جامعة الملك سعود
King Saud University

Biochemistry437

Lipoprotein Metabolism

Biochemistry Team 437

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Cardiovascular block

EDITING FILE

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Objectives :

- Define and list the types, structure and composition of lipoproteins.
- Understand various functions of lipoprotein particles.
- Compare the functions of lipoprotein particles and their implications in disease.
- Understand the metabolism of chylomicrons, VLDL and LDL particles.
- Discuss the functions The of lipoprotein lipase and its role in disease.
- List the diseases due to imbalance in the metabolism of lipoproteins.

Overview :

- Lipoprotein types and composition
- Apolipoproteins
- Chylomicrons
- VLDL particles and their metabolism
- Lipoprotein lipase
- VLDL diseases

Lipoproteins

- Lipids are hydrophobic molecules (They are afraid of water).
- They are transported in the plasma as lipoprotein structures.
- Lipoproteins are spherical (كروي) macromolecular complexes[1] of :
  - Lipids[2]
  - Specific protein (Apolipoproteins)
- Lipoproteins keep lipid contents soluble while transporting them to and from the tissues.

[1]Big molecules that contain more than 1 type of compounds,in this case Lipids + Proteins.
[2]Lipid molecule present in a lipoprotein complex:
1- triglyceride (Triacylglycerol)
2- cholesterol
3- cholesteryl esters
4- phospholipids (Most important)

Remember!

- Lipoproteins is a complex of lipid+proteins.
- Function: since lipids are hydrophobic molecules, they need lipoproteins to transport them in plasma.
- Lipoproteins can solubilize lipids and carry them in their core, while at the same time they can interact with water to transport those lipids.
- Lipoproteins have a hydrophobic core to carry the lipids, and a hydrophilic shell to interact with water.

Types of lipoproteins :

- Chylomicrons (lowest density, largest)
- Very low density lipoproteins (VLDL)
- Low density lipoproteins (LDL)
- High density lipoproteins (HDL)

Lipoproteins differ in :

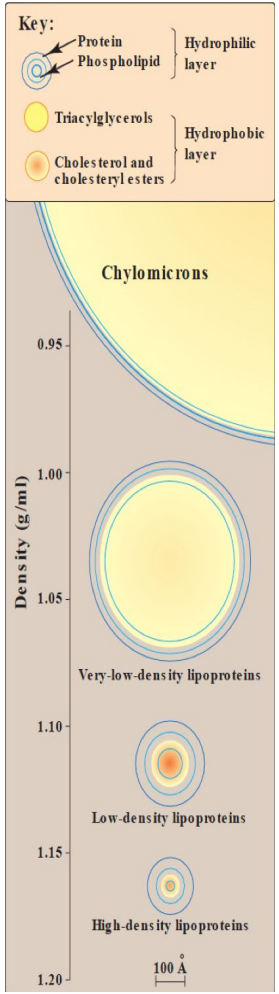
To measure the total cholesterol in the body we measure HDL, LDL and calculate VLDL.

- Density (means weight)
- Size (The most density molecule is the smallest in size)
- Site of origin
- Composition of lipids and proteins

Q : Why when we mix water with oil , oil goes up to the surface ?
Answer : Thats because oil (which is a lipid) has a low density .. therefore if the molecule is more rich in Lipids (e.g : TAG) it will have LOWER DENSITY and LARGER SIZE.

Density:

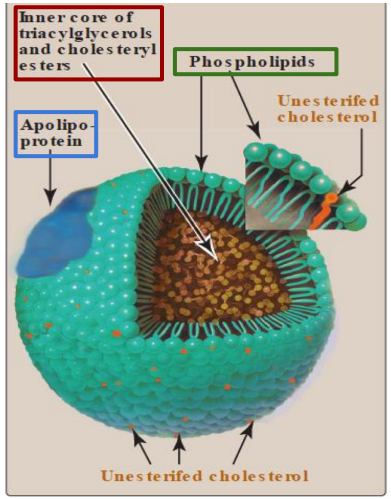
- The density of lipoprotein doesn't depend on the size, it depends on the concentration of lipid and protein.
- Chylomicron (Lowest density lipoprotein) has more fats than protein , while HDL(High density lipoprotein) has more proteins than fats.
- Low density molecules like fat, float on water.
- The more proteins the more density.
- The more fat the lesser density.



Composition of lipoproteins

Lipoproteins are composed of:

1. Neutral lipid core :
   - Triacylglycerides (TAG)
   - Cholesteryl esters
2. Outer Hydrophilic shell :
   - Amphipathic apolipoproteins
   - Phospholipids "One layer"
   - Free (unesterified) cholesterol



Triacylglycerides (TAG) are mainly transported by :

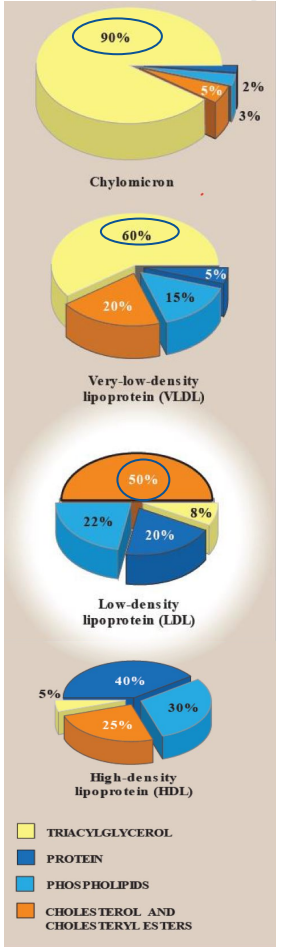
- Chylomicrons Transport exogenous fats
- VLDL Transport endogenous fats

Cholesterol is mainly transported by :

- LDL Transport endogenous fats (mainly cholesterol)
- HDL

- Every lipoprotein differs in its composition
- Chylomicrons are very rich with TAG (90%)
- VLDL are (60%) TAGs
- LDL are (50%) cholesterol
- HDL are (40%) proteins and (30%) phospholipids. The abundance of phospholipids in HDL is important to solubilize and carry lipids

*المطلوب معرفة العنصر الأكثر وفرة في المركب فقط



Apolipoproteins

Types:

- Apo B-48[1], B-100[2] (Produced from the product of the same gene)
- Apo C-I, C-II, C-III
- Apo E

[1]Apo B48 specific in Chylomicron.

[2]Apo B100 present in LDL.

Functions:

- Provide structure to lipoprotein particles (Stability).
- Provide recognition sites for cell-surface receptors (they bind to the cell receptor in the tissue).
- Activators or coenzymes for the enzymes involved in lipoprotein metabolism (Like Lipoprotein lipase).

Some apolipoproteins are fixed for particular lipoproteins, e.g. B-48, while others are not specific e.g. Apo E because it can transfer into other lipoprotein, so we can say There is not a fixed structure or composition for lipoproteins in general.

Chylomicrons

- Assembled in the intestinal mucosal cells
  site of origin: intestine, because they carry dietary lipids
- Transport to peripheral tissue:
  - Dietary TAGs (90%) (Exogenous)
  - Cholesterol
  - Fat-soluble vitamins
  - Cholesteryl esters
- The milky appearance of plasma after a meal is due to chylomicrons
  (After 6 hours it will disappear)

Plasma after meal (Milky appearance) due to presence of fat

Plasma at fasting

VLDL

- Produced and secreted by the liver “site of origin”
  Composed of:
  - Mainly endogenous TAGs (60%)
  - Some cholesterol (free and esterified)
- Carry these lipids from the liver to peripheral tissues.
- Peripheral tissues degrade TAGs by lipoprotein lipase (LPL)* enzyme.
- Imbalance in hepatic TAG synthesis and secretion of VLDL which occurs in case of obesity and Type 2 diabetes mellitus , can cause NASH “nonalcoholic steatohepatitis”.

*When TAGs are transported to tissues by chylomicrons or VLDL, the tissues cannot use it unless it was broken down to fatty acids. So the tissues have an enzyme called lipoprotein lipase on their surface “extracellular enzyme” that can metabolize TAGs - with the help of heparan sulfate- into fatty acids, and glycerol.
The fatty acids are then used by different tissues and the glycerol is transported to the liver for gluconeogenesis.

You can read the steps to give you a good understanding of the whole process, when memorizing, focus the most on what is written in slides and the picture.

VLDL metabolism

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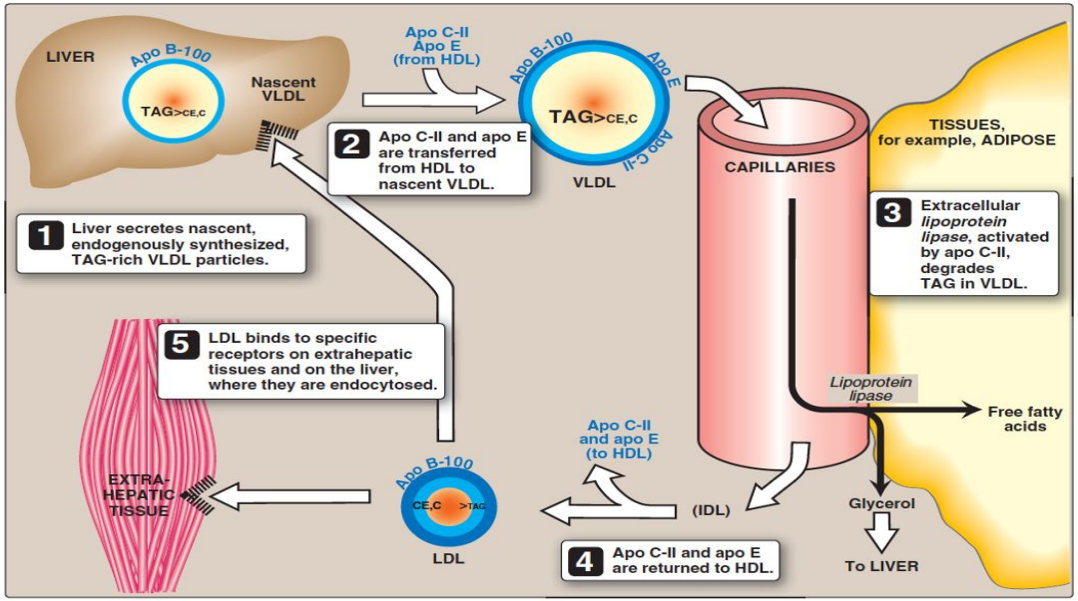
Steps:

- Nascent [immature] VLDL is produced in the liver. It has Apo B-100 and carries TAG in its core.
- VLDL is secreted out of the liver.
- Secreted VLDL receives 2 apolipoproteins, Apo C-II and Apo E from and HDL molecule, becoming a mature VLDL [now it carries Apo B-100, apo c-II and apo E].
- Mature VLDL goes to the tissue.
- Apo C-II activates lipoprotein lipase enzyme that is present on the surface of the tissue, which in turn degrades the TAGs inside the VLDL.
- The VLDL has lost its TAGs and is now called a remnant VLDL. [but it still has all of the apolipoproteins]
- Apo c-II is returned to HDl, the remaining molecule is called IDL “intermediate density”
- Apo E is returned to HDL from IDL, the remaining molecule is called LDL.
- VLDL also transfers TAGs to HDL in exchange for cholesteryl ester “this modification is explained next slide”.
- LDL now carries apo b-100 only.
- Liver and extrahepatic tissues have receptors for Apo b-100 to facilitate endocytosis.



Chylomicrons have almost the same steps, but instead of b-100 we have b-48
And it is synthesised in the intestine instead of the liver.

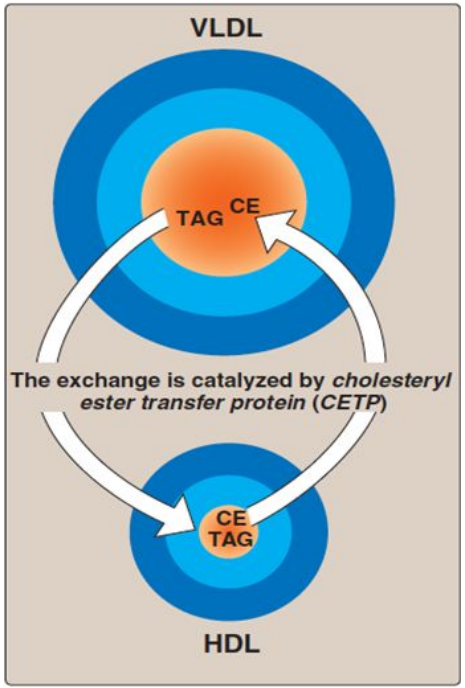
VLDL metabolism:

1.Release from the liver:

- They are secreted into the blood by the liver As nascent particles containing:
  - TAGs and cholesterol
  - Apo B-100
- TObtain apo C-II and apo E from circulating HDL particles
- (mature VLDL) .
- Apo C-II is required for activation of LPL .

2. Modification in the circulation:

- TAGs in VLDL are degraded by lipoprotein lipase (LPL)
- VLDL becomes smaller and denser
- Surface components (apo C and E) are returned to HDL
- VLDL transfers TAGs to HDL in exchange for cholesteryl esters
- This exchange is catalyzed by cholesteryl ester transfer protein (CETP)



VLDL Metabolism

3. Conversion to LDL

- After modifications, VLDL is converted to:
  - LDL
  - IDL (taken up by liver cells thru apo E)
  - VLDL remnants
- **Apo E exists in three isoforms:**
  - Apo E-2 (Poorly binds to receptors)
  - Apo E-3
  - Apo E-4

Site of origin:
- VLDL: liver
- LDL: blood

Liver receptors:
- Chylomicrons: B-48
- IDL: Apo E
- LDL: B-100

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Summary:

1. Release of VLDL:

VLDL are secreted directly into the blood by the liver as nascent VLDL particles containing apo B-100. They must obtain apo C-II and apo E from circulating HDL . As with chylomicrons, apo C-II is required for activation of lipoprotein lipase.

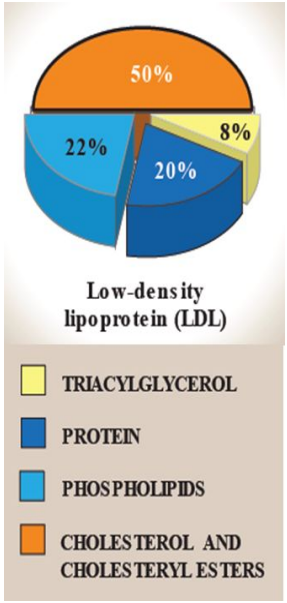
2. Modification of circulating VLDL:

As VLDL pass through the circulation, triacylglycerol is degraded by lipoprotein lipase, causing the VLDL to decrease in size and become denser. Surface components, including the C and E apoproteins, are returned to HDL, but the particles retain apo B-100. Finally, some triacylglycerols are transferred from VLDL to HDL in an exchange reaction that concomitantly transfers some cholesteryl esters from HDL to VLDL. This exchange is accomplished by cholesteryl ester transfer protein .

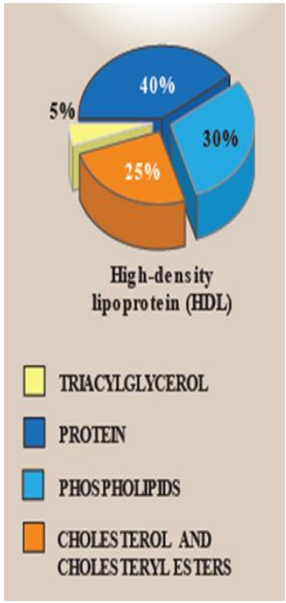
3. Production of LDL from VLDL in the plasma:

With these modifications, the VLDL is converted in the plasma to LDL. Intermediate- sized particles, the intermediate-density lipoproteins (IDL) or VLDL remnants, are observed during this transition. IDLs can also be taken up by cells through receptor-mediated endocytosis that uses apo E as the ligand.

Low density lipoprotein (LDL) Vs High density lipoprotein (HDL)



	Low Density Lipoprotein*	High Density Lipoprotein
Mainly contains	Cholesterol & Cholesteryl esters	Protein, phospholipids, cholesterol, cholesteryl esters
Production	Produced from VLDL particles	Produced in the liver and intestine (Site of origin)
Contains	Contains Apo B-100 lipoprotein	Contains Apo A-1, C-2 and E lipoproteins
Function	- Provides cholesterol to peripheral tissue (From liver (VLDL)) - LDL binds to cell surface receptors through Apo B-100 (receptor-mediated endocytosis)	Take up cholesterol from peripheral tissues to the liver



* Produced in the blood by VLDL

- HDL is a good Lipoprotein because it takes cholesterol from tissues to the liver (cleans your arteries from cholesterol) (good guy).
- LDL is a bad cholesterol because it takes cholesterol from liver to the tissues it may be deposited and cause atherosclerosis. (BAD GUY).

Lipoprotein lipase (LPL)

- Extracellular enzyme that degrades lipids.
- Anchored by heparan sulfate to the capillary walls of most tissues.
- Mainly present in adipose tissue, cardiac and skeletal muscle.
- Requires apo C-II[1] for activation.
- Degrades TAGs into free fatty acids and glycerol.
- Insulin[2] stimulates LPL synthesis.
- Deficiency of LPL or apo C-II causes:

  Type 1 hyperlipoproteinemia [3] (familial LPL deficiency)

[1]Remember , it is present on both chylomicrons and VLDL. it also comes from HDL.
[2]Insulin is released when there is ↑ glucose levels
↑ insulin → ↑ LPL synthesis to clear blood stream from lipids.
"There will usually be an increase in both lipids and glucose after a meal, this is why insulin stimulates LPL as well"

[3]"TAGs can't be solubilized and they accumulate"

There will be at least 1 question about the diseases!

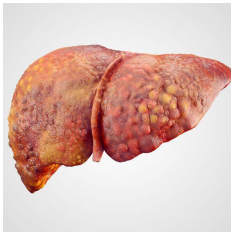
VLDL Diseases

Hypolipoproteinemia
"In plasma"

- Abetalipoproteinemia is due inability to attach the Apo-B to the lipids[1]
- Therefore , FEWER chylomicrons and VLDL are produced (because they dont have the apo-b loaded into them).
- TAG will accumulate in the liver and intestine , because they aren't released into tissues (no chylomicrons or VLDL !).

Steatohepatitis
(Fatty Liver)

- There is imbalance between the TAG synthesis in the liver & TAG secretion (release through VLDL) from the liver.
- This will lead to accumulation of lipids[2](TAG) in the liver → causing fatty liver.



[1]Due to deficiency of microsomal triglyceride transfer protein (MTTP) which help with loading Apo B48 with lipids. ,"extra"
[2]Which cause inflammation in the liver.

VLDL Diseases

Type I Hyperlipoproteinemia

- Rare , Autosomal recessive disease.
- It happens because of a familial (genetic) deficiency of LPL or its coenzyme Apo C-II, which helps it to be activated
- It will cause EXCESSIVE accumulation of chylomicrons in plasma (>1000 mg/dl) → Hyperchylomicronemia.
- High fasting plasma TAG are seen in these patients.

Type III Hyperlipoproteinemia

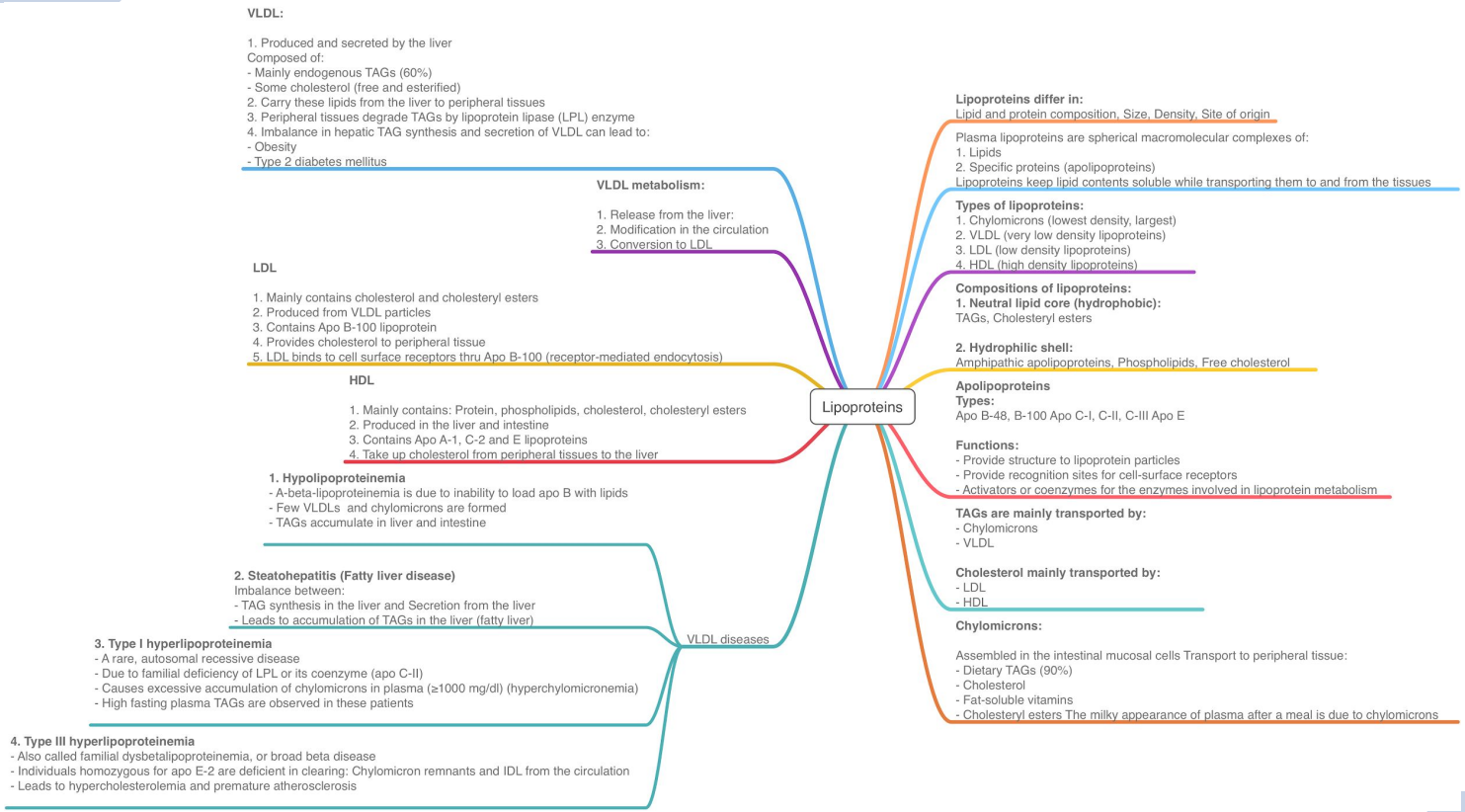
- Familial dysbetalipoproteinemia , or broad beta disease
- Individuals homozygous in Apo E-2*(have low apo E-2) have problems in clearing these from circulation :
  - Chylomicrons remnants
  - IDL
- This will lead to Hypercholesterolemia & premature atherosclerosis

*Apo E2:Required for recognition of IDL and chylomicron remnants.
Apo B100: Required for recognition of LDL.

Take Home Messages

- Lipoproteins are important for transportation of lipids to and from liver and peripheral tissues.
- Different types of lipoproteins perform different functions in the body.
- Imbalance in the metabolism of lipoproteins leads to accumulation of lipids in the tissues and circulation increasing the risk for atherosclerosis and coronary heart disease.

Summary


Lipoproteins
VLDL:
1. Produced and secreted by the liver
Composed of:
- Mainly endogenous TAGs (60%)
- Some cholesterol (free and esterified)
2. Carry these lipids from the liver to peripheral tissues
3. Peripheral tissues degrade TAGs by lipoprotein lipase (LPL) enzyme
4. Imbalance in hepatic TAG synthesis and secretion of VLDL can lead to:
- Obesity
- Type 2 diabetes mellitus
VLDL metabolism:
1. Release from the liver:
2. Modification in the circulation
3. Conversion to LDL
LDL
1. Mainly contains cholesterol and cholesteryl esters
2. Produced from VLDL particles
3. Contains Apo B-100 lipoprotein
4. Provides cholesterol to peripheral tissue
5. LDL binds to cell surface receptors thru Apo B-100 (receptor-mediated endocytosis)
HDL
1. Mainly contains: Protein, phospholipids, cholesterol, cholesteryl esters
2. Produced in the liver and intestine
3. Contains Apo A-1, C-2 and E lipoproteins
4. Take up cholesterol from peripheral tissues to the liver
VLDL diseases
1. Hypolipoproteinemia
- A-beta-lipoproteinemia is due to inability to load apo B with lipids
- Few VLDLs and chylomicrons are formed
- TAGs accumulate in liver and intestine
2. Steatohepatitis (Fatty liver disease)
Imbalance between:
- TAG synthesis in the liver and Secretion from the liver
- Leads to accumulation of TAGs in the liver (fatty liver)
3. Type I hyperlipoproteinemia
- A rare, autosomal recessive disease
- Due to familial deficiency of LPL or its coenzyme (apo C-II)
- Causes excessive accumulation of chylomicrons in plasma (≥1000 mg/dl) (hyperchylomicronemia)
- High fasting plasma TAGs are observed in these patients
4. Type III hyperlipoproteinemia
- Also called familial dysbetalipoproteinemia, or broad beta disease
- Individuals homozygous for apo E-2 are deficient in clearing: Chylomicron remnants and IDL from the circulation
- Leads to hypercholesterolemia and premature atherosclerosis
Lipoproteins differ in:
Lipid and protein composition, Size, Density, Site of origin
Plasma lipoproteins are spherical macromolecular complexes of:
1. Lipids
2. Specific proteins (apolipoproteins)
Lipoproteins keep lipid contents soluble while transporting them to and from the tissues
Types of lipoproteins:
1. Chylomicrons (lowest density, largest)
2. VLDL (very low density lipoproteins)
3. LDL (low density lipoproteins)
4. HDL (high density lipoproteins)
Compositions of lipoproteins:
1. Neutral lipid core (hydrophobic):
TAGs, Cholesteryl esters
2. Hydrophilic shell:
Amphipathic apolipoproteins, Phospholipids, Free cholesterol
Apolipoproteins
Types:
Apo B-48, B-100 Apo C-I, C-II, C-III Apo E
Functions:
- Provide structure to lipoprotein particles
- Provide recognition sites for cell-surface receptors
- Activators or coenzymes for the enzymes involved in lipoprotein metabolism
TAGs are mainly transported by:
- Chylomicrons
- VLDL
Cholesterol mainly transported by:
- LDL
- HDL
Chylomicrons:
Assembled in the intestinal mucosal cells Transport to peripheral tissue:
- Dietary TAGs (90%)
- Cholesterol
- Fat-soluble vitamins
- Cholesteryl esters The milky appearance of plasma after a meal is due to chylomicrons

MCQs:

Q1: which of the following is an incorrect way of differentiating lipoproteins?

A- Size **B-** Density **C-** Site of origin **D-** Shape

Q2: the milky appearance of plasma after a meal is because of?

A- HLDL **B-** Chylomicrons **C-** LDL **D-** Phospholipids

Q3: which of the following is required for activation of LPL in VLDL metabolism?

A- Apo C-II **B-** Apo E **C-** Apo C-III **D-** Apo B-100

Q4: LDL binds to cell surface receptors through which of the following?

A- Apo B-48 **B-** Apo E **C-** Apo B-100 **D-** Apo E 2

MCQs & SAQ:

Q5 which of the following VLDL diseases will cause premature atherosclerosis?

A- familial dysbetalipoproteinemia **B-** Steatohepatitis **C-** Hyperlipoproteinemia **D-** both (A&C)

Q6 which of the following statements is incorrect about HDL ?

A- Produced in the liver and intestine **B-** Contains Apo A-1

C- take up cholesterol from the liver to peripheral tissue **D-** all are incorrect

What is the cause of fatty liver and why is it called that ?

Answers:
1- D
2- B
3- A
4- C
5- A
6- C

Ans; Imbalance between TAG synthesis in the liver and Secretion from the liver
Leads to accumulation of TAGs in the liver (fatty liver)

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Team leaders

- رهام الحلبي
- معاذ الحمود

Boys team

- طارق العميم
- فيصل الطحان
- محمد الصويغ
- انس القحطاني
- صالح الوكيل
- عبد الملك الشرهان
- سعيد القحطاني
- نواف اللويمي
- عبدالرحمن التركي
- عبدالله الحربي

Girls team

- رهف الشنيبر
- شهد الجبرين
- لينا الرحمة
- منيرة المسعد
- ليلى الصّباغ
- العنود المنصور
- أرجوانة العقيل
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