Bilirubin Metabolism

Mohammed Alzoghaibi, Ph.D

zzoghaibi@gmail.com

malzoghaibi@ksu.edu.sa

0506338400

Bilirubin

- **Bilirubin: is the end product of heme degradation derived from breakdown senescent (aging) erythrocytes by mononuclear phagocytes system specially in the spleen, liver and bone marrow.**
- **The major pigment present in bile is the orange compound bilirubin.**
- **It is highly soluble in all cell membranes (hydrophobic) and is also very toxic. Therefore, its excretion in the bile is one of the very important functions of the liver.**

Bilirubin

Conjugated

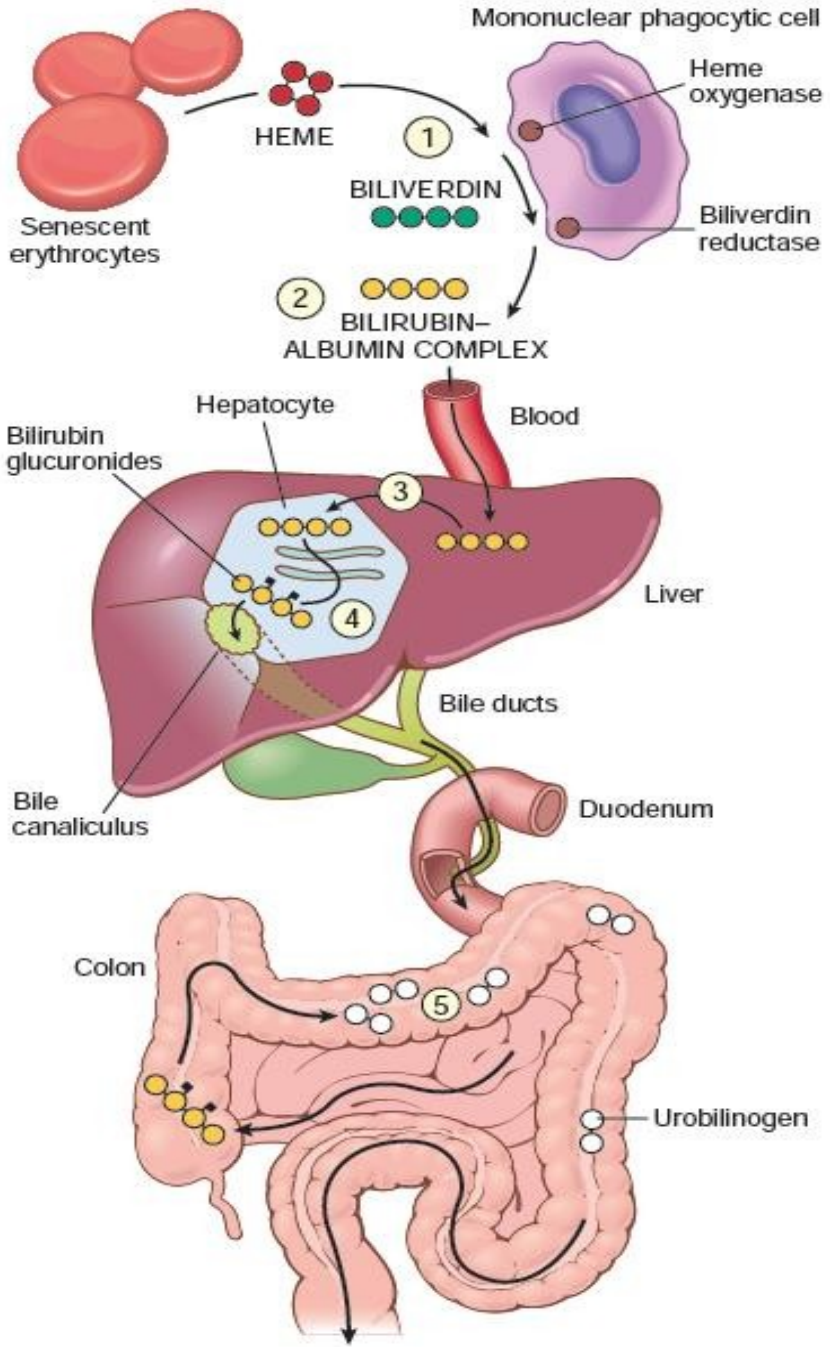
- Water soluble
- Loosely bound to albumin
- Filtered through renal glomeruli and excreted in urine
- Non-toxic
- Present in low concentration in the blood

Unconjugated

- Insoluble in water
- Tightly complex to albumin
- Not filtered through renal glomeruli, is not excreted in urine
- Toxic substance
- The chief form of bilirubin in the blood (represents the normal bilirubin in the blood; 0.5 mg/dl of plasma)

Bilirubin Is the Major Component of Bile Pigments, Steps of Excretion:

1. **Hemoglobin is first dissociated into heme and globin.**
2. **In the presence of NADPH and O_2, the Heme oxygenase enzyme hydroxylates Heme, with a concomitant oxidation of ferrus Fe^{2+} iron to ferric Fe^{+3}, and converts it into Biliverdin.**
3. **Biliverdin is then reduced or converted into bilirubin by biliverdin reductase enzyme. Bilirubin is transported in blood bound to albumin forming a water soluble compound called hemobilirubin (unconjugated bilirubin, free bilirubin, indirect bilirubin) which is rapidly transported to hepatocytes for further metabolism (even when bound to albumin, it's called free bilirubin).**


Mononuclear phagocytic cell
Heme oxygenase
HEME
1
BILIVERDIN
Biliverdin reductase
Senescent erythrocytes
2
BILIRUBIN–ALBUMIN COMPLEX
Hepatocyte
Blood
Bilirubin glucuronides
3
Liver
4
Bile ducts
Bile canaliculus
Duodenum
Colon
5
Urobilinogen

Bilirubin Is the Major Component of Bile Pigments, Steps of Excretion (cont.):

4. **The liver removes bilirubin from the circulation rapidly, mediated by a carrier protein (Mutiple organic anion transporting protein (MOAT), but this process is inefficient, therefore, there is always some unconjugated bilirubin in the viens), and conjugates most of it with glucuronic acid and only 10% with sulfate. This reaction is catalyzed by the enzyme UDP-Glucuronyl Transferase (UGT) in the smooth endoplasmic reticulum to have conjugated bilirubin, which is more water soluble than bilirubin.**
5. **The bilirubin-glucuronide (conjugated bilirubin, direct bilirubin) is secreted into the bile canaliculi through an active carrier- mediated process, via (Multidrug resistance-associated protein 2, MRP-2), (rate – limiting step for bilirubin metabolism by hepatocytes).**

Note:

1. **A defect in MRP-2 causes Dubin Johnson Syndrome, that the conjugated bilirubin concentration increases.**
2. **A deficiency or absence of UDP-Glucuronyl transferase causes Criggler Najjar Syndrome.**
3. **The unconjugated bilirubin is normally not secreted.**

Bilirubin Is the Major Component of Bile Pigments, Steps of Excretion (cont.):

6. **In the small intestine, bilirubin glucuronide is poorly absorbed. In the gut (colon), however, bacteria deconjugate it back to bilirubin, and convert it to the highly soluble colorless compound called Urobilinogen.**
7. **Only 20% of Urobilinogen can be absorbed by the small intestine (this represents the enterohepatic circulation of bile pigments). 70% of the Urobilinogen can be oxidized in the large intestine to Stercobilin (by bacteria).**

Note: Urobilinogen is excreted in either urine (where it is converted to yellow Urobilin in the urine, after exposure to air in the urine) or fesses (after it is converted to Stercobilin which is responsible for the brown color of fesses).

Bilirubin Is the Major Component of Bile Pigments (cont.)

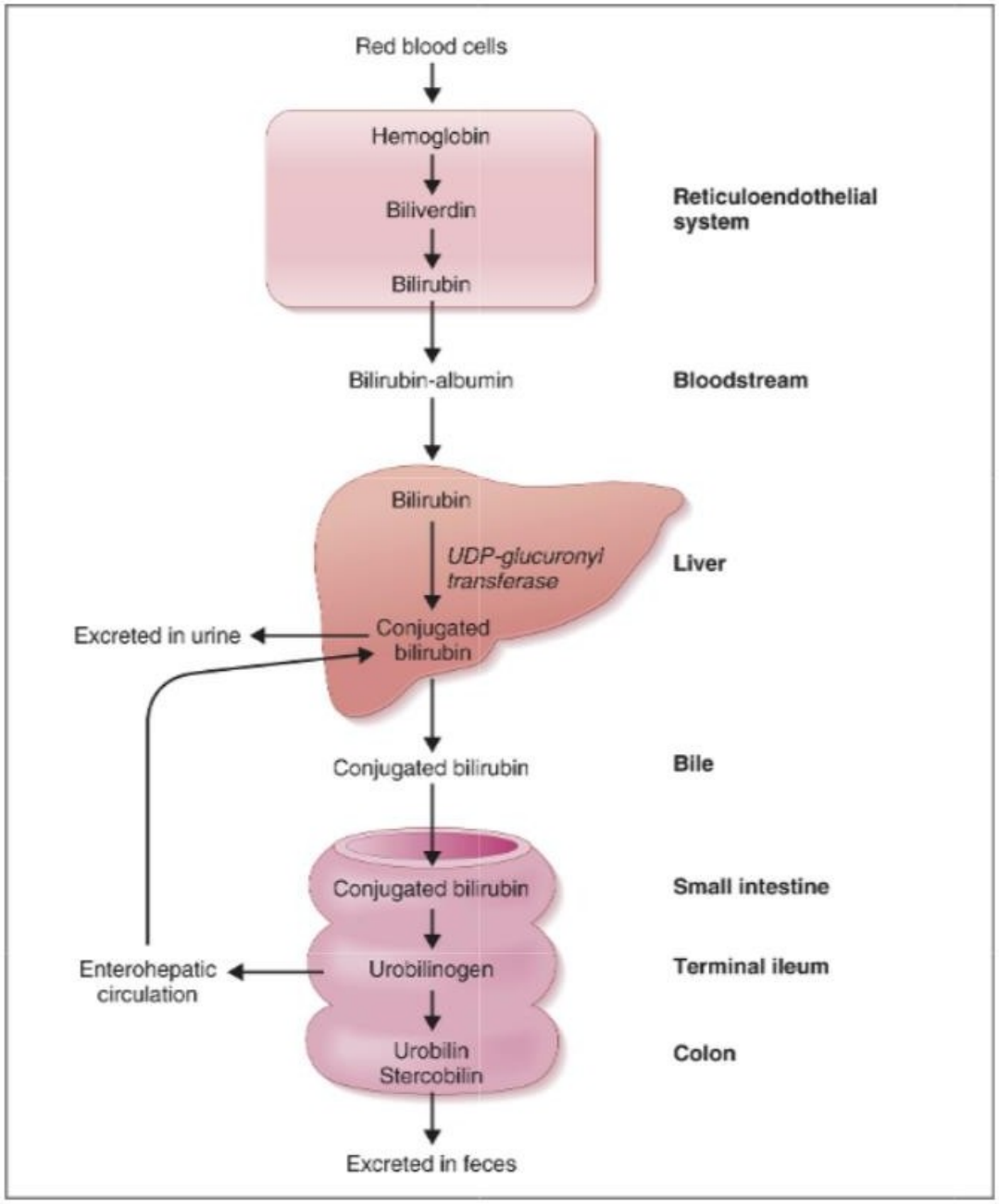
Fate of the bilirubin-glucuronide after they leave the hepatocyes:

- **A small portion of the conjugated bilirubin returns to the plasma either directly into the liver sinusoids or indirectly by absorption into the blood from the bile ducts or lymphatics. This represents 10% only.**
- **This causes a small portion of the bilirubin in the extracellular fluid always to be of the conjugated type rather than of the free type. These conjugated bilirubin that escaped into the blood, they bind less tightly to albumin and are excreted readily in the urine.**

Enterohepatic circulation of bile pigments

- **Small amount of bilirubin glucuronide (20%, which is de-conjugated and converted to Urobilinogen) is absorbed by the small intestine into the portal blood to the liver where it is extracted by the liver cells and is re-conjugated again and excreted in the bile. However, 5% of the reabsorbed Urobilinogen is excreted by the kidneys into the urine.**

Summary of Bilirubin Formation and Excretion



Bilirubin

Conjugated

- Water soluble
- Loosely bound to albumin
- Filtered through renal glomeruli and excreted in urine
- Non-toxic
- Present in low concentration in the blood

Unconjugated

- Insoluble in water
- Tightly complex to albumin
- Not filtered through renal glomeruli, is not excreted in urine
- Toxic substance
- The chief form of bilirubin in the blood (represents the normal bilirubin in the blood; 0.5 mg/dl of plasma)

- Plasma bilirubin contains both conjugated and unconjugated bilirubin.
- Total bilirubin (1-1.5 mg/dL) – conjugated = unconjugated.
- Usually, 90% of total bilirubin is unconjugated and 10% conjugated.

Bilirubin

- Normal serum bilirubin is 0.3-1.2 mg/dL of blood.
- The rate of bilirubin production is equal to the rates of hepatic uptake, conjugation, and biliary excretion.
- Jaundice becomes evident when the serum bilirubin levels rise above 2.5 to 3 mg/dL; levels as high as 30 to 40 mg/dL can occur with severe disease.

Main causes of Jaundice:

1. Excessive production of bilirubin
2. ↓ hepatocyte uptake
3. Impaired conjugation
4. ↓ hepatocyte excretion of bilirubin glucuronides
5. Impaired bile flow (obstruction of bile duct)

Causes and Pathogenesis of Jaundice

Learning Objectives

- **Definition of Jaundice**
- **The normal plasma concentration of total bilirubin**
- **Classification of jaundice**
  - **Prehepatic (hemolytic) jaundice**
  - **Hepatic (hepatocellular) jaundice**
  - **Poshepatic jaundice**

Jaundice (Icterus)

- **It is the yellow coloration of the skin, sclera, mucous membranes and deep tissues.**
- **The usual cause is large quantities of bilirubin in the ECF, either free or conjugated bilirubin.**
- **The normal plasma concentration of total bilirubin is 0.3-1.2 mg/dL of blood.**

Figure 21.10
Jaundiced patient, with the sclerae of his eyes appearing yellow.

Jaundice (cont.)

- However, in certain abnormal conditions this can rise up to 40 mg/dL of blood. But the skin usually begins to appear jaundiced when the concentration of total bilirubin in the plasma is greater than 2.5 to 3 mg/dL of blood.
- Bilirubin level from 1 to 2 mg/dL is called subclinical jaundice.

Classification of jaundice

I. Pre-hepatic (hemolytic) jaundice
II. Hepatic (hepatocellular) jaundice
III. Post-hepatic jaundice (cholestatic jaundice)

I. Pre-hepatic (hemolytic) jaundice

I. Pre-hepatic (hemolytic) jaundice

- **In hemolytic jaundice, the excretory function of the liver is not impaired (normal liver function).**
- **It results from excess production of bilirubin (beyond the liver's ability to conjugate it) following hemolysis of erythrocytes (RBCs).**
- **Causes:**
  - **Autoimmune disease**
  - **Hemolytic disease of the newborn**
  - **Hemolytic anemias**
  - **Rh- or ABO- incompatibility (mismatched)**
  - **Structurally abnormal RBCs (Sickle cell disease)**
  - **Toxic substances in the circulation (e.g., snake venom)**

I. Pre-hepatic (hemolytic) jaundice (cont.)

- **Therefore, the plasma concentrations of free bilirubin rises to levels much above normal but it is not filtered through the kidney, because they are unconjugated bilirubin.**
- **The urine is free from bilirubin, but high levels of urobilinogen.**
- **The stools appear darker than the normal color due to excessive stercobilin formation.**

II. Hepatic (hepatocellular) jaundice

II. Hepatic (hepatocellular) jaundice

- **Hyper-bilirubinemia (increased levels of bilirubin in the blood) may be due to:**
  - **Impaired uptake of bilirubin into hepatic cells.**
  - **Disturbed intra cellular protein binding or conjugation.**
  - **Disturbed active secretion of bilirubin into bile canaliculi.**
- **The main causes of Hepatic jaundice are:**
  - **Damage of liver cells: e.g., viral hepatitis, drugs, chemical, alcohol, or toxins.**
  - **Ethanol induced liver injury.**
  - **Genetic errors in bilirubin metabolism.**
  - **Genetic errors in specific proteins.**
  - **Autoimmune hepatitis.**

II. Hepatic (hepatocellular) jaundice

- **The diseased liver cells are unable to take all the unconjugated bilirubin formed, increasing its concentration in the blood.**
- **Also, there is intrahepatic biliary duct obstruction that leads to regurgitation of conjugated bilirubin to blood (swelling of cells and edema due to inflammation cause mechanical obstruction of intrahepatic biliary tree).**
- **Both types of bilirubin (conjugated & unconjugated) are present in blood in high concentration.**

II. Hepatic (hepatocellular) jaundice (cont.)

Clinical Features:

- **Stools appear pale grayish in color due to deficiency of Stercobilin.**
- **Urine appears dark brown due to filtration of excess conjugated bilirubin through the kidney (probably due to rupture of the congested bile canaliculi and direct emptying of the bile into the lymph leaving the liver).**
- **In this case, hyper-bilirubinemia is usually accompanied by other abnormalities in biochemical markers of liver function such as:**

1. **Alanine amine transferase (ALT) which specific for liver function.**
2. **Aspartate amine transferase (AST).**
3. **Alkaline phosphatase (ALP) and Gamma-glutamyltransferase (GGT), which cellular membrane enzymes in the cholengiocytes.**

- **All of these enzyme become elevated in chronic condition.**

III. Post-hepatic (Obstructive) jaundice

III. Post-hepatic jaundice

Caused by an obstruction of the biliary tree:

1. **Intrahepatic bile duct obstruction: due to swelling, fibrosis, or obstruction of liver canaliculi. The main causes are:**

- **Drugs.**
- **Cirrhosis.**
- **Cholangitis.**
- **Hepatitis.**

2. **Extrahepatic, cholestasis: obstruction of common bile duct which leads to compression. The main causes are:**

- **Gallstones (Calculus cholecystitis, Cholelithiasis).**
- **Edema of pancreatitis.**
- **Cancinoma of head of pancreas, (which is usually accompanied by high levels of serum alkaline phosphatase enzyme).**
- **Sclerosing cholangitis.**

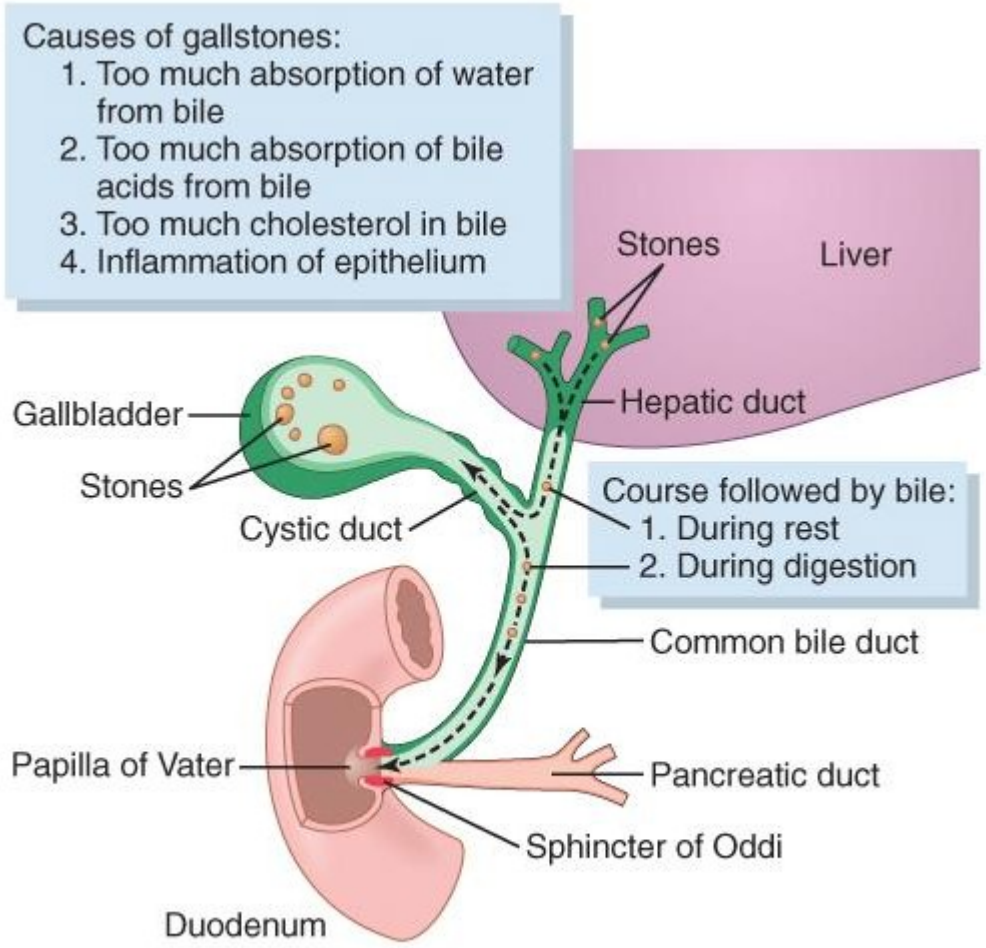
Post-hepatic jaundice

- **The rate of bilirubin formation is normal. Bilirubin enters the liver cells and become conjugated in the usual way.**
- **The conjugated bilirubin formed simply can not pass into small intestine and it returns back into blood, probably by rupture of the congested bile canaliculi and direct emptying of the bile into the lymph leaving the liver.**
- **Most of the bilirubin in the plasma becomes the conjugated type rather than the unconjugated type.**
- **In this type of jaundice, conjugated bilirubin is filtered through the kidney and appears in urine giving it dark brown color.**
- **Urine is free from urobilinogen.**
- **Stools are clay color due to absence of stercobilin.**

Liver Secretion of Cholesterol and Gallstone Formation (Cholelithiasis)

- **Under abnormal conditions, the cholesterol may precipitate in the gallbladder, resulting in the formation of *cholesterol gallstones*. The amount of cholesterol in the bile is determined partly by the quantity of fat that the person eats, because liver cells synthesize cholesterol as one of the products of fat metabolism in the body. For this reason, people on a high-fat diet over a period of years are prone to the development of gallstones.**
- **Inflammation of the gallbladder epithelium, often resulting from low-grade chronic infection, may also change the absorptive characteristics of the gallbladder mucosa, sometimes allowing excessive absorption of water and bile salts but leaving behind the cholesterol in the bladder, and then progressing to large gallstones.**

Liver Secretion of Cholesterol and Gallstone Formation



The End