**Cholesterol and Lipid Transport**

Clinical Case Xanthoma - irregular yellow patch on skin caused by deposition of lipids

8 y.o. girl
- Admitted for heart/lung transplantation

Medical history
- Xanthomas at 2 yo
- MI symptoms at 7 yo
  - TC=1240mg/dl (normal less than 100)
  - TG=350mg/dl (normal less than 150, High – 200)
  - Diet & statin & cholestyramine
  - Mother TC= 355, father TC=310
  - Coronary artery bypass at 7 yo
  - 8 yo severe angina, second bypass
  - TC = 1000mg/dl

Transplantation successful
- TC=260mg/dl, xanthomas regressing

Bile salts: amphipathic detergent compounds derived from cholesterol
- cholic, deoxycholic, chenodioxochnolic and lithocholic acids
- May conjugate with glycine or taurine

Synthesized in liver and secreted to the gallbladder for release into the small intestine
- Digest dietary fat, solubilizing and forming micelles into colloidal chyme

Involved in elimination of cholesterol with waste and micelles support lipase digestion of lipids and fats

**Greasy Spoon Digestion and transport**

Initial absorption of dietary fats
Digestion occurs at lipid water interface in intestine
- Transport & solubility in intestinal cells increased by Fatty acid-binding protein Lipid solubility aided by micelles composed of bile salts - cholesterol esters
- Pancreatic lipase hydrolyzes TAG into DAG then MAG
- PLA$_2$ - digests phospholipids to lysophospholipids and FFAs
Transport INSIDE the intestinal cell

Intestinal Fatty acid binding protein “carries” the non-polar fatty acid through the polar cytoplasmic environment

Trapped between beta pleated sheets, I-FABP protects the cell from the high concentration of fatty acids (detergent/micelle)

**Apoproteins**
- Mostly helical proteins loosely associated with lipoprotein.
- Most (not ApoB100) are water soluble
- Can transfer from one lipoprotein to another by contact or other mechanism
- Each apoprotein has a purpose – often for receptor docking or activation of another protein / enzyme regulation

**Apoprotein A1**
Found associated with chylomicrons and HDL

Facing the end of a helix shows the arrangement of the polar and non-polar side chains – indicating the helix associates with the apoprotein (floating on lipid pond)

| TABLE 20-1 Characteristics of the Major Classes of Lipoproteins in Human Plasma |
|---------------------------------|-----------------|---------------|---------------|---------------|-----------------|
|                                 | Chylomicrons    | VLDL          | IDL           | LDL           | HDL             |
| Density (g · cm⁻³)              | <0.95           | <1.006        | 1.006–1.019   | 1.019–1.063   | 1.063–1.210     |
| Particle diameter (Å)           | 750–12,000      | 300–800       | 250–350       | 180–250       | 50–120          |
| Particle mass (kD)              | 400,000         | 10,000–80,000 | 5000–10,000   | 2300          | 175–360         |
| % Protein                       | 1.5–2.5         | 5–10          | 15–20         | 20–25         | 40–55           |
| % Phospholipids                 | 7–9             | 15–20         | 22            | 15–20         | 20–35           |
| % Free cholesterol              | 1–3             | 5–10          | 8             | 7–10          | 3–4             |
| % Triacylglycerols              | 84–89           | 50–65         | 22            | 7–10          | 3–5             |
| % Cholesteryl esters            | 3–5             | 10–15         | 30            | 35–40         | 12              |
| Major apolipoproteins           | A-I, A-II, B-48, C-I, C-II, C-III, E | B-100, C-I, C-II, C-III, E | B-100, C-I, C-II, C-III, E | B-100 | A-I, A-II, C-I, C-II, C-III, D, E |

*Surface components.
*Core lipids.

Transported in bodily fluids as lipoprotein vesicles (chylomicrons, HDL, LDL, VLDL)
Separated by centrifugation
Density determined by total lipid content (low density) and protein content (high density)
Greasy Spoon Digestion and Transport

**Chylomicrons** (98-99% lipid 1-2% protein)
- transport of dietary lipids into circulation
- mostly TAGs some phospholipid and cholesterol esters
- Initially synthesized in intestine, 1/2 in rats min, in humans 30 mins
- transport FA from lymphatic system to blood stream
- Deliver to peripheral *extrahepatic* tissue (heart and skeletal muscle and adipose)
- transfer of TAGs catalyzed by lipoprotein lipase -> MAG and FFAs (not active in adult liver)
- lipoprotein lipase requires apoprotein C-II for activity
- remnants taken up by liver (high in dietary cholesterol. This requires *apoprotein E* gets it from HDL

**Cooperation of apo proteins and lipase**

Note role of both proteins in activating release of FFA from Chylomicron
Phospholipids and ApoCII are required for LPL activation

Uncontrolled Type 1 Diabetes (IDDM) often have very high fats (FF & apoproteins) in part due to decreased LPL activity.
- LPL is activated by insulin signaling.
- Insulin increases TAG production in liver and transport to adipose and inhibits adipose release of TAGs (later)

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**Exogenous pathway**

- Dietary fat
- Bile acids and cholesterol
- Intestine
- Chylomicrons
- Remnants
- Capillaries
- Lipoprotein lipase
- Free fatty acids
- Adipose tissue, muscle

**Endogenous pathway**

- LDL
- Extrahepatic tissue
- HDL
- LDL receptors
- Capillaries
- Lipoprotein lipase
- Free fatty acids
- Adipose tissue, muscle

- Dietary cholesterol
- Endogenous cholesterol
- Liver
- VLDL
- IDL
- LDL
**VLDL** (very low density lipoprotein)
- Serves similar role to chylomicrons except transports lipids from liver to extrahepatic tissue
- 90-93% lipid, 7-10% protein
- ~ 50% lipid are TAGs, 20% P lipids, 21% cholesterol, and it's esters
- apoprotein C and E
- As TAGs decrease cholesterol is enriched (formation of IDL ~ VLDL remnants)
- some IDL (with apoE) is taken up by liver by LDL receptors (apo B-100 and apoE)
- some IDL converted to LDL (no apoE)

**LDL** (low density lipoprotein) THE BAD CHOLESTEROL
- 70% lipid, 21% protein
- 13% TAG, 28% P lipids, 58% cholesterol esters, and free cholesterol
- Serves as source of cholesterol for tissue
- 45% of plasma pool is degraded by liver and extrahepatic tissue each day
- Apo B-100 binds to LDL receptor - receptor level is regulated by cholesterol levels (more later)

**HDL** (high density lipoprotein) THE GOOD CHOLESTEROL
- 76% lipid, 33% protein
- 16% TAG, 43% P lipids, 41% cholesterol esters, and free cholesterol
- Serves to remove cholesterol and it's esters from tissue to liver where cholesterol can then be lost as bile
- nascent HDL is devoid of cholesterol esters - picks up from tissue by LCAT (lecithin:cholesterol acyl transferase) - transfers FA from phosphatidyl choline onto unesterified cholesterol.
- LCAT activated by apoA
- cholesterol esters then transferred to VLDL and LDL
- High HDL levels are inversely proportional to coronary atherosclerosis

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**Apolipoprotein AI (Apo-AI)**
- Found in HDL and Chylomicrons.
- 70% of the protein moiety in HDL.
- 245 amino acids with molecular weight 28.3 kDa.
- Apo-AI shows a high content of α-helix structure.
- The amphipathic regions in the α-helix structure seem to be responsible for lipid binding capacity.
- Apo-AI activates lecithin-cholesterol (LCAT) acyltransferase, which is responsible for cholesterol esterification in plasma.
- Apo-AI levels may be inversely related to the risk of coronary disease.
Apolipoprotein B (Apo-B)

- Two major forms: B-100 found in LDL, VLDL and IDL, B48 found in Chylomicrons and chylomicron remnants.

Apo-B levels correlate with the risk of coronary disease.

- Apo-B100 is the major physiological ligand for the LDL receptor. Apo-B100 is a large monomeric protein, (MW 515,000).
- Apo-B100 is synthesized in the liver and is required for the assembly of VLDL. It does not interchange between lipoprotein particles, as do the other apolipoproteins, and it is found in IDL and LDL after the removal of the Apo-A, E and C.
- Apo-B48 is essential for the intestinal absorption of dietary lipids. Apo-B48 is synthesized in the small intestine. It comprises approximately half of the N-terminal region of Apo-B100 and is the result of posttranscriptional mRNA editing by a stop codon in the intestine not found in the liver.

Apolipoprotein CI (Apo-CI)

- Found in VLDL, HDL and Chylomicrons. Apo-CI has been found to activate LCAT.
- LCAT functions to esterify cholesterol and is important in the generation of LDL from VLDL.

Apolipoprotein CII (Apo-CII)

- Found in VLCL, HDL and Chylomicrons. Apo-CII activates lipoprotein lipase.
- Lipase hydrolyzes fatty acids from triacylglycerols in chylomicrons.

Apolipoprotein D (Apo-D)

- Apo-D is a 29-kDa glycoprotein primarily associated with HDL.
- Apo-D has been found to bind cholesterol, progesterone, pregnenolone, bilirubin and arachidonic acid. However it has not been confirmed which of these may be natural ligands.
- Accumulation of Apo-D may be associated with increased risk of breast cancer and Alzheimer’s disease.

Apolipoprotein E (Apo-E)

- Found in all but LDL.
- Apo-E is a 34-37 kDa glycosylated protein.
- Apo-E is involved with triglyceride, phospholipid, cholesteryl ester, and cholesterol transport in and out of cells and is a ligand for LDL receptors.
- Apo-E has also been implicated in immune and nerve degeneration.
  - It has been found to suppress lymphocyte proliferation. Late-onset familial and sporadic Alzheimer disease patients have been found to have a higher occurrence of one of the three common Apo-E isoforms, Apo-E4.
  - The Apo-E4 isoform has been detected in senile plaques and neurofibrillary tangles of Alzheimer disease patients. Apo-E4 is associated with rapid chylomicron-remnant clearance and increased total cholesterol levels.
**Release the Grease**

**Hormone sensitive Lipase (HLS)**

Lipolysis - fatty acid (TAG) release from adipose storage

• Activation of PKA leads to release of TAGs via activation of HLS

Perilipin A coats lipid droplets and blocks lipase activity from fats. PKA phosphorylated Perilipin A allows access of lipase to fats in droplets.

• PKA phosphorylates hormone sensitive lipase (active when phosphorylated)

HLS activation – glucagon, adrenal corticoid hormones (corticotropin) dopamine, norepinephrine

Insulin inhibits fatty acid release by reducing cAMP levels - insulin deficiency causes increased FFA liberation and under utilization of chylomicrons and VLDL (this results in hyperlipoproteinemia)

**Release the Grease**

Once the first FA is liberated two additional unregulated lipases quickly act

- 1) diacyl glycerol lipase and 2) monoacyl glycerol lipase

• end up with 3 FA and 1 glycerol (can enter carbo metabolism via dihydroxyacetone phosphate)

• free (unesterified) fatty acids move through blood to site of metabolism by protein carriers including albumin

**Resolution of Clinical Case**

Familial hypercholesterolemia (FH)

- Family history
- Early xanthomas and very high TC
- Absence of LDL-receptors
  • Homozygous FH

Parent TC consistent with heterozygous FH

- 1/500 Americans with heterozygous FH, treatable with diet/drugs
- 1/10^5 with homozygous FH

Diet and drugs relatively ineffective

Liver has ~70% of LDL-receptors

- Combined liver/heart recommended because of advance CHD