
بسم الله الرحمن الرحیم

# LIPID TRANSPORT & STORAGE

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**KGMC- 2022**

# LIPID TRANSPORT & STORAGE

- The exogenous & endogenous fats must be transported b/w tissues and organ for Utilization & storage.
- Lipid are insoluble in liquid so nonpolar lipids (TG, Ch esters), amphipathic lipid (phospholipid , cholesterol) and proteins make water miscible lipoproteins for transportation of lipid in plasma.

# LIPID TRANSPORT & STORAGE

- Lipoproteins transported ingested fats in the form of Chylomicron,
- VLDL transported synthesised fats from the liver to most tissues for oxidation or storage in adipose tissues.
- From adipose tissues storage the FFA bound to serum albumin and travel towards the needy cell or tissue.

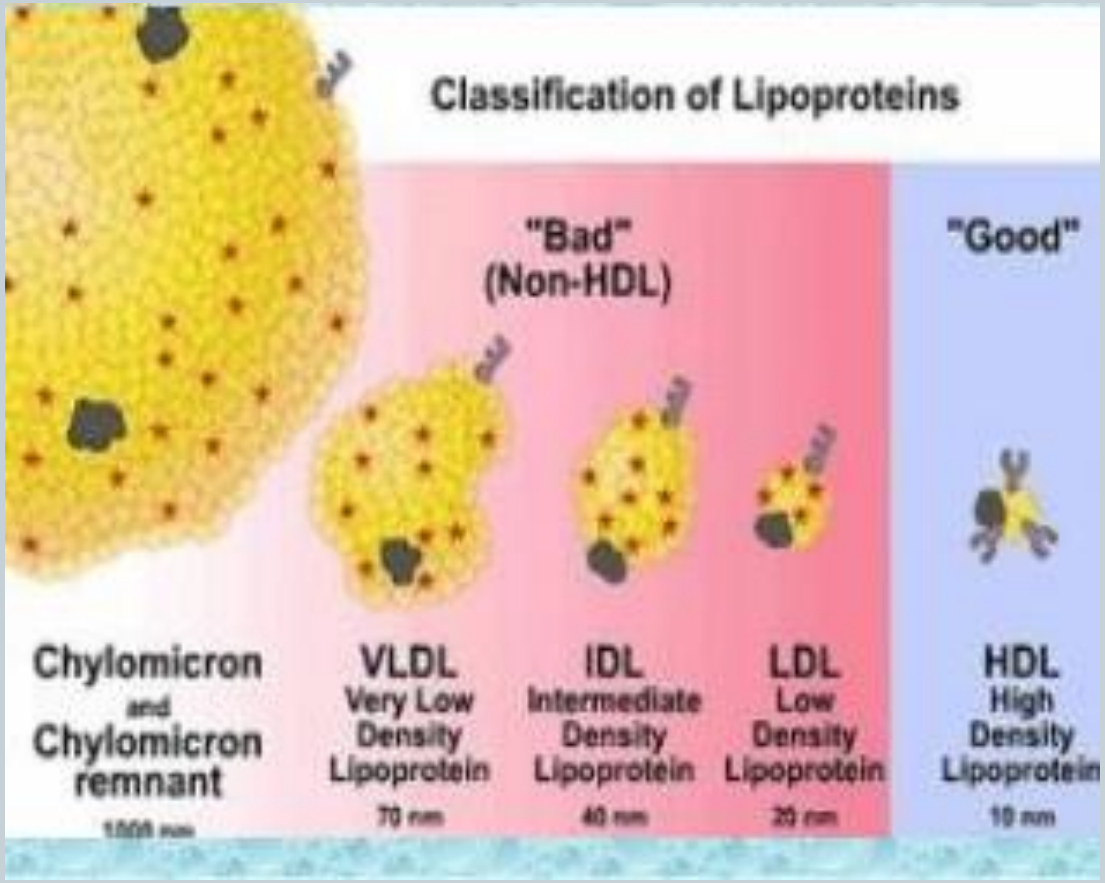
# LIPOPROTEINS

- The molecular complex that consist of lipids and conjugated proteins.
- They transport lipids in blood and deliver the lipid components (TG, Ch etc ) to various tissues for utilization and storage.

# CLASSIFICATION of LIPOPROTEINS

Five major classes on the bases of density separated by electrophoresis.

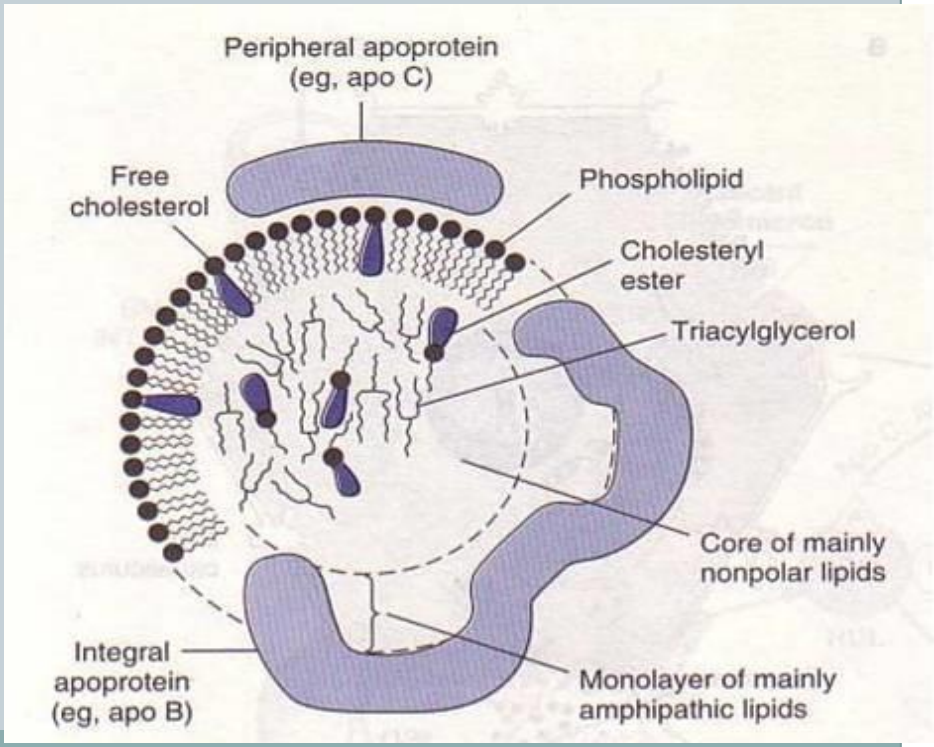
1. Chylomicrons
2. VLDL
3. IDL
4. LDL
5. HDL



# STRUCTURE of LIPOPROTEIN

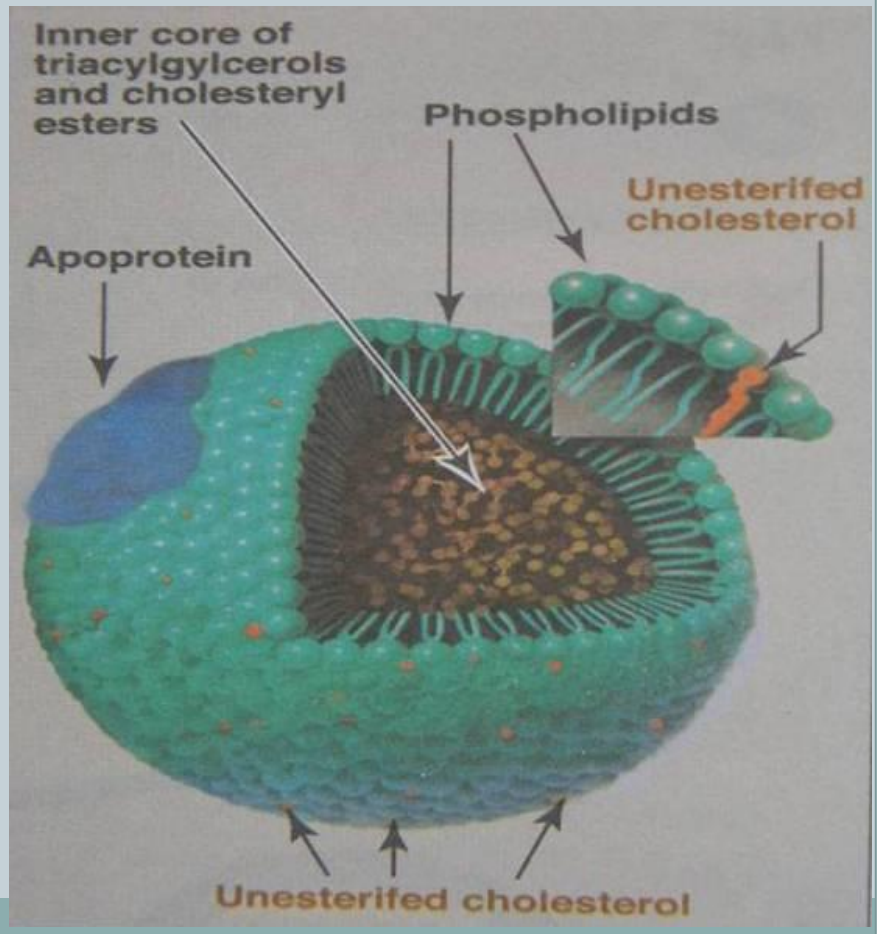
Lipoproteins basically consist

1. neutral non polar lipid core (TG, Ch esters).
2. amphipathic single surface layer (phospholipids, Ch).
3. The protein moiety of lipoprotein is known as apolipoprotein or apoprotein.



# CHYLOMICRON

- Synthesized in intestine and it transport dietary TG e.g. towards the tissues.
- Consist 99% lipid and 1% protein.
- Least in density (<0.95g/mL) and largest in size.



# Chylomicron

- They are synthesized in intestinal wall and are hydrophobic so converted to lipoprotein complex Chylomicron.

- Size 90-1000nm in diameter.
- It is composed of central hydrophobic TG covered by single layer of hydrophilic PL, cholesterol ester and apoprotein ApoA-I, A-II, A-III , Apo- B-48,, Apo CI, CII, CIII, Apo-E.

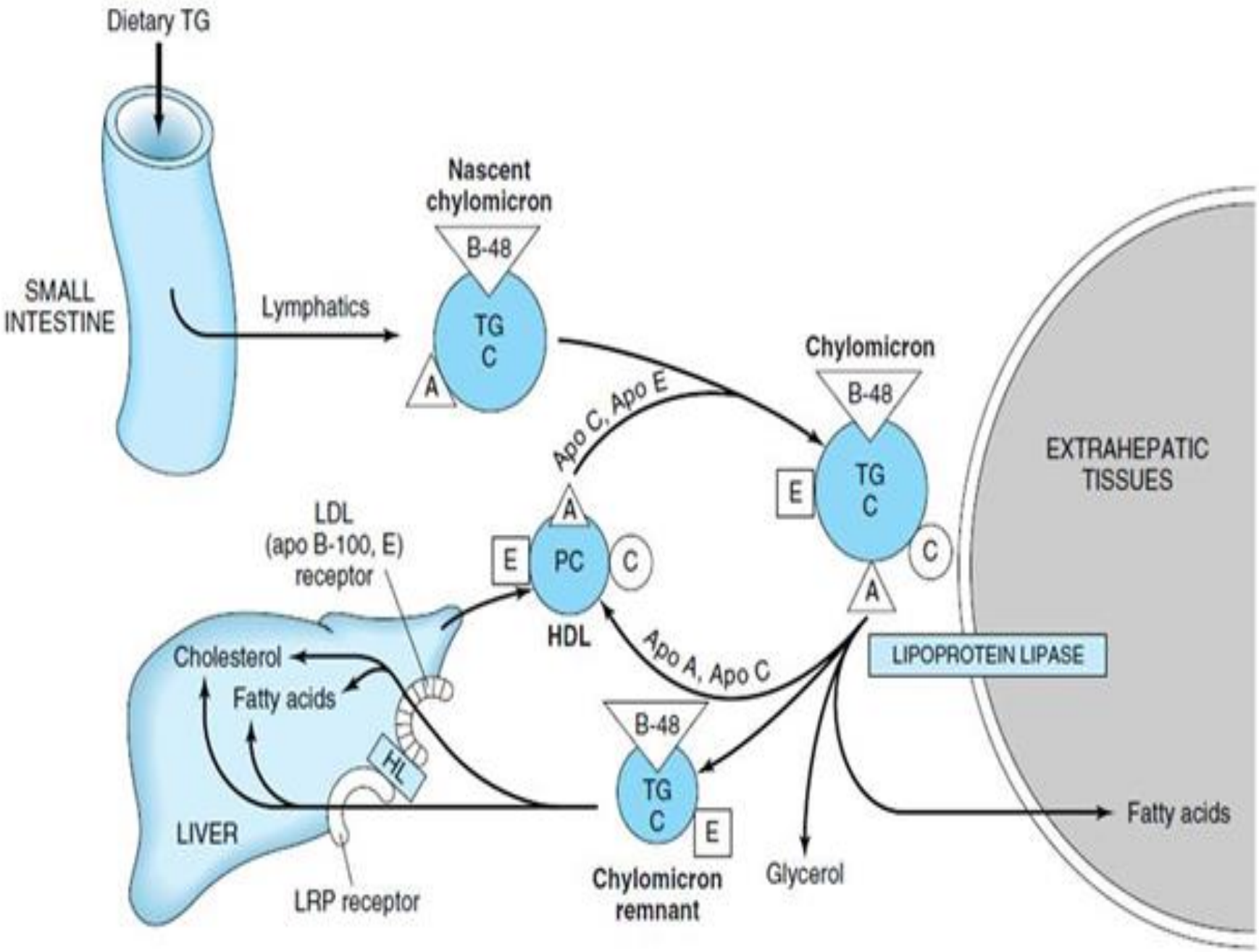
# Chylomicron

- Chylomicrons are formed in intestinal wall and through lymphatic vessels enter systemic circulation.

- Rich in: TGs
- Function: Re synthesized TG and Deliver TG's to body cells to be used as fuel.

# CHYLOMICRON REMNANTS:

- The remnant of chylomicron
- 45-150nm in density .
- <1.006 g/mL in plasma.
- protein 6-8% and lipids 92-94%.
- TG, PL, Ch, B-48, E.

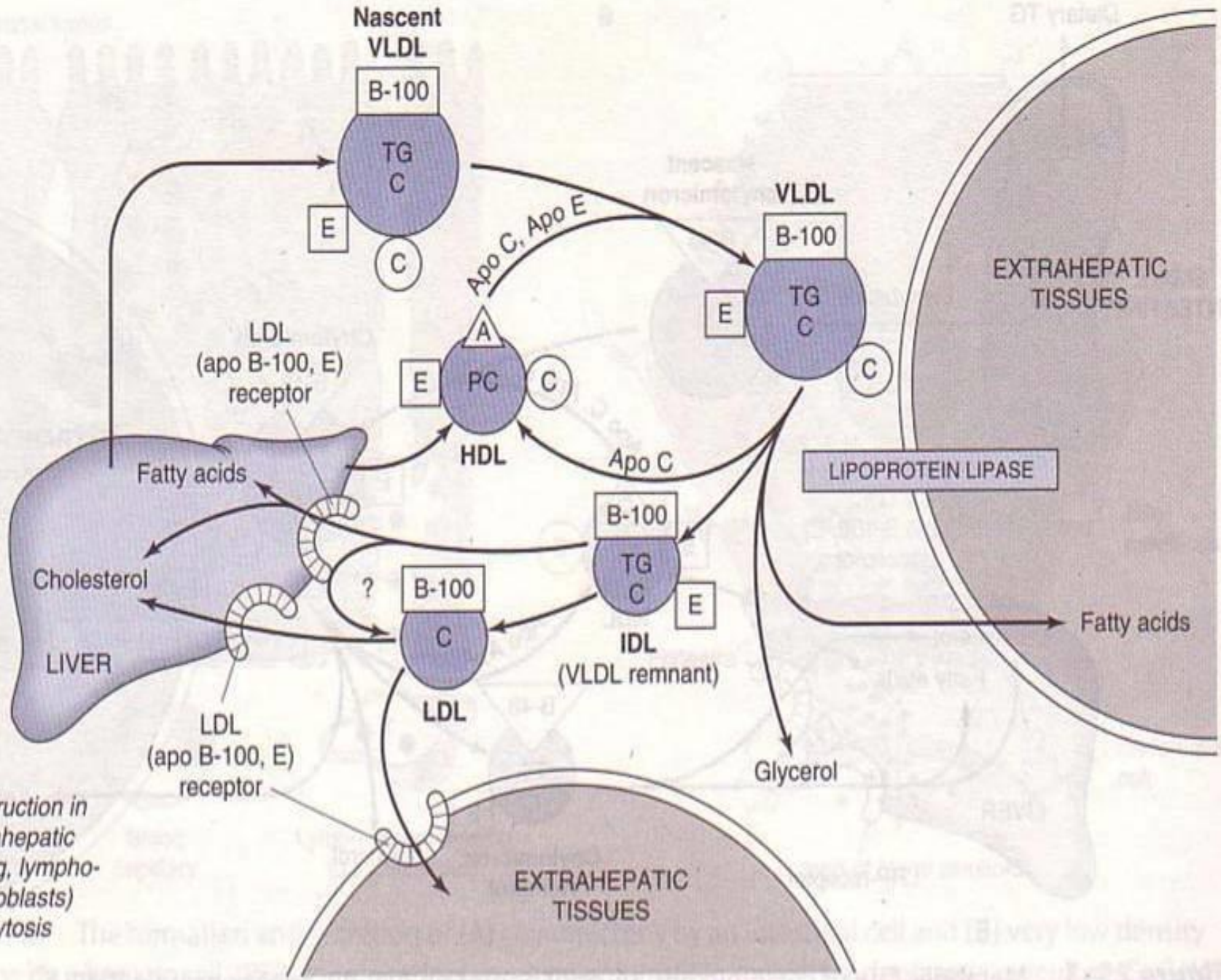

Dietary TG
SMALL INTESTINE
Lymphatics
Nascent chylomicron
B-48
TG
C
A
Apo C, Apo E
Chylomicron
B-48
E
TG
C
C
A
EXTRAHEPATIC TISSUES
LDL
(apo B-100, E)
receptor
A
E
PC
C
HDL
Apo A, Apo C
LIPOPROTEIN LIPASE
Cholesterol
Fatty acids
HL
LIVER
LRP receptor
B-48
TG
C
E
Chylomicron remnant
Glycerol
Fatty acids

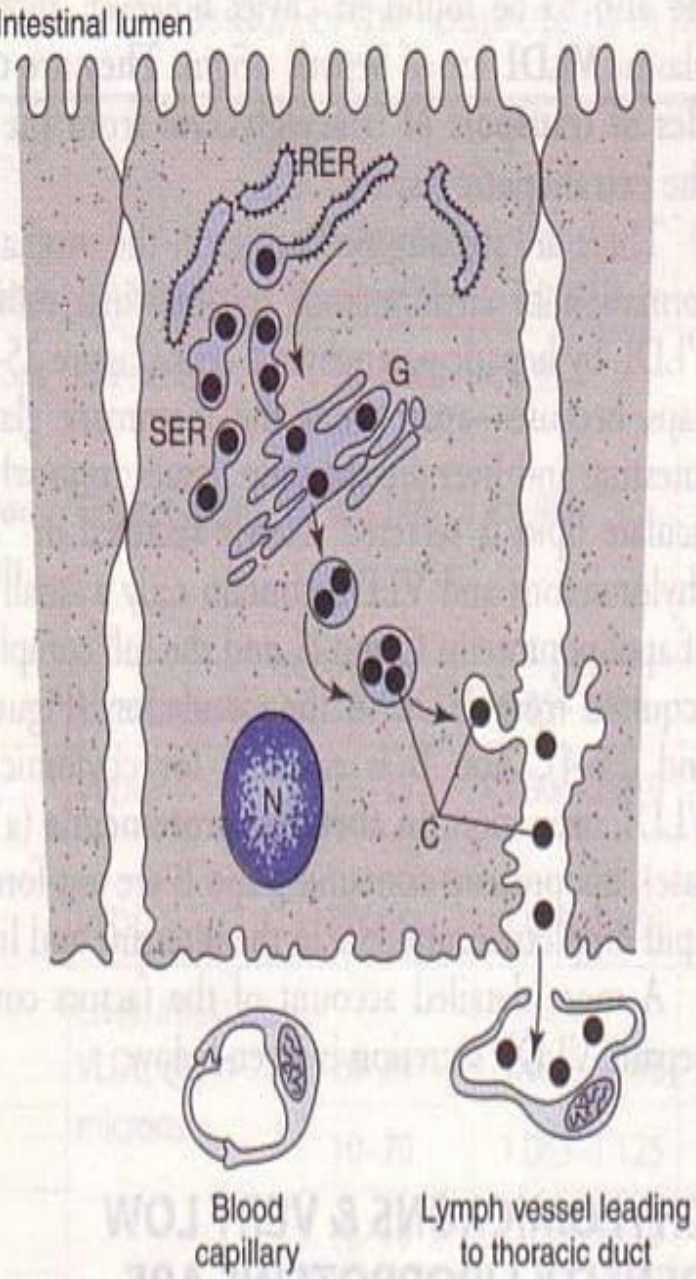
# VLDL

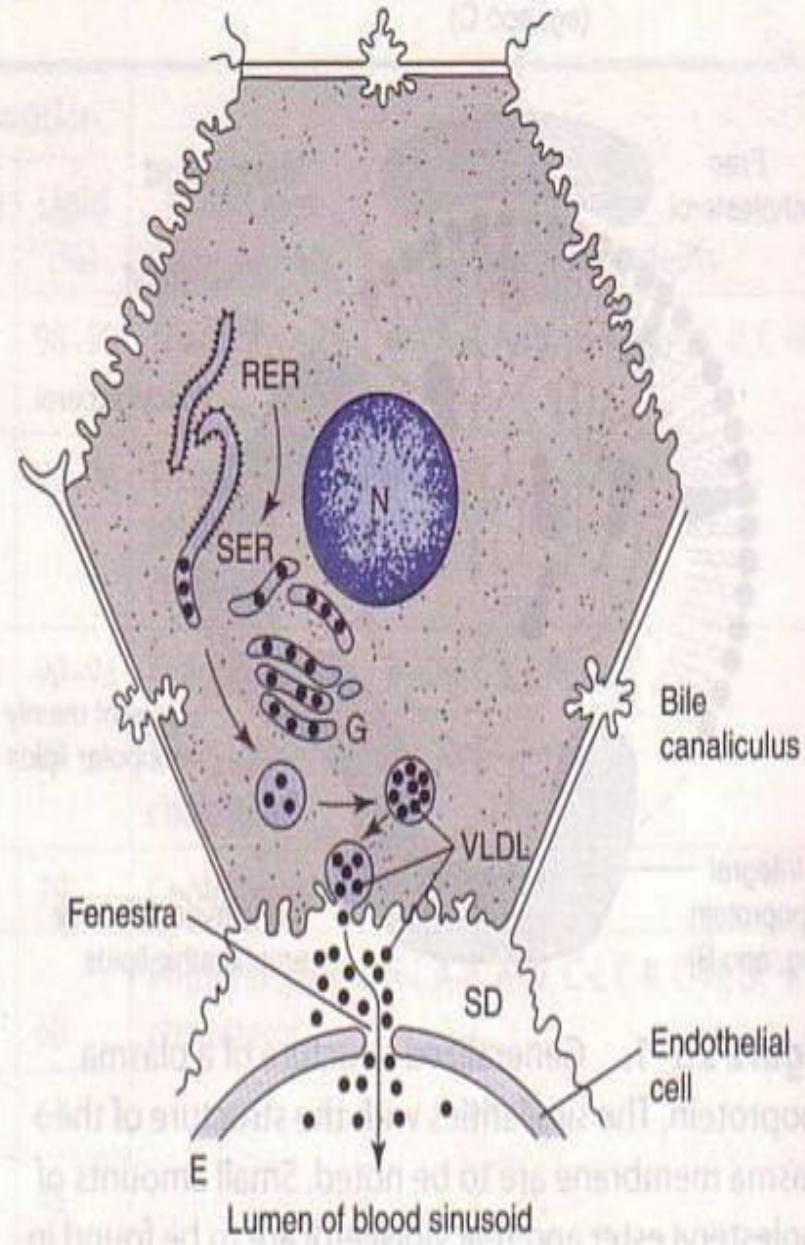
- Very Low Density Lipoprotein
- Made in: the liver from excess dietary CHO and protein along with the Chylomicron remnant
- Secreted into: the blood stream
- Rich in: TGs
- Function: Deliver TGs to body cells
- Contains Apo B-100, C-I, C-II, C-III.
- Size 20-75nm in diameter, density 0.95-1.006 g/mL, protein 7-10% and lipid 90-93%.

# LDL (Low Density Lipoprotein)

- Source: VLDL
- Made in: the Liver as VLDL
- Arise from: VLDL once it has lost a lot of its TG's
- Secreted into: the blood stream
- Rich in: Cholesterol
- SIZE: 30-90nm in dia, density 1.019-1.063 g/Ml, protein 21% , lipids 79% and apolipoprotein B-100
- Function: Deliver cholesterol to all body cells

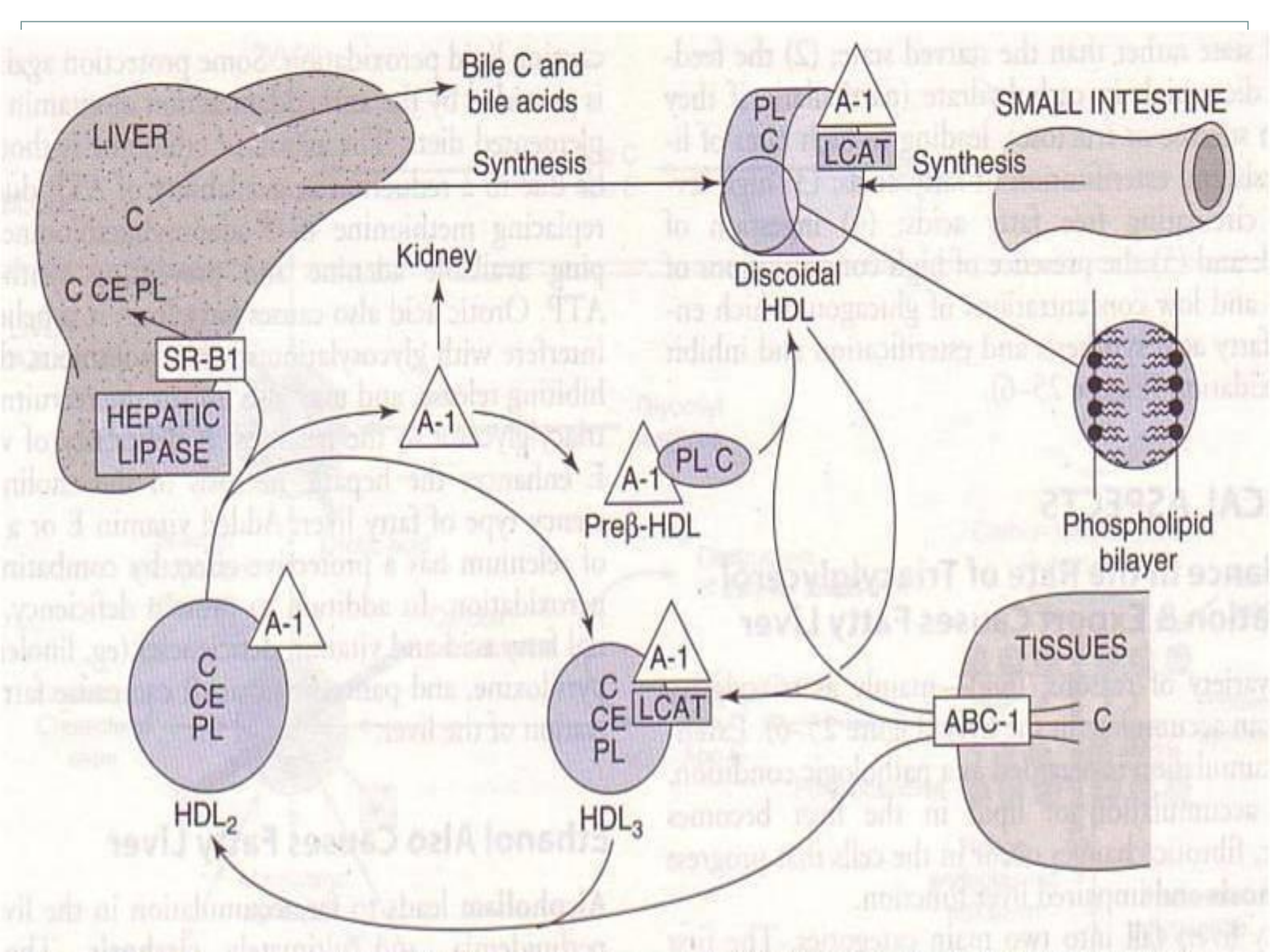

Nascent VLDL
B-100
TG
C
E
C
Apo C, Apo E
VLDL
B-100
TG
C
E
C
EXTRAHEPATIC TISSUES
LDL (apo B-100, E) receptor
A
E
PC
C
HDL
Apo C
LIPOPROTEIN LIPASE
Fatty acids
B-100
TG
C
E
IDL
(VLDL remnant)
Cholesterol
?
B-100
C
LDL
LIVER
Fatty acids
LDL (apo B-100, E) receptor
Glycerol
Final destruction in liver, extrahepatic tissues (eg, lymphocytes, fibroblasts) via endocytosis
EXTRAHEPATIC TISSUES


A
Intestinal lumen
RER
G
SER
N
C
Blood capillary
Lymph vessel leading to thoracic duct


B
RER
N
SER
G
Bile canaliculus
VLDL
Fenestra
SD
Endothelial cell
E
Lumen of blood sinusoid

# HDL (High Density Lipoprotein)

- Made in: the Liver and Small Intestine
- Secreted into: the blood stream
- Function: Pick up cholesterol from body cells and take it back to the liver = “reverse cholesterol transport”.
- Size: 5-25nm, density 1.019-1.210 g/mL, protein 32-57%, lipid 43-68% and A-1.
- Potential to help reverse heart disease.


Bile C and
bile acids
LIVER
C
C CE PL
SR-B1
HEPATIC
LIPASE
Synthesis
Kidney
A-1
PL
C
A-1
LCAT
Synthesis
SMALL INTESTINE
Discoidal
HDL
A-1
PL C
Preβ-HDL
Phospholipid
bilayer
A-1
C
CE
PL
HDL2
A-1
C
CE
PL
LCAT
HDL3
TISSUES
ABC-1
C

# Roles of HDL Apo proteins

- Brings cholesterol from peripheral tissues (including arteries) to the liver
  - Removing cholesterol from arterial wall
  - Inhibiting growth of new plaques
- Enhances stability of plaques and inhibits plaque rupture

# Roles of HDL Apo proteins

- HDL plays an antioxidant role due to an enzyme paroxanase activity and protacts LDL oxidation and as a result atherogenesis is reduced.

# FFA- albumin

- Arise in plasma from the break down of TG of adipose tissue by lipoprotein lipase.
- Albumin makes it soluble in plasma.

# Apolipoprotein

The protein component of lipoprotein.

A-I , AII, AIV, B-48 (intestine), B-100 (liver), CI, CII, CIII and E etc.

# Function of Apolipoprotein

- structural part of lipoprotein.
- They are enzyme cofactor e.g. C-I for lipoprotein lipase etc.
- They are enzyme inhibitor e.g. A-II and C-III for lipoprotein lipase.
- Act as ligand for interaction with lipoprotein receptors in tissues e.g. B-48, B-100.

# Function of Apolipoprotein

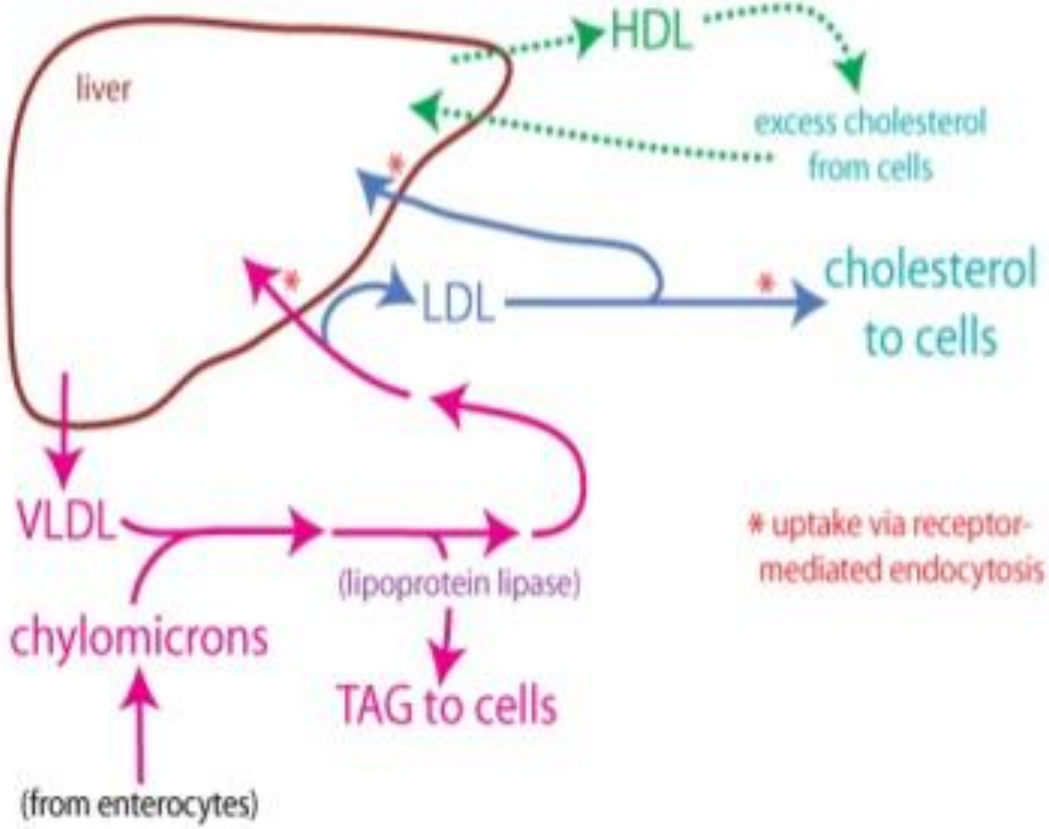
- Recognize the cell membrane surface receptors.
- Activate enzymes involved in lipoprotein metabolism.
- Protects LDL-cholesterol from oxidation by acting as a good anti-oxidant when HDL attaches to LDL.

# Function of Apolipoprotein

- Reduce expression of adhesion molecules on the vascular endothelium
  - Reduced adhesion of leukocytes (early phase of atherogenesis),
  - prevent formation of new plaques,
  - maintain integrity vascular endothelium

| Lipoprotein | Functions | Apoproteins | Functions |
|---|---|---|---|
| **Chylomicrons** | Transport dietary triglyceride and cholesterol from intestine to tissues | **apoB-48**<br>**apoC-II**<br>**apoE** | Secreted by intestine<br>Activates lipoprotein lipase<br>Uptake of remnants by the liver |
| **VLDL** | Transports triglyceride from liver to tissues | **apoB-100**<br>**apoC-II**<br>**apoE** | Secreted by liver<br>Activates lipoprotein lipase<br>Uptake of remnants (IDL) by liver |
| **IDL (VLDL remnants)** | Picks up cholesterol from HDL to become LDL<br>Picked up by liver | **apoE**<br>**apoB-100** | Uptake by liver |
| **LDL** | Delivers cholesterol into cells | **ApoB-100** | Uptake by liver and other tissues via LDL receptor (apoB-100 receptor) |
| **HDL** | Picks up cholesterol accumulating in blood vessels<br>Delivers cholesterol to liver and steroidogenic tissues via scavenger receptor (SR-B1)<br>Shuttles apoC-II and apoE in blood | **apoA-1** | Activates lecithin cholesterol acyltransferase (LCAT) to produce cholesterol esters |

# Summary of formation and fate of lipoproteins




- Chylomicrons is a transporter of dietary lipids whereas VLDL is a transporter of endogenous lipids(mainly TGs).
- LDL transports cholesterol to peripheral cells while HDL transports cholesterol from peripheral cells back to liver.

# Plasma concentration of Lipids

| *Lipid fraction* | *Reference values (mg/dl)* |
|---|---|
| Total lipid | 400-600 |
| Total cholesterol | 150–200 |
| LDL-cholesterol | 80–150 |
| HDL-cholesterol | 30–60 |
| VLDL-cholesterol | 20–40 |
| Triglycerides | 75–150 |
| Phospholipids | 150–200 |
| Free fatty acids | 5–15 |

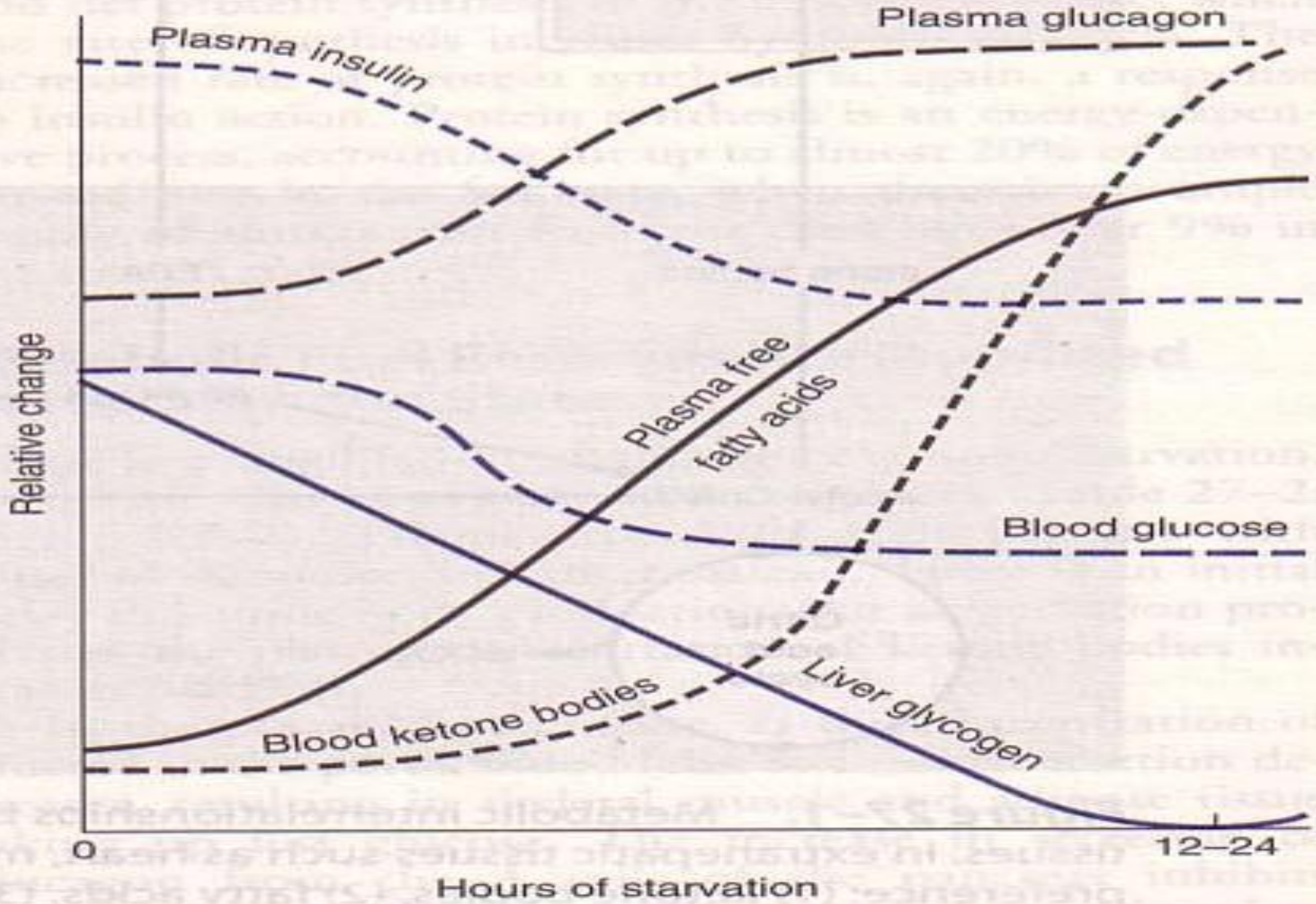



***Figure 27–2.*** Relative changes in metabolic parameters during the onset of starvation.

## *Lipids related disorders*;-

- ***lipid disorders***

**Common disorders**

Hypercholetrolemia

Hypertriglyceridemia

Hyperlipoproteinemia

ketosis

CVD

Fatty liver

Obesity

cancer

**Uncommon disorders**

Metabolic disorders of cerebrosides.

Lipidoses / lipid storage diseases

Multiple sclerosis.

Infant respiratory distress syndrome

Xanthomatosis.

Retinitis pigmentosa.

Phrynoderma / Toad skin.

Disorders of EFAs deficiency.

Zwellweger's disease.

# Lipid storage diseases

- Lipid storage diseases, or lipidoses, are a group of inherited metabolic disorders in which harmful amounts of fatty materials called lipids accumulate in some of the body's cells and tissues. People with these disorders either do not produce enough of one of the enzymes needed to metabolize lipids, or they produce enzymes that do not work properly. Over time, this excessive storage of fats can cause permanent cellular and tissue damage, particularly in the brain, peripheral nervous system, liver, spleen, and bone marrow.

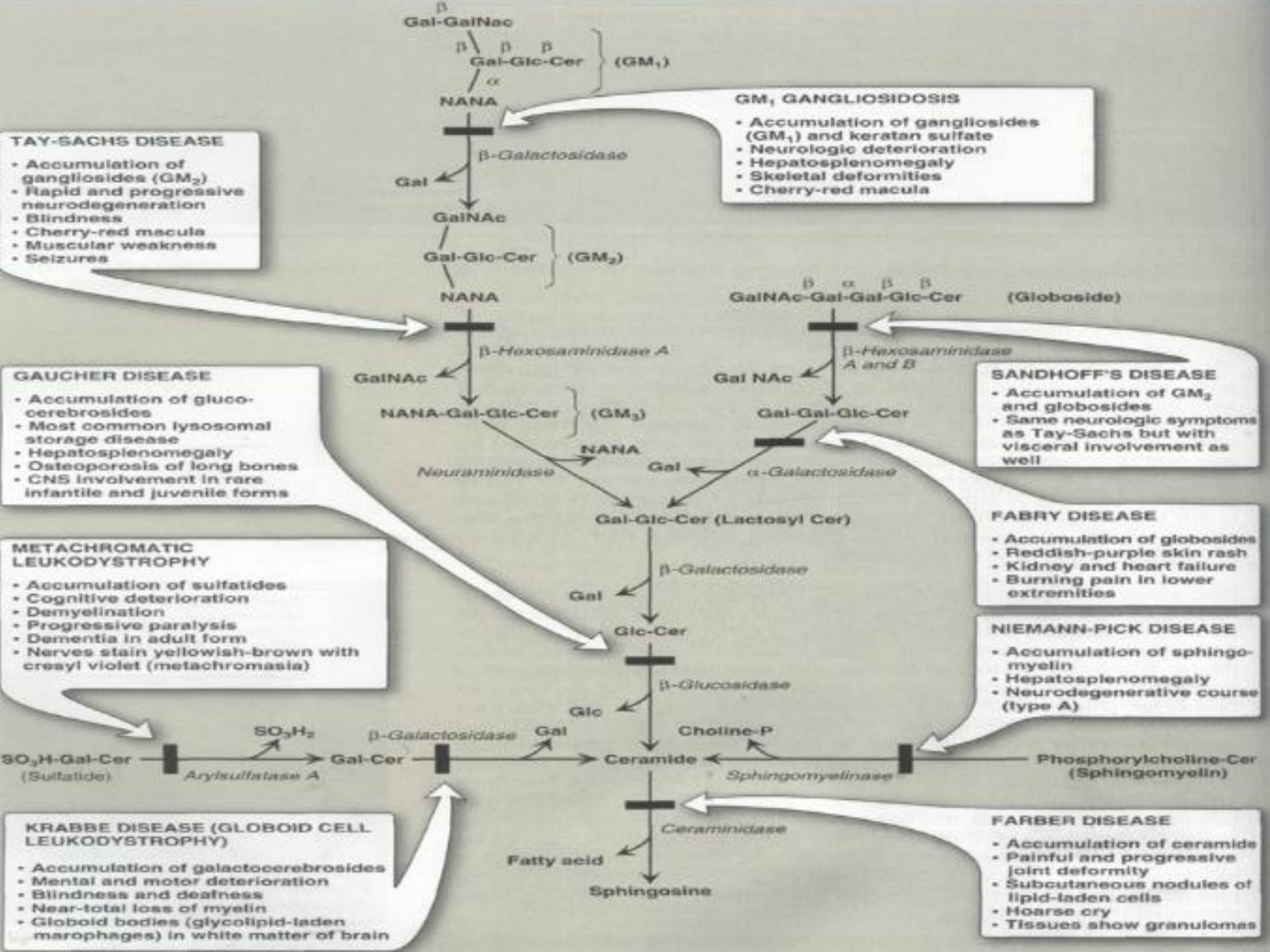
# Pathophysiology

- Because glycosphingolipids are essential components of all cell membranes, inability to degrade these substances and their subsequent accumulation results in physiologic and morphologic alterations of specific tissues and organs that lead to characteristic clinical manifestations. In particular, progressive lysosomal accumulation of glycosphingolipids in the central nervous system can lead to a neurodegenerative course; whereas, storage in visceral cells can lead to organomegaly, skeletal abnormalities, bone marrow dysfunction, pulmonary infiltration, and other manifestations.

# Diagnosis

- Diagnosis is made through clinical examination, biopsy, genetic testing, molecular analysis of cells or tissues, and enzyme assays (testing a variety of cells or body fluids for enzyme deficiency). In some forms of the disorder, a urine analysis can identify the presence of stored material.

| Disease | Enzyme Deficiency | Lipid Accumulating | Clinical Symptoms |
|---|---|---|---|
| Tay Sach's Disease | Hexosaminidase A | $G_{M2}$ Ganglioside | Mental retardation, blindness, muscular weakness |
| Fabry's disease | α-Galactosidase | Globotriaosylceramide | Skin rash, kidney failure (full symptoms only in males; X-linked recessive). |
| Metachromatic leukodystrophy | Arylsulfatase A | Sulfogalactosylceramide | Mental retardation and Psychologic disturbances in adults; demyelination. |
| Krabbe's disease | β-Galactosidase | Galactosylceramide | Mental retardation; myelin almost absent. |
| Gaucher's disease | β -Glycosidase | Glucosyl ceramide | Enlarged liver and spleen, erosion of long bones, mental retardation in infants. |
| Niemann-Pick disease | Sphingomyelinase | Sphigomyelin | Enlarged liver and spleen, mental retardation; fatal in early life. |
| Farber's disease | Ceramidase | Ceramide | Hoarseness, dermatitis, skeletal deformation, mental retardation; fatal in early life |


β
Gal-GalNac
β β β
Gal-Glc-Cer
(GM1)
α
NANA
β-Galactosidase
Gal
GalNAc
Gal-Glc-Cer
(GM2)
NANA
β-Hexosaminidase A
GalNAc
NANA-Gal-Glc-Cer
(GM3)
NANA
Neuraminidase
Gal
Gal-Glc-Cer (Lactosyl Cer)
β-Galactosidase
Gal
Glc-Cer
β-Glucosidase
Glc
Ceramide
Ceraminidase
Fatty acid
Sphingosine
β α β β
GalNAc-Gal-Gal-Glc-Cer
(Globoside)
β-Hexosaminidase A and B
Gal NAc
Gal-Gal-Glc-Cer
α-Galactosidase
Gal
SO3H-Gal-Cer
(Sulfatide)
Arylsulfatase A
SO3H2
Gal-Cer
β-Galactosidase
Gal
Choline-P
Sphingomyelinase
Phosphorylcholine-Cer
(Sphingomyelin)
GM1 GANGLIOSIDOSIS
• Accumulation of gangliosides (GM1) and keratan sulfate
• Neurologic deterioration
• Hepatosplenomegaly
• Skeletal deformities
• Cherry-red macula
TAY-SACHS DISEASE
• Accumulation of gangliosides (GM2)
• Rapid and progressive neurodegeneration
• Blindness
• Cherry-red macula
• Muscular weakness
• Seizures
GAUCHER DISEASE
• Accumulation of gluco-cerebrosides
• Most common lysosomal storage disease
• Hepatosplenomegaly
• Osteoporosis of long bones
• CNS involvement in rare infantile and juvenile forms
SANDHOFF'S DISEASE
• Accumulation of GM2 and globosides
• Same neurologic symptoms as Tay-Sachs but with visceral involvement as well
FABRY DISEASE
• Accumulation of globosides
• Reddish-purple skin rash
• Kidney and heart failure
• Burning pain in lower extremities
METACHROMATIC LEUKODYSTROPHY
• Accumulation of sulfatides
• Cognitive deterioration
• Demyelination
• Progressive paralysis
• Dementia in adult form
• Nerves stain yellowish-brown with cresyl violet (metachromasia)
NIEMANN-PICK DISEASE
• Accumulation of sphingo-myelin
• Hepatosplenomegaly
• Neurodegenerative course (type A)
KRABBE DISEASE (GLOBOID CELL LEUKODYSTROPHY)
• Accumulation of galactocerebrosides
• Mental and motor deterioration
• Blindness and deafness
• Near-total loss of myelin
• Globoid bodies (glycolipid-laden marophages) in white matter of brain
FARBER DISEASE
• Accumulation of ceramide
• Painful and progressive joint deformity
• Subcutaneous nodules of lipid-laden cells
• Hoarse cry
• Tissues show granulomas

# Types

- Type 1 ( familial hyperchylomicronemia)
- Type 2A (familial hypercholesterolemia)
- Type 2B ( familial combined(mixed) hyperlipidemia)
- Type 3 (familial dysbetalipoproteinemia)
- Type 4 (familial hypertriglyceridemia)
- Type 5 ( familial mixed hypertriglyceridemia)

# Primary Disorders of Plasma Lipoproteins (Dyslipoproteinemias)

| Name | Defect | Characteristics |
|---|---|---|
| **Hypolipoproteinemias** | | |
| Abetalipoproteinemia | No chylomicrons, VLDL, or LDL are formed because of defect in the loading of apo B with lipid. | Rare; blood acylglycerols low; intestine and liver accumulate acylglycerols. Intestinal malabsorption. |
| Familial alpha-lipoprotein deficiency<br>Tangier disease<br>Fish-eye disease<br>Apo-A-I deficiencies | All have low or near absence of HDL. | Hypertriacylglycerolemia due to absence of apo C-II, Low LDL levels. Atherosclerosis in the elderly. |

# Primary Disorders of Plasma Lipoproteins (Dyslipoproteinemias)

| Name | Defect | Characteristics |
|---|---|---|
| **Hyperlipoproteinemia** | | |
| Familial lipoprotein lipase deficiency (type I) | Hypertriacylglycerolemia due to deficiency of LPL, abnormal LPL, or apo C-II deficiency causing inactive LPL. | Slow clearance of chylomicrons and VLDL. Low levels of LDL and HDL. No increased risk of coronary disease. |
| Familial hypercholesterolemia (type II a) | Defective LDL receptors or mutation in ligand region of apo B-100. | Elevated LDL levels and hypercholesterolemia, resulting in atherosclerosis and coronary disease. |

# Primary Disorders of Plasma Lipoproteins (Dyslipoproteinemias)- contd.

| Name | Defect | Characteristics |
|---|---|---|
| Familial type III hyperlipoproteinemia (broad beta disease, remnant removal disease, familial dysbetalipoproteinemia) | Deficiency in remnant clearance by the liver is due to abnormality in apo E. | Increase in chylomicron and VLDL remnants , Causes hypercholesterolemia, xanthomas, and atherosclerosis. |
| Familial Hypertriacylglycerolemia (type IV) | Overproduction of VLDL often associated with glucose intolerance and hyperinsulinemia. | High cholesterol, VLDL, Subnormal LDL and HDL. Associated with Alcoholism, diabetes mellitus and obesity. |
| Hepatic lipase deficiency | Deficiency of the enzyme leads to accumulation of large triacylglycerol-rich HDL and VLDL remnants | Patients have xanthomas and coronary heart disease. |

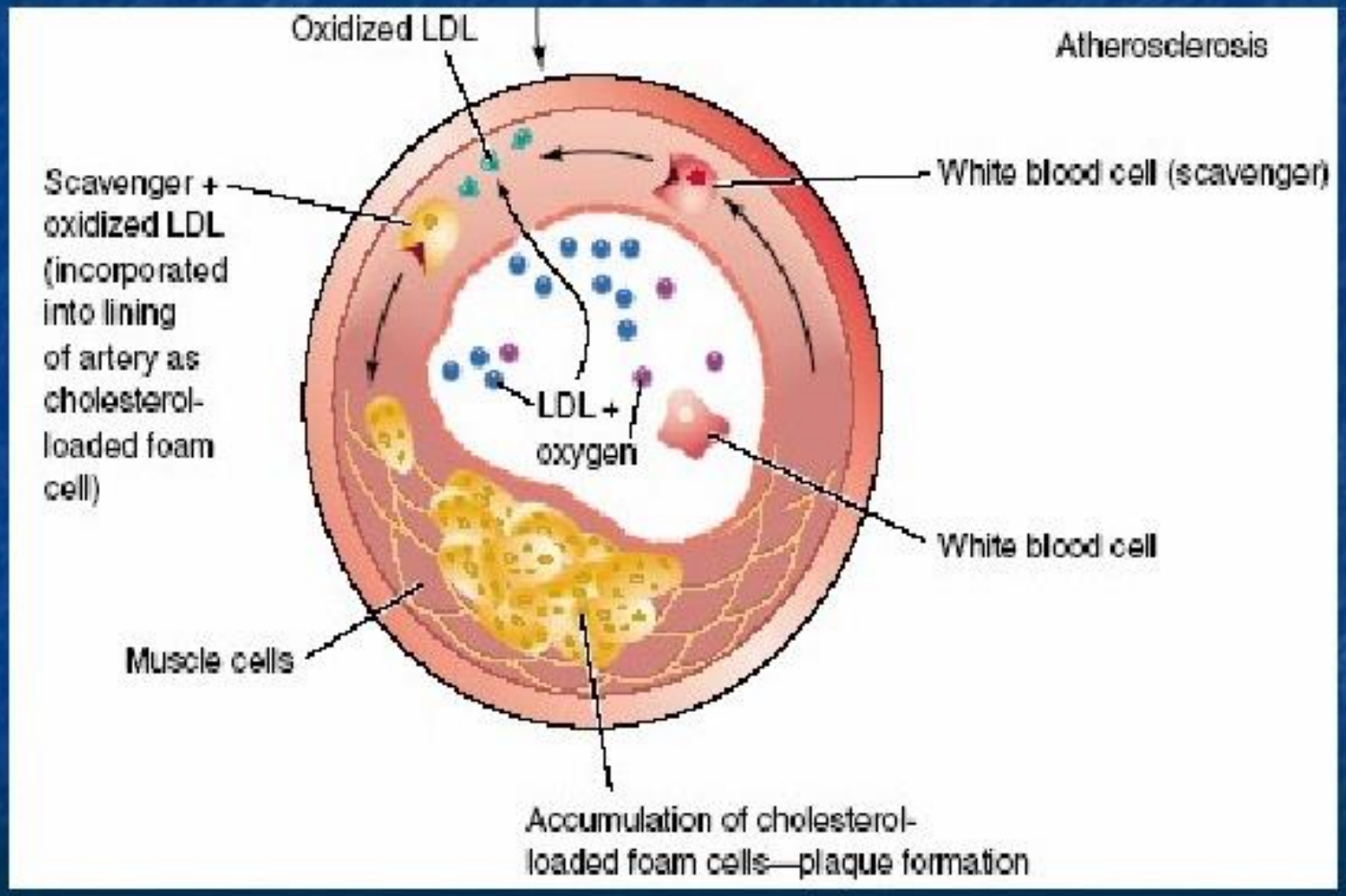
- ***ATHEROSCLEROSIS*:**

- As LDL particles penetrate the walls of the arteries, they become oxidized-LDL and next are scavenged by the body's white blood cells.

- • These foam cells are then deposited into the lining of the artery wall.

- • This process, known as *atherosclerosis,* causes plaque deposits to enlarge, artery walls to lose elasticity, and the passage through the artery to narrow.

# Diagrammatic representation of the disease (atherosclerosis)-

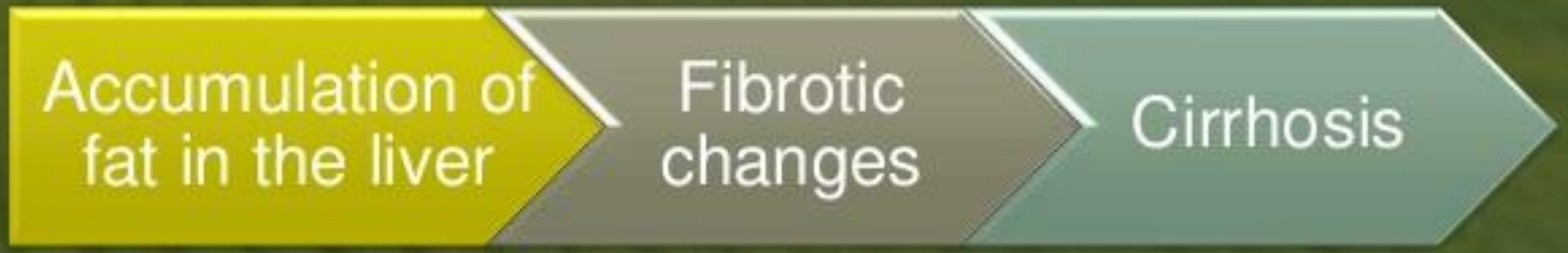


# Fatty liver

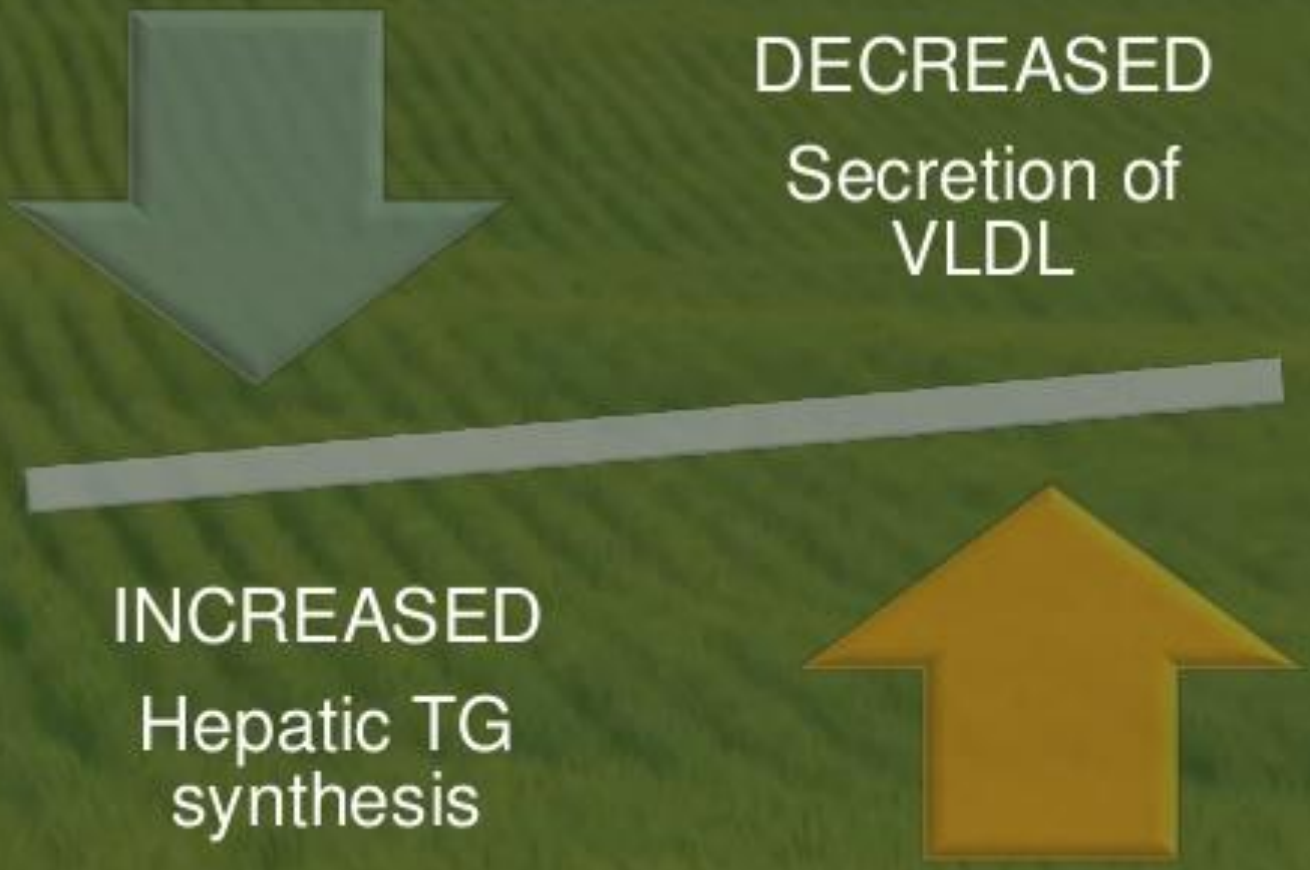
Excessive accumulation of fat in the liver parenchymal cells

- Liver is not a storage organ for fat
- Liver contains about 5% fat

# Fatty liver


Accumulation of fat in the liver
Fibrotic changes
Cirrhosis

# FATTY LIVER: CAUSES



# Conditions that cause FATTY LIVER

# Conditions that cause FATTY LIVER

Dietary deficiency of

- Lipotropic factors
- Essential fatty acids
- Essential amino acids
- Vitamin E and selenium

# LIPOTROPIC FACTORS

Substances that prevent the accumulation of fat in the liver

- Choline
- Methionine
- Betain
- Vitamin $B_{12}$
- Folic acid

# Management of Hyperlipidemias

- **I- Diet:**
- **Avoid saturated** fatty acids (animal fats) and give unsaturated fatty acids (plant fats).
- - Regular consumption of fish oil which contains **omega 3** fatty acids and vitamins E and C **(antioxidants).**
- **II. Exercise:**
- - ↑ HDL and insulin sensitivity.
- **III- Drug therapy**: the primary *goal* of therapy is to *decrease levels of LDL* . Also,increase in HDL is recommended.

# ANY QUESTION

- **CHATTERJEA BIOCHEMISTRY**
- **LIPPINCOTT BIOCHEMISTRY**
- **HARPERS BIOCHEMISTRY**
- **SATYANARAYANA BIOCHEMISTRY**

# Thank you