LIPIDS PROFILE

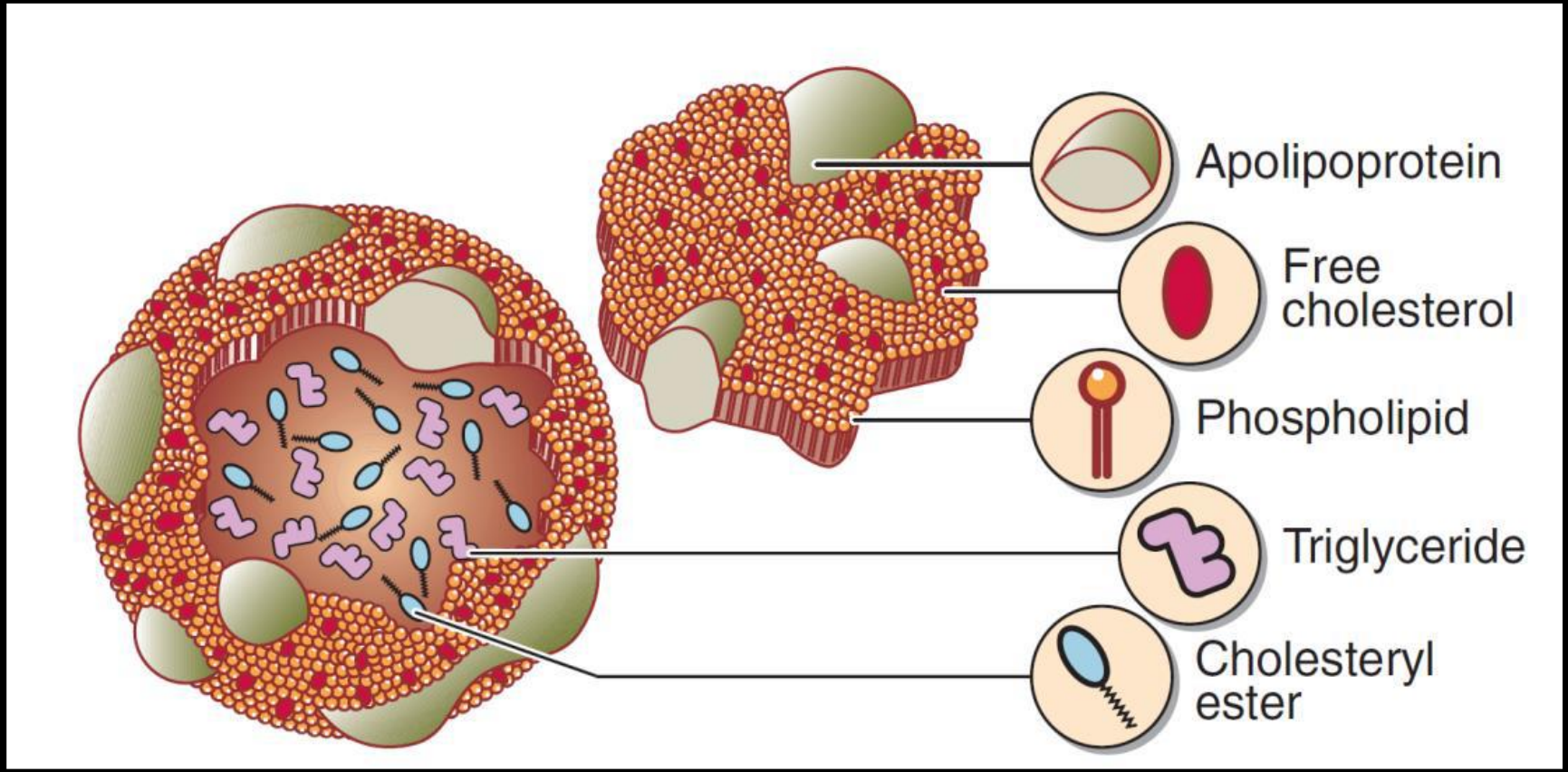
- Lipids absorbed from the diet (exogenous), and lipids synthesized by the liver and adipose tissue (endogenous), must be transported between the various tissues and organs, through the blood, for utilization and storage.

- ▪ Since lipids are insoluble in water, the problem arises of how to transport lipids in an aqueous solution (such as the blood).
- ▪ This is solved by associating non-polar lipids (TAG and cholesterol esters) with amphipathic lipids (phospholipids and cholesterol) and protein (Called apolipoproteins or apoproteins) to make water-miscible lipoproteins.

- ▪ **Cholesterol** is an essential component of all cell membranes and is a precursor for steroid hormone and bile acid biosynthesis.

- ▪ **Triglyceride** is central to the storage and transport of energy within the body.

STRUCTURE OF LIPOPROTEIN

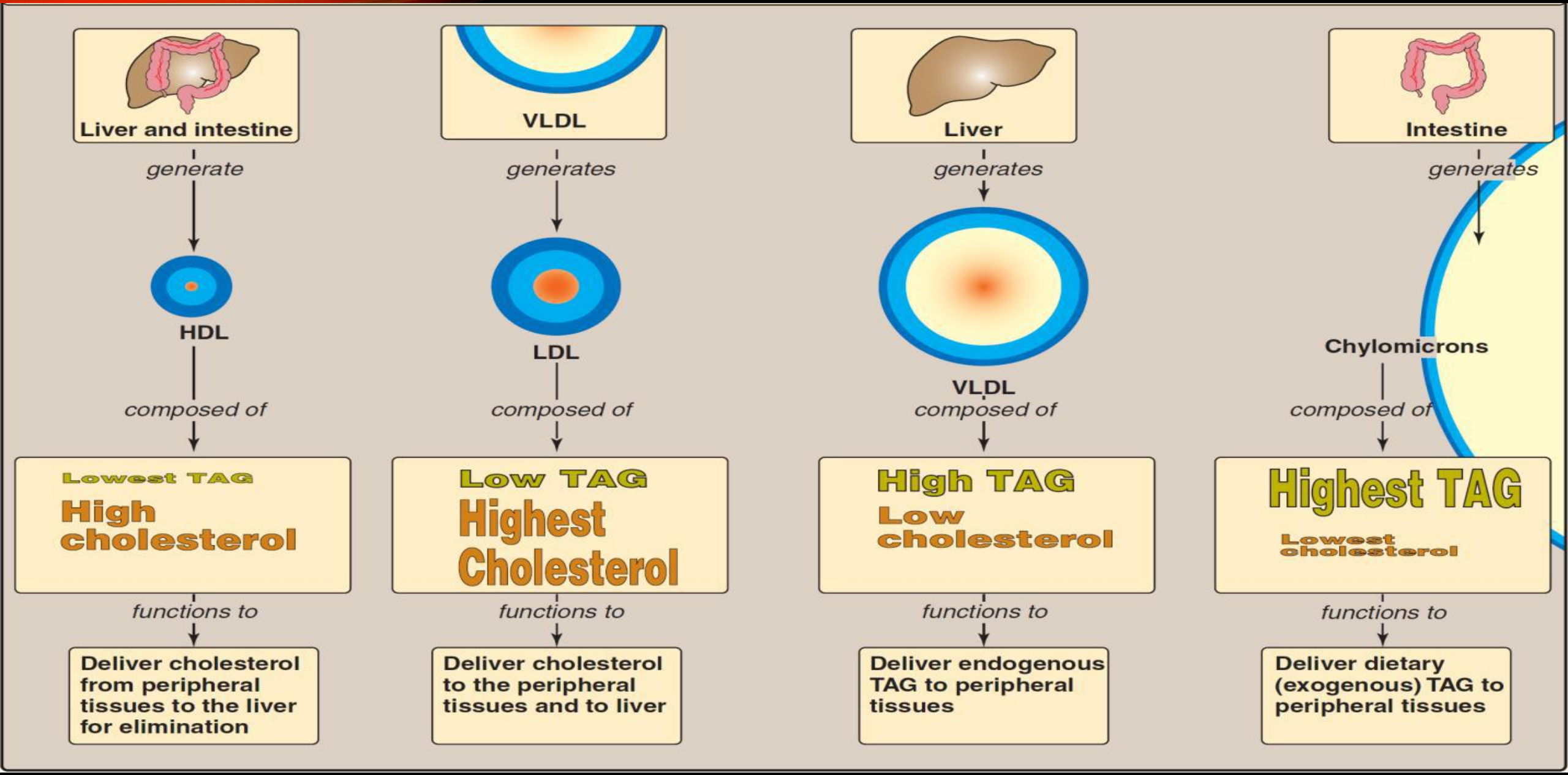


LIPOPROTEINS ARE CLASSIFIED INTO 4 AS FOLLOWS:

- 1. **Chylomicrons (CMs):** They are the largest and least dense lipoproteins. They transport dietary (exogenous) TAG and cholesterol from intestine to other tissues in the body.
- 2. **Very low density lipoproteins (VLDLs):** They transport endogenous TAG and cholesterol, synthesized in the liver, to other tissue in the body.
- 3. **Low density lipoproteins (LDLs):** Derived from VLDL, they transfer cholesterol from liver to other tissues.
- 4. **High density lipoproteins (HDLs):** They are the smallest and the densest of plasma lipoproteins. They transfer cholesterol from peripheral tissues and other lipoproteins to liver.

Lipoprotein	Source	Major lipid	Structural protein
CM	Intestine	Dietary TAG	Apo-B48
VLDL	Liver	Endogenous TAG	Apo-B100
LDL	VLDL	Cholesterol to tissues	Apo-B100
HDL	Liver and Intestine	Cholesterol from tissues	Apo-A1

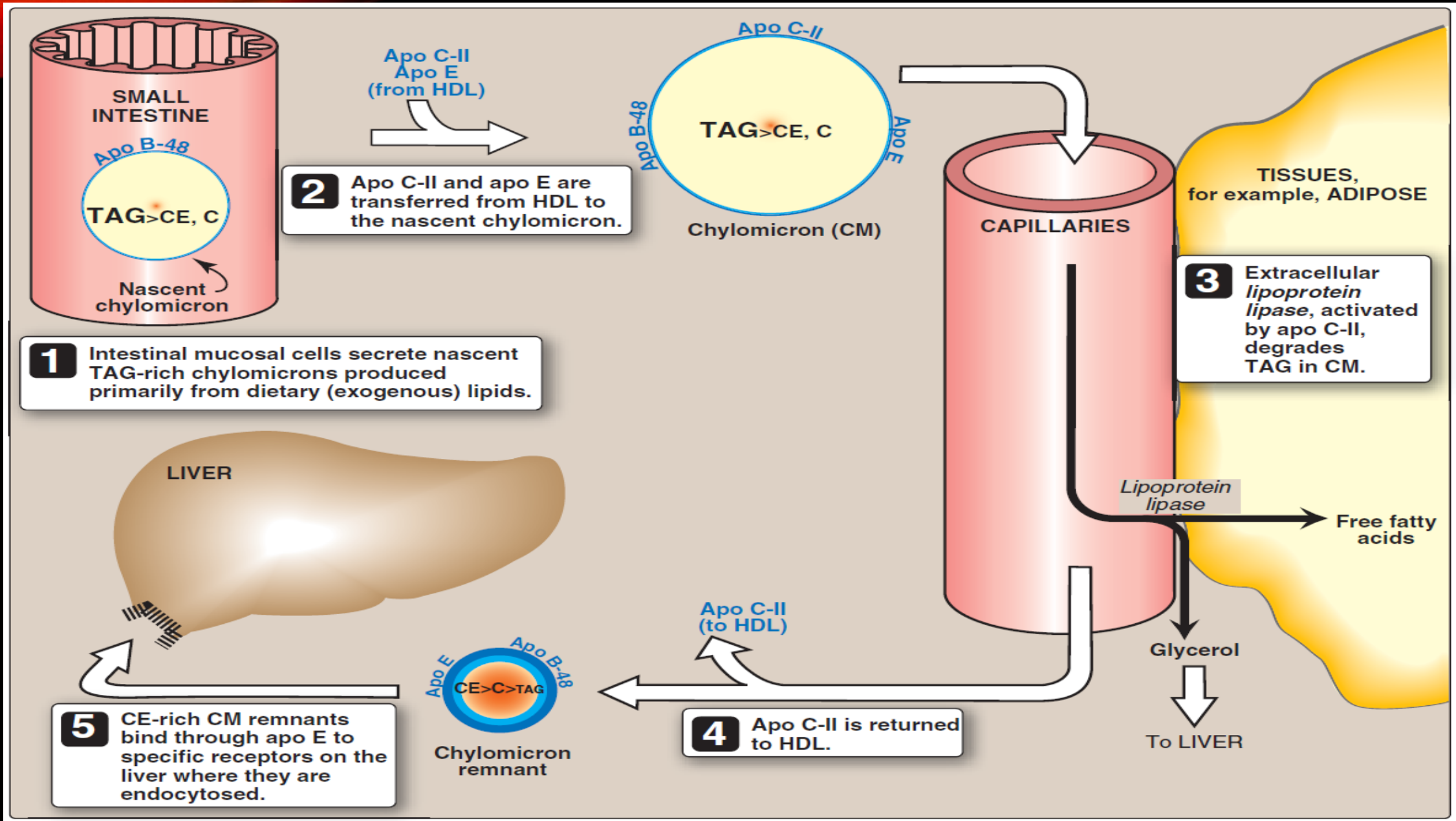
- ▪ The functions of apolipoprotcins:
- 1) Solubilize the hydrophobic lipids (Apo-B48, Apo-B100, Apo-A-1).
- 2) Act as cellular targeting signals, providing recognition sites for cell surface receptors (Apo-E).
- 3) Serving as activators for enzymes involved in lipoprotein metabolism (Apo-CII).


Liver and intestine
generate
HDL
composed of
Lowest TAG
High cholesterol
functions to
Deliver cholesterol from peripheral tissues to the liver for elimination
VLDL
generates
LDL
composed of
Low TAG
Highest Cholesterol
functions to
Deliver cholesterol to the peripheral tissues and to liver
Liver
generates
VLDL
composed of
High TAG
Low cholesterol
functions to
Deliver endogenous TAG to peripheral tissues
Intestine
generates
Chylomicrons
composed of
Highest TAG
Lowest cholesterol
functions to
Deliver dietary (exogenous) TAG to peripheral tissues

METABOLISM OF LIPOPROTEINS

- **1) Metabolism of CM (The exogenous lipid cycle):**
- **-** CMs are assembled in intestine then secreted into the lymphatic vessels. They carry dietary TAG, cholesterol, CE, PL to the peripheral tissues.
- **-** The CM is called nascent and it contains Apo-B48
- **-** In plasma, it receives Apo-E (which is recognized by hepatic receptors) and Apo-CII (which is necessary for the activation of LPL) from HDL.

- **-** LPL is activated by Apo-CII and hydrolyzes the TAG into FFA and glycerol leading to degradation of CM, decreasing its size and increasing its density.
- **- FFA and glycerol enter the target tissues (muscles or adipose)**
- **-** Apo-CII is returned back to HDL and the remaining particle is CM remnant.
- **-** CM remnant is rapidly removed from the circulation by the liver, whose cell membranes contain lipoprotein receptors that recognize Apo-E.


SMALL INTESTINE
Apo B-48
TAG>CE, C
Nascent chylomicron
1 Intestinal mucosal cells secrete nascent TAG-rich chylomicrons produced primarily from dietary (exogenous) lipids.
Apo C-II
Apo E
(from HDL)
2 Apo C-II and apo E are transferred from HDL to the nascent chylomicron.
Apo C-II
Apo B-48
TAG>CE, C
Apo E
Chylomicron (CM)
CAPILLARIES
TISSUES, for example, ADIPOSE
3 Extracellular lipoprotein lipase, activated by apo C-II, degrades TAG in CM.
Lipoprotein lipase
Free fatty acids
Glycerol
To LIVER
LIVER
Apo C-II
(to HDL)
4 Apo C-II is returned to HDL.
Apo E
Apo B-48
CE>C>TAG
Chylomicron remnant
5 CE-rich CM remnants bind through apo E to specific receptors on the liver where they are endocytosed.

- **2) Metabolism of VLDL:**
- - VLDLs are formed in the liver. Carry the endogenous TAG and cholesterol from the liver into the peripheral tissues.
- - They are released as nascent VLDL containing Apo-B100.
- - In plasma, they receive Apo-E and Apo-CII from HDL.
- - LPL is activated by Apo-CII and hydrolyzes the TAG into FFA and glycerol leading to degradation of VLDL, decreasing its size and increasing its density.
- - Apo-CII and Apo-E is returned back to HDL

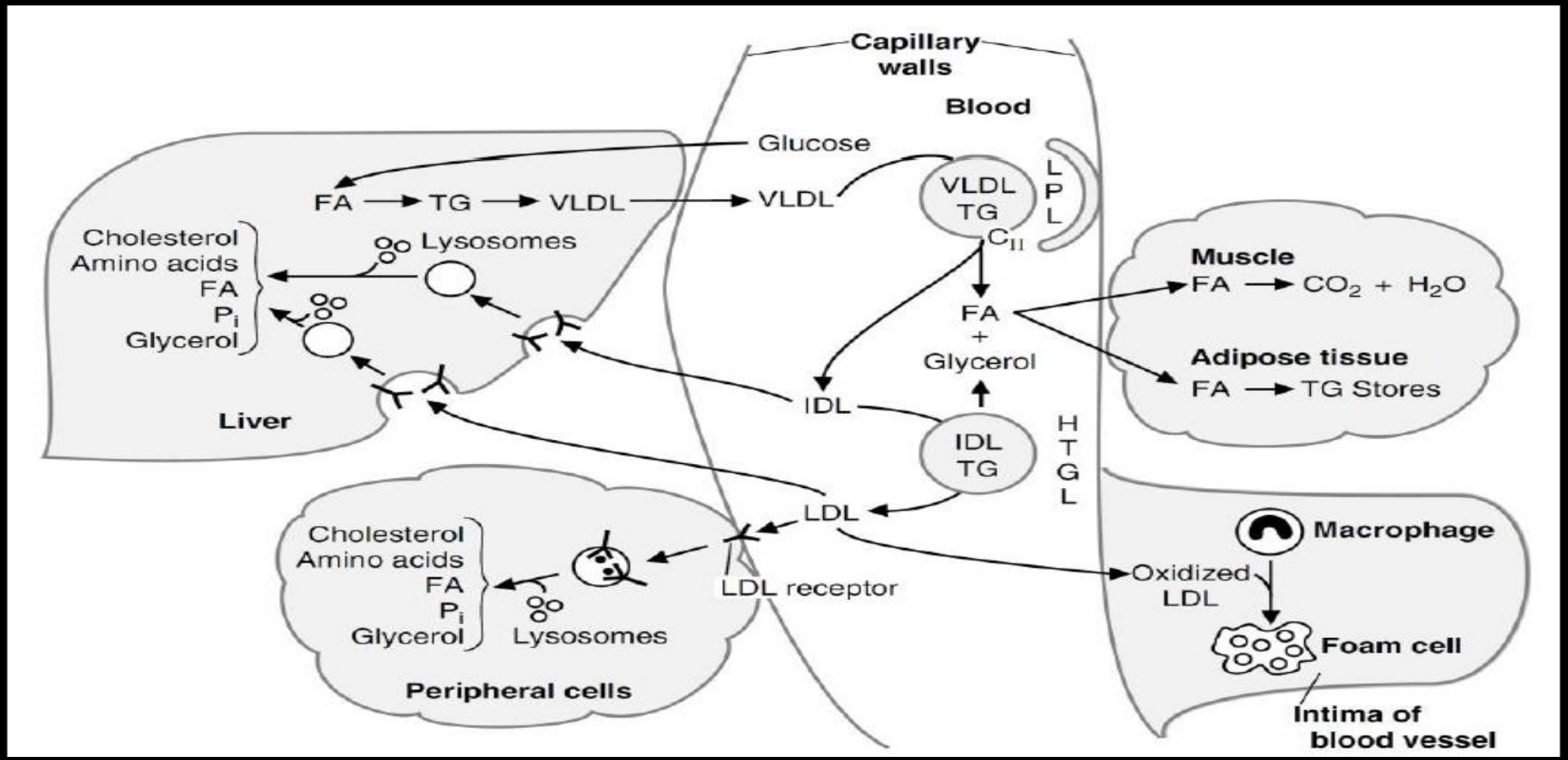
- **-** Finally, TAGs and phospholipids are transferred from VLDL to HDL in an exchange reaction that concomitantly transfers CE from HDL to VLDL. This exchange is accomplished by cholesteryl ester transfer protein (CETP).
- **- With these modifications, the VLDL is converted in the plasma to LDL.**
- **-** An intermediate-sized particle, the IDL (or VLDL-remnant), is observed during this transition.
- **- IDL** can also be taken up by cells through receptor-mediated endocytosis that uses Apo-E as the ligand.

- **3) Metabolism of LDL (Bad Cholesterol):**
- **-** They are derived from VLDL by delipidation (LDL particles contain less TAG than their VLDL, and have a high concentration of cholesterol and CE)
- **-** They contain Apo-B100 then they receive Apo-E from HDL.
- **- They transfer cholesterol and CE to the peripheral tissues**

- **- They are cleared from plasma by:**
- **a) LDL-Receptors:**
- They are negatively charged glycoproteins that are present on the surface of all cells.
- They bind to lipoproteins that contain Apo-B100 or Apo-E and internalized them by endocytosis for breakdown within the cells
- The number of LDL receptors depends on the requirement of the cells to cholesterol (if the cholesterol within the cell is sufficient, the receptors are down-regulated and vise versa)
- Effects of endocytosed cholesterol on cellular cholesterol homeostasis:
- 1) Inhibits HMG-CoA reductase to reduce the synthesis of cholesterol
- 2) Stimulates the storage of cholesterol as cholesterol ester via ACAT
- 3) It causes down-regulation of LDL receptors

- **b) LDL Receptor-Related Protein (LRP):**
- LRP is structurally related to the LDL receptor but recognizes a broader spectrum of ligands.
- The LRP receptor recognizes the Apo-E lipoproteins (remnants produced by the action of LPL on TAG of CM and VLDL i.e CM remnants and IDL)
- Thus, one of its functions is believed to be the clearance of these remnants from the blood.
- The LRP receptor is abundant in the cell membranes of the liver, brain, and placenta.
- In contrast to the LDL receptor, synthesis of the LRP receptor is not significantly affected by an increase in the intracellular concentration of cholesterol

- **c) Macrophage Scavenger Receptors:**
- Macrophages have non-specific receptors known as scavenger receptors that bind various types of molecules, including chemically modified LDL particles.
- Chemical modifications of LDL involves oxidation polyunsaturated fatty acid
- In contrast to the LDL receptors, the scavenger receptors are not subject to down regulation. The continued presence of scavenger receptors in the cell membrane allows the cells to take up oxdatively modified LDL.
- When the macrophages become engorged with lipids, they are called foam cells
- An accumulation of these foam cells in the sub endothelial space of blood vessels participates in the formation of atherosclerotic plaque


Capillary walls
Blood
Glucose
FA → TG → VLDL
VLDL
VLDL TG
C_{II}
LPL
Cholesterol
Amino acids
FA
P_i
Glycerol
Lysosomes
Liver
FA + Glycerol
IDL
IDL TG
HTGL
LDL
Muscle
FA → CO_2 + H_2O
Adipose tissue
FA → TG Stores
Cholesterol
Amino acids
FA
P_i
Glycerol
Lysosomes
Peripheral cells
LDL receptor
Macrophage
Oxidized LDL
Foam cell
Intima of blood vessel

- **4) Metabolism of HDL (Good Cholesterol):**
- **-** HDL particles are secreted directly into blood from the liver and intestine.
- **-** Newly HDL particles contain free cholesterol, phospholipids (Lecithin) and Apo-AI, Apo-CII, Apo-E.
- **-** In plasma, HDL transfers Apo-CII and Apo-E to CM and VLDL

- - HDL collects free cholesterol from other lipoproteins and cells to convert it to cholesterol ester via LCAT (which is activated by Apo-AI) as the HDL particles fill with cholesterol ester; they become larger and called HDL-3.
- - HDL-3 transfers cholesterol ester to VLDL in exchange with TAG & phospholipids by the action of CETP (Reverse Cholesterol Transport)
- - The remnant particle is smaller and called HDL-2 which can be catabolized by liver

- Dyslipidemias
- **-** Dyslipidemias are group of metabolic diseases result from any disturbances in the lipoproteins metabolism.
- **- In practice, lipoprotein disorders are simplistically classified as being:**
- 1) **Primary** – when the disorder is not due to an identifiable underlying disease.
- 2) **Secondary** – when the disorder is a manifestation of some other disease.

- **- Xanthomas**: They are cutaneous manifestations of lipidosis in which there is an accumulation of lipids in large foam cells within the skin.

TYPES OF DYSLIPIDEMIAS:

Hyperlipoproteinemia	Hypolipoproteinemia
Primary Hyperlipoproteinemia (Type I, IIa, IIb, III, IV and V) Secondary Hyperlipoproteinemia Diabetes mellitus Hypothyroidism Nephrotic syndrome Obesity Obstructive jaundice	A-α-lipoproteinemia (Tangier's) A-β-lipoproteinemia

PRIMARY HYPERLIPOPROTEINEMIA (FREDRICKSON CLASSIFICATION):

Type	Name	Causes	Lipoprotein	TC	TG
1	Familial Hyperchylomicronemia	↓ LPL or ↓ Apo-CII	CM	N or ↑	↑
2a	Familial Hypercholesterolemia	↓ LDL receptors.	LDL	↑	N
2b	Familial Combined Hypercholesterolemia	↓ LDL receptors ↑ Apo-B	LDL & VLDL	↑	↑
3	Familial Dysbetalipoproteinemia	↓ Apo-E	IDL & CM remnants	↑	↑
4	Endogenous Hyperlipemia	↑ VLDL production	VLDL	N or ↑	↑
5	Familial Hypertriglyceridemia	↑ VLDL production ↓ LPL	CM & VLDL	↑	↑

- **- Hypolipoproteinaemia:**
- 1) **A-**alpha**-lipoproteinemia (Tangier's):** Complete absence of ApoA-1, HDL is undetectable in plasma. Accumulation of cholesterol in tissues.
- 2) A-β-lipoproteinemia
- Complete absence of Apo-B. The lipoproteins that normally contain ApoB (i.e. CM, VLDL, IDL and LDL) are absent from plasma. Both plasma cholesterol and TAG are very low.

ATHEROSCLEROSIS

- - Atherosclerosis or arteriosclerosis refers to the development of an atheroma in an artery and the sclerosis of its wall.
- - An atheroma (from the Greek word for porridge) is a hard yellow plaque that gradually builds up on the inside of medium-sized arteries.
- - The plaque consists of a necrotic (dead) core rich in cholesterol, surrounded by fibrous tissue.
- - Sclerosis (from the Greek word for hard) means an abnormal hardening or fibrosis, which is the formation of excess fibrous material within a tissue.
- - Sufferers may experience a sudden heart attack or stroke, in most cases the arteries of the victims have gradually become blocked by atherosclerosis

- PATHOGENESIS OF ATHEROSCLEROSIS

- 1) Injury of arterial endothelium by hypercholesterolemia or other risk factors (hypertension, smooking, diabetes mellitus or immunological factors)
- 2) This injury encourages monocytes attachment, and endothelial cell dysfunction with altered prostacyclin (Normally, endothelial cells produce prostacyclin, that inhibits platelet aggregation).
- 3) Also, when endothelial cells are damaged, platelets begin to aggregate and release thromboxane A2 (TXA2), a substance that further stimulates platelet aggregation.

- 4) Endothelial cells can also bind LDL, and, when activated by injury, these cells and the attached monocytes/macrophages generate free radicals which oxidize the attached LDL, and destruction of the receptor needed for normal receptor-mediated clearance of LDL.
- 5) Modified LDL is taken up by macrophages via their "scavenger receptors“ to form foaming cells
- 6) Platelets, macrophages, and endothelial cells release growth factors, which cause proliferation of smooth muscle and deposition of connective tissue, resulting in atherosclerotic plaque.

- 7) The plaque forms the substrate on which thrombosis develops subsequent to rupture.
- 8) Rupture and hemorrhage of the encapsulated plaque in a coronary vessel may cause the acute formation of a clot (thrombus), which further occludes the vessel, causing a myocardial infarction.

- DIET AND LIFE STYLE CHANGES IN ATHEROSCLEROSIS

- - Diet rich in cholesterol raises its concentration in the blood and increases the formation of fatty deposits.
- - Dietary fat rich in saturated or trans unsaturated FA raises the blood cholesterol.
- **- Sucrose and fructose raise the blood lipids, particularly TAG.**

- - Therefore, in order to reduce the risk of heart attack, the intake animal fat that contains saturated FA should be reduced and replaced by vegetable oil (e.g., cottonseed, corn, and soybean oil) and fish that are rich in PUFA.

- - The cholesterol-lowering effect of PUFA: 1) They stimulate cholesterol excretion and conversion to bile acids.
- 2) Cholesterol esters of PUFA acids are rapidly metabolized by the liver and other tissues more than that of saturated fatty acids

- - Risk factors for coronary heart disease include: high blood pressure, smoking, obesity, and lack of exercise.
- - Elevation of plasma FAs: this leads to increased VLDL secretion by the liver, involving extra TAG and cholesterol output into the circulation.

- - Factors leading to high levels of FAs include: emotional stress, nicotine, cigarette smoking, coffee drinking, and eating a few large meals rather than more continuous feeding.
- - Exercise and estrogen (present in premenopausal women) increase HDL levels, thus protecting against cardiovascular disease: Exercise is recommended to aid in the prevention or treatment heart disease. Estrogen replacement therapy is prescribed to menopause.
-

LIPIDS PROFILE (LIPIDS PANEL)

- **- Lipids profile** is a group of blood tests requested together to determine risk of CHD and atherosclerosis. Two types of lipids, cholesterol and TAG, are measured in blood. It typically includes estimation of:
- **1) Total TAG** (most is in the VLDL, as the patient must be fast for 14 hrs).
- **2) Total Cholesterol** (all of the cholesterol in all the lipoprotein particles)
- **3) VLDL-Cholesterol** (The amount of cholesterol in the VLDL is 1/5 its TAG)
- **4) LDL-Cholesterol** (Usually, the amount LDL-C is calculated using the results of total cholesterol, HDL-C, and TAG) **Friedewald Formula**

- LDL-C = T.C – (HDL-C + VLDL-C) **or** LDL-C = T.C – (HDL-C + TAG/5)
- This formula is valid only if TAG value is less than **400** mg% and fasting specimen

- 5) HDL-Cholesterol
- 6) Risk Ratio 1 (Total-C/HDL-C)
- 7) Risk Ratio 2 (LDL-C/HDL-C)

- **- Pre-test requests:** 1) An overnight fasting (12-14 hours), only water is permitted
- 2) A normal diet should be consumed for 3 weeks
- 3) If possible, withhold all medication for at least 24 hours before testing
- 4) The patient should abstain from alcohol for 48 hours before testing
- 5) Do not use heparinized plasma (for TAG estimation)?? Why
- 6) Do not use citrate, oxalate or fluoride plasma (for cholesterol)

- **New laboratory test: Apolipoprotein A-I and B (Apo A-I / Apo B) Ratio:**
- **-** Apo A is the main component of HDL.
- **-** Apo B is the main component of CM, LDL and VLDL.
- **-** Apo A-I deficiencies are often associated with premature CHD.
- **-** The ratio of Apo A-I to Apo B correlates more closely with increased risk for CHD than do cholesterol levels or the LDL/HDL ratio.
- **-** The lower the ratio, the higher the risk

Reference ranges:

Parameter	level	Interpretation
TAG	Less 150 mg%	Optimal
	150–199 mg%	High
	200 mg% and above	Very high
Total-C	Less than 200 mg%	Desirable level
	200-239 mg%	Borderline high
	240 mg% and above	High blood cholesterol
LDL-C	Less than 100 mg%	Optimal
	100-129 mg%	Near or above optimal
	130-159 mg%	Borderline high
	160-189 mg%	High
	190 mg% and above	Very high

HDL-C	Less than 40 mg%	A major risk factor for heart disease
	40-59 mg%	Desirable
	60 mg% and above	Protective against heart disease
Risk Ratios 1 Total C / HDL-C	< 4	Low risk
	4 - 11	Moderate risk
	> 11	High risk
Risk Ratios 2 LDL-C / HDL-C	0.5 - 3	Low risk
	3 - 6	Moderate risk
	> 6	High risk
Apo A-I	< 90 mg%	Indicate increased CAD risk
Apo B	> 110 mg%	Indicate increased CAD risk
Apo A-I / Apo B	Male 0.80 - 1.5	Desirable
	Female 0.90 - 2.5	Desirable