28

Biochemistry

Doctor 2017 | Medicine | JU

Sheet Slides

DONE BY

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DOCTOR

Faisal

Digestion of dietary lipids

Lipid digestion and absorption are complex processes. They involve soluble enzymes, substrates with different degree of solubility, and occur primarily in **the stomach** and **small intestine**.

+++ : (Dietary lipids are : triglycerides 90% , phospholipids, steroids, especially cholesterol and cholesterol esters, fat-soluble vitamins, namely: vitamin A, D, E and K, and carotenoids.)

1) TAG with **short or medium chain Fatty Acids (FA)** (<=12 carbon)

- Begins in **the stomach (acid environment)** so they **are acid stable lipases**
- Both: **Lingual Lipase** and **Gastric Lipase** hydrolyze FA from TAG
- Always remember that **milk has medium chain of FA**, so these Lipases play a particularly important role in **NEONATES** whom milk fat is primary source of calories.
- Also, **they** become important digestive enzymes in individual with **PANCREATIC INSUFFICIENCY** in which they work to digest those lipids in the absence of pancreatic lipases.
- They remove 1 FA producing = FA + DAG

As their names indicate: -

- Lingual Lipase is originated from glands at the back of the tongue and activated in stomach.
- Gastric Lipase is secreted by the gastric mucosa

Pancreas normally secretes Lipases to digest fats, when sth wrong with this secretion as in **CYSTIC FIBROSIS** (a cause of pancreatic insufficiency)**,** the above enzymes help in degrading TAG in the intestine.

2) In the small intestine

A- Emulsification in the duodenum –the first part of the small intestine-

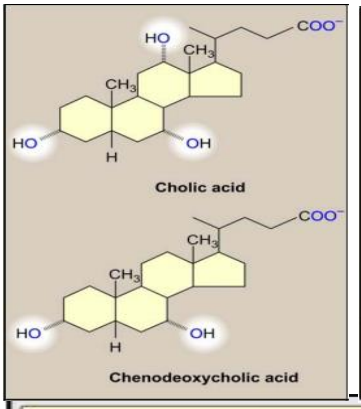
- Lipids are hydrophobic so they **aren't soluble** in the aqueous environment like in the intestine, to solve this problem **Emulsification** occurs.
- It's happened by **bile acids or bile salts made in liver and stored in Gallbladder** secreted with pancreatic lipases to the duodenum (more details in the next lecture).
- **Emulsification** breaks the fat globule to smaller molecule called emulsion droplets.
- Emulsification increases **the surface area** of the hydrophobic lipid droplets **so** the digestive enzymes (pancreatic lipases) can act effectively.

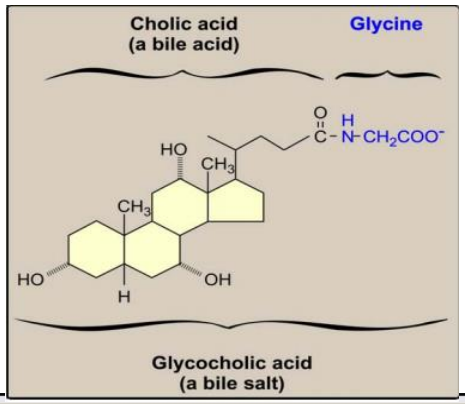
- Bile salts and acids *stabilize* lipid particles as they become smaller and preventing them from coalescing.

B- Degradation by pancreatic enzymes (happens Because TAG molecules are too large to be absorbed by "mucosal cells") .

Pancreas secretes **LIPASE and CO-LIPASE** to small intestine .

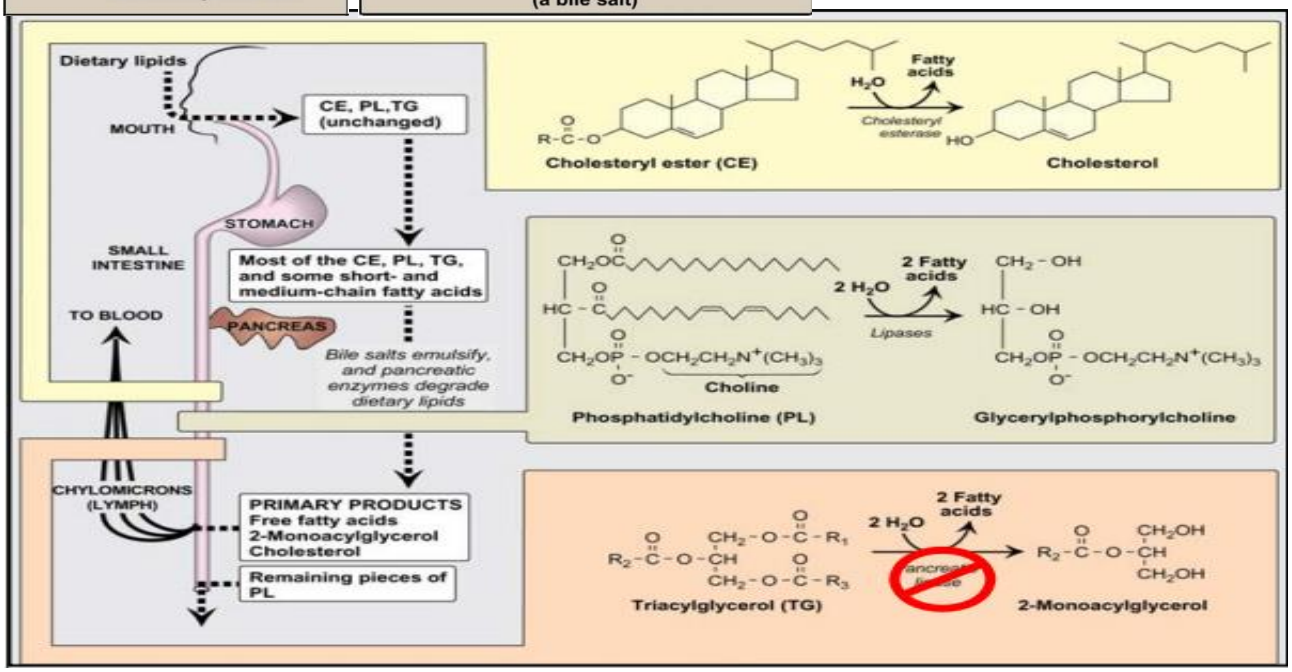
- Lipase removes 2 FA from TAG at carbon 1+3, forming **2-MONOACYLGLYCEROL+2FA**.
- Ester linkage at Position 2 can't be hydrolyzed.
- Cholesteryl esters are hydrolyzed by **pancreatic cholesteryl ester hydrolase (cholesterol esterase)**, which produces **(CH)+FA** .
- **COLIPASE helps the lipase (hydrophilic molecule) binding to TAG (hydrophobic), it is an amphipathic molecule.**





*** Examples on bile acids and salts.**

Don't worry just study sheet 29 ☺



As a summary

https://courses.washington.edu/conj/bess/fats/fats.html?fbclid=IwAR3LxfRnclVo7hm_2LiMBnh34ISA3fURuhFP9MbAXQF_ZazV3FtUyz4It1s

https://www.youtube.com/watch?v=Zqvr20ZOtvM&t=261s

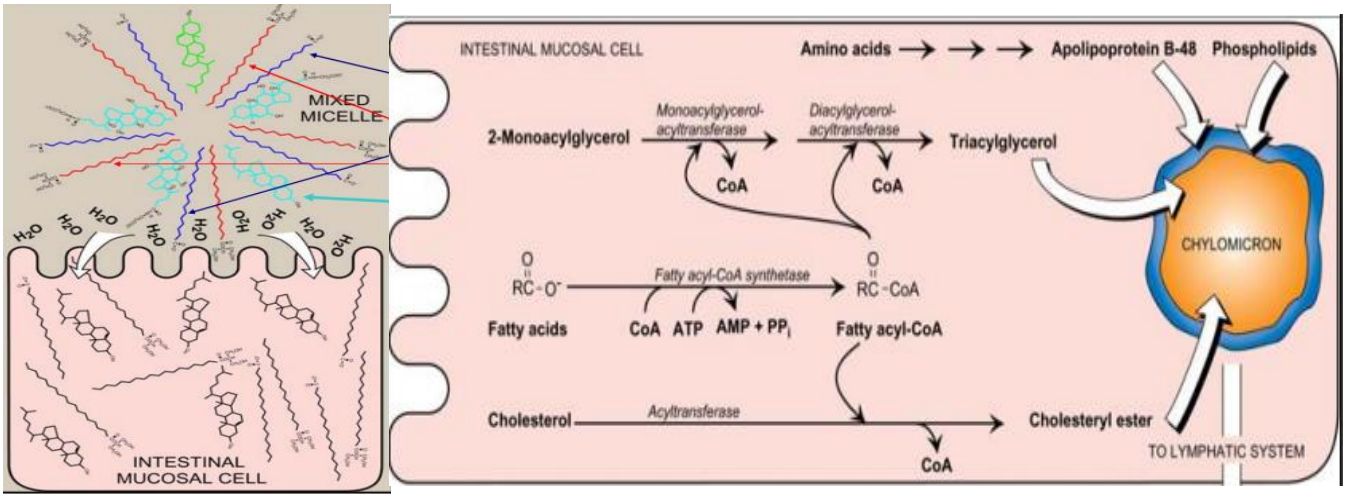
The doctor said that we have to self-study the previous topic, I tried to explain it as well as I could, SORRY for any extra information

- **FA, 2-MAG & CH** are the primary products of lipids digestion in the jejunum.
- All are **amphipathic** so they aggregate in the lumen (with bile acids+ bile salts+ vitamins) to form **MIXED MICELLE** (hydrophilic surface and hydrophobic core)
- MIXED MICELLE will **diffuse** through the membrane of enterocytes. (remember that carbohydrates and amino acids need special transporters to enter enterocytes unlike Lipids)
- Inside the enterocytes (specifically in the S-ER) **FA** is activated by CoA (revise sheet 22) and added to **2-MAG** to form **DAG**, another activated FA is added to resynthesize **TAG**.
- **CE** is also reformed by adding **FA** to **CH**.

★Think of it as breaking of TAG and CE to enter the enterocyte and then reforming them again.

- TAG and CE are hydrophobic so they aren't soluble in water→ **they are coated by phospholipid, CH and protein B-48 to form *CHYLOMICRON*** (a lipoprotein used to carry lipids in plasma)
- By exocytosis, **Chylomicron** leaves the enterocyte to the **LYMPHATIC SYSTEM to thoracic duct and then to large left subclavian vein where they enter the blood.**
- **The chylomicron metabolism is completed in page 8 ….**

Final product of digestion for Carbohydrates and amino acids enter the circulatory system directly by capillaries
But lipids are so large (if entered without dilution it will block the capillaries)



Summaries from the slides

LIPOPROTEINS

- **Glycerol** is a very hydrophilic molecule with 3 carbon atoms + 3 hydroxyl groups

(soluble)

- **Fatty Acid (FA)** has a negative charge on its carboxyl group, it's amphipathic

(soluble)

- When combining together and forming **TriAcylGlycerol (TAG),** it's neither polar nor amphipathic (ester bond is no longer hydrophilic)

(completely insoluble)

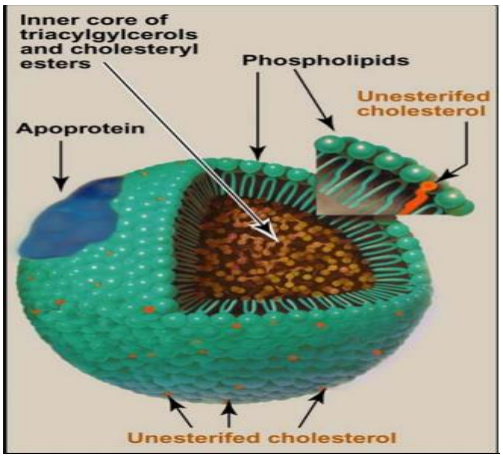
- We know that 90% of the plasma is water, so we need a carrier to transport lipids to and from tissues, this transport system is called **LIPOPROTEINS**

LIPOPROTEINS are composed of multimolecular complexes of **lipids** and **proteins**.

-lipids are

1) TAG, Cholesterol Ester (CE), both are non-polar so they are existed in the core of the **LIPOPROTEINS**

2)Cholesterol (CH), Phospholipids (PL), both are amphipathic so they are existed on the surface (the shell) with their polar part exposed on the surface to make it soluble in water.



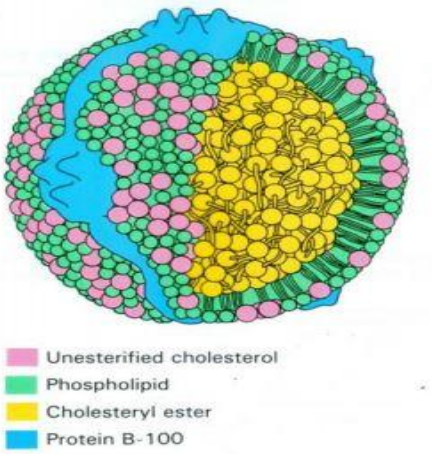
-Proteins : are called Apo-lipoproteins

- They are amphipathic, exists of the surface (the shell)
- Several classes **(Apo A , Apo B-48 , Apo c , Apo E)** some will discussed later.
- They have <u>structural role</u> (can't be removed)
- Or <u>Regulatory role</u> (can be transferred between different lipoproteins)
- Or <u>Binding to cell surface receptors</u>.

recall from the summer :-

if the protein is bound to something else the protein part of that complex is called ***apoprotein***

LIPOPRETEINS are Similar to Micelles ☺



★ **Lipoproteins are composed of a neutral lipid core (containing TAG & CE) surrounded by a shell of amphipathic Apolipoproteins, Phospholipids & free Cholesterol.**

LIPOPROTEINS are classified according to their densities so we can separate them by **centrifugation.**

Classes of Lipoproteins

Lipoprotein	Density	Protein	Major Lipid
Chylomicrons (FLOATS)	<0.95	2 %	TAG (85%)
VLDL (In-between)	0.95- 1.006	9%	TAG (55%)
IDL (Sinks)	1.006-1.019	11%	TAG (26%) CE (30%)
LDL (Sinks)	1.019- 1.063	20%	CE (35%)
HDL (Sinks)	1.063- 1.21	45%	PL (25%)

VLDL: very low density lipoprotein
IDL: Intermediate-density lipoprotein
LDL: low density lipoprotein
HDL: high density lipoprotein

-Please don't memorize the numbers.
-You should know the arrangement according to density, size, lipid and protein percentage. (IDL>LDL and so on..)

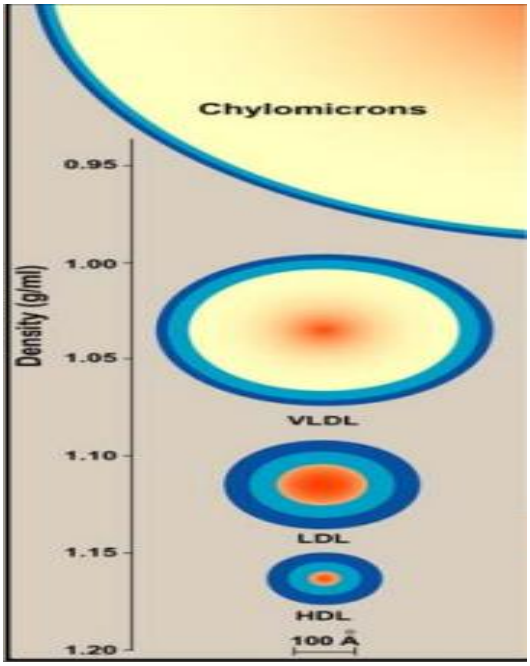
- **Remember that density of water=1g/cm^3,**
- **oil (fat) always float in water, so its density<1, therefore increasing lipid component will decrease the density of lipoprotein and the opposite for increasing protein components.**
- TAG is in the core so 85% of **Chylomicrons** is a core lipid therefore it has a low surface area ratio to volume (bigger in size), the name micron indicates this also.
- While PL and proteins are on the surface, so 70% of HDL is a shell therefore high surface area ratio to volume (smaller in size).

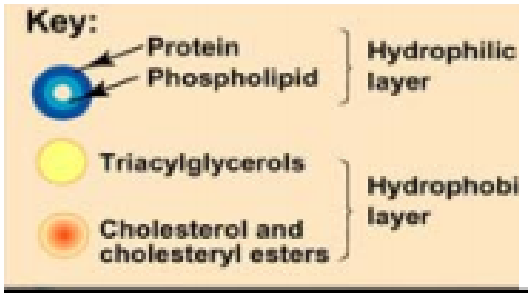
★**As an overview :- increasing the size will increase the volume and surface area, but the increase in volume is much bigger than the increase in surface area**.

As in the picture below Chylomicrons have high surface area and volume than others but we are talking about ratios.

so the ratio surface area/volume will decrease when increasing the size

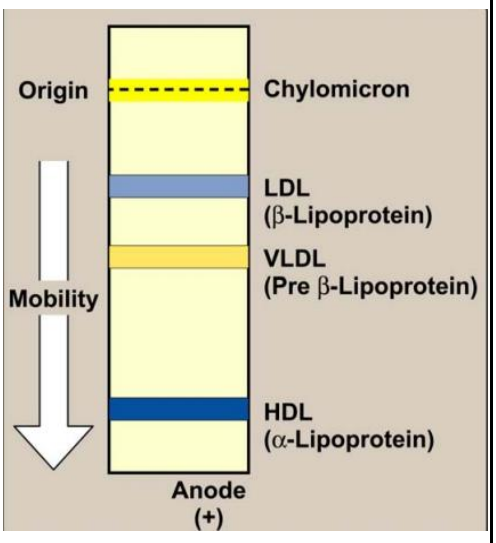
★Chylomicrons are the lipoprotein particles lowest in density and largest in size and that contain the highest percentage of lipid (as TAG) and the lowest percentage of protein. VLDLs and LDLs are successively denser, having higher ratios of protein to lipid. HDL particles are the smallest and densest.





CH has a polar part which exists on the surface as in page 4

- The easiest way to separate **LIPOPROTEINS** is **electrophoresis** (based on charge and size as in plasma proteins) but here we use a special stain that reacts only with lipids so whenever there is a lipid, it will appear as a band.
- It is done in a ph of 8.6(high) so most of the proteins will be negatively charged moving to the positive anode.
- **HDL** called **ALPHA-lipoprotein** because it migrates with **ALPHA proteins** of the plasma
- Same with **LDL** **(BETA-lipoprotein)**
- **VLDL** (pre BETA-lipoprotein) a little faster than BETA-lipoprotein (remember pre albumin in the plasma)



❖ This way doesn't depend on density (**VLDL** is below **LDL**)

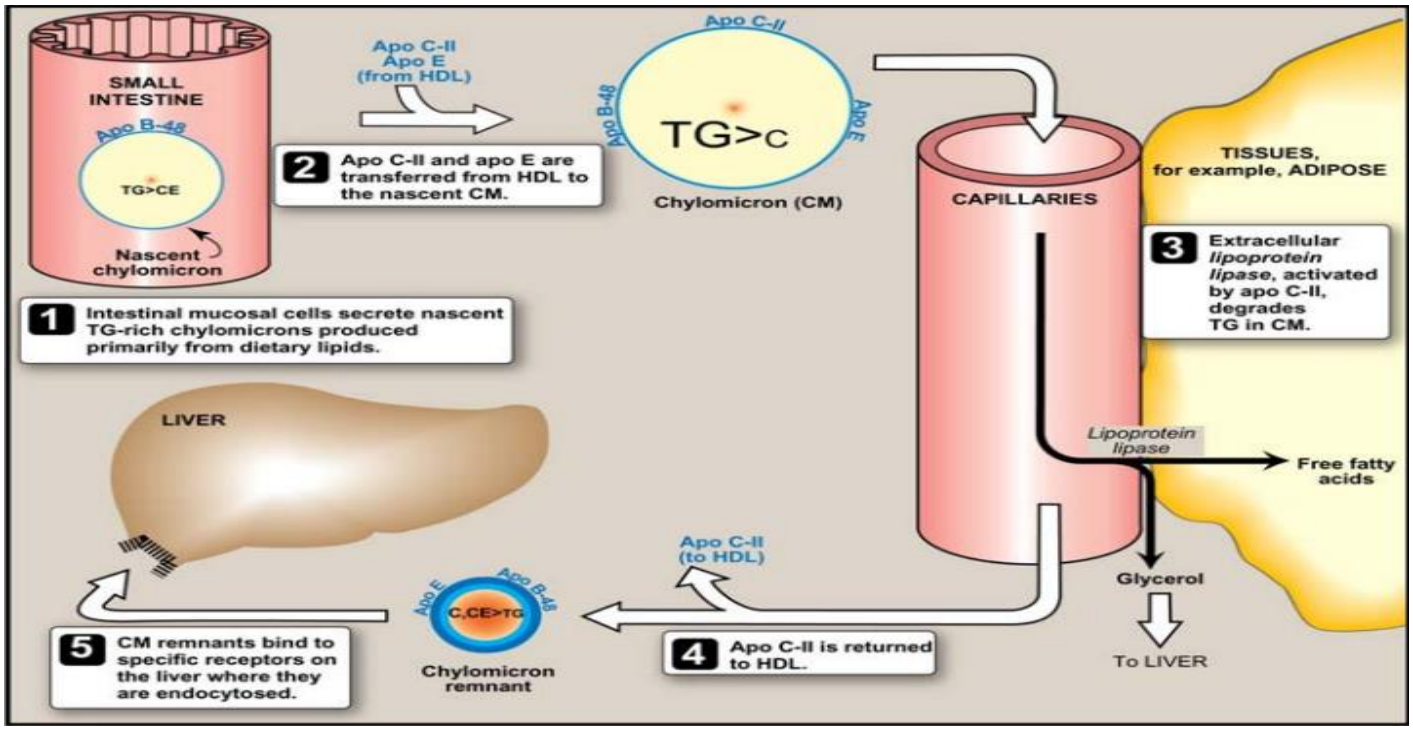
Lipoprotein	Apo Protein Types	
Chylomicrons	Apo B, Apo C, Apo E	Dietary Lipids
VLDL	Apo B, Apo C, Apo E	Endogenous TAG
IDL	Apo B, Apo E	
LDL	Apo **B**	Cholesterol
HDL	Apo **A**, Apo C, Apo E	Cholesterol Return to Liver

Endogenous TAG is the TAG synthesized in the liver from excess carbohydrates

From the second column you should only know that

- **Apo A** type exists only in **HDL**
- **Apo B** type exists in all except **HDL** → **HDL has Apo A and doesn't have Apo B**
- **LDL** has only **Apo B**

CHYLOMICRON METABOLISM for exogenous TAG (you should know all steps and purposes of Apoproteins in LIPOPROTEINS)



Numbers are referred to the picture

- The newly synthesized chylomicrons are called "**nascent chylomicrons**".

3- Most of the TAG is broken down by **LIPOPROTEIN LIPASE (LPL)**

- synthesized by adipose tissue and skeletal muscle, it is an **extracellular enzyme**
- requires an activator which is **protein C-II** comes from HDL in step 2
- The products are ↓

FA diffuses to **skeletal muscle to be oxidized or to adipose tissue to be oxidized or re-esterified to produce TAG**

Glycerol goes to the liver **(which has glycerol kinase)** to form glycerol 3-phosphate

Then it enters GLYCOLYSIS or GLUCONEOGENESIS or be used in TAG synthesis

Connect the previous lectures.

After this step **TAG** is decreased in chylomicron so the size **is decreased**

The density **increases** due to removing lipids (density lower than water)

focus on the changing of chylomicron shape in the picture

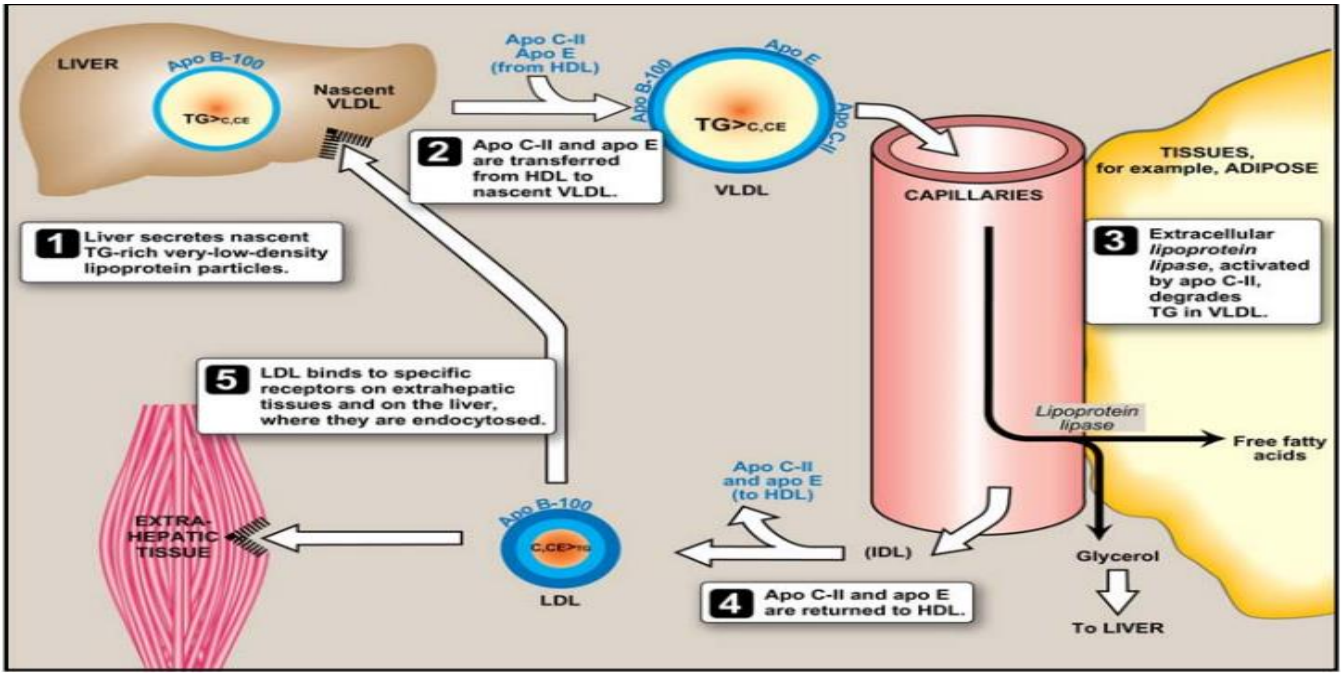
5- liver has a receptor for **Apo E,** when binding, endocytosis happens to the remnant of chylomicron (بقايا).

- **"chylomicron remnants "contains larger amounts of Cholesterol and cholesterol esters than TAG which have been already degraded by LPL.**

This metabolism takes several hours, so in order to measure cholesterol, the patient must fast 12-14 hours, otherwise the cholesterol measured in the plasma= the cholesterol we eat (very high)

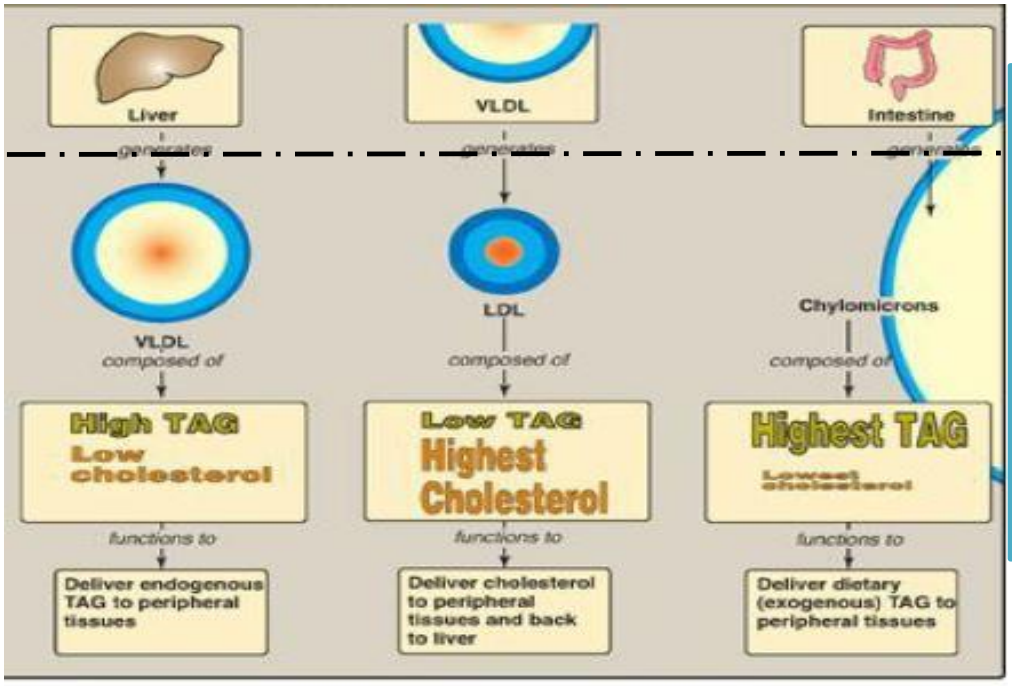
Summary from book: Chylomicrons are assembled in intestinal mucosal cells from dietary lipids (primarily TAG). Each nascent chylomicron particle has one molecule of apolipoprotein (apo) B-48. They are released from the cells into the lymphatic system and travel to the blood, where they receive apo C-II and apo E from HDLs. Apo C-II activates endothelial lipoprotein lipase (LPL), which degrades the TAG in chylomicrons to fatty acids and glycerol. The fatty acids that are released are stored (in the adipose) or used for energy (by the muscle). The glycerol is metabolized .by the liver

VLDL metabolism (for endogenous TAG), again you should know the steps



- Almost the same as CHYLOMICRON **except** It is synthesized in the **liver and released directly to the blood (small in size),** CHYLOMICRON (is assembled in the small intestine and doesn't enter the blood directly) When TAG is degraded **the density is increased** as mentioned in chylomicron metabolism
- **This converts VLDL to IDL**
- **IDL** is taken by endocytosis or continues until the density increases a lot to become **LDL** which has higher CE and C than TAG (denser).
- All the components of **LDL** is taken by endocytosis to **extrahepatic tissues** or liver.

Another summary from the book



Know that both chylomicrons and VLDL lose TAG in the blood

Chylomicron becomes Chylomicron remnant while VLDL is converted to IDL BECAUSE of the different proteins on their surfaces

CHOLESTEROL

CHOLE= gallbladder Ster=steroid Ol= alcohol

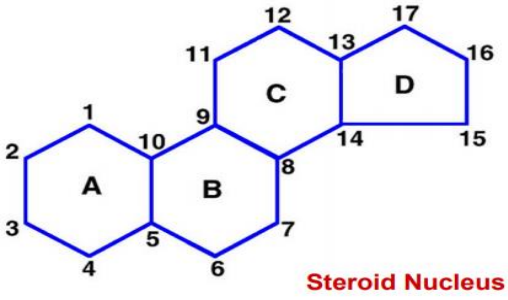
so it's the steroid alcohol of the gall bladder

cholesterol is related to atherosclerosis, strokes and many diseases,

A lot researches have been done on it.

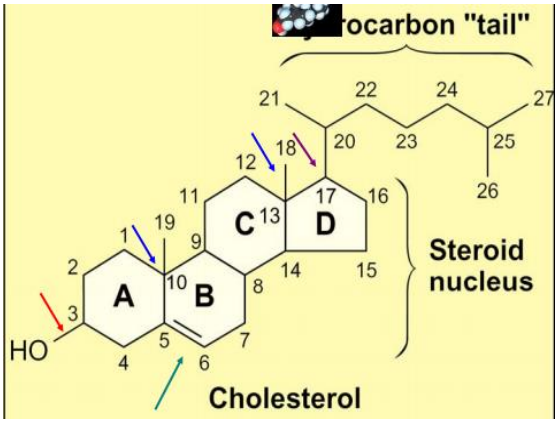
★ Cholesterol was firstly isolated from gall bladder stones in 1774

- **All steroids have steroid nucleus →17 carbon**

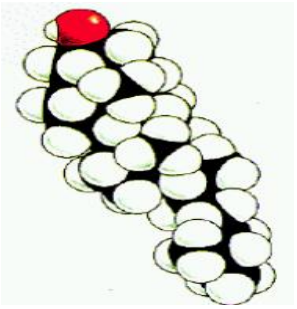


- **The cholesterol has the following structure**

1)Steroid nucleus
2) Hydroxyl group OH on carbon 3
3) Double bond between carbos 5&6 (at ring B)
4) Two methyl groups on carbons 18&19
5) Hydrocarbon side chain (at carbon 17) carbon 20-27



^You have to distinguish cholesterol structure from other steroids^



- In the space filling model it has a rod shape with terminal hydrophilic OH (in red)
- It is composed of non-polar hydrophobic region and a small **OH** group which is polar, so it is poorly soluble →carried with lipoproteins in the plasma and can precipitate forming stones in gallbladder.
- When this is happened, the treatment is to remove all gallbladder with the stones.
- This makes it suitable to be existed in the **all animal plasma membranes**

- **Sources of Cholesterol**

1)synthesis ≈ 1000 mg

Mainly by liver, also by small intestine and adrenal cortex

In fact, all cells are capable to synthesize cholesterol but since they take it easily in big amounts, the synthesis is inhibited

2) Dietary ≈ 300 mg (considered low cholesterol diet)

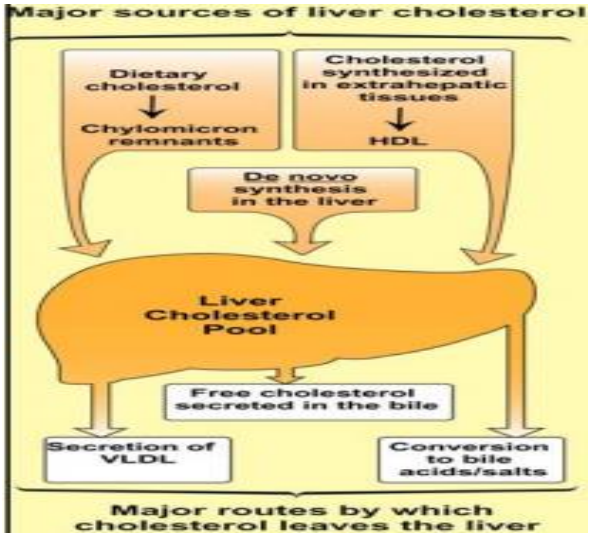
Synthesis and dietary are regulated, if you increase your dietary (CH) a little, the synthesis will be inhibited to balance this increase and vice versa.

- **Elimination of Cholesterol**

CH is eliminated via the bile as free cholesterol or bile salts (more details in lecture 29)

Since the liver is the major organ that synthesize CH

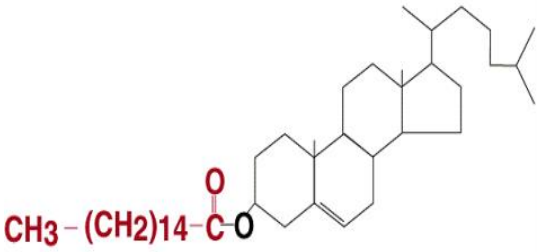
Liver of the sheep and chicken are very rich in CH



- **CHOLESTEROL ESTER (CE)**

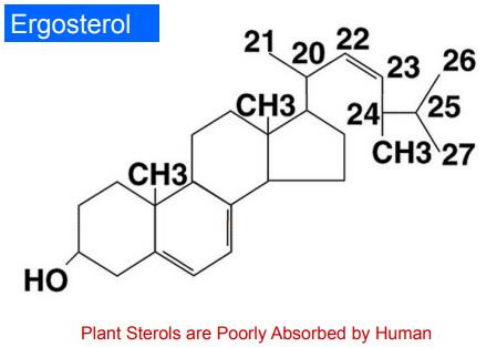
Cholesterol +FA on the hydroxyl group by an ester bond (at carbon 3)

It is no longer hydrophilic due to ester bond



Remember:-
CH is on the surface of lipoproteins
CE is in the core of lipoproteins

- **PHYROSTEROLS (plant steroids)**
  - ❖ Produced by plants (they don't make CH)
  - ❖ Ergosterol is similar to CH with additional carbon(28) and double bonds, it is found in fungi.
  - ❖ Plant oil e.g. corn oil is free cholesterol because it is from plant which can't produce cholesterol



Plant Sterols are Poorly Absorbed by Human

  - ❖ Phyrosterols 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 lecture is about LIPID METABOLISM and it has covered: -

1) lipid digestion and absorption in the stomach and small intestine

2) lipoproteins that carry lipids in the blood to the tissues, and their components

3)specific metabolism of two lipoproteins (chylomicrons and VLDL)

4-Intoduction to cholesterol which will be continued in the next lecture

FINALLY, THE END.