BILIRUBIN METABOLISM

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After the end of the session student will able to know the

• Formation of bilirubin in our body (From HB)
• Bilirubin metabolism
• Jaundice and its types
• Pathogenesis of different types of jaundice
• Biochemical difference of different types of jaundice
Formation of bilirubin

Heme is catalysed by microsomal heme oxygenase system of R.E. cell.

Cleavage of the porphyring ring & production of biliverdin.

Biliverdin is reduced to form bilirubin.
Bilirubin metabolism

Degradation of heme:

Specially in liver & spleen.
Normally

5% bilirubin is conjugated
95% is unconjugated
1. Senescent red cells are a major source of heme proteins.

2. Breakdown of heme to bilirubin occurs in macrophages of the reticuloendothelial system (tissue macrophages, spleen, and liver).

3. Unconjugated bilirubin is transported through the blood (complexed to albumin) to the liver.

4. Bilirubin is taken up by the liver and conjugated with glucuronic acid.

5. Conjugated bilirubin is secreted into bile and then the intestine.

6. In the intestine, glucuronic acid is removed by bacteria. The resulting bilirubin is converted to urobilinogen.

7. Some of the urobilinogen is reabsorbed from the gut and enters the portal blood.

8. A portion of this urobilinogen participates in the enterohepatic urobilinogen cycle.

9. The remainder of the urobilinogen is transported by the blood to the kidney, where it is converted to yellow urobilin and excreted, giving urine its characteristic color.

10. Urobilinogen is oxidized by intestinal bacteria to the brown stercobilin.
Pathophysiology of hemolytic jaundice
Pathophysiology of Neonatal jaundice
Uptake of bilirubin by liver

• Bilirubin is slightly soluble in plasma so it is bind to albumin to transport to liver.

• Bilirubin + albumin = Free bilirubin.
Formation of bilirubin diglucuronide

Bilirubin bind with glucoronic acid catalysed by bilirubin glucuronyltransferase
Excretion of bilirubin into bile

Active transported into bile canaliculi and then into bile.
Formation of urobilins in the intestine

Bilirubin glucuronide is hydrolysed and reduced by bacteria in the gut to urobilinogen. Some urobilinogen is reabsorbed from the gut into the portal blood and transported to the kidney where it is converted into urobin.
Jaundice

Refers to the yellow color of the skin and mucous membrane caused by deposition of bilirubin secondary to increase bilirubin level.
Types of jaundice

a. Hemolytic jaundice

b. Obstructive jaundice

c. Hepatocellular jaundice
Hemolytic jaundice

Normal production of bilirubin is only 300 mg per day but normal liver can excrete 3000 mg per day.
Prehepatic (hemolytic) jaundice

hemolysis of red blood cell

blood

unconjugated bilirubin

liver

conjugated bilirubin

gut

conjugated bilirubin

urobilinogen

urobilin (sterocobilin)

kidney

major pathway

minor pathway

urine

feces
Positive finding of Hemolytic jaundice

Unconjugated bilirubin is elevated in blood

Urinary urobilinogen is increased
Hepatocellular jaundice

Damage to liver cell causes a decrease uptake and production of conjugated bilirubin

Unconjugated bilirubin and Urobilinogen is increases in blood.
Obstructive jaundice:

Results from obstruction of the bile duct. e.g. Hepatic tumor, stone in bile duct.
Posthepatic jaundice

- Red blood cell
  - Blood
    - Conjugated bilirubin
    - Unconjugated bilirubin/alalbumin
  - Liver
    - Conjugated bilirubin
    - γGT
    - ALP
  - Gut
- Kidney
- Urine

Major pathway: blue arrows
Minor pathway: dotted blue arrows
<table>
<thead>
<tr>
<th>Condition</th>
<th>Serum Bilirubin</th>
<th>Urine Urobilinogen</th>
<th>Urine Bilirubin</th>
<th>Fecal Urobilinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Direct: 0.1-0.4 mg/dL</td>
<td>0-4 mg/24 h</td>
<td>Absent</td>
<td>40-280 mg/24 h</td>
</tr>
<tr>
<td></td>
<td>Indirect: 0.2-0.7 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemolytic anemia</td>
<td>↑Indirect</td>
<td>Increased</td>
<td>Absent</td>
<td>Increased</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>↑Direct and indirect</td>
<td>Decreased if micro-obstruction is present</td>
<td>Present if micro-obstruction occurs</td>
<td>Decreased</td>
</tr>
<tr>
<td>Obstructive jaundice²</td>
<td>↑Direct</td>
<td>Absent</td>
<td>Present</td>
<td>Trace to absent</td>
</tr>
</tbody>
</table>

²The most common causes of obstructive (posthepatic) jaundice are cancer of the head of the pancreas and a gallstone lodged in the common bile duct. The presence of bilirubin in the urine is sometimes referred to as choluria—therefore, hepatitis and obstruction of the common bile duct cause choluric jaundice, whereas the jaundice of hemolytic anemia is referred to as acholuric. The laboratory results in patients with hepatitis are variable, depending on the extent of damage to parenchymal cells and the extent of micro-obstruction to bile ductules. Serum levels of alanine aminotransferase and aspartate aminotransferase are usually markedly elevated in hepatitis, whereas serum levels of alkaline phosphatase are elevated in obstructive liver disease.
## Biochemical finding of Diff. types of jaundice

<table>
<thead>
<tr>
<th></th>
<th>Hemolytic</th>
<th>Hepatocellular</th>
<th>Obstructive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin &lt;75μmol/L</td>
<td>Bllirubin later</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑</td>
<td></td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Normal enzyme level</td>
<td>AST</td>
<td>ALP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑↑↑</td>
<td>↑↑</td>
<td></td>
</tr>
<tr>
<td>NO bili in urine</td>
<td>Bili + in urine</td>
<td>Bili + in urine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDH</td>
<td>↑</td>
<td></td>
<td>↑</td>
</tr>
</tbody>
</table>
Blood

Bilirubin • Albumin

1. UPTAKE

Hepatocyte

Bilirubin

UDP-GlcUA
UDP-GlcUA

2. CONJUGATION
Neonatal jaundice
“Toxic” jaundice
Crigler-Najjar syndrome
Gilbert syndrome

Bilirubin diglucuronide

3. SECRETION
Dubin-Johnson syndrome

Bile ductule

Bilirubin diglucuronide
<table>
<thead>
<tr>
<th>Unconjugated</th>
<th>Conjugated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemolytic anemias</td>
<td>Obstruction of the biliary tree</td>
</tr>
<tr>
<td>Neonatal &quot;physiological jaundice&quot;</td>
<td>Dubin–Johnson syndrome</td>
</tr>
<tr>
<td>Crigler-Najjar syndromes types I</td>
<td>Rotor syndrome</td>
</tr>
<tr>
<td>and II</td>
<td></td>
</tr>
<tr>
<td>Gilbert syndrome</td>
<td>Liver diseases such as the various types of hepatitis</td>
</tr>
<tr>
<td>Toxic hyperbilirubinemia</td>
<td></td>
</tr>
</tbody>
</table>

These causes are discussed briefly in the text. Common causes of obstruction of the biliary tree are a stone in the common bile duct and cancer of the head of the pancreas. Various liver diseases (e.g., the various types of hepatitis) are frequent causes of predominantly conjugated hyperbilirubinemia.
Bilirubin Excretion

- Bilirubin (unconjugated) is produced in the liver.
- Bilirubin mono- or diglucuronide (conjugated) is excreted by the kidneys.
- Urobilinogen is produced in the liver and enters the enterohepatic circulation.
- Urobilinogen is excreted in the bile and enters the large intestine.
- Urobilin is formed from urobilinogen in the large intestine.
- Stercobilinogen is produced in the large intestine and is excreted in the stool.
- Stercobilin is formed from stercobilinogen in the large intestine and is excreted in the stool.