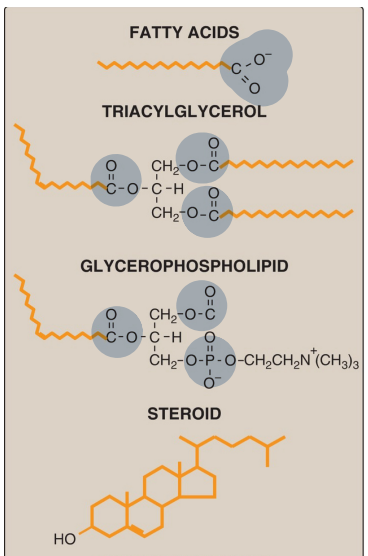
Lipid metabolism

بس نتعرف على أشكالهم :



Lipid metabolism

- Lipids are water-insoluble organic molecules that can be extracted from tissues by nonpolar solvents
- Present as membrane associated (1), lipoproteins (2) (transport) in blood or droplets of triglycerides in adipose tissues (3) (storage)
- They are the major source of energy (lipids)
  - واحنا طايبين لما ناكل تكون carbs glycolysis
- Responsible for dissolving fat-soluble vitamins (AKED) which have regulatory or coenzyme functions in the body
- Prostaglandins (made of lipids) and steroid hormones play role in body's homeostasis

A = eyes
K = blood coagulation
E = strong anti-oxidant activity
D = bones

Free fatty acids ↓

stomach duodenum

Lipid digestion / Emulsification

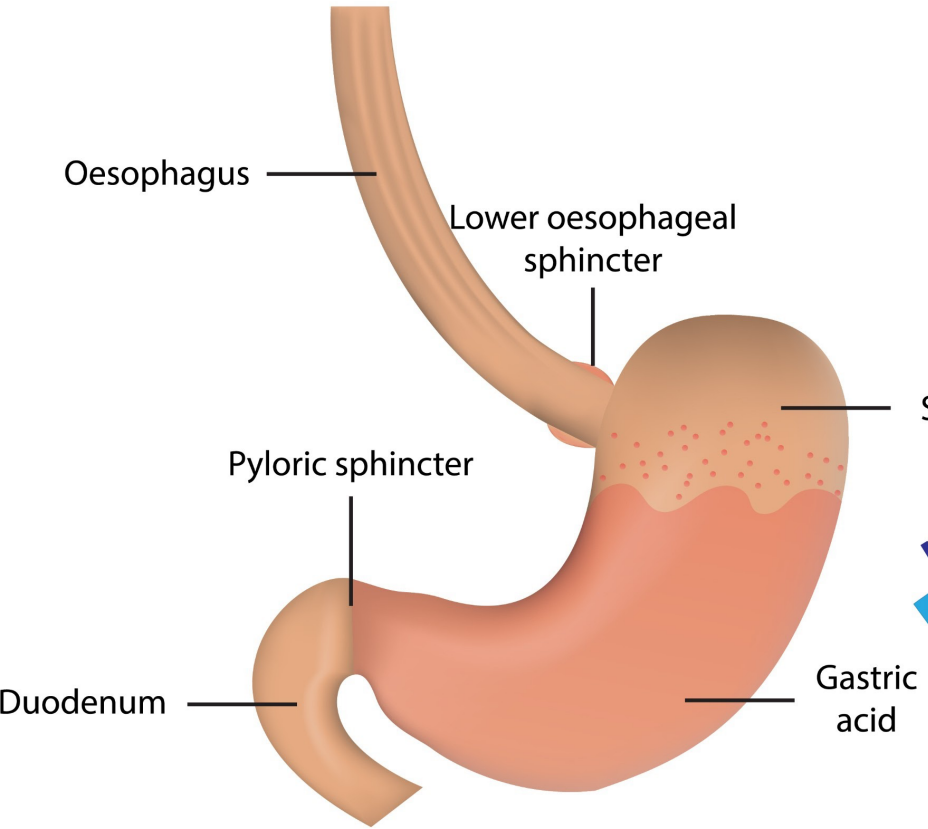
(stable mixture of lipids)

- An adult ingest 60-90 g of fat /day, 90% as triglycerides and the rest as cholesterol, phospholipids and free fatty acids. 10%
- Digestion starts in stomach by lingual lipase and gastric lipase
  - acid stable
  - bc carbs digestion start in mouth
- Triglycerides of short and medium chain length fatty acids (<12C) are the target of these enzymes.
  - طيب لو كانت أعلى من 12C نستخدم pancreatic lipase
- The enzymes are important in neonates (new borns) to digest fat in milk and for people with cystic fibrosis (no pancreatic lipase)

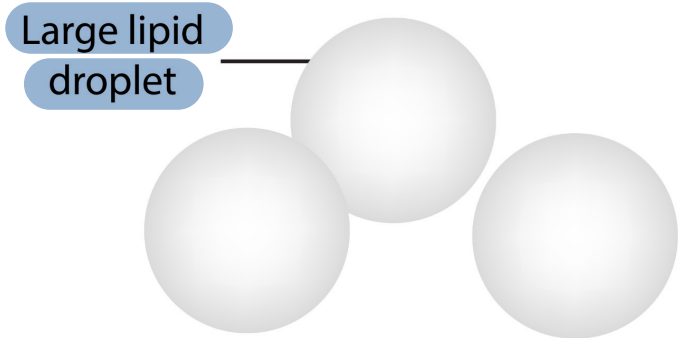
> In **Cystic Fibrosis**, thick mucus blocks the pancreatic duct, meaning no pancreatic enzymes reach the gut. In these patients, the stomach lipases are the only thing keeping them from starving, as they are the only enzymes left to break down any fat at all. +2

- Emulsification of dietary lipid occurs in duodenum in presence of bile salts and perstalsis which will increase the surface area of digestion
  - act like soap
  - physical squeezing
- Bile salts are produced in liver and stored in gallbladder (physiology)

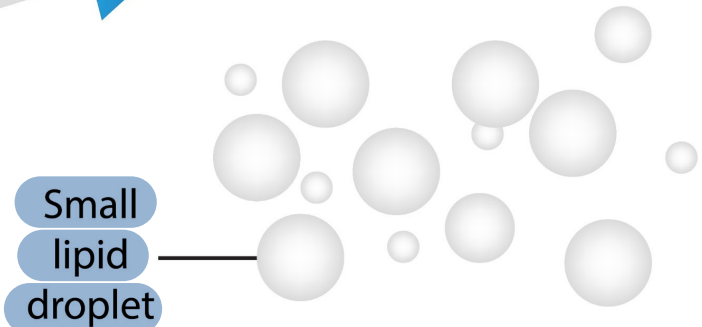
Digestion of Lipids



Lipase



Lipase breaks down big lipid droplets to smaller lipid droplets



Degradation by pancreatic enzymes

- **Triacylglycerol degradation:**
- Degraded by pancreatic lipase to 2-monoacylglycerol and free fatty acids

> · **The Enzyme Action: Pancreatic lipase** is a specific hydrolase. It doesn't just break the fat into pieces; it specifically chops off the fatty acids at **positions 1 and 3** of the glycerol backbone.

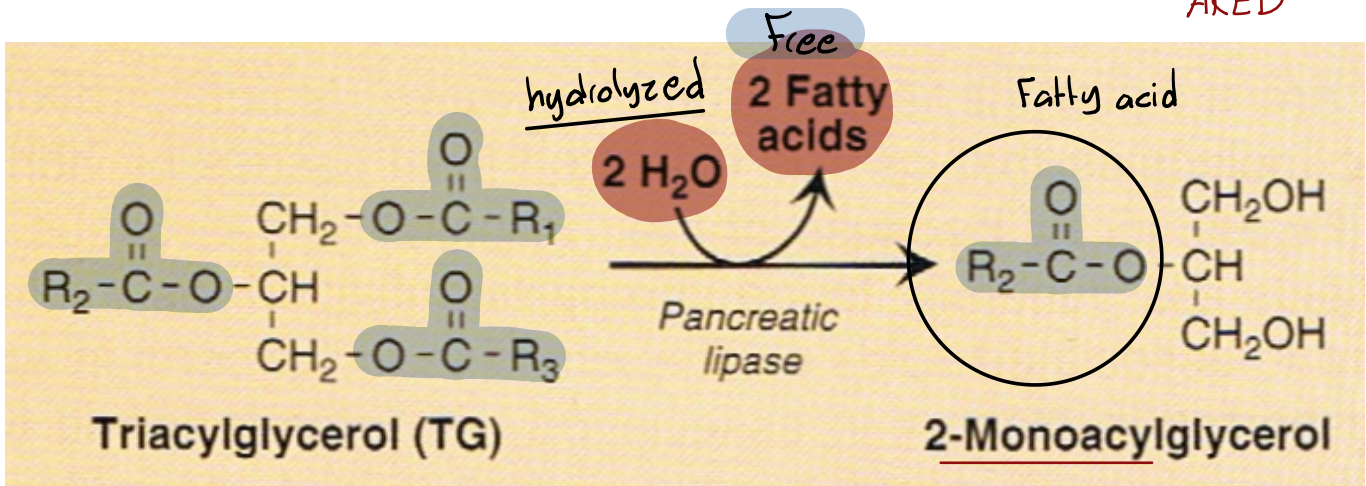
حكي الدكتورة

- Colipase (activated by trypsin) binds to the lipase in ratio 1:1 and anchors it to the lipid-aqueous interface

- Orlistat (antiobesity drug) inhibits gastric and pancreatic lipase and so decrease the absorption of fat (also the fat soluble vitamins)

تستخدم لفترات قصيرة

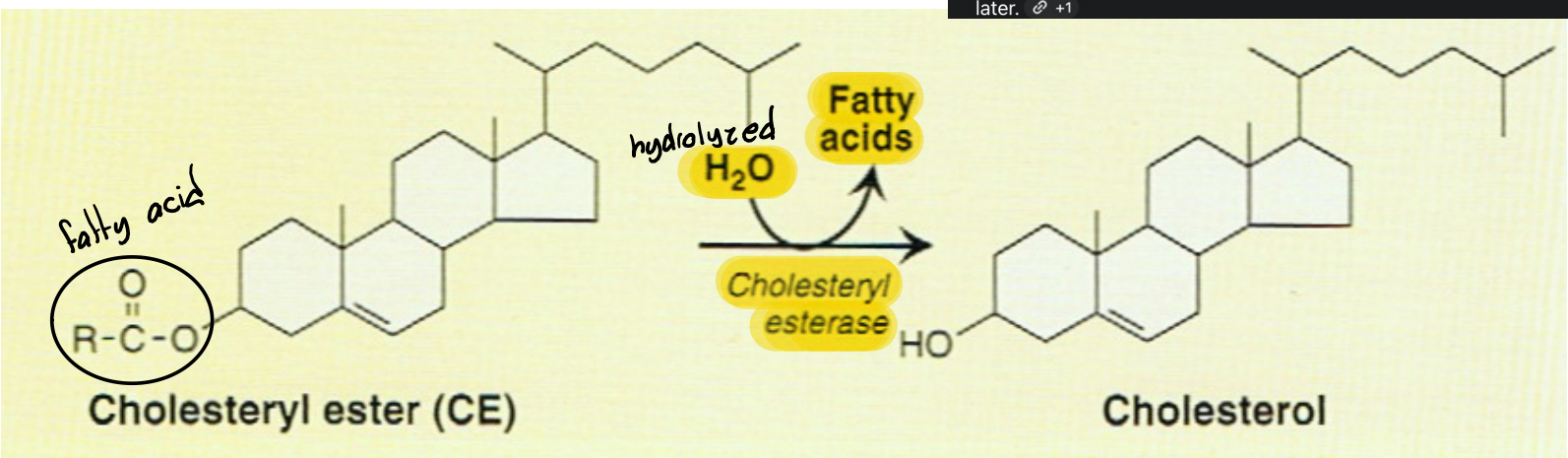
AKED



Degradation by pancreatic enzymes

- **Cholesteryl ester degradation:**
- 10-15% of cholesterol is present in esterified form (Not free)
- It is hydrolyzed by pancreatic cholesterol esterase to cholesterol and free fatty acids
- The activity of the enzyme is increased in the presence of bile salt

> • Explanation: The enzyme **Cholesteryl Esterase** performs a hydrolysis reaction. It adds a water molecule (H_2O) to break the bond between the cholesterol and the fatty acid. This produces two separate pieces: **Free Cholesterol** and one **Free Fatty Acid**. Both of these are now small enough to be processed for absorption later. +1



Degradation by pancreatic enzymes

phospholipid $\xrightarrow[\text{phospholipase A2}]{\text{bile salt}}$ lysophospholipid

- **Phospholipid degradation (like phosphotidylcholine):**

  • The Mechanism: This enzyme specifically targets the fatty acid attached to **Carbon #2** of the phospholipid.

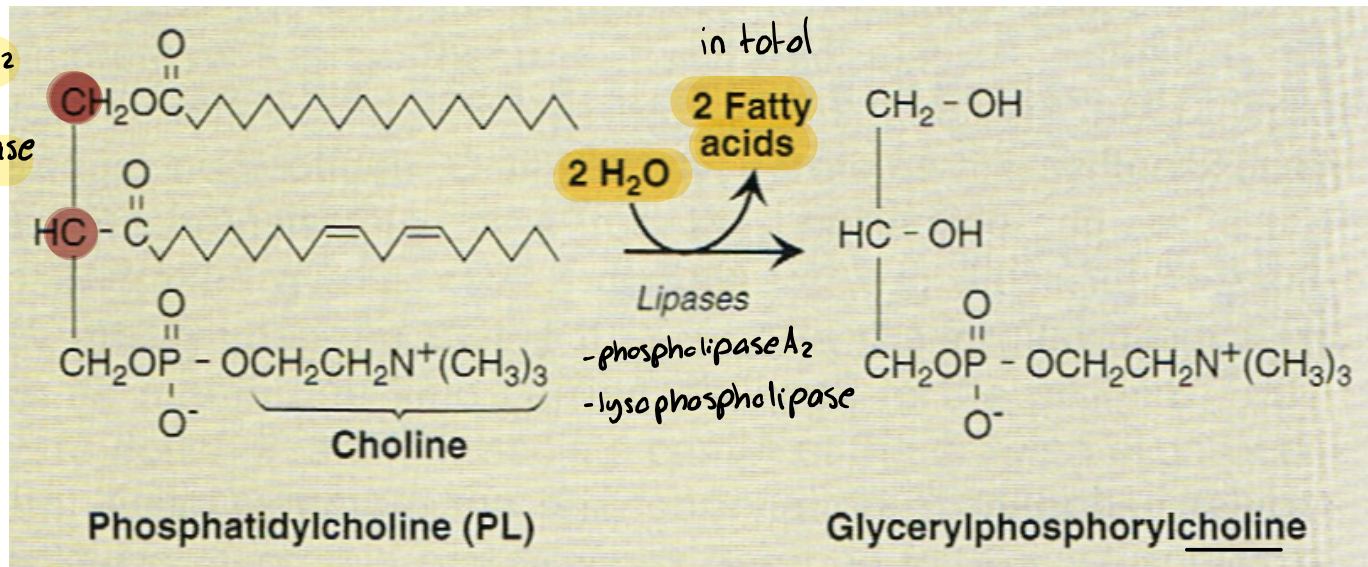
  like pancreatic esterase

- Degraded by **phospholipase A2** in presence of bile salts by removal of one fatty acid from C2 of PL to form lysophospholipid

- Lysophospholipid is hydrolyzed by **lysophospholipase** leaving free fatty acid and glyceryl phosphoryl base that can be excreted in feces, further degraded or absorbed

carbon 2 & phospholipase A_2

carbon 1 & lysophospholipase



could be
- reabsorbed
- excretion
- further degradation

Lipid Type	Key Enzymes	Requirements / Activators	Byproducts (What is cut off)	Final Product (What stays)
Triglyceride	Pancreatic Lipase	Activated by trypsin Colipase (the anchor) and Bile Salts	2 Free Fatty Acids (from positions 1 & 3)	2-Monoacylglycerol (Glycerol + 1 fatty acid)
Cholesterol Ester	Cholesterol Esterase	Bile Salts (required for activity)	1 Free Fatty Acid	Free Cholesterol
Phospholipid	Phospholipase A2 & Lysophospholipase	Trypsin (to activate the enzymes)	2 Free Fatty Acids (one at a time)	Glycerylphosphoryl base (e.g., Glycerylphosphorylcholine)

Control of lipid digestion

- It is hormonally controlled (CCK / secretin)
- (1) Cholicystokinin (CCK) which is secreted from the mucosa of jejunum and lower duodenum and acts on:
  - Gallbladder to release bile (gallbladder)
  - Pancreas to release pancreatic enzymes (pancreas)
  - Decrease gastric motility and so decrease gastric emptying (stomach)

    hey, slow down!!
- (2) Secretin which is secreted by other intestinal cells in response to the lower pH of the chyme (- Food -) cause pancreas and liver to release bicarbonate which will neutralize the pH making it optimum for the pancreatic enzymes to work

Absorption of lipids by intestinal mucosal cells (Enterocytes)

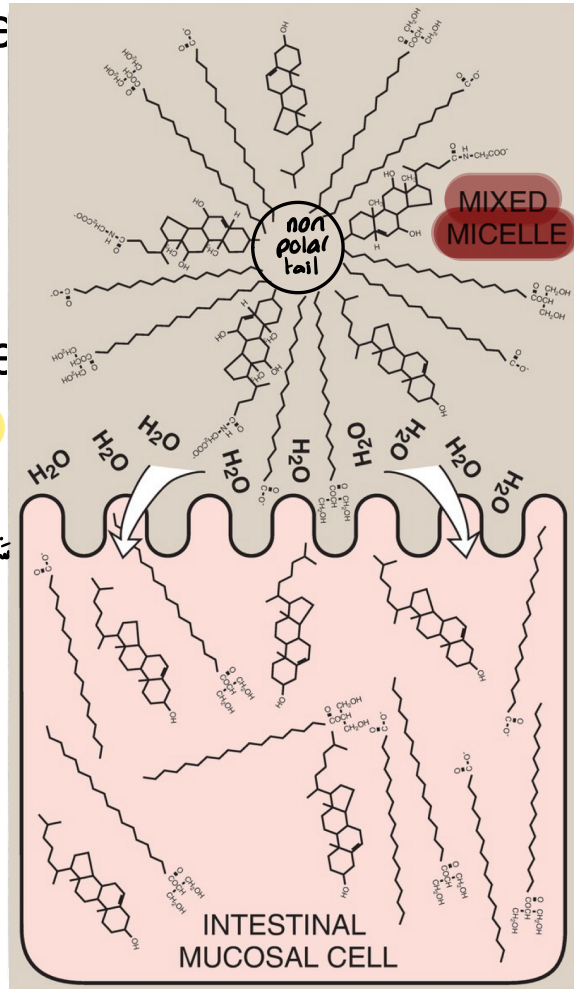
- The degradation products of lipids together with bile salts form mixed micelle (hydrophobic inside and hydrophilic outside) (long chains)

لتنتقل في watery environment

- The hydrophilic surface facilitate the transport of the hydrophobic lipids through the unstirred water layer (ثابت) to the brush boarder membrane where they are absorbed. The micelle itself is not absorbed.

(شوية polar) ليمر من الـ membrance for solubility

- Formation of mixed micelles is not required for the absorption of short and medium chain length fatty acids long chains need micelles



Passive Diffusion:

- **The Mechanism:** When the micelle touches the **brush border membrane** (the microvilli of the intestinal cell), the lipids simply "jump" out of the micelle and dissolve into the cell membrane.
- **Passive:** This doesn't require energy (ATP). It happens because the concentration of lipids is higher in the gut than inside the cell.
- **The Exception: Bile Salts** do not enter the cell here. They stay in the gut to be recycled later [redacted]

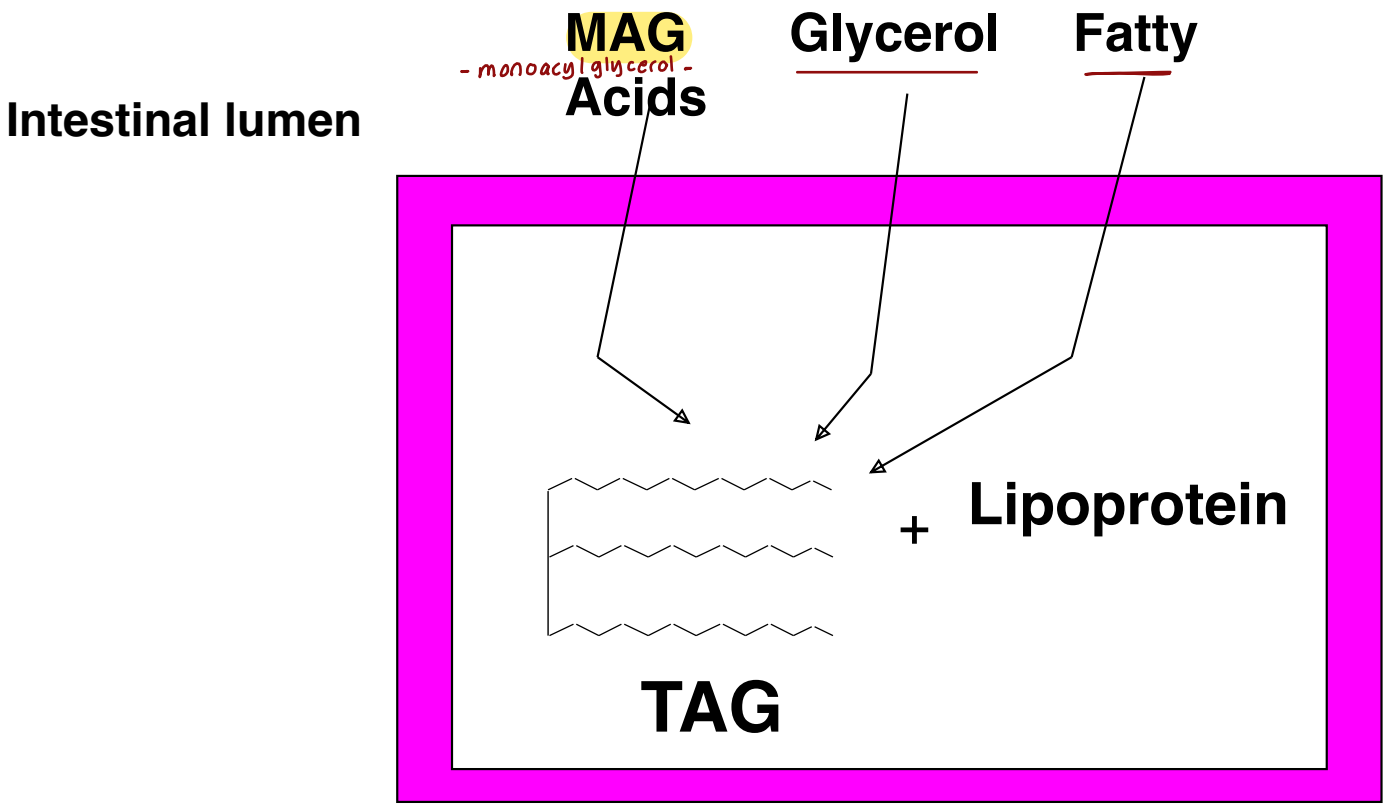
Absorption of lipids by intestinal mucosal cells

- In enterocytes triacylglycerol and cholesteryl esters are resynthesized

carbon 1,3 على fatty acids بدنا نرجع نحط

- Short and medium chain length fatty acids are not converted to their CoA derivatives but released into portal circulation and carried by serum albumin to the liver to be metabolized.

Just long chains get converted



phospholipids

chylomicron

Free cholesterol

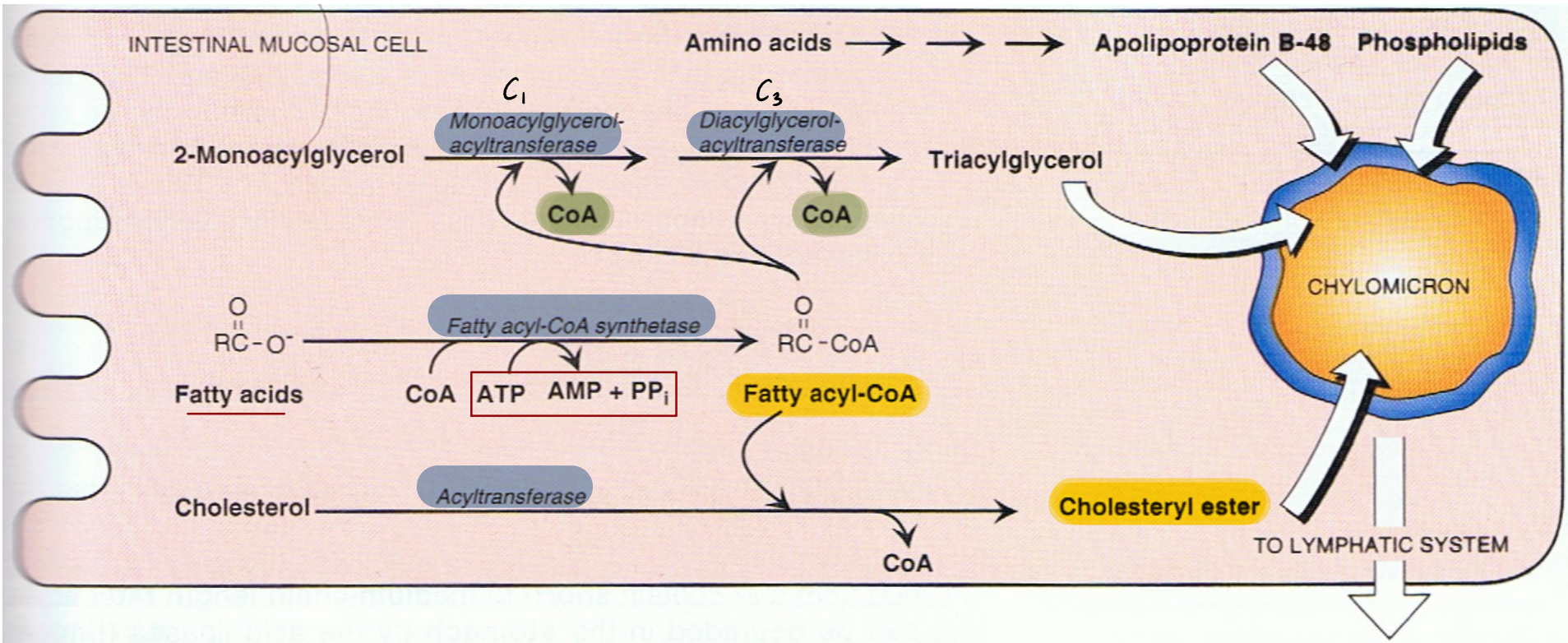
triacylglycerol
cholesterol ester

Apolipoprotein B-48

Secretion of lipids from enterocytes

- Phospholipids, unesterified cholesterol, and (apolipoprotein B-48) are at the outer layer and triacylglycerol and cholesterol ester form chylomicrons. And this is released to the chyle (milky appearance)

- This is released to blood



Component	Requires Activation?	Final Form in Cell	Exit Route
Long-Chain FA	Yes (to Fatty Acyl CoA)	TAG, PL, or CE	Lymph (via Chylomicrons)
Short-Chain FA	No	Stays as Free FA	Blood (via Albumin)

serum

portal circulation

سوء امتصاص

Lipid malabsorption (Steatorrhea)

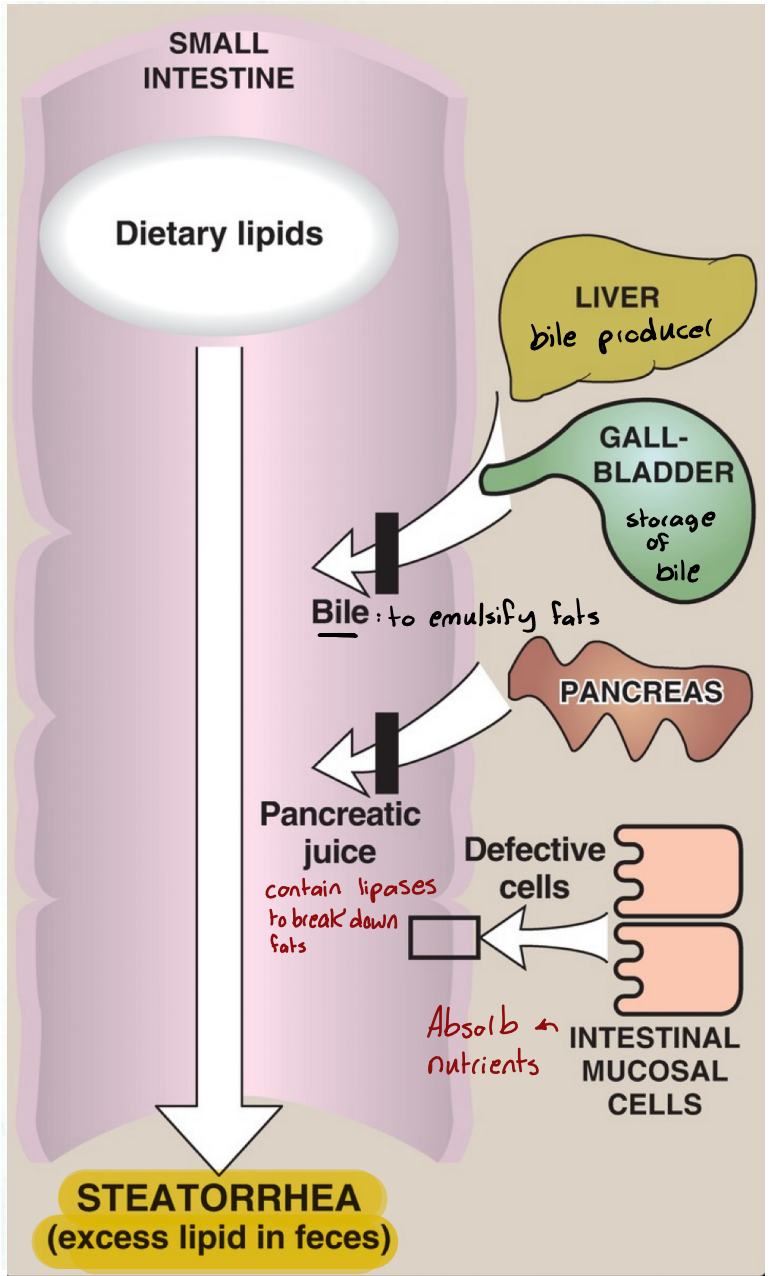
Cystic fibrosis — No pancreatic juice

Shortened bowl — low surface area for absorption

Both causes decrease in absorption of lipids (including fat soluble vitamins and essential fatty acids) leading to increase in lipids in feces (Steatorrhea)

B. Cystic fibrosis

CF is the most common lethal genetic disease in Caucasians of Northern European ancestry and has a prevalence of ~1:3,300 births in the United States. CF is an autosomal-recessive disorder caused by mutations to the gene for the CF transmembrane conductance regulator (CFTR) protein that functions as a chloride channel on epithelium in the pancreas, lungs, testes, and sweat glands. Defective CFTR results in decreased secretion of chloride and increased uptake of sodium and water. In the pancreas, the depletion of water on the cell surface results in thickened mucus that clogs the pancreatic ducts, preventing pancreatic enzymes from reaching the intestine, thereby leading to pancreatic insufficiency. Treatment includes replacement of these enzymes and supplementation with fat-soluble vitamins. [Note: CF also causes chronic lung infections with progressive pulmonary disease and male infertility.]



Use in tissue

main form of stored fats

- Triacylglycerol is broken down primarily in the capillaries of skeletal muscle, adipose tissues, heart, lung, kidney, and liver.

immediate energy storage

- Triacylglycerol in chylomicrons is degraded to free fatty acids and glycerol by lipoprotein lipase. This enzyme is synthesized primarily by adipocytes and muscle cells.

pathophysiology

- Familial lipoprotein lipase deficiency (type I hyperlipoproteinemia) is a rare, autosomal recessive disorder that results from a deficiency of lipoprotein lipase or its coenzyme, apo C-II. The result is massive chylomicronemia.

Type		
Familial lipoprotein lipase deficiency (hyperchylomicronemia, hypertriglyceridemia)	TG++, C normal	CM++, HDL–/normal

Now that the **lipoprotein lipase** has broken down the triacylglycerols in the blood, we look at where those components actually go.

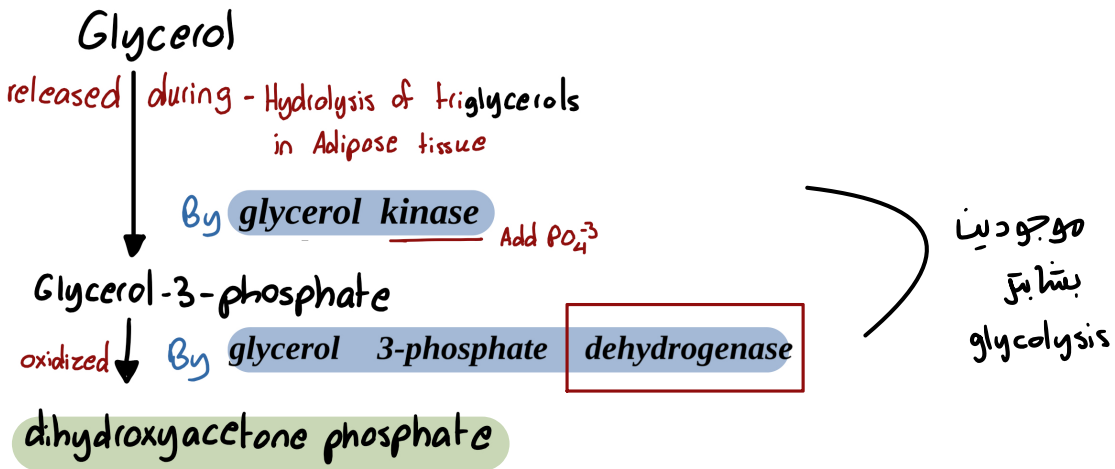
Fate of free fatty acids

- The free fatty acids derived from the hydrolysis of triacylglycerol may directly enter adjacent muscle cells or adipocytes
- The free fatty acids may be transported in the blood in association with serum albumin until they are taken up by cells.

  short chains fatty acids
- Most cells can oxidize fatty acids to produce energy
- Adipocytes can also reesterify free fatty acids to produce triacylglycerol molecules, which are stored until the fatty acids are needed by the body.

Fate of glycerol

- فقط By liver Glycerol that is released from triacylglycerol used almost exclusively by the liver to produce glycerol 3-phosphate, which can enter either glycolysis or gluconeogenesis by oxidation to dihydroxyacetone phosphate (DHAP)



(gastric enzymes)

Enzyme	Source	Action/Function	Specific Notes
Lingual Lipase	Mouth/Stomach	Breaks down TGs with short/ medium-chain fatty acids.	For the two enzymes: Vital for infants ([redacted] digest fat in milk
Gastric Lipase	Stomach	Breaks down TGs with short/ medium-chain fatty acids.	Crucial backup for Cystic Fibrosis patients. (lack pancreatic lipase)

Enzyme (pancreatic enzymes)	Target	Action/Function	Specific Notes
Pancreatic Lipase	Triglycerides (Long-chain) (12C >>>)	Removes fatty acids from positions 1 and 3. (TGs → 2-MAG)	Produces 2-Monoacylglycerol + 2 FFAs.
Colipase	Lipase Anchor	Not an enzyme itself, but a protein that "docks" lipase to the fat.	Must be activated by Trypsin; 1:1 ratio with lipase.
Cholesterol Esterase	Cholesteryl Esters	Removes the fatty acid from cholesterol.	Activity is strictly increased by bile salts.
Phospholipase A2	Phospholipids	Removes the fatty acid from position 2. (C2 of PL)	presence of bile salts [redacted] produces Lysophospholipid.
Lysophospholipase	Lysophospholipids	Removes the remaining fatty acid from position 1. (C1 of PL)	Leaves a water-soluble glycerylphosphoryl base.

Enzyme	Action/Function	Specific Notes
Fatty acyl CoA synthetase (Thiokinase)	Attaches CoA to long-chain fatty acids.	"Activates" the fatty acid so it can be re-attached to glycerol.
Acyltransferases (Family)	Re-attaches fatty acids to 2-MAG, Lysophospholipids, or Cholesterol.	The "Assembly Line" that recreates TAG, PL, and CE.

Enzyme	Source	Action/Function	Specific Notes
Lipoprotein Lipase (LPL)	Adipocytes & Muscle cells	Degrades TGs inside chylomicrons into FFAs and glycerol.	Requires Apo C-II as a coenzyme.

BIOCHEMISTRY EXAMINATION BANK

Module: Lipid Metabolism & Digestive Biochemistry

Question 1: Stomach Lipases

Which of the following statements regarding the digestion of lipids in the stomach is CORRECT?

A) Lingual and gastric lipases are denatured by the high acidity of the stomach.

B) The primary targets of gastric lipases are triglycerides containing long-chain fatty acids.

C) Stomach lipases are especially critical for lipid digestion in neonates and patients with cystic fibrosis.

D) Gastric lipase requires bile salts to be activated in the stomach.

> **Correct Answer: C**
>
> Rationale: These enzymes are acid-stable. In CF or neonates, they are primary drivers because pancreatic lipase is often deficient.

Question 2: Hormonal Regulation

Which statement about the hormonal control of digestion is INCORRECT?

A) CCK is released in response to the presence of lipids and partially digested proteins.

B) Secretin primarily acts by stimulating the gallbladder to contract and release bile.

C) CCK slows down gastric motility to facilitate processing time in the intestine.

D) Secretin is released in response to the low pH of chyme entering the duodenum.

> **Correct Answer: B**
>
> Rationale: CCK contracts the gallbladder. Secretin focuses on bicarbonate release from the pancreas to neutralize acid.

Question 3: Pancreatic Lipase Specificity

Regarding the action of Pancreatic Lipase, which of the following is CORRECT?

A) It removes all three fatty acids from a triglyceride to produce free glycerol.

B) The final products of its reaction are 2-monoacylglycerol and two free fatty acids.

D) It is secreted in its active form and does not require activation by trypsin.

> **Correct Answer: B**
>
> Rationale: It targets only positions 1 and 3 on the glycerol backbone, leaving the fatty acid at position 2 attached.

Question 4: Colipase Function

Which of the following describes the role of Colipase INCORRECTLY?

A) It is a protein secreted by the pancreas.

B) It is a digestive enzyme that hydrolyzes cholesteryl esters.

C) It binds to the lipase in a 1:1 ratio.

D) It is activated by trypsin in the intestinal lumen.

> **Correct Answer: B**
>
> Rationale: Colipase is an anchor protein, not an enzyme. It allows lipase to access the fat droplet surface.

Question 5: Cholesterol Digestion

Which statement about cholesterol digestion is CORRECT?

A) Most dietary cholesterol is already in the "free" form and needs no digestion.

B) Cholesterol esterase activity is strictly decreased by the presence of bile salts.

C) Cholesterol esterase breaks down cholesteryl esters into free cholesterol and one fatty acid.

D) Cholesterol esterase is secreted by the liver.

> **Correct Answer: C**
>
> Rationale: Esterase hydrolyzes the ester bond, releasing the single fatty acid and free cholesterol.

Question 6: Phospholipids

Which of the following is INCORRECT regarding phospholipid degradation?

A) Phospholipase A2 removes the fatty acid at position 2.

B) The final product is a water-soluble glycerylphosphoryl base.

C) Lysophospholipase removes the fatty acid at position 1.

D) Phospholipase A2 is activated by Cholecystokinin (CCK).

> **Correct Answer: D**
>
> Rationale: Phospholipase A2 is activated by the protease trypsin in the duodenum.

Question 7: Micelle Physiology

What is the primary function of Mixed Micelles?

A) To transport long-chain fatty acids from blood to liver.

B) To package lipids for secretion into lymph.

C) To facilitate transport through the unstirred water layer of the gut.

D) To act as storage in adipose tissue.

> **Correct Answer: C**
>
> Rationale: Micelles shuttle hydrophobic lipids across the aqueous environment to the cell membrane.

Question 8: Chain Length Exceptions

Which fatty acid bypasses the need for mixed micelles and chylomicrons?

A) Stearic acid (18C)

B) Oleic acid (18C)

C) Capric acid (10C)

D) Palmitic acid (16C)

> **Correct Answer: C**
>
> Rationale: Medium-chain FAs (<12C) are water-soluble enough to enter the portal blood directly.

Question 9: Intracellular Synthesis

Regarding the resynthesis of lipids in the enterocyte, which statement is CORRECT?

A) FAs are re-attached without an activation step.

B) Thiokinase is only active on short-chain fatty acids.

C) Synthesis occurs in the Smooth Endoplasmic Reticulum (SER).

D) 2-MAG is broken into glycerol before rebuilding.

> **Correct Answer: C**
>
> Rationale: The Smooth ER is the site of complex lipid assembly in the intestinal cell.

Question 10: Enzymatic Matches

Which enzyme is correctly matched with its product?

A) Pancreatic Lipase : Free Glycerol

B) Phospholipase A2 : Lysophospholipid

C) Cholesterol Esterase : 2-monoacylglycerol

D) Thiokinase : Chylomicrons

> **Correct Answer: B**
>
> Rationale: Phospholipase A2 leaves a 'lyso' (broken) phospholipid after removing one tail.

Question 11: Transport Routes

Chylomicrons exit the enterocyte via which route?

A) Portal vein directly to the liver.

B) Lymphatic vessels (lacteals) to the thoracic duct.

C) Capillaries to the systemic blood.

D) Biliary tract back to the gut.

> **Correct Answer: B**
>
> Rationale: Chylomicrons are too large for capillaries and must enter the lymph system first.

Question 12: Pathology

What is the clinical hallmark of lipid malabsorption (Steatorrhea)?

A) Blood in the stool.

B) Excessive lipids in the feces.

C) High serum chylomicrons.

D) Reduced pancreatic bicarbonate.

> **Correct Answer: B**
>
> Rationale: Failure to digest or absorb fat leads to its excretion in feces.

Question 13: Capillary Processing

Which enzyme clears triglycerides from chylomicrons in the blood?

A) Hormone-sensitive lipase.

B) Lipoprotein Lipase (LPL).

C) Pancreatic lipase.

D) Hepatic lipase.

> **Correct Answer: B**
>
> Rationale: LPL is anchored to capillary walls to hydrolyze TG in lipoproteins.

Question 14: LPL Activation

LPL requires which apolipoprotein for activation?

A) Apo B-48

B) Apo C-II

C) Apo E

D) Apo A-I

> **Correct Answer: B**
>
> Rationale: Apo C-II is the essential co-enzyme for lipoprotein lipase activity.

Question 15: Type I Hyperlipoproteinemia

A deficiency in LPL results in which primary symptom?

A) Low blood triglycerides.

B) Fasting chylomicronemia.

C) Lack of bile salts.

D) Intestinal blockage.

> **Correct Answer: B**
>
> Rationale: Without LPL, chylomicrons cannot be cleared and accumulate massively.

Question 16: Orlistat Mechanism

Orlistat is a weight-loss drug that works by:

A) Speeding up metabolism.

B) Inhibiting gastric and pancreatic lipases.

C) Reducing appetite.

D) Binding to bile salts.

> **Correct Answer: B**
>
> Rationale: It prevents the digestion (and thus absorption) of dietary fats.

Question 17: Activation Enzyme

Which enzyme converts fatty acids into Fatty Acyl CoA in the SER?

A) Thiokinase.

B) Acyltransferase.

C) Lipase.

D) Kinase.

> **Correct Answer: A**
>
> Rationale: Thiokinase (Fatty acyl CoA synthetase) activates the FA for synthesis.

Question 18: Absorption Limits

Short-chain fatty acids are transported in blood bound to:

A) Chylomicrons.

B) Albumin.

C) VLDL.

D) HDL.

> **Correct Answer: B**
>
> Rationale: Small fatty acids enter the portal blood directly and hitch a ride on albumin.

Question 19: Chylomicron Structure

The core of a chylomicron is primarily composed of:

A) Phospholipids.

B) Triglycerides.

C) Free Cholesterol.

D) Apo B-48.

> **Correct Answer: B**
>
> Rationale: The hydrophobic core is packed with TGs and cholesteryl esters.

Question 20: Master Switch

Which enzyme activates both Colipase and Phospholipase A2?

A) CCK.

B) Secretin.

C) Trypsin.

D) Pepsin.

> **Correct Answer: C**
>
> Rationale: Trypsin is the protease that activates pancreatic pro-enzymes.