BILE ACID METABOLISM

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Clinical Significance of Bile Acids

Bile acids perform four physiologically significant functions:

1. Their synthesis and subsequent excretion in the feces represents a major mechanism for the elimination of excess cholesterol.

2. Bile acids and phospholipids solubilize cholesterol in the bile, thereby preventing the precipitation of cholesterol in the gallbladder.
Clinical Significance cont

3. They facilitate the digestion of dietary triacylglycerols by acting as emulsifying agents that render fats accessible to pancreatic lipases.

4. They facilitate the intestinal absorption of fat-soluble vitamins.
Bile (or gall) is a bitter, yellow or green alkaline fluid secreted by hepatocytes from the liver of most vertebrates.

In many species, it is stored in the gallbladder between meals and upon eating is discharged into the duodenum where it excretes waste and aids the process of digestion.

**The components of bile:**
- Bile salts (sodium glycocholate & sodium taurocholate)
- water
- cholesterol
- lecithin (a phospholipid)
- Bile pigments (bilirubin & biliverdin)
BILE ACIDS

• At the pH of the small intestine, most of the bile acids are ionized and mostly occur as their sodium salts which are then called “primary conjugated bile salts.”

• In the lower small intestine and colon, bacteria dehydroxylate and deconjugate some of the primary bile salts to form “secondary bile acids”.
BILE ACIDS

• primary conjugated bile acid
  Taurocholic acid
  Glycocholic acid
  Taurochenodeoxycholic acid
  Gylcochenodeoxycholic acid

• secondary bile acids
  Deoxycholic acid
  Lithocholic acid
BILE ACIDS

• The primary bile acids are synthesized in the liver from cholesterol.
• These are cholic acid (largest amount) and chenodeoxycholic acid, both formed from a common precursor 7-hydroxycholesterol itself derived from cholesterol.
• The 7α hydroxylation of cholesterol is the first committed step in the biosynthesis of bile acids.
12α-hydroxylase

7α-hydroxylase

Vit C

7-Hydroxycholesterol

several steps

Cholyl-CoA

Chenodeoxycholyl-CoA
Glycocholic acid

Taurocholic acid
BILLE ACID SECRETION

• Liver hepatocytes metabolize cholesterol to cholic acid and chenodeoxycholic acid.
• These lipid soluble bile acids are conjugated mainly to glycine or taurine molecules to form water soluble primary conjugated bile acids.
• These bile acids travel to the gall bladder during the interdigestive phase for storage and to the second part of the duodenum via the common bile duct during digestion.
DIGESTION AND ABSORPTION OF FATS

• Bile acids act to some extent as a detergent, helping to emulsify fats (increasing surface area to help enzyme action), and thus aid in their absorption in the small intestine.

• Bile salts combine with phospholipids to break down fat globules in the process of emulsification by associating its hydrophobic side with lipids and the hydrophilic side with water.
Emulsification

Fat globule

Nonpolar region

Polar (charged) regions

Bile salt

Fat droplets coated with bile salts are suspended in water

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MICELLES

• Emulsified droplets then are organized into many micelles which increases absorption.
• Mixed micelles are molecular aggregates composed of fatty acids, monoglycerides, phospholipids, cholesterol, and conjugated bile salts.
• They are formed when the concentration of conjugated bile acids is greater than its critical micellar concentration.
MICELLES

• The microvillus membrane of the small intestine is covered by a so-called unstirred water layer—a relatively stagnant aqueous phase.

• Water soluble mixed micelles provide a mechanism for the water-insoluble products of lipolysis to reach the luminal plasma membrane of villus epithelial cells.
1. Large fat globules are emulsified by bile salts in the duodenum.

2. Digestion of fat by the pancreatic enzyme lipase yields free fatty acids and monoglycerides, which then form micelles.

3. Fatty acids and monoglycerides leave micelles and enter epithelial cells by diffusion.

4. Chylomicrons containing fatty substances are transported out of the epithelial cells and into lacteals, where they are carried away from the intestine by lymph.
BILE ACIDS

• Since bile acids increase the absorption of fats, it is an important part of the absorption of the fat-soluble vitamins D, E, K and A.

• Bile salts are also bacteriocidal to the invading microbes that enter with food.

• 95% of the bile acids which are delivered to the duodenum will be recycled by the enterohepatic circulation.
ENTEROHEPATIC CIRCULATION

• Along the proximal and distal ileum, a large proportion of the biliary excretion of bile acids is reabsorbed into the portal circulation, taken up by the liver and reexcreted in the bile.

• This is known as enterohepatic circulation.

• The bile salts not reabsorbed, or their derivatives are excreted in the feces.

• The net effect of enterohepatic recirculation is that each bile salt molecule is reused about 20 times, often multiple times during a single digestive phase.
Bile acid pool 2 – 4g

Fecal loss

Enterohepatic circulation
Bile acid Pool

- Fecal loss of bile acids is 0.3 to 0.6g/day.
- It is compensated by an equal daily synthesis of bile acids by liver and bile acid pool is maintained.
- Normal bile acid pool is approximately 2 to 4g.
- Bile acids returning to the liver suppress de novo hepatic synthesis of primary bile acids from cholesterol by inhibiting the rate limiting enzyme 7α-hydroxylase.
- Maximum rate of synthesis is approximately 5g/day
ABNORMAL CONDITIONS ASSOCIATED WITH BILE ACIDS

• The cholesterol contained in bile will occasionally accrete into lumps in the gall bladder, forming gallstones. (hypersecretion of cholesterol, hypossecretion of bile acids or both)
• Malabsorption of fats.
• Absorption of fat soluble vitamins affected
STEATORRHEA

• Steatorrhea— an increase in stool fat excretion of > 6% of dietary fat.
• Steatorrhea is caused by one or more defects in the digestion and absorption of fats.
• In the absence of bile acids, fats become indigestible and are instead excreted in feces.
• In this case, the feces lacks its characteristic brown colour and instead are white or grey, and greasy. This condition is known as steatorrhea
STEATORRHEA

- This causes significant problems in the distal parts of the intestine as normally virtually all fats are absorbed in the intestines and bacterial flora are not adapted to processing fats past this point.
- Diarrhea of steatorrhea is the result of the effect of nonabsorbed dietary fats on intestinal, usually colonic, ion transport.
- E.g. oleic acid & ricinoleic acid (a bacterially hydroxylated fatty acid that is also the active ingredient in castor oil a widely used laxative) induce active colonic Cl secretion, most likely secondary to increasing intracellular Ca
Defects in lipid digestion and absorption in steatorrhea

- **Bile duct obstruction**
  - ↓ Bile acid
  - ↓ Micellar formation

- **Chronic pancreatitis**
  - ↓ Lipase
  - ↓ Lipolysis

- **Mucosal dysfunction**
  - ↓ Mucosal uptake & resterification

**STEATORRHEA**
Bile acid sequesterants

• Bile acid sequestrants are polymeric compounds which serve as ion exchange resins.
• Bile acid sequestrants exchange anions such as chloride ions for bile acids.
• By doing so, they bind bile acids and sequester them from enterohepatic circulation.
• Since bile acid sequestrants are large polymeric structures, they are not well-absorbed from the gut into the bloodstream.

• Thus, bile acid sequestrants, along with any bile acids bound to the drug, are excreted via the feces after passage through the gastrointestinal tract.
• Since bile acids are biosynthesized from cholesterol, the disruption of bile acid reabsorption will decrease cholesterol levels, particularly low density lipoprotein. (commonly known as "bad cholesterol").
• Bile acids returning to the liver suppress de novo hepatic synthesis of primary bile acids from cholesterol by inhibiting the rate limiting enzyme 7α-hydroxylase.
AVAILABLE DRUGS

• Therefore, they may be used for the treatment of hypercholesterolemia and dyslipidemia.

• Available drugs.
  – Cholestyramine
  – Colesevelam
  – Colestipol
SIDE EFFECTS

• Constipation, diarrhea, and flatulence
• Bile acid sequestrants may also bind drugs in the GI tract, preventing their absorption into the bloodstream.
• It is generally advised that bile acid sequestrants be spaced several hours apart from other drugs
CONT

• They may also bind fat-soluble vitamins, such as vitamin A, vitamin D, vitamin E, and vitamin K.

• This effect may result in vitamin deficiency.

• Hence, vitamin supplementation may be warranted.
Additionally, because bile acid sequestrants are not well-absorbed from the gut, they are generally regarded as being safe in pregnant women.

However, by interfering with vitamin absorption, they may cause vitamin deficiencies that may affect the fetus.

Hence, vitamin supplementation may be warranted, with appropriate intervals between dosing of the vitamins and bile acid sequestrants.
CONCLUSION

• Bile acid synthesis and subsequent excretion in the feces represent the only significant mechanism for the elimination of excess cholesterol.

• Interfering with the enterohepatic circulation of bile acids helps us in increasing in the excretion of cholesterol.

• Absorption of fats.

• Absorption of fat soluble vitamins.
THANK YOU