Biochemistry Teamwork
Lipoprotein Metabolism

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Lipoprotein Metabolism

Lipid compounds: **Relatively water insoluble, they are transported in plasma (aqueous) as Lipoproteins**

Clinical Problems Related to Lipoproteins

- **Atherosclerosis and hypertension**
- **Coronary heart diseases**
- **Lipoproteinemias (hypo- and hyper-)**
- **Fatty liver**

Lipoprotein Structure

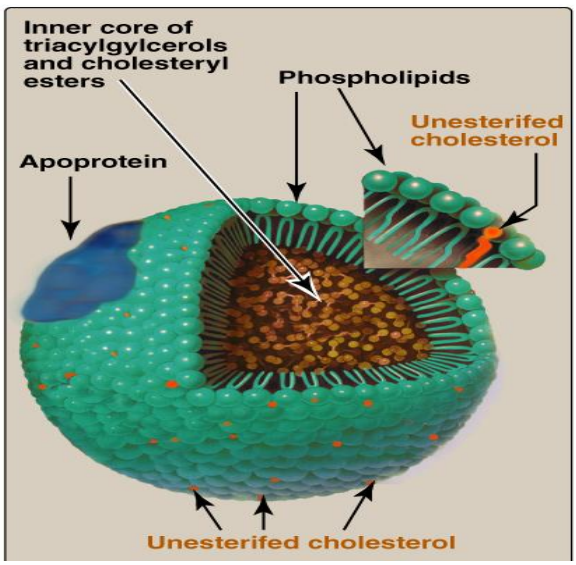
Protein part: **Apoproteins or apolipoproteins**
Abbreviations: Apo-A, B, C, D, E
Functions: Structural and transport function
Enzymatic function
Ligands for receptors

Lipid part:
According to the type of lipoproteins
Different lipid components in various combinations

Enzymatic function: They are not enzyme but act as a cofactor, for example, ApoC II cofactor for lipoprotein lipase.

Ligands for receptors : so, the receptor will identify Apoprotein.
For example,
-Apo B-100 is a ligand for LDL Receptor
-Apo A is ligand for HDL receptor
-Apo E ligand for IDL receptor
Lipid part is "variable"

Spherical molecules of lipids and proteins (apoproteins)



Outer coat: Hydrophillic
Apoproteins, Phospholipid Heads, Free (unestrified) Cholesterol

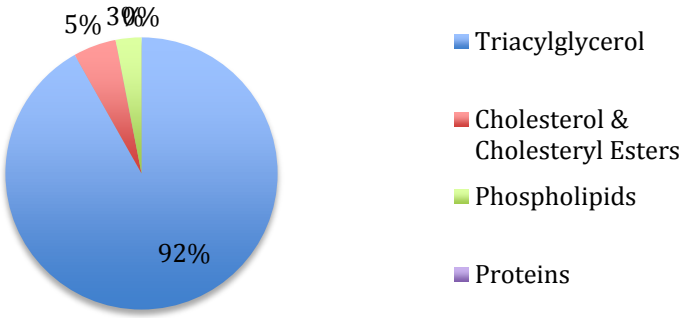
Inner core: Hydrophobic
TG, Cholesterol ester

Lipoproteins differ in size, density & electrophoretic mobility according to their composition.

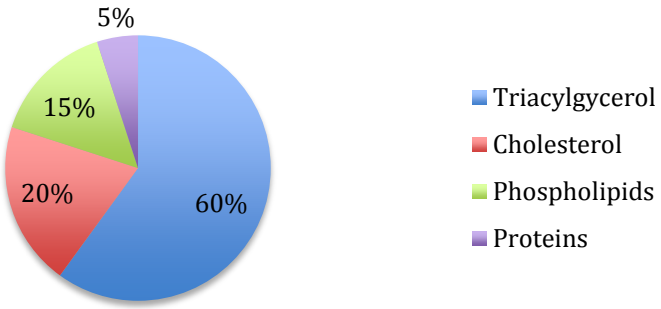
Lipids are low in density but big in size
Proteins have high density but small size

Types and Composition of Lipoproteins

Chylomicrons

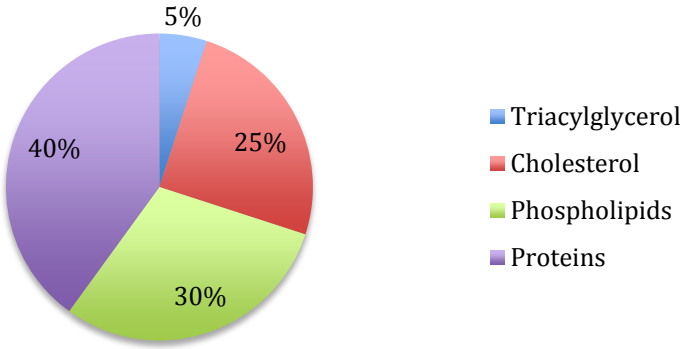


Very low density Lipoprotein (VLDL)



Low density Lipoprotein (LDL)

High density Lipoprotein (HDL)

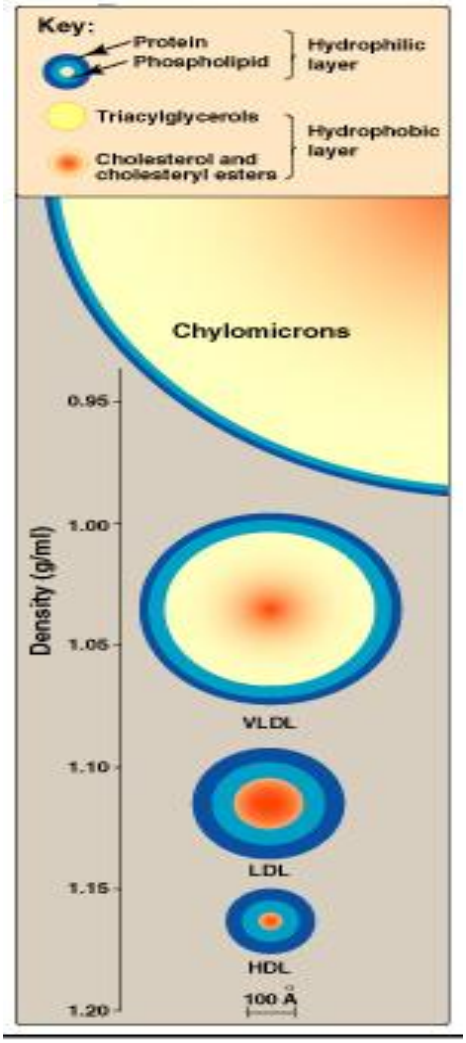


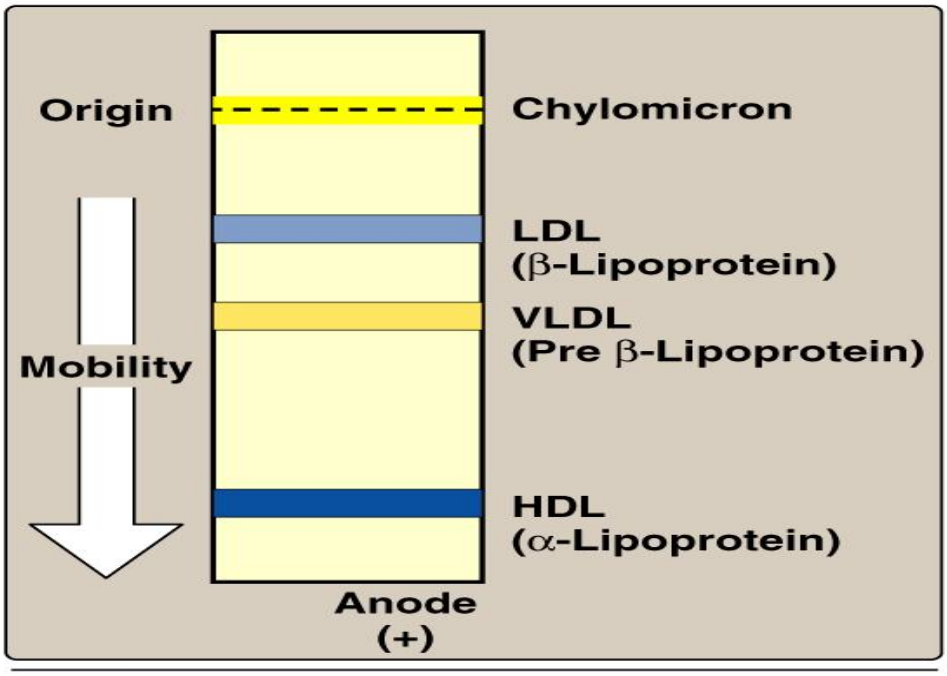
- Chylomicrons + VLDL are MAINLY composed of triacylglycerol. VLVD in endogenous but Chylomicrons are ingested. TG cannot be transported in the body on it's own.
- Chylomicrons has the lowest density but biggest size.
- LDL + HDL → Rich of cholesterol. LDL mainly has free cholesterol. HDL manily has esterified cholesterol.

Note:

Lipid → if it's high, low density
Protein → if it's high, high density

Ultracentrifugation & Electrophoresis of Lipoproteins





'phoresis' meaning migration/movement in gel media
Mainly depends on size with some exceptions*

Chylomicron → very big to the extent it does not move
*LDL & VLDL → VLDL is more mobile although LDL is smaller in size. Why? VLDL is more negative in charge so is attracted more to the +ve anode
HDL → fast molecule

Plasma Lipoproteins

For triacylglycerol transport (TG-rich):

Chylomicrons: TG of dietary origin (exogenous)
VLDL: TG of endogenous (hepatic) synthesis

*Chylomicron and VLVD are used to measure TG in the blood since TG cannot be transporter on it's own.

For cholesterol transport (cholesterol-rich):

LDL: Mainly free cholesterol
HDL: Mainly esterified cholesterol

Chylomicrons

- Assembled in intestinal mucosal cells after ingestion (dietary origin)
- Lowest density, largest size
- Highest % of lipids and lowest % proteins
- Highest triacylglycerol (dietary origin)
- Carry dietary lipids to peripheral tissues
- Responsible for physiological milky appearance of plasma (up to 2 hours after meal) which may be confused for hypercholestermia [for a lipid profile to be reliable, patient must be fasting for 12 hours]

Very Low Density Lipoproteins

- Assembled in liver (endogenous origin)
- High triacylglycerol (hepatic origin)
- Carry lipids from liver to peripheral tissues
- Nascent VLDL (newly fromed): contains Apo B-100
- Mature VLDL: Apo B-100 PLUS Apo C-II and Apo E (which is gained from contact with HDL on it's way to the tissue)

Metabolism of VLDLs

VLDLs are assembled then secreted by the liver in it's nascent form (Apo B100 only)
They circulate in the blood gaining Apo CII and E from circulating HDL.
After VLDLs are mature, they contain Apo B100 in addition to Apo CII and E, and are ready for modification.
The enzyme in charge of the degradation of TG into glycerol and fatty acids is LIPOPROTEIN LIPASE and requires Apo CII for activation.

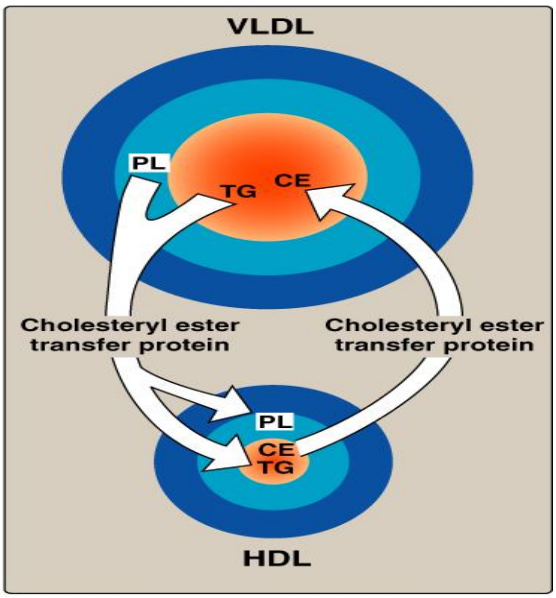
An extracellular enzyme, anchored by heparan sulfate to the capillary walls of most tissues.
Predominantly present in adipose tissue, cardiac & skeletal muscle
The fatty acid produced is used up by the cell for energy or storage
Regulation: by insulin → stimulates its synthesis and transfer to the luminal surface of the capillary
Defect in lipoprotein lipase or in Apo CII will result in type I hyperlipoproteinemia (familial lipoprotein lipase deficiency)

Modification of circulating VLDLs:

- VLDL attaches to lipoprotein lipase on the capillary wall, which hydrolyzes TG and resulting in a smaller but more dense IDL [intermediate]
- IDL comes in contact with circulating HDL returning the Apo CII and E and becoming LDL
- Some TG are transferred from VLDL to HDL in exchange for cholesterol ester by cholesterol ester transfer protein
- The Apo B100 remaining on the LDL is recognized by LDL receptors in the liver and other peripheral tissue and is engulfed

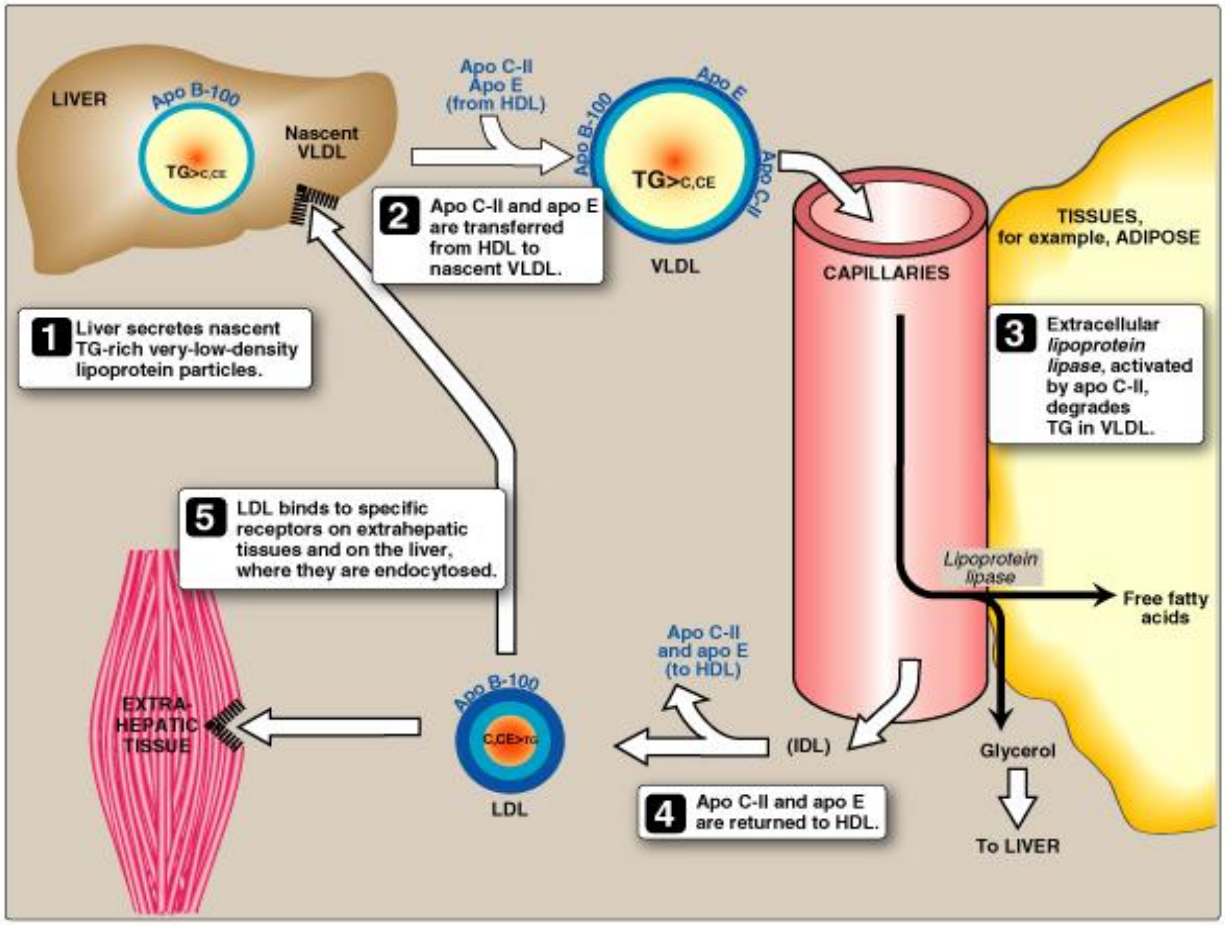
Lipid-Transfer Protein

Cholesteryl ester transfer protein → it's Apo D



Summary of VLDL Metabolism

degradation by lipoprotein lipase → breakdown of TG into fatty acid and glycerol →LDL assembled in circulation



VLDLs-Related Diseases

Hypolipoproteinemia

Abetalipoproteinemia

Defect in TG-transfer protein, which is required for the assembly of the TG into apoprotiens
Apo B-100 cannot be loaded with lipid
Accumulation of TG in liver
Inability to produce nascent VLDL

Fatty Liver (hepatic steatosis)

Imbalance between hepatic synthesis of TG and secretion of VLDLs.
Accumulation of TG in liver

> Abetalipoproteinemia → congenital
>
> Fatty liver → could be acquired
>
> Abetalipoproteinemia could cause fatty liver or not

Hyperlipoproteinemia

Type I Hyperlipoproteinemia

Familial Lipoprotein lipase deficiency
Due to deficiency of lipoprotein lipase or its cofactor (Apo C-II)
> reminder: TG load is broken down in the circulation by this enzyme
Shows a dramatic accumulation (≥1000 mg/dl) of chylomicrons in the plasma
Usually associated with acute abdominal pain due to acute pancreatitis
↑ plasma TG, showing pathological creamy blood, even in the fasted state

Type III Hyperlipoproteinemia

Familial dysbetalipoproteinemia
Due to Apo E deficiency
Associated with hypercholesterolemia & premature atherosclerosis

*This is not present in the presentation but the male doctor mentioned it

Chylomicron Clinically

If blood was taken from someone two hours after he/she had a meal. The blood then was left for some time to separate it's component. In that condition the serum would usually look milky (yellow white and turbid*). This is caused by the high amount of chylomicron in the blood that was absorbed by the intestinal mucosa. The milky appearance would usually not appear if blood was taken few hours later in healthy individuals.

However, if the milky appearance persist for more than two hours, it is usually a pathological condition. The pathology in that case is type 1 hyperlipoproteinemia or familial lipoprotein lipase deficiency, due to lipoprotein lipase or apo C2 deficiency. This pathology is manifested by the dramatic accumulation of chylomicrons in the plasma.

*This appearance of turbidity is caused by the large chylomicron molecules (chilomycron has the largest size).

Questions

Which of the following lipoproteins has the largest size?

a.chylomicrons
b.VLDL
c.LDL
d.HDL

which of the following is a function of VLDL?

a. carry dietary lipids to peripheral tissue
b. carry lipids to the liver
c. carry lipids from the liver to peripheral tissue
d. cause hyperlipoproteinemia

A patient with a family history of hypercholestrolemia and premature atherosclerosis most likely has:

a. type III hyperlipoproteinemia
b. type I hyperlipoproteinemia
c. fatty liver
d. heart failure

which of the following is required for lipoprotein lipase activation?

a. Apo B-100
b. Apo CII
c. Apo E
d. Heparin sulfate

Ans: a,c,a,b