METABOLISM

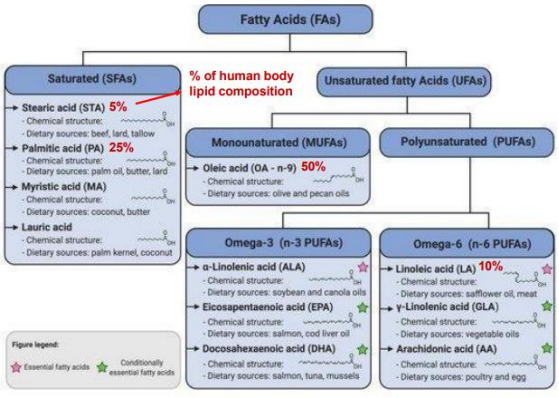
2025-2024

DR.Ahmad Al Qawasmi

ARKAN ACADEMY

Lipids Metabolism

- Lipids are heterogeneous, hydrophobic molecules compartmentalized in membranes, as droplets of triacylglycerol (TAG), or in lipoprotein (LP) particles
- Functions: Energy, structural, molecular precursors for vitamins and signaling molecules
  - The major dietary lipids are triacylglycerol, cholesterol, and phospholipids
- Lipids involve:
  - ***Glycerophospholipids:*** Consist of a *glycerol* molecule, *2 Fatty acids* and a *polar head*
    - ✓ Polar head = ***Phosphate*** group + ***hydrophilic*** group such as choline and serine
    - ✓ The most common phospholipid is lecithin (phosphatidylcholine)
  - ***Sphingolipid:*** a lipid built on a *sphingosine* molecule
    - ✓ *Ceramide:* Sphingosine + ***1 Fatty acid***
    - ✓ *Sphingomyelin:* Sphingosine + 1 Fatty acid + ***Phosphatidylcholine***
  - ***Sterols:*** Lipids build on a *steroid nucleus* (4 fused rings) with side chains
    - ✓ **Cholesterol** is the most common sterol
- ***Fatty Acids:*** Long *hydrocarbon chain* starting with a *carboxyl group*
  - Fatty acids can be short (SCFA, < 6 C), medium (MCFA, 6 – 12 C), long (LCFA, 14 – 20 C) and very long (VLCFA, > 20 C) chain
  - They consist of odd or even number of carbons
  - They can be either saturated, unsaturated (double bonds) or modified (branched, hydroxylated)
    - ✓ Double bonds in FA are always spaced at three-carbon intervals
  - They can be *essential* (**only from diet**) or *non-essential*
    - ✓ FAs with double bonds beyond the 10th carbon are essential such as linoleic and α-linolenic acid
- The addition of *double bonds* decreases the melting temperature of a fatty acid (↓ T_m, ↑ *fluidity*)
- Increasing the chain's *length* increases the melting temperature (↑ *Tm*, ↓ *fluidity*)
  - Membrane lipids typically contain unsaturated long-chain fatty acids (LCFA) to maintain fluidity
- The most abundant FA in our bodies:
  - *Oleic* acid (50%), 18 C, monounsaturated
  - *Palmitic* acid (25%), 16 C, saturated
  - *Linoleic* acid (10%)
  - *Stearic* acid (5%), 18 C, saturated



- Fatty acids can present in many forms:
  - ***Structural FAs:*** membrane lipids such as phospholipids and glycolipid
  - ***Protein-associated FAs:*** facilitate attachment of proteins with membrane covalently
    - ✓ Include palmitoylation and myristylation

- ***Esterified FAs*** in the form of cholesterol esters and TAGs stored in the adipose tissue as the major reserve of energy in the body
  - ✓ > 90% of the plasma fatty acids are in the form of fatty acid esters (primarily TAG, cholesteryl esters, and phospholipids) carried by circulating lipoprotein particles
- ***FAs are precursors*** for the synthesis of many hormones
  - ✓ Arachidonic acid is the precursor for prostaglandins, thromboxane and leukotrienes
- ***Free Fatty Acids (FFA)*** can be oxidized into acetyl CoA to *provide energy* (in liver and muscle) or ketone bodies synthesis (in liver)
  - ✓ FFAs is transported in the plasma on ***albumin*** from adipose tissue to most tissues

- ***Triacylglycerol (TAGs):*** consists of Glycerol + 3 FAs attached by ester bonds
  - *Simple TAG:* 3 identical FAs such as tristearin
  - *Mixed TAG:* different FAs

Digestion and Absorption of Lipids

- Digestion occurs in:
  - *Oral cavity* by *lingual lipase* (minimal digestion)
    - ✓ Lingual lipase is released by the back of the tongue and mixes with the saliva
    - ✓ It can cut (hydrolyze) TAGs with *SCFAs and MCFA*
    - ✓ It is ***acid stable*** and active in the stomach
  - *Stomach* by *lingual* and *gastric lipases* (10-30% digestion)
    - ✓ They cut (hydrolyze) TAGs with *SCFAs and MCFA*
    - ✓ They are ***acid stable*** (optimum at 2.5–5 pH)
    - ✓ Gastric lipase is ***inhibited by LCFAs***
    - ✓ Don't require Colipase or bile
    - ✓ Important for the digestion of lipids in:
      - *Newborn infants:* SCFAs and MCFAs are the main FAs in breast feeding
      - *Pancreatic lipase deficiency* or *pancreatic insufficiency* patients such as cystic fibrosis

Breast feeder women can introduce some of their genome to the neonate by:

1. ***Epigenetics*** (methylation)
2. ***Reverse transcriptase*** in the milk

  - *Intestine* by *pancreatic enzymes* (50–70%) such as:

A. *Pancreatic lipase*

- ✓ They cut (hydrolyze) TAGs with *LCFA*
- ✓ Cut the 1st and 3rd FAs of TAG producing 2 FAs and Monoacylglycerol
- ✓ Requires *Co-lipase* to be active which ***anchors the lipase*** into micelle interface in a ratio of 1:1
  - Co-lipase is a zymogen (proenzyme) activated by ***trypsin*** which activates lipase and restore its activity against inhibitors
  - Lipase-colipase complex deficiency causes ***orphan disease***

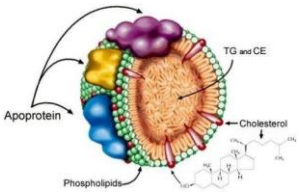
B. *Phospholipases*

- ✓ Phospholipids are firstly hydrolyzed by *phospholipase A2*
  - It is a proenzyme activated by ***trypsin***
  - It cuts FA on the 2nd carbon, producing lysophospholipid and FFA
- ✓ *Lysophospholipase* cuts FA on 1st carbon
  - It produces FFA and glycerophosphoryl base
  - Glycerophosphoryl can be either absorbed, excreted in feces or further degraded

C. ***Cholesterol esterase*** breaks cholesterol ester into cholesterol and FFA

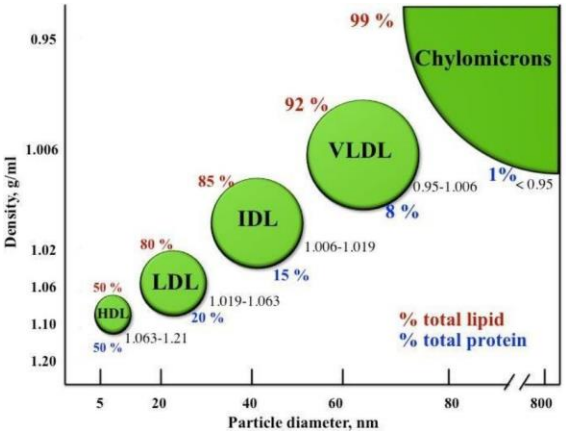
- In the intestine, the lipids must be ***emulsified*** to be digested
- Emulsification is a process where one liquid is dispersed as small spherical droplets in a second immiscible (not homogeneous) liquid.
  - ➢ It is done by peristalsis (mixing movement) or bile salt conjugation
- **Biles** are synthesized in the *liver* and stored in the *gallbladder*
  - ➢ When needed, it is released to the duodenum to ***activate all pancreatic*** digestive enzymes (lipase, colipase, cholinesterase, phospholipase)
  - ➢ Biles are ***amphipathic*** molecules (polar and non-polar), that form a micelle around lipids
  - ➢ They are derived mainly from ***cholesterol***
    - ✓ Cholesterol-lowering drugs increases synthesis of bile acids to increase cholesterol consumption
- Hormonal control of lipid digestion:
  - ➢ ***Cholecystokinin (CCK)*** is released from the duodenum and jejunum by the ***entry of chyme*** (food)
    - ✓ Increase gallbladder contraction to *release bile*
    - ✓ Stimulate exocrine pancreatic cells to *release digestive enzymes*
    - ✓ *Decrease gastric motility* to decrease the release of gastric contents (increase efficiency)
  - ➢ ***Secretin*** is released by the intestinal cells due the ***low pH*** of chyme
    - ✓ Stimulates pancreatic cells to *release bicarbonate* rich solution to neutralize the acidity of chyme
    - ✓ *Inhibit gastric motility*
- The contents of the micelle (FFAs, monoacylglycerol, cholesterol, bile salts and fat-soluble vitamins) get absorbed from the apical surface (brush-border membrane) of the intestinal cells then get reformed into TAGs and Cholesterol esters and released from the basolateral surface by chylomicrons
  - ➢ FFAs are absorbed via ***passive diffusion*** (mainly SCFA, MCFA) or protein mediated
  - ➢ Monoacylglycerol and lysophospholipids are also absorbed passively
  - ➢ Cholesterol require ***Niemann-Pick C1 like 1 protein (NPC1L1)*** for absorption by vesicular transport
    - ***Ezetimibe*** inhibits cholesterol absorption by internalizing the NPC1L1
    - ***Dietary fats*** facilitate cholesterol absorption, but ***high fibers*** content inhibits it

- ***Microsomal Triglyceride Transfer Protein (MTP)*** is a protein in the SER responsible for the *assembly of chylomicrons* from lipids and apolipoproteins
  - ✓ LCFAs enter the SER by Fatty acid binding protein 2 (***FABP2***)



- Lipoproteins consist of lipids and apolipoproteins
  - As lipid content increases, protein density decreases
- Lipoproteins are responsible for ***transporting lipids*** in the blood stream
  - The first lipoprotein to be formed is *chylomicron* carrying a high TAGs and low cholesterol
  - In the blood stream, lipoprotein lipase in the surface of endothelial cells will hydrolyze some TAGs
  - The remnant of chylomicrons will go to the liver converted into *VLDL*
  - VLDL enter the circulation and TAGs are hydrolyzed by ***lipoprotein lipase (LPL)***
  - Then converted in the liver into *IDL* which also go to circulation and return to the liver and converted into *LDL* to be distributed into the peripheral tissues
    - ✓ LPL is activated by apolipoprotein C-II

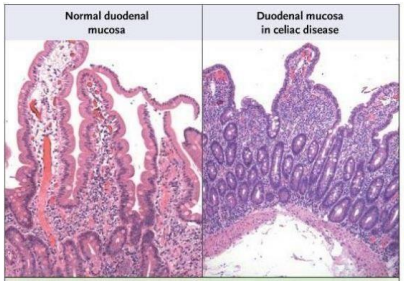
	Chylomicrons	VLDL	LDL	HDL
Density (g/ml)	< 0.94	0.94-1.006	1.006-1.063	1.063-1.210
Diameter (Å)	2000-6000	600	250	70-120
Site of synthesis	Intestine	Liver	Liver	Liver, intestine
Total lipid (wt%)	99	92	85	50
Triacylglycerols	85	55 Liver	10	6
Cholesterol esters	3	18	50 (bad)	40 (good)
Apolipoproteins	A, C, E, **B48**	C, **B100**, E	B100	A, C, E
Function	Transport of dietary TG to the liver	Transport of TG from the liver to peripheral tissues	Transport of cholesterol from the liver to peripheral tissues	Transport of cholesterol from peripheral tissues back to the liver (cholesterol scavengers)



- Apolipoprotein B48 (chylomicrons) and B100 (VLDL) are produced from the **same gene** in different tissues, due to the presence of ***cytidine deaminase*** in the intestine concerting C to U producing a stop codon UAA which produces a shorter polypeptide chain
- *HDL is the good cholesterol* because it transports lipids and cholesterol from the tissues to the liver, where it is used to produce bile and vitamin D
  - It also provides cholesterol to the testes, ovaries and adrenal gland for steroid hormones synthesis
  - HDL has a high protein density and low lipid content
- ***FFAs*** produced from the hydrolysis of TAGs from the chylomicrons are:
  - Broken down into *acetyl CoA* (at low energy state)
  - Stored in the *adipose* tissues (at the high energy state)
- ***Glycerol*** produced from the hydrolysis of TAGs from the chylomicrons is:
  - Used to produce other *TAGs* and phospholipids
  - Converted into *G3P and DHAP* and then enters glycolysis and gluconeogenesis

- ***Familial chylomicronemia (type I hyperlipoproteinemia)*** is a rare, autosomal- recessive disorder caused by a *deficiency of LPL or its coenzyme apo C-II* resulting in fasting chylomicronemia and severe hypertriacylglycerolemia, which can cause pancreatitis

- ***Celiac Disease:*** Auto-immune response to gliadin peptide in ***gluten*** (in wheat, rye, barley) causes damage in the intestinal absorptive surface causing ***malabsorption of lipids*** and steatorrhea



  - Gliadin has a high proline (14%) and glutamine (40%) content
  - It is characterized by the presence of anti-tissue transglutaminase antibodies (*anti-tTG*)
  - Tissue biopsy reveals *absence of the villous surface* epithelium

- Diseases that cause steatorrhea:
  - *Short bowl disease*
  - *Liver or biliary tract disease*
  - *Pancreatic exocrine insufficiency*
  - *Cystic fibrosis* which is a congenital disease common in western countries especially in jews causes accumulation of mucus in the lung and intestinal mucosa

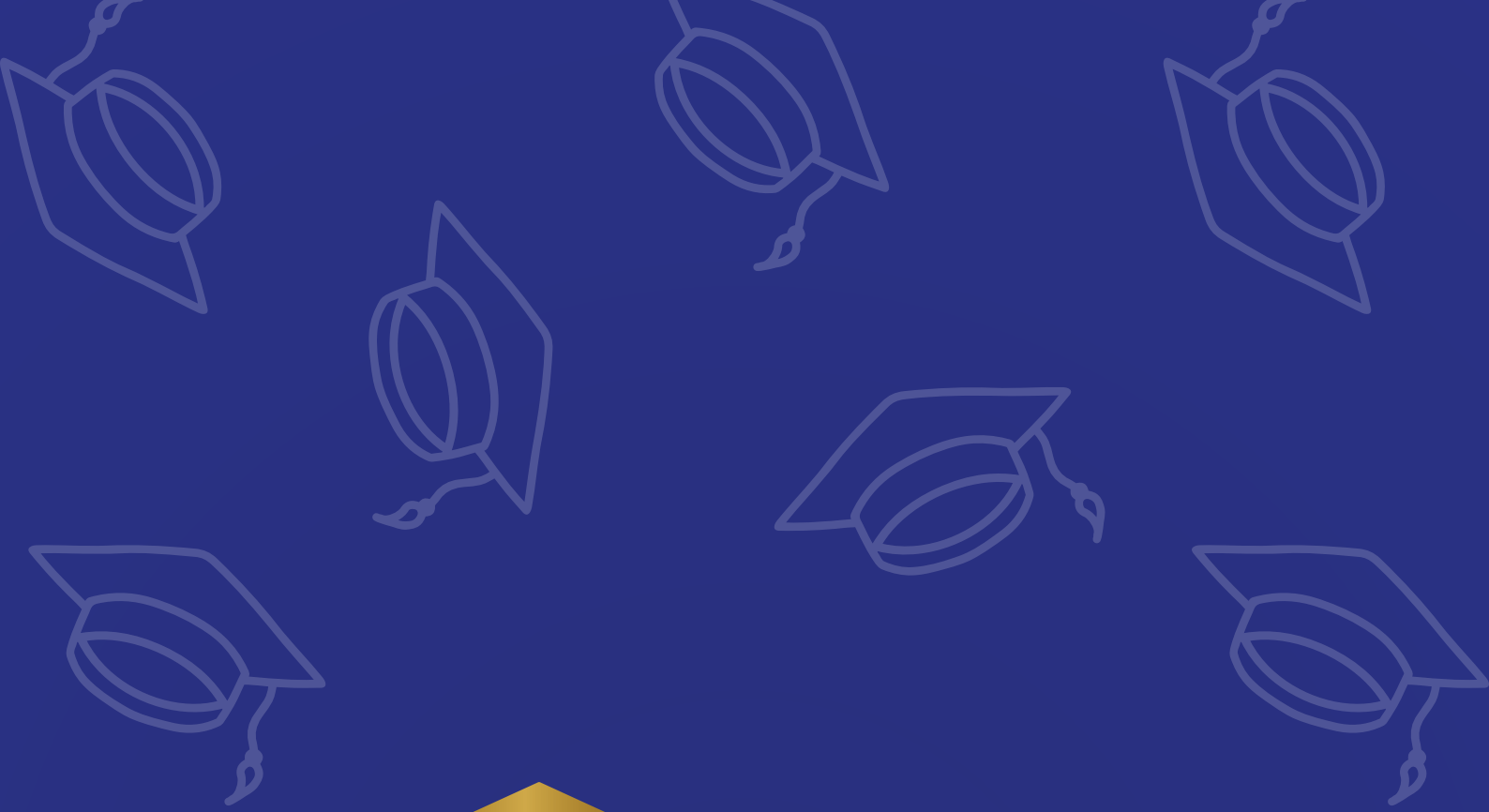
Past Papers

1. Which one of the following protein activates lipoprotein lipase?
   A. Apolipoprotein A-I
   B. Apolipoprotein B-48
   C. Apolipoprotein C-II
   D. Cholesteryl ester transfer protein

2. something true about lipoproteins:
   A. chylomicron has the lowest apolipoprotein percentage
   B. chylomicron has the lowest TAG
   C. HDL has the lowest apolipoprotein percentage
   D. All of the Above

3. Apo-B100 is found only by itself in:
   A. LDL
   B. HDL
   C. IDL
   D. Chylomicron
   E. All of the Above

4. Lisophosphatidyl choline is produced from lecithin by the action of
   A. Phospholipase D
   B. Phospholipase C
   C. Phospholipase A2
   D. Phospholipase B
   E. Lysophospholipase



ARKAN

ACADEMY

علم في كل مكان

Arkan academy

Arkanacademy

www.arkan-academy.com

+962 790408805