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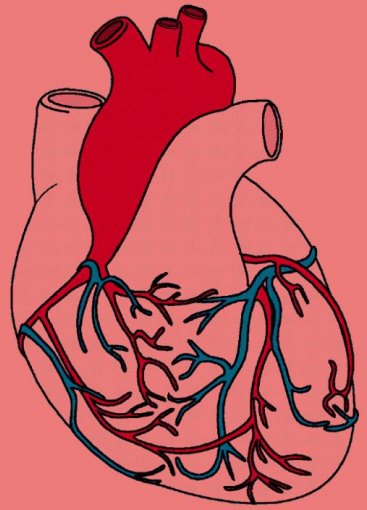
3

Lipoprotein metabolism



Color index :

Main text

IMPORTANT

Extra Info

Drs Notes

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MED439

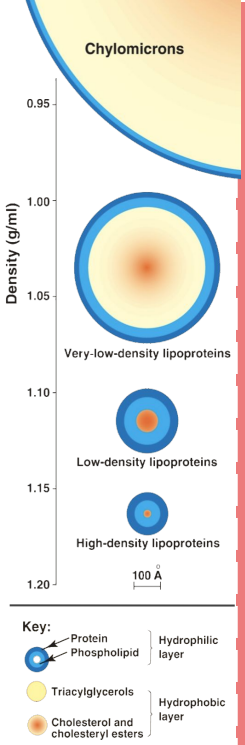
Objectives:

- 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 of lipoprotein lipase and its role in disease
- List the diseases due to imbalance in the metabolism of lipoproteins

A helpful video

Lipoproteins

- Lipids are hydrophobic macromolecule, so they need to be transported in plasma as lipoprotein particles.
  Dr: "We cannot say that lipoproteins carry lipids, because they are structures made up of protein and lipids. And theses proteins are helping in solubilizing these lipids (lipid is a component of their structure not something that's just being carried)"
- Lipoproteins keep lipid contents soluble while transporting them to and from the tissues.
  Small free fatty acids can be carried by albumin but most other types of lipids such as cholesterol, cholesterol esters, TAGs, etc.. are carried "**as**" lipoproteins NOT "**by**" lipoproteins. !!!
- Plasma lipoproteins are spherical in shape, they contain lipid and a special type of proteins (apolipoprotein).
  (Apolipoproteins are amphipathic, because if they were hydrophilic they will run away from lipids)
- Lipoproteins differ in their lipid and protein composition, size, density, and site of origin.
  Keep in mind that proteins are much heavier than lipids. As you see in the figure, HDL is mostly composed of proteins so it's the heaviest / smallest one. In contrast, chylomicrons are mostly composed of lipids so it's the lightest / largest.



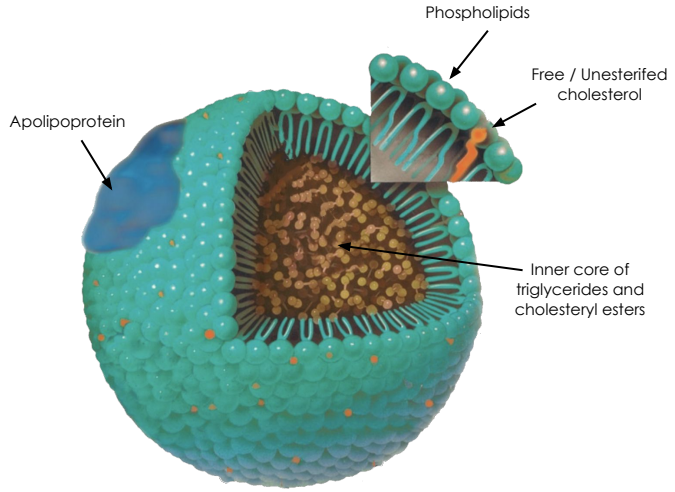
Types of lipoprotein

- **Chylomicrons** — Lowest density, Largest. (Lightest but largest in size)
- **VLDL** — Very low density lipoproteins .
- **LDL** — Low density lipoproteins.
- **HDL** — High density lipoproteins. (Heaviest but smallest in size)

Composition of Lipoprotein

Lipoprotein is made of :

1. **Hydrophobic core:** (Natural lipid)
   - Triacylglycerols (TAGs)
   - Cholesteryl esters
2. **Hydrophilic shell:**
   - Amphipathic apolipoproteins
   - Phospholipids (Polar head to the outside, nonpolar tails to the inside)
   - Free cholesterol (it's important for membrane stability)



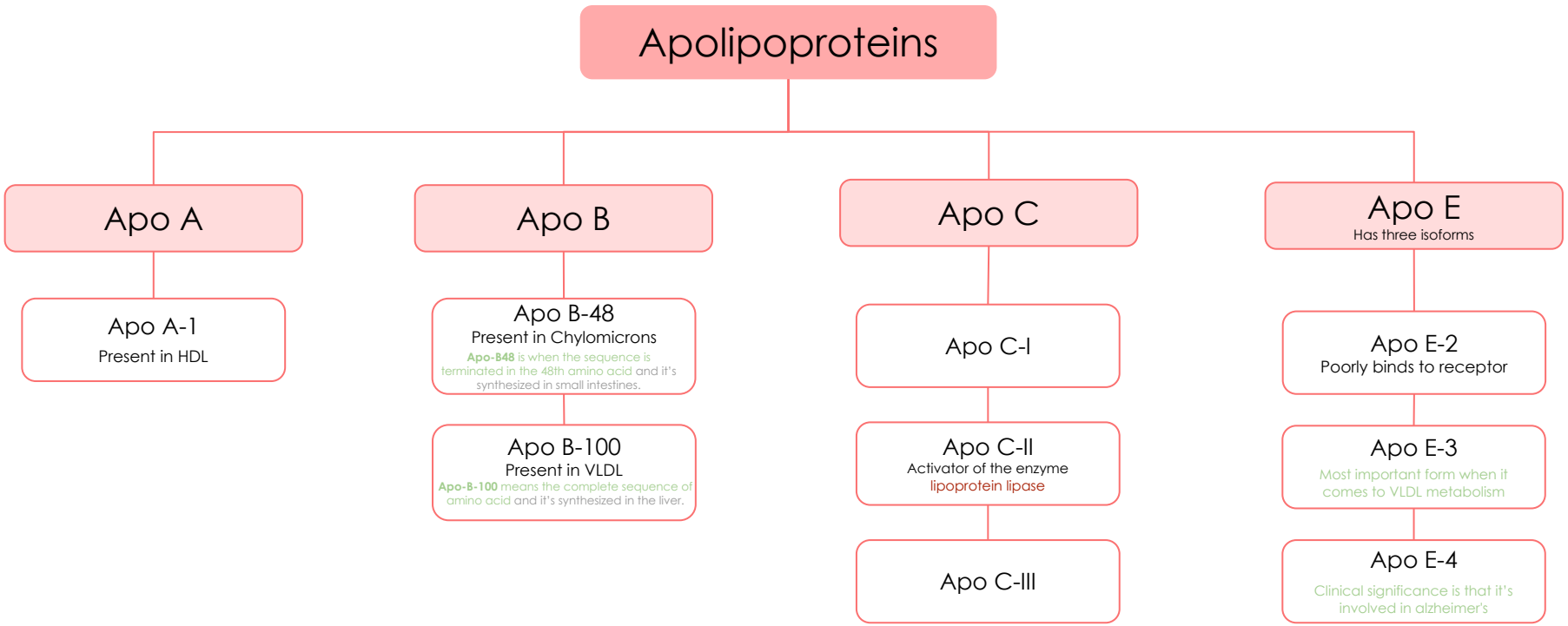
Structure of a typical lipoprotein particle.

TAGs and cholesterols are carried as lipoprotein, but in what form are they carried?

The basic difference between Chylomicrons and VLDL is:
Chylomicrons are transporting Dietary TAGs.
VLDLs are transporting endogenous TAGs (that is made by liver).

Triglycerides are mainly transported as
- Chylomicrons — TAGs = 90% of chylomicrons
- VLDL — TAGs = 60% of VLDL

Cholesterol are mainly transported as
- LDL — Cholesterols = 50% of LDL
- HDL — Cholesterols = 25% OF HDL



Functions of Apolipoproteins:

1. Provide structure to lipoprotein particles. (on the shell). Some of the apolipoproteins are fixed structures In the lipoproteins (for example: chylomicrons will never give up their Apo B-48 as they are structurally required to prevent the lipoprotein structure from dissociation), but other apolipoproteins are transferred between the different lipoproteins (e.g. Apo C-II and Apo E can jump between lipoproteins).
2. Provide recognition sites for cell-surface receptors.
   Lipoproteins circulating in the blood need to be recognised by the adipocytes or hepatocytes, here comes another function of apolipoproteins!
3. Activators or coenzymes for the enzymes involved in lipoprotein metabolism. (E.g. Apo C-II can activate lipoprotein lipase)

Chylomicrons

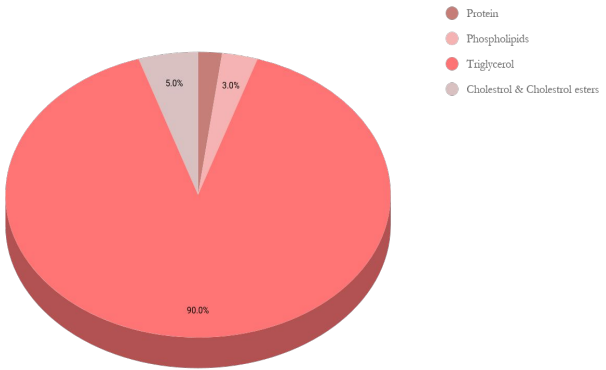
- Assembled in the intestinal mucosal cells (enterocytes).
- The milky appearance of plasma after a meal is due to lots of chylomicrons.
  As you can see in the pic

After taking a meal | Fasting patient's plasma

Function of Chylomicrons:

Is to transports the following to the peripheral tissues:

- Dietary TAGs (triacylglycerol) (90%)
- Cholesterol (C)
- Fat-soluble vitamins
- Cholesteryl esters (CE)



A chart showing the composition of Chylomicrons

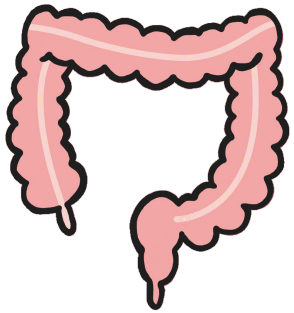
* In the next two slides we will discuss the metabolism of chylomicrons.
Be aware that it is extra information and that you are not required to cover it for the exam. However, it was explained by **girls' doctor**, and it is **extremely helpful** as it is very similar to VLDL metabolism.

original pic

Chylomicron Metabolism

★ extra explanation

Intestinal Mucosa



1

Nascent Chylomicrons (TAG>CE,C)

Apo B-48

(ApoE + ApoC-II) from HDL

2

Chylomicrons

Apo B-48

ApoE

ApoC-II

Capillary

3

Chylomicrons

Apo B-48

ApoC-II

ApoE

Lipoprotein lipase

Extrahepatic tissue for example: adipose

(Apo C-II) back to HDL

4

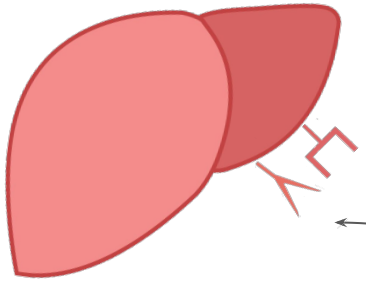
5

Chylomicrons (CE>C,TAG)

Apo B-48

ApoE

Chylomicron remnant



Liver

★ extra explanation

Chylomicron Metabolism

A helpful video OR A helpful video

Note that chylomicron metabolism is very similar to VLDL metabolism. the main difference is the major structural apolipoprotein & the source of the nascent molecule

1. Intestinal mucosal cells secrete nascent TAG (triacylglycerol) -rich chylomicrons which produced from dietary (exogenous) lipids. And they only have **Apo B-48** on them.

   While nascent chylomicrons are produced in intestinal mucosal cells with Apo B-48, nascent VLDL is produced in the liver with Apo B-100.

2. **Apo C-II** and **Apo E** are then transferred from HDL to this nascent chylomicron. Now, it has all three apolipoproteins: **Apo B-48**, **Apo C-II**, and **Apo E**.

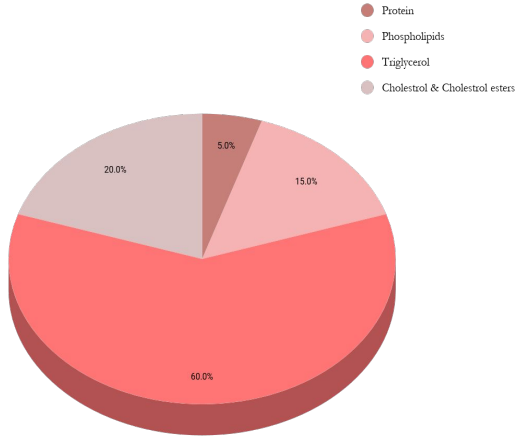
3. Extracellular lipoprotein lipase (LPL) gets **activated by Apo C-II**, and starts degrading the TAGs in chylomicrons into three fatty acids + glycerol.

4. **Apo C-II** is returned back to HDL, however **Apo E** and **Apo B-48** are still there.

5. CE (cholesteryl ester)-rich in chylomicrons remnants bind through **Apo E** to specific receptors on the liver and then they are endocytosed.

Very low density lipoprotein (VLDL)

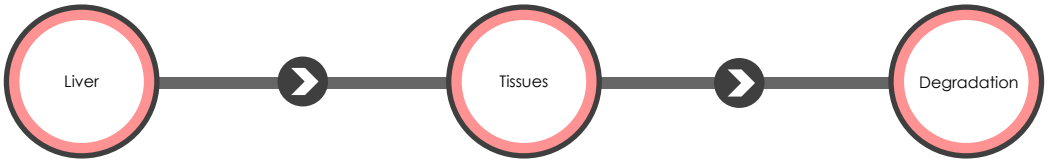
- Produced and secreted by the Liver.



A chart showing the composition of VLDL

Composed of the following:

- Mainly Endogenous TAGs (60%)
- Some cholesterol (both free and esterified)



VLDL carries these lipids (TAGs & cholesterols) from the liver to peripheral tissues

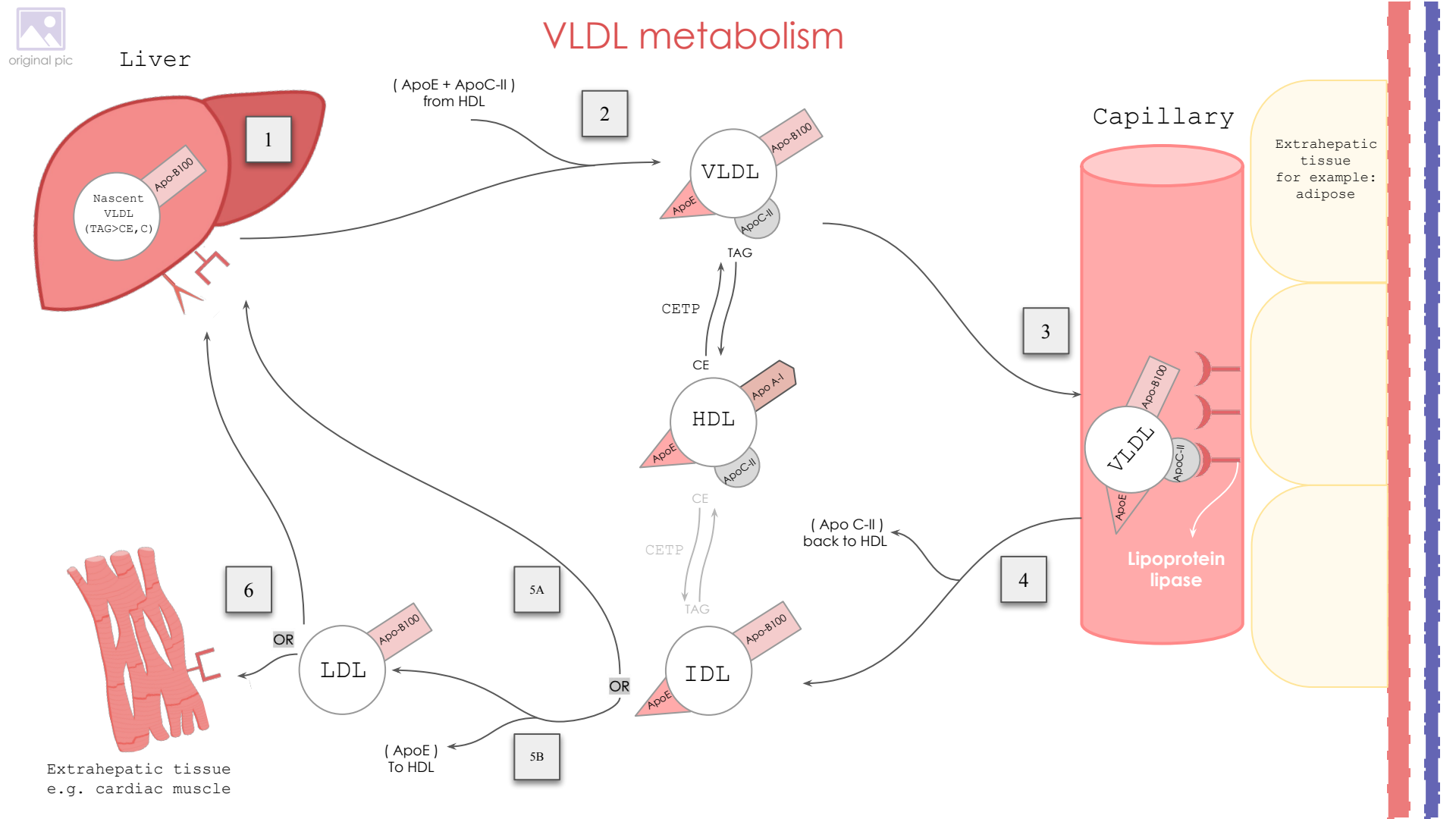
TAGs are delivered to the peripheral tissues by VLDL

it will be degraded by an enzyme called Lipoprotein lipase (LPL)

Imbalance in hepatic TAG synthesis and secretion of VLDL can lead to:

- Obesity.
- Type 2 diabetes mellitus.

VLDL metabolism



VLDL metabolism

A helpful video

OR

A helpful video

1. VLDL is produced in the liver and it is called nascent / immature VLDL. because they are the first form that is produced, and it contains TAGs (triacylglycerol), cholesterol, and **Apo B-100 only**. Then it is released to the bloodstream.

2. Once the nascent VLDLs are released in the blood, they obtain **Apo C-II** and **Apo E** from circulating HDL particles (Apo C-II is required for activation of enzyme Lipoprotein Lipase).

   - After the acquisition of these two apolipoprotein, it is now considered as mature VLDL which has all of the three apolipoproteins (Apo B-100, Apo C-II, and Apo E).
   - Meanwhile, some VLDL transfer TAGs (triacylglycerol) to HDL in exchange for cholesteryl esters(CE) . This exchange is catalyzed by cholesteryl ester transfer protein (**CETP**).

3. Now our mature VLDL can start distributing TAGs to extrahepatic tissues (e.g. adipocytes). The enzyme Lipoprotein lipase (**LPL**) which is found on the wall of capillaries will be **activated by Apo C-II** and it will start the degradation of TAGs into three fatty acids + glycerol.

   As a result, VLDL molecule will become smaller.

VLDL metabolism, contd..

4 Denser Surface components such as **Apo C-II is released** and returned back to HDL. (the original place it came from).

- Now, the molecule is called **IDL** (intermediate density lipoprotein) also called **VLDL remnant**, with **Apo B-100** and **Apo E** only. In Chylomicron remnant we have Apo **B-48** & Apo E
- **However there are two fates of IDL now:**

5A Some of these IDLs will go to to the liver, and **Apo E** will interact with the remanent receptors to induce **endocytosis** of the molecule. The end for this path!

OR

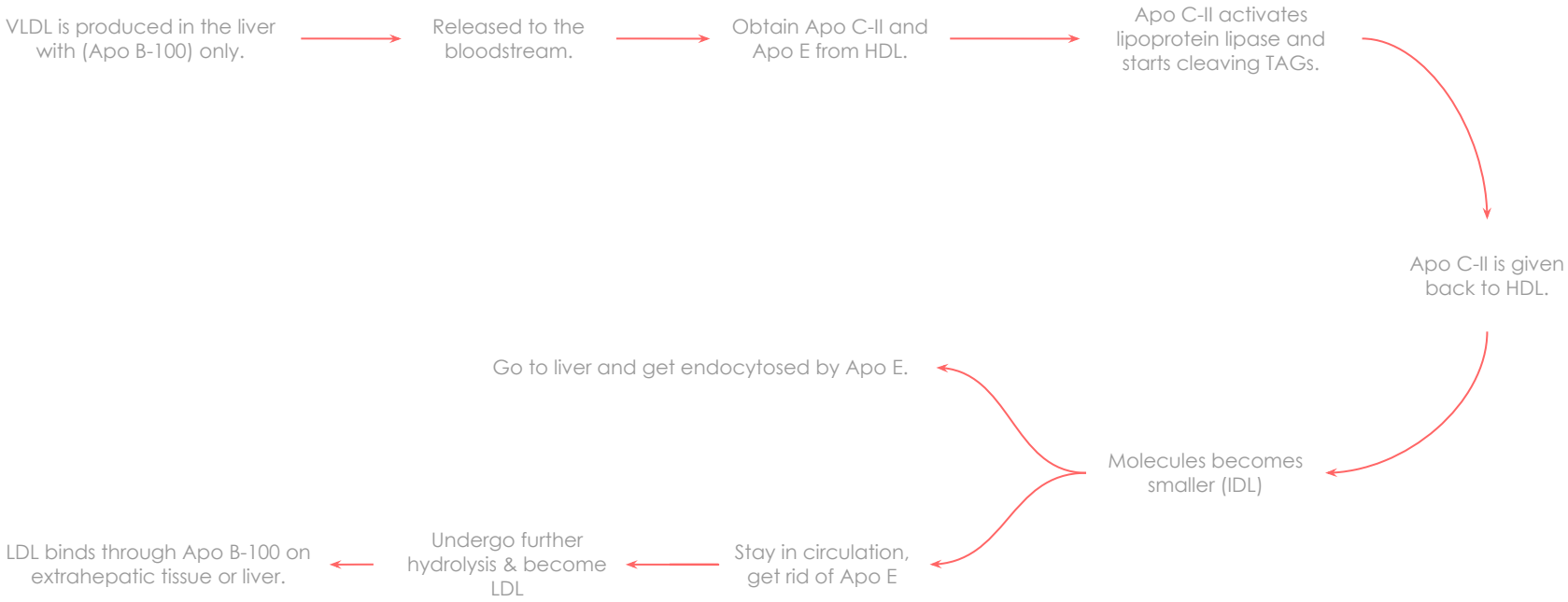
5B The left majority will remain in circulation, where they will get rid of **Apo E** and give it back to HDL, After that, they will continue and undergo further triglyceride hydrolysis by enzyme called hepatic lipase to become LDL. (hepatic lipase will cleave TAGs so it will lose some density and become low density lipoprotein) and then proceed to step 6!

- **Lastly:**

6 After step 5B: LDL will use its **Apo B-100** to bind to specific receptors either on extrahepatic tissue such as the cardiac muscle (drawn by the amazing Manal Altwaim♡) OR on the liver to be finally endocytosed.

- Remember that metabolism of chylomicrons is the same, except that it is produced by intestinal mucosal cells, and that . chylomicrons has Apo B-48 instead of Apo B-100 in case of VLDL.
- Note that cardiac muscle prefers fatty acids and ketones as a fuel, and that is due to the fact that unlike skeletal muscle, it does not store glucose as glycogen, So it's glucose consumption is way less than skeletal muscle

Summary of the pathway In order for you to gain a better understanding

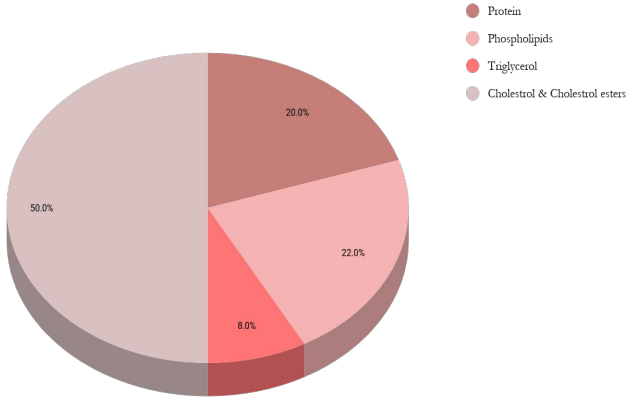


Low density lipoprotein (LDL)

- Produced from VLDL particles in the plasma in the circulation.

Composed of the following:

- Mainly cholesterol (C) & cholesteryl esters (CE)
- Contains Apo B-100 lipoprotein.



A chart showing the composition of LDL

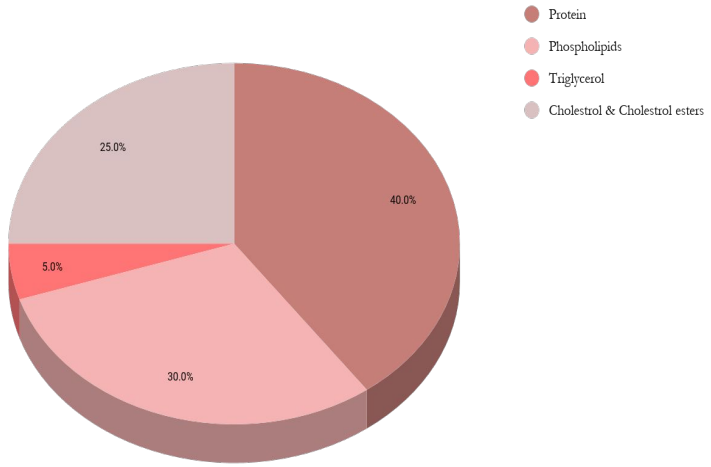
Functions of LDL:

- Is to provide cholesterol to peripheral tissue. as we saw, it is taken by the liver and extrahepatic tissue. it also transports cholesterol from the liver to the arteries, where it can build up there (bad cholesterol)

- it binds to cell surface receptors through Apo B-100 when it's taken by the liver or extrahepatic tissues we call this process (receptor-mediated endocytosis).

High density lipoprotein (HDL)

- Produced in the liver and intestine.
  (it is still unknown properly how is it exactly synthesized).



A chart showing the composition of HDL

Mainly composed of the following:

- Protein.
- Phospholipids.
- Cholesterol (C) & cholesteryl esters (CE).
- Apo A-1, Apo C-II and Apo E lipoproteins.

The major structural protein for HDL (the inherent protein) which is not given to anyone is Apo A1.
However, Apo C-II and Apo E present in HDL too, but they are given temporarily to VLDL and chylomicrons and be taken back later.

Function of HDL:

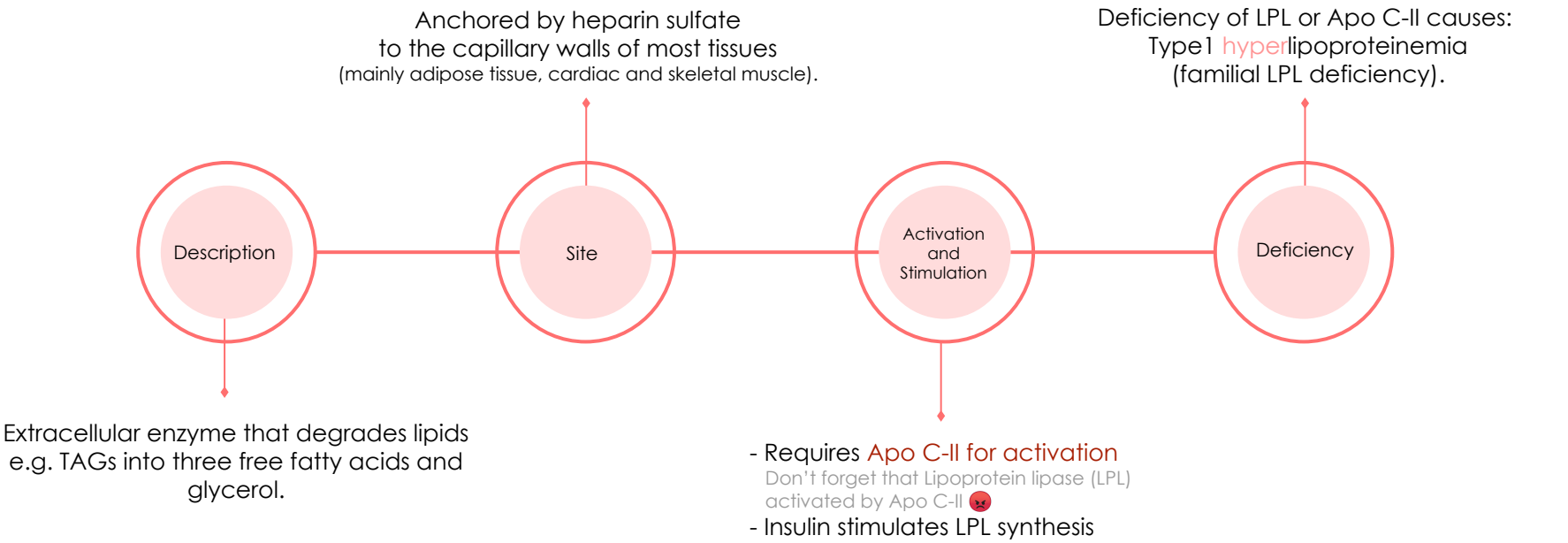
Is to take up cholesterol from peripheral tissues to the liver.
It removes cholesterol from the arteries and take it to the liver (Good Cholesterol)

Remember that the inherent Apolipoprotein for chylomicrons is Apo B-48.
And for VLDL and LDL it's Apo B-100.

Summary of Lipoproteins

Lipoprotein	Composition	Apolipoprotein	Density	Size	Origin / Production	Final destination
Chylomicrons	• Dietary TAGs (90%) • Cholesterol • Fat-soluble vitamins • Cholesteryl esters	• **Apo B-48**	Lowest	Largest	Intestinal mucosal cells	Peripheral tissue
VLDL	• Endogenous TAGs (60%) • Some cholesterols	• **Apo B-100** • Apo C-II • Apo E-2, 3, 4	Low	Large	Liver	Peripheral tissue
LDL	• Cholesterols • Cholesteryl esters	• **Apo B-100**	High	Small	From VLDL particles (Liver)	Peripheral tissue
HDL	• Cholesterol • Cholesteryl esters. • Protein. • Phospholipids.	• **Apo A-1** • Apo C-II • Apo E	Highest	Smallest	Liver & intestines	From peripheral tissue to Liver

Lipoprotein Lipase (LPL)



VLDL Diseases

Disease	About	Cause	Lead to
Steatohepatitis	(Fatty liver disease) Characterized by inflammation of the liver with concurrent fat accumulation in liver	Imbalance between: TAG synthesis in the liver and Secretion from the liver So the TAGs are made, but they are not taken out!	Leads to accumulation of TAGs in the liver (fatty liver)
Hypolipoproteinemia	Lack of lipoprotein in the blood due to genetic problem in the enzymes or some other diseases such as malnutrition and malabsorption.	Abetalipoproteinemia is a disorder that interferes with the normal absorption of fat and fat soluble vitamins from food. Due to inability to load Apo B with lipids. There is an enzyme called MTTP that is responsible for bringing the lipids and loading it into Apo B. if there was a deficiency or inhibition of this enzyme, loading will fail.	Fewer VLDLs and chylomicrons are formed, so TAGs will accumulate in the liver and intestine.
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 which will lead to a lot of cardiovascular problems.
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. Homozygous means if both alleles were defected in someone, his Apo E2 will not function at all. However if he was heterozygous, then the normal allele will make some protein and Apo E2 will function partially or less than normal person. Remember that Apo E2 is required for recognition of IDL and chylomicron remnants.	Leads to hypercholesterolemia and premature atherosclerosis

Summary

Lipoproteins

Definition

Plasma spherical macromolecular complexes of Lipids and Specific proteins (apolipoproteins) and it's amphipathic

Composition

- Lipid core
  - Triacylglycerols
  - Cholesteryl esters
- Amphipathic shell
  - Phospholipids
  - Free cholesterol
  - apolipoproteins

Function

Keep the hydrophobic lipid contents soluble while transporting them to and from the tissues

Types

1- Chylomicrons Synthesized in Intestinal mucosal cell (Apo B-48)

2- VLDL synthesized in the Liver (Apo B-100)

3 -LDL produced from VLDL particles (liver) (Apo B-100)

4- HDL is Synthesized in the Liver and intestine (Apo A1)

VLDL

- Metabolism
  - 1-In the liver it will produce Nascent = immature lipoprotein
  - 2-Release from the liver : In the bloodstream the lipoprotein become mature (obtain apo C-II and apo E from circulating HDL)
  - 3-Modification in the circulation : some VLDL transfer TAGs to HDL in exchange for cholesteryl esters(CE)
  - 4-Conversion to LDL :In the bloodstream IDL will be converted into LDL
- VLDL diseases
  - Hypolipoproteinemia
  - Steatohepatitis
  - Type I hyperlipoproteinemia
  - Type III hyperlipoproteinemia

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.

Quiz

Q1 : VLDL is produced in the ..... with ..... ?			
A) Liver, Apo B-100	B) Liver, Apo B-48	C) Intestinal mucosa, Apo B-100	D) Intestinal mucosa, Apo B-48
Q2 : Which of the following is Assembled in the intestinal mucosal cells ?			
A) LDL	B) VLDL	C) Cholymicrons	D) HDL
Q3 : Which one of these isoforms of Apo E is the one that poorly binds to receptors ?			
A) Apo E-1	B) Apo E-2	C) Apo E-3	D) Apo E-4
Q4 : The enzyme Lipoprotein lipase is activated by:			
A) Apo B-48	B) Apo B-100	C) Apo C-2	D) Apo C-3
Q5 : a disease that is caused when there is a deficiency in LPL or its coenzyme is:			
A) Hypolipoproteinemia	B) Type I hyperlipoproteinemia	C) Type III hyperlipoproteinemia	D) Steatohepatitis
Q6 : A disease that will lead to TAGs accumulation in the liver and intestine due to fewer VLDLs and chylomicrons being formed.			
A) Hypolipoproteinemia	B) Type I hyperlipoproteinemia	C) Type III hyperlipoproteinemia	D) Steatohepatitis

SAQs :

Q1: Describe the composition of Lipoproteins.

Q2: List the functions of apolipoproteins.

Q3: Give two VLDL diseases and describe their cause and result.

★ **MCQs Answer key:**

1) A 2) C 3) B 4) C 5) B 6) A

★ **SAQs Answer key:**

1) **Hydrophobic core:** triacylglycerols (TAGs), cholesteryl esters
Hydrophilic shell: Amphipathic apolipoproteins,Phospholipids, free cholesterol.

2) Provide structure to lipoprotein particles, provide recognition sites for cell-surface receptors, activators or coenzymes for the enzymes involved in lipoprotein metabolism.

3) Check **slide 18**

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