HDL metabolism
HDL

• Synthesized *de novo* in the liver and small intestine, primarily as protein-rich disc-shaped particles.
• Newly formed HDL are nearly devoid of C & CE.
• Apoproteins: apoA-I, apoC-I, apoC-II and apoE.
• Transports C from peripheral tissues to liver.
• Acts as circulating stores of apoC-I, apoC-II and apoE.
HDL

- **Pre-β-HDL**: Hydrolyzed CM & VLDL donate PL & apo-A1. This induces cholesterol efflux leading to discoidal HDL.
- **Discoidal HDL (nascent HDL)**: newly secreted HDL from intestine with additional C & PL. Contains Apo-A1. Does not contain apo C or E; synthesized in liver & transferred to HDL.
- **HDL3**: formed due to the action of lecithin cholesterol acyl transferase (LCAT). CE thus formed being more hydrophobic gets shifted into interior of the lipoprotein changing the shape to a disc.
- **HDL2**: formed due to the action of cholesterol ester transfer protein (CETP). Exchanges CE with CM & VLDL remnants; gets TGL in return.
  - By transferring CE out of HDL, product inhibition of CE on LCAT is eliminated.
  - Conversion back to HDL3 is done by HL which hydrolyzes PL & TGL. HDL 3 takes part in HDL cycle. Any surplus A1 is degraded by kidney.
  - CE transferred to CM & VLDL remnants is degraded to bile acids.
  - When C efflux followed by esterification by LCAT is effective, HDL2 will be high. HDL2 concentration is a marker of effectiveness of reverse cholesterol transport.
HDL metabolism

Surplus surface constituents from the action of LPL on CM & VLDL

Pre-β HDL

A-1

PL, C

ABC-1

Tissues PL,C

SR-B-1

ABC-A1: ATP Binding Cassette-A1
SR-B1: Scavenger Receptor type B-1

t1/2: 5 days
Lecithin:Cholesterol Acyl Transferase (LCAT)

LCAT: Disk to sphere transformation

Free cholesterol $\rightarrow$ Cholesteryl ester

Nascent HDL

Mature HDL

Phospholipid plus cholesterol

Cholesteryl ester (CE)

Cholesterol

Phospholipid

ApoA-I

Cholesteryl ester (CE) plus lysophospholipid
HDL AND REVERSE CHOLESTEROL TRANSPORT

Liver → FC → CE → SR-BI

Bile

Mature HDL

A-I

LCAT

Nascent HDL

A-I

ABCA1

Macrophage
Reverse Cholesterol Transport (RCT)

The process whereby excess cholesterol in peripheral cells, especially foam cells, is returned to the liver for degradation and excretion.

RCT involves apoA-I, ABCA1 and LCAT as well as receptors on the liver for uptake of the excess cholesterol.
Reverse cholesterol transport (RCT)

- HDL can then acquire cholesterol and apoE from the macrophages.
- ApoE in HDL leads to an increase in their uptake & catabolism by the liver.
- HDL also acquires C from cell surface membranes. This lowers intracellular cholesterol, since the C stored within cells as CE will be mobilized to replace the C removed from the plasma membrane.
- CE in HDL can also be transferred to VLDL and LDL through the action of CETP. This has the added effect of allowing the excess cellular C to be returned to the liver through the LDL-R pathway.
Modification of LDL

Apo B-100

Derivatization:
- Aldehydes
- Glucosylation
  eg. diabetes

Derivatized LDL

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

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

- Scavenger receptor (SR-A1)
- Oxidized LDL
- Fatty streaks
- Lipid droplets

Macrophage → Macrophage Foam Cell

Fatty streaks
Dietary fats and blood lipoproteins

Cholesterol metabolism in coronary artery lesions

- Atheromatous plaque
- Lipid deposit
- Macrophages
- Smooth muscle cells
- Plasma
- Nascent HDL
- HDL
- Cholesterol
- Small dense LDL
- B100
Lipid profile

Total cholesterol : < 200 mg/dl
Triglycerides : < 150 mg/dl
LDL c : < 100 mg/dl
HDL c : > 40 mg/dl
Indications for measuring plasma lipids

• Clinical indication:
  • Evidence of arterial disease in a relatively young individual.
  • Corneal arcus in a patient under 40 years of age.
  • Xanthelasma or tendinous xanthomata.

• Family H/O arterial disease.

• Risk factors for coronary artery disease.
  • DM
  • Hypertension
Disorders of plasma lipoproteins

• Hyperlipoproteinemias
  – Hypercholesterolemia
  – Hypertriglyceridemia
  – Mixed (common)

• Hypolipoproteinemias
Hyperlipoproteinemias

- **Primary**: Friederickson’s classification
  - 6 categories-based on the type of lipoprotein increased.
- **Secondary**:
  - DM
  - Nephrotic syndrome
  - Multiple myeloma
  - Cushings syndrome
  - Obesity
  - Alcoholism
  - Use of progestational drugs
# Classes of Primary Hyperlipidemias

<table>
<thead>
<tr>
<th>Class</th>
<th>Cause</th>
<th>Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Familial Hyperchylomicronemia</td>
<td>LPL deficiency</td>
<td>↑CM; ↑TGL; Pancreatitis, DM. No risk for CAD.</td>
</tr>
<tr>
<td>IIa. Familial Hypercholesterolemia</td>
<td>LDL receptor defect</td>
<td>↑LDL; ↑TC Atherosclerosis &amp; CAD</td>
</tr>
<tr>
<td>IIb. Familial Combined Hyperlipidemia</td>
<td>Similar to type IIa, asso. ↑ in VLDL</td>
<td>↑VLDL, ↑LDL, ↑TC, ↑TG.</td>
</tr>
<tr>
<td>III. Familial dys-beta-lipoproteinemia</td>
<td>Defect in remnant clearance. Defective Apo E. Lack E3 &amp;E4, have E2.</td>
<td>↑CM &amp; VLDL remnants, ↑TC, ↑TG ↑IDL, Xanthomas &amp; atherosclerosis</td>
</tr>
<tr>
<td>IV. Familial Hypertriglyceridemia</td>
<td>Overproduction of VLDL asso. with glucose intolerance &amp; hyperinsulinemia.</td>
<td>↑↑ TG + ↑TC ↓LDL &amp; HDL, asso. With CAD, DM type II, obesity, alcoholism</td>
</tr>
<tr>
<td>V. Familial mixed Hypertriglyceridemia</td>
<td>Abnormal VLDL &amp; CM metabolism</td>
<td>↑↑TG + ↑ TC. ↑VLDL, ↑CM; ⇐ LDL.</td>
</tr>
</tbody>
</table>
## Fredrickson Classification of the Hyperlipidemias

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Lipoprotein(s) elevated</th>
<th>Serum cholesterol concentration</th>
<th>Serum triglyceride concentration</th>
<th>Relative frequency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Chylomicrons</td>
<td>Normal to ↑</td>
<td>↑↑↑↑↑</td>
<td>&lt;1</td>
</tr>
<tr>
<td>IIa</td>
<td>LDL</td>
<td>↑↑</td>
<td>Normal</td>
<td>10</td>
</tr>
<tr>
<td>IIb</td>
<td>LDL and VLDL</td>
<td>↑↑</td>
<td>↑↑</td>
<td>40</td>
</tr>
<tr>
<td>III</td>
<td>IDL</td>
<td>↑↑</td>
<td>↑↑↑↑</td>
<td>&lt;1</td>
</tr>
<tr>
<td>IV</td>
<td>VLDL</td>
<td>Normal to ↑</td>
<td>↑↑</td>
<td>45</td>
</tr>
<tr>
<td>V</td>
<td>VLDL and chylomicrons</td>
<td>↑ to ↑↑</td>
<td>↑↑↑↑↑</td>
<td>5</td>
</tr>
</tbody>
</table>
Type I hyperlipidemia

Chylomicrons mature

Adipose tissue/skeletal muscle cannot process chylomicrons because LPL or apo CII is defective

Nascent chylomicrons mature

Chylomicrons accumulate in the blood.

Chylomicrons travel to capillaries

non-hepatic tissues
Type II Familial hypercholesterolemia (FH)

- Heterozygotes- 1/500 have 2X normal cholesterol levels, heart attacks around age of 35.
- Homozygotes-are present in about 1/106, and have heart attacks beginning between 2-20 yrs.
- Genetic defects
  - Class 1: no receptors are made
  - Class 2: Receptor synthesized, but not transported from ER to Golgi apparatus.
  - Class 3: Receptors reach surface of the cell but fail to bind LDL.
  - Class 4: Receptors reach surface, bind LDL, but don't cluster in coated pits and can't internalize. The mutation is on the cytoplasmic portion of the receptor.
  - Class 5: Receptor can't recycle.
Type III hyperlipidemia

Chylomicron Remnant

Mature HDL

E Receptor

A1

CII

CII
Striate palmar xanthomata in type III hyperlipoproteinaemia
Tuberose xanthomata (over elbow) in type III hyperlipoproteinaemia
TYPE IV HYPERLIPIDEMIA

- Most common hyperlipidemia
- Increases in both triacylglycerol and cholesterol
- Not due to defects in lipoprotein processing
- VLDL levels↑ by overproduction - obesity, alcohol abuse, diabetes

Diabetes:
- Cannot shutdown hormone sensitive lipase → mobilize FFA
- FFA → liver → TAGs → VLDL → circulation
- VLDL → pathologically excessive LDL

- Incidence of CAD elevated in all Type IV hyperlipidemic patients
### Secondary Hyperlipidemia

<table>
<thead>
<tr>
<th>Disease-Induced Hyperlipidemia</th>
<th>Drug-Induced Hyperlipidemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endocrine / Metabolic disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>Thiazides: ↑ LDL &amp; TC</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Glucocorticoids: ↑ VLDL, LDL, TC,</td>
</tr>
<tr>
<td>Cushing's syndrome</td>
<td>β-Blockers: ↑ TG and ↓ HDL</td>
</tr>
<tr>
<td>Renal Disease</td>
<td>Anabolic Steroids: ↑ TC and ↓ HDL</td>
</tr>
<tr>
<td>Uremia, nephrotic syndrome.</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatic Disease</strong></td>
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<tr>
<td>Primary biliary cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Acute hepatitis</td>
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</table>
Secondary hyperlipoproteinemia

• **Hypothyroidism** :
  - Down-regulation of LDL-R; decreased LDL-R mediated catabolism of LDL/IDL
  - Decreased TGL catabolism due to decreased LPL activity.

• **Nephrotic syndrome**
  - Increased secretion of VLDL
  - Decreased catabolism of VLDL
  - Impaired HDL maturation due to reduced activity of LCAT.

• **Diabetes mellitus**
  - Increased lipolysis $\rightarrow$ increased TGL formation $\rightarrow$ increased VLDL formation
  - Decreased LPL activity $\rightarrow$ decreased TGL clearance
  - Decreased HDL $\rightarrow$ due to decreased level of remnants.
Atherosclerosis
Atherosclerosis

- Atherosclerotic lesions consist of cholesterol deposits in the intimal lining of the arteries.
- Lumen may become occluded to the extent that the blood flow is impaired.
- This causes restricted oxygen supply to peripheral organs like the brain, back pressure on the major arteries that can lead to high blood pressure and congestive heart failure.
- Blood platelets and debris can accumulate at the plaque deposits further narrowing the circulation.
- Chronic high ratios of LDL ('bad cholesterol') over HDL particles is thought to be the major cause of these cholesterol deposits.
CARDIOVASCULAR DISEASE
Treatment of the Three Components of the Atherosclerotic Process

Dyslipoproteinemia  Inflammation  Thrombosis
Lipoprotein Classes and Inflammation

- Chylomicrons, VLDL, and their catabolic remnants
  - > 30 nm
  - Potentially proinflammatory

- LDL
  - 20–22 nm

- HDL
  - 9–15 nm
  - Potentially anti-inflammatory

References:
HDL Stimulates Reverse Cholesterol Transport

LDL
- cholesterol clogs arteries (plaque)

HDL
- Removes LDL from the bloodstream

Increased HDL
- = more cholesterol excretion
blood vessel lumen

endothelial cells

elastic lamina

smooth muscle cells
Early and late atherosclerotic lesions

A

Fatty streak

B

Thrombotic athero lesion, myocardial infarct
**HDL Protective Role**

- **oxLDL** = oxidized LDL
- **UC** = unesterified cholesterol
- **ABCA1**
- **apoA-I**
- **Endothelial cells**
- **Artery wall**
- **Nascent HDL**
- **HDL + UC**
- **HDL**
- **Monocyte**
- **oxLDL**
- **UC**
- **apoA-I**
- **ABCA1**
- **PL**
- **Macrophage foam cell**

**Definitions**:
- oxLDL = oxidized LDL
- UC = unesterified cholesterol
Endothelial cells, smooth muscle cells or macrophages

Native LDL → Acetyl LDL → oxLDL

Slow

Native LDLR (downregulated)

Acetyl LDLR = SR-A (not downregulated)

CD36, SR-A and other oxLDL receptors (not downregulated)
# Positive and Negative risk Factors in Atherosclerosis

<table>
<thead>
<tr>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: Males &gt; 45 years</td>
<td>Elevated HDL cholesterol</td>
</tr>
<tr>
<td>Females &gt; 55 years</td>
<td>Low LDL cholesterol</td>
</tr>
<tr>
<td>Family history of early CHD</td>
<td>Good genes</td>
</tr>
<tr>
<td>Elevated LDL cholesterol (&gt;130 mg/dl)</td>
<td>Female gender (estrogen)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Exercise</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
</tbody>
</table>
Relationship Between LDL-C and HDL-C Levels and CHD Risk

- LDL-C: 1-mg decrease reduces CHD risk by 1%
- HDL-C: 1-mg increase reduces CHD risk by 3%