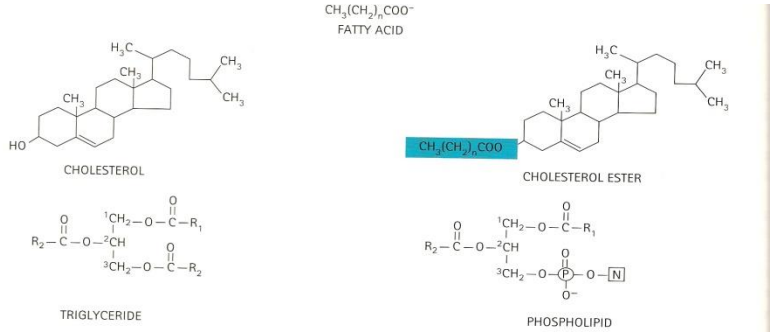
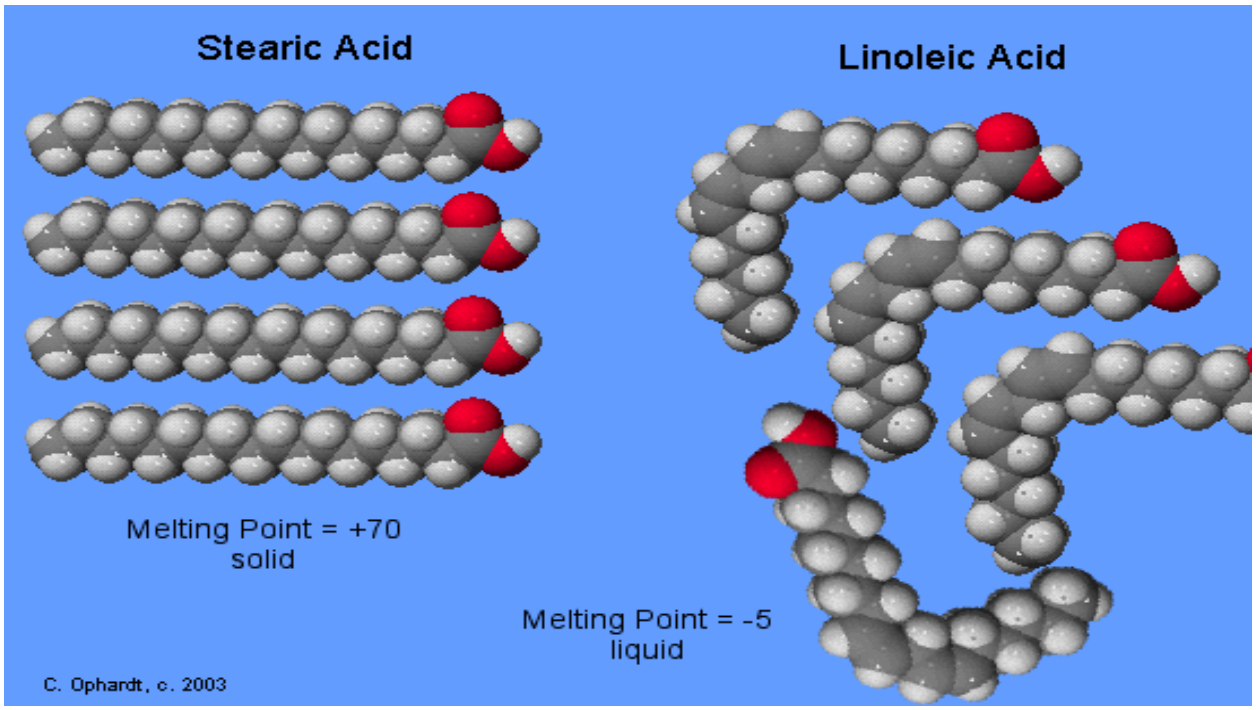
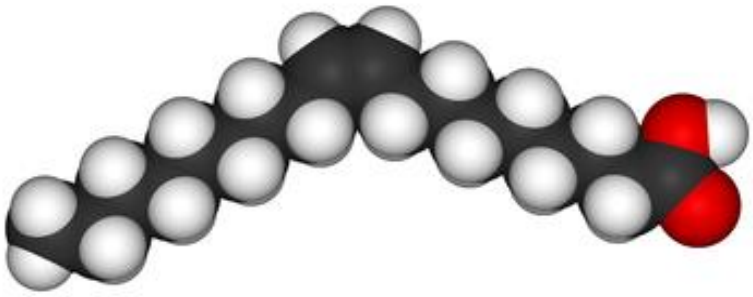
Plasma Lipids:



☐Fatty acids:

- ☐ Straight chain carbon compounds:
- ☐ - saturated: No double bond , Palmitic acid.
- ☐ - monounsaturated : one double bond ,Oliec.
- ☐ - polyunsaturated : more than one double bond , Linoliec.

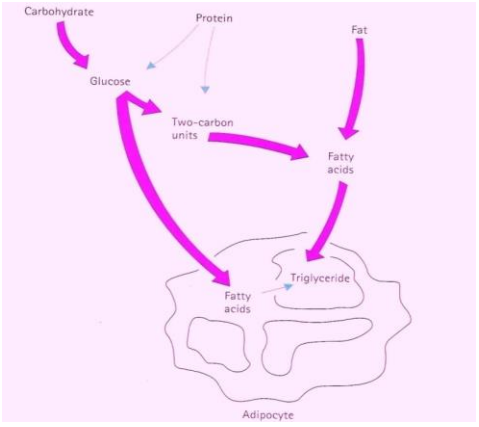




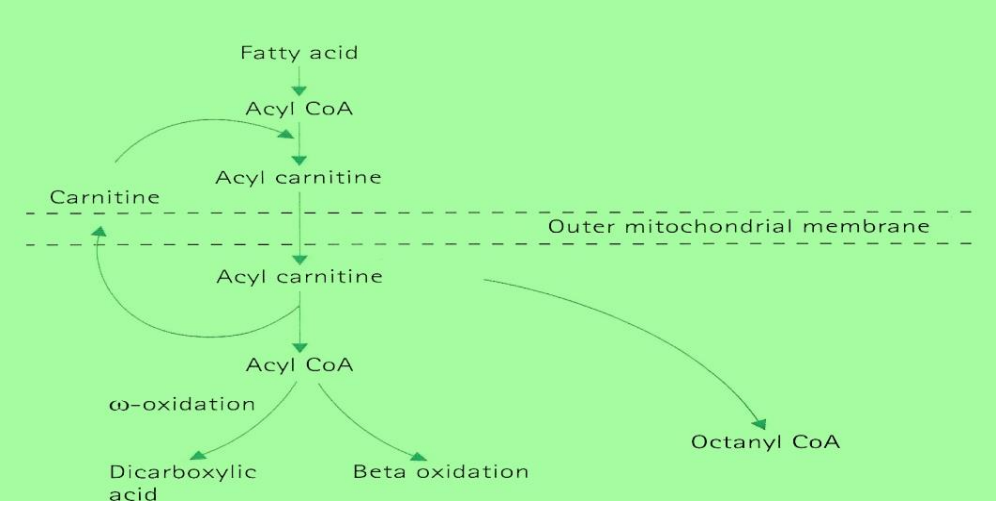
oleic acid

- **Non-esterified fatty acids NEFAs:**
- **-**either provided by food.
- - from adipose tissue (adipocytes).
- -from protein or glucose.
- NEFAs activate a group of nuclear receptors called : Peroxisome Proliferator activated receptors (PPARs) .They associate insulin resistance and dyslipidemia.

  Fatty acids are re-esterified in the adepocytes to tri-glycerides & stored there.
- Triglycerides are released, **as Fatty acids** , to the blood when there is energy deficit .



Fatty acid oxidation



Defects in fatty acid oxidation

- group of very rare inborn errors of metabolism.

  The most common, medium-chain-acyl-CoA dehydrogenase (MCAD) deficiency.

- Fatty acids provide an important alternative source of fuel for the body, especially during fasting states.

  heart, skeletal muscle, and gut can use FA as fuel.

- When **oxidized** by the liver to **ketone bodies**, they provide a critical energy source for ***brain (when no glucose).***

- A deficiency in the enzymes for fatty acid beta-oxidation can be dangerous during **hypoglycemic states.**

- In Beta oxidation defect, there will be **fasting hypoglycemia WITHOUT** the expected ketosis .

- The defects & prolonged fasting can also lead to **heart failure, liver failure, and skeletal muscle rhabdomyolysis (** *due to accumulation of FA).*

Transport of lipids :

- **lipoproteins :**
- **chylomicrones:** ***in the intestines : exogenous trigs., apoproteins A $_1$, A_2 ,B48 , C2 ,C3 & E***
- **VLDL** ***: in the liver , endogenous trigs. apoproteins : B48, B100 ,C2, C3, &E.***
- **LDL** ***: in the liver , carry cholesterol to the cells , apoproteins: B100 .***
- **HDL** ***:in the liver ,carry cholesterol to the liver, apoproteins : A1, A2 ,C2,C3,& E.***
- **Functions of apoproteins**:
- A1 , & A2 : LCAT activators.
- B48 : secretion of chylomicrons & VLDL.
- B100 : LDL receptor bindings.
- C2 & C3 : Lipoprotein lipase activators.
- E : IDL & remnant particle receptor binding.
-

Chylomicrons

- Small fat globules composed of protein and lipid (fat).They consist of :
- triglycerides (85–92%), phospholipids (6–12%), Cholesterol (1–3%), and proteins (1–2%).

- They transport dietary lipids from the intestines to other locations in the body.
- are found in the blood and lymphatic fluid,
- They transport fat from the intestine to the liver and to adipose (fat) tissue.
- After a fatty meal, milky blood indicates chylomicrons.

- **Chylomicronemia syndrome**
- is a disorder in which the body does not break down fats (lipids) correctly.
- This causes chylomicrons to build up in the blood.
- The disorder is passed down through families
- 1- Absensce of lipoprtein lipase (LPL) enzyme…... *genetic defect*
- 2- Defects in apolipoprotein CII and apolipoprotein A V.

LDL : low density lipoprotein (β-lipoprotein)

- the most important ,
- associated with atherosclerosis ,
- have 4 types :
- LDL1 : apoprotein B100 , large particles , less atherogenic , less susceptible to oxidation .
- LDL2 & LDL3 with apoprotein **B45,** smaller dense , more atherogenic and more prone to oxidation.
- Lp (a) : similar to LDL ,but higher protein.Normally < 0.3 g / L
- independent risk factor for cardiovascular disease.

☐ Cholesterol & LDL

- ☐ Most cell can synthesize cholesterol.
- ☐ But most endogenous production occurs in the liver and intestine & distributed to other tissues by LDL
- ☐ * In familial hypercholesterolemia or on a high-cholesterol diet,
- ☐ * the VLDL produced is higher in cholesterol content, smaller in size, and within the LDL density range (1.019–l.063 g/mL).
- ☐ When IDL is converted to LDL ,It looses Apo- E & acquires Apo B-100.
- ☐ The LDL produced stays longer in blood.
- ☐ *LDL supplies all tissue with cholesterol*

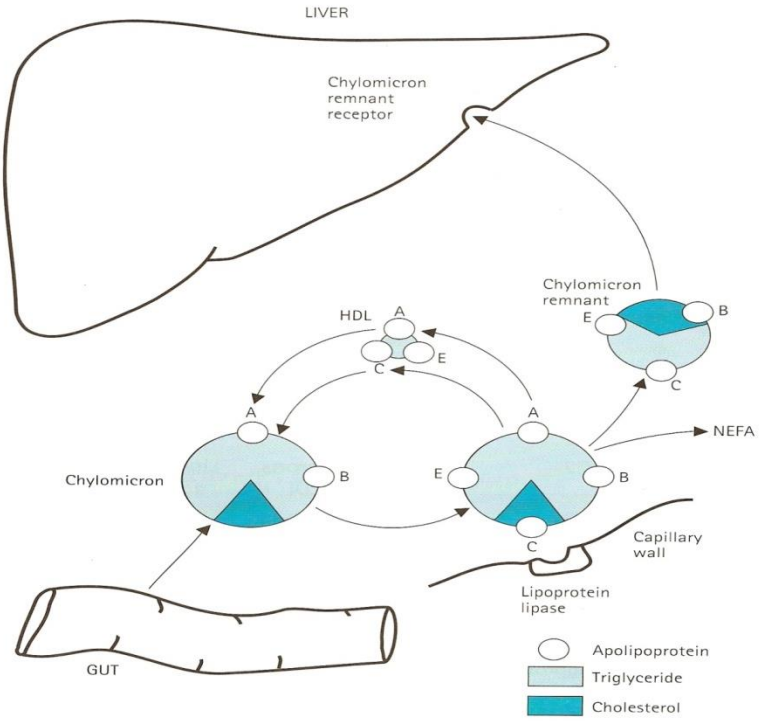
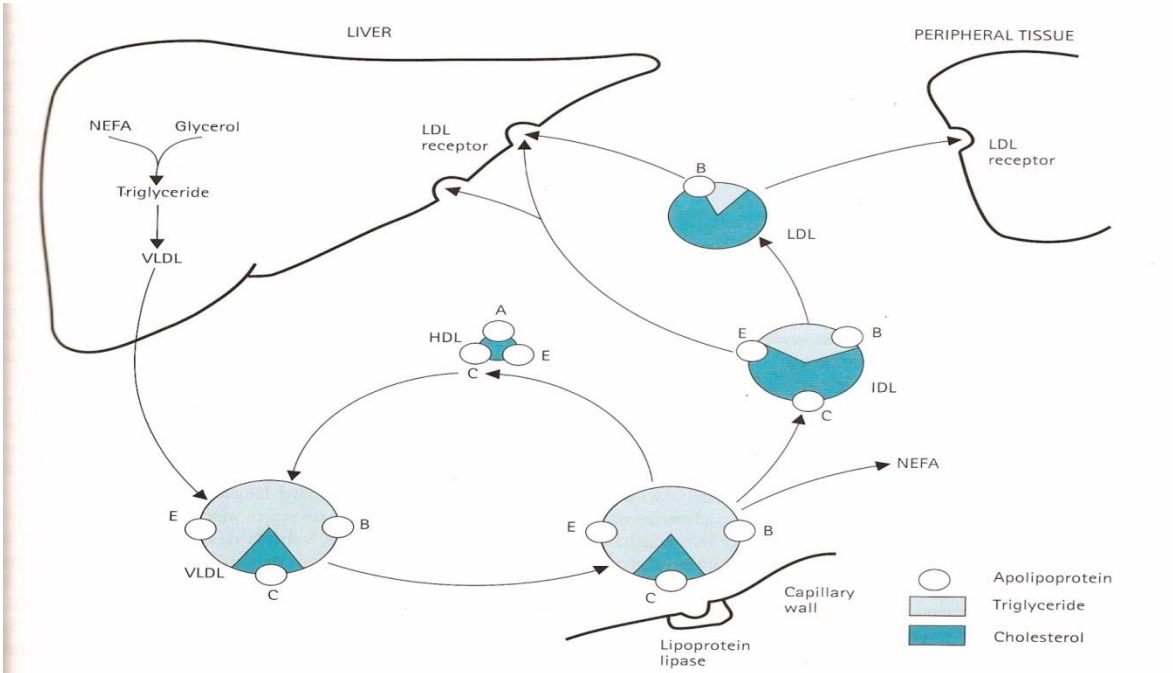


Fig. 13.5 Exogenous lipid pathways. (HDL = high-density lipoprotein; NEFA = non-esterified [free] fatty ac

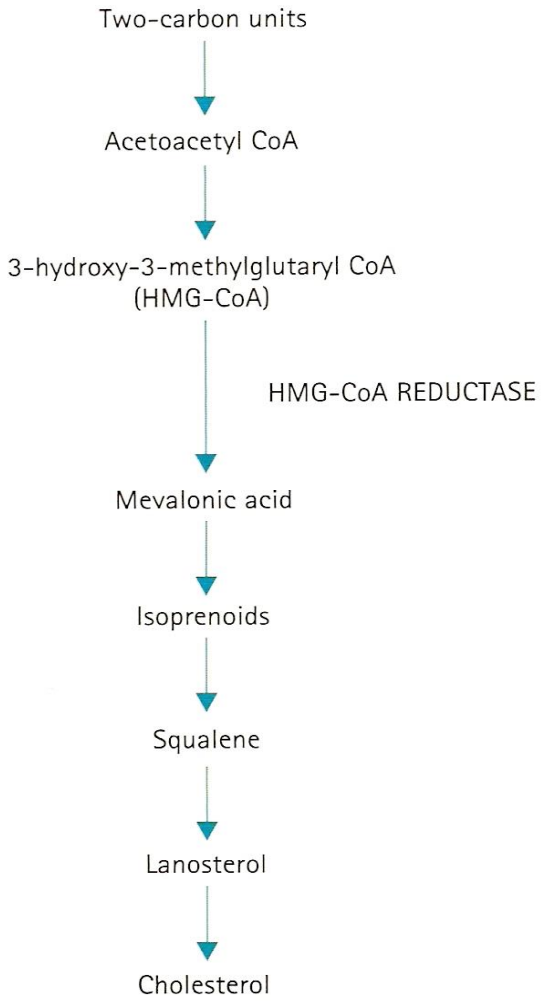


6 Endogenous lipid pathways. (LDL = low-density lipoprotein; VLDL = very low-density lipoprotein; intermediate-density lipoprotein; HDL = high-density lipoprotein; NEFA = non-esterified [free] fatty acid.)

-

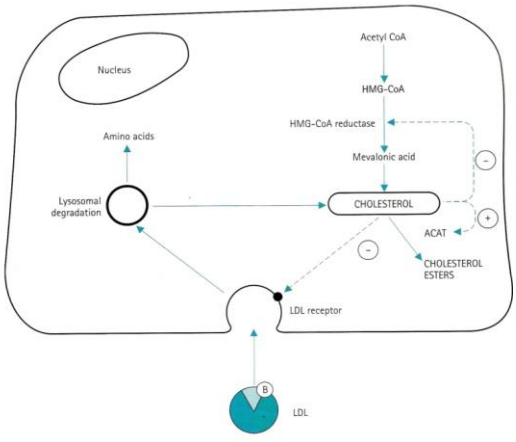
Cholesterol synthesis:

- (hydroxymethylglutarylCoA reductase (HMG-CoA reduxtase) ***is the rate limiting enzyme.***
- **Low enzyme activity seen at excessive synthesis.**



☐

☐ Accumulation of cholestero inside the cells reduces hepatic LDL receptors activity & results in reducing their number.

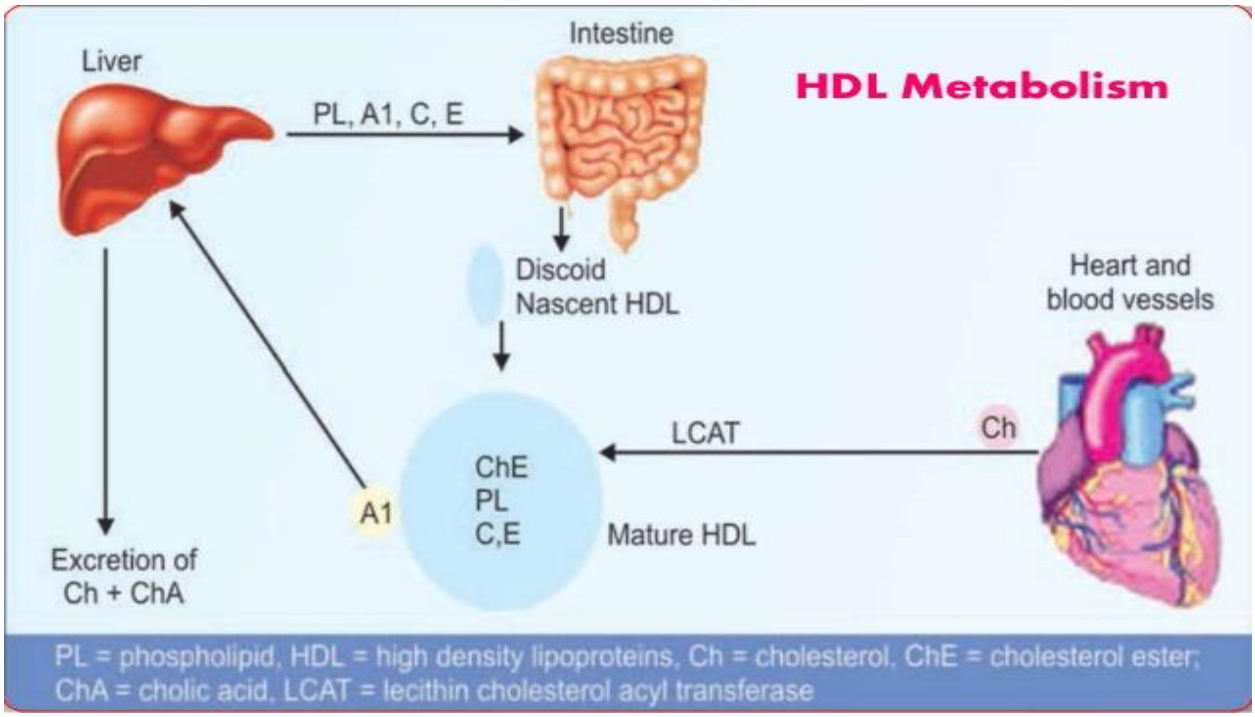


☐ HDL :high density lipoprotein (α- lipoprotein)

- ☐ are synthesized in the liver and the small intestine.
- ☐ They have higher protein content (around 50 % of the particle total weight).
- ☐ When secreted, they contain little cholesterol and no cholesteryl esters.
- ☐ formed by different apolipoproteins, Apo A1, ApoE and Apo C-II.
- ☐ They transport ApoE and Apo C-II from the liver to the plasma,
- ☐ ApoE & Apo C-II are used by other lipoproteins.
- ☐ Its main lipid content is phospholipids (35 % of the total weight),
- ☐ The enzyme Lecithin Cholesterol Acyl Transferase (**LCAT**) catalyzes the transfer of acyl groups from lecithin to cholesterol.

LCAT

- ☐ Lecithin + Cholesterol ———->Lyso-lecithin + Cholesterol ester.
- ☐ The **cholesterol esters** are scavengered from :
- ☐ a- cell membrane of extra-hepatic tissues,
- ☐ b- IDL and Chylomicrons remnants.
- ☐ The result is the formation of the cholesterol rich **HDL2 and HDL3.**
- ☐ The Apo-A receptors in the liver take up HDL2 & HDL3
- ☐ **{ A process of cholesterol transportation from the peripheral parts to the liver }**
- ☐ **Cholesterol is excreted through bile.**
- ☐ **functions of HDL in summary:**
- ☐ a) A reservoir of apoproteins for other lipoproteins.

- b) Acceptor of unesterified cholesterol.
- c) Esterification of cholesterol, (through the action of LCAT).
- d) Reverse Cholesterol Transport .
- 

- **Very-low-density lipoproteins (VLDL) ,**Pre –β lipoproteins
- carry 90% of the serum TGs in the fasting state.
- VLDL TGs are made in the liver from FAs :

  1- synthesized *de novo,*

  2- extracted from the circulation as non- esterified FAs,

  3- recycled from lipoprotein remnants cleared by hepatic receptors.
- As in chylomicron , TG is cleared from the circulation by the action of lipoprotein lipase (LPL),

The triglyceride content is lower and cholesterol content higher than that of chylomicrons .

the major structural protein is apo B (apo B_{100}**) as opposed to the **apo B_{48}** in the chylomicrones .

- VLDLs carry triglycerides synthesized in the liver and intestines to capillary beds in adipose tissue and muscle,
- they are hydrolyzed to provide fatty acids that can be oxidized to produce ATP.
- ***Or*** *re-esterified to fat & stored.*
- VLDL remnants (called *IDLs*) contain no TG & can be further metabolized to LDL.
- VLDLs serve as acceptors of cholesterol transferred from HDL,
- This transfer process is mediated by an enzyme called ***cholesterol ester transfer protein*** **(CETP).**
- VLDLs are produced by the parenchymal cells of the liver from lipid and apoprotein constituents in a way similar to that of chylomicron formation in intestines.

Factors affecting liver secretion of VLDL

- 1-the flux of free fatty acids entering the liver (direct relation), polysaturated FA produce more TG).
- 2-A high-carbohydrate diet results in a substantial elevation of plasma VLDL concentrations. (High carbohydrates = high VLDL).

- 3-high-cholesterol diet alters the composition of VLDL , (cholesterol esters substitute TG as core components, and increase apo E synthesis).

- **VLDL remnants ……..In humans :**

- the core TG are removed and the Apo-C are lost,

- About half of the VLDL is rapidly removed by the liver via the **apo B-100–apo E receptor pathway.**

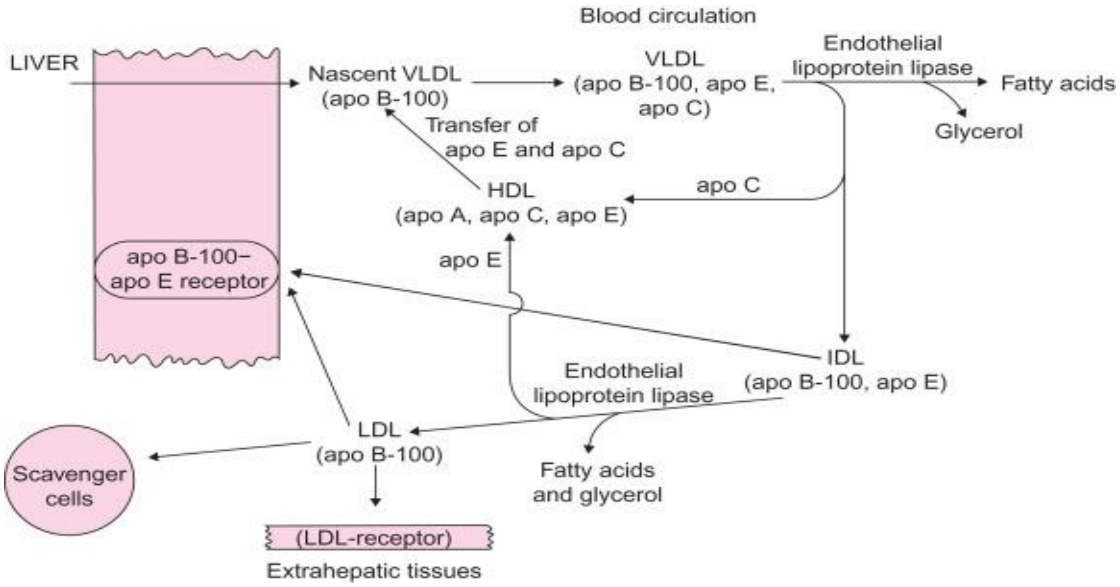
- The rest remains in circulation as VLDL remnants **.**

- remnants with a density of between 1.006 and 1.019, are called IDLs . they are analogous to chylomicron remnants.

- The remaining IDLs are subjected to further catabolism by hepatic lipase.

- In VLDL and IDL, the cholesterol is converted to cholesteryl esters by LCAT.

- **LDL is formed** (cholesteryl-ester + apo B-100).



☐ DYSLIPIDEMIA:

☐ - A disorder of lipoprotein metabolism, -lipoprotein overproduction or deficiency.

☐ may be manifested by **elevation** in blood of :

1- the total cholesterol,

2- the "bad" low-density lipoprotein (LDL) cholesterol.

3- the triglycerides.

4- a **decrease** in the "good“ HDL chol .

☐ LDL cholesterol for adults with diabetes ,< 100 mg/dL (2.60 mmol/L),

☐ HDL cholesterol > 40 mg/dL (1.02 mmol/L),

☐ desirable triglyceride conc. <150 mg/dL (1.7 mmol/L).

☐ Dyslipidemia is divided up into **primary and secondary** types.

☐ Primary is inherited.

☐ Secondary is an acquired condition. Develops from other causes, such as obesity or diabetes.

☐ **Familial combined hyperlipidemia.**

☐ inherited cause of both high LDL cholesterol and high triglycerides.

☐ develop problems in the teens or 20s.with a high risk for early coronary artery disease, or a heart attack .

☐ **Familial and polygenic hyper- cholesterolemia.**

☐ both characterized by high total cholesterol. (A total cholesterol of **<** 200 milligrams per deciliter (mg/dL) is acceptable).

☐ Familial hyperapobetalipoproteinemia.

- ☐ high levels of apolipoprotein B, a protein that is part of the LDL cholesterol.
- ☐ can be primary or secondary.,
- ☐ the body has a difficulty in breaking down LDL cholesterol or triglycerides .

☐ Causes of secondary dyslipidemia

- ☐ cigarette smoking.
- ☐ obesity and a sedentary lifestyle .
- ☐ foods high in saturated fat and trans fat .
- ☐ Alcohol consumption.
- ☐ type 2 diabetes
- ☐ Hypothyroidism.
- ☐ Chronic kidney disease.

☐ Frederickson Classification of Lipid Disorders (WHO)

- ☐ **Type 1:** hyper chylomicronemia , **milky serum**
- ☐ Deficiency of lipoprotein lipase .
- ☐ Apo-CII deficiency.
- ☐ *serum TG **++** , TC .. N*

- ***Type II a***: *hypercholesterolemia , High LDL with defect in LDL receptor.*
- *clear serum .*
- *Serum TG - N . TC **++***

- ***Type II-b*** *: Combined hyperlipidemia , LDL - High , VLDL – High*
- *LDL receptor defect & high Apo-B*
- *serum: turbid . TG ++ , TC ++*

- ***Type III*** *: Dysbetalipoproteinemia . IDL +*
- *IDL +, HDL – low , mutation in ApoE*
- *turbid serum with : TG + , TC +*

- ***Type IV*** *: Hypertriglyceridema , High VLDL*
- *Familial hypertriglyceridemia*
- *Increased VLDL synthesis over elimination .*
- *Turbid serum , with TG ++ , TC N or +*

- ***Type V** : hypertriglyceridemia , chyl. & high VLDL*
- *Increased VLDL synthesis + low LPL*
- *creamy & turbid serum*
- *serum TG ++ , TC +*

Tangier disease :

- Inherited disease causing decreased HDL & Moderate increase in risk of cardiovascular disease.
- Caused by mutations in the ABCA1 gene .