Lipid metabolism
lect. 1

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❖ Digestion of lipids

- On the average, an adult eats about 100-150 g lipids/day.
- The main lipids in diet are triacylglycerols in addition to some phospholipids and cholesterol.

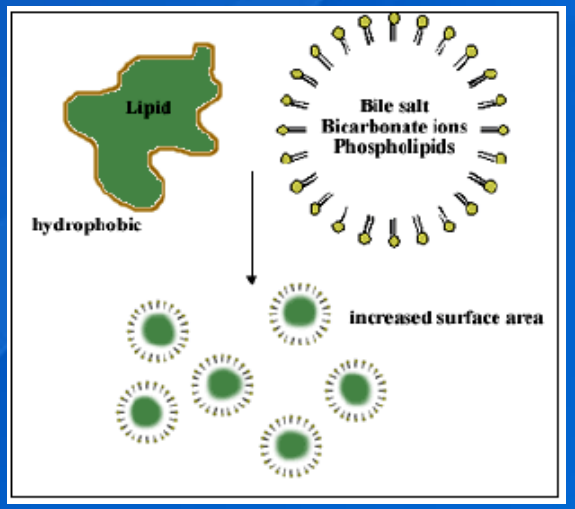
➢ **Sources of dietary lipids:**

1) Plant oils: cotton seed oil, olive oil, corn oil, sesame oil and linseed oil.
2) Animals fats: butter and other animal fats.

❖ Digestion of triacylglycerols:

- Ingested triacylglycerols are digested in two subsequent major steps (emulsification and enzymatic hydrolysis):

I. Emulsification: means breakdown of large fat globules into smaller ones:



a) In the mouth by chewing.

b) In the stomach by gastric contraction.

c) In the intestine by peristalsis, bile salts and phospholipids.

II. Enzymatic hydrolysis (by lipase enzymes):

- This include lingual, gastric, pancreatic, and intestinal lipases.

1) Lingual lipase

- Secreted by Ebner's glands in the buccal mucous.
- It has minimal effect in lipid digestion because lipids remain for short time in the mouth.

2) Gastric lipase

- It is secreted by gastric mucosa in an active form.
- Its optimum pH ranged is between 3-6, so it can not act in adult stomach (pH 1-2).
- It may act on the milk fats in infant stomach (pH 5).
- It hydrolysis acylglycerol containing short, medium and generally unsaturated long-chain FAs to form free FA and 1,2 diacylglycerol.

3) **Pancreatic lipase**

- It is the most active and important lipase.
- It is secreted from pancreatic acini in an inactive form.

➢ **Synthesis of pancreatic lipase is stimulated by:**

a) Pancreozymin hormone: (secreted by the duodenum).

b) Vagus nerve stimulation.

- **Pancreatic lipase is activated in the duodenum by:**

a) **Bile salts:** which are produced by the liver, they shift the pH from 8 to 6.5 and have a great role in emulsification of fat (increase the surface area upon which the enzyme acts).

b) **Co-lipase:** It is a protein produced by the pancreas.

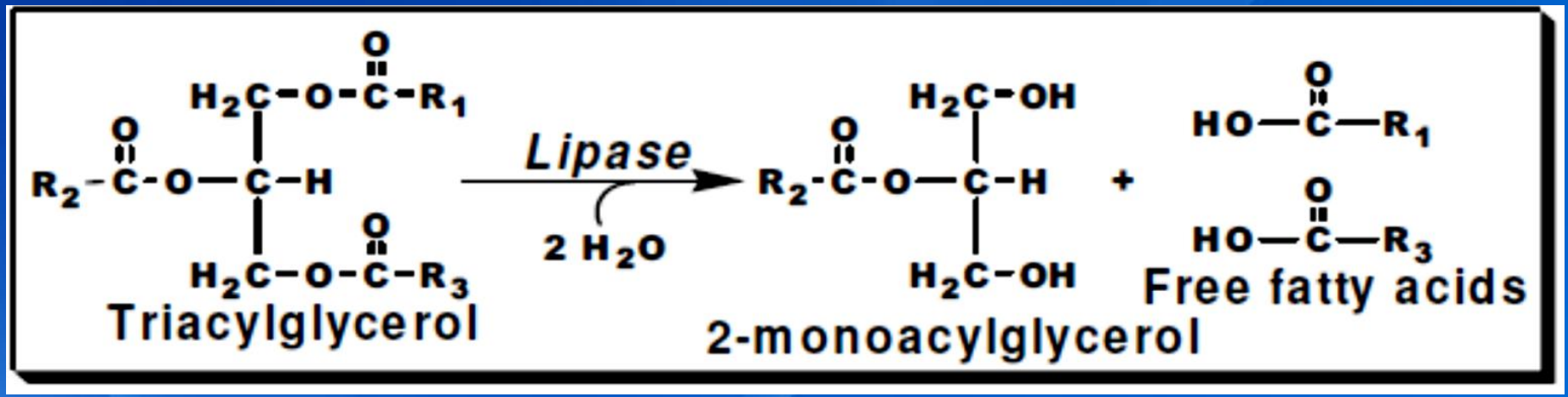
c) **Phospholipids**

d) **Ca^{2+} ions:** help to remove the FAs through the formation of insoluble calcium salts.

- Deficiency of these factors causes inadequate fat digestion.

Action of pancreatic lipase:

- It attacks the 1st and the 3rd primary ester bonds of triacylglycerols leading to the formation of 2-monoacylglycerol and two free FAs.



- Thus the end products of digestion of triacylglycerols are:

i. 72% as 2-monoacylglycerols (absorbed as it is).

ii. 2-6% as 1-monoacylglycerols

iii. 22% as glycerol and free FAs (saturated and unsaturated).

4) Intestinal lipases

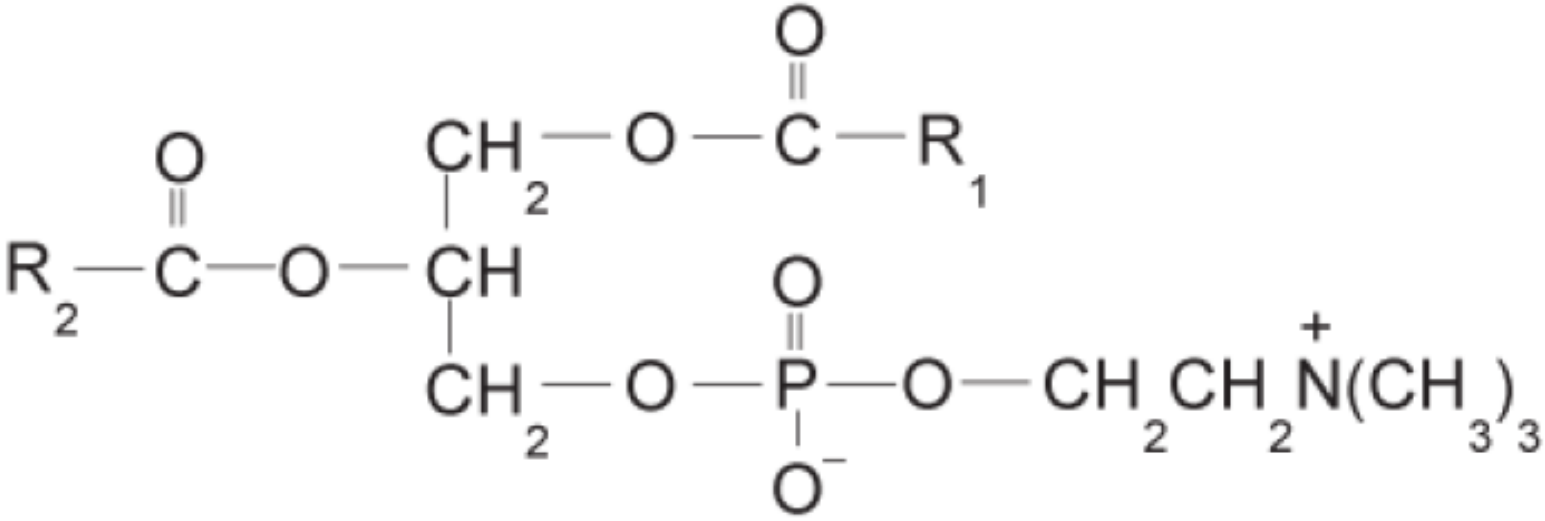
- It acts on 1-monoacylglycerols converting them into Glycerol and free FAs.

Digestion of cholesterol and cholesteryl esters:

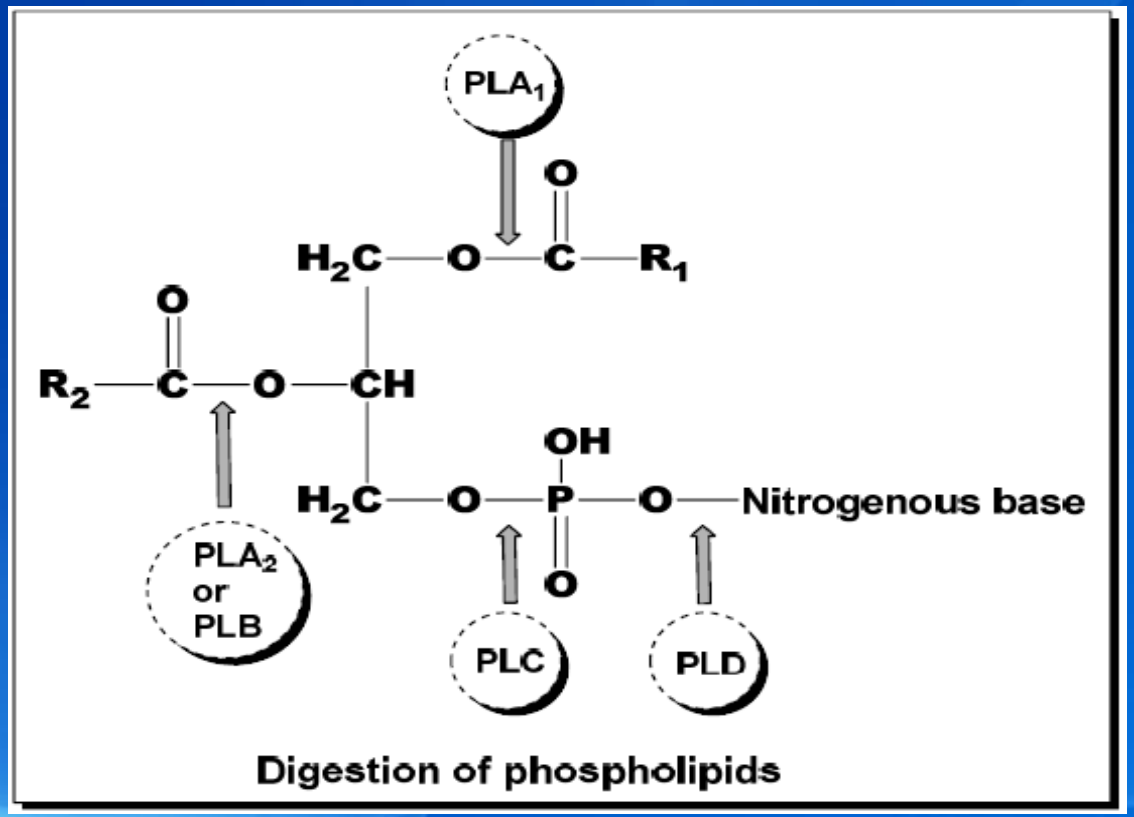
- Cholesterol itself undergoes no digestion and absorbed as it is.
- Cholesteryl esters are digested by cholesterol esterase enzyme into cholesterol and free FAs.
- Cholesterol esterase enzyme is secreted by pancreatic acini in an active form and its optimal pH is pH: 8.

Digestion of phospholipids:

- Phospholipids are conjugated lipids.
- They are formed of an alcohol e.g. glycerol + 2 fatty acids + phosphoric acid in addition to nitrogenous base.
- Phospholipids may be absorbed as it is or:



- It could be also digested by phospholipase enzymes [A_1, A_2 (B), C and D] into free FAs, glycerol, phosphate and nitrogenous bases.
- Phospholipases are secreted from pancreas and intestine in an inactive forms then activated by bile salts and Ca^{2+} ion.



Digestion of phospholipids

Steatorrhoea:

- It is a condition in which fat content of the stool is abnormally increased (normally it is less than 5 g/day).
- Its manifestations are:

a) Passage of fluid or semi-fluid bulky, pale and usually offensive stools.

b) Stool volume may reach 500-1000 ml/day (normally 100-200 ml/day).

Causes of Steatorrhoea:

I. Deficiency of Pancreatic Lipase:

- This lead to defective lipids digestion and it is characterized by:

a) Presence of undigested fats in stool.

b) There is no loss of fat soluble vitamins in the stool as these vitamins need no digestion.

- **Causes of deficiency of pancreatic secretion:**

i. Pancreatic duct obstruction.

ii. Acute or chronic pancreatitis.

iii. Zollinger Ellison disease (excessive production of HCl).

II. Deficiency of Bile Salts:

- It is characterized by:

a) Presence of digested fat in the stool.

b) Loss of fat soluble vitamins.

- **Causes of deficiency of bile salts:**

I. Liver disease: (the site of bile secretion).

II. Bile duct obstruction: by a tumor or stone.

III. Unhealthy Intestinal Mucosa:

- Diseased intestinal mucosa prevent absorption of digested fat.

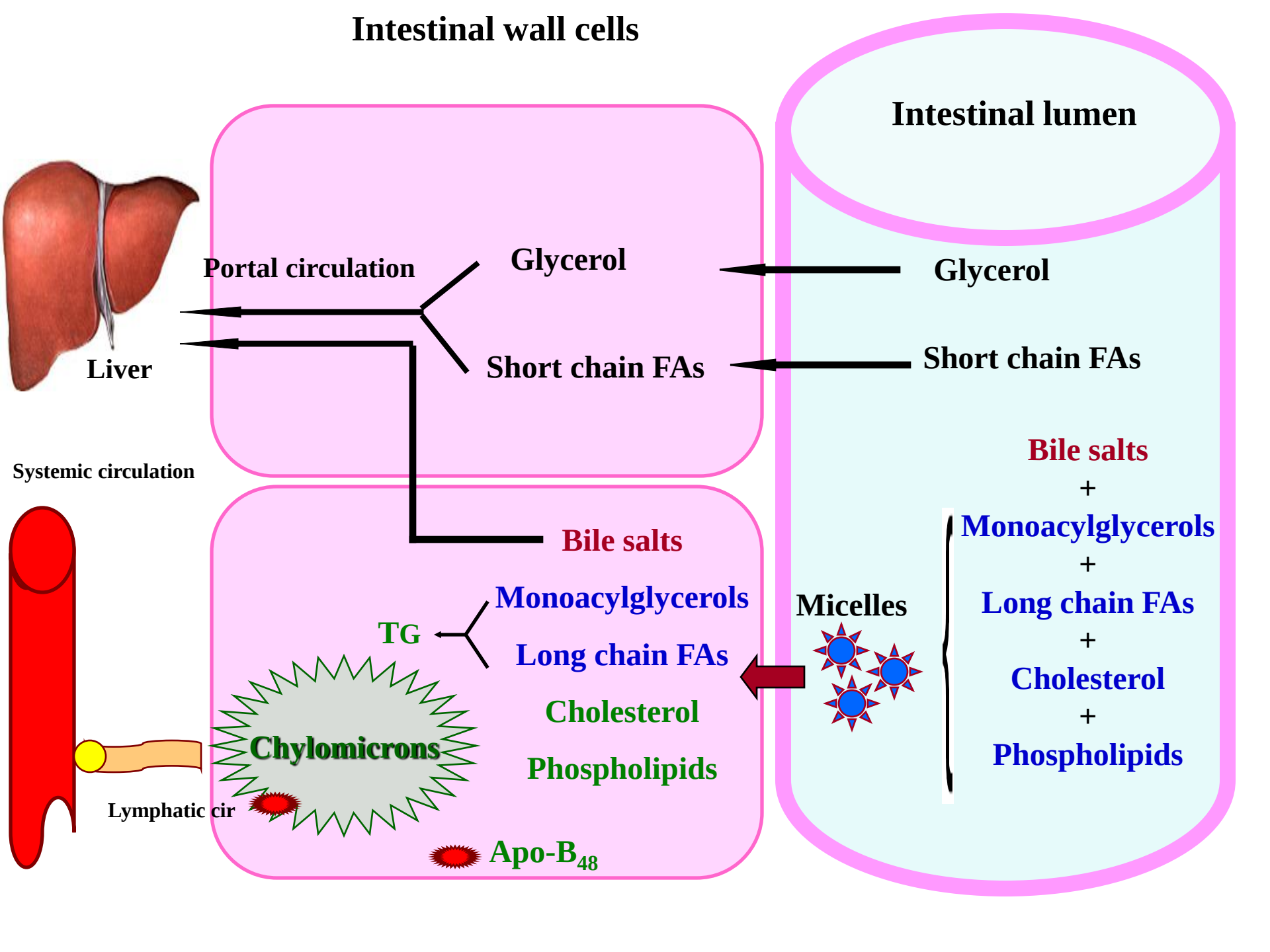
❖ Absorption of digested lipids:

- The end products of lipids digestion are:

1) 1-Monoacylglycerol.
2) Fatty acids (Short and Long chain fatty acids).
3) Glycerol.
4) Lysophospholipids, phosphate, nitrogenous bases.
5) Cholesterol

- They are absorbed from jejunum and ileum.

- Short chain FAs (<12 carbons) and glycerol are water soluble (pass via the portal system to the liver).
- Other lipids are water insoluble (form micelles with bile salts which then enter the mucosal cells).
- Bile salts are reabsorbed to the liver again (entero-hepatic circulation).
- Long chain FAs are activated in the mucosal cells and recombine with monoacylglycerols and diacylglycerols (re-esterification).
- Cholesterol and lysophospholipids are re-esterified in a similar manner.


Intestinal wall cells
Intestinal lumen
Portal circulation
Glycerol
Glycerol
Short chain FAs
Short chain FAs
Liver
Systemic circulation
Bile salts
+
Monoacylglycerols
+
Long chain FAs
+
Cholesterol
+
Phospholipids
Bile salts
Monoacylglycerols
TG
Long chain FAs
Micelles
Cholesterol
Chylomicrons
Phospholipids
Lymphatic cir
Apo-B48

Formation of chylomicrons:

- Re-esterification of TG occurs inside the endoplasmic reticulum of the mucosa cells as the following:
- TGs (88%) are coated by apolipoprotein (0.5-2%, apo-B_{48}), phospholipids (8%) and cholesterol to form globules that is 0.1-1.0 μm in diameter (Chylomicron).
- Chylomicrons are released from mucosal cells by exocytosis to the lymphatic system and then to the systemic circulation.

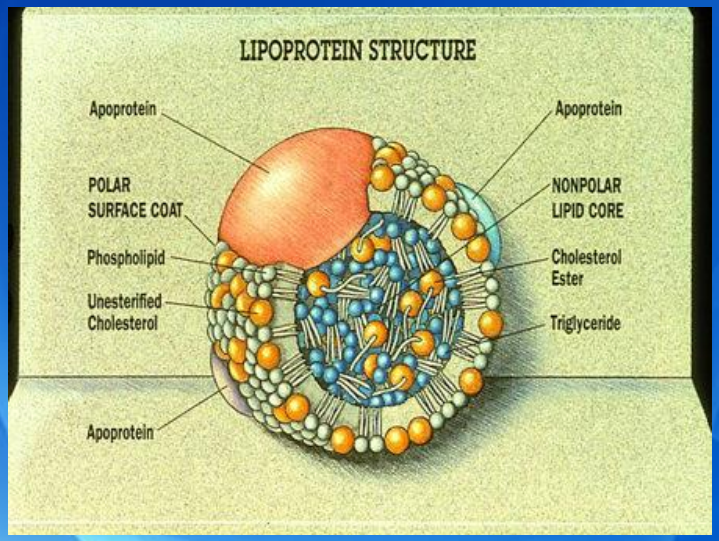
- **Fate of absorbed chylomicrons:**
- Excess chylomicrons stimulate mast cells to release heparin.
- Heparin stimulate the lining epithelium of BV in (heart, lungs, spleen, etc.) to produce an enzyme called **lipoprotein lipase** (plasma-clearing factor, inactive form).
- Lipoprotein lipase is activated by **Apo-C_{II}**.
- Active lipoprotein lipase hydrolyze the TGs of chylomicrons into glycerol and free FAs.

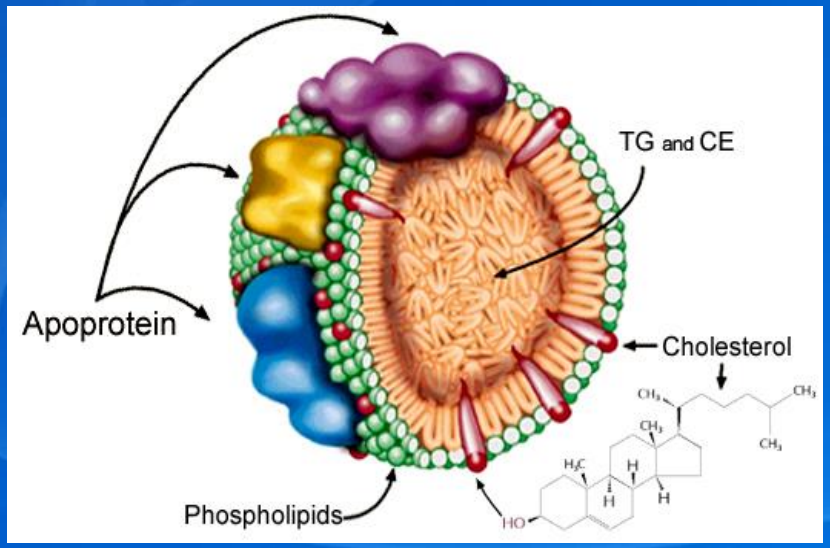
- **Glycerol and free FAs are taken by tissues for the following:**

1) Formation of depot fats (adipose tissues).
2) Synthesis of tissue fats (structural fats).
3) Oxidation for energy production.
4) Glucose formation (gluconeogenesis).
5) Syntheses of biologically active compounds (prostaglandins, leukotreins).

Lipoproteins

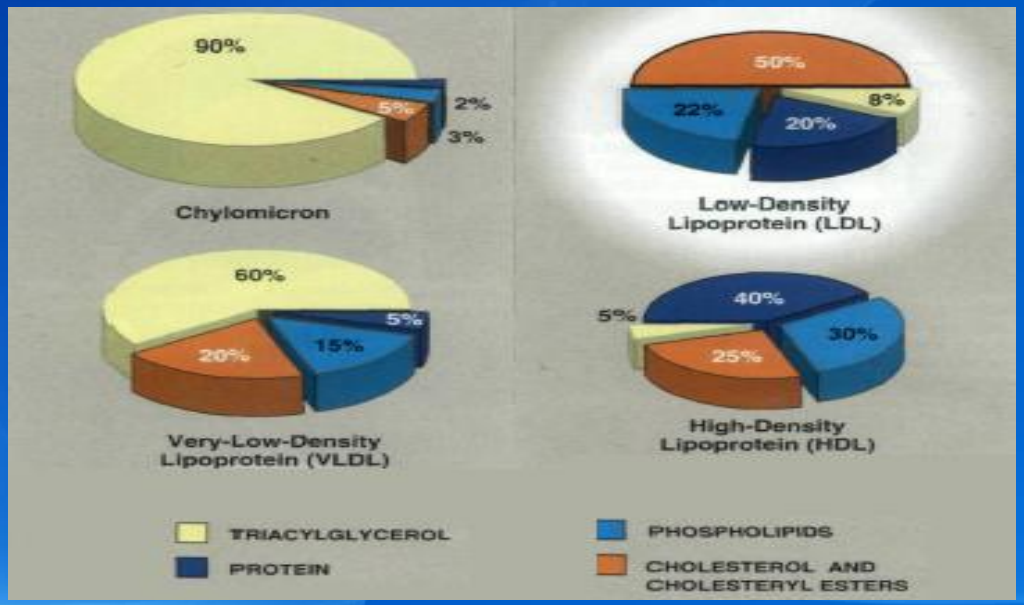
- Lipoproteins are lipids combined with protein to form water soluble complex “plasma lipoproteins”.
- This protein fraction is synthesized in the liver and intestinal mucosa and called apoprotein (apolipoprotein).
- **Structure of lipoproteins:**





- **Types or fractions of lipoproteins:**

1) Chylomicrons.
2) Very low density lipoprotein (VLDL, or pre-β-lipoprotein).
3) Low density lipoprotein (LDL, β-lipoprotein or bad ch).
4) High density lipoprotein (HDL, α-liporotein or good ch).
5) Albumin-Free fatty acid complex.



- **All types of lipoproteins differ in:**

a) The main lipid content of each type.

b) Source of each type.

c) Type and amount of the associated protein.

d) Functions.

- **Importance of lipoproteins:**

1) Keep lipid soluble in blood

2) Transport lipids in blood

Apolipoproteins or Apoproteins:

- They are the protein moiety of lipoproteins.

Types of Apoliporproteins: (5 types):

1) **Apolipoprotein A:** (Apo-A_I, Apo-A_{II} and Apo-A_{IV}, present in HDL).
2) **Apolipoprotein B:** (Apo-B_{48} and Apo-B_{100}). Apo-B_{48} is present in chylomicrons and chylomicron remnants. Apo-B_{100} is present in VLDL, LDL and IDL.

3) **Apolipoprotein C:** (Apo-C_I, Apo-C_{II} and Apo-C_{III}). All of them are present in VLDL, HDL and chylomicrons.

4) **Apolipoprotein D:** It is present in the subfraction of HDL.

5) **Apolipoprotein E:** It is present in VLDL, HDL, chylomicrons and chylomicron remnants.

1- Chylomicron

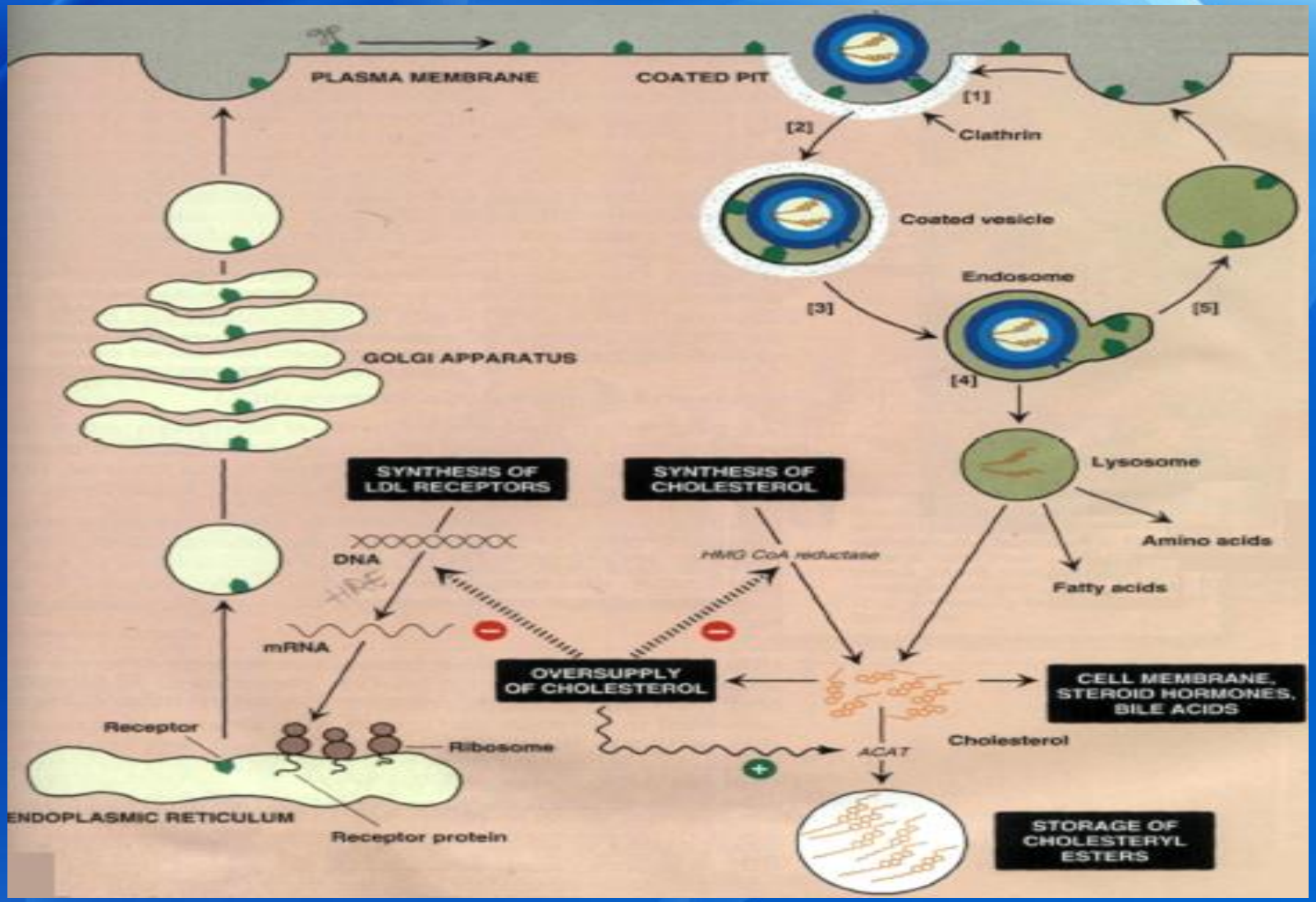
- **Site of synthesis:** Intestinal mucosa.
- **Function:** They carry TG, cholesterol ester and ph-lipids from the intestine to the peripheral tissues.
- **Apoproteins:** Apo-B, Apo-C, Apo-E, and Apo-A.
- **Main lipid component:** TG.
- **Catabolism:** It occurs in the plasma by lipoprotein lipase enzyme which is activated by Apo-C_{II} to act on TG converting them into glycerol and FAs.

2- VLDL

- **Site of synthesis:** Liver
- **Function:** It carries TG from the liver to extrahepatic tissues.
- **Apoproteins:** Apo-C, Apo-E and Apo-B.
- **Main lipid component:** TG.
- **Catabolism:** It is catabolized in the plasma by lipoprotein lipase which is activated by Apo-C_{II}.
- The enzyme acts on TG leading to formation of IDL which is further changed into LDL.

3- LDL

- **Site of synthesis:** It is synthesized from VLDL in the circulation and also in the liver.
- **Function:** It carries cholesterol to various tissues.
- **Apoproteins:** Apo-B_{100}.
- **Main lipid component:** Cholesterol.
- **Catabolism:** LDL binds to specific receptors in the tissues such as liver, suparenal cortex, ovary and testis. This allows the cells to uptake and metabolize plasma LDL. Deficiency of these receptors leads to severe hypercholesterolaemia.



- Estrogen (female sex hormone) increases the number of LDL-receptors in the liver, so it decrease blood cholesterol in females.

4- HDL

- **Site of synthesis:** Intestine and Liver.
- **Function:** It carries cholesterol from tissues to the liver to be catabolized.
- **Apoproteins:** Apo-A, Apo-C, Apo-E, and Apo-D.
- **Main lipid component:** Cholesterol ester and ph-lipids.
- Deficiency of HDL leads to accumulation of cholesterol in the tissues (Tanger's disease).

5. FFA-HSA complex

- They are carried on plasma albumin
- They are produced from:

1) **During fasting:** hydrolysis of TG of adipose tissues.
2) **After meal:** hydrolysis of chylomicrons and VLDL.

- **Fate of fatty acids:**

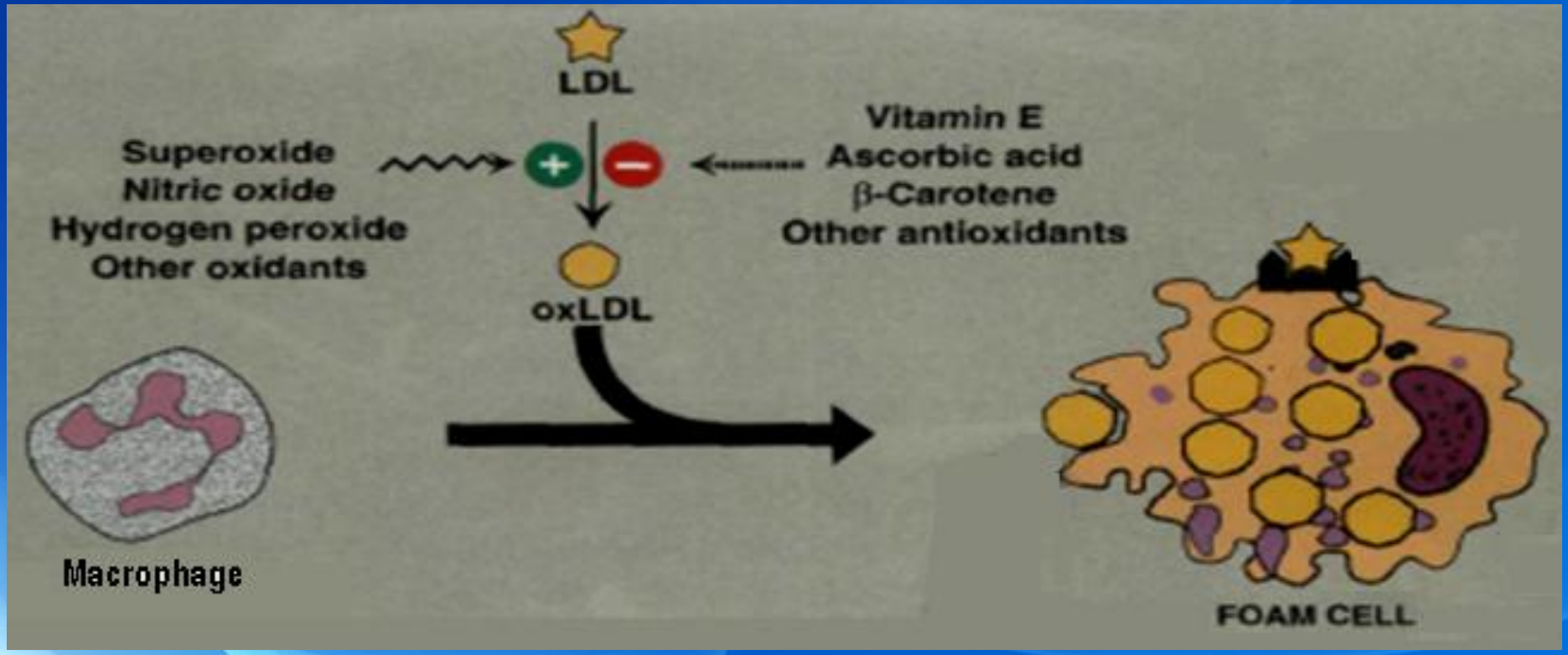
1) Oxidation for energy production (during fasting).
2) Esterification: formation of phopholipids, TG, glycolipids and cholesterol ester (after meal).

Clinical significances of lipoprotein metabolism

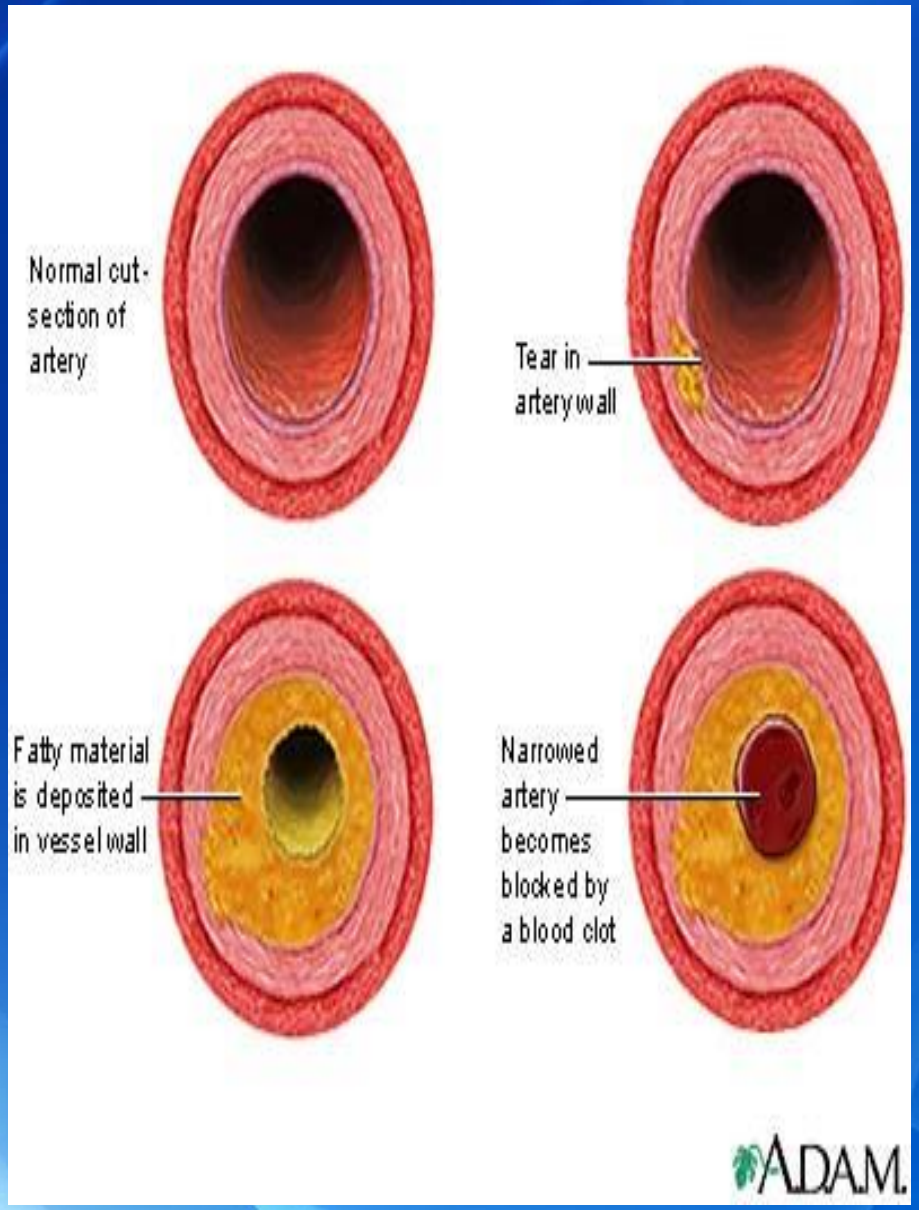
- Diabetes mellitus, hypothyroidism and kidney disease often lead to abnormal lipoprotein metabolism.
- Insulin and thyroid hormones positively affect hepatic LDL-receptor interactions; therefore, uncontrolled diabetes or hypothyroidism are commonly associated with hypercholesterolemia and increased risk of atherosclerosis due to decreased hepatic LDL uptake and metabolism.

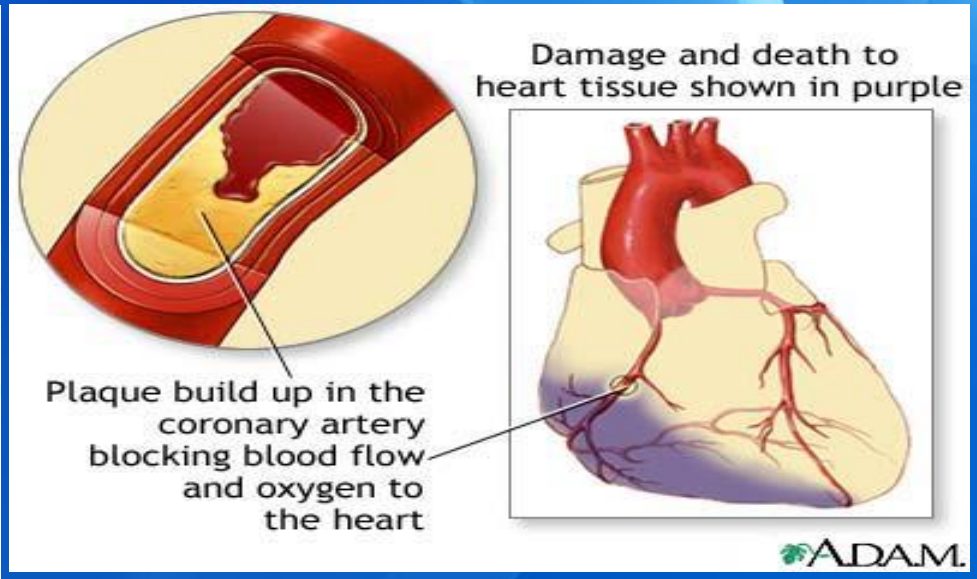
Chemically modified or oxidized LDL:

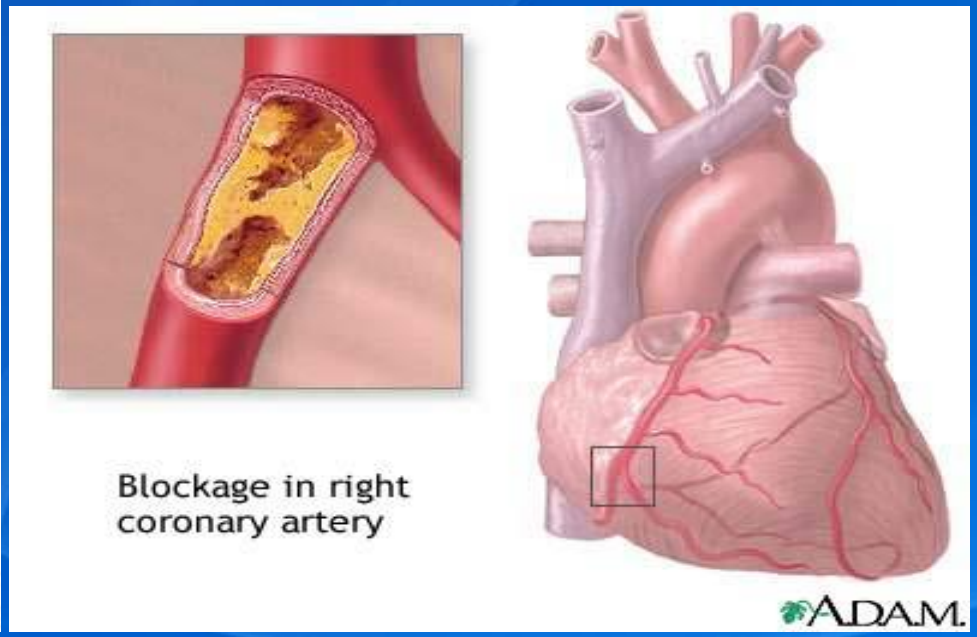
- Free radicals damage (oxidize) the excess LDL cholesterol either through genetics or diet, or shortage in the body antioxidant system.



➢ Atherosclerosis – Oxidized LDL







➢ Role of liver in lipid metabolism

I. Role in TG metabolism:

1) Uptake of FAs after fatty meal by pinocytosis.
2) Synthesis of TG.
3) Oxidation of FAs (β & ω).
4) Mobilization of depot fat.
5) Gluconeogenesis for glycerol and propionyl CoA.
6) Desaturation of FAs.
7) Oxidation of glycerol.
8) Ketogenesis.

II. Facilitates digestion and absorption of fats by production of bile salts.

III. Role in phospholipid metabolism:

1) Synthesis and catabolism of plasma phospholipids.
2) Synthesis and degradation of (VLDL, LDL and HDL).

IV. Role in cholesterol metabolism:

1) Biosynthesis of cholesterol.
2) Oxidation of cholesterol to bile acids.
3) Esterification of cholesterol into its esters.
4) Oxidation of cholesterol to Vitamin D3.

V. Detoxication of steroid hormones especially estrogen.

VI. Storage of fat soluble vitamins and transformation of carotenes to vitamin A by carotenase enzyme.

VII. Prothrombin biosynthesis.

Next lecture

Lipolysis of TG


Thank You