-Biochemical Aspects of Bile Acids and Salts-

Biochemistry Teamwork

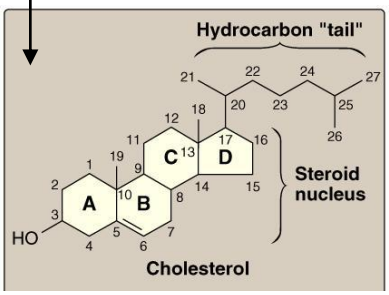
Osamah Al-Jarallah	Al-Anood Asiri
Abdulaziz Al-Shamlan	Lama Mokhlis
Abdullah Al-Mazyad	Noha Khalil
Turki Al-Otaibi	Reem Al-Mansour
Khalid Al-Khamis	Hadeel Helmi
Saud Al-awad	Nuha Al-Furayh
Khaled Almohaimede	Jumana Al-Shammari
Meshal Al-Otaibi	Deema Jomar

By : Reem AlMansour & Abdullah AlMazyad

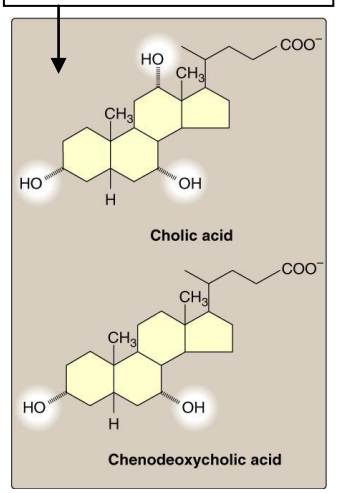
Objectives:

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

It is the parent for steroid hormones, vitamin D, bile salts and the bile



So to form the bile acids we increase the OH and decrease the carbon atoms in comparison to the cholesterol.



Cholesterol:

Cholesterol (27 C) is the:

Parent steroid compound

Precursor of bile acids and salts

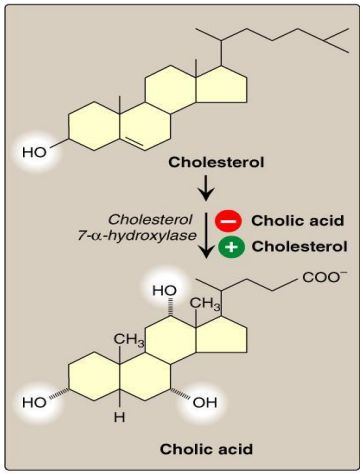
Primary Bile Acids (24 C):

Amphipathic

-COOH at side chain

Cholic acid: 3 OH

Chenodeoxycholic: 2 OH



Hepatic Synthesis of Bile Acids:

The rate-limiting step is catalyzed by:

Cholesterol 7-α-hydroxylase

Regulation:→also happens at the gene level.

Down-regulated by end products (bile acids)

"Enzyme repression"

Up-regulated by cholesterol "Enzyme induction"

Some people have mutation in the gene that form the enzyme Cholesterol 7-α-hydroxylase, so the cholesterol is increased in the bile and it could precipitate in the form of stones. Therefore, since there is no formation of the bile acids, there is no formation of the bile salts.

Primary Bile Acids and Salts:

They are steroid in nature

Cholic acid ← Bile acids → Chenodeoxycholic acid

Glycocholic, Taurocholic ← Bile salts → 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

The conjugation happens in the liver.

Bile Salts:

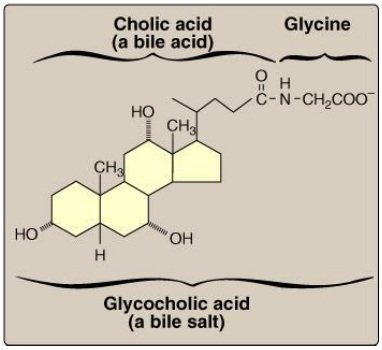
- **Addition of glycine or taurine results in the presence of fully ionized groups at pH 7.0:**
  -COO- of glycine &
  -SO3- of taurine → The amphipathic feature of the bile salts is more than of the bile acids, due to these compounds

  (hence, its name as bile salts e.g., Sodium or potassium glycocholate)
- **More effective detergent than bile acids. (because it's full ionized)**
- **Only bile salts, but not acids, found in bile.**

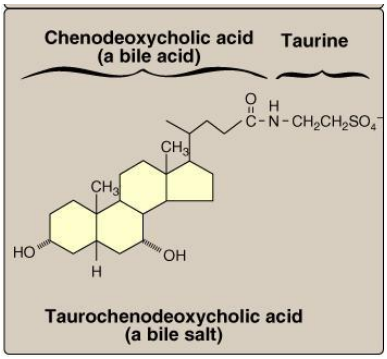
Bile Salts:

Primary bile salt found in the body associated with K or Na .

Na or K Glycocholate



Na or K Taurochenodeoxycholate



Hormonal Control of Bile Secretion:

Stimulus:

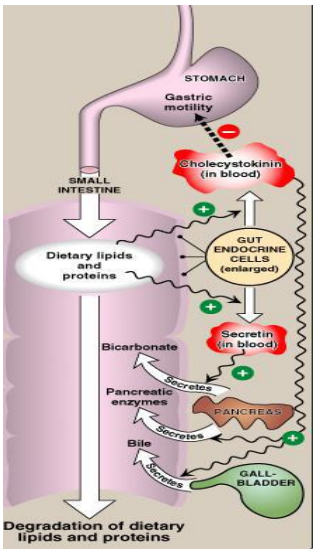
Undigested lipids and partially digested proteins in duodenum.

Hormone from gut cells:

Cholecystokinin (CCK).

Responses:

1.Secretion of pancreatic enzymes
2.Bile secretion
3.Slow release of gastric contents



Functions of Bile Salts:

- **Important for cholesterol excretion:**
  1. As metabolic products of cholesterol →it essential in the excretion of the cholesterol
  2. Solubilizer of cholesterol in bile
- **Emulsifying factors for dietary lipids, a prerequisite step for efficient lipid digestion**
- **Cofactor for pancreatic lipase and PLA2**
- **Facilitate intestinal lipid absorption by formation of mixed micelle**

Emulsification of Dietary Lipids in Duodenum: Role of Bile Salts

•Emulsification increases the surface area of lipid droplets, therefore the digestive enzymes can effectively act.

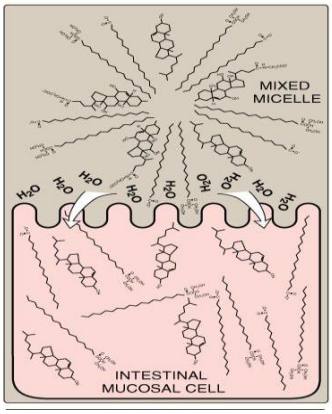
•Mechanisms:

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.

Absorption of Lipids by Intestinal Mucosal Cells: Role of Bile salts:

- **Mixed micelles:**
  Disc-shaped clusters of amphipathic lipids.
  Arranged with their hydrophobic groups on the inside and their hydrophilic groups on the outside.
  Micelle includes end products of lipid digestion, bile salts and fat-soluble vitamins.
- **Note:**
  Short- and medium-chain fatty acids do not require mixed micelle for absorption by intestinal cells.

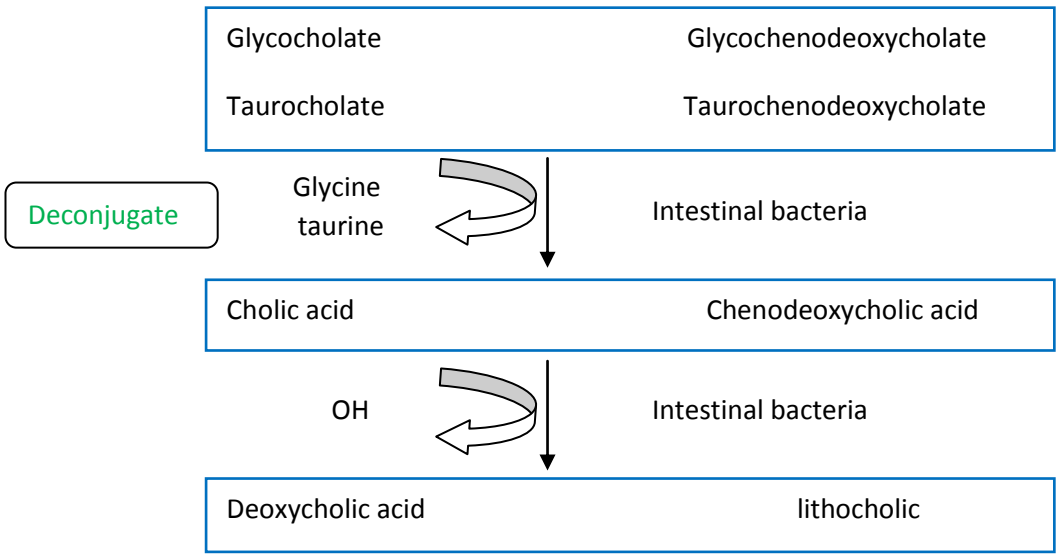
The Role of Bile Salts in Absorption of Lipids by Intestinal Cells:



Mixed Micelle Formation:

Bile salts End products of lipid digestion Fat-soluble vitamins.

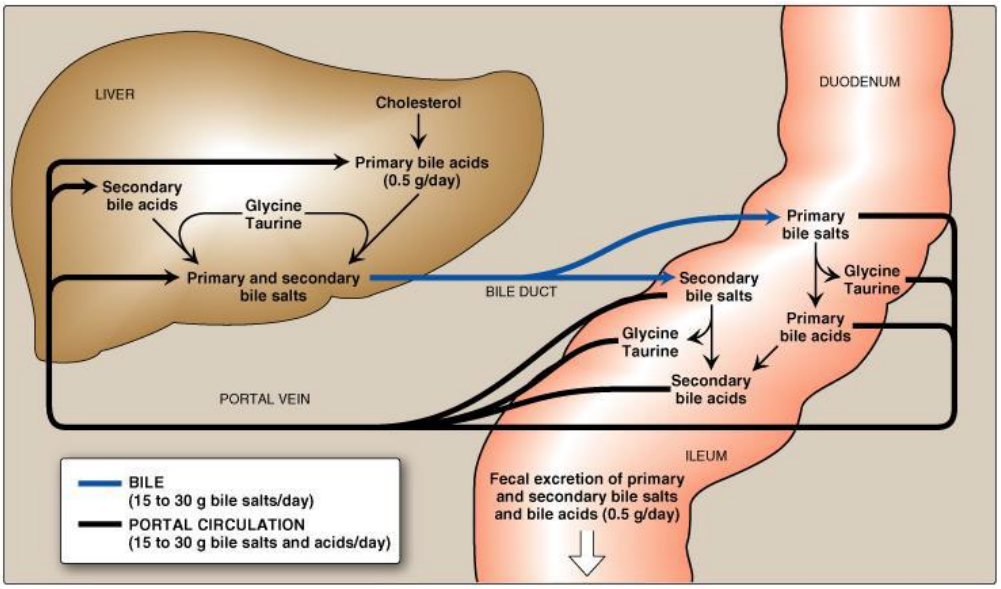
Secondary Bile Acids:



We find all the types in the portal circulation; the bile acids, bile salts, primary and secondary.

The bile is recycled.

Enterohepatic Circulation:



But only we find in the bile duct the bile salts primary and secondary.

Enterohepatic Circulation

Cholestyramine: Bile acid sequestrants

It binds to bile acids in the gut, preventing their reabsorption &Promoting their excretion , It is used for treatment of hypercholesterolemia

Dietary fiber: It binds to bile acids, increasing their excretion

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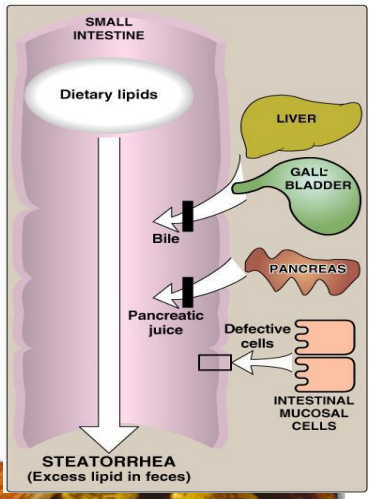
Maldigestion/Malabsorption of Lipids:→steatorrhea

Decreased bile secretion by:

- **Liver diseases:**
  e.g., Hepatitis or cirrhosis
- **Gall bladder diseases:**
  e.g., Gall stones

⟶ **Malabsorption of lipids**

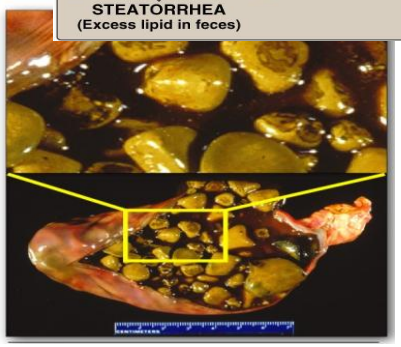


Cholelithiasis:

Causes:

1. ↓**Bile salts in bile:**
   Biliary tract obstruction
   (intereferes with enterohepatic circulation)
   Hepatic dysfunction ↓(synthesis)

2. ↑**Biliary cholesterol excretion**



Treatment:

- **Bile acid replacement therapy.→(supplements) takes months to years.**
- **Surgical.**

Summary

Cholesterol can be eliminated from the body either by conversion to bile salts or by secretion into the bile. Bile salts and phosphatidyl-choline are quantitatively the most important organic components of bile. Bile salts are conjugated bile acids produced by the liver and stored in the gallbladder. The primary bile acids, cholic or chen-odeoxycholic acids, are amphipathic, and can serve as emulsifying agents. The rate-limiting step in bile acid synthesis is catalyzed by cholesterol-7--hydroxylase, which is inhibited by bile acids. Before the bile acids leave the liver, they are conjugated to a molecule of either glycine or taurine, producing the primary bile salts: glycocholic or taurocholic acid, and glyco chenodeoxycholic or taurochenodeoxycholic acid. Bile salts are more amphipathic than bile acids and, therefore, are more effective emulsifiers. In the intestine, bacteria can remove the glycine and taurine, and can remove a hydroxyl group from the steroid nucleus, producing the secondary bile acids—deoxycholic and lithocholic acids. More than 95% of the bile acids and salts are efficiently reabsorbed from the intestine by a sodium-bile salt cotransporter. They are then actively transported out of the ileal mucosal cells into the portal blood, where they are carried by albumin back to the liver (enterohepatic circulation; bile acid sequestrants reduce this) and are taken up by the hepatic form of the cotransporter. In the liver, the primary and secondary bile acids are reconverted to bile salts, and secreted into the bile. If more cholesterol enters the bile than can be solubilized by the available bile salts and phosphatidylcholine, cholesterol gallstone disease (cholelithiasis) can occur.

Test yourself:

1-Which of the following is the precursor of bile acid and salt?

(a) Cholesterol
(b) Cholic acid
(c) Chenodeoxycolic
(d) Glycocholate

2- which of these options lead to inhibition of the activity of Cholesterol 7-α-hydroxylase "down-regulate" ?

(a) Cholic acid
(b) Cholesterol
(c) Taurochenodeoxycolic
(d) Glycocholate

3- Which of the following is the function of bile salts?

(a) Emulsifying factors for dietary lipids
(b) Cofactor for pancreatic lipase and PLA2
(c) Facilitate intestinal lipid absorption
(d) a , b , c

4- Which of the following is considered as a secondary bile acid?

(a) Taurocholate
(b) Glycochenodeoxycolic
(c) Cholic acid
(d) Deoxycolic acid

5- A 35-year-old woman was seen in emergency room because of recurrent abdominal pain. The history revealed a 2-year pattern of pain in the upper right quadrant, beginning several hours after the ingestion of a meal rich in fried/fatty food. Ultrasonographic examination demonstrated the presence of numerous stones in the gallbladder. The patient initially elected treatment consisting of exogenously supplied chenodeoxycholic acid, but eventually underwent surgery for the removal of gallbladder, and had a full recovery. The rational for the initial treatment of this patient with chenodeoxycholic acid is that this compound:

(a) Interferes with the enterohepatic circulation
(b) Inhibits cholesterol synthesis
(c) Increases de novo bile acid production
(d) Increase cholesterol solubility in bile

Explanation of Q5 :

Chenodeoxycholic acid is a bile acid used in treatment of gallstone. It's an amphipathic molecule that can act like an emulsifying agent and help solubilize cholesterol. It will not affect the enterohepatic circulation, interfere with cholesterol synthesis or increase bile acid producton

Answers:

1-a 2-a 3-d
4- d 5- d

Done by: Reem AlMansour and Abdullah AlMazyad