LIPOPROTEIN METABOLISM

BY

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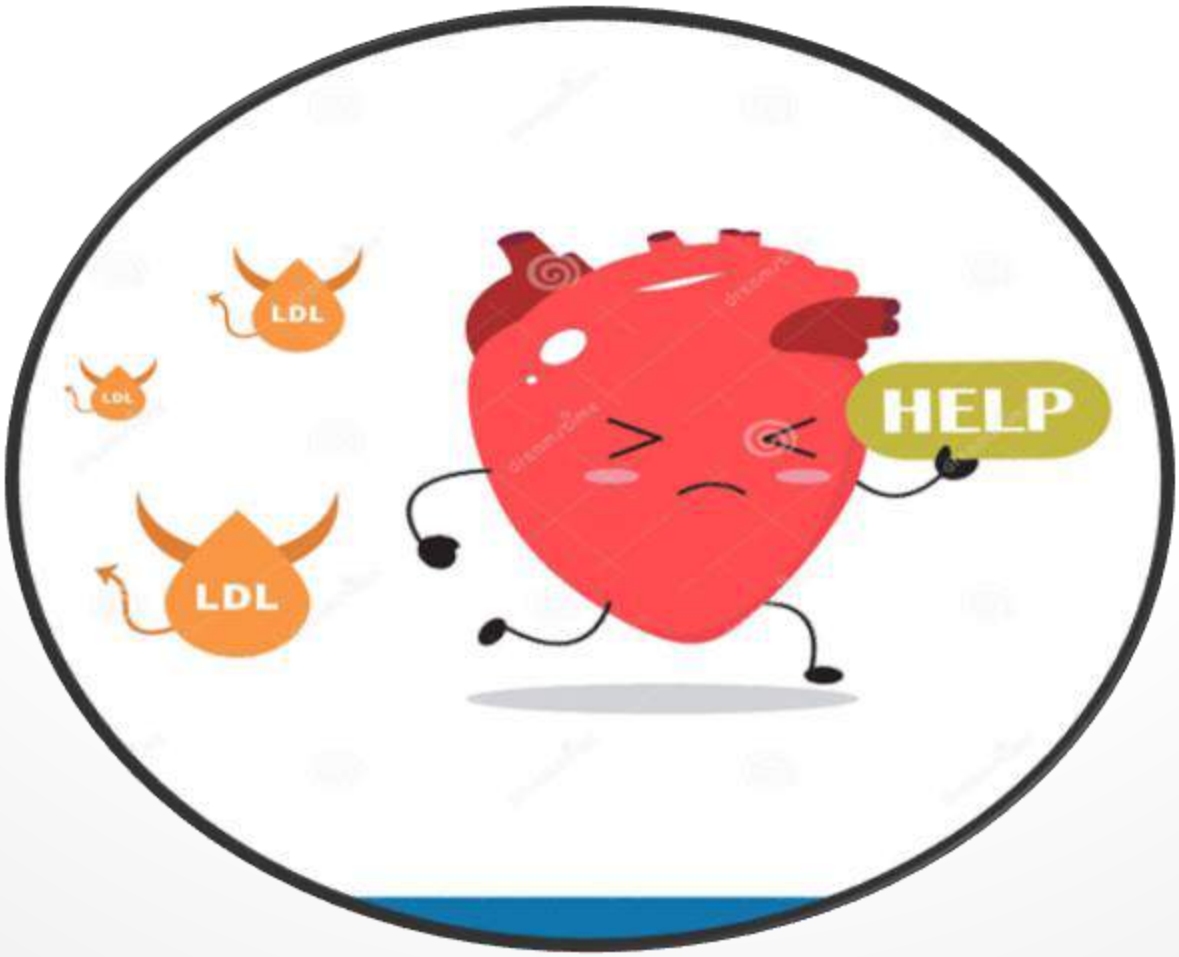


Lipoprotein metabolism

Lipid compounds:
Relatively water insoluble

Therefore, they are transported in plasma **(aqueous)** **as Lipoproteins**

Plasma lipoproteins

- All lipids in plasma are transported in the form of lipoproteins.
- Lipoproteins solubilize lipids in plasma.

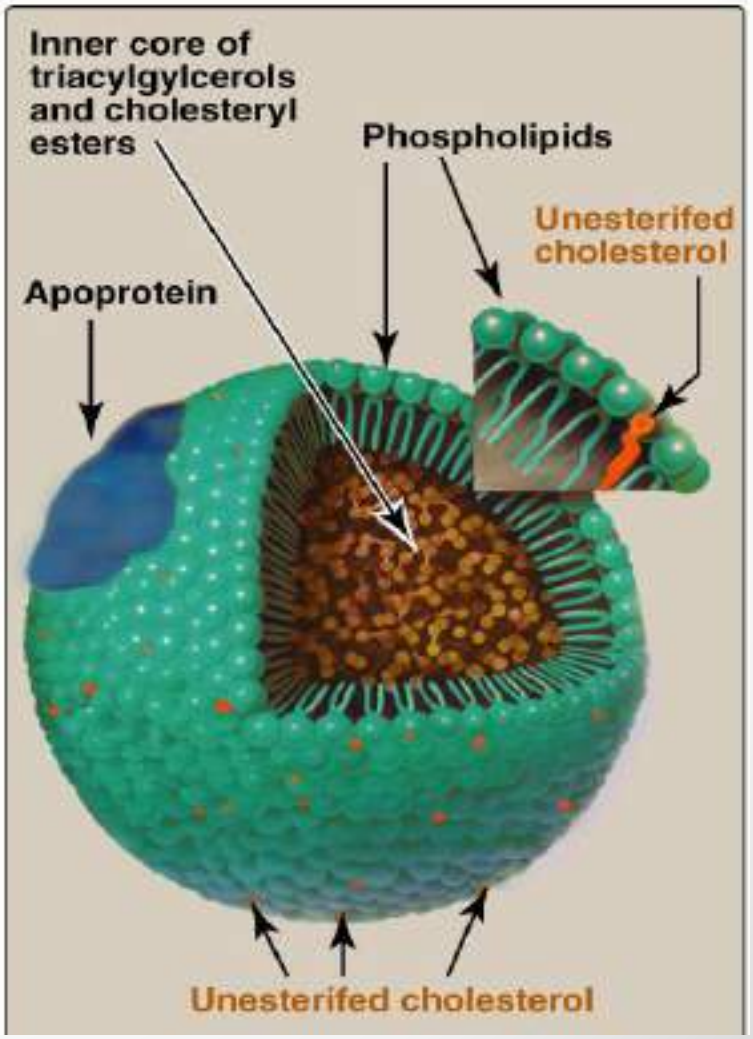
The structure of lipoprotein is:

- **Central core** formed of non-polar lipids:

1. triacylglycerols (TG; TAG) and
2. cholesterol esters (CE).

- **Outer layer** contains polar lipids:

1. phospholipids (PL).
2. non-esterified cholesterol (C).
3. proteins (apoproteins).

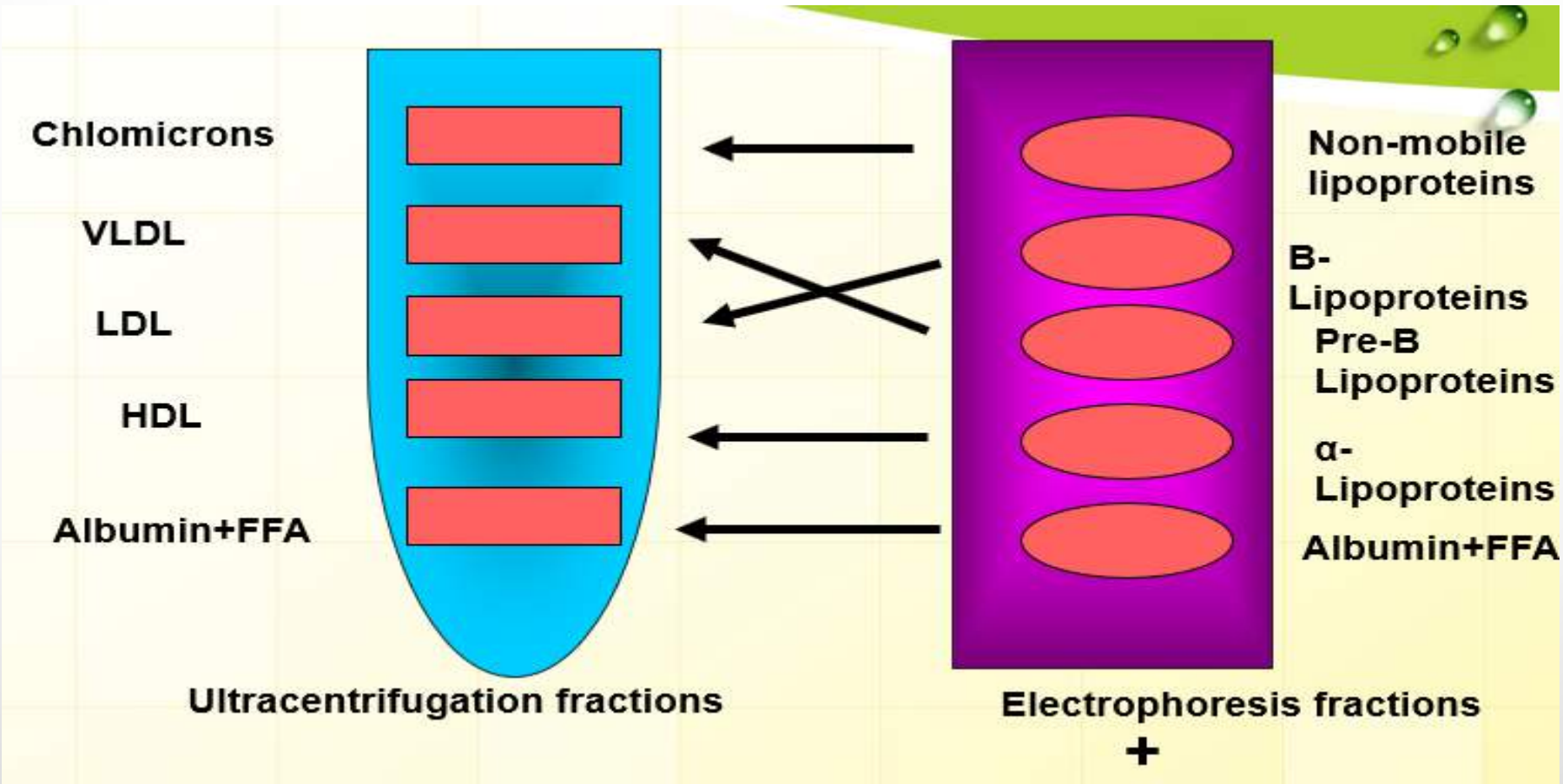


Classification of plasma lipoproteins

Lipoproteins differ in the **ratio of protein to lipids**, & in the particular **apoproteins** & **lipids** that they contain.

They are classified based on their **density**:

- **Chylomicron (CM)** (largest; lowest in density due to high lipid/protein ratio; highest % weight triacylglycerols)
- **VLDL** (very low-density lipoprotein; 2nd highest in triacylglycerols as % of weight)
- **IDL** (intermediate density lipoprotein)
- **LDL** (low density lipoprotein, highest in cholesteryl esters as % of weight)
- **HDL** (high density lipoprotein; highest in density due to high protein/lipid ratio)



Function of lipoproteins

- **Serve to transport lipids and lipid-soluble compounds** between tissues and organs
  - Substrates for energy metabolism (TG)
  - Essential components for cells (PL, C)
  - Precursors for hormones (C)
  - Lipid soluble vitamins (D, E, K, A)
  - Precursors for bile acids (C)

Transport functions of lipoproteins

Class	Origine	Transport
CM	enterocyte	exogenous TAG from GIT to peripheral tissues
VLDL	liver	endogenous TAG from liver to periph. tissues
LDL	plasma	cholesteryl esters to peripheral tissues
HDL	liver	cholesterol from tissues to liver

Apoproteins:

Apoproteins may be present peripherally and called **peripheral protein** (e.g., apo C & apo E) and integrated among the amphipathic lipid and called **integral protein** (e.g., apo B-48 and apo B-100. The followings represent the main apoprotein and their percentage in different lipoprotein molecules as:

1-Chylomicrons: The protein part forms 1%. They are apo A-1, apo A-II, apo A-IV, apo B-48, apo C-I, apo C-II, apo C-III and apo E.

2-VLDL: The protein part forms 10%. They are apo B-100, apo C-I, apo C-II and apo C -III.

3-LDL: The protein part forms 20%. The apoprotein present is apo B-100.

4-HDL: The protein part forms 40%. They are apo A-I, apo A-II, apo A-IV, apo C-I, apo C-II, apo C-III and apo E.

Functions of apoproteins:

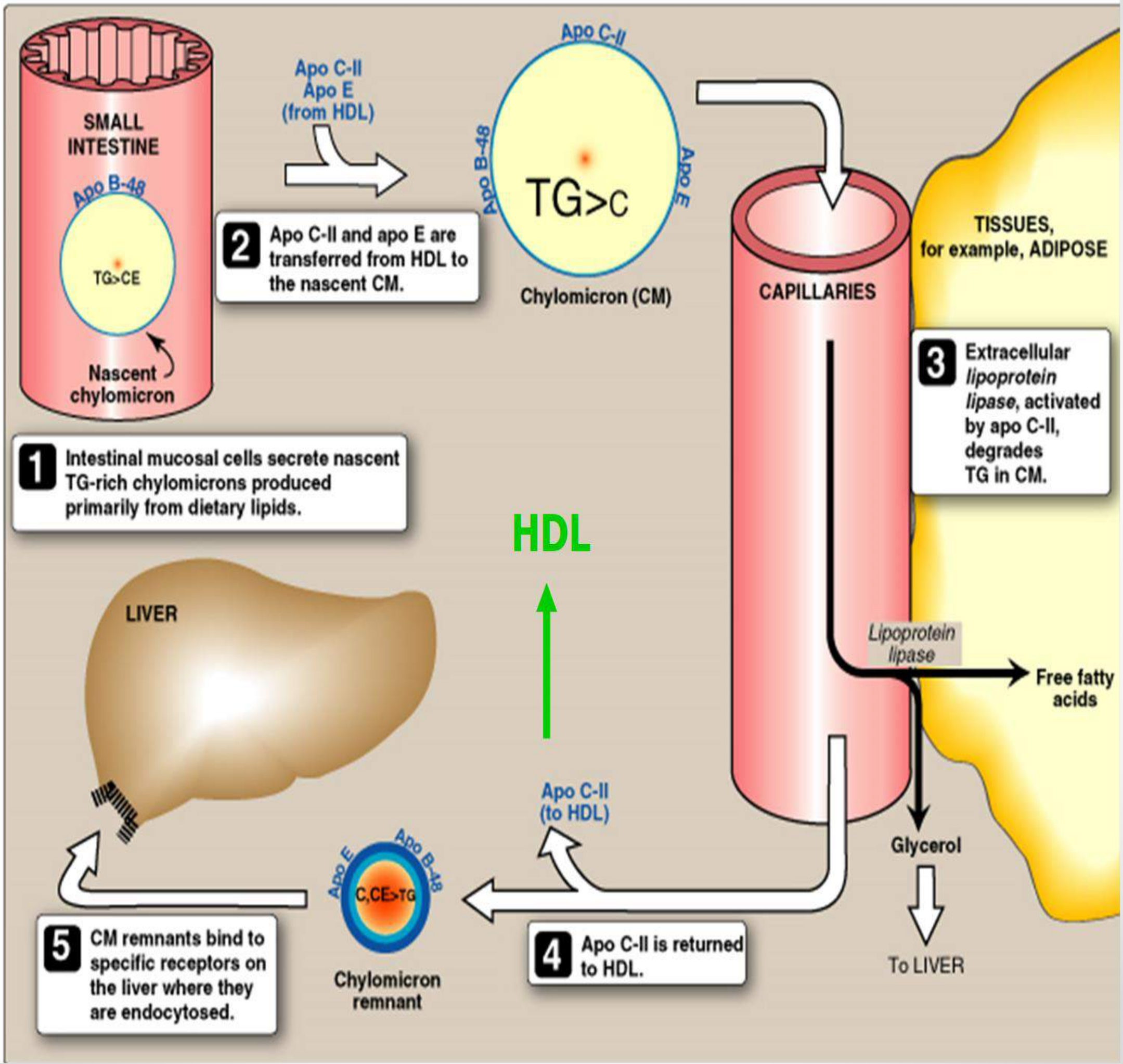
1 -They can form part of the structure of the lipoprotein e.g., apo B.

2-They are enzyme cofactor (e.g., apo C-II for lipoprotein lipase)

3- They are enzyme inhibitors (e.g., apo A-II & apo C –III for lipoprotein lipase).

4 -They act as ligands for interaction with lipoprotein receptors in tissues (e.g., apo B-100 and apo E for the LDL receptor)

Metabolism of chylomicron



Metabolism of CM

I- Synthesis of nascent chylomicrons

1. Nascent chylomicrons are formed in the **intestinal mucosa** and pass to the **chyle** and then to the **blood stream** through the thoracic duct.
2. **Triglycerides** are the predominant lipid in chylomicrons and form 90% of the total lipid present in them. (***Exogenous ; dietary triglycerides***)
3. Its protein content is about 1%.
4. **Apo-A** and **apo-B48** are component of the nascent cylomicrons

II- conversion of nascent chylomicrons to mature chylomicrons

- After entering the blood stream, the chylomicron particles **transfer apo-A to HDL** and **acquire apo-C from HDL**.

III- Degradation of chylomicrons

1. Apo-C_{II} activates **lipoprotein lipase** (LPL= clearing factor)

- **LPL** located in the ***capillaries*** of adipose and other peripheral tissues as cardiac and skeletal muscles and lactating mammary gland.
- **LPL** ***Hydrolyze triglyceride*** (TG) in the core of CM and VLDL to free fatty acids and glycerol.
- ***Insulin*** enhances the synthesis of this enzyme and ***heparin*** increases its activity.

III- Degradation of chylomicrons

Triglycerides in chylomicrons are hydrolyzed into glycerol and FFA.

- **The fatty acids** are released and oxidized in muscles or stored as triglycerides in adipose tissue. They are transported bound to plasma albumin.
- **Glycerol** is taken by the liver cells mainly (due to high activity of glycerol kinase).

IV- Formation of chylomicron remnants

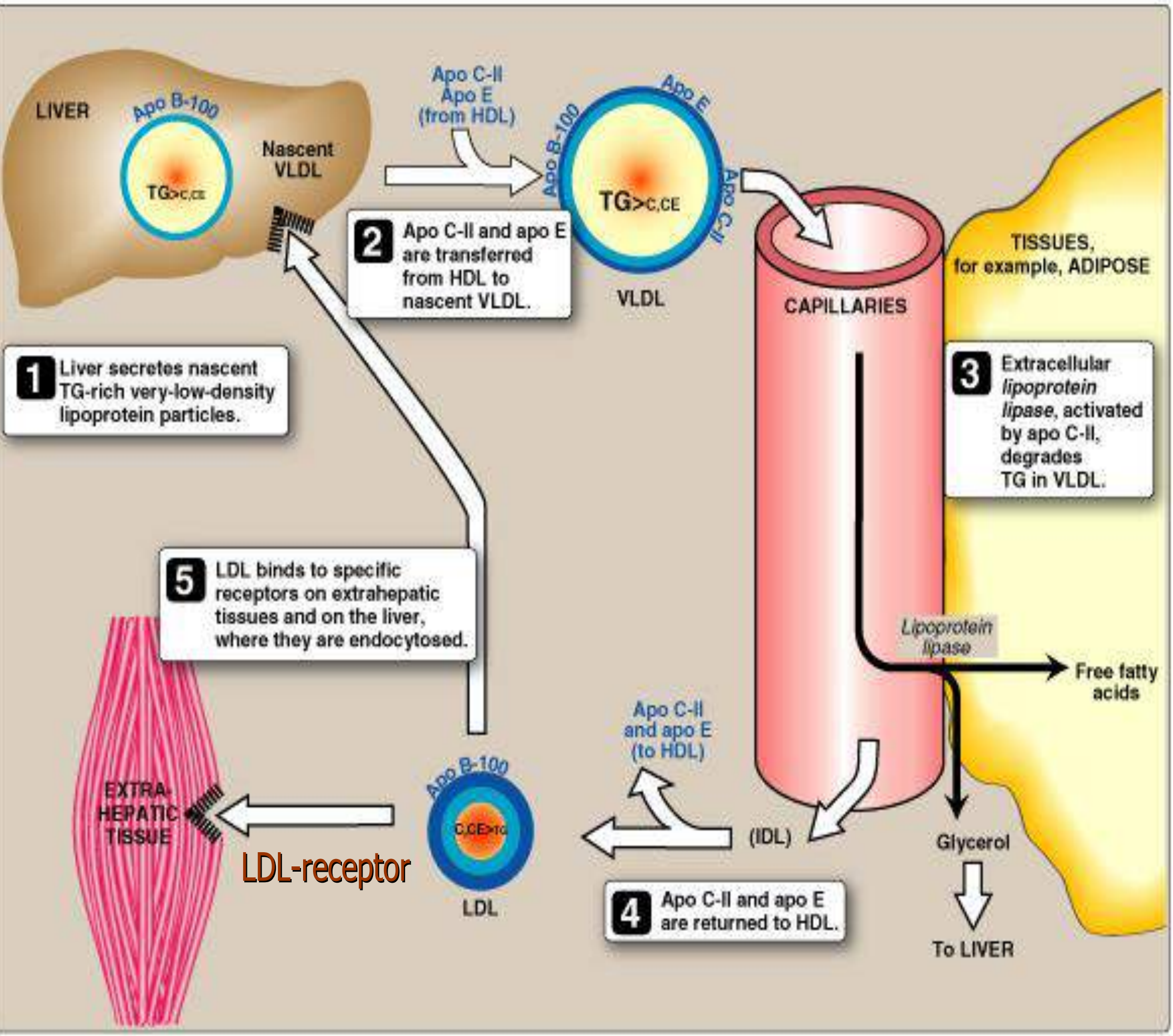
1. As triglycerides are removed from the hydrophobic core of chylomicrons, the surface area of cylomicrons decreases.
2. The more hydrophilic surface components **(apo-C, unesterified cholesterol and phospholipids)** are transferred **to HDL**.

- The remaining particles are termed chylomicron remnants.

V- Fate of chylomicron remnants

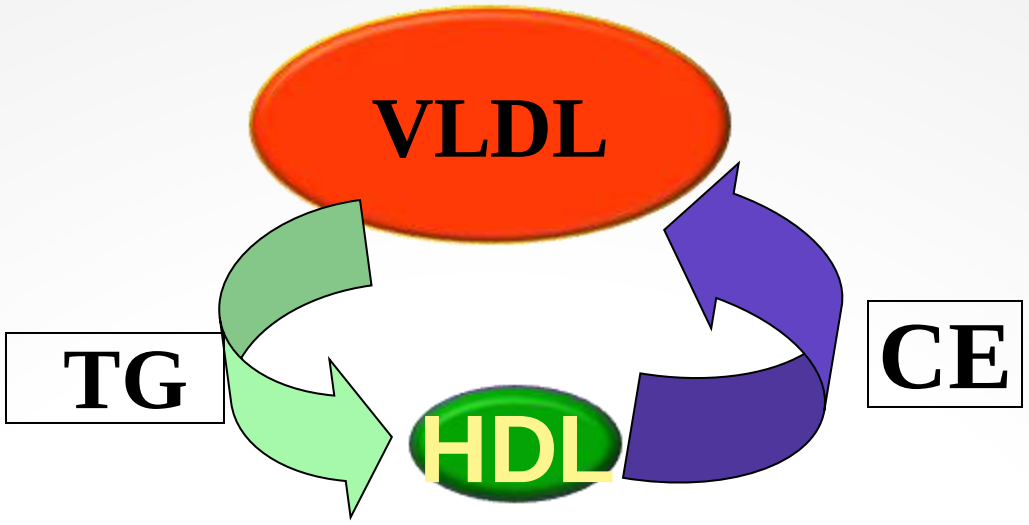
- They are triglycerides poor particles and consist mainly of **cholesterol esters, apo-B48, apo-E**.
- They interact with **receptors on liver** cells and are taken by *endocytosis*, where they are catabolized within the hepatic lysosomes and the products (amino acids, fatty acids, cholesterol) are released into the cytosol and reutilized by the hepatic cells.
- remnants are taken up by liver cells due to **apoE** recognition sites.

Metabolism of VLDL and LDL



Metabolism of VLDLs

- Assembled and secreted ***by liver*** directly into blood as nascent form.
- Carry lipids (hepatic origin***; endogenous TG***) from liver to peripheral tissues.
- Mature VLDLs: contain Apo B-100 plus Apo C-II and Apo E (both from HDL). ApoC-II is required for activation of lipoprotein lipase.
- Lipoprotein lipase is required to degrade TG into glycerol and fatty acids.
- As TG is degraded, VLDLs become
  - Smaller in size
  - More dense
  - Apo C back to HDL
- Exchange of TG with cholesterol ester (HDL) by cholesterol ester transfer protein (CETP)
- End products: IDL (returns Apo E to HDL) and become LDL
  - Most core lipid in LDL is **cholesterol ester.**
  - **ApoB100** is **only** apolipoprotein in the surface.



Choleteryl Ester Transfer Protein (CETP)

Summary of CM, VLDL, LDL

Chylomicron

- Synthesized **in small intestine**
- Transport **dietary lipids**
- 98% lipid, large sized, lowest density
- **Apo B-48:** Receptor binding
- **Apo C-II:** Lipoprotein lipase activator
- **Apo E:** Remnant receptor binding

VLDL

- Synthesized in liver.
- Transport endogenous TG.
- 90% lipid, 10% protein.
- **Apo B-100**
  - Receptor binding
- **Apo C-II**
  - LPL activator
- **Apo E**
  - Remnant receptor binding

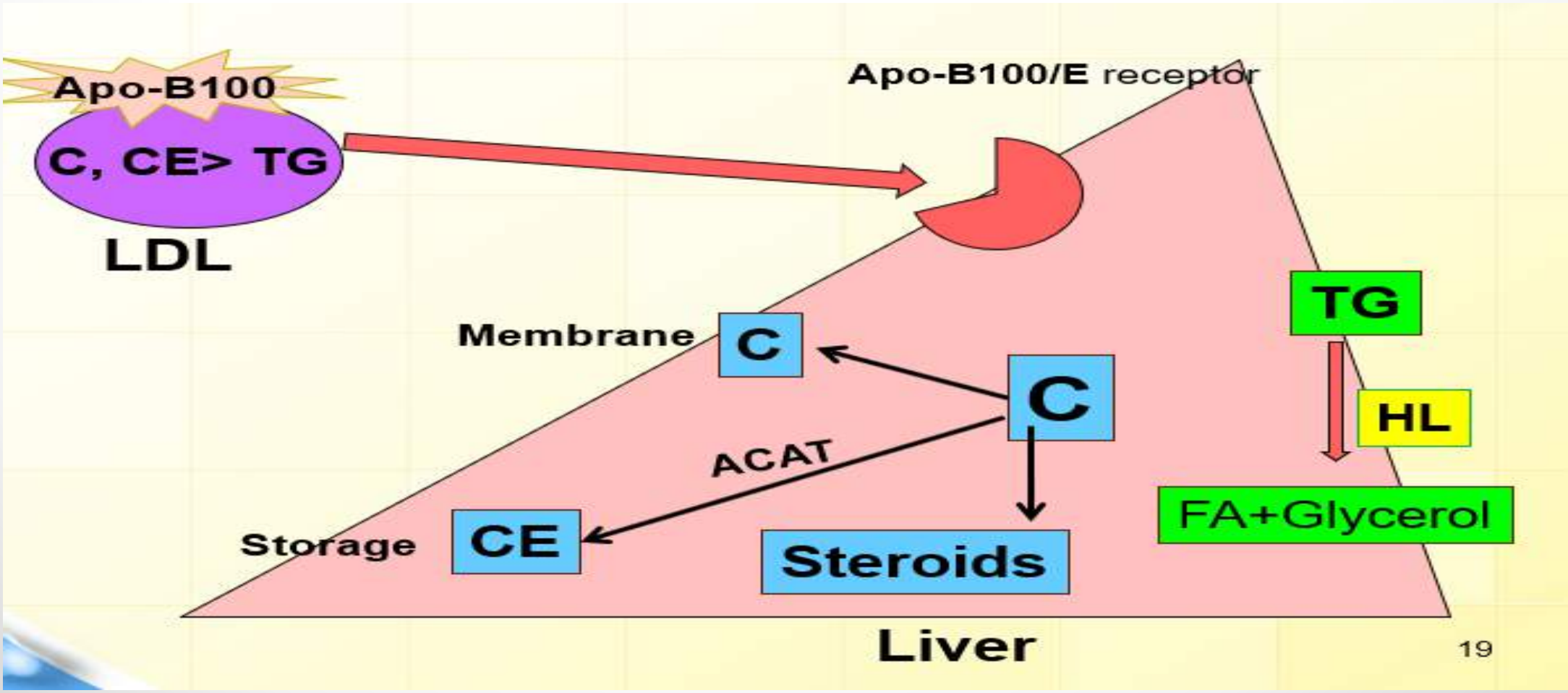
LDL

- Synthesized from IDL.
- Cholesterol transport.
- 78% lipid, 58% cholesterol & CE.
- **Apo B-100**
  - Receptor binding

LDL receptor

- LDL receptors exist in the **liver** and in most **peripheral tissues**
- The complexes of LDL and receptor are taken into the cells by endocytosis, where LDL is degraded but the receptors are recycled
- LDL cholesterol levels are positively related to risk of cardiovascular disease
- Therefore, cholesterol in LDL has been called **“bad cholesterol”**

Fates of cholesterol intracellular.



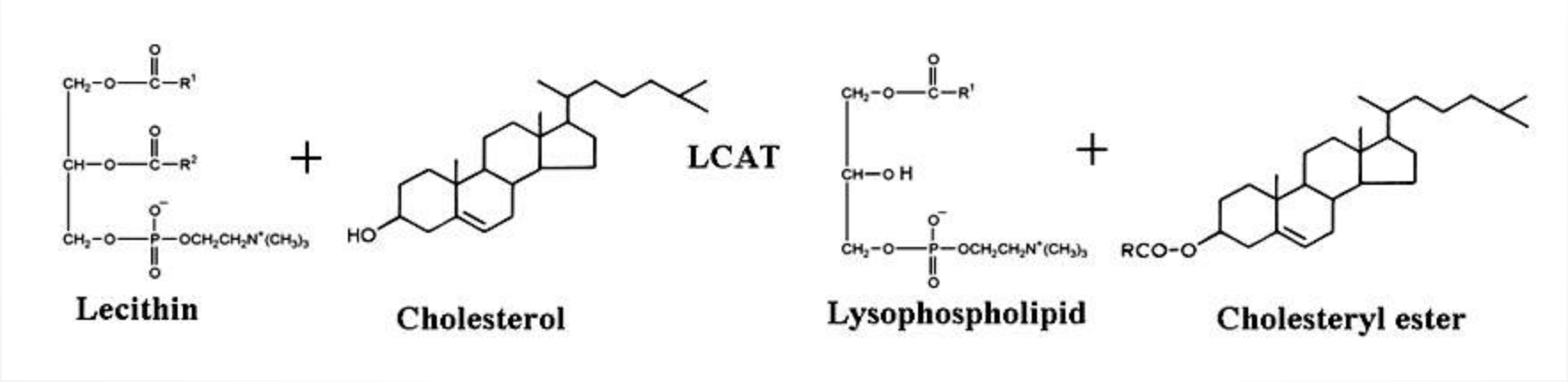
High density lipoprotein (HDL)

- Synthesized de novo in the **liver** and small **intestine**, primarily as protein-rich **disc-shaped** particles.
- **Nascent HDL** consists of discoid PL bilayers containing apo E & free cholesterol (C).
- **On entering the circulation:**

➢ **apo-A**, the major HDL apoprotein is acquired from **CM**

➢ **apo-C** is transferred to **CM** and **VLDL.**

- **LCAT** and its activator **apo-A1**, bind to the discoidal particles, Apo-AI activates **LCAT** (lecithin – cholesterol acyl transferase) which is present on the HDL surface. Free cholesterol, present on the HDL surface is esterified by LCAT.



- The non-polar **CE** move into the hydrophobic interior of the bilayer, whereas lysolecithin is transferred to plasma albumin. Thus, a **spherical HDL** is formed.

Liver

Bile acids

C + FA

CE

HDL receptor

Apo-A

CM
VLDL

Apo-C

Apo-E

LCAT

Nascent HDL

Apo-A

CE

LCAT

Mature HDL

C

C

C

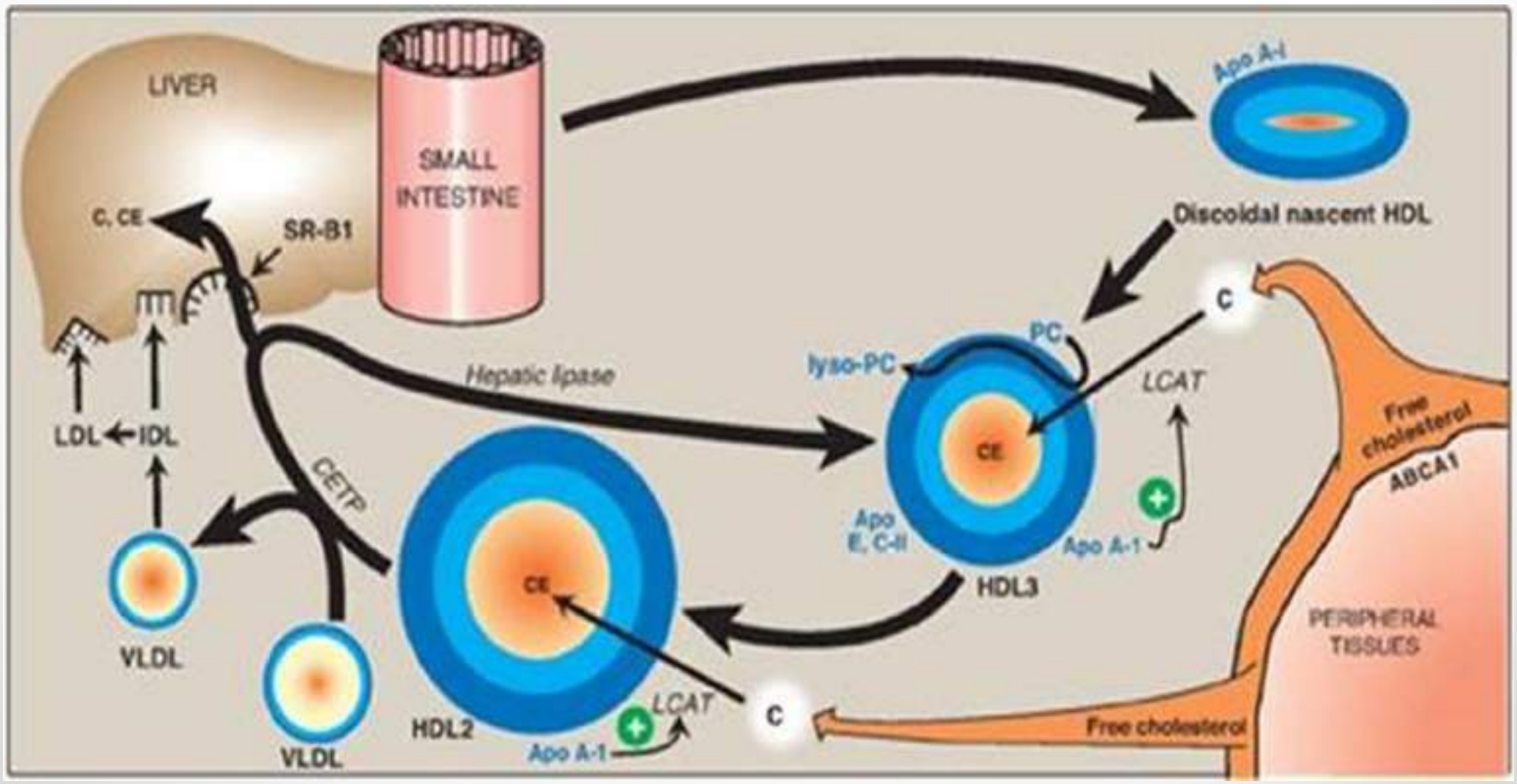
Other lipoproteins

Peripheral tissue

interchange of HDL2 & HDL3

- **HDL3** generated from discoidal HDL, by the action of LCAT, accepts cholesterol from the tissues and C is then esterified by LCAT, increasing the size of particles to form the less dense **HDL2**.
- **HDL2** by the action of cholesterol ester transfer protein (CETP). Exchanges CE with CM & VLDL remnants; gets TG in return allowing more cholesterol removal from peripheral tissues. When C efflux followed by esterification by LCAT is effective, HDL2 will be high.

HDL3 is then reformed, either after selective delivery of CE to the liver via the SR-B1**(scavenger receptor class B**) or by hydrolysis of HDL2 PL & TG by hepatic lipase and endothelial lipase. (**Reverse Cholesterol Transport (RCT)**



Athersclerosis

DEF: It is a chronic inflammatory response in the wall of arteries due to accumulation of macrophages, promoted by LDL without adequate removal of fat and cholesterol from the macrophages by functional HDL. Caused by formation of multiple atheromatous plaques inside the arteries.

Athersclerosis produce many problems:

A) Plaque rupture ⟶ clots heal with fibrous tissue ⟶ Arterial stenosis.

B) Compensatory artery enlargement ⟶ aneurysm.

C) Plaque rupture ⟶ thrombus, myocardial infarction, stroke.

Risk factors:

1- Serum cholesterol over 220 mg/ dl., LDL over 160mg/ dl.

2- HDL cholesterol below 35mg/ dl. Decreased HDL/ LDL ratio below 0.3.

3- Low poly unsaturated fatty acids in diet.

4- Smoking, coffee , stress.

5- Diabetes mellitus.

6- Sedentary life, obesity, hypertension.

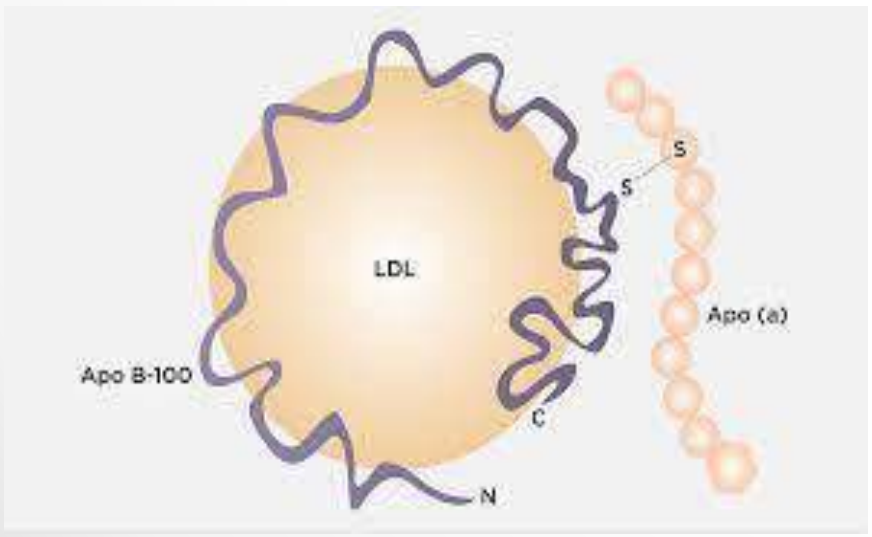
Lipoprotein (a) & heart disease

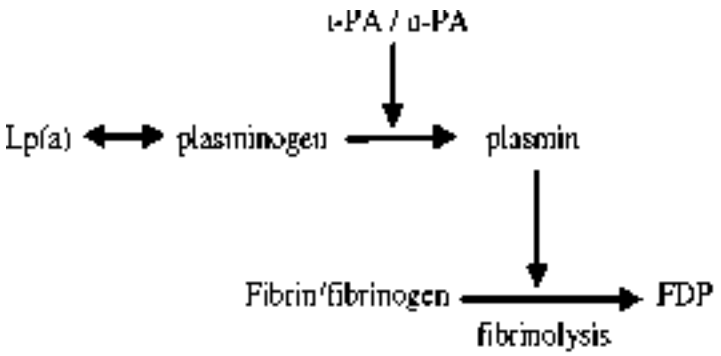
-Lipoprotein (a) or lipoprotein small a [LP (a)] particle attached to apo B-100 which form an integral protein in LDL. When present in large quantities in plasma, lead to increase the risk of coronary heart disease.

-LP (a) plasma levels are determined by genetic factors. However, factors as diet may play some role as trans fatty acids have been shown to increase LP (a) and estrogen decrease both LDL & LP (a).

-Apo (a) is a highly homologous to plasminogen, the precursor of blood protease which causes fibrinolysis.

-Elevated LP (a) competes with plasminogen for plasminogen activator. Thus, prevent plasminogen from fibrinolysis and hence coronary attack persists.





t-PA = tissue plasminogen activator
u-PA = urokinase type plasminogen activator

Disorders of lipoprotein metabolism

I. Hypolipoproteinemias

	Types	Cause	Effect & remarks
1	Abetalipoproteimia	Failure of loading of apo B-48 and apo B-100 with lipids.	No chylomicrons, VLDL or LDL are formed. 1.Plasma triacylglycerol is low 2.Accumulation of acylglycerols in liver & intestine leading to fatty liver (steatosis) & malabsorption of fats (steatorrhea), respectively. 3.Early death which can be avoided by administration of large doses of fat- soluble vitamins, particularly vitamin E.
2	Hypobetalipoprotei-nemia	familial disease caused by decrease loading of apo B-100 with lipid due to impaired synthesis by the liver	Decreased VLDL and LDL formation and hence plasma lipids were low.
3	Alphalipoprotein deficiency, Tangier disease, fisheye disease and apo A-1 deficiency	Absence of apo C-II & apo A due to failure of their synthesis.	All have low or near absence of HDL. 1. Hypertriacylglyceridemia due to absence of apo C-II which is activator for lipoprotein lipase. 2. Atherosclerosis in elderly. 3- Fish eye disease is characterized by partial deficiency of LCAT enzyme while complete deficiency of LCAT is called «familial LCAT deficiency» 4- A broad β band replaces LDL & VLDL due to apo C & apo E deficiencies taken by VLDL from HDL. 6. Accumulation of cholesterol esters in tissues cause a disease called Tangier's disease.

II. Hyperlipoproteinemias

	Types	Cause	Effect & remarks
1	Hyperchylomicro nemi a	The familial type is due to deficiency of lipoprotein lipase	-Increased plasma levels of chylomicrons and VLDL. - LDL &HDL are reduced. - Increased plasma level of triacylglycerols and slight increase in plasma cholesterol. - So, the plasma is turbid.
2	Hyperbetalipoprot eine mia	- The familial type is due to defective LDL receptor or mutation in ligand region of apo B-100. - The acquired type occurs in hypothyroidism as T3 increases the sensitivity of LDL receptor to LDL.	There are two subtypes of hyperbetalipoproteinemia: 1)Type IIa: It is characterized by increased plasma LDL without increase in VLDL. So, the plasma is clear. 2)Type IIb: It is characterized by increased plasma LDL with a slight increase in plasma VLDL. So, the plasma is slightly turbid. There is marked hypercholesterolemia which if familial called familial hyper cholesterolemia. Also, there is a slight increase in plasma triglycerides levels especially in type IIb. Atherosclerosis & coronary heart disease were sequelae of elevated LDL & hypercholesterolemia.
3	Dysbetalipoprotein emi a: Broad β-band disease or, remnant removal disease	The familial type is due to abnormality in apo E leading to the defective uptake of chylomicrons & VLDL by apo E receptor	Increase chylomicron remnants & VLDL remnants in plasma. - Electrophoresis shows broad β-band. So , the disease sometimes refers to it as "broad β-band disease" - The plasma is turbid. - Plasma triacylglycerols & cholesterol are increased which are responsible for occurrence of xanthomas & atherosclerosis.

4	**Hyperprebetalipoprotei nemia**	**-The familial type is due to over production of VLDL due to increase formation of triacylglycerols from carbohydrates** **-The acquired type is due to type II diabetes mellitus, obesity, alcoholism and administration of progestational hormones.**	**- VLDL concentration & cholesterol levels rise** **- Plasma is turbid.** **- The patients had xanthomas, atherosclerosis, & coronary heart disease.**
5	Hyperchylomicronemia & Hyperprebetalipoprotei nemia	It may be due to increase apo-B	1 Increase chylomicrons & VLDL leading to increase in triacylglycerol & cholesterol. 2 The plasma is turbid. 3 This type is associated with obesity & glucose hypotolerance.
6	Hyperalphalipoproteinemia	It is due to familial increase in HDL concentration.	-The plasma is clear. -HDL concentration is increased -It is a rare condition apparently beneficial to health & longevity. -It occurs in patients taken estrogen.
7	Hepatic lipase deficiency	Deficiency of hepatic lipase enzyme.	1 Accumulation of large triacylglycerol rich –HDL & VLDL remnants. 2 Patients have xanthomas & coronary heart disease.
8	Familial LCAT Deficiency	Absence of LCAT enzyme.	1 Block in reverse cholesterol transport (centripetal transport). 2 HDL remains as nascent disk incapable of taking up & esterifying cholesterol. 3 Plasma concentrations of cholesterol esters & lysolecithin are low.
9	Familial lipoprotein (a) excess	It is a genetic disease characterized by increase LP (a) which consists of 1 mol of LDL attached to 1 mol of apo (a)	premature coronary heart disease due to atherosclerosis, plus thrombosis due to inhibition of fibrinolysis


WISH YOU ALL
THE BEST