Lipoproteins
Metabolism
LEARNING OBJECTIVES

• By the end of this Lecture, the student should be able to describe:
  • What are Lipoproteins?
  • Describe Lipoprotein Particles.
  • Composition of Lipoproteins.
  • The chemical component of chylomicrons, VLDL & HDL.
  • The synthesis & role of chylomicrons, VLDL & HDL in Lipid transport.
  • Disorders of plasma Lipoproteins.
What are lipoproteins?

• Molecular complexes that consist of lipids and proteins. They function as transport vehicles for lipids in blood plasma.

• Lipoproteins deliver the lipid components (cholesterol and triglyceride etc.) to various tissues for utilization.
Structure of lipoprotein

- Lipoproteins Consist of:
  - a Non-polar Core & a Single Surface Layer of Amphipathic Lipids.
  - The protein moiety Apo-Protein)
• **The non polar Lipid Core** Consist of mainly triacylglycerol and Cholesteryl ester

• Non-polar lipid Core is surrounded by a **single surface layer of amphipathic** phospholipids and cholerterol molecules.

• These are oriented so that their polar groups face outward to the aqueous medium, as in cell membrane.

• **The protein moiety** of a Lipoprotein is known as apolipoprotein or apoprotein.
Classification of plasma lipoproteins according to their density

- Chylomicron (CM)
- Very low density lipoprotein (VLDL)
- Intermediate density lipoprotein (IDL)
- Low density lipoprotein (LDL)
- High density lipoprotein (HDL)
<table>
<thead>
<tr>
<th>Lipoprotein class</th>
<th>Density (g/ml)</th>
<th>Diameter (nm)</th>
<th>Protein %</th>
<th>Phospholipids %</th>
<th>Triglycerides %</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL</td>
<td>1.063-1.21</td>
<td>5 – 15</td>
<td>33</td>
<td>29</td>
<td>8</td>
</tr>
<tr>
<td>LDL</td>
<td>1.019 – 1.063</td>
<td>18 – 28</td>
<td>25</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>IDL</td>
<td>1.006-1.019</td>
<td>25 - 50</td>
<td>18</td>
<td>22</td>
<td>31</td>
</tr>
<tr>
<td>VLDL</td>
<td>0.95 – 1.006</td>
<td>30 - 80</td>
<td>10</td>
<td>18</td>
<td>50</td>
</tr>
<tr>
<td>CHYLOMIKRONS</td>
<td>&lt; 0.95</td>
<td>100 - 500</td>
<td>1 - 2</td>
<td>7</td>
<td>84</td>
</tr>
</tbody>
</table>
Lipoproteins

- Each contains different kinds and amounts of lipids and proteins
  - The more protein, the higher the density
  - The more lipid, the lower the density
- Each has different function
Because fat is less dense than water, the density of lipoproteins increases in proportion to their ratio of Proteins to Lipids.
Apolipoproteins

- Act as structural components of lipoproteins
- Recognize the lipoprotein receptors on cell membrane surface as ligand.
- Activate/inhibit enzymes involved in lipoprotein metabolism
Apolipoproteins

• Apo AI: Activator LCAT
• Apo AII: Inhibitor of hepatic lipase (HL)
• Apo A-IV: Activator of LCAT
• Apo B-100: structure, ligand
• Apo B-48: structure
• Apo C-I: Activator of LCAT
• Apo C-II: Activator of LPL
• Apo C-III: Inhibitor of LPL
• Apo D: Function unknown
• Apo E: Ligand
Important enzymes and proteins involved in lipoprotein metabolism
LPL  (Lipoprotein Lipase)

- Locate in extracellular on the walls of blood capillaries, anchored to the endothelium.
- Hydrolyze triglyceride (TG) in the core of CM and VLDL to free fatty acids and glycerol.
- LPL  (Lipoprotein Lipase) activated by apo protein C –II.
HL
(Hepatic Lipase)

• Bound to the surface of liver cells,
• Hydrolyzes TG to free fatty acids and glycerol
• Unlike LPL, HL does not react readily with CM or VLDL but is concerned with TG hydrolysis in VLDL remnants and HDL metabolism
LCAT
(Lecithin:Cholesterol Acyl transferase)

Formation of cholesterol esters in lipoproteins

\[
\text{Lecithin} + \text{Cholesterol} \xrightarrow{\text{LCAT}} \text{Lysophospholipid} + \text{Cholesteryl ester}
\]
CETP

(Cholesterol Ester Transfer Protein)
Metabolism of chylomicrons

- Transport dietary TG and Cholesterol from the intestine to the peripheral tissues

- The dietary TG are first acted by intestine lipase and absorbed as monoacylglycerol, fatty acid and glycerol. Within the intestine cells, they are resynthesized into TG.

- CM are synthesized in the intestine using TG, PL, C, ApoB48, and ApoAs and secreted into the lymph and reach blood through thoracic duct.

- Nascent CM pick up apoE, apo CII and some apoAs from HDL and become matured CM.
Metabolism of chylomicrons

- In the capillaries of peripheral tissue, lipoprotein lipase (LPL) degrades triglycerol (TG) of chylomicrons to fatty acids (FA) and glycerol which enter tissues by diffusion.

- Lipoprotein lipase (LPL) is activated by apo C-II.

- After most of the TG is removed, chylomicrons become chylomicron remnants. During the process, CM give apoC-II and apoA to HDL.
Metabolism of chylomicrons

- CM remnants bind to specific receptors on the surface of liver cells through apo E and then the complex is endocytosed.
  - remnant receptor or
  - apo E receptor or
  - LRP (LDL receptor-related protein)

- Chylomicron remnants deliver dietary cholesterol and some cellular cholesterol (via HDL) to the liver.
Metabolism of VLDL and LDL
**VLDL**

- VLDL are made by liver. Liver synthesizes TG and cholesterol, and packages them into VLDL for export into blood.

- Most lipid in the core of VLDL is triglyceride.

- Nascent VLDL contain apoB100. In blood nascent VLDL pick up apo E and apo C-II from HDL and become matured VLDL.
VLDL

• In the capillaries of various tissues, LPL degrades TG to fatty acids and glycerol, which enter the tissues by diffusion. ApoC-II is needed in this step to activate LPL.

• When VLDL loses triglyceride, it transforms into VLDL remnant, also named as IDL (intermediate-density lipoprotein).

• During the process, some apolipoproteins (apo A and apoC-II) are transferred back to HDL.

• VLDL function: Deliver TG from liver to peripheral tissue cells.
Three Fates of VLDL remnants (IDL)

• Taken up by liver or transform into LDL

  1) A proportion of the VLDL remnant (IDL) is taken up by liver through the LDL receptor (apoE-mediated).

  2) The other remnant is further acted upon by hepatic lipase (HL) and converted into LDL. LDL loses all apolipoproteins except apoB100.

  3) Some TG are transferred from VLDL to HDL in exchange with cholesterol ester (By cholesterol ester transfer protein)
Lipid-Transfer Protein
Final destruction in liver, extrahepatic tissues (e.g., lymphocytes, fibroblasts) via endocytosis
LDL are formed in the blood from IDL and in liver from IDL (enzyme – *liver lipase*)

LDL are enriched in cholesterol and cholesteryl esters (contain about 50% of cholesterol)

Protein component - apo B-100

LDL is the major carrier of cholesterol (transport cholesterol to peripheral tissue)
**Function of HDL**

- REVERSE CHOLESTEROL TRANSPORT
- donor of apoproteins to other LPs
- HDL contains a large number of different proteins including apolipoproteins such as:
  - Apo-AI (apolipoprotein A1),
  - Apo-CI,
  - Apo-CII,
  - Apo-D, and
  - Apo-E.
HDL

• Liver and Intestinal cells synthesize HDL & release into blood.
• Nascent HDL are discoid in shape.
• Discoidal HDL contains Free cholesterol, Apo A-1 and LCAT.
• Nascent HDL is going to get cholesterol from peripheral tissues through ABCA-1 receptor, LCAT converts cholesterol into cholesterol esters and forms spherical HDL 3.
• Cholesterol from cell is also transferred to HDL by scavenger receptor-B1 (SR-B1)
HDL

- CETP move some of the CE from HDL to VLDL in exchange for TAG.
- Spherical HDL particles rich in TAG are called as HDL-2.

Two Fates of HDL

1. HDL-2 taken up by the liver by SR-B1 receptor present at the surface of the liver and are acted upon by hepatic lipase and molecule comes out as nascent discoidal HDL.
HDL

2. HDL2 only acted upon by HL loosing only TG part of it and rest of the molecule will come as HDL3.

- The transport of cholesterol from peripheral cells to liver, called as reverse cholesterol transport.
- Serum HDL levels are inversely related to the incidence of atherosclerosis.
- HDL is termed as “good cholesterol”
Figure 25-5. Metabolism of high-density lipoprotein (HDL) in reverse cholesterol transport.
Type I hyperlipoproteinemia = lipoprotein lipase deficiency

Due to deficiency of lipoprotein lipase or apo C-II

-> accumulation of triarylglycerol –rich lipoprotein in plasma

↑ plasma TG even in the fasted state
Familial alpha-Lipo-protein deficiency.

• Apo A-I deficiency:
  • All have low or near absence of HDL
  • Complete deficiency
  • Partial deficiency → fish eye disease
Hypo α-lipoproteinimimia

- Tangier disease
- ABCA-1 deficiency (Pre HDL synthesis hampered)
- HDL deficiency
- Orange tonsils
Abetalipoproteinemia

There’s ↓ apo B-100 synthesis
↓ VLDL → ↓ TG & ↑ TG in liver
↓ LDL → ↓ cholesterol •

Sign and symptoms •
Retina pigmentosa •
Acanthosis •
Spinocerebral Ataxia
Malabsorption •