# METABOLISM

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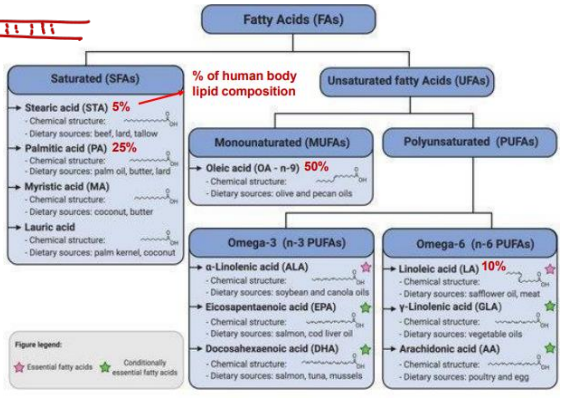
ARKAN ACADEMY

# 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 (*↓ Tm, ↑ 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 (FFAs)*** 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

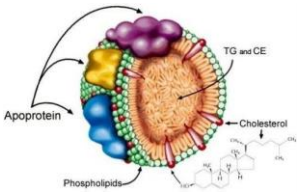
### C. *Cholesterol esterase* breaks cholesterol ester into cholesterol and FFA

- 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*

$HCO_3^-$

- 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

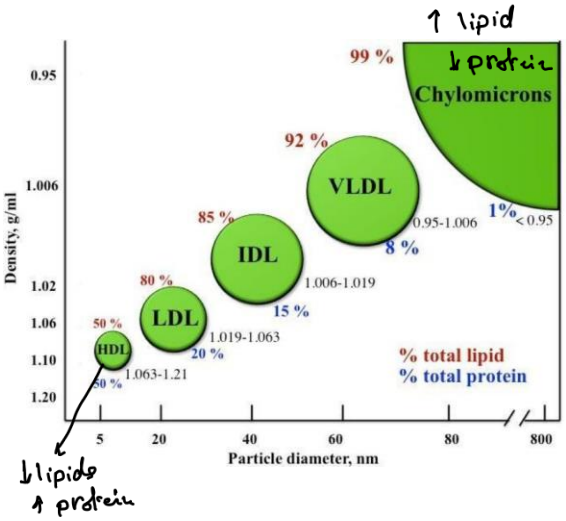
- ***Microsomal Triglyceride Transfer Protein (MTTP)*** is a protein in the SER responsible for the *assembly of chylomicrons* from lipids and apolipoproteins
  - ✓ LCFAs enter the SER by Fatty acid binding protein 2 (*FABP2*)




- Lipoproteins consist of lipids and apolipoproteins (Protein)
  - 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 | IDL | 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<br>Liver | 10 | 6 |
| Cholesterol esters | 3 | 18 | 50<br>(bad) | 40<br>(good) |
| Apolipoproteins | A, C, E, **B48** | C, **B100**, E | E | 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) |



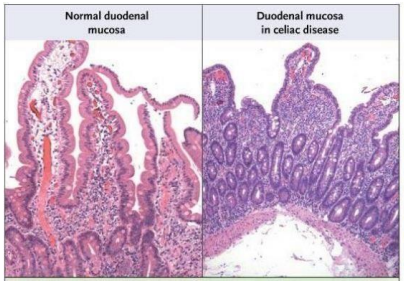

- Apolipoprotein B48 (chylomicrons) and B100 (VLDL) are produced from the same gene in different tissues, due to the presence of *cytidine deaminase* in the intestine concerting C to U producing a stop codon UAA which produces a shorter polypeptide chain
- *HDL is the good cholesterol* because it transports 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

- *LCFAs* 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

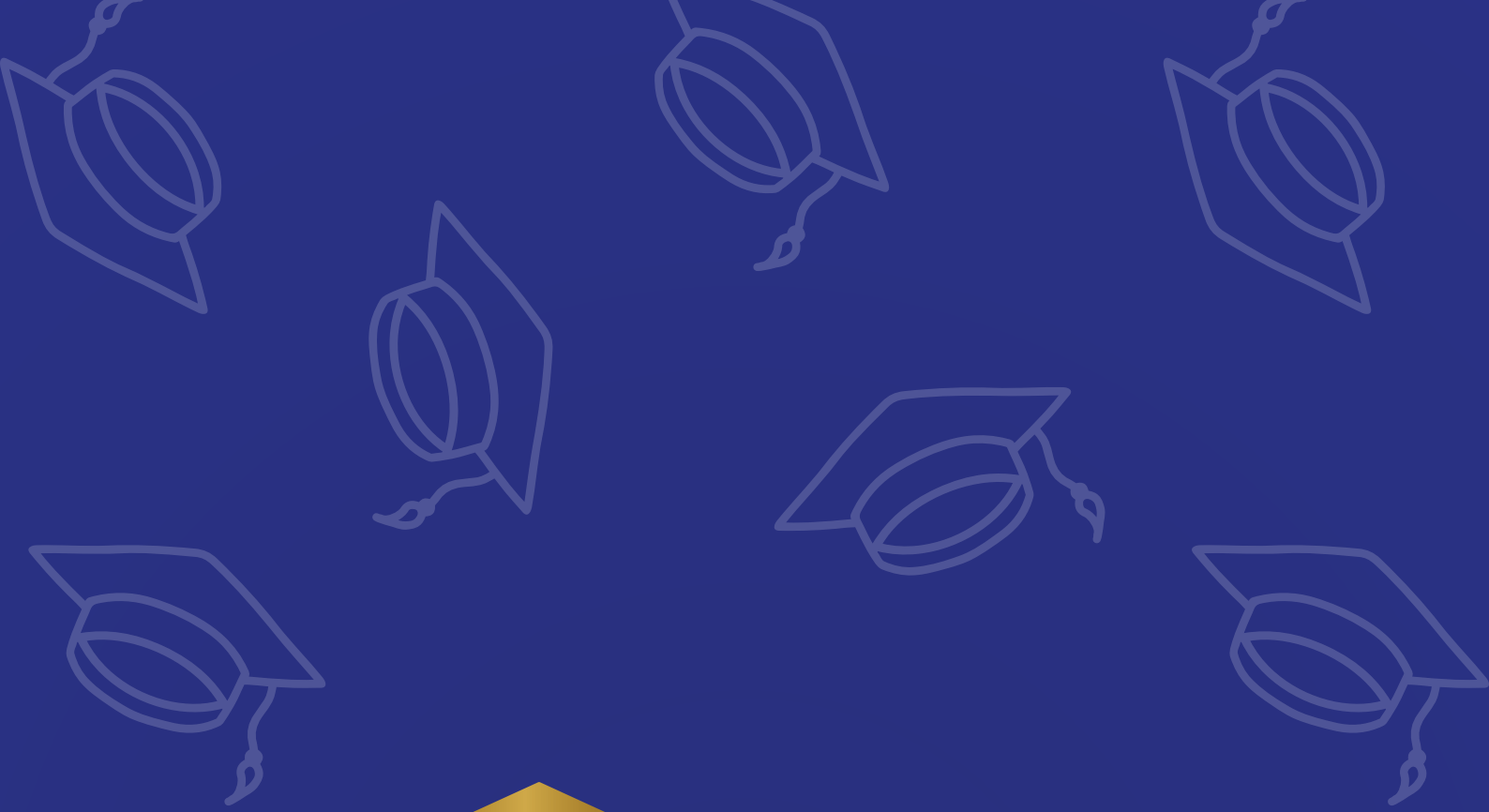
# Past Papers

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



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