Lipid metabolism

Lipids constitute a heterogeneous group of compounds of biochemical importance. Lipids may be defined as compounds which are relatively insoluble in water, but freely soluble in nonpolar organic solvents like benzene, chloroform, ether, hot alcohol, acetone, etc.,

Functions of Lipids:

1. Storage form of energy (triglycerides)
2. Structural components of biomembranes (phospholipids and cholesterol)
3. Metabolic regulators (steroid hormones and prostaglandins)
4. Act as surfactants, detergents and emulsifying agents (amphipathic lipids)
5. Act as electric insulators in neurons
6. Provide insulation against changes in external temperature (subcutaneous fat)
7. Give shape and contour to the body
8. Protect internal organs by providing a cushioning effect (pads of fat)
9. Help in absorption of fat soluble vitamins (A, D, E and K)
10. Improve taste and palatability to food.

Clinical Applications:

1. Excessive fat deposits cause obesity.
2. Abnormality in cholesterol and lipoprotein metabolism leads to atherosclerosis and cardiovascular diseases.
3. In diabetes mellitus, the metabolisms of fatty acids and lipoproteins are deranged, leading to ketosis.

CLASSIFICATION OF LIPIDS

Based on the chemical nature, lipids are classified:

I. Simple Lipids
They are esters of fatty acids with glycerol or other higher alcohols. They are subclassified as:

a) Triacylglycerol or Triglycerides or neutral fat.
b) Waxe

II. Compound Lipids

They are fatty acids esterified with alcohol; but in addition they contain other groups. Depending on these extra groups, they are subclassified as:

A) Phospholipids, Containing Phosphoric Acid

B) Non-phosphorylated Lipids such as Glycosphingolipids (carbohydrate)

III. Derived Lipids

They are compounds which are derived from lipids or precursors of lipids, e.g. fatty acids, steroids, prostaglandins, leukotrienes, terpenes, dolichols, etc. For details of cholesterol and steroids.

IV. Lipids Complexed to Other Compounds Proteolipids and lipoproteins.

Fatty acids:

Fatty acids are straight-chain hydrocarbons with a terminal carboxyl group. They are frequently identified by the number of carbon atomes and number of douple bonds, as diunsaturated linolic acid. The location of the douple bound in the n- or omega (ω) numbering system designates the number of carbon atoms from the terminal methyl, thus linolic acid designated as 18:2n-6 and called an ω-6 fatty acid.

Fatty acids exist mostly as ester of glycerol in both triglycerides and some phospholipids and as ester of high –molecular –weight alcohols. The fatty acidds of triglycereides are mostly C16 or C18, and in phospholipids, they are C18 to C22.

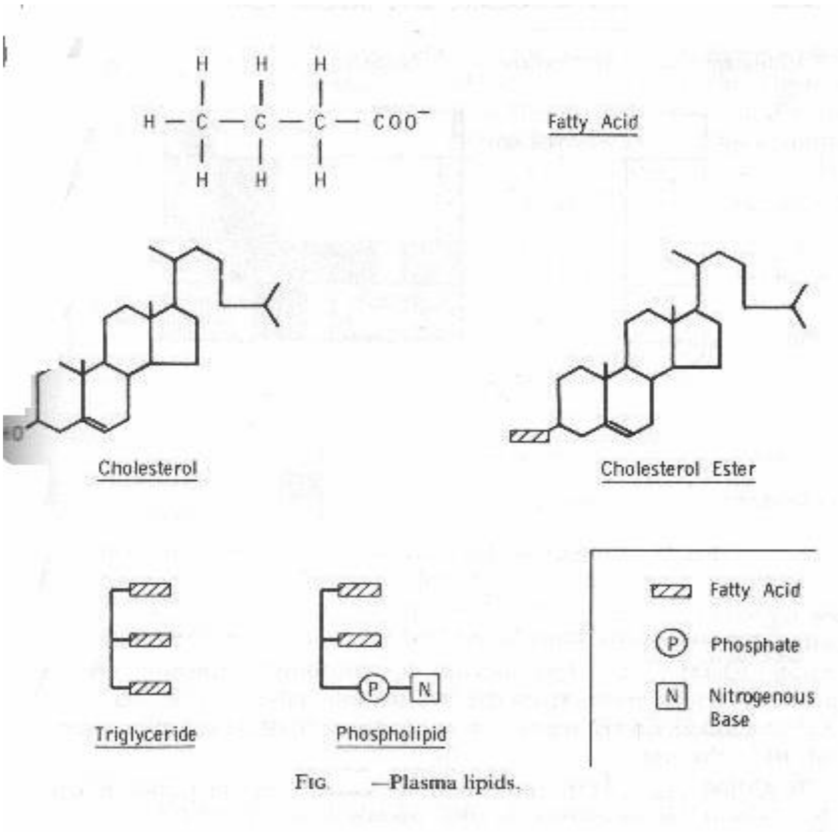
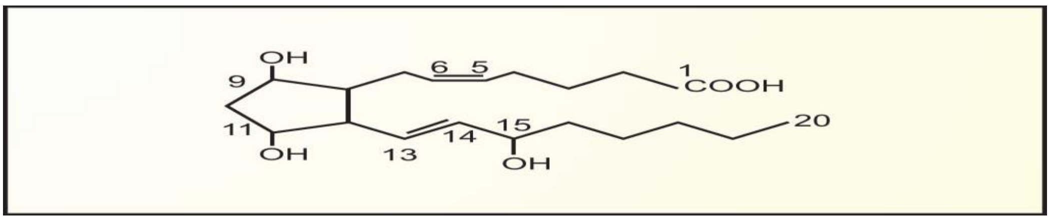


FIG —Plasma lipids.

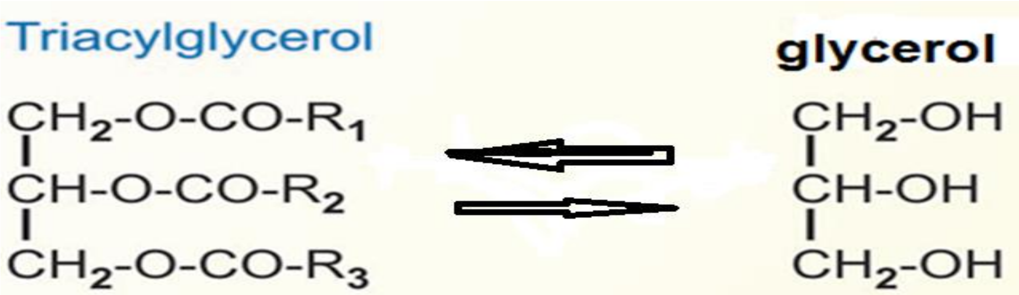
Prostaglandins

Prostaglndies (PGs) were originally isolated from prostate tissue and hence the name. But they are present in almost all tissues. They are the most potent biologically active substances; as low as one nanogram/ml of PG will cause smooth muscle contraction. The diverse physiological roles of prostaglandins confer on them the status of local hormones. Chemical Structure: All prostaglandins are considered to be derived from the 20 C cyclic saturated fatty acid, The five carbon ring is saturated. All naturally occurring PGs have an alpha oriented OH group at C15. Classification of Prostaglandins: According to the attachment of different substituent groups to the ring, PGs are named with capital letters such as A, B, E and F. In the same series, depending on number of double bonds on the side chains they are denoted by a subscript after the capital letter, *e.g*. PGE 1 , PGE 2 , PGE 3 , etc. Series 2 have 2 double bonds at 13–14 (trans) and 5–6 (cis). Structure of PGF 2 is shown in Figure below:



Triglycerides

Most of the fatty acids in the body are components of triglyceride and are stored in the depots (adipose tissue) as fat. Adipose cells convert fatty acids into triglyceroide by esterification with glycerol-3-phosphate, compounds that arises from glucose metabolism. cells must contain glucose for triglyceride formation. glucose is absent during periods of fasting, starvation, or uncontrolled diabetes mellitus, and in these condition, hydrolysids of triglycerides, and withdrawal of their fatty acids from the depots predominate. Excess carbohydrate ingested during a meal may be stored tempoarily as triglycerides after conversion of glucose to fattty acids. The hormone insulin promotes the synthesis of triglycerides by adipose cells, whereas its deficiency accelerated triglyceride hydrolysis. The first step in the catabolism of triglycerides begins with their hydrolysis. The fatty acids apperear in the plasma as nonesterfied (free) fatty acids bounded to albumin as a carrier.



Phosphosholipids

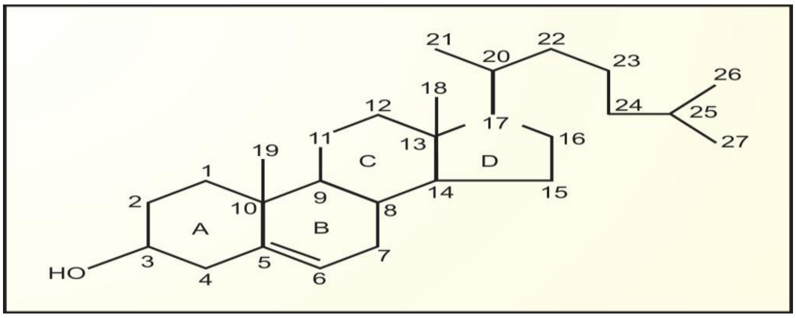
The principal phospholids are composed of triglyceride esterified with phosphoric acid, which in turn, is bound as an ester to a nitrogen containing base (choline, ethanolamine) or to serine, and inositol are some times collectively referred to as cephalins. Phospholipds are essential compounds of cell membrane becouse of their ability align themselves between water and lipids phase. Phosphoethanolamine, a constituent of blood platelts, is a necessary participant in the clooting process. Phospholips in lipoprotiens also supply the fatty acids necessary for the esterification of cholesterol. The phospholipids play a role in mitochondrial metabolism, in blood cogulation, and lipid transport as part of lipoprotins, and are important structural components of membranes.

Sphongolipids

The sphingolipids are all compounds containing the long chain, dihydroxyamino alcohol sphingosine. All the sphingolipids bind a fatty acid in amide linkage to the amino group and are also known as ceramides, becouse they are cerebral lipids containg an amide group.

Cholesterol

Cholesterol, the principal body sterol, is a complex alcohol formed of four fused rings and a side chain, pure cholesterol is a solid at body temperature. The major sites of synthesis of cholesterol are liver, adrenal cortex, testis, ovaries and intestine.



Structure of cholesterol

Approximately 70 % of plasma cholesterol exists in an acyl ester form. The esterification takes place almost exclusively in high density lipoprotein (HDL) complex. Most of the cholsterol in the body is syntheszed from acetyl CoA, but we also ingest some when we eat meat, dairy products, or eggsplants do not contain cholesterol, although they do have closely related sterols. Cholesterol is catabolized in hepatic cells by oxidation to bile acids (cholic and chenodeoxycholic acids that conjugate with glycine or taurine before secreation into bile. These bile acids and conjugates are emulsifying agents that are essential for the digestion and absorption of fats. Some of cholesterol is also secreated as such into the bile. Both the bile acids and biliary cholesterol are reabsorbed to some extent in the intestine by an entrohepatic circulation. *Thus*, the liver is the site of cholresterol disposal or degradation, as well as its major sit of synthesis.

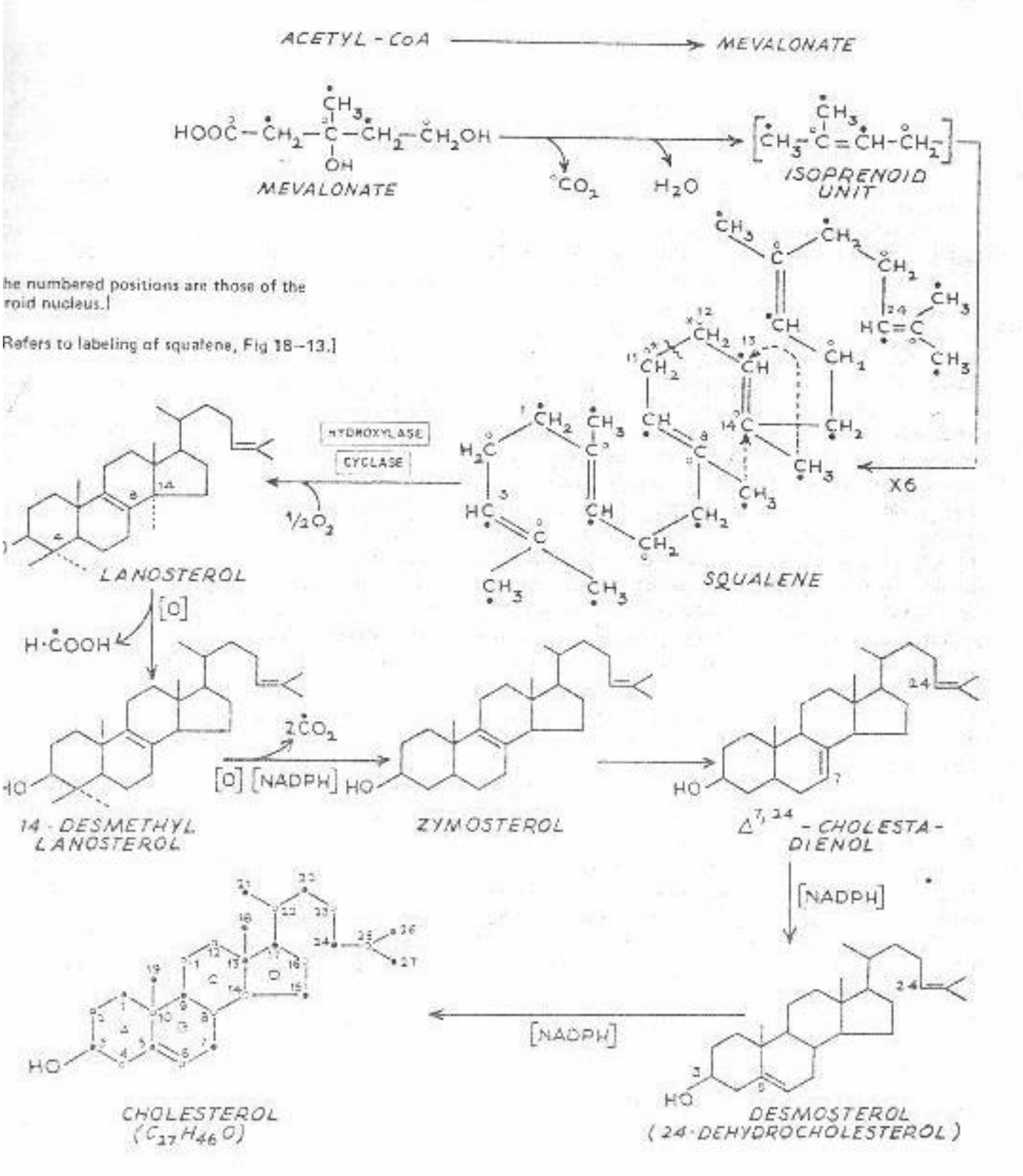


Figure Biosynthesis of cholesterol

A negative feed back mechanism controls to a limited extent the rate of synthesis of cholesterol. When the diet is high in cholesterol, the increased amoun of cholesterol brought to the liver decrease the receptors – mediate hepatic intake of cholesterol and inhibits the rate – limiting enzyme (β-hydroxy- β-methylglutaryl CoA reductase) essential for te synthesis of mevalonic acid, step in the synthesis of cholesterol. *Furthermore*, the reabsorption of bile acids and cholesterol in the enteroheatic circulation is decreased, so more cholesterol is excreated in the form of bile acids and free cholesterol.

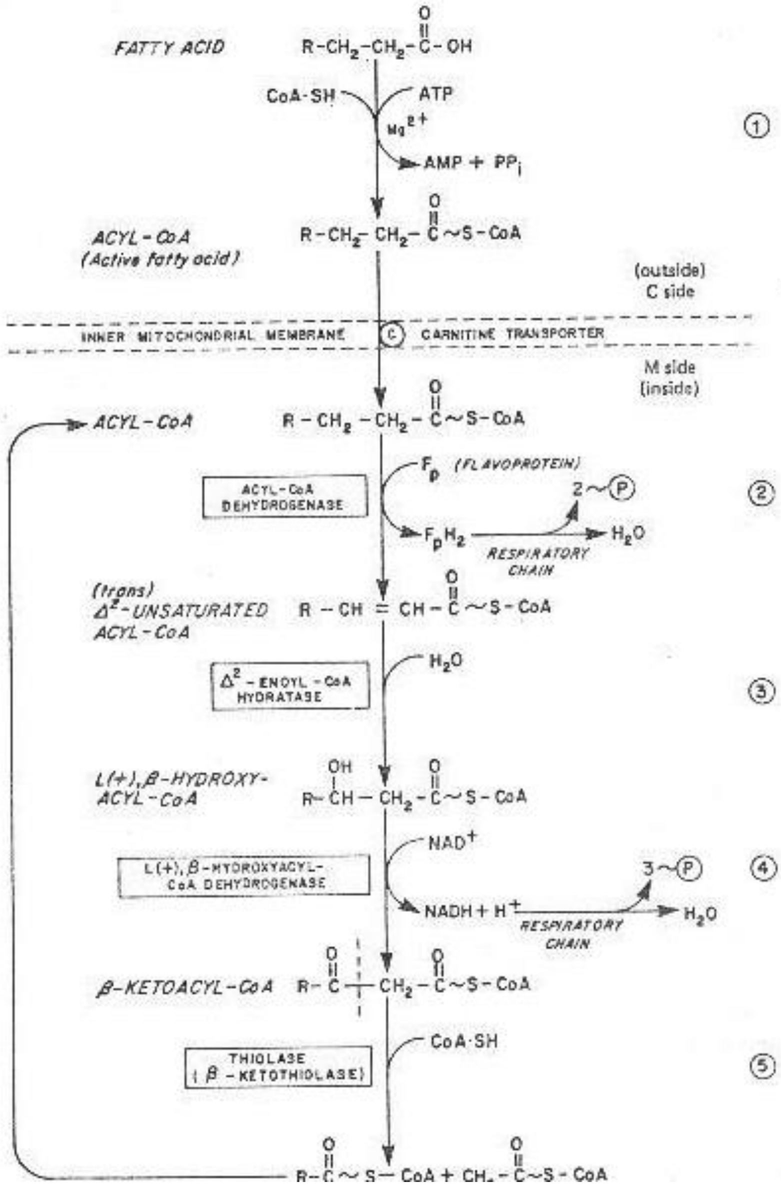
Serum cholesterol concentration can rise to high levels in some pathological states. An elevated cholesterol concentration has been implicatede as one of sever risk factors leading to coronary artery disease (atherosclerosis or myocardial infraction); *thus* the measurment of serum cholesterol is a fairly common lab. procedure.

<u>Significance and Functions of Cholesterol:</u>

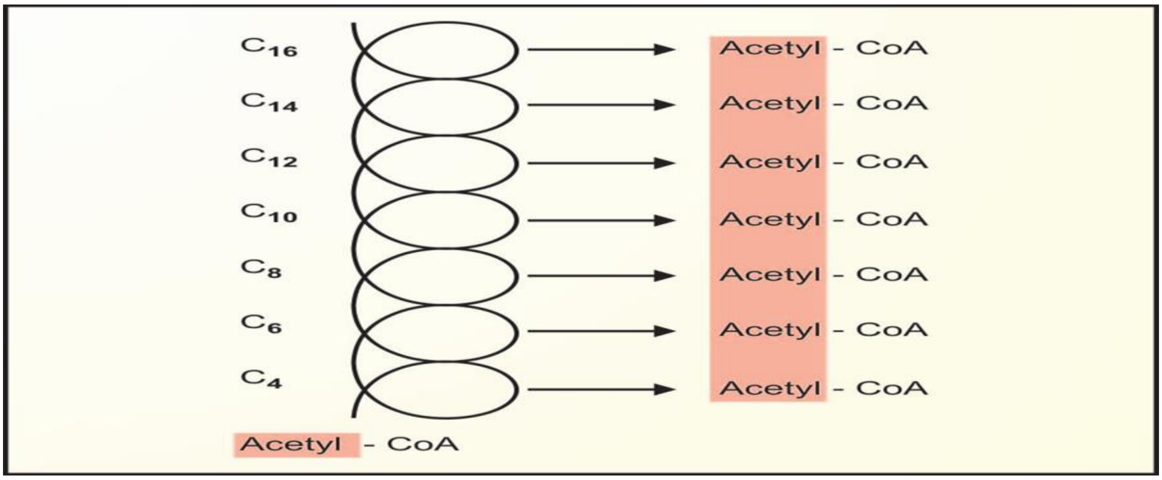
1. Heart diseases: The level of cholesterol in blood is related to the development of atherosclerosis. Abnormality of cholesterol metabolism may lead to cardiovascular accidents and heart attacks.
2. Cell membranes: Cholesterol is a component of membranes and has a modulating effect on the fluid state of the membrane.
3. Nerve conduction: Cholesterol is a poor conductor of electricity, and is used to insulate nerve fibers.
4. Bile acids and bile salts: The 24 carbon bile acids are derived from cholesterol. Bile salts are important for fat absorption.
5. Steroid hormones: 21 carbon glucocorticoids, 19 carbon androgens and 18 carbon estrogens are synthesized from cholesterol.
6. Vitamin D: It is synthesized from cholesterol.

<u>β oxidation</u>

The major pathway for the catabolism of the saturated fatty acid is a mitochonderial pathway called β-oxidation, which was proposed by Knoop. In this process, oxidation of fatty acids occures at β-carbon atom and two carbon fragments are successively removed from the carboxyl end of fatty acel-CO A. this in result in the elemination of two terminal carbon atoms as acetyl CoA, thereby leaving fattyacyl CoA that has two carbons less than the original fatty acid.



The β-oxidation

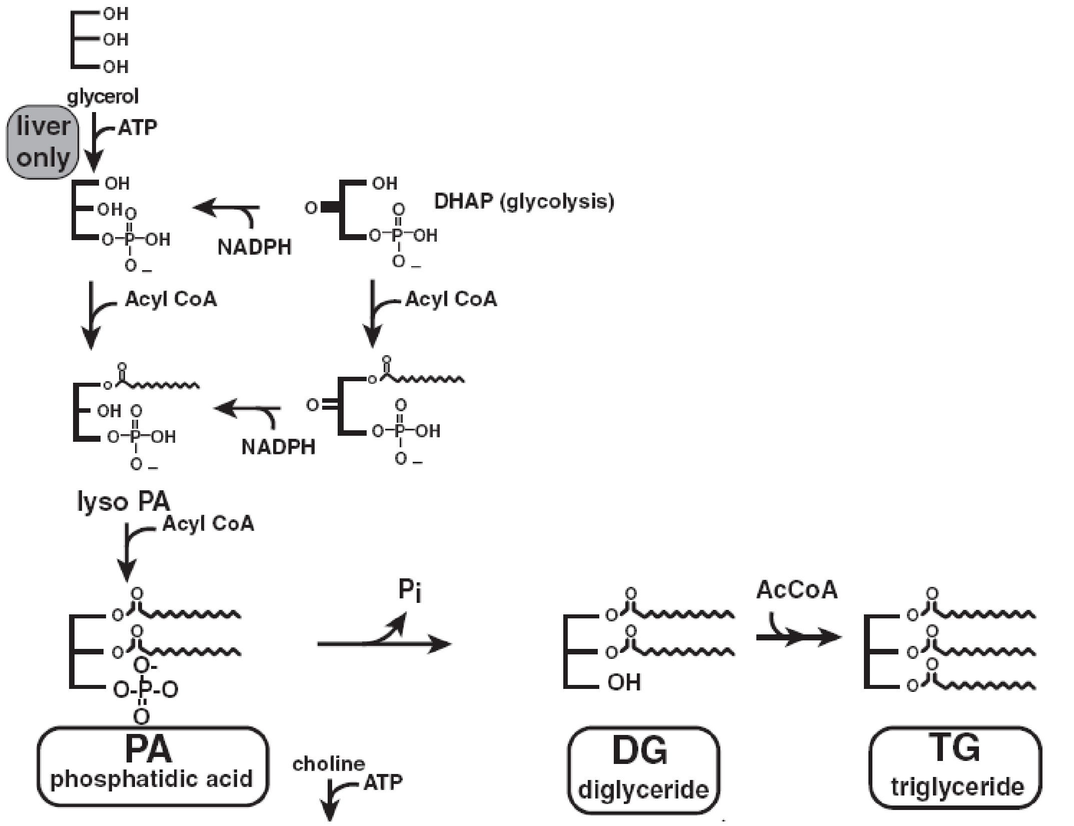


Summary of beta-oxidation of palmitic acid (16 C). It undergoes 7 cycles, which give rise to 8 molecules of acetyl CoA

TRIGLYCERIDE AND PHOSPHOLIPID SYNTHESIS

Glycerol phosphate comes from glycerol (*not in adipose*) or from dihydroxyacetone phosphate (in *liver* and *adipose*).

Nitrogen-containing phospholipids are made from diglyceride. Other phospholipids are made from phosphatidic acid.



Exogenous and endogenous pathways

The body lipids are derived from two sources that require separate metabolic pathways. The first source is fats, oils, and tissue lipids in the diet. After ingestion, the dietary lipids are hydrolyzed in the intestine and absorbed and transported to various tissues. The rout is the exogenous pathway, dealing with lipids from outside. The liver, however, readily synthesized saturated and monounsaturated fatty acids from Acetyl CoA and converts them to triglycerides that atre distrbuted to tissues. Cholesterol is also synthesis in liver from acetyl CoA units. The internal synthesis and distribution of lipids is the endogenous pathway. Both pathways require a means for soluilization and transportation of water insoluble lipids throught the body stream. Lipoprotiens are the particles that transport and distribute the lipids.

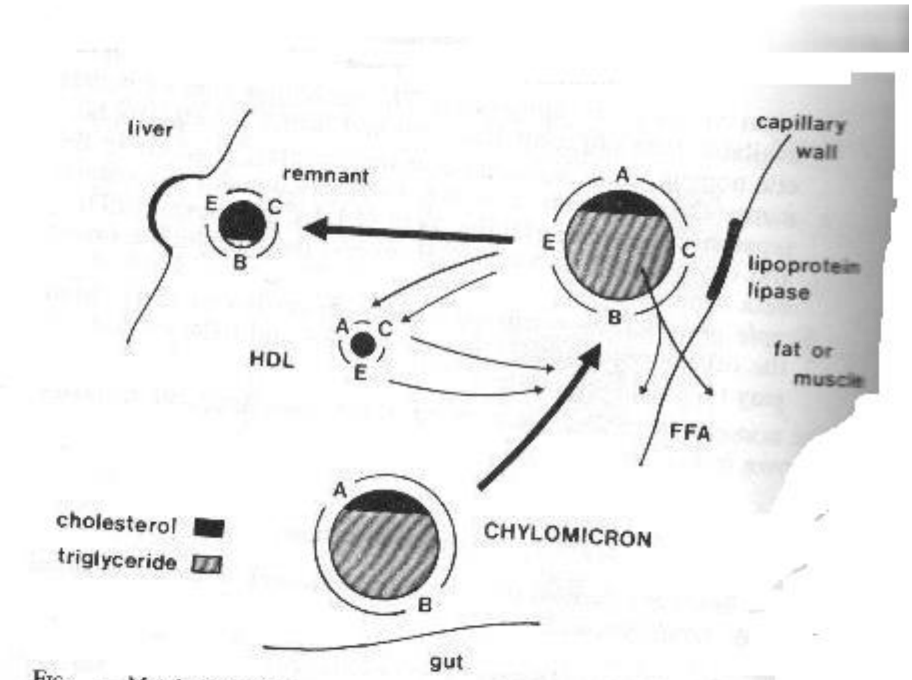
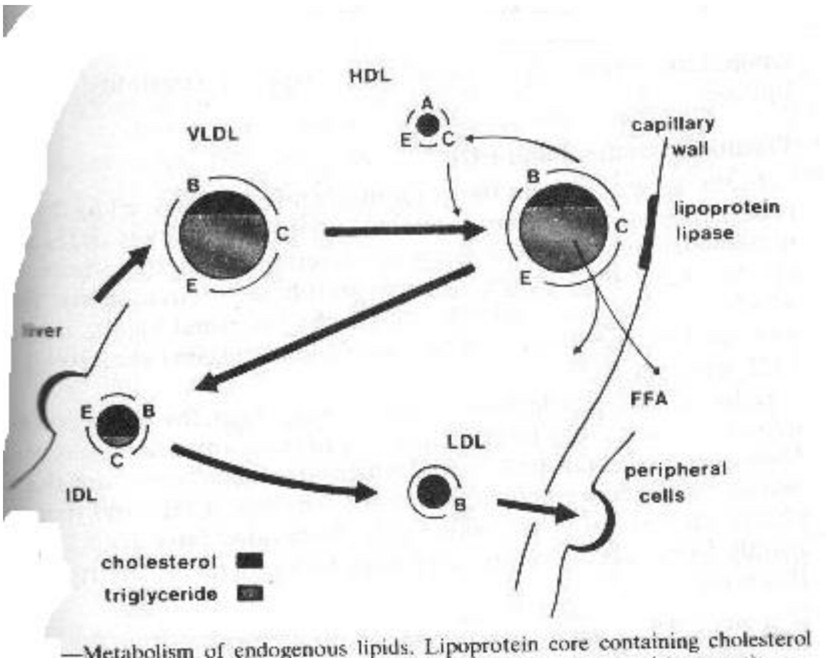


FIG. —Metabolism of exogenous lipids. Lipoprotein core containing cholesterol and triglycerides, surrounded by phospholipids and apoproteins (clear area).



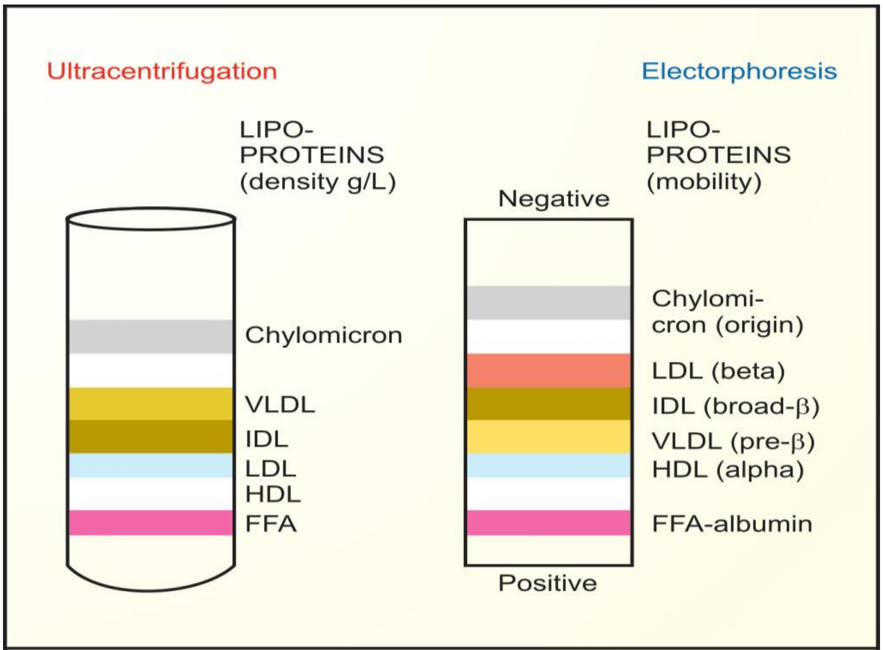
—Metabolism of endogenous lipids. Lipoprotein core containing cholesterol and triglycerides, surrounded by phospholipids and apoproteins (clear area).

<u>Lipoproteins and apoplipoproteins:</u>

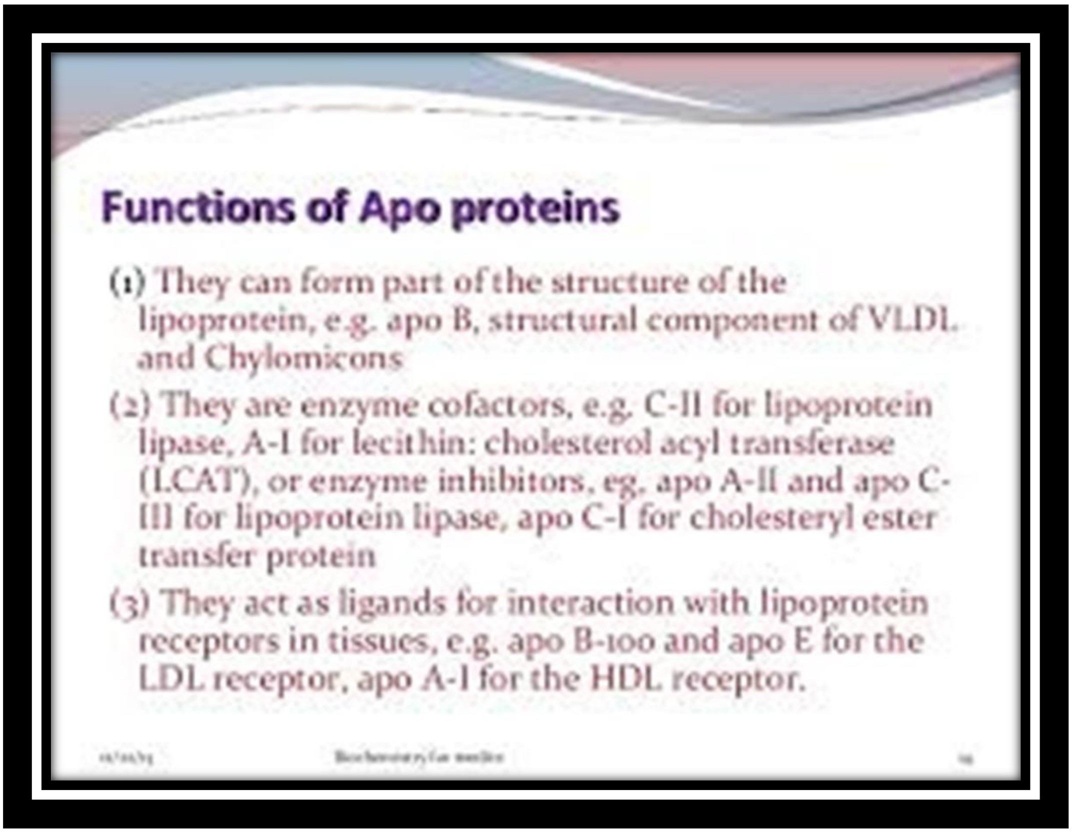
Lipoprotiens are lipids – filled particles that have an outer membrane consisting of monolayer of special protiens called apolipoprotiens intrespersed with the polar lipids (phospholipids and nonesterified cholesterol) the polar lipids are aligned with their charged heads facing outward and the hydrophobic tails pointing inward. The outer membrane sourrouns a central core of neutral lipids (triglycerides and cholesterol esters).

Classes of lipoprotiens

The five different classes of lipoprotiens have distinctive physical properties structures. Each class of lipoproteins has a specific set of apolipoproteins in the membrane and different of lipids in the core. The most commonly used names of lipoproteins clases are derived frome their relative densities upon ultracenterfugation. The structure and function of lipoproteins are described in more details in a subsequent section.



VLDL = very low density lipoproteins; IDL = intermediate density lipoproteins; LDL = low density lipoproteins; HDL = high density lipoproteins; FFA = free fatty acid)



<u>1. chylomicrons</u>

chylomicrons are the largest and least dense of all lipoproteins . they arise in the intestine and transport ingested triglycerides to adipose tissue and they muscle cells.

1. <u>very low density lipoprotein (VLDL)</u>

VLDL is a lipoproteins made in the liver and is designed primarly to transport triglycerides synthesized by the liver to muscle and adipose cells.

<u>3. intermediate density lipoprotein (IDL)</u>

IDL is a transitory remnant of VLDL , circulating in plasma after about half ofr VLDL triglyceride have been transferred to adipose tissue or muscle cells. Most of the IDL undergose further delipidation, transfers to HDL all its apolipoproteins except ApoB, and thus beccoumes LDL. A small percentage of IDL binds to liver cells, where it is degraded.

<u>4. Low density lipoprotin (LDL)</u>

LDL, rich in cholesterol, arise in plasma from IDL, LDL delivers cholesterol either to liver for bile acid formation or to other tissues for use as a structural components of new cells membrane, as a precursor of steroid hormones, or for storage as cholesterol esters.

5. High density liopoprotien (HDL)

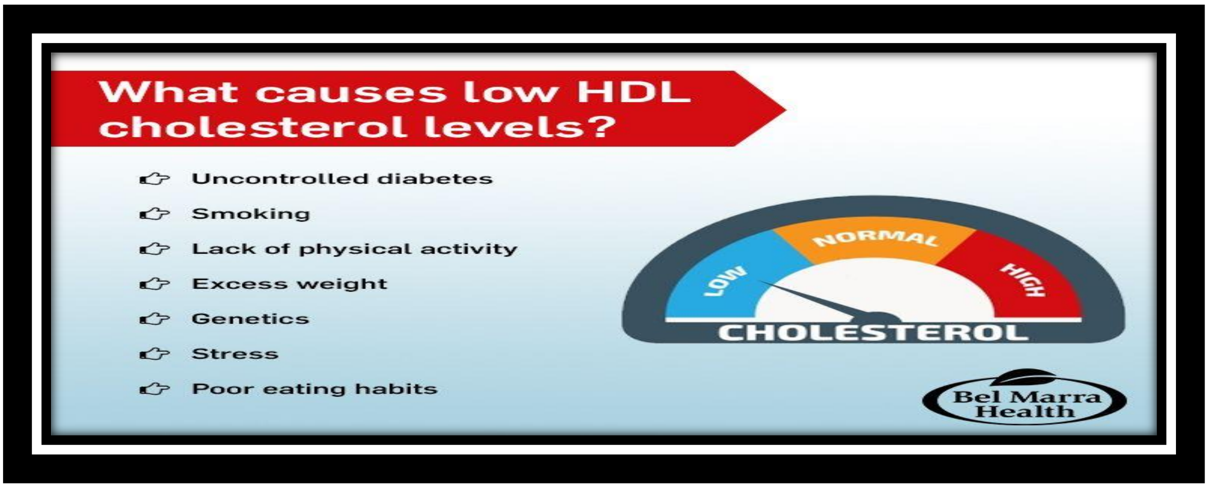
HDL has a complicated life cycle and undergose growth and change after its initial formation. HDL particles are made both by liver and intestinal mucosa cells. A newly formed (nascent) HDL particle forms a complex with some lipoproteins, LCAT (lecithin cholesterol acyl transferase) esterifies cholesterol by transferring to it a fatty acids from lecithin. HDL also trasfer some apolipoproteins baack and froth to other lipoproteins at various stages in their life cycles.

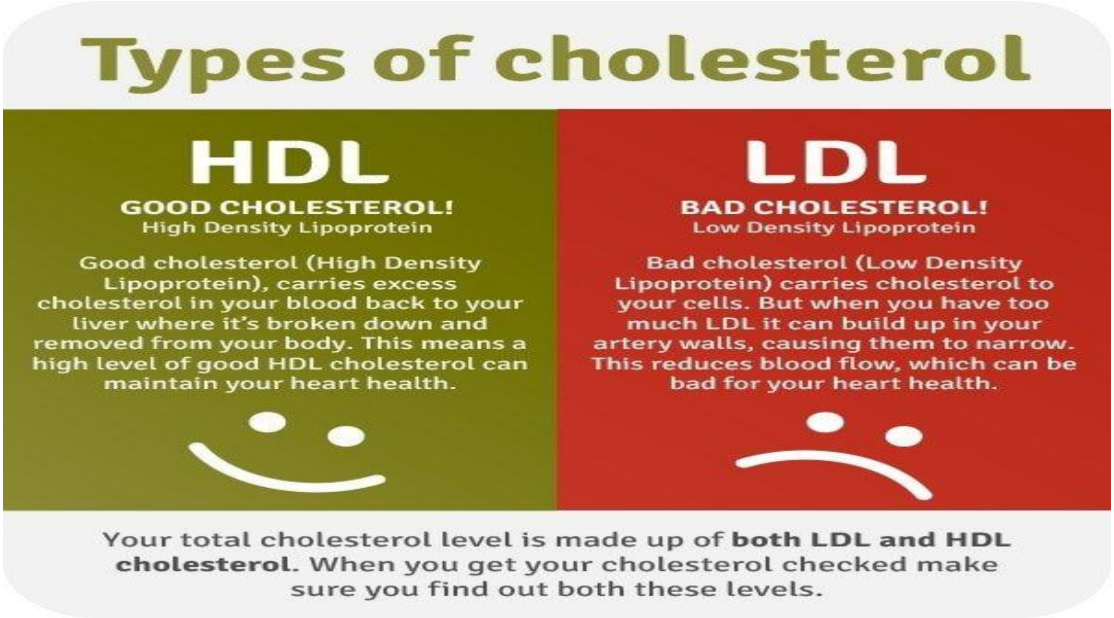
Function of HDL

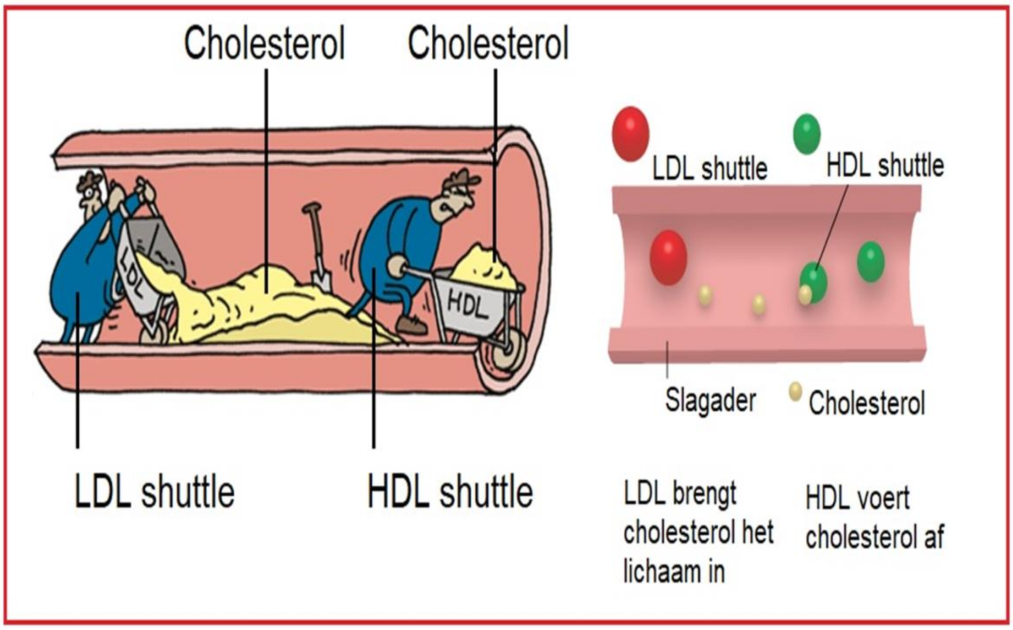
i. HDL is the main transport form of cholesterol from peripheral tissue to liver, which is later excreted through bile. This is called reverse cholesterol transport by HDL.

ii. The only excretory route of cholesterol from the body is the bile.

iii. Excretion of cholesterol needs prior esterification with poly unsaturated fatty acids. Thus poly unsaturated fatty acids will help in lowering of cholesterol in the body, and so poly unsaturated fatty acids is anti-atherogenic.




Types of cholesterol
HDL
GOOD CHOLESTEROL!
High Density Lipoprotein
Good cholesterol (High Density Lipoprotein), carries excess cholesterol in your blood back to your liver where it's broken down and removed from your body. This means a high level of good HDL cholesterol can maintain your heart health.
LDL
BAD CHOLESTEROL!
Low Density Lipoprotein
Bad cholesterol (Low Density Lipoprotein) carries cholesterol to your cells. But when you have too much LDL it can build up in your artery walls, causing them to narrow. This reduces blood flow, which can be bad for your heart health.
Your total cholesterol level is made up of both LDL and HDL cholesterol. When you get your cholesterol checked make sure you find out both these levels.


Cholesterol
Cholesterol
LDL
HDL
LDL shuttle
HDL shuttle
LDL shuttle
HDL shuttle
Slagader
Cholesterol
LDL brengt cholesterol het lichaam in
HDL voert cholesterol af