SHEET NO. 19

METABOLISM

DOCTOR 2019 | MEDICINE | JU

DONE BY : Afnan Atallah & Bushra Faisaal

SCIENTIFIC CORRECTION :

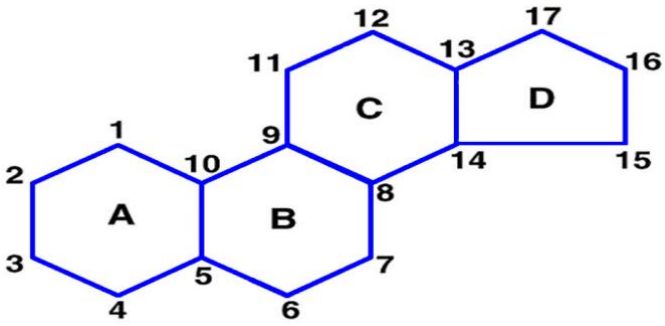
GRAMMATICAL CORRECTION :

DOCTOR : Faisal Al khatib

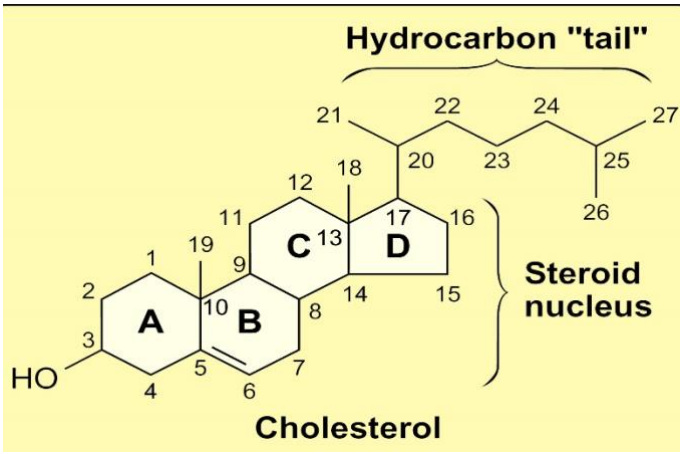
Cholesterol Metabolism

The structure of cholesterol :

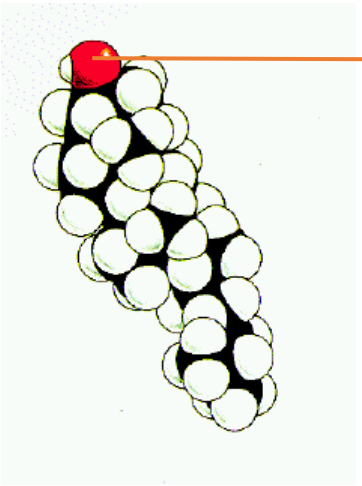
Cholesterol is a lipid with a unique structure consisting of four linked hydrocarbon rings forming the bulky steroid structure. These four rings which contain 17 carbons called “Steroid nucleus “.
Three of them are 6 carbon rings and the fourth one is 5 carbon ring.



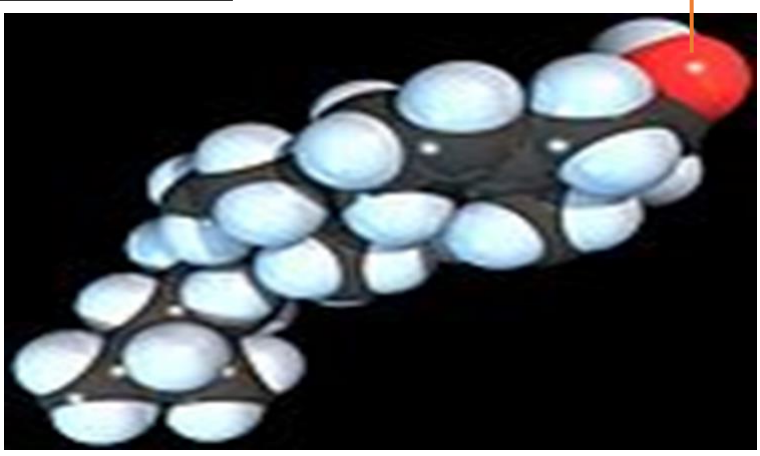
- It contains a hydroxyl group linked to the carbon number 3 which is the only hydrophilic part of the molecule.
- There is a hydrocarbon tail composed of 8 carbons linked to other end of the steroid at carbon number 17.
- There is a double bound between carbon No.5 and carbon No.6.
- It also contains two methyl groups at carbon No. 10 and carbon No. 13.
- Cholesterol is known as a "sterol" because it is made out of alcohol and steroid

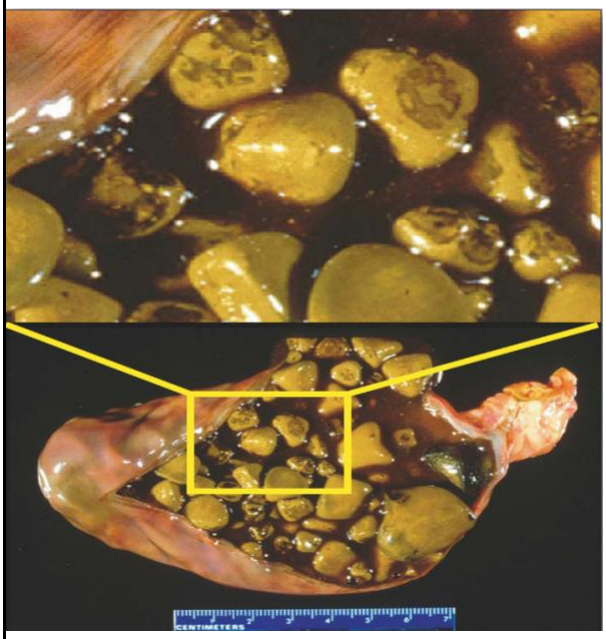


- As the cholesterol molecule is mostly hydrophobic except the hydroxyl group, it is able to insert itself into the phospholipids bilayer perpendicular to the membrane plane. The hydroxyl group forms hydrogen bonds with the carbonyl oxygen of a phospholipid head group while the hydrocarbon tail positions itself in the non-polar core of the bilayer.



Hydroxyl group



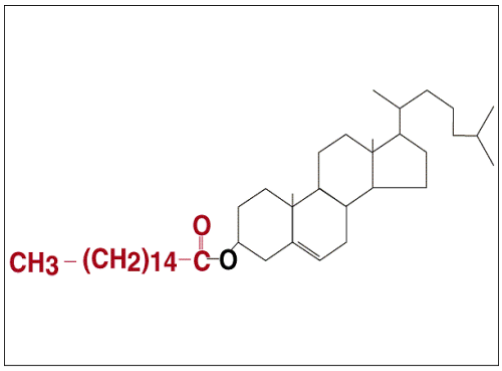


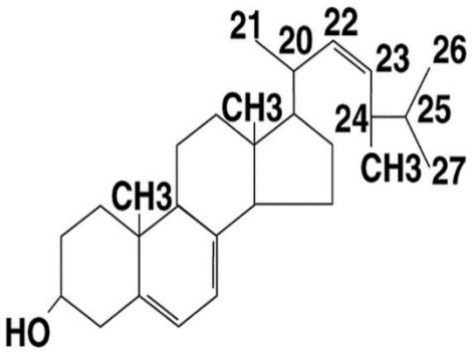
These structures are the gallbladder stones which cause a problem so it should be removed by a surgery called “cholecystectomy”.

BUT how they are formed??
As the cholesterol is insoluble it is kept at the gallbladder in a soluble form by a help from phospholipids and bile salts. But having too much cholesterol in your bile can lead to yellow cholesterol stones.

Cholesterol was isolated from gall bladder stones in 1774.

- Cholesterol can form Cholesteryl Ester by binding to a fatty acid from the hydroxyl group by an ester bond (Esterification). This molecule is more insoluble than cholesterol.





This is Ergosterol which is a plant sterol that are poorly absorbed by Human.

Plants manufacture phytosterols (substances chemically similar to cholesterol produced within plants), which can compete with cholesterol for reabsorption in the intestinal tract, thus potentially reducing cholesterol reabsorption.

When intestinal lining cells absorb phytosterols, in place of cholesterol, they usually excrete the phytosterol molecules back into the GI tract, an important protective mechanism

The function & importance of cholesterol:

- It maintains the fluidity of cell membrane.
- It involves in the production of steroid hormones.

Sources of Cholesterol:

- Synthesis: ≈ 1000 mg / day

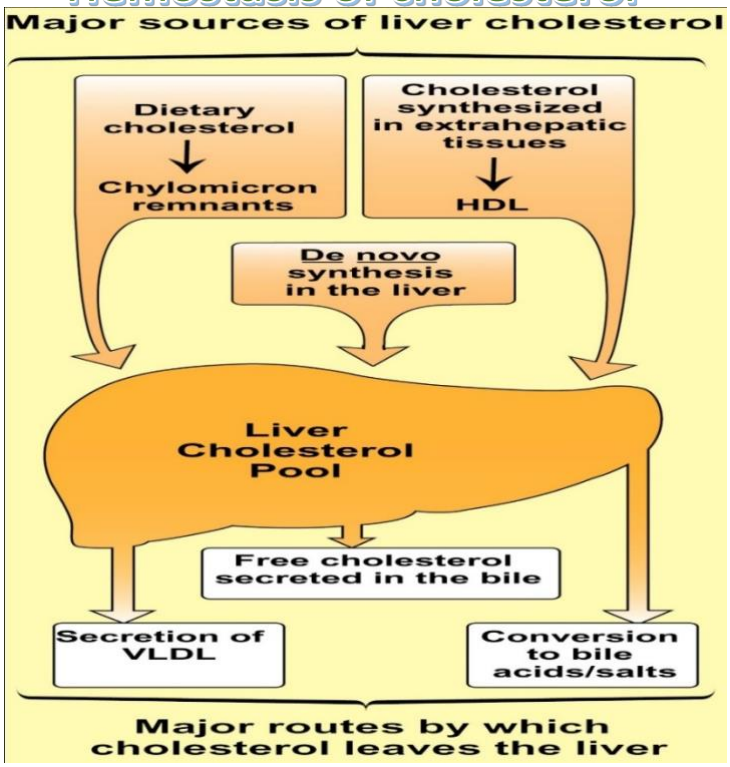
It can be synthesized in all cells mainly the Liver, Small Intestine and Adrenal Cortex. Usually it synthesized in the liver and transported to other cell.

- Dietary: ≈ 300 mg / day (Low Cholesterol Diet)
  It is found in all food of animal origin not plant origin.

Elimination of cholesterol:

- It is not degraded in the body as a source of energy.
- It eliminated via the bile and excreted as a cholesterol or bile salts

Hemostasis of cholesterol



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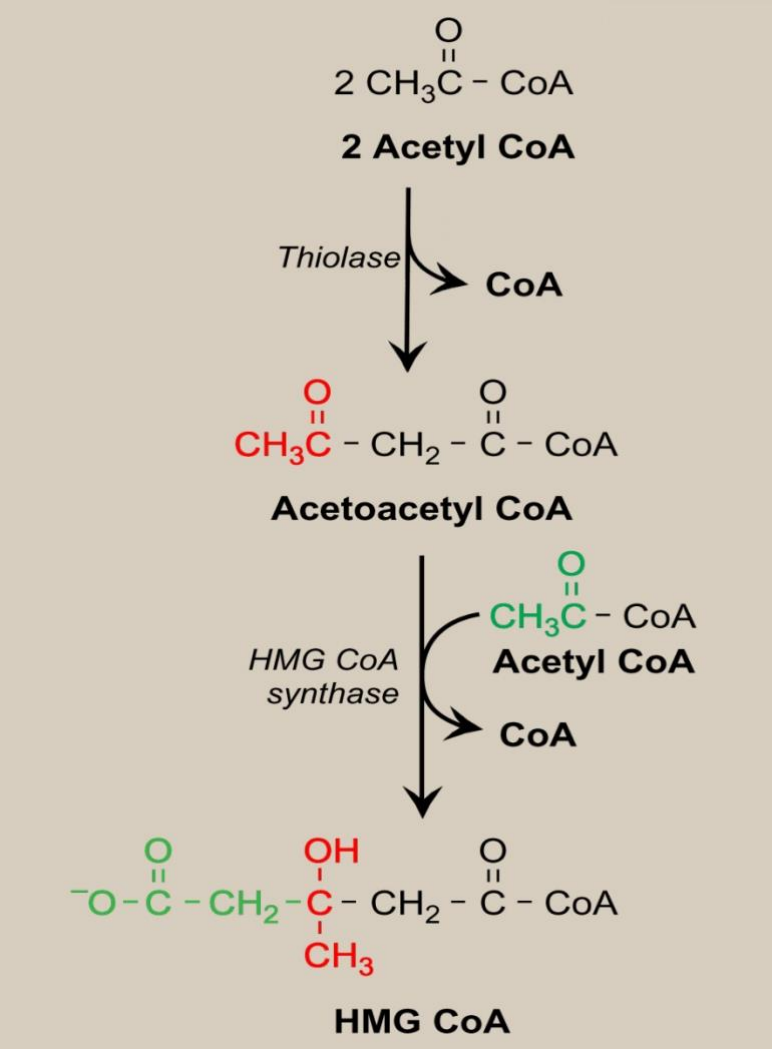
Synthesis of cholesterol

The synthesis of cholesterol requires:

- Carbon Source: Acetyl CoA
- Energy: ATP
- Reducing Power: NADPH
- O2

Stages of Cholesterol Synthesis

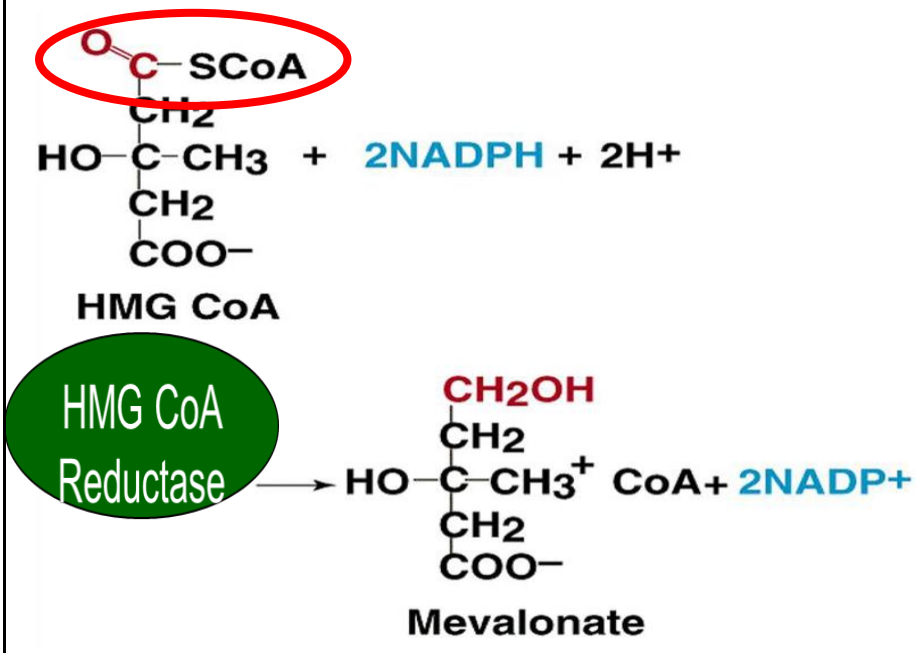
Acetyl CoA (C2)
↓
Mevalonate (C6)
↓
Isoprene Units (C5)
↓
Squalene (C30)
↓
Lanosterol (C30)
↓
Cholesterol (C27)



First step : we start with two acetyl-COA
With a help pf enzyme called Thiolase they produced the Acetoacetyl COA.

Second step: one more acetyl COA condensed with the acetoacetyl COA by an enzyme called HMG CoA Synthase and produced the HMG CoA.

The enzyme is called synthase because there is no ATP consumption in the reaction



Third step : the carboxylic group of the HMG is reduced by consumption of two NADPH molecules to convert it to a hydroxyl group and form the mevalonic acid.
This step is irreversible and mediated by enzyme called HMG CoA Reductase.

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Fourth step:

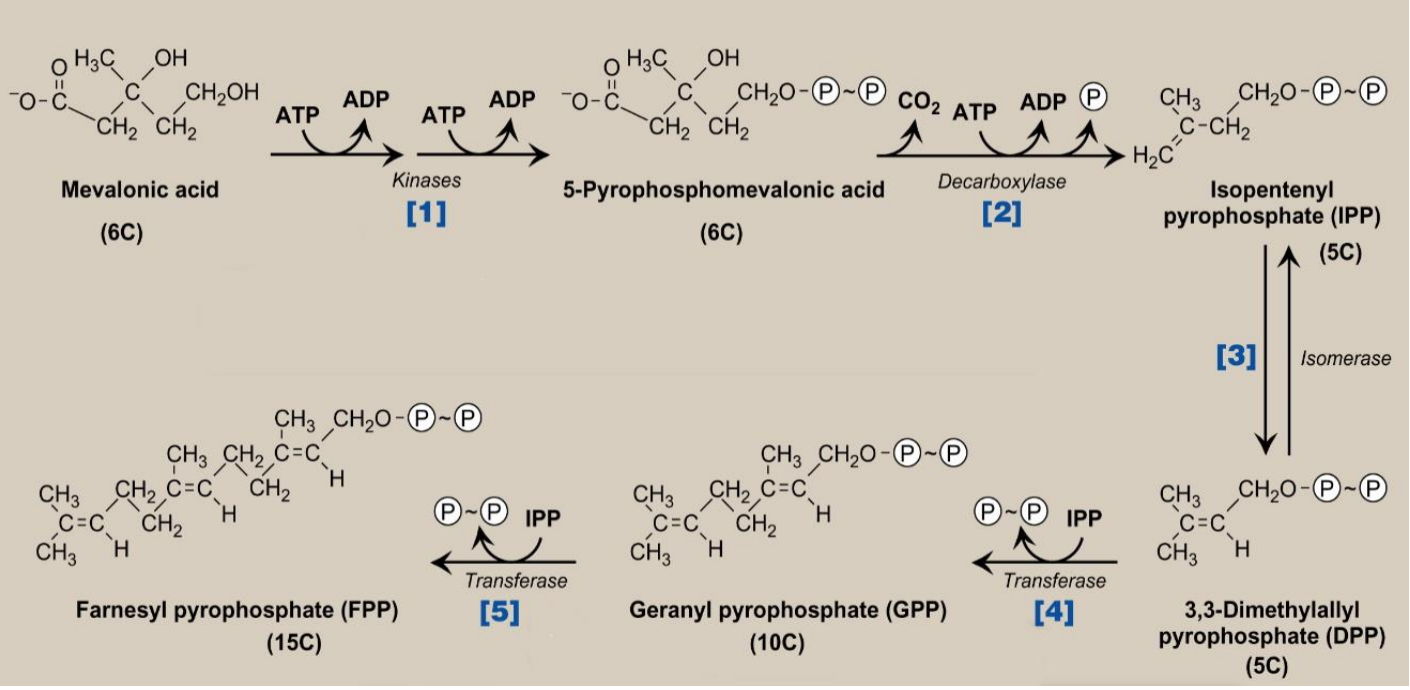
The mevalonic acid is phosphorelated by consumption of 2 ATP
And produce the
5- pyrophosphomevalonic acid

Fifth step:

5- pyrophosphomevalonic acid is decarboxylated and form the Isopentenyl pyrophosphate (IPP)
It involves the consumption of one ATP molecule.

Sixth step:

The IPP is isomerized to an anther isomer

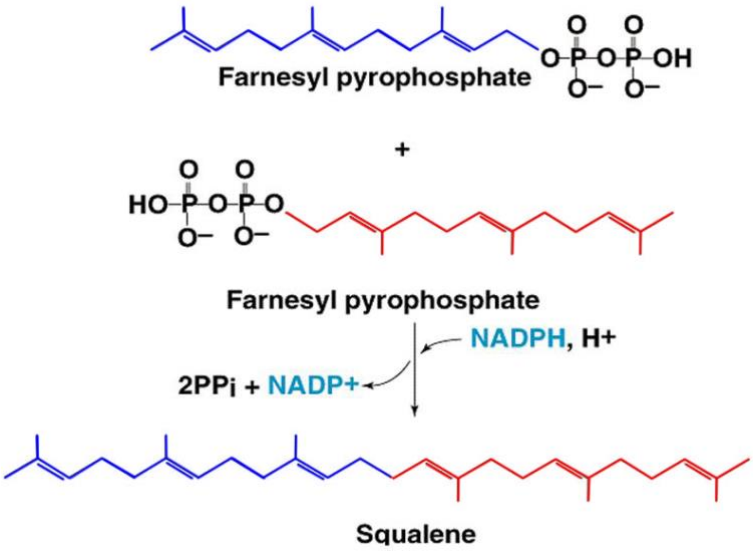


Eighth step:

The GPP is condensed with anther IPP molecule and pyrophosphate is released to form the Farnesyl pyrophosphate (FPP)

Seventh step: the IPP condensed with its isomer and released the pyrophosphate by transferase.

To form the Geranyl pyrophosphate (GPP)



Now two molecules of FPP is condensed and the two pyrophosphate groups are released
and two NADPH molecules are consumed
The product is Squalene (polyisoprene) which is a highly hydrophobic molecule

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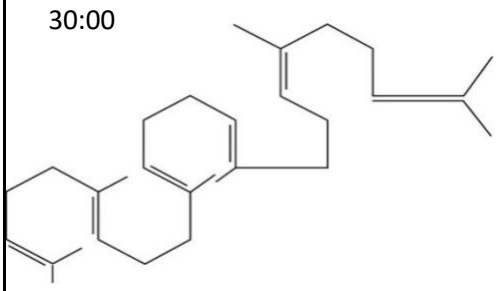
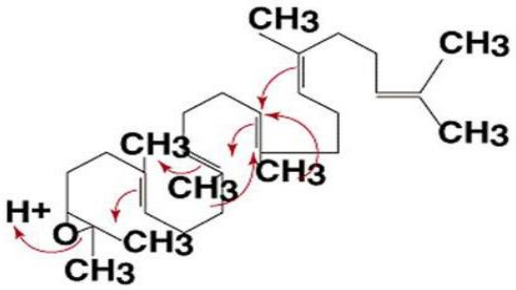


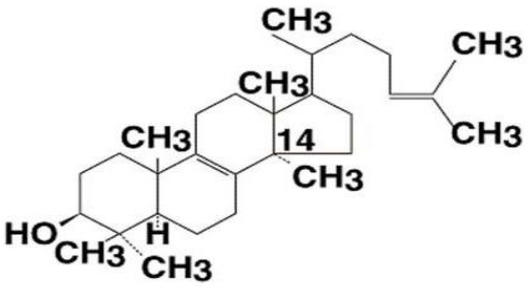
squalene is converted to squalene 2,3-epixoide by adding an oxygen atom at carbons No. 2 and 3



Squalene 2,3-epoxide

cyclase

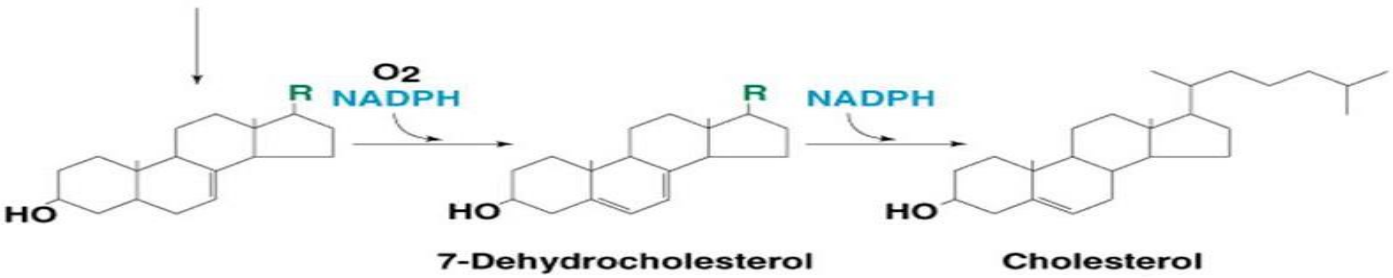
squalene 2,3-epixoide is highly unstable so it is converted to Lanosterol by an enzyme called cyclase.
This involves the closing of the rings



Lanosterol

The lanosterol under goes several steps and produces many intermediates.
They are nor required ☺

The last intermediate is 7-Dehydrocholesterol that contain an additional double bond at the seventh carbon. THEN it is reduced and converted to cholesterol.

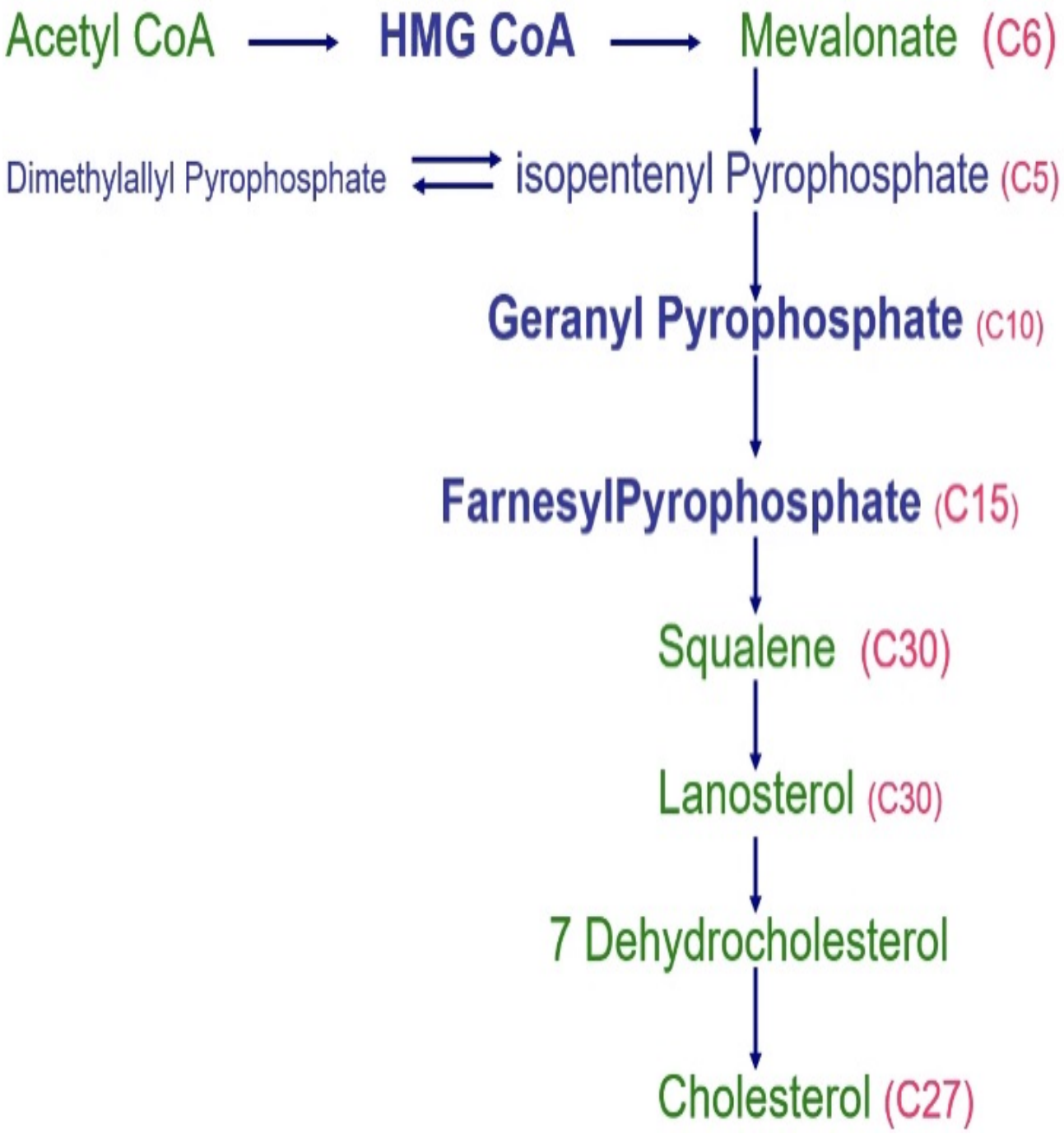


7-Dehydrocholesterol

Cholesterol

* <u>The exposure to sun light (UV) converts the 7-Dehydrocholesterol to Vitamin D</u> (in an inadequate amount)

- So it should be taken with the diet if there is a very little exposure to sun light.

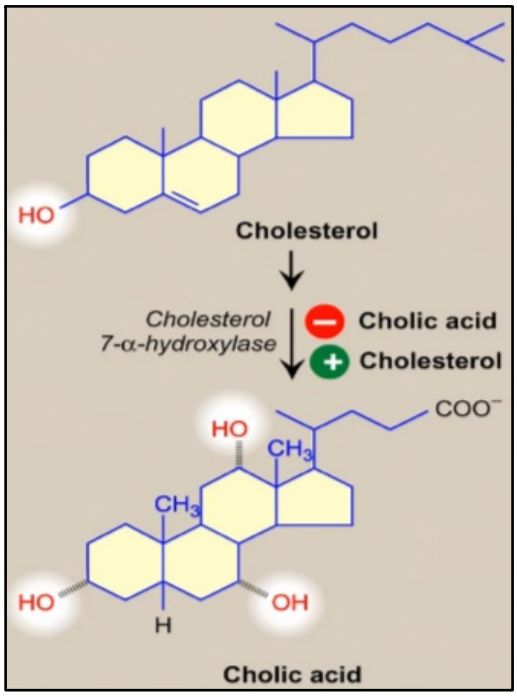


This is the summary

Synthesis of bile acids

• Bile acids are synthesized in the liver by a multistep pathway (several modifications)
1-hydroxyl group are inserted at C 7 (this is the first step catalysed by cholesterol 7-a-hydroxylase)and other hydroxyl groups are inserted at specific positions on the steroid structure .
2-the double bond of the cholesterol B ring is reduced
3- the hydrocarbon chain is shortened by three carbons(from 8 carbons to five carbones)
4- introducing a carboxyl group at the end of the chain.
• this step is regulated, cholic acid which is the end product , act as inhibitor for the hydroxylase , whereas as high level of cholesterol stimulates the hydroxylase

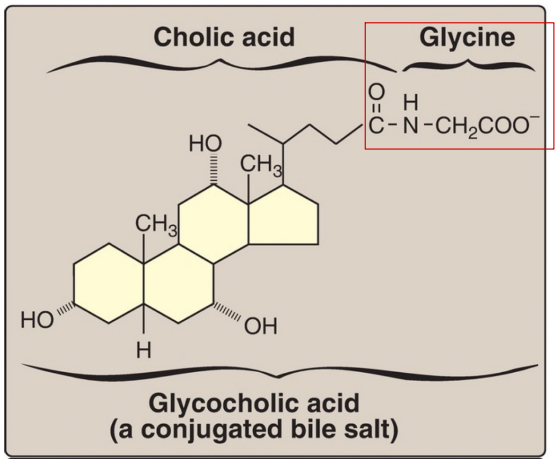
• cholic acid here contains two additional hydroxyl groups and one carboxyl group (no double bonds)

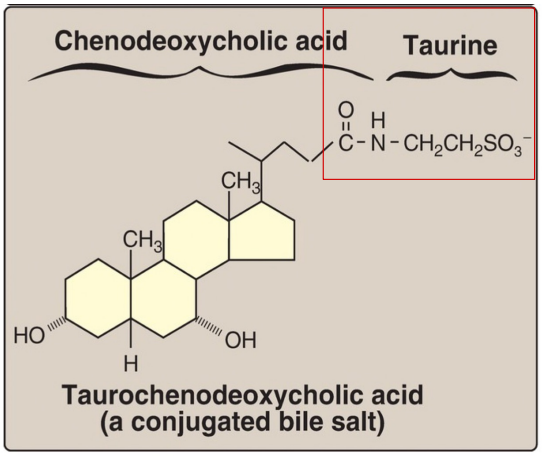


Hydroxylation at carbon 7 is the rate limiting step

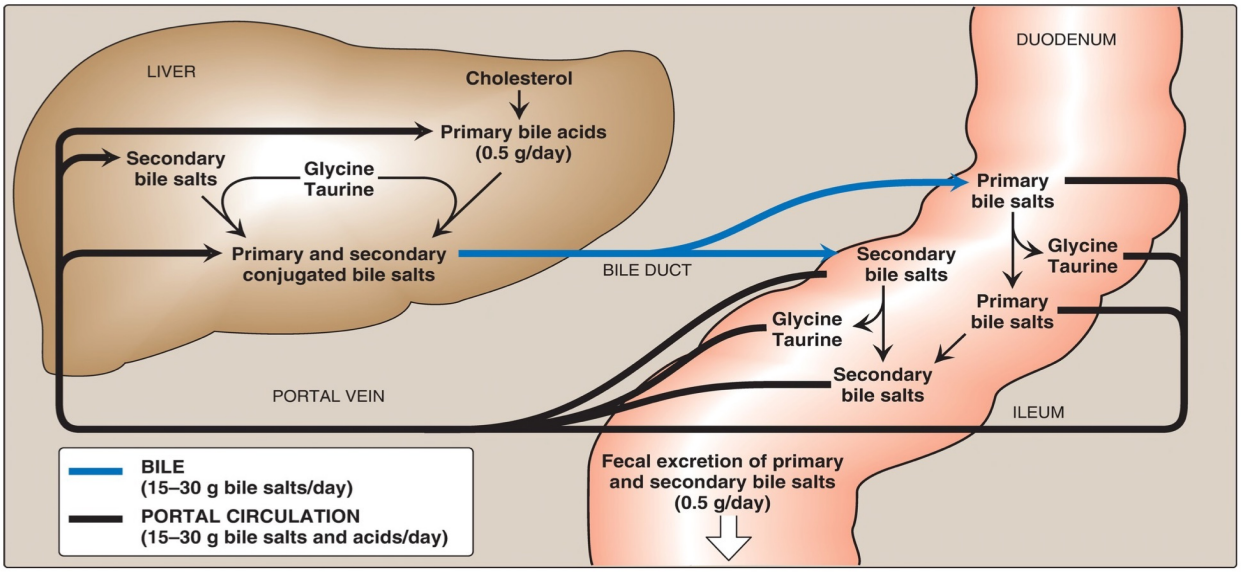
• the next step is Conjugation

- Before the bile acids leave the liver, they are conjugated to a molecule of either glycine (the simplest amino acid) or taurine (sulfonic acid) by an amide bond (covalent bond) between the carboxyl group of the bile acid and the amino group of the added compound.
- The conjugated, ionized bile salts are stronger than the unconjugated ones because of their enhanced amphipathic nature
- the conjugated bile salts are always fully ionized (negatively charged)





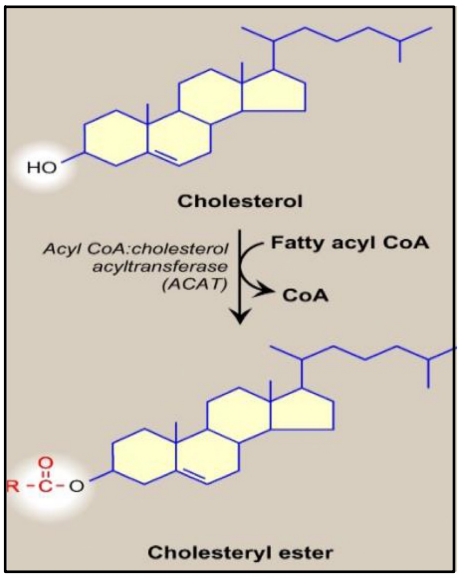
The homeostasis of the bile acids



• in the liver, cholesterol is converted to bile acids, we call them primary bile acids
- the rate is about (0.5g/day)
• then they are conjugated with either glycine or taurine , then they are released into the bile
• the bile duct takes the bile (including bile acids) into the gallbladder
• gallbladder contracts after fatty meals to release the bile acids and bile salts into the small intestine where they participate in digestion of triacylglycerols by emulsification (formation of micelles)
• after they finish their function they are deconjugated (glycine and taurine are removed) by Bacteria of the intestinal microbiota
• bacterial enzymes can also dehydroxylate carbons ,producing secondary bile acids (we call them secondary because they are acted upon by the bacteria)
- almost all secondary bile acids are reabsorbed from the small intestine and carried back to the liver through the portal vain to be reused again.
- not 100% is reabsorbed but about 95% , which makes about 0.5g/day do not reabsorbed, rather, they are excreted in the feces .
- every day about 0.5g of cholesterol is converted to bile acids and about 0.5g is lost in the feces, the rest are circulating.

Esterification of Cholesterol in the Cells

Two substrates:
- fatt acyl CoA
- cholesterol
- the name of the enzyme:
Acyl CoA:cholesterol acyltransferase
- what happens to the cholesterol ester?
- it becomes less soluble
• this esterification in the cells occurs for the purpose of storage

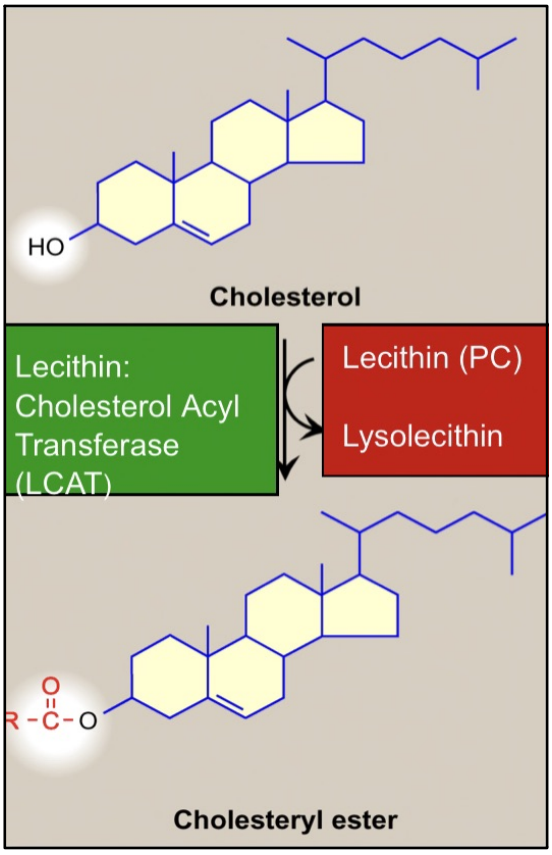


Esterification of Cholesterol in the Plasma

- esterification of cholesterol can occur in the plasma

- occurs in the surface of lipoproteins
- phospholipids that are adjacent to cholesterol is the source of fatty acids , so lecithin which is a phosphatidylcholine is the source of fatty acid (donate fatty acid from carbon 2) producing lysolecithin

- the name of the enzyme:
Lecithin :cholesterol acyltransferase (LCAT)



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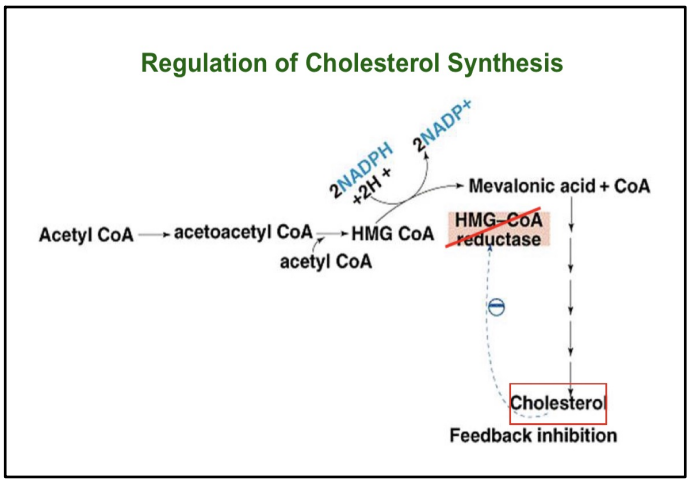
Regulation of Cholesterol Synthesis

- cholesterol performs a number of essential functions in all cells of the body , on the other hand, high level of cholesterol can be fatal , so cholesterol synthesis should be restrictely regulated.

• regulation happens by several mechanisms:

- Regulation of Gene Expression
- Covalent Modification
- Hormonal Regulation
- Proteolytic Regulation

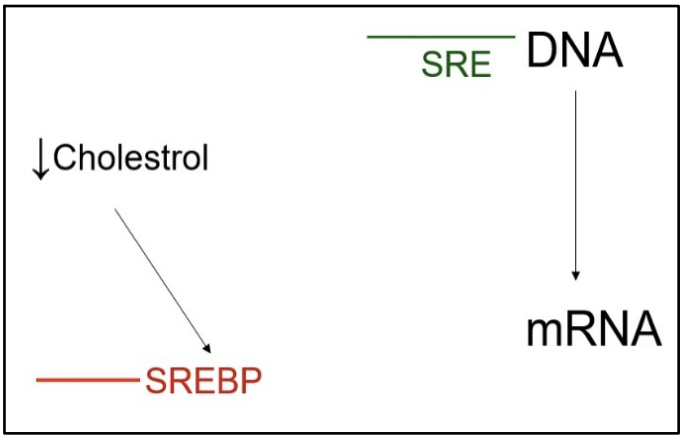


•what is the enzyme that is regulated?
- HMG-CoA reductase

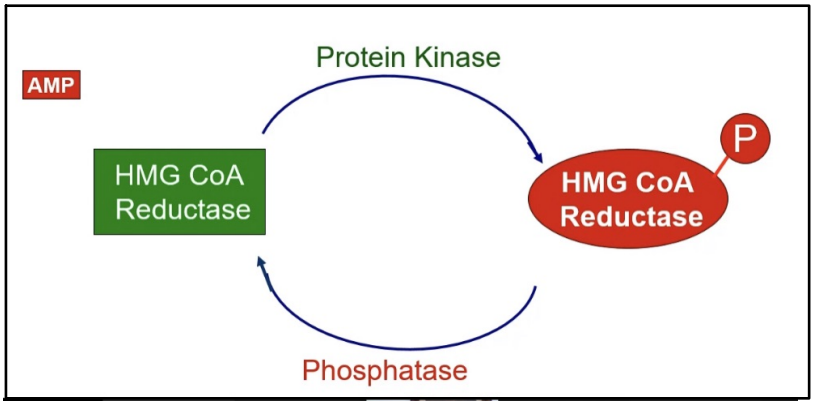
❀ Regulation of the enzyme occurs mainly by the level of cholesterol , high cholesterol levels inhibit the enzyme (feedback inhibition)

• Regulation of gene expression

• Expression of the gene for HMG CoA reductase is controlled by the transcriptional factor, sterol regulatory element–binding protein (SREBP), which binds DNA at the region responsible for regulation (sterol regulatory element (SRE)) upstream of the reductase gene.
• Inactive SREBP is an integral protein of the endoplasmic reticulum membrane .
• When cholesterol levels in the SER are low, this will lead to the cleavage of the bond connecting SREBP to the endoplasmic reticulum
• SREBP then enters the nucleus, binds the SRE, and functions as a transcription factor.
•This results in increased synthesis of HMG CoA reductase and, therefore, increased cholesterol synthesis



•Covalent Modification



• HMG CoA reductase activity is controlled covalently through the actions of adenosine monophosphate (AMP)–activated protein kinase and a phosphoprotein phosphatase .
• The phosphorylated form of the enzyme is inactive, whereas the dephosphorylated form is active.
• Note: Because Protein kinase is activated by AMP, cholesterol synthesis, is decreased when ATP availability is decreased.

• Hormonal regulation

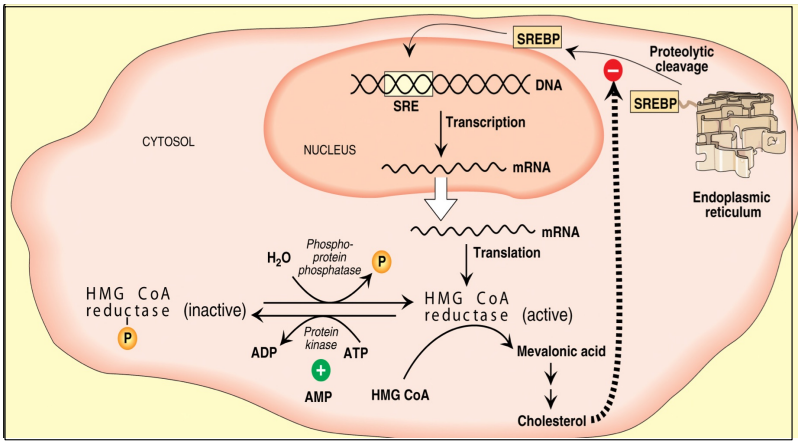
- The activity of HMG CoA reductase is controlled hormonally.
- An increase in insulin favors dephosphorylation (activation) of the reductase, whereas an increase in glucagon and epinephrine has the opposite effect.

Glucagon: ↑Phosphorylated Form

Insulin:↑ **Dephosphorylated** Form (↑Phosphatase)

•Proteolytic Regulation

- the high cholesterol increases the proteolysis (the degradation) of HMG CoA reductase



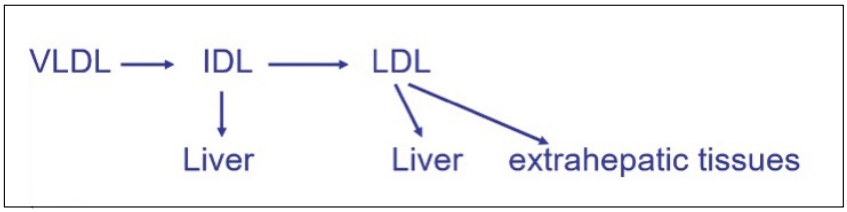
Transport of Cholesterol in the Blood

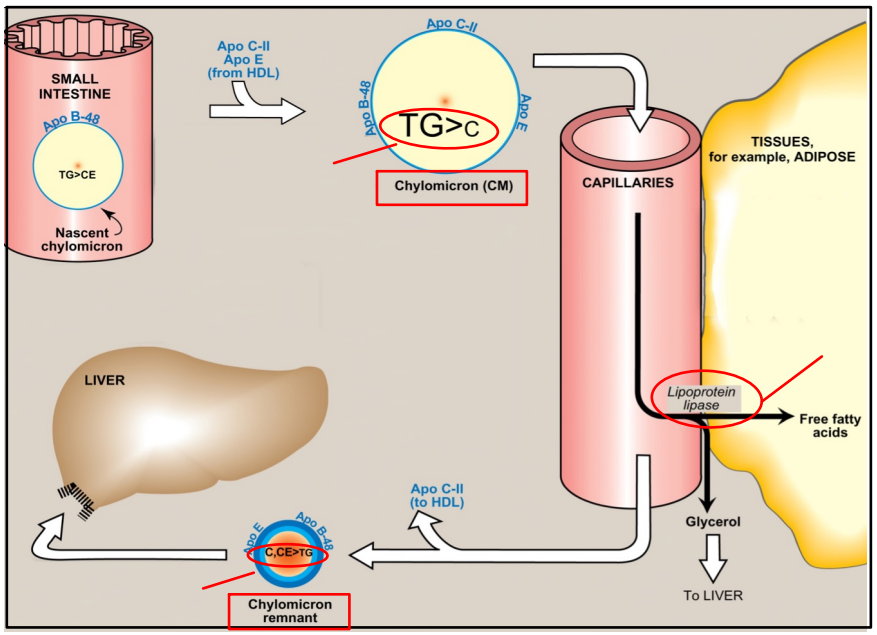
• Can the cholesterol be free in the blood?
-No, it is always part of the lipoproteins
• chylomicrons that are synthsized in the small intestine carry the dietary cholesterol
- as we said, chylomicrons carry triacyglycerol as well , which is removed by lipoprotein lipase in different tissues .
- when the majority of triacyglycerols are removed , chylomicrons become smaller and dense, and now are called "chylomicrons remenants"
- because chylomicron remenants have apolipoprotein E , they are endocytosed by the liver

Chylomicrons ——» remenants ——» liver

• the liver in the other hand deliveres cholesterol to other tissues when it synthesize VLDL (very low density lipoproteins)
• VLDL are acted upon by lipoprotein lipase (extracellular enzyme on the vascular endothelial surface) which degrades triglycerides that are embedded in very low-density lipoproteins (VLDL)
• the density of VLDL is increased (it becomes IDL)
• IDL can be taken by the liver or it can be converted to LDL with the effect of lipoprotein lipase .

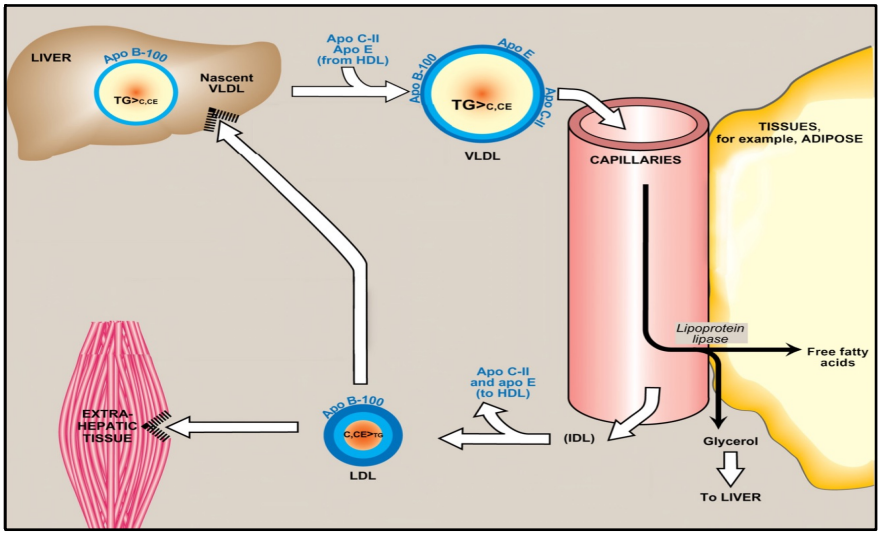
• LDL are more dense, smaller in size and very rich in cholesterol, they are taken by the liver cells and extrahepatic tissues by endocytosis .
• HDL carry cholesterol back to the liver





• explanation of the figure above:

- Chylomicrons are assembled in intestinal mucosal cells and carry mainly dietary (exogenous) TAG and cholesterol .
- Lipoprotein lipase (LPL) is an extracellular enzyme on the vascular endothelial surface that degrades TAG that are embedded in chylomicrons that travel through the bloodstream
- most TAG are removed from the chylomicron ——» chylomicron remenant (more cholesterol and cholesterol esters)
- chylomicron remenant are taken by endcytosis by the liver cells .



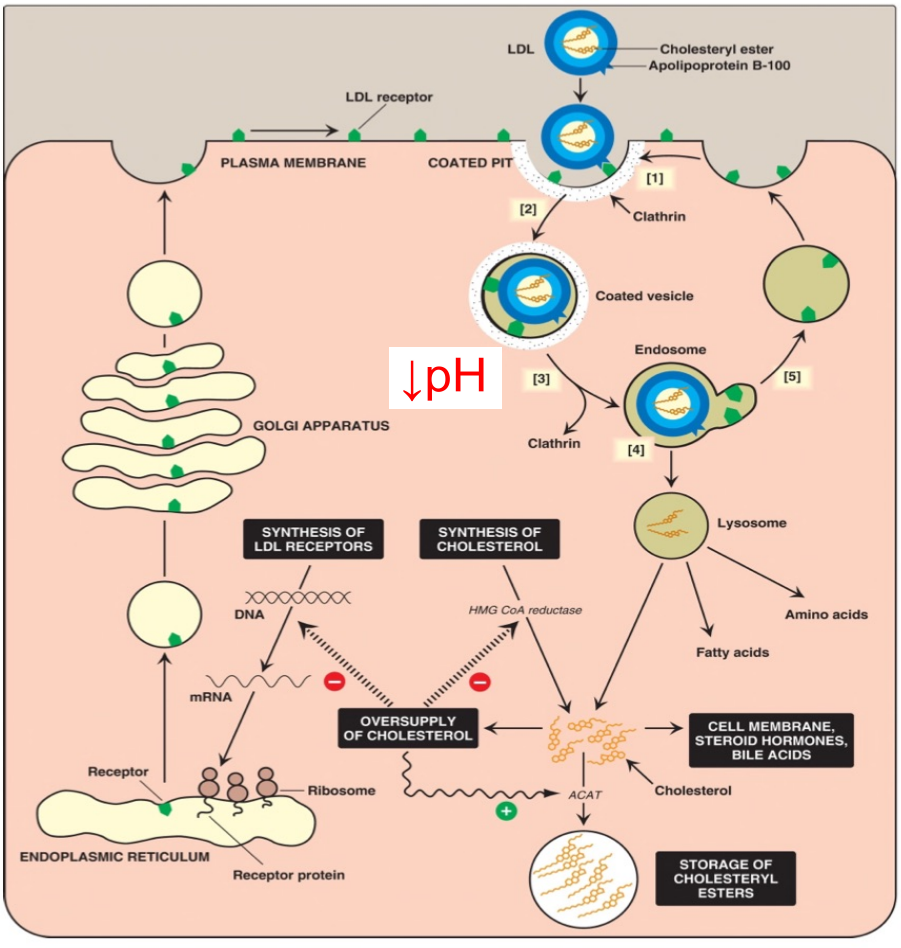
• In the case of VLDL, the process is similar to that of chylomicrons, but the difference is that VLDL is secreted from the liver and when circulating in the blood, they acquire apolipoprotein C-II and apolipoprotein E from HDL .

• Lipoprotein lipase (LPL) is an extracellular enzyme on the vascular endothelial surface that degrades TAG that are embedded in VLDL that travel through the bloodstream converting VLDL to IDL .

• IDL has two fates: either taken by the liver or losing apolipoprotein C-II and apolipoprotein E to become LDL

• the LDL is taken by endocytosis both by liver cells and extra-hepatic tissues .

- extra-hepatic tissues that receive LDL don't synthesize cholesterol.



Cellular uptake and degradation of low-density lipoprotein (LDL) particles.

1- LDL particles have apolipoprotein B-100 that can bind to LDL receptors (LDL receptors are found in the cell surface of the cells that are clustered in pits on cell membranes)
- The cytosolic side of the pit is coated with the protein clathrin, which stabilizes the pit.
2- After binding, the LDL–receptor complex is endocytosed .
3- The vesicle containing LDL loses its clathrin coat and fuses with other similar vesicles, forming larger vesicles called endosomes.
4- The pH of the endosome falls (due to the proton-pumping activity of endosomal ATPase), which allows separation of the LDL from its receptor. The receptors then migrate to one side of the endosome, whereas the LDL stay free within the lumen of the vesicle.

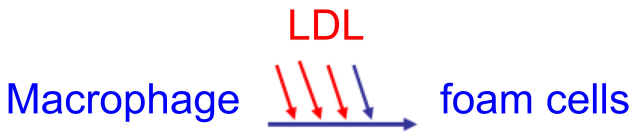
5- The receptors can be recycled, whereas the lipoprotein remnants in the vesicle are transferred to lysosomes and degraded by lysosomal acid hydrolases, releasing free cholesterol, amino acids, FA, and phospholipids. These compounds can be reutilized by the cell.

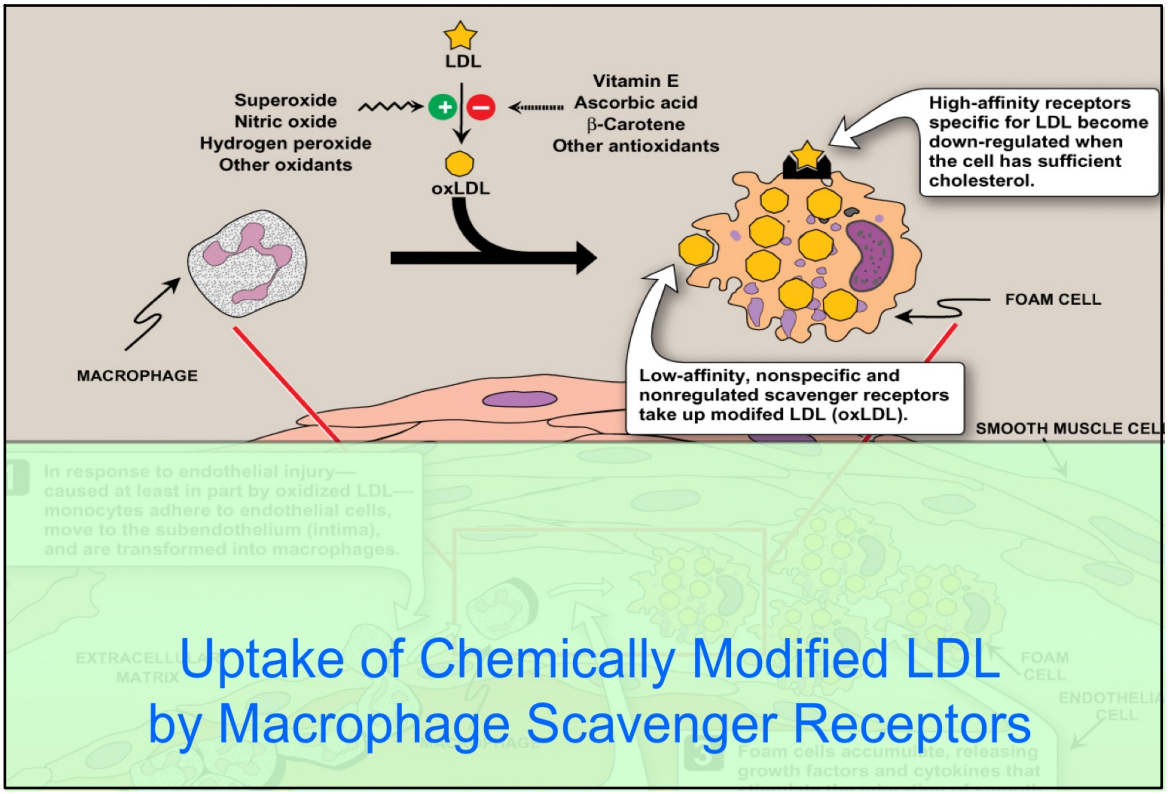
- free cholesterol in the cell has three actions :

1- it decreases the synthesis of cholesterol by inhibiting the HMG CoA reductase.
2- it decreases the synthesis of the receptor itself (this is called down regulation)
3- stimulates the enzyme ACAT (which is required for esterification)

Macrophage scavenger receptor

- besides the LDL receptor which is found in all cells, there is another receptor called macrophage scavenger receptor , as the name indicates, is found on the surface of macrophages and it removes the damaged LDL molecules from the plasma .
- this receptor undergoes no down regulation
- when macrophage takes large amounts of LDL it is converted to foam cell
- Accumulation of foam cells in the subendothelial space indicates Early evidence of atherosclerotic plaque





Familial Hypercholesterolemia

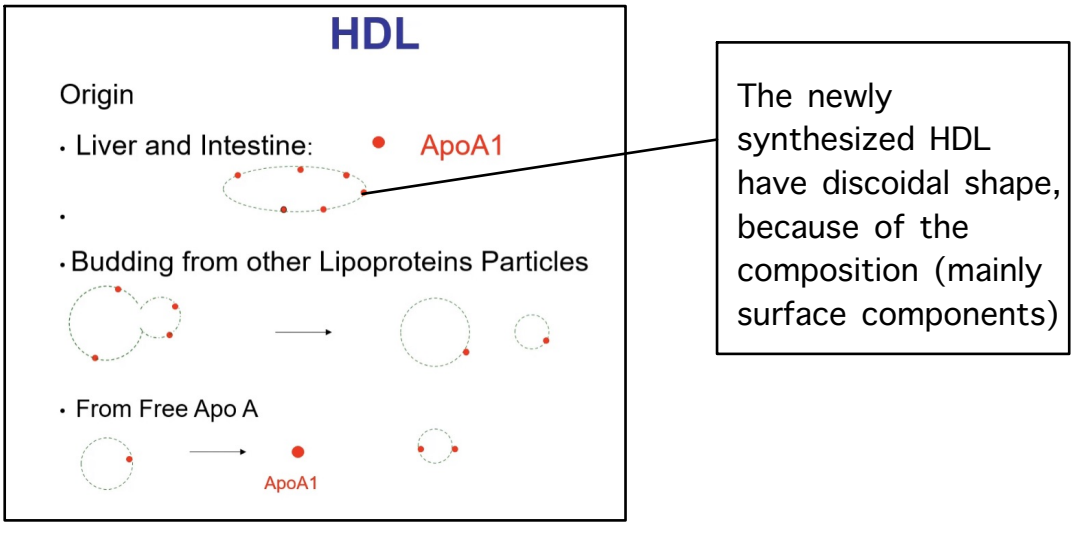
- familial : hereditary
- emia : the concentration in the blood
- familial hypercholesterolemia : a genetic condition that causes high cholesterol .
- usually, cholesterol level is about 200 mg/dl ,in those individuals it can be around 300mg/dl if they are heterozygotes , or 700 mg/dl if they are homozygotes .
- the problem is that their cells lack or have less than the normal amount of LDL receptors .

Homozygotes	No Receptors
Hetero	½ Normal Number

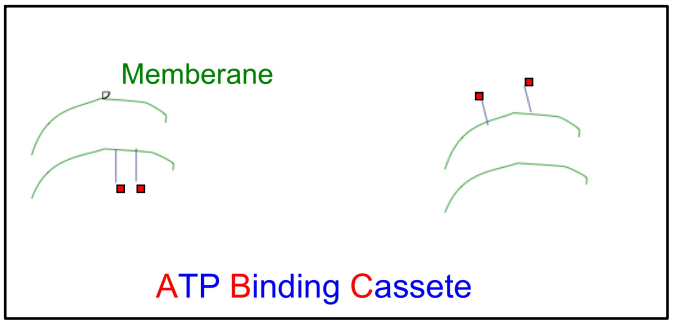
• LDL will accumulate in the plasma
- it will undergo oxidation and be damaged
- IDL also binds to the LDL receptor, so it will accumulate too.
- cholesterol deposition in tissues
- atherosclerosis
- death in childhood

HDL

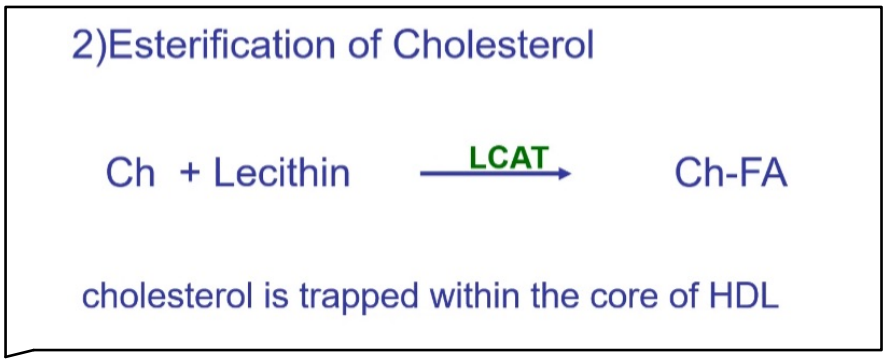
- originate from the liver and intestine that produce a protein called apolipoprotein A1
- this apolipoprotein that is found only in HDL acquires phospholipids in the plasma and make the newly synthesized HDL.



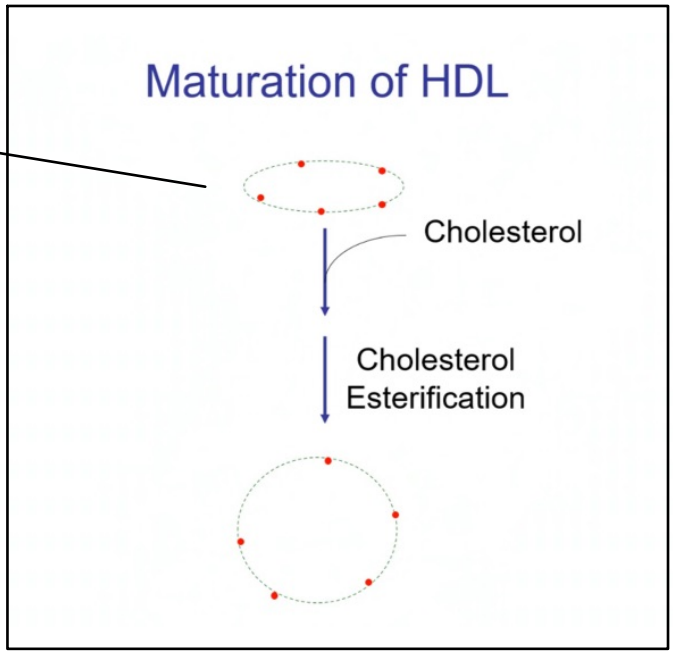
- the function of the HDL is to take cholesterol found in excess in tissues or in dying cells and deliver it to the liver.
- to transfer the cholesterol, a group of proteins (ATP Binding Cassete) or ABC are required for the directional movement from the anterior leaflet of the membrane to outside.
- once the cholesterol is in the surface of the cell , HDL will take it away.



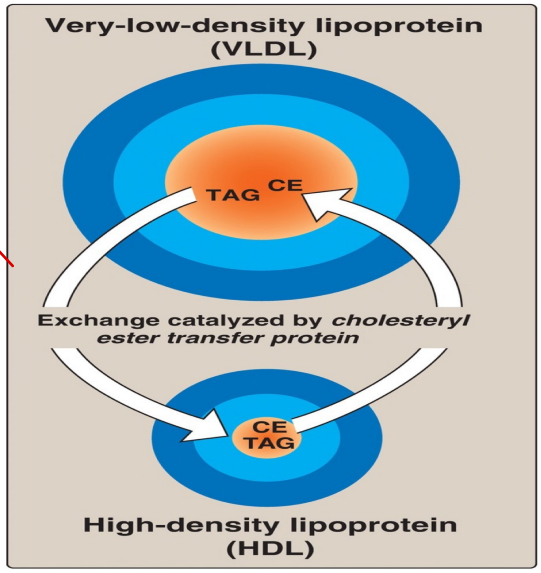
- to transfer cholesterol to the core of HDL , it must be esterified .



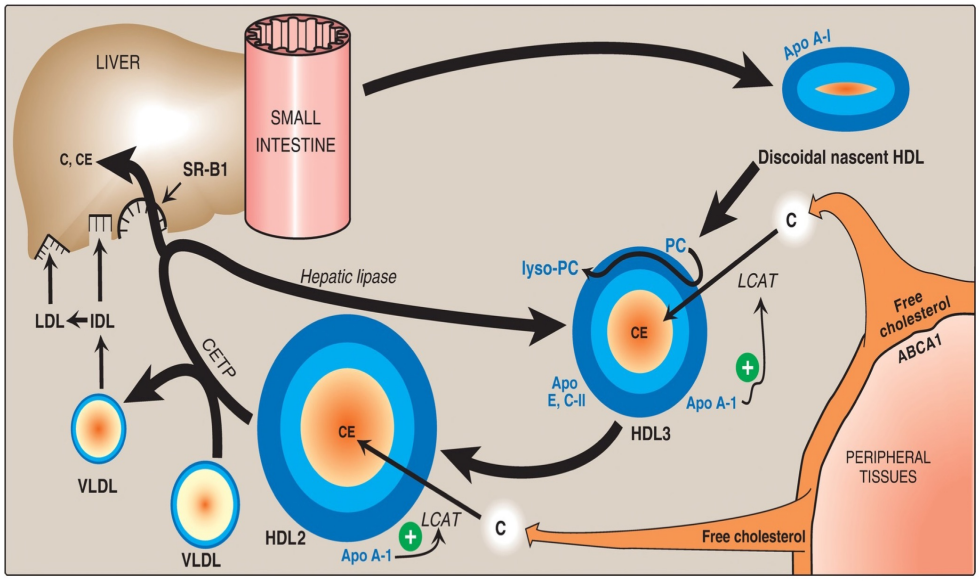
Discoidal shape is converted to spherical by cholesterol esterification



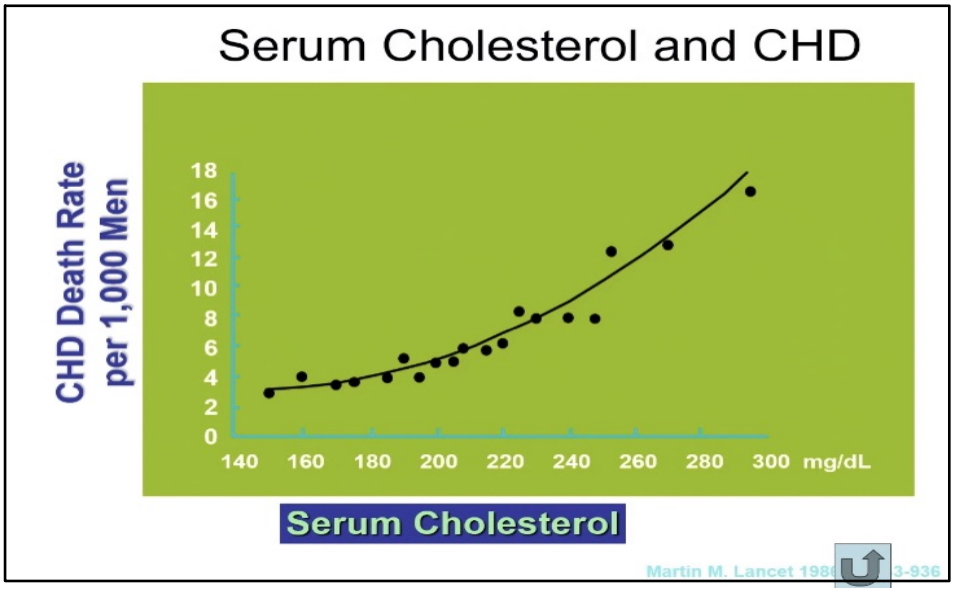
- away to reduce the level of cholesterol from the HDL is the Transfer of cholesteryl ester (CE) from HDL to VLDL in exchange for triacylglycerol (TAG).
- This exchange is accomplished by cholesteryl ester transfer protein (CETP)



- this figure shows how HDL originate from liver and intestine in discoidal shape
- the ABC protein transfer cholesterol from tissues to the HDL converting its shape to spherical shape ——» HDL3
- HDL3 receives more cholesterol ——» HDL2
- HDL2 can transfer cholesterol to VLDL or can bind to scavenger receptor B1in the surface of the liver.



-This figure shows the relationship between cholesterol level and the risk of death when the patients are admitted to the hospital with myocardial infarction



Modifiable and non-modifiable CAD risk factors

Cigarette smoking	Males > 45 years Females > 55 years
Obesity	Males
Hypertension (blood pressure >= 140 / 90 mmHg)	Family history of coronary artery disease
Physical inactivity	
Kidney disease	
Diabetes mellitus	
Alcohol consumption	
Stress	
Elevated LDL	
Reduced HDL	

Lowering Cholesterol Level

- how we can lower the cholesterol level?

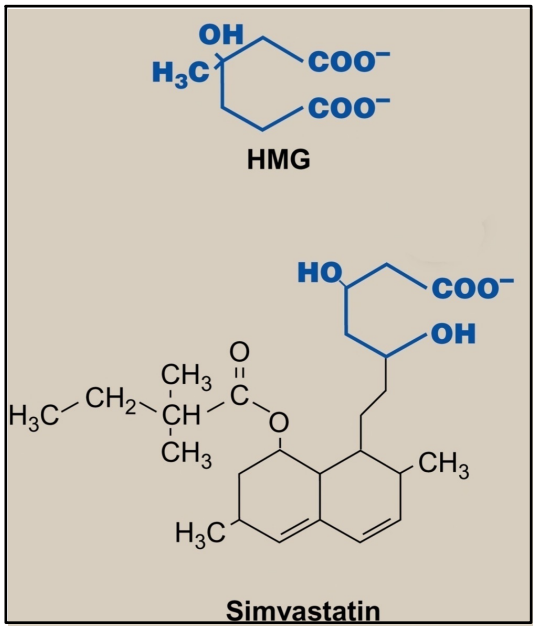
Dietary

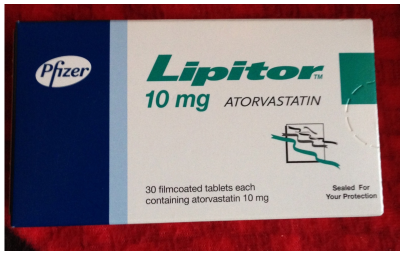
- ↓Cholesterol intake (Will not affect the level too much 5-10%)
- ↑ PUSFA / SFA
- ↑ Fiber (inhibit steroids synthesis)
- Daily Ingestion of Plant Steroid Esters

Inhibition of Synthesis (the inhibition is targeted to HMG CoA reductase)

↓ Enterohepatic Circulation of Bile Acids

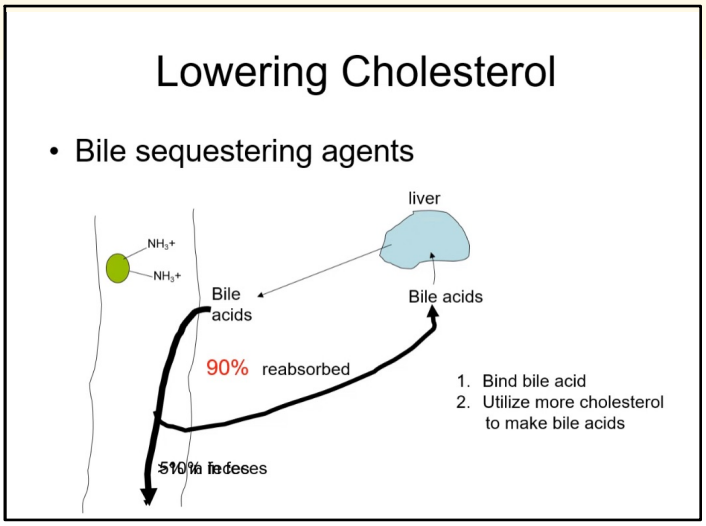
• The statin drugs (atorvastatin) are structural analogs of HMG CoA and are reversible, competitive inhibitors of HMG CoA reductase .
-They are used to decrease plasma cholesterol levels in patients with hypercholesterolemi





Another way to lower cholesterol:

- Bile acid sequestrants, such as cholestyramine(insoluble substance that has multiple amine groups), bind bile salts in the gut and prevent their reabsorption, thereby promoting their excretion.



رسالة ...

وبالتوفيق جميعاً 🌸🌸🌸