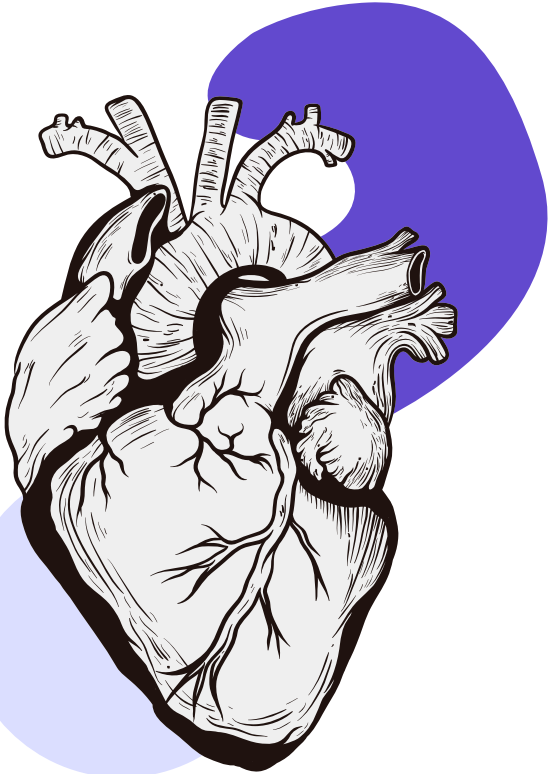
Lipoprotein metabolism



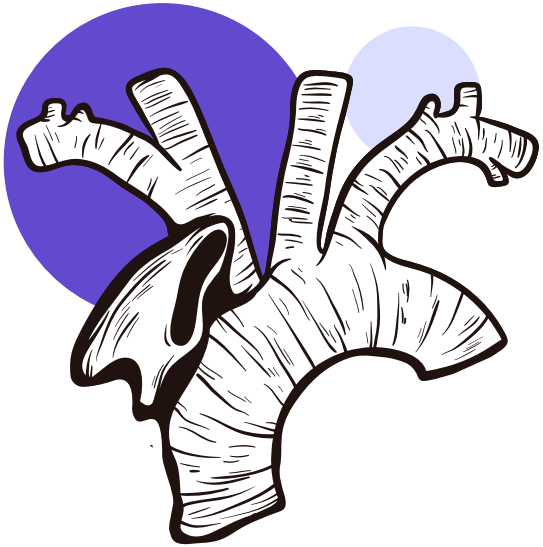
Editing File

COLOR INDEX:
MAIN TEXT (BLACK)
FEMALE SLIDES (PINK)
MALE SLIDES (BLUE)
IMPORTANT (RED)
DR'S NOTE (GREEN)
EXTRA INFO (GREY)

Helpful video by Ninja Nerd

شرح عربي

Objectives



01 Define and list the types, structure and composition of lipoproteins

02 Understand various functions of lipoprotein particles

03 Compare the functions of lipoprotein particles and their implications in disease

04 Understand the metabolism of chylomicrons, VLDL and LDL particles

05 Discuss the functions of lipoprotein lipase and its role in disease

06 List the diseases due to imbalance in the metabolism of lipoproteins

Characteristics of Lipoproteins

01 Lipids are hydrophobic molecules (Lipo: Lipid)

02 Transported in plasma as lipoprotein particles (outside is protein which is hydrophilic like plasma and inside is transported lipid which is hydrophobic)

03 Plasma lipoproteins are spherical macromolecular complexes of:

- Lipids (transported part)
- Specific proteins (apolipoproteins)

04 (function of LPs): Lipoproteins keep lipid contents soluble while transporting them to and from the tissues

Types of Lipoproteins

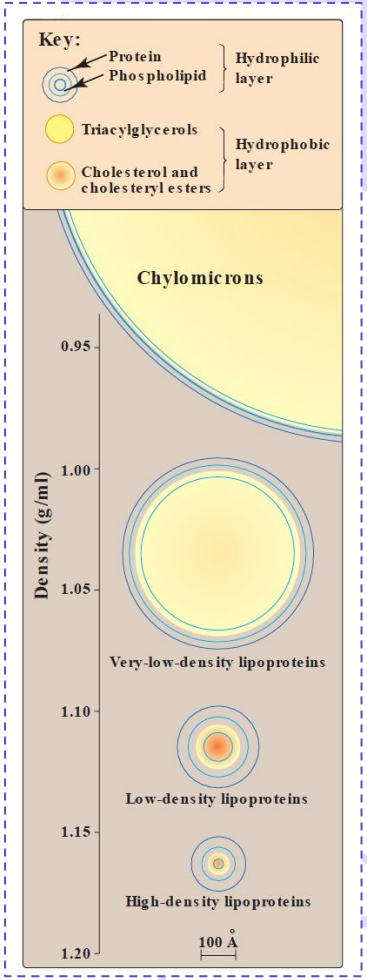
Density refers to the protein content against the lipid content

Lipoproteins

- **Chylomicrons** — Lowest density (more fat), Largest
- **VLDL** — Very low density lipoproteins
- **LDL** — Low density lipoproteins
- **HDL** — High density lipoproteins

Lipoproteins differ in:

- Lipid & Protein composition
- Size
- Density
- Site of origin



Compositions of lipoproteins

01 Neutral lipid core (hydrophobic):

- ★ Triacylglycerols (TAGs)
- ★ Cholesteryl esters

02 Hydrophilic shell: (it is kind of a single layer membrane)

- ★ Amphipathic apolipoproteins
- ★ Phospholipids
- ★ Free cholesterol or Unesterified cholesterol (The orange dots in the picture, its function is to stabilize the Lipoprotein, without it the structure will dissolve)

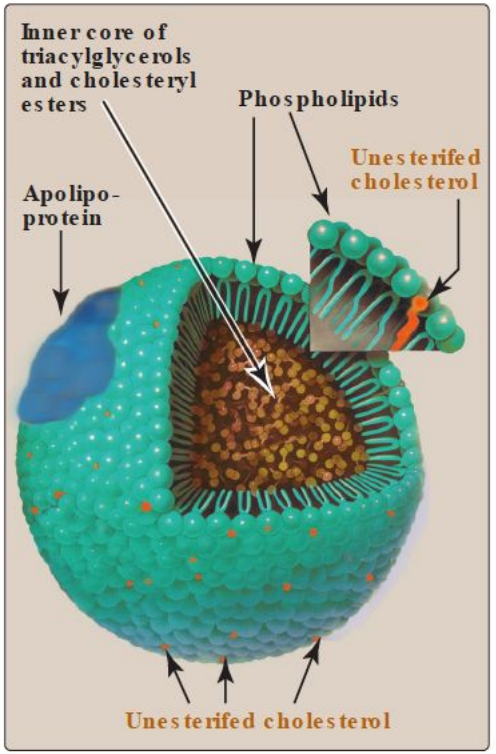
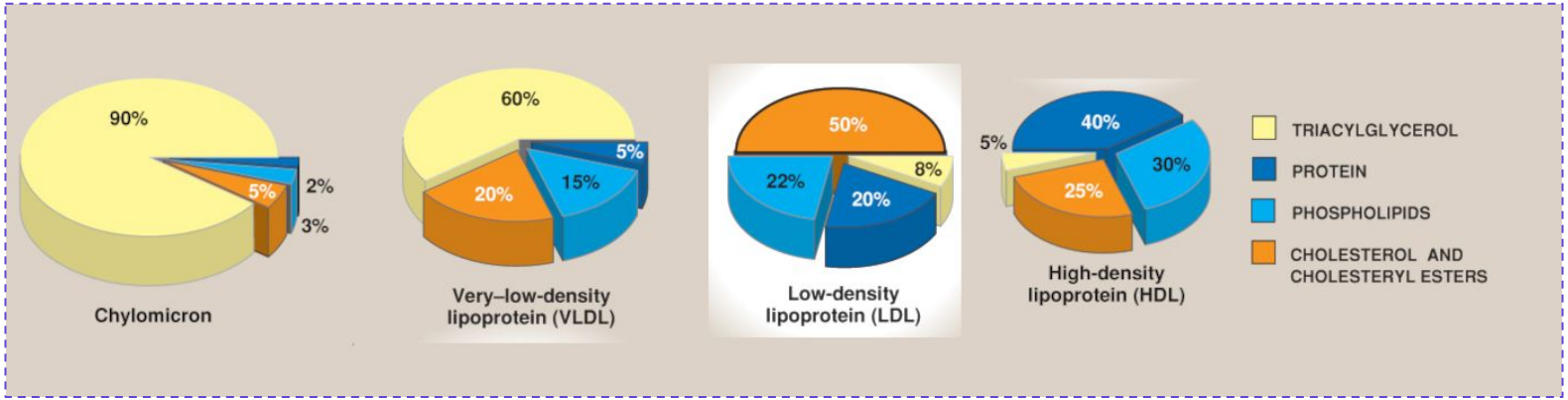


Figure 18.14
Structure of a typical lipoprotein particle.

Cont. Compositions of lipoproteins



TAGs are mainly transported by:

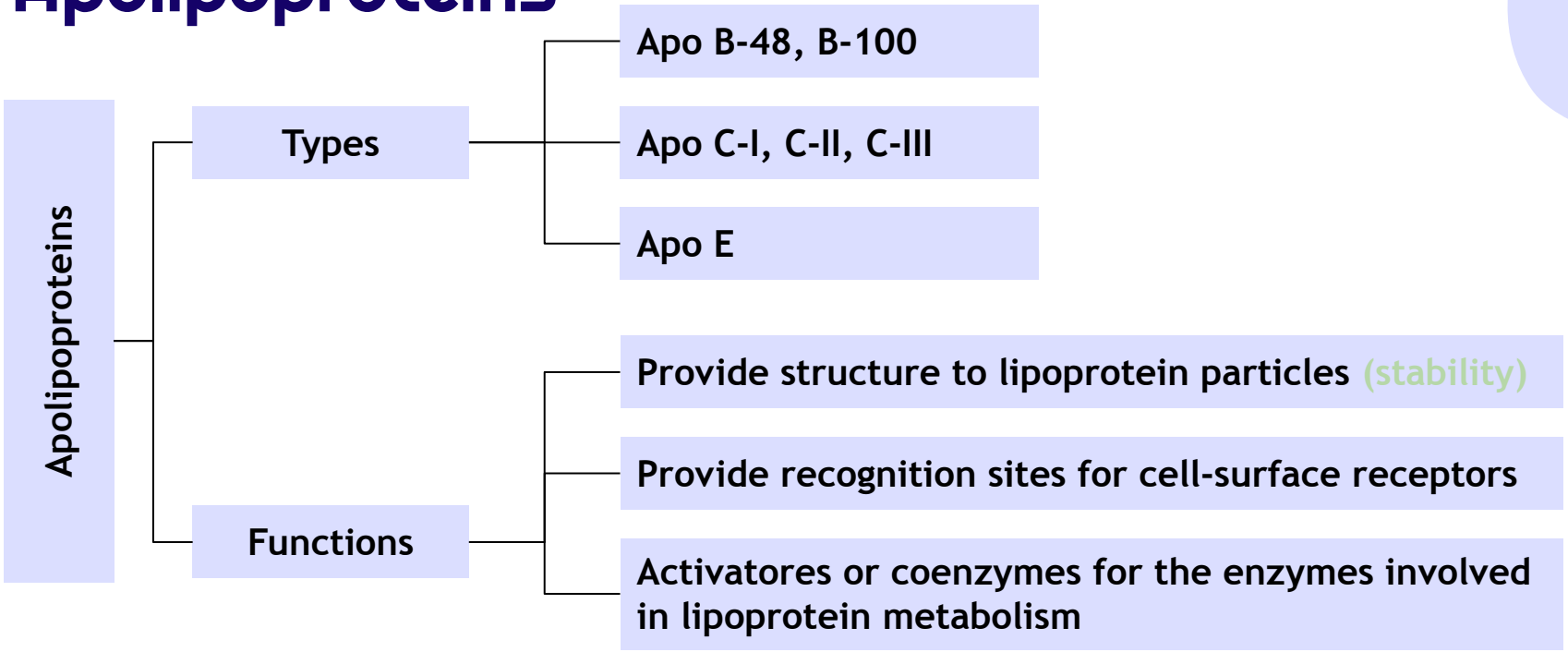
- ★ Chylomicrons (Dietary lipids, Exogenous, outside of the body)
- ★ VLDL

Cholesterol is mainly transported by:

- ★ LDL
- ★ HDL

Other than chylomicrons, Lipoproteins are endogenous

Apolipoproteins



Chylomicrons

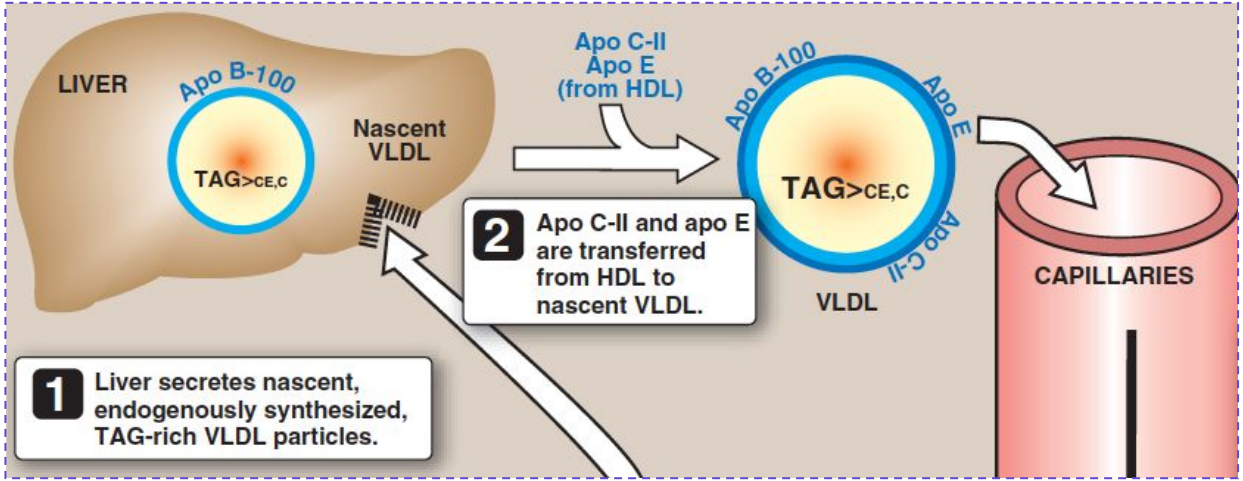
- Source of exogenous fat, they mainly carry dietary lipids as Triglycerides, the cholesterol content is very low
- Assembled in the intestinal mucosa cells (they’re only produced after we eat a meal)
- Transport to peripheral tissue:
  - Dietary TAGs (90%)
  - Cholesterol
  - Fat-soluble vitamins
  - Cholesteryl esters
- The milky appearance of plasma after a meal is due to chylomicrons

VLDL

- VLDL & the rest of the particles are endogenous (produced inside the body)
- Produced and secreted and packaged by the liver
- Mainly composed of:
  - Mainly Endogenous TAGs (60%)
  - Some cholesterol (Free and esterified)
- Carry these lipids from the liver to peripheral tissues
- The function of these particles is to supply the whole body with these lipids through circulation after coming out of the liver
- The difference between Chylomicrons and VLDL is that Chylomicrons carry exogenous lipids and VLDL carry endogenous lipids
- Peripheral tissue degrade TAGs by lipoprotein lipase (LPL) enzyme which exist on the cell surface
- Imbalance in hepatic TAG synthesis and secretion of VLDL can lead to:
  - Obesity
  - Type 2 diabetes mellitus

VLDL metabolism

1. Release from the Liver
   - As Nascent particles containing:
     - TAGs and cholesterol
     - Apo B-100
   - Obtain apo C-II and apo E from circulating HDL particles
   - Apo C-II is required from activation of LPL



VLDL metabolism

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)

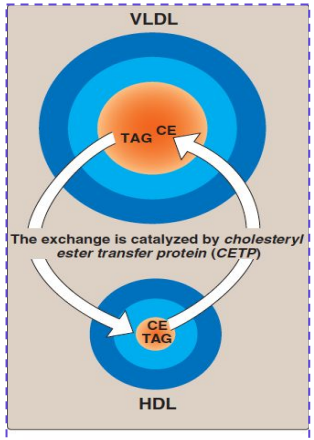
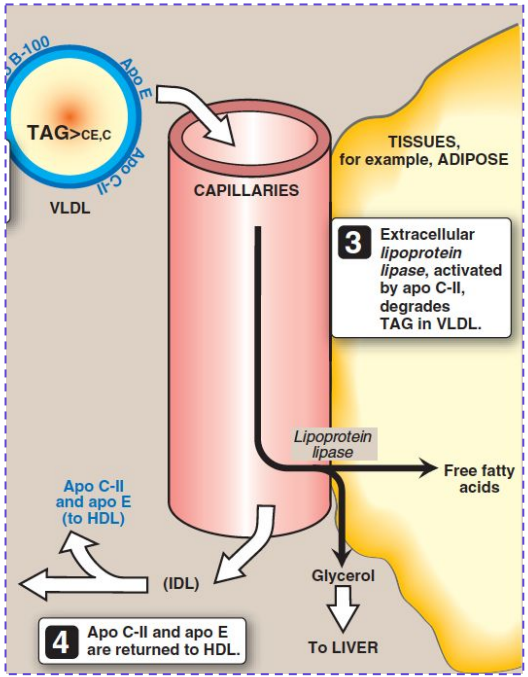


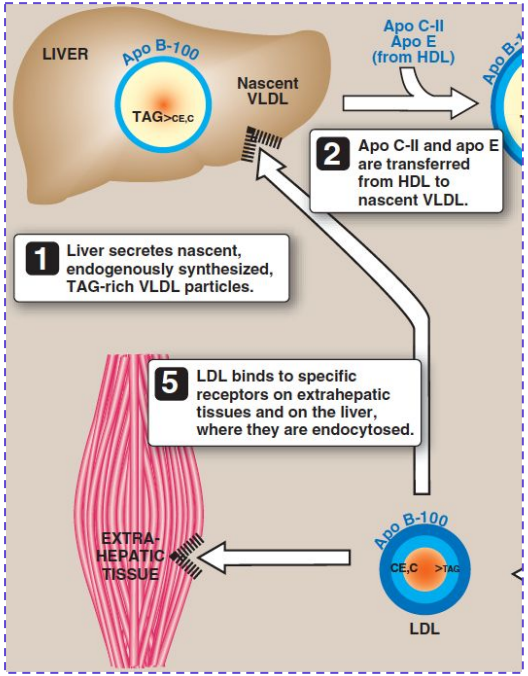
Figure 18.18
Transfer of cholesteryl esters (CE) from HDL to VLDL in exchange for triacylglycerol (TAG).



VLDL metabolism

3. Conversion to LDL
   - After modifications, VLDL is converted to:
     - LDL
     - IDL intermediate density lipoprotein (taken up by liver cells through apo E)
     - VLDL remnants

Apo E has poor binding so we tend to accumulate IDL



Apo E exists in three isoforms

- Apo E-2 (poorly binds to receptors)
- Apo E-3
- Apo E-4

APOE Clinical Correlation

- **Apo-E Genotype:**

- your APO-E gene is the strongest and most prevalent(>50%) genetic risk factor for **Alzheimer's Disease**.

- There are 3 main allele variants
(**E2**: Protective | **E3**: Neutral | **E4**: Detrimental)

- **2x ApoE4** Gene = **8x-12x** fold increase **risk** in Alzheimer's Disease

- Some people test for it. But, there is no current interventions specific for Alzheimer's Disease other than lifestyle interventions.

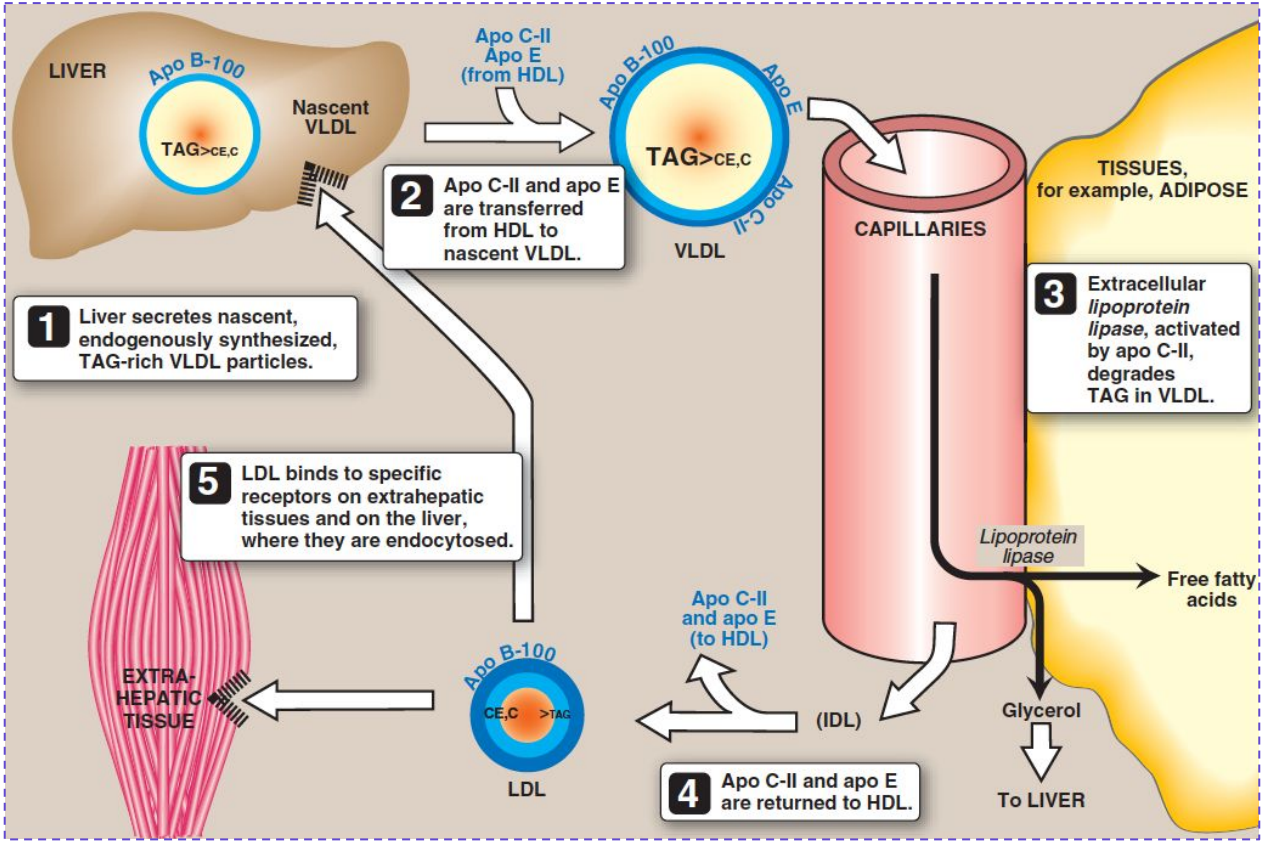
You can read More on APOE and AD here:
ApoE in Alzheimer's disease: pathophysiology and therapeutic strategies | Molecular Neurodegeneration

Recently, there has been a popular story where actor Chris Hemsworth (Thor) discovered he had 2x APOE4 Gene.

You can read more here: Chris Hemsworth's APOE4 Alzheimer's Gene | MedPage Today

By: Khalid Ibraheem 44

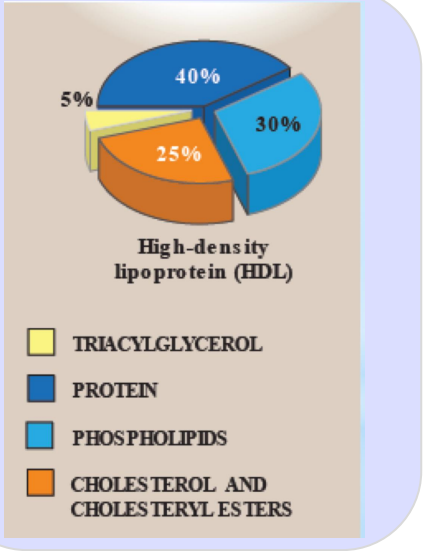
VLDL metabolism Overview

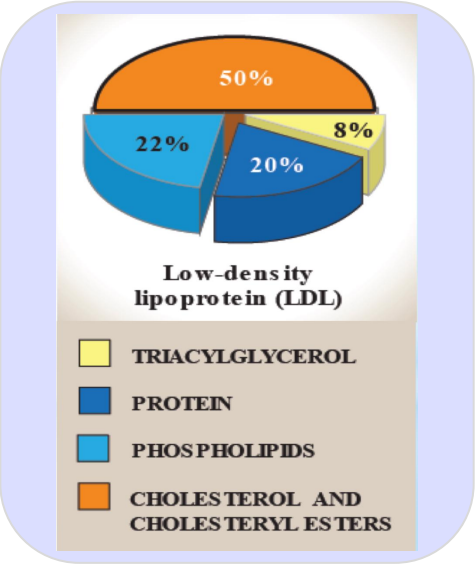


Low density lipoproteins (LDL) & High density lipoproteins (HDL)

(LDL) (Bad cholesterol) *Check L3 (Lipoproteins and Atherosclerosis) to know why the terms "good and bad cholesterol" are **inaccurate** to use.*		(HDL) (Good cholesterol)
Produced from VLDL particles	Production	Produced in the liver and intestine
Mainly contains : • cholesterol and cholesteryl esters • Apo B-100 lipoprotein	Contents	Mainly contains: • Protein, phospholipids, cholesterol, cholesteryl esters • Apo A-1, C-2 and E lipoprotein
- Provides cholesterol to peripheral tissue - LDL binds to cell surface receptors through Apo B-100 (receptor-mediated endocytosis)	Functions	Take up cholesterol from peripheral tissues to the liver Reverse cholesterol transfer (HDL and LDL have opposite functions)

Low density lipoproteins (LDL) & High density lipoproteins (HDL)





Lipoprotein lipase (LPL)

Deficiency

Deficiency of LPL or apo C-II causes:

Type 1 hyperlipoproteinemia
(familial LPL deficiency)

that's why this enzyme is important

Description

-Extracellular enzyme that degrades lipids

-Degrades TAGs into free fatty acids and glycerol will be sent to the liver

Site

-Anchored by heparin sulfate to the capillary walls of most tissues

-Mainly present in adipose tissue, cardiac and skeletal muscle

Synthesis

Insulin stimulates LPL synthesis
(Increase lipogenesis)

Activation

Requires apo C-II for activation

VLDL Diseases

Disease	About	Cause	Leads to
Hypolipoproteinemia	-	441 dr : (A=not or without ; beta= apo B) Abetalipoproteinemia is due to inability to load apo B with lipids	you won't be able to synthesize your lipoproteins which are • Few VLDLs and chylomicrons are formed • TAGs accumulate in liver and intestine
Steatohepatitis	(Fatty liver disease) To much fat in the liver with will cause inflammation	Imbalance between: -TAG synthesis in the liver and -Secretion from the liver	Leads to accumulation of TAGs in the liver (fatty liver)
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
Type III hyperlipoproteinemia	Also called **familial dysbetalipoproteinemia**, or broad beta disease	Individuals homozygous for apo E-2 are deficient in clearing: -Chylomicron remnants - IDL from the circulation	Leads to hypercholesterolemia and premature atherosclerosis

MCQ

1-C 2-C 3-A

Q1:what is the lowest density lipoprotein but largest in size ?			
A- VLDL	B- HDL	C- chylomicrons	D- LDL
Q2: Type I hyperlipoproteinemia is caused by :			
A- VLDL Overproduction	B- APOB deficiency	C- Apo CII deficiency	D- LPL overactivity
Q3: Extracellular lipoprotein lipase activated by ?			
A- apo C-II	B- apo C-III	C- apo E	D- apo B-100

MCQ

1-A 2-C 3-A

Q1: Compared to HDL, LDL particles are characterized by which of the following criteria?			
A- They contain less protein	B- They contain mainly esterified cholesterol	C- They contain excess phospholipids	D- They contain Apo AI
Q2: VLDL is produced in the ..... with ..... ?			
A- Liver, Apo B-48	B- Intestinal mucosa, Apo B-48	C- Liver, Apo B-100	D- Intestinal mucosa, Apo B-100
Q3: Where does the chylomicrons assemble ?			
A- Intestinal mucosal cells	B-peripheral tissue	C- liver	D- kidney

SAQ

Q3: A patient presents with fatty deposition on his liver and is later diagnosed with steatohepatitis. Explain from a biochemical standpoint how was this caused?

A1:
There is an imbalance between Triglyceride Synthesis and Secretion in the liver which leads to the accumulation of lipids in the liver

Q2: Mention 2 of apolipoproteins function ?

A2: 1-Provide structure to lipoprotein particles
2-Provide recognition sites for cell-surface receptors

Q3: where can LPL be found ?

A3: Adipose tissue, cardiac and skeletal muscle

Aram Alzahrani

Lujain Darraj

Eyad Zubaidi

Osama Alotaibi

Mays Altokhais

Shadin Alabbas

Khalid Alkanhal

Lana Alfouzan

Ghala Alyousef

Waleed Alanazi

Faris Alturaiki

Aseel Alanazi

Saleh Alotaibi

Faisal Alghamdi

Leena Shagrani