Pathophysiology of Lipid Disorders

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Ruptured Atherosclerotic Plaque

Epicardial Coronary Artery Section
Magnification × 30

Epicardial Coronary Artery Section
Magnification × 120

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

National Center for Health Statistics. National Health and Nutrition
Examination Survey (III); 1994. (Data collected 1991-1994.)

Number of Adults (Millions) Who Need
Lifestyle and Drug Treatment

<table>
<thead>
<tr>
<th>Therapeutic Lifestyle Changes (TLC)</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD and CHD Risk Equivalents</td>
<td></td>
</tr>
<tr>
<td>10-year risk &gt;20%</td>
<td>24.1</td>
</tr>
<tr>
<td></td>
<td>35</td>
</tr>
<tr>
<td>2+ Risk Factors 10-year risk 10–20%</td>
<td>10.9</td>
</tr>
<tr>
<td>2+ Risk Factors 10-year risk &lt;10%</td>
<td>14.6</td>
</tr>
<tr>
<td></td>
<td>30.2</td>
</tr>
<tr>
<td>0–1 Risk Factor</td>
<td>15.6</td>
</tr>
<tr>
<td>Total</td>
<td>65.3M</td>
</tr>
</tbody>
</table>
Development of Atherosclerotic Plaques

Normal Fatty streak
Lipid-rich plaque
Foam cells
Fibrous cap
Lipid core
Thrombus

Unoccluded Coronary Artery
Fibrous Lesion with Necrotic Core

- Fibrous cap
- Necrotic core

Occluded Coronary Artery

- Thrombus
- Necrotic atherosclerotic lesion
**Filtration theory of atherogenesis**

PLASMA -- VESSEL -- FILTRATE

Normal lipid Normal lipid

Hyperlipemia Lipid retention Hyperlipemic

Normal lipid Thickened intima Normal lipid

Page, I. Connor Lecture, Circ X, 1954

**Atherosclerosis: Lesion Initiation**

- LDL
- E-Selectin, P-Selectin
- OxLDL
- L-Selectin, Integrins
- VCAM-1, ICAM-1
- Monocyte
- MCP-1
- M-CSF
- Macrophage Activation & Division
- Smooth Muscle Cell Migration

Impact of Diabetes on Cardiovascular Mortality

* Risk factors analyzed were: smoking, dyslipidemia and hypertension

*Diabetes Care* 12:573-579, 1989

![Lipoprotein Structure Diagram](image_url)
### 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</td>
<td>0.98</td>
<td>5%</td>
<td>90%</td>
<td>4%</td>
</tr>
<tr>
<td>VLDL</td>
<td>&lt;1.006</td>
<td>13%</td>
<td>65%</td>
<td>12%</td>
</tr>
<tr>
<td>IDL/LDL</td>
<td>1.006-1.063</td>
<td>43%</td>
<td>10%</td>
<td>22%</td>
</tr>
<tr>
<td>HDL</td>
<td>1.063-1.210</td>
<td>18%</td>
<td>2%</td>
<td>30%</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 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 B100</td>
<td>540,000</td>
<td>VLDL, IDL, LDL</td>
<td>Essential structural protein Ligand for LDL receptor</td>
</tr>
<tr>
<td>Apo B48</td>
<td>250,000</td>
<td>chylomicrons</td>
<td>Essential structural protein</td>
</tr>
<tr>
<td>Apo C1, CII, CIII</td>
<td>8-12,000</td>
<td>VLDL, IDL, HDL chylomicrons</td>
<td>CI inhibits remnant uptake, CII activate LPL, CIII inhibits LPL and remnant uptake</td>
</tr>
<tr>
<td>Apo E</td>
<td>34,000</td>
<td>VLDL, IDL, HDL</td>
<td>Ligand for LDL and LRP receptors</td>
</tr>
</tbody>
</table>
## Apolipoproteins

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<thead>
<tr>
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<th>Lipoproteins</th>
<th>Metabolic Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apo A-I</td>
<td>28</td>
<td>HDL, chylomicrons</td>
<td>Structural component of HDL, LCAT activator</td>
</tr>
<tr>
<td>Apo A-II</td>
<td>17</td>
<td>HDL, chylomicrons</td>
<td>Unknown</td>
</tr>
<tr>
<td>Apo A-V</td>
<td>40</td>
<td>HDL, chylomicrons</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>

**Diagram:**

- **Chylomicron**
  - apo B-48
  - apo A-I
  - apo C-II
  - apo E
  - Triglyceride
  - Cholesterol Ester
  - apo C-III
  - apo A-IV

**Notes:**

- HDL: High-Density Lipoprotein
- Chylomicrons: Lipoprotein particles containing triglycerides
- Metabolic Function: Structural component, LCAT activator, Unknown, Unknown, but strong Association with hITG, Competitive inhibitor of plasminogen
- hITG: High-Intensity Triglyceride
Transport of Intestinal Cholesterol
Clinical signs of severe hypertriglyceridemia

Eruptive xanthomas
Lipemia Retinalis
Structure Differences Between Apo E Alleles

NH₂ Apo E (E3) COOH
1 299
(E4)112 Cys → Arg
(E2)158 Arg → Cys
Receptor binding domain
Tuberous Xanthomas
Plasma TG Values Over Time

Men

Women

Fig. 2. Sudan-stained arterial segments from aortic arch and upper thoracic (A) and lower thoracic (B) regions. The accompanying en face radioautograms (2) were performed as described in the Methods section.
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
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
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
LDL Receptor

Domains
- Ligand - Binding (292 Amino Acids)
- EGF - Precursor Homology (~400 Amino Acids)
- 0 - Linked Sugars (58 Amino Acids)
- Membrane - Spanning (22 Amino Acids)
- Cytoplasmic (50 Amino Acids)

Hypercholesterolemia

- Overproduction of VLDL Particles
- Reduced Activity of LDL Receptors
- Increased Conversion to LDL
- Other Sites

VLDL
apo C
apo E
apo B-100

LDL

Increased Conversion to LDL

Reduced Activity of LDL Receptors

VLDL Remnant
Xanthelasma
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

- Fat Cells
- Liver
- Insulin

Lipoprotein (a)

Apo B

Apo (a)
Risk for CAD is mediated by small size (<22 K4) apo(a) isoform-containing Lp(a) particles, “s-i-Lp(a)”.