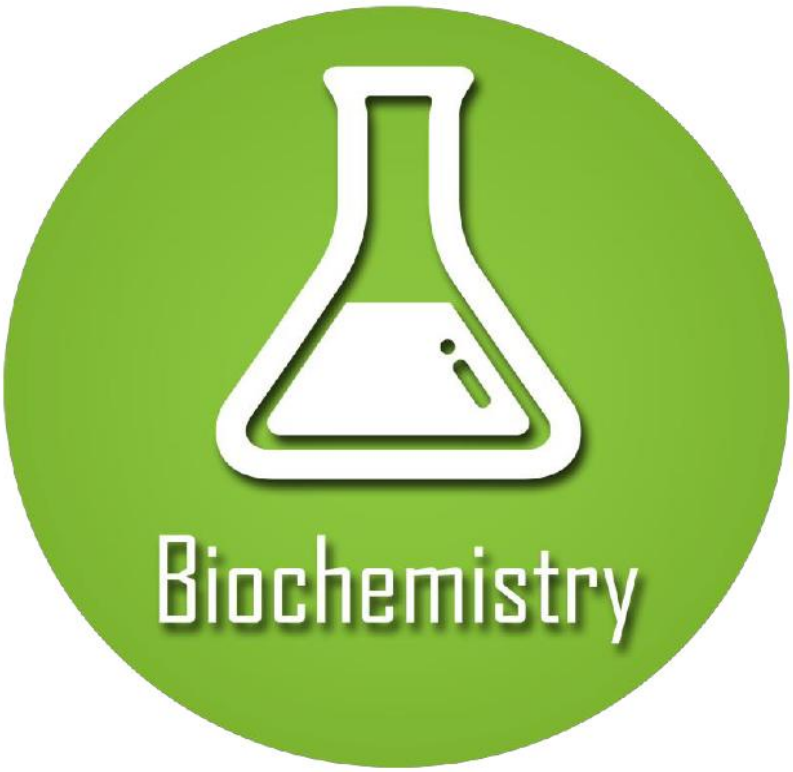
2014 2020
Medical Committee
The University Of Jordan



◉Sheet ○Slides

Number: **20**

Done by: **Ayat M Zghoul**

Corrected by: **Nadia Al_kouz**

Subject: **Cholesterol Metabolism #2**

Doctor: **Dr. Faisal Al Khateeb**

- Topics we are going to discuss :
    1. Lowering Cholesterol Level
    2. Esterification of Cholesterol
    3. Regulation of Cholesterol Synthesis
    4. Transport of Cholesterol in the Blood
    5. Macrophage Scavenger Receptor
    6. Familial Hypercholesterolemia
    7. HDL

Let's start …

1. Lowering Cholesterol Level :

- **Firstly, why do we care about cholersterol level?!**

Because high level of cholesterol is associated with **atherosclerosis and coronary artery diseases** , so it has to be lowered and it has to be lowered less than normal (if the normal cholesterol level = 200 mg/dl so it has to be less than 200 mg/dl in order to protect against myocardial infarction).

- **How to lower cholesterol level?!**

A. Control the diet :

1- **Reducing the cholesterol intake** but that cannot make cholesterol level = zero even though we are vegetarians **why?!**

- ✓ because cholesterol is found in all kinds of food . it's specially rich in certain kinds of food that we can avoid but even we take low cholesterol diet we will get some cholesterol (low cholesterol diet = 100 mg \ dl)
- ✓ if we decrease the cholesterol intake the synthesis will increase so if we don't eat anything contain cholesterol its level **cannot reach zero** .

2- **Increase the ratio of polyunsaturated fatty acids to saturated fatty acids (PUSFA / SFA)** >>>SFA are mainly found in animals fat associated with the Cholesterol but even without cholesterol SFA tends to increase the cholesterol (specially the LDL which is the bad one) .

3- **Increase the fiber content in the food** , these fibers(derived of carbohydrates) are not digested so they inhibit the absorption of the cholesterol by binging to cholesterols in small intestine so make them also not digested so increase excretion of cholesterols and decrease their amount in the body .

4- **Ingestion of plant steroid esters (Erigsterol)** >> that decrease the rate of absorption of cholesterol by the competition with it for absorption >>increase excretion .

5- Increases the intake of omega 3

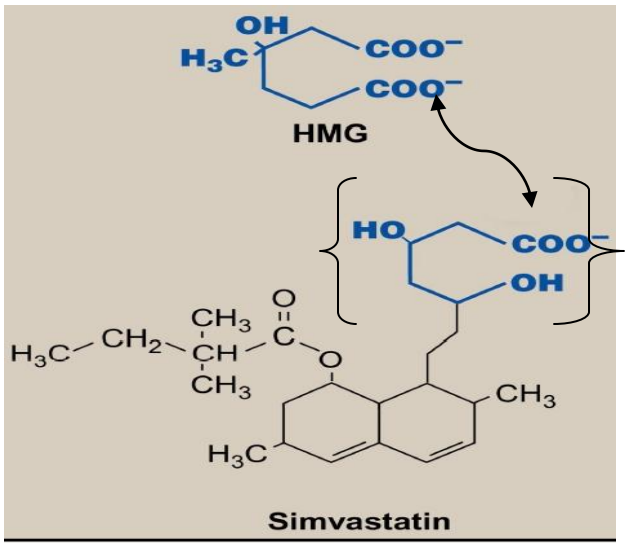
6-**Doing exercises** >> help in decreasing of LDL (BAD cholesterol) and increasing of HDL (GOOD cholesterol) .

B. Inhibition of synthesis :

If all ways above don't work adequately so we move up to the inhibition of the synthesis.

➢ How do we inhibit the synthesis?!

- Of course we will target **the rate limiting step** in the synthesis >> so the **HMG CoA Reductase** is our target .



- We all know that the substrate of this enzyme is **HMG CoA** , there is another compound which is called **Simvastatin** has **part**

similar to HMG (see the picture) , so this compound is used as **competitive inhibitor** .

- **Statin** is a drug family >>> **simavastatin** is one member of this family , **Atorvastatin is** another member which one of the most common prescribing drugs , used **for lowering cholesterol level specially LDL** (many people **after age of 50** start to use this drug to decrease the risk of **myocardial infarction**) . Actually, a lot of drugs that we use are inhibitors to enzymes.

C. ↓ Enter hepatic Circulation of Bile Acids :

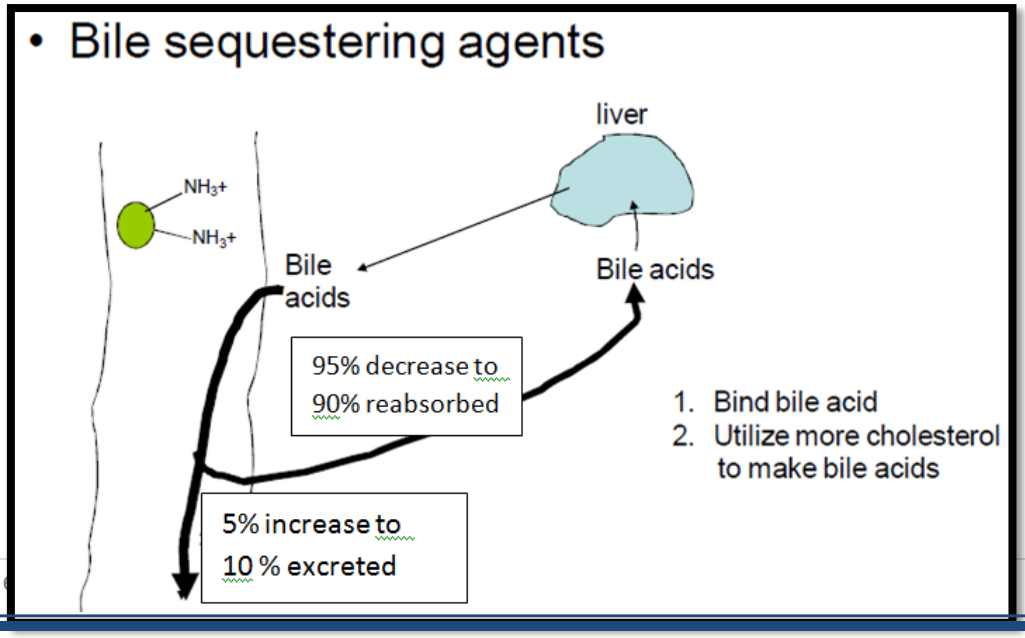
that by using **Bile sequestering agents**

➢ What is Bile sequestering agent ?!

it's insoluble molecule , cannot be absorbed , has positive charge (due to amine groups) so it's able to bind to bile acid .

➢ How does it work ?!

when it binds to bile acids ,it prevents their reabsorption >>> increase the amount the excreted bile acids to 10% and decrease the amount the reabsorbed to 90% … **So What ?!** the **bile acids** as we know **inhibit the conversion** of cholesterol into bile acids so if we **decrease the inhibitor we activate** the conversion so **more cholesterols are converted to bile acids which are excreted by the feces** so we **decrease the cholesterol level .**



2. Esterification of Cholesterol .

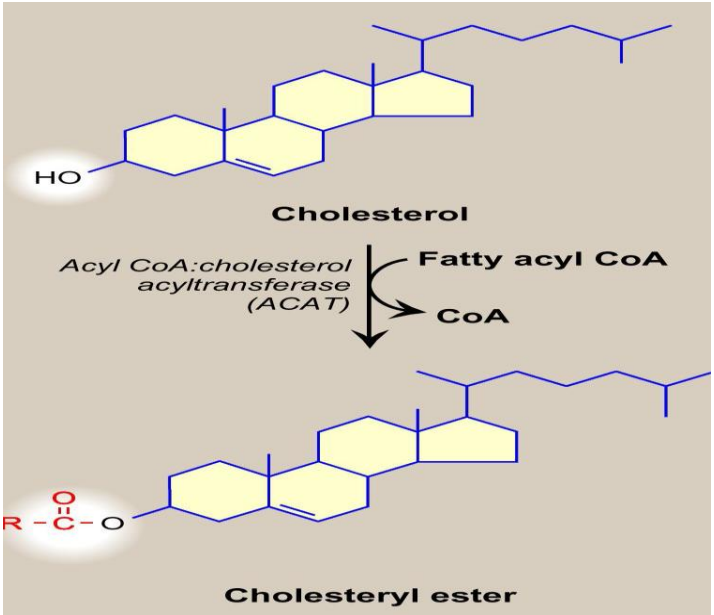
➢ **What do we mean by Esterification of Cholesterol ?!**

Joining fatty acids to cholesterol by ester bond.

❖ We should know that the esterification may occur inside cells or in the plasma. But each way has its special donor of fatty acid and special enzymes ,,, How ?!

A. The esterification of cholesterol in the cells :

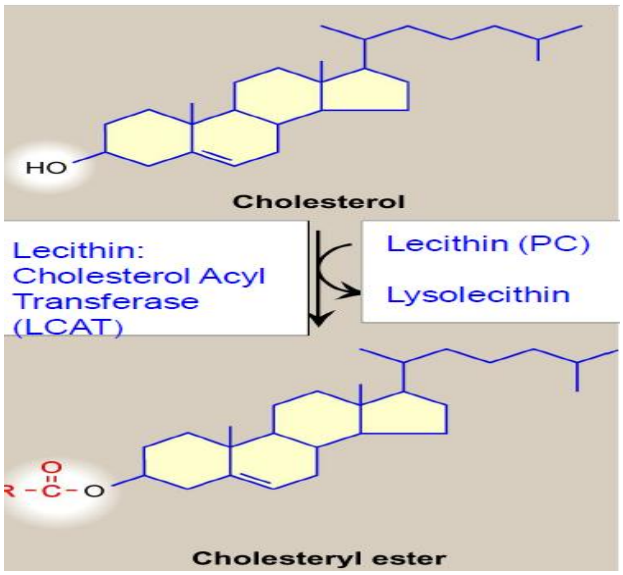
- The donor of fatty acid is **fatty acyl CoA**
- This reaction is transfer of acyl from fatty acyl CoA to the cholesterol so the enzyme is called :
  Acyl CoA : Cholesterol acyltransferase (ACAT)
- For **storage** purpose <---we esterify the cholesterol .



B. Esterification of the cholesterol in the plasma

- In the plasma the cholesterol is circulated **in the LDL and HDL**

- We cannot use the manner we used in the cell because **CoA is not found** in the plasma , so we have to get fatty acid from different source by different enzymes .
- The donor >>> **<u>lecithin (phosphotidylcholine)</u>** which is phospholipids and also found in lipoprptein particles along with cholesterol <<< so the fatty acyl acid is transferred from lecithin to cholesterol . Usually it's **unsaturated fatty acid**.
- The enzyme is called **<u>(acyltransferase (LCAT)</u> found in plasma and HDL particles .**



- When lecithin gives fatty acid it becomes **lysophosphotidylcholine (lysolecithin) .**

- ## Inhibition of the cholesterol synthesis :

  Cholesterol is very important for cell function >>> it's found in cell membrane and found in all animal cells but on the other hand high level of cholesterol can be fatal , so the cholesterol level should be regulated .
  - This regulation include :

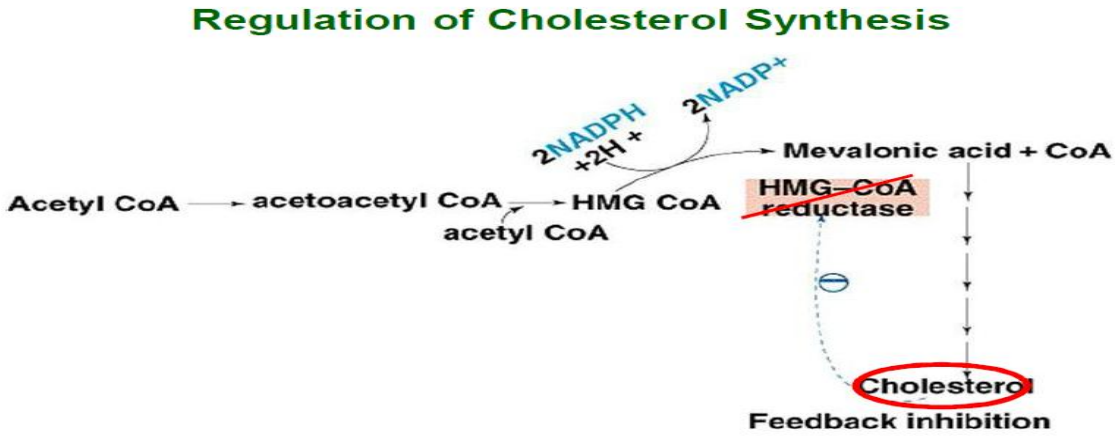
    1- regulation gene expression

    2- Covalent modification.

    3- Hormonal regulation.

    4- Proteolyic regulation.

- There is something common between all of these strategies that the **enzyme HMG CoA reductase is inhibited by the end product which is cholesterol** >>> cholesterol binds to HMG CoA reductase and inhibits it. >>>> **Feedback inhibition.(when the end product inhibit an early enzyme) .**



1- Regulation of Gene Expression.

- Gene expression: making mRNA from the gene that synthesizes specific protein. (we have the gene but it will not be translated) .
- Before the gene –upstream side – there is a sequence of nucleotide **we call it sterol Regulatory Element (SRE).**

- The gene isn't transcribed unless **transcriptional factor** is there; transcriptional factor usually is **Sterol Regulatory Element Binding Protein (SREBP).** This **SREBP** usually is attached to the **ER** (endoplasmic reticulum) ,

  >>>> In the case of **low cholesterol** it will **leave the ER** then **bind to SRE** so **gene expression** (mRNA will be synthesized) .
  >>>if the cholesterol **level is high** the **SREBP won't** leave ER so **no gene expression.**

- That is why all cells have the ability to synthesize the cholesterol but the synthesis mainly occurs in liver, adrenal cortex and small intestine.

2- Covalent modification of the enzyme.

- HMG CoA reductase is the target again.
- This enzyme can be found in two forms : **dephosphorylated and phosphorylated forms**
- The addition of phosphate group covalently to the HMG CoA reductase requires another enzyme **called AMP dependent protein kinas** (that transfer the phosphate group from the ATP to the HMG CoA reductase) .
- In the presence of **AMP the protein kinase will be activated** because the **high level of AMP reflexes the low level of energy**.
  Why AMP ?!
  if the cell consumes energy ATP will be converted to ADP then the ADP level will be elevated , ADP still has some energy but cannot replace ATP so phosphate group can be transferred from one ADP to another ADP and produce ATP and AMP >>> high level of AMP .

- **Note:** the kinas here is **AMP dependent** - not cAMP dependent - , it will be activated when **AMP binds to it**.

- **Dephosphorylated form** of the reductase in the **active form** and the phosphorylated form is inactive. **Why?!**
  If the **energy level of the cell is low** so it **isn't time to make Cholesterol.**
- The synthesis of the Cholesterol occurs during cell division , production of new membrane ,,,
- **Low** level of energy >>> **activate the kinas** >>> inhibit the fatty acid synthesis and cholesterol synthesis.

- **High** energy level **>>> activate the phosphatase** so activate the cholesterol synthesis.

3- Hormonal Regulation :

- **Glucagon** >>>> **increase the phosphorylated** form of the reductase then **inhibit the synthesis** ,
- **Insulin** (growth hormone) >>>> **activate the phosphatase** so stimulate the active form (without p group) so **activate the synthesis**.

4- Proteolytic regulation

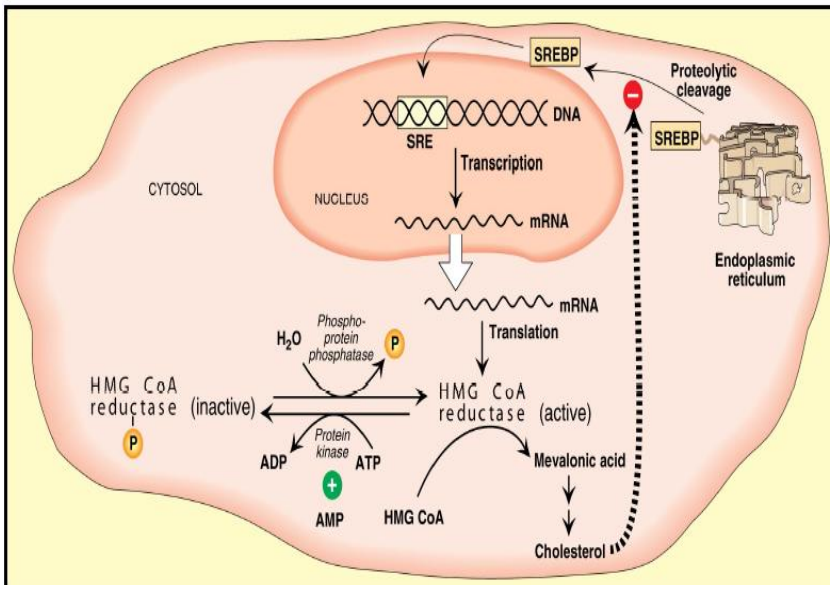
❖ The amount of the enzyme is usually **balanced** between the **synthesis rate of enzyme and the degradation rate of enzyme.**

- When the rate of synthesis of enzyme **=** rate of degradation of enzyme so the amount of enzyme is **constant**
- When the rate of **degradation increases** so the amount of the enzyme will be **decreased.**
- When the rate of **synthesis increases** so the amount of enzyme will be **increased.**

- **How do cholesterols control this?!**

High level of Cholesterol stimulates **HMG CoA Reductase Proteolysis** so **decreasing** the amount of **the HMG CoA Reductase** so the rate of Cholesterol **synthesis will decrease.**

This picture summarizes all the strategies



---

3. The transport of the cholesterol in the blood

When we want to measure the cholesterol level in the blood we can measure either total cholesterol level or the level in each lipoprotein separately.

- Total cholesterol level >>> in the Chylomicron, Chylomicron remnant, LDL, VLDL, HDL, IDL.

❖ We measuring the cholesterol level **during the fasting** why?! Because the cholesterol that we get from the food in the small intestine will bind to Chylomicron then to liver , the amount of cholesterol that we get from food is variable (differ from time to time , from meal to meal), so if you eat diet that rich in cholesterol the level of cholesterol after that meal will be very high **. So we should take baseline, the baseline is during fasting.**

❖ How many hours of fasting do we need?! Usually **10 hours and more**.

- ❖ so we ask patient to **fast 14 hours** before taking the blood sample for measuring of glucose to prevent **the high level of Chylomicron**

, after 14 hours of fasting Chylomicron normally taken by the liver ,so the remnant cholesterol may be found in :

1- the VLDL LDL IDL Apo B100

2- in HDL Apo A

Now we can measure the total cholesterol level

- but that is not enough because Cholesterol is found in two major fractions : LDL and HDL
  - We should measure amount of cholesterol in LDL and HDL separately because LDL is bad cholesterol and HDL is good cholesterol. Usually we measure that by separation through special techniques so LDL, VLDL, IDL will be participated but HDL will remain so can be measured.

- Without separation.-→ we can measure the total and by separation we measure the HDL -→then by subtraction we can measure the LDL.

❖ **Chylomicron** transports the cholesterol from the **small intestine** then Chylomicron converted to the **remnant** by losing TAGs then enter **the liver.**

❖ **Cholesterol that formed in the liver** will be transported by the **VLDL** which enter the blood **directly** then take Apo E and Apo C from the HDL then by **the lipoprotein lipase** it will lose TAG so converted to **IDL** , **IDL** can go directly to **the liver** or also **loss TAGs and converted to the LDL** which have **only Apo B100** then enter **the liver or any extra hepatic tissue** .

See the figures in the slides

- **How LDL is taken by the cells?!**

The particle **is large** so cannot enter by diffusion but by **endocytosis** .

- **endocytosis** require that **LDL** should bind to **the LDL receptors on the cells membrane** specially in the **coated pit** which contain protein **called clathrin** .

  >>> After the binding **coated vesicle is produced**

  >>> **Coated vesicle contains LDL and LDL receptors**, before making anything **receptors are separated with part of the membrane and then they are recycled.**

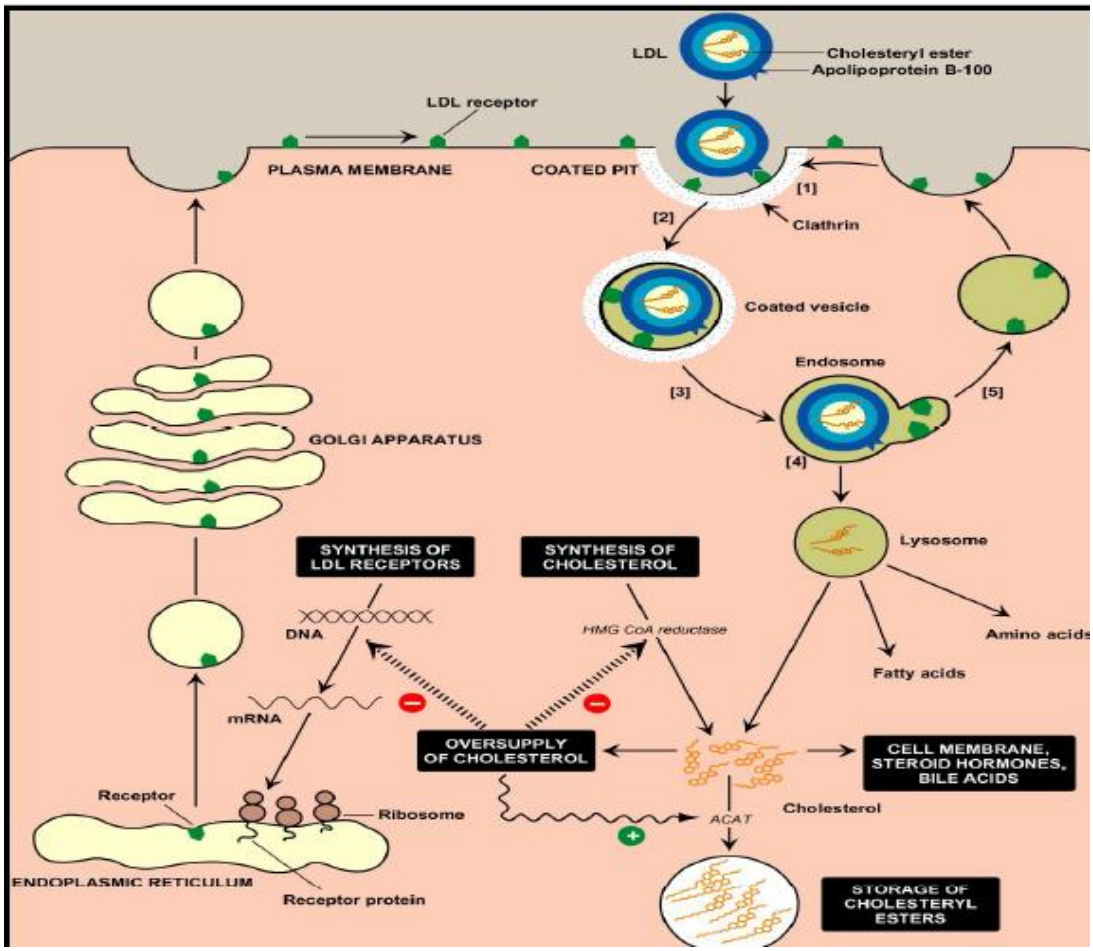
  >>> The remnant **coated vesicle which contain cholesterol ester** will be digested by lysosome so the **Apo B will be degraded into amino acids** and the **CE (cholesterol Ester) will be digested into FA and free cholesterol.**

- Free cholesterol may:

  1. incorporate in the cell membrane or for steroid hormones or bile acids
  2. Production of CE, so it can be stored,,,, to store it free cholesterol stimulate the **ACAT** (esterification enzyme)**inside the cell** .
  3. a lot of cholesterol will inhibit the MHG CoA reductase.
  4. Inhibit the synthesis of LDL receptors. what the significant in this inhibition ?!

     - to limit the amount of the LDL entering the cells , this regulation of the receptors is down regulation

This picture to summarize all we disscued above:



4. Macrophage Scavenger Receptor

- When we talked about the taking of LDL previously we talked about LDLs **which are intact** but when the **LDLs are damaged** they will be taken by the **Macrophage Scavenger Receptor**
- These receptors are **not specific ,** found in the macrophages
- There is **no down regulation** that means if there are a lot of damaged LDLs that **won't inhibit** these receptors.
- When macrophages take **a lot of LDLs so they converted to foam cells**>>> accumulation of foam cells in the **sub endothelial space** is early evidence of **atherosclerotic plaque**. Details in the figure are NOT important.

---

5. Familial Hypercholesterolemia

Familial: inherited / Genetic disorder (discovered in some families) .
Hypercholesterolemia: high level of cholesterol in the blood ' >>>> emia : something related to the blood

- Abnormal gene from **both parents so homozygous** or from **one parent so heterozygous**
- Homozygotes …. 680 mg/dl
- Heterozygotes …..300 mg/dl
- Normally..... 200 mg/dl

❖ The causes :

1- Absence of LDL receptor >>>> Homozygotes there are No Receptors

2- Abnormal Receptor >>>> Heterozygotes they have ½ Normal Number of receptors.

➢ So LDL won't enter into the cell so stay longer period of time in the plasma ,,, it may be oxidized , damaged or taken by microphages and converted into foam cells >>> so the accumulation of LDL in the plasma leads atherosclerosis and may lead to death specially in childhood …

➢ Death caused by Myocardial infarction occur in the 2nd decade of life, unusual to hear someone die because of M.I , < age of 25 except in case of **Familial hypercholesterolemia** .

6. HDL

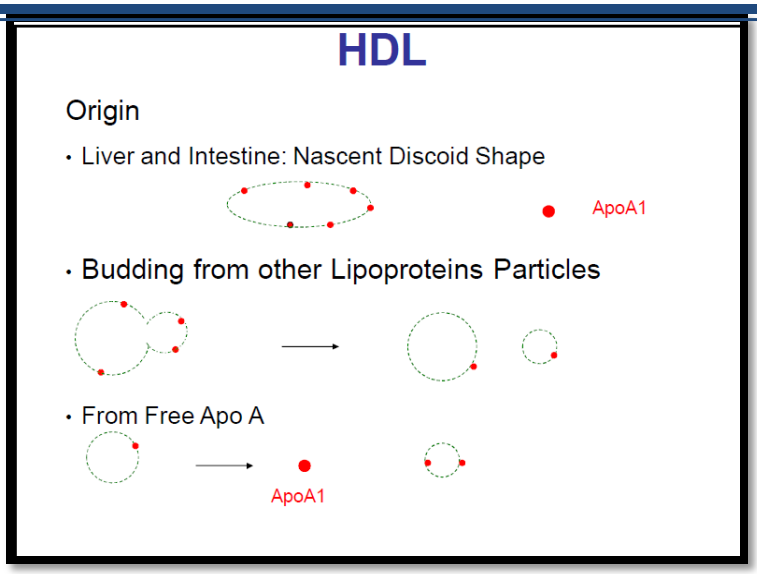
- The origin of HDL:

1- Liver and Intestine: Nascent Discoid (disk _like)

Shape , It's not spherical **that means -- large surface area = lots of phospholipids and free cholesterol** .

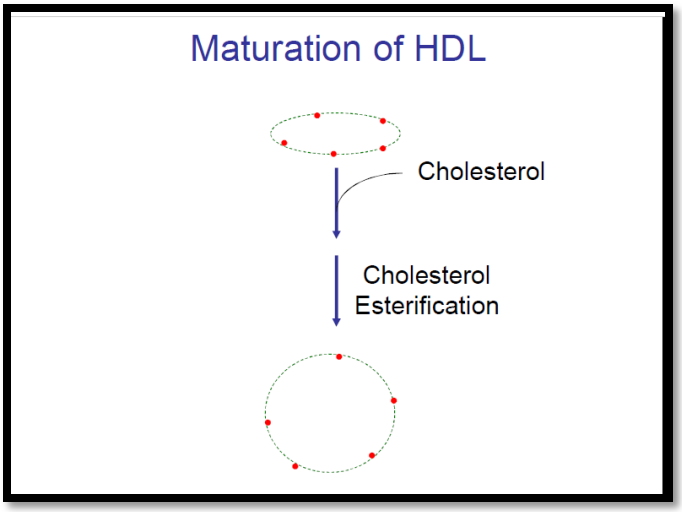
2 - Budding from other Lipoproteins Particles

3 - From Free Apo A with some phospholipids so HDL



- **The origin is not clearly known.**

- **Maturation** of the HDL by the **esterification** of the cholesterol so it will be converted from **discoid shape** to **spherical shape** >>> the donor of FA is **Lecithin** because we are talking about **plasma ..**
- Cholesterol when it's esterified it won't still surface component .



- Fate of the HDL >>> liver but not all HDL enters to liver
- It's **good** >>>> because it will be transformed **to the liver** rather than **STAYING** in the circulation as LDL.

Sorry for any mistake ^^
Ayat M Zghoul …