
Mechanisms other than Reverse Cholesterol Transport by which HDL may be Anti-atherogenic

- Anti-oxidant effects
- Inhibition of endothelial adhesion molecule expression
- Prostacyclin stabilization
- Promotion of NO production
Common Lipid Phenotypes

Hypercholesterolemia with normal triglycerides and HDL cholesterol levels:
- High LDL cholesterol

Low HDL cholesterol with high triglycerides and variable LDL cholesterol:
- Insulin resistance, Metabolic Syndrome
- Combined hyperlipidemia

Mechanisms Relating Insulin Resistance and Dyslipidemia
Risk for CAD is mediated by small size (<22 K4) apo(a) isoform-containing Lp(a) particles, “s-i-Lp(a)”. 