Liver Function Tests (LFTs)
Objectives

Upon completion of this lecture, the students should be able to:

• Understand the major metabolic functions of the liver and causes of liver dysfunction.
• Discuss markers of liver function tests such as liver enzymes, bilirubin, albumin and prothrombin time that can diagnose hepatic injury and assess hepatic function.
Major Metabolic Functions of the Liver

- **Synthetic Function**
  - Plasma proteins (albumin, globulins), cholesterol, triglycerides and lipoproteins
- **Detoxification and excretion**
  - Ammonia to urea (urea cycle), bilirubin, cholesterol, drug metabolites
- **Storage Function**
  - Vitamins A, D, E, K and $B_{12}$
- **Production of bile salts**
  - Helps in digestion
Some example of liver dysfunction

- Hepatocellular disease
- Cholestasis (obstruction of bile flow)
- Cirrhosis
- Hepatitis
- Jaundice
- Liver cancer
- Steatosis (fatty liver)

- Genetic Disorders
  - Hemochromatosis (iron storage)
Liver Function Tests (LFTs)

Broadly classified as:

1. Tests to detect hepatic injury:
   - Mild or severe; acute or chronic
   - Nature of liver injury (hepatocellular or cholestasis)

2. Tests to assess hepatic function
Classification of LFTs

Group I: Markers of liver dysfunction

- Serum bilirubin: total and conjugated
- Urine: bile salts and urobilinogen
- Total protein, serum albumin and albumin/globulin ratio
- Prothrombin Time (concern about your blood's ability to clot)
Classification of LFTs

Group II: Markers of hepatocellular injury

- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
Classification of LFTs

Group III: Markers of cholestasis (fatty liver)

- Alkaline phosphatase (ALP)
- \( \gamma \)-glutamyltransferase (GGT)
Limitations of LFTs

• Normal LFT values do not always indicate absence of liver disease
  ▫ Liver a has very large reserve capacity

• Asymptomatic people may have abnormal LFT results
  ▫ Diagnosis should be based on clinical examination
Bilirubin

- A byproduct of red blood cell breakdown
- It is the yellowish pigment observed in jaundice
- High bilirubin levels are observed in:
  - Gallstones, acute and chronic hepatitis
• Bilirubin

• Bilirubin exists in the blood in two forms, conjugated and unconjugated. Only the conjugated form is water soluble, so bilirubinuria signifies the presence in urine of conjugated bilirubin.

• Conjugated bilirubin is normally excreted through the biliary tree into the gut where it is broken down; a small amount is reabsorbed into the portal circulation, taken up by the liver and re-excreted in bile. Interruption of this so-called enterohepatic circulation usually stems from mechanical obstruction, and results in high levels of conjugated bilirubin in the systemic circulation, some of which spills over into the urine.
Urobilinogen

• In the gut, conjugated bilirubin is broken down by bacteria to products known collectively as faecal urobilinogen, or stercobilinogen. This too undergoes an enterohepatic circulation. However, unlike bilirubin, urobilinogen is found in the systemic circulation and is often detectable in the urine of normal subjects. Thus the finding of urobilinogen in urine is of less diagnostic significance than bilirubin. High levels are found in any condition where bilirubin turnover is increased, e.g. haemolysis, or where its enterohepatic circulation is interrupted, e.g. by liver damage.
Bilirubin metabolism

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 via facilitated diffusion by the liver and conjugated with glucuronic acid.

5. Conjugated bilirubin is actively 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.
METABOLISM OF BILIRUBIN

Haemoglobin → Haem → Bilirubin

Reticulo-endothelial system

Albumin → Unconjugated bilirubin

Plasma

Re-uptake

Liver

Unconjugated bilirubin

Bilirubin digluconuride (conjugated)

Bile

Excretion

Small intestine

Kidney

Urobilinogen (portal vein)

Large intestine

Conjugated bilirubin

Bacterial action

Urobilinogen

Oxidation

Urobilin stercobilin → Faecal excretion
Causes of jaundice.

Causes of jaundice:
- Haemolysis
  - e.g. acquired autoimmune haemolytic anaemia
  - drug-induced, e.g. methyldopa
  - congenital spherocytosis
- Globin
- Haem
- Bilirubin
- Hepatocellular
  - Toxins
  - Infections
- Cholestasis
  - Cirrhosis
  - Tumour 1° or metastases
  - Gallstones
Serum bilirubin levels

- Normal
  - 0.2 – 0.8 mg/dL
- Unconjugated (indirect):
  - 0.2 – 0.7 mg/dL
- Conjugated (direct):
  - 0.1 – 0.4 mg/dL
- Latent jaundice:
  - Above 1 mg/dL
- Jaundice:
  - Above 2 mg/dL
## Bilirubin levels and jaundice

<table>
<thead>
<tr>
<th>Class of Jaundice</th>
<th>Causes</th>
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<tbody>
<tr>
<td>Pre-hepatic or hemolytic</td>
<td>Abnormal red cells; antibodies; drugs and toxins; thalessemia Hemoglobinopathies, Gilbert’s, Crigler-Najjar syndrome</td>
</tr>
<tr>
<td>Hepatic or Hepatocellular</td>
<td>Viral hepatitis, toxic hepatitis, intrahepatic cholestasis</td>
</tr>
<tr>
<td>Post-hepatic</td>
<td>Extrahepatic cholestasis; gallstones; tumors of the bile duct, carcinoma of pancreas</td>
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Urobilinogen (UBG) and bile salts

- Most UBG is metabolized in the large intestine but a fraction is excreted in urine (less than 4 mg/day)

- Normally bile salts are NOT present in urine

- Obstruction in the biliary passages causes:
  - Leakage of bile salts into circulation
  - Excretion in urine
Serum Albumin

- The most abundant protein synthesized by the liver

- Normal serum levels: 3.5 – 5 g/dL

- Synthesis depends on the extent of functioning liver cell mass

- Longer half-life: 20 days

- Its levels decrease in all chronic liver diseases
Serum Globulin

• Normal serum levels: 2.5 – 3.5g/dL

• \( \alpha \) and \( \beta \)-globulins mainly synthesized by the liver

• They constitute immunoglobulins (antibodies)

• High serum \( \gamma \)-globulins are observed in chronic hepatitis and cirrhosis:
  ▫ IgG in autoimmune hepatitis
  ▫ IgA in alcoholic liver disease
Albumin to globulin (A/G) ratio

- Normal A/G ratio: 1.2/1 – 1.5/1

- Globulin levels increase in hypoalbuminemia as a compensation
Prothrombin Time (PT)

- **Prothrombin**: synthesized by the liver, a marker of liver function
- **Half-life**: 6 hrs. (indicates the present function of the liver)
- **PT is prolonged only when liver loses more than 80% of its reserve capacity**
- **Vitamin K deficiency also causes prolonged PT**
- **Intake of vitamin K does not affect PT in liver disease**
Aspartate aminotransferase (AST)

- Normal range: 8 – 20 U/L
- A marker of hepatocellular damage
- High serum levels are observed in:
  - Chronic hepatitis, cirrhosis and liver cancer
Alanine aminotransferase (ALT)

- More liver-specific than AST
- Normal range (U/L):
  - Male: 13-35
  - Female: 10-30
- High serum levels in acute hepatitis (300-1000U/L)
- Moderate elevation in alcoholic hepatitis (100-300U/L)
- Minor elevation in cirrhosis, hepatitis C and non-alcoholic steatohepatitis (NASH) (50-100U/L)
Alanine aminotransferase (ALT)

- Appears in plasma many days before clinical signs appear
- A normal value does not always indicate absence of liver damage
Alkaline phosphatase (ALP)

- A non-specific marker of liver disease
- Produced by bone osteoblasts (for bone calcification)
- Present on hepatocyte membrane
- Normal range: 40 – 125 U/L
- Modearte elevation observed in:
  - Infective hepatitis, alcoholic hepatitis and hepatocellular carcinoma
Alkaline phosphatase (ALP)

• High levels are observed in:
  ▫ Extrahepatic obstruction (obstructive jaundice) and intrahepatic cholestasis

• Very high levels are observed in:
  ▫ Bone diseases
γ-glutamyltransferase (GGT)

- Used for glutathione synthesis
- Normal range: 10 – 30 U/L
- Moderate elevation observed in:
  - Infective hepatitis and prostate cancers
- GGT is increased in alcoholics despite normal liver function tests
  - Highly sensitive to detecting alcohol abuse