Biochemistry Team 435

جامعة الملك سعود
King Saud University 1957

BILE ACIDS AND SALTS.

* Please check out this link to know if there are any changes or additions.

Revised by
هشام الغفيلي & خولة العماري

Color index: Important | Doctors notes | Further explanation.

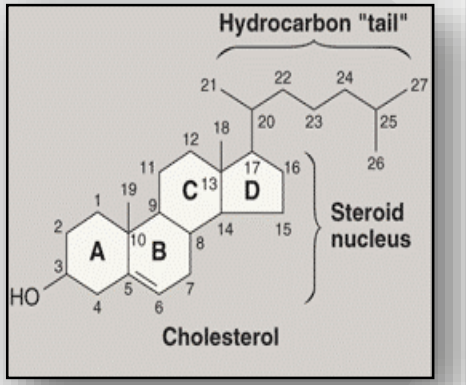
OBJECTIVES:

- ✓ Structure of primary bile acids and salts
- ✓ Structure of secondary bile acids and salts
- ✓ Functions of bile salts
- ✓ Enterohepatic circulation
- ✓ Malabsorption syndrome
- ✓ Cholelithiasis

Cholesterol:

- Cholesterol (27 C) is the:
  - **Parent steroid compound**.
  - Precursor of **bile acids** and **salts**.
- It has a **27-carbon structure**, which contains:
  1. Four fused hydrocarbon rings "Steroid nucleus".
  2. Hydroxyl group "attached to C3".
  3. Hydrocarbon tail "attached to C17".

What is bile? 1-bile is a watery solution 2-synthesized in the liver 3-heads to the intestines 4-but stored in the gallbladder.
What are the main components of bile?
1-phosphotidylcholine (the major component of bile !!!) 2-bile salts
3-cholesterol
Note that bile doesn't contain bile acids!



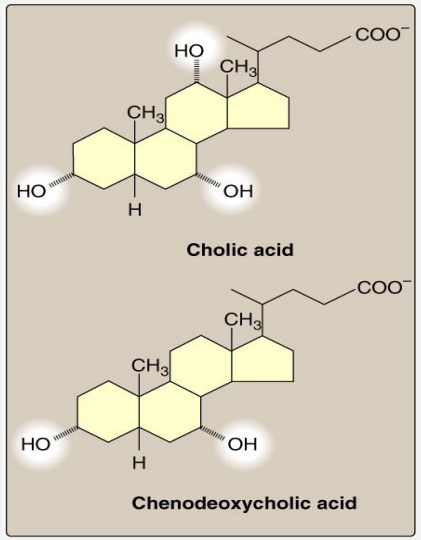
Note that cholesterol is a molecule that has a steroid nucleus with a hydrocarbon tail .This molecule is amphipathic but mostly hydrophobic because there is only **one hydroxyl group.**

PRIMARY BILE ACIDS

What are "Primary bile acids"?

- An **amphipathic** **24-carbon** structure <u>which contains:</u>
  - **COOH** at side chain.
  - **3 OH** as in **Cholic acid**. or
  - **2 OH** as in **Chenodeoxycholic**.

لتسهيل الحفظ: الكلمة فيها ٢ إي "اول حرف بعد السي والاتش" يعني ٢ كربوكسيل قروب

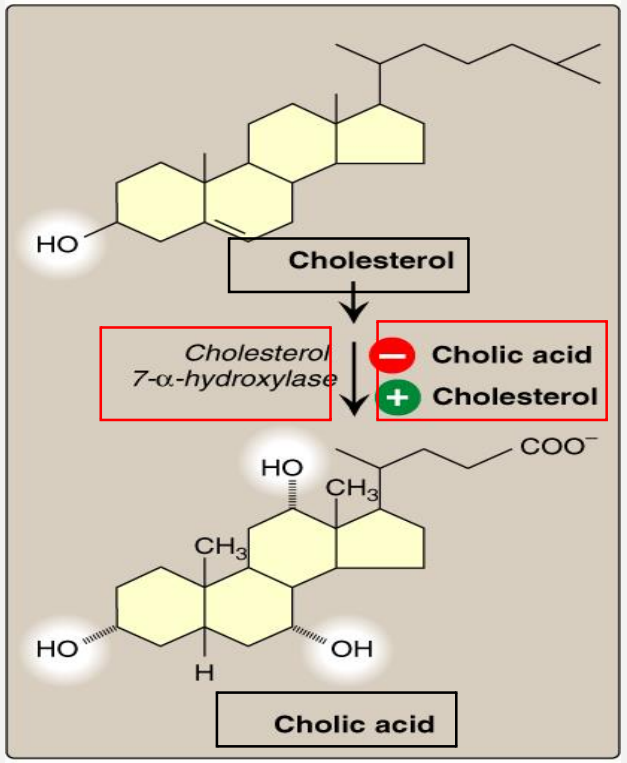


Note that the presence of more than one hydroxyl group with the presence of the carboxyl group makes these primary bile acids **more amphipathic than cholesterol!**

HEPATIC SYNTHESIS OF BILE ACIDS

تكوين البايل اسيدز يتم في الكبد خلال سلسة طويلة من التفاعلات.. التفاعل الوحيد اللي لازم نعرفه هو الرايت لمتنق ستب "اللي بالصورة".

Rate limiting step:		
Catalyzed by:	Cholesterol 7-α-hydroxylase Adds a hydroxyl group on position 7 of the steroid nucleus	
Substrate:	Cholesterol	
Product:	Bile acids: • **Cholic acid** or • **Chenodeoxycholic**.	
Regulation:	Down-regulated	by end products (**bile acids**). لو النواتج كثيرة بتسوي انهبشن للتفاعل "خلاص احنا كثار"
	Up-regulated	by **cholesterol** "Enzyme induction".



- The rate limiting step of bile acid synthesis is the HYDROXYLATION of carbon number SEVEN of cholesterol!
- This enzyme adds a hydroxyl group at carbon 7 so what you get is cholic acid or chenodeoxycholic acid
- **How is this enzyme regulated?**
  - It is down regulated by the end product (cholic acid or chenodeoxycholic acid)
  - It is up regulated by the substrate (cholesterol)
- So basically if you have a lot of cholesterol available ,you will form more of the bile acids by the work of the enzyme (cholesterol 7 alpha hydroxylase) .
- Note that bile acids DO NOT GET SECRETED IN THE BILE! They get converted into salts which are then secreted in the bile.

PRIMARY BILE ACIDS AND SALTS

BILE Acids		BILE SALTS
Cholic acid	Conjugation: Addition of glycine or taurine	Glycocholic, Taurocholic
Chenodeoxycholic acid	Conjugation: Addition of glycine or taurine	Glycochenodeoxycholic, Taurochenodeoxycholic

Bile salts (Conjugated bile acids):
amide-linked with **glycine** or **taurine**
The ratio of glycine to taurine forms in the bile is **3:1**

- ✓ Addition of **glycine** or **taurine** results in the presence of **fully ionized** "negatively charged" groups at **pH 7.0**: dr. Sumbul said that the pH should be 6
  - **Carboxyl group** (COO^-) of glycine &
  - **Sulfonate group** (SO_3^-) of taurine
- ✓ (hence, its name as bile salts e.g., **Sodium** or **potassium glycocholate**)

➢ Those conjugated, ionized bile salts are **more effective** detergent than bile acids "the unconjugated ones". Why? Because they have an extra sulphonate or an extra carboxyl group.

➢ **ONLY bile salts "اللي بالمربع الأحمر فوق", but NOT acids, found in bile.**

البايل وش فيه؟ 👇👇

Notes

- Cholic acid and chenodeoxycholic acid make salts with two other molecule one is glycine (amino acid) and the other is taurine (a product derived from amino acid cysteine).
- These two molecules are conjugated to bile acids (by amide linkage) to form bile salts.
  - Note that the amine linkage is between the carboxyl group (found in the bile acids) and the amino group(found in glycine and taurine).
- **The names of these salts are:** glycocholic acid or taurocholic acid or Glycochenodeoxycholic Taurochenodeoxycholic (depending upon the components obviously.)
- The majority of bile salts are derived from glycine (hence the ratio of bile salts composed of glycine versus those composed of taurine is 3:1).
- At PH of 6, bile salts are ionized → that is why we call the bile salts glycolate or taurocholate (because they are in the ionized form)
- The formed bile salts will interacts with ions such as sodium and potassium....etc → when this interaction occurs the bile acids are called sodium glycocholate ,sodium taurocholate, potassium taurocholate or potassium glycocholate.

EXTRA EXPLANATION " SUMMARIZED FROM LIPPINCOTT & BRS":

You can skip it if you understood what was written in last 2 slides

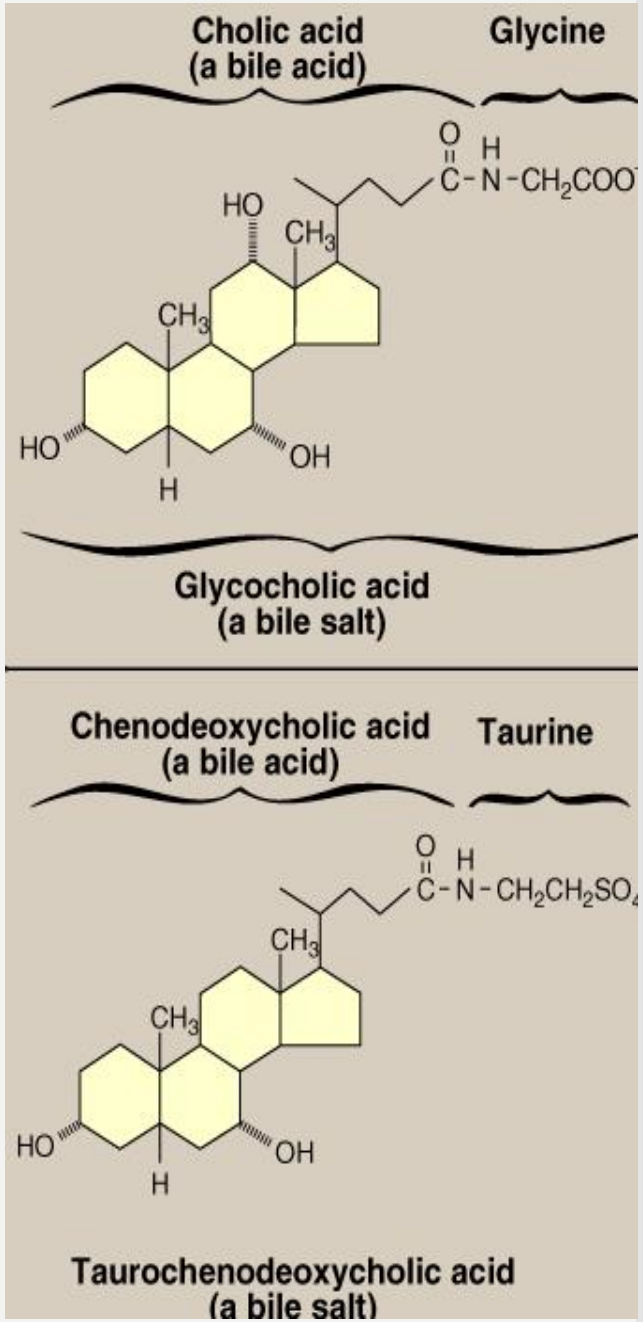
Before the acids leave the liver, they're *conjugated to a molecule of either glycine or taurine (end product of cysteine metabolism) by an **amide bond** between the carboxyl group of the bile acid and the amino group of the added compound.

These new structures include: Glycocholic and Glycochenodeoxycholic acids and Taurocholic and Taurochenodeoxycholic acids.

Addition of glycine or taurine results in the presence of carboxyl group with a lower Pka (from glycine) or a sulfonate group (from taurine), both of which are fully ionized "negatively charged" at the alkaline pH in the gut lumen and serve as a better detergent than the unconjugated ones because of their enhanced amphathic nature.

The conjugated, ionized bile salts are more effective detergents than the unconjugated because they're in the ionized form and can interact with ions such as Na or K. "

*A conjugate refers to a compound formed by the joining of two or more chemical compounds.



Functions of Bile Salts

Important for cholesterol excretion:

- As a metabolic products of cholesterol.
- As a solubilizer of cholesterol in bile.

We can conclude that bile salts are needed for BOTH the absorption and EXCRETION of cholesterol!! How do bile salts contribute the cholesterol excretion? If the cholesterol is not emulsified ,then it will NOT be excreted.

Emulsifying factors for dietary lipids

- Emulsification **increases** the surface area of lipid droplets, therefore the digestive enzymes can **effectively** act.
- **Mechanisms:** إعادة للكلام اللي تكلمنا عنه بمحاضرة اللبدز
  1. **Mechanical mixing by peristalsis**
  2. **Detergent effect of bile salts:**

Bile salts interact with lipid particles and aqueous duodenal contents, **stabilizing** the particles as they become smaller, and **preventing** them from coalescing.

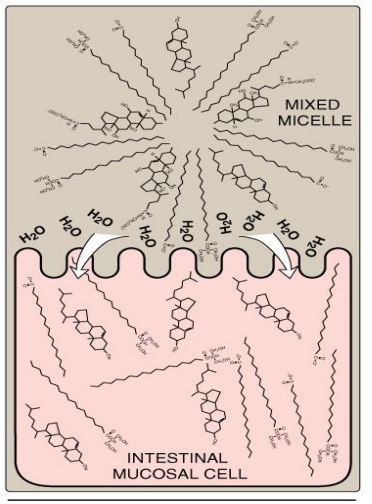
Cofactor for: **pancreatic lipase** and **PLA2**

Facilitate intestinal lipid absorption by **Mixed micelles:**

Mixed micelles: برضوا إعادة لكلام محاضرة اللبدز

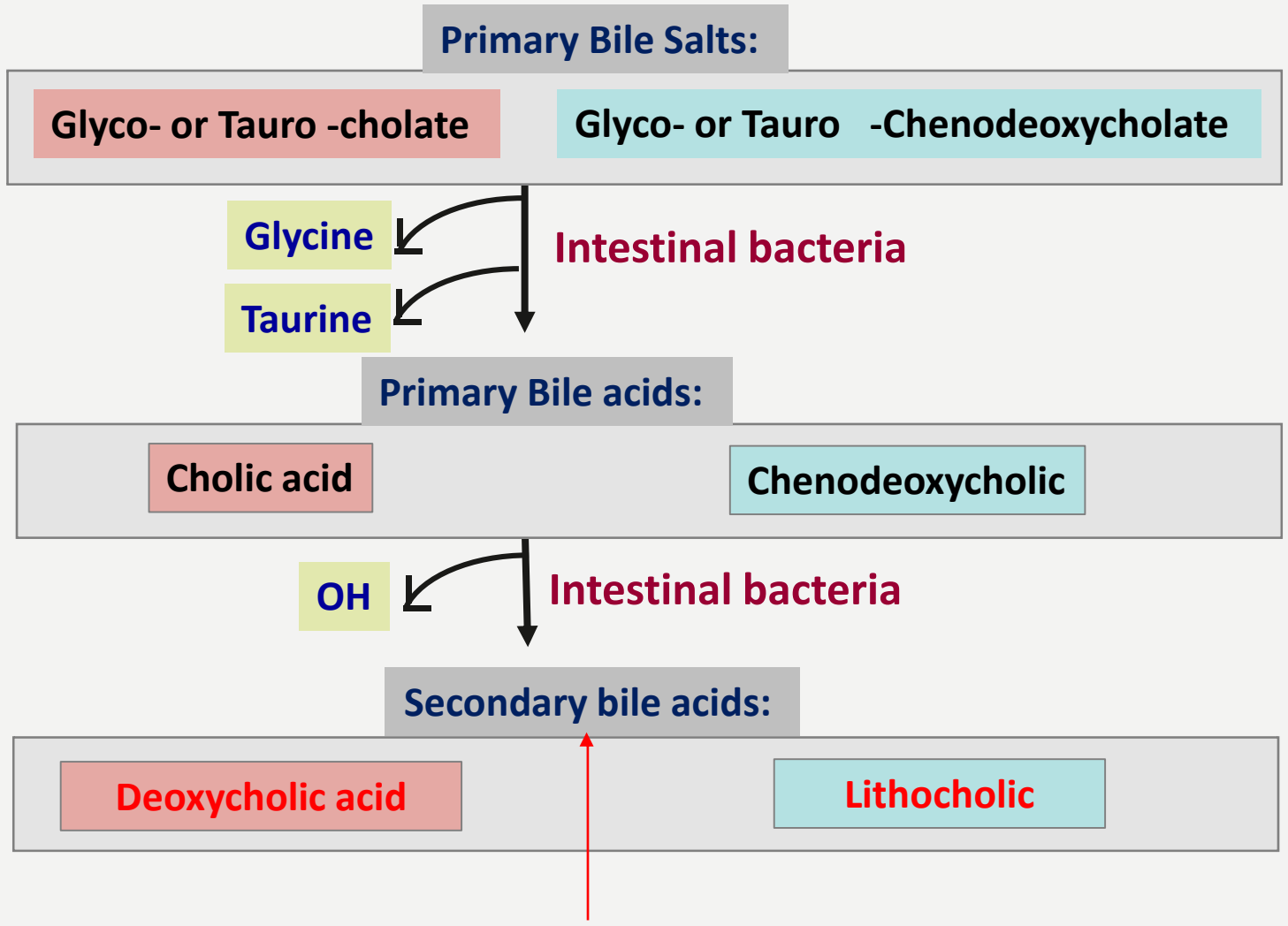
- **Disc-shaped** clusters of **amphipathic** lipids.
- **Arranged with:**
  - Their **hydrophobic** groups on **the inside**
  - Their **hydrophilic** groups on **the outside.**
- **Micelle includes:**
  - **end products of lipid digestion**, **bile salts** and **fat-soluble vitamins.**

Recall :what are the end products of lipid digestion?
2monoacylglycerol – TAG - cholesterol



Note: Short- and medium-chain fatty acids do not require mixed micelle for absorption by intestinal cells.

SECONDARY BILE ACIDS



احفظوا اسمائهم وكل واحد منهم من أي اسيد مشتق مو علشانهم ببوكس وحركات تسحبون عليهم ☺

- the liver excretions are mainly bile salts.
- The bile salts go to the intestine where we will find bacteria that will remove the glycine and taurine found in bile salts So that only primary bile acids remain (cholic acid - chenodeoxycholic acid)

- Then the intestinal bacteria works upon these two primary bile acids by removing the hydroxyl group **"Decarboxylation"** at the seventh carbon atom.
- we are left with Deoxycholic acid from cholic acid & Lithocholic acid from chenodeoxycholic acid
- **so SECONDARY bile acids are produced in the intestines**! ! !
- These secondary bile acids will be absorbed, then will head to the liver where they will form bile SALTs again!!
- Note that the **bile duct contains BOTH primary and secondary bile salts**

ENTEROHEPATIC CIRCULATION

This is basically a summary of the whole lecture:

1-Cholesterol turns into primary bile acids

2-Primary bile salts are formed by adding Glycine and Taurine.

3- Salts go through the bile ducts to the intestines.

4-the primary bile salts are acted upon by the bacteria and converted into primary bile acids once again(by removing taurine or glycine).

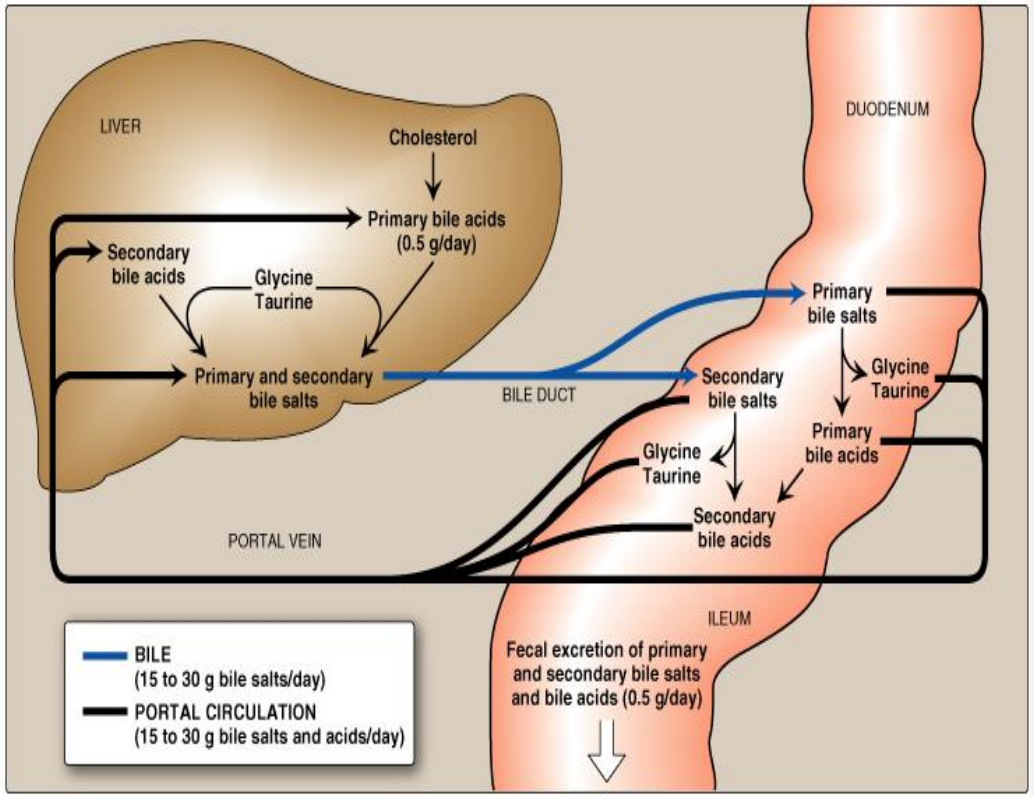
5-the primary bile acids are turned into secondary bile acids by the intestinal bacterial by removing OH.

6-the secondary bile acids go into the portal circulation by a carrier (albumin) But are first absorbed by a sodium co-transporter that helps in the absorption of both primary and secondary bile acids.

(So what goes into the portal vein is acid but what goes out into the bile duct is salt!!!!!!!!)

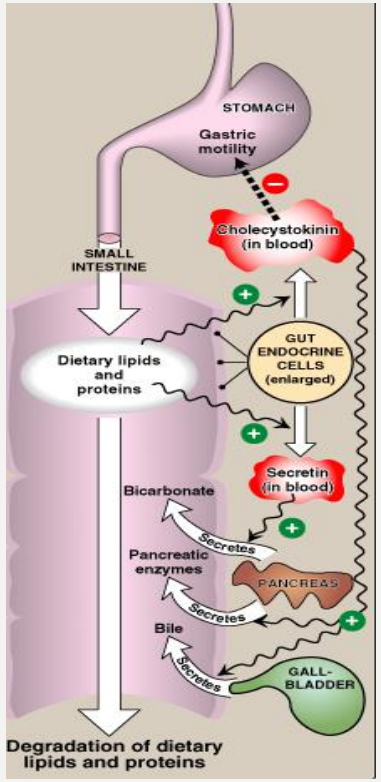
7-from the portal vein, the acids head to the liver where they conjugate with glycine and taurine to form primary and secondary bile salts which go to the intestines again! (the cycle is repeated).

8- the bile acids and salts not absorbed will be excreted in the feces(15-30gram per day).



HORMONAL CONTROL OF BILE SECRETION

Hormone from gut cells:	
Cholecystokinin (CCK)	
Stimulus:	Responses:
Undigested lipids and **partially digested proteins** in <u>duodenum</u>.	1. Secretion of pancreatic enzymes 2. Bile secretion. 3. Slow release of gastric contents



MALDIGESTION/MALABSORPTION OF LIPIDS

Liver diseases:

e.g., Hepatitis or cirrhosis

Decreased secretion of bile Due to decreased synthesis

Gall bladder diseases:

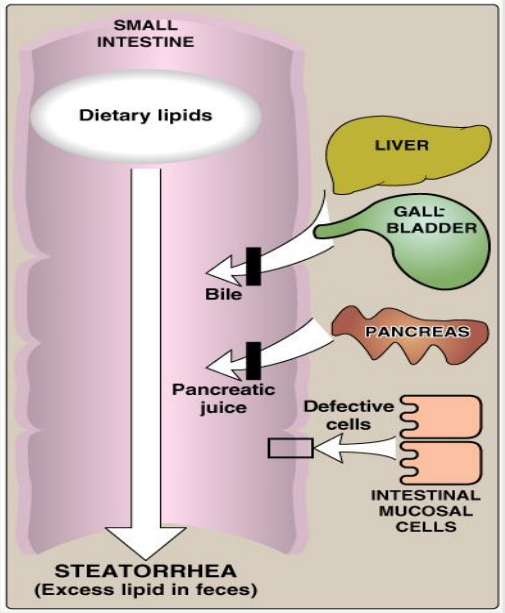
e.g., Gall stones

Decreased bile secretion Due to obstruction

Decreased bile secretion

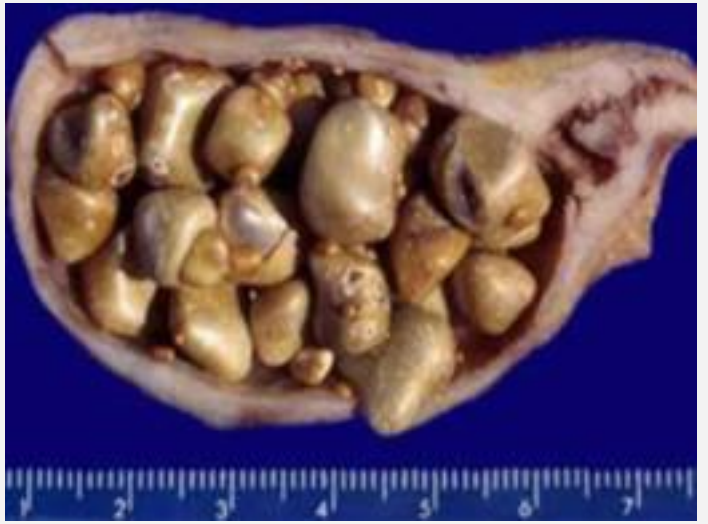
Malabsorption of lipids

Due to decreased emulsification , hence malabsorption occurs -----> steatorrhea



CHOLELITHIASIS

- **Cholelithiasis**
  - **Causes**
    - **Decreased bile salts in bile:**
      - Biliary tract obstruction (interferes with enterohepatic circulation)
      - Hepatic dysfunction (synthesis)
    - **Increased Biliary cholesterol excretion**
  - Treatment:
    - **Bile acid replacement therapy** they mostly give chenodeoxycholic acid
    - **Surgical**



CHOLELITHIASIS – DR SUMBUL'S EXPLANATION

- **What is cholelithiasis?**
  - Presence of stones in the gallbladder.
- **What are these stones made of?**
  - cholesterol mainly(85%), with bilirubin and other molecules.
- **Mechanism of cholelithiasis:**
  - Cholesterol is not soluble itself, in order to become soluble it needs bile salts.
  - So in the decrease or absence of bile salts, cholesterol will precipitate in the gallbladder, thus forming biliary stones.
  - So if the liver is not producing enough bile salts or if the bile salts are being produced but there is obstruction , this cholesterol will definitely precipitate because there must be enough bile salts in the gallbladder to solubilize the cholesterol coming in to the gallbladder.
- **Causes of cholelithiasis:**
  - **Obstruction:** Most of the bile salts that are secreted are reabsorbed and reused by the liver But if there is some obstruction of the enterohepatic circulation, the bile salts will not be reabsorbed, so less bile salts are present in the liver → cholilithiasis .
  - **Decreased synthesis due to dysfunction of the liver.**
  - **Increased excretion if cholesterol:** for example some drugs that increase cholesterol excretion (such as **fibrates** which are given to patients with high serum cholesterol because fibrates bind to bile salts which are then excreted in the feces → decreased bile salts in the body → body synthesizes more bile by using cholesterol → thus depleting swum cholesterol
  - But because of the mechanism of these drugs (which increases cholesterol in the gallbladder but decreases bile salts simultaneously) ,these drugs will lead to stone formation → cholelithiasis.

Check your understanding!

Q1: Cholesterol, the parent compound of Bile acids, is composed of a:

A. 26 Carbon structure
B. 22 Carbon structure
C. 29 Carbon structure
D. 27 Carbon structure

Q2: Cholic Acid is a primary bile acid containing:

A. 1 COOH group and 2 OH groups
B. 1 COOH group and 3 OH groups
C. Cholesterol structure + 3 OH groups only
D. Cholesterol structure + 2 OH groups only

Q3: The rate-limiting step of Bile Acid synthesis is the hydroxylation of Cholesterol by Cholesterol 7-α-hydroxylase.

A. True
B. False

Q4: Primary Bile Acids are found in Bile.

A. True
B. False

Q5: Conjugation of Bile acids occurs in the:

A. Intestine
B. Gallbladder
C. Liver
D. Blood

Q5: Conjugation of Bile acids occurs in the:

A. Intestine
B. Gallbladder
C. Liver
D. Blood

Q6: Bile Salts have a role in the digestion of fat-soluble vitamins.

A. True
B. False

Q7: Cholecystokinin (CCK) activity is stimulated by the presence of:

A. Undigested Lipids
B. Partially Digested Proteins
C. Acidic chyme
D. A+B

Q8: Deoxycholic acid is derived from Lithocholeic acid.

A. True.
B. False.

1.D 2.B 3.A 4.B 5.C 6.A 7.D 8.B

Done by:

- شهد العنزي.
- عبدالله الغزي.
- ريفان هاشم.
- ابراهيم الشايع.
- عبدالله الطويل.
- رهف بن عباد.

Revised by:

- فارس المطيري.

Resources:

- 435's slides and notes.
- Lippincott's illustrated reviews: Biochemistry – sixth edition.
- BRS Biochemistry molecular biology and genetics – 7th edition.
- Cholelithiasis – MSD manual website.

@435biochemteam
435biochemistryteam@gmail.com
@biochemteam435