Lipoprotein Metabolism

Cardiovascular System Block

Objectives

By the end of this lecture, the First Year students will be able to:

- 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

Overview

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

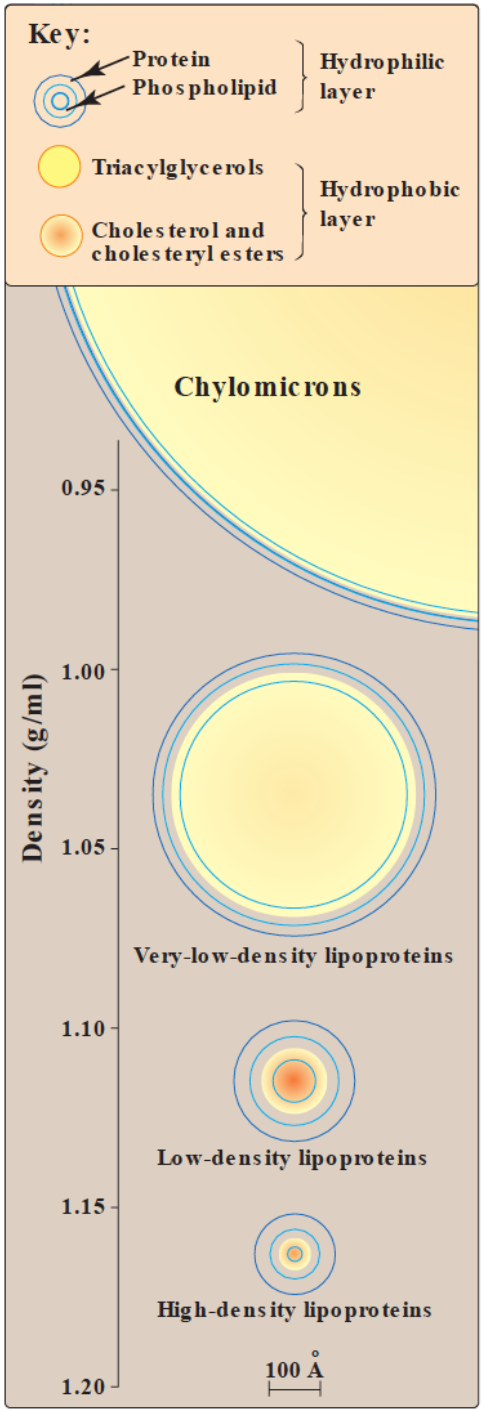
Lipoproteins

- Lipids are hydrophobic molecules
- Transported in plasma as lipoprotein particles
- Plasma lipoproteins are spherical macromolecular complexes of:
  - Lipids and
  - Specific proteins (apolipoproteins)
- Lipoproteins keep lipid contents soluble while transporting them to and from the tissues

Types of lipoproteins

- Chylomicrons (lowest density, largest)
- VLDL (very low density lipoproteins)
- LDL (low density lipoproteins)
- HDL (high density lipoproteins)

- Lipoproteins differ in:
  - Lipid and protein composition
  - Size
  - Density
  - Site of origin



Compositions of lipoproteins

- Neutral lipid core (hydrophobic):
  - Triacylglycerols (TAGs)
  - Cholesteryl esters
- Hydrophilic shell:
  - Amphipathic apolipoproteins
  - Phospholipids
  - Free cholesterol

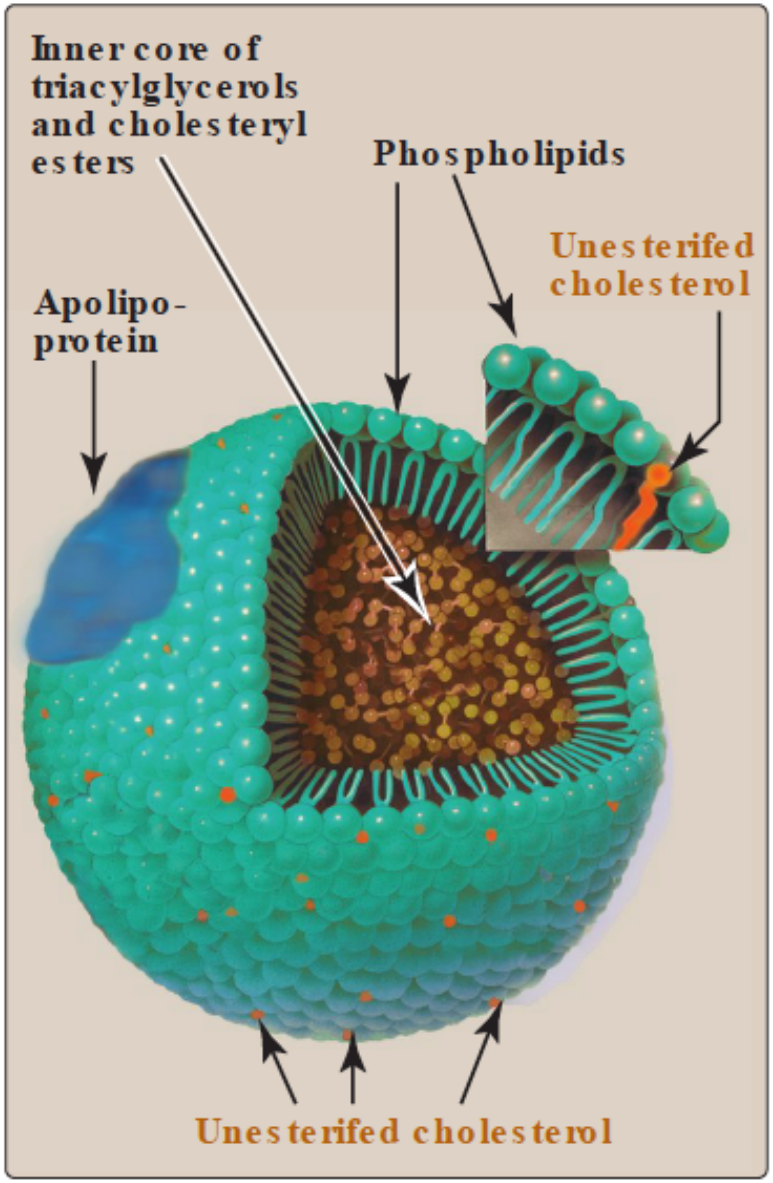
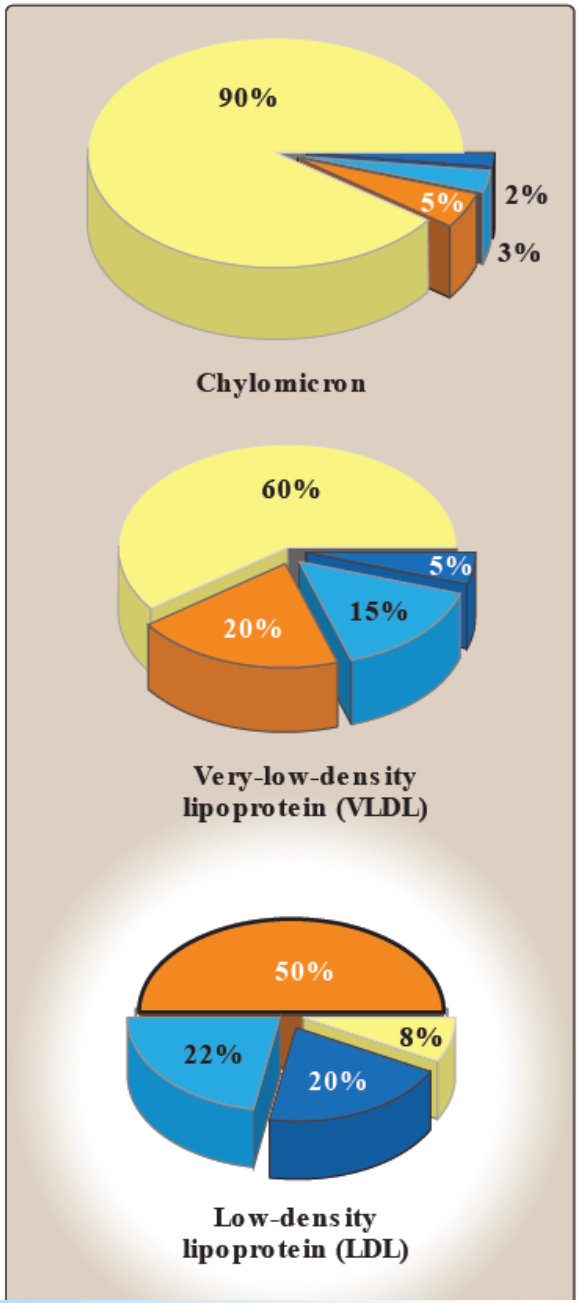


Figure 18.14
Structure of a typical lipoprotein particle.



- TAGs are mainly transported by:
  - Chylomicrons
  - VLDL
- Cholesterol mainly transported by:
  - LDL
  - HDL

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

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

VLDL

- Produced and secreted by the liver

Composed of:

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

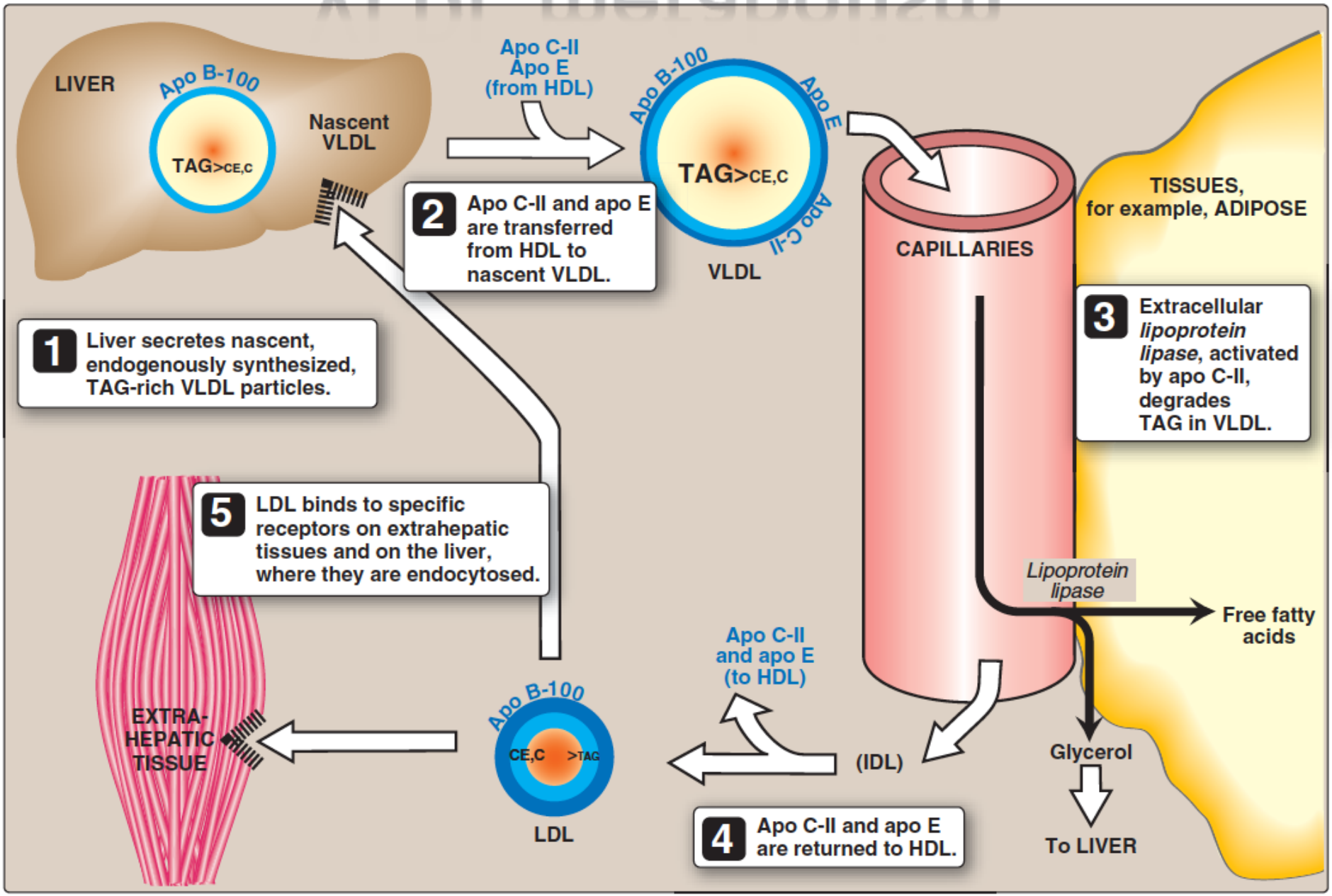
- Carry these lipids from the liver to peripheral tissues

VLDL

- Peripheral tissues degrade TAGs by lipoprotein lipase (LPL) enzyme

- Imbalance in hepatic TAG synthesis and secretion of VLDL can lead to:
  - Obesity
  - Type 2 diabetes mellitus

VLDL metabolism



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 for 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)

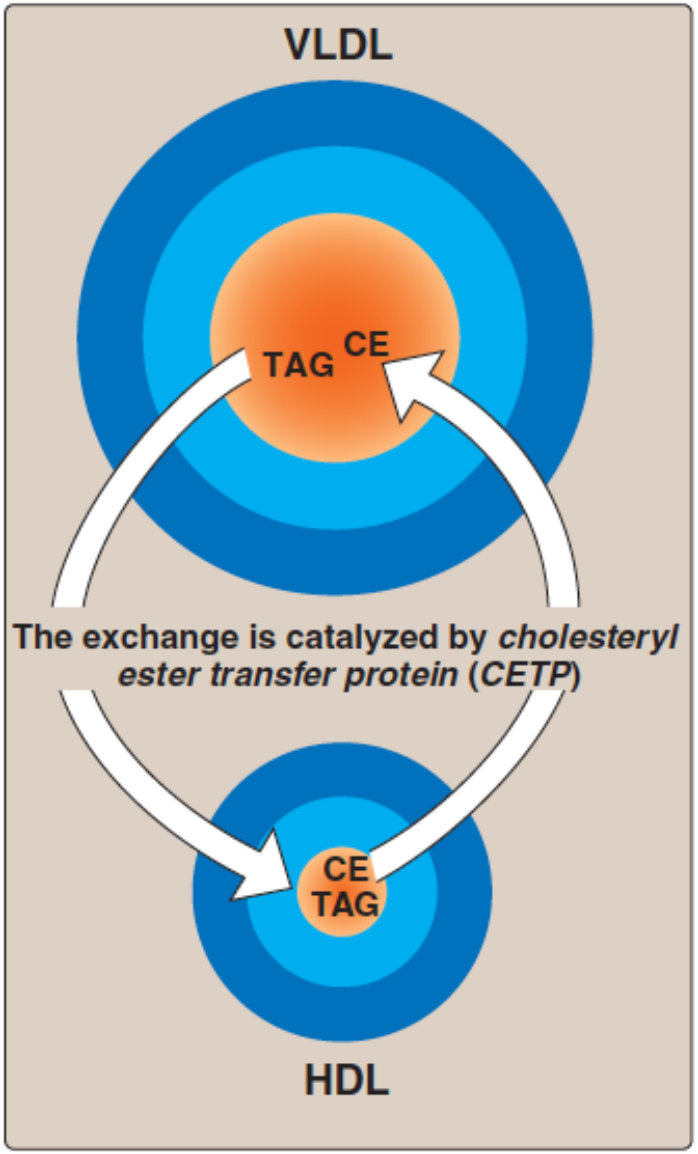


Figure 18.18
Transfer of cholesteryl esters (CE) from HDL to VLDL in exchange for triacylglycerol (TAG).

VLDL metabolism

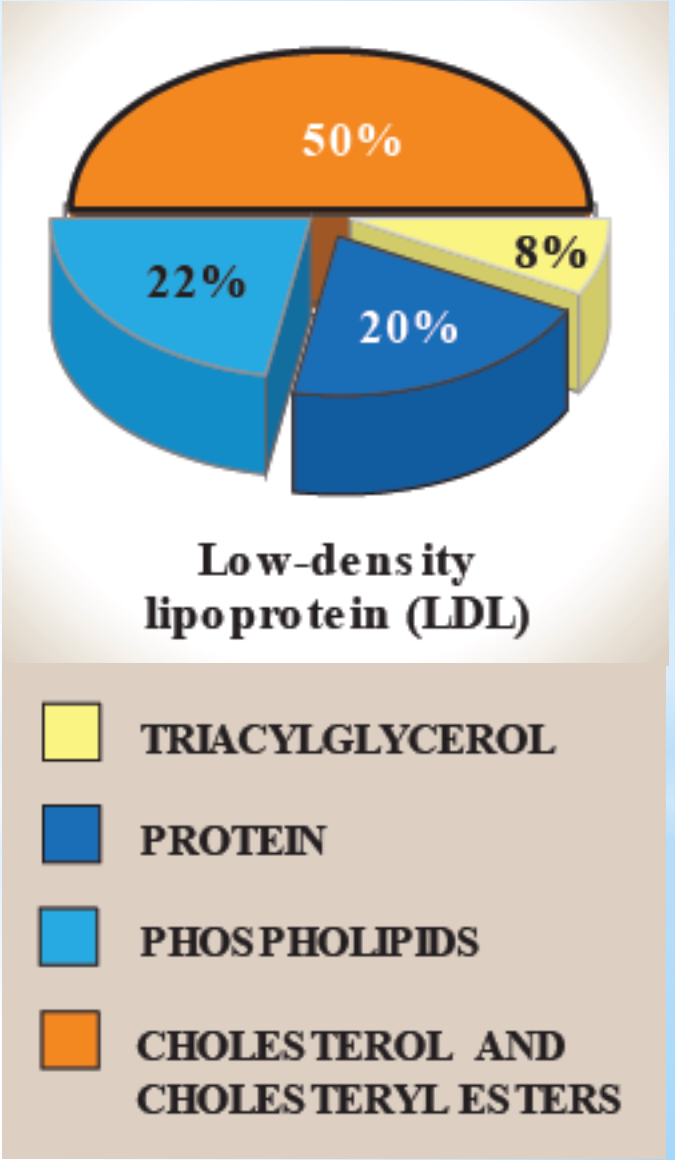
3. Conversion to LDL

- After modifications, VLDL is converted to:
  - LDL
  - IDL (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

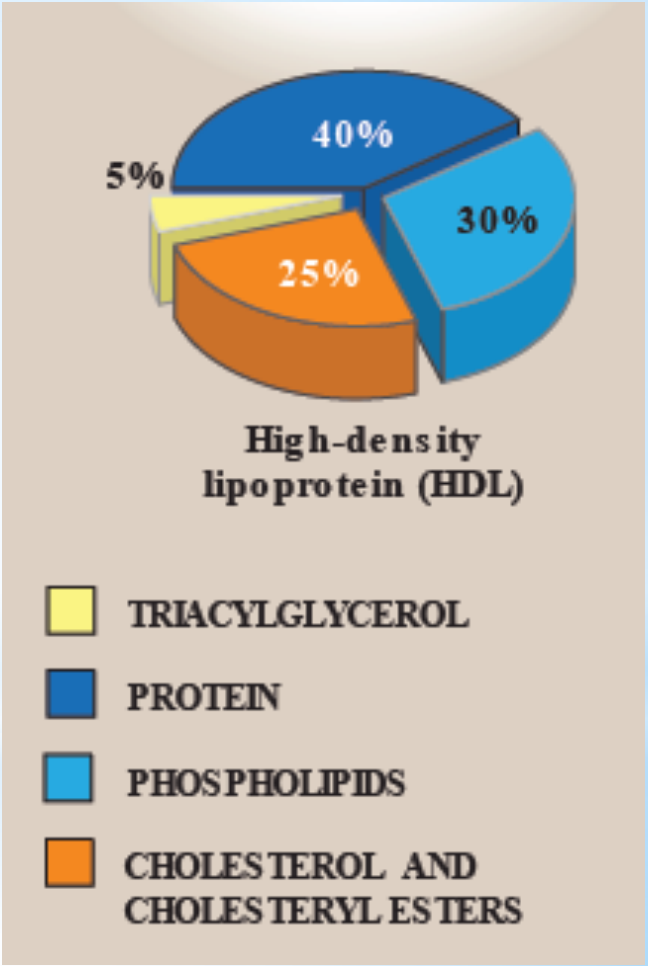
Low density lipoprotein (LDL)

- Mainly contains cholesterol and cholesteryl esters
- Produced from VLDL particles
- Contains Apo B-100 lipoprotein
- Provides cholesterol to peripheral tissue
- LDL binds to cell surface receptors thru Apo B-100 (receptor-mediated endocytosis)



High density lipoprotein (HDL)

- Mainly contains:
  - Protein, phospholipids, cholesterol, cholesteryl esters
- Produced in the liver and intestine
- Contains Apo A-1, C-2 and E lipoproteins
- Take up cholesterol from peripheral tissues to the liver



Lipoprotein lipase (LPL)

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

VLDL diseases

Hypolipoproteinemia

- Abetalipoproteinemia is due to inability to load apo B with lipids
- Few VLDLs and chylomicrons are formed
- TAGs accumulate in liver and intestine

VLDL diseases

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)

VLDL diseases

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

VLDL diseases

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

Take home message

- 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

References

Lippincott's Biochemistry. 6th Edition, Chapter 18, pp. 226-232. Lippincott Williams & Wilkins, New York, USA.