Liver Function Tests

Liver is the centre of metabolic activity for carbohydrates, protein, and lipids.

1. **Carbohydrates:** The following metabolic processes occur in the liver:
   a. Glycogen synthesis from glucose via glycogenesis.
   b. Glucose formation in fasting states via gluconeogenesis "from non-carbohydrate compounds" or glycogenolysis "glycogen breakdown".
   c. Pentose phosphate pathway for formation of pentoses and NADPH "for reducing reactions".
   d. Production of pyruvate and lactate from glucose via glycolysis.
   e. Citric acid cycle.

2. **Proteins:** The following metabolic processes occur in the liver:
   a. Deamination of amino acids and urea formation.
   b. Synthesis of albumin and globulin in the hepatocytes.

3. **Lipids:** The following metabolic processes occur in the liver:
   a. Storage of triglycerides.
   b. Synthesis of cholesterol.

Other liver functions include detoxification of many drugs and carcinogens to inactive compounds which will be excreted into bile. For example, most steroid hormones are metabolized to inactive, water soluble substances and some carcinogens are conjugated. These products are excreted in the bile or in the urine.
Liver Function Tests

Liver function tests can be classified according to the specific function of the liver involved as follows:

1- Abnormalities of pigment metabolism:
   a. Serum total, direct, and indirect bilirubin.
   b. Urine bilirubin.

2- Tests based on the liver’s part in carbohydrate metabolism:
   a. Glucose tolerance test.
   b. Fructose tolerance test.

3- Tests based on changes in plasma proteins:
   a. Determination of plasma proteins, albumin, globulin, A/G ratio and fibrinogen.
   b. Amino acids in blood and urine.

4- Tests based on abnormalities of lipids:
   a. Determination of serum total, free and ester cholesterol.
   b. Determination of serum high and low density lipoproteins-cholesterol (HDL-C & LDL-C).
   c. Determination of serum triglycerides and phospholipids.

5- Determination of serum enzyme activities:
   a. Serum alkaline phosphatase (ALP).
   b. Serum transaminases (AST, ALT).

6- Detoxication and conjugation:
   a. Hippuric acid test.
Liver Function Tests

**Total Protein in Serum:**

**Normal ranges:**

<table>
<thead>
<tr>
<th>Age</th>
<th>Total protein (g/dl)</th>
<th>Albumin (g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 days</td>
<td>5.4 – 7.0</td>
<td>2.6 – 3.6</td>
</tr>
<tr>
<td>1 – 3 years</td>
<td>5.9 – 7.0</td>
<td>3.4 – 4.2</td>
</tr>
<tr>
<td>4 – 6 years</td>
<td>5.9 – 7.8</td>
<td>3.5 – 5.2</td>
</tr>
<tr>
<td>7 – 9 years</td>
<td>6.2 – 8.1</td>
<td>3.7 – 5.6</td>
</tr>
<tr>
<td>10 – 19 years</td>
<td>6.3 – 8.6</td>
<td>3.7 – 5.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Globulin (g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>0.4 – 3.7</td>
</tr>
<tr>
<td>1 – 3 years</td>
<td>1.6 – 3.5</td>
</tr>
<tr>
<td>4 – 9 years</td>
<td>1.9 – 3.4</td>
</tr>
<tr>
<td>14 – 49 years</td>
<td>1.9 – 3.5</td>
</tr>
</tbody>
</table>

**A/G ratio:** 1.2 – 2.5

**Pathophysiology:**

- An increase in total proteins may occur in dehydration (vomiting or diarrhea), followed by increase in both albumin and globulin because of the haemoconcentration.

- A decrease in total proteins is due to a low albumin level, accompanied by no increase in globulin, or by a moderate increase, which is less than the fall in albumin, thus A/G ratio is decreased. Plasma protein may also be reduced in severe and acute hemorrhage as well.

A low serum albumin level is due to:

1- Heavy loss of albumin in the urine, as in nephrotic syndrome.

2- Loss of protein or malabsorption of protein from the alimentary tract.

3- Decreased formation of protein in the liver, as in severe liver diseases, due to impaired ability of the liver to form albumin.

4- Increased catabolism of protein.

5- Insufficient protein intake by food (malnutrition).
A reduction in the protein is one of the causes of edema, because protein is the cause of oncotic pressure which attract body fluids from tissue to capillary and by decreased concentration (when osmotic pressure is decreased than blood pressure) fluids are forced to the tissues from the capillary and cause odema. In severe liver disease although the concentration of serum albumin is reduced, that of globulin is usually increased, so that the total protein is either normal or more commonly high.

Globulin concentration is increased in infectious diseases or other processes that result in antibody formation.

**Bilirubin in Serum:**

**Normal ranges:**
Total bilirubin: up to 1 mg/dl. Direct bilirubin: < 0.25 mg/dl.

**Pathophysiology:**

<table>
<thead>
<tr>
<th>Types of Jaundice</th>
<th>Serum Bilirubin</th>
<th>Urobilinogen</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Uncojugated</td>
<td>Conjugated</td>
<td>Urine</td>
</tr>
<tr>
<td>Hemolytic</td>
<td>Increased</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Obstructive</td>
<td>Increased</td>
<td>Increased</td>
<td>Decreased Or absent</td>
</tr>
</tbody>
</table>
Liver Function Tests

Bilirubin and urobilinogen measurements (examples of results in various conditions):

<table>
<thead>
<tr>
<th>Condition</th>
<th>Urine tests (side-room)</th>
<th>Plasma (bilirubin)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urobilinogen</td>
<td>Bilirubin</td>
</tr>
<tr>
<td>Healthy individuals</td>
<td>Trace</td>
<td>Nil</td>
</tr>
<tr>
<td>Gilbert's syndrome</td>
<td>Trace</td>
<td>Nil</td>
</tr>
<tr>
<td>Hemolytic diseases</td>
<td>Increased</td>
<td>Nil</td>
</tr>
<tr>
<td>Hepatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prodromal</td>
<td>Increased</td>
<td>Detectable</td>
</tr>
<tr>
<td>Icteric stage</td>
<td>Undetectable</td>
<td>Present</td>
</tr>
<tr>
<td>Recovery stage</td>
<td>Detectable</td>
<td>Falling</td>
</tr>
<tr>
<td>Biliary obstruction</td>
<td>Undetectable</td>
<td>Present</td>
</tr>
</tbody>
</table>

Type of hyperbilirubinaemia:
- Pre-hepatic hyperbilirubinaemia only plasma [unconjugated bilirubin] often increased.
- Hepatocellular hyperbilirubinaemia both plasma [conjugated bilirubin] and [unconjugated bilirubin] often increased.
- Cholestatic hyperbilirubinaemia, plasma [conjugated bilirubin] is particularly increased.

Bilirubin is used in:
- Differential diagnosis of diseases of hepatobiliary system and pancreas and other causes of jaundice.
- Jaundice becomes apparent clinically at > 2.5 mg/dl.

Serum total bilirubin:
- It is not a sensitive indicator of hepatic dysfunction and may not reflect the degree of liver damage.
- In uncomplicated hemolysis > 5 mg/dl seldom occurs unless hepatobiliary disease is also present.
Liver Function Tests

- Is generally less markedly increased in hepatocellular jaundice (<10 mg/dl) than in neoplastic obstructions (<20 mg/dl) or intrahepatic cholestasis.

- In extrahepatic biliary obstruction, bilirubin may rise progressively to a plateau of 30 – 40 mg/dl due in part to balance between renal excretion and diversion of bilirubin to other metabolites. Such a plateau tends not to occur in hepatocellular jaundice and bilirubin may exceed 50 mg/dl (partly due to concomitant renal insufficiency and hemolysis).

- Concentrations are generally higher in obstruction due to carcinoma than that due to stones.

- In viral hepatitis, higher serum bilirubin suggests more liver damage and longer clinical course.

- In acute alcoholic hepatitis >5 mg/dl suggests a poor prognosis.

- Increased serum bilirubin with normal ALP suggests constitutional hyperbilirubinemias or hemolytic states,

- Normal serum bilirubin, AST and ALT with increased ALP (of liver origin) and LDH suggests obstruction of one hepatic duct or metastatic or infiltrative disease of liver. Metastatic and granulomatous lesions of liver cause 1.5 – 3.0 times increase of serum ALP and LDH.

**Direct (conjugated) bilirubin is increased in:**

- Hereditary disorders

- Hepatic cellular damage. Increased conjugated bilirubin may be associated with normal total bilirubin in up to one-third of patients with liver diseases.

- Hemolytic diseases (RBC enzyme deficiencies and autoimmune hemolysis).

- Ineffective erythropoiesis.

- Incompatible blood transfusions.

- Hematomas.
Serum Transaminases:

Transamination is a process in which an amino group is transferred from an $\alpha$-amino acid to an $\alpha$ keto acid. As a result different amino acids and $\alpha$ keto acids are formed. This process is catalyzed by transaminases or aminotransferases. These enzymes formed in liver, require pyridoxal 5–phosphate as a cofactor.

There are two important enzymes:

1- Serum aspartate transaminase (AST) or glutamate–oxaloacetate transaminase (SGOT): this enzyme catalyzes the transfer of amino group from glutamate to oxaloacetate. It is present in greatest concentration in cardiac muscle, liver, kidney and skeletal muscle.

2- Serum alanine transaminase (ALT) or glutamate–pyruvate transaminase (SGPT): it catalyzes the transfer of amino group from glutamate to pyruvic acid.

Normal distribution of these enzymes in body tissues:
Both enzymes are found in most tissues but the relative amounts vary.

<table>
<thead>
<tr>
<th></th>
<th>Heart</th>
<th>Liver</th>
<th>Kidney</th>
<th>Pancreas</th>
<th>Spleen</th>
<th>Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (IU/L)</td>
<td>151</td>
<td>137</td>
<td>88</td>
<td>27</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>7</td>
<td>43</td>
<td>19</td>
<td>2</td>
<td>1.2</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Normal range:
GOT: 4 – 20 IU/L
GPT: 2 – 17 IU/L

Pathophysiology:
- GOT increases in:
  1- Myocardial infarction (not specific for this condition). The increase begins 3-6 hrs after the onset of the attack and returns to normal in 3 – 6 days.
Liver Function Tests

2- Congestive heart failure.
3- Hypoxia (in few days of the onset).
4- Trauma of skeletal muscle.

• GOT and GPT increase in:
  1- Liver disease particularly in infective hepatitis (GPT > GOT).
  2- The action of drug and toxic substances (the most marked increase is found with those acting directly on the liver cells).
  3- Toxic hepatitis (due to CCl4).
  4- Advanced cirrhosis.
  5- In the early stages of obstructive jaundice due to destruction of the large bile passages (200 – 300 units) then falling, when recovery takes place. So, the determination can be useful in showing the severity of the disease.
  6- In newborn, values up to 120 units for GOT and 90 units for GPT must be considered normal.

AST/ALT (sGOT / sGPT) Ratio:

Normal range = 0.7 – 1.4 (depending on methodology). It is used in differential diagnosis of diseases of hepatobiliary system and pancreas. It increases in:

• Drug hepatotoxicity (> 2.0)
• Alcoholic hepatitis (>2.0 is highly suggestive)
• Cirrhosis (1.4 – 2.0)
• Intrahepatic cholestasis [retention and accumulation of the bile in the liver due to factors within the liver] (> 1.5)
• Hepatocellular carcinoma
• Chronic hepatitis.
Liver Function Tests

And it decreases in:

- Acute hepatitis due to virus, drugs, toxins (with AST increased 3-10 times the upper limit of normal) (usually < 0.65 ratio 0.3 – 0.6 is said to be a good prognostic sign but higher ratio of 1.2 – 1.6 is a poor prognostic sign)
- Extrahepatic cholestasis (normal or slightly decreased).

Alkaline phosphatase (ALP) activity in serum:

It catalyzes the splitting of phosphate group from phosphate esters, in alkaline medium (pH 10). Its sites of action include bone (osteoblast), liver (bile canaliculi), intestine and kidney. Most of ALP in adult blood comes from liver, but in children it comes from bone due to growth.

It is used for diagnosis and monitoring cholestasis as well as diagnosis of various bone disorders.

Normal ranges:

<table>
<thead>
<tr>
<th>Age</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 – 3 yrs.</td>
<td>145 – 320 U/L</td>
<td></td>
</tr>
<tr>
<td>4 – 6 yrs.</td>
<td>150 – 380 U/L</td>
<td></td>
</tr>
<tr>
<td>7 – 9 yrs.</td>
<td>175 – 420 U/L</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 – 11 yrs.</td>
<td>135 – 530 U/L</td>
<td>130 – 560 U/L</td>
</tr>
<tr>
<td>12 – 13 yrs.</td>
<td>200 – 495 U/L</td>
<td>105 – 420 U/L</td>
</tr>
<tr>
<td>14 – 15 yrs.</td>
<td>130 – 525 U/L</td>
<td>70 – 230 U/L</td>
</tr>
<tr>
<td>16 – 19 yrs.</td>
<td>65 – 260 U/L</td>
<td>50 – 130 U/L</td>
</tr>
</tbody>
</table>

In children: ALP is 2.5 times more than that in adult.

Pathophysiology:

ALP increases in:

1. Bone origin:
   - Increased deposition of calcium.
Liver Function Tests

- Hyperparathyroidism. "excessive secretion of PTH → ↑ serum Ca\(^{+2}\) level → ↑ deposition of Ca\(^{+2}\) in bone".
- Prostatic carcinoma that metastases to bone.
- Osteomalacia, rickets. Osteomalacia is due to a defect in active vit D in adults. Rickets is due to a defect in active vit D in children.
- Hyperthyroidism. Thyroid hormones stimulate: increased bone turnover, increasing bone resorption, and to a lesser degree bone formation. So, in chronic hyperthyroidism, there is osteopenia. In severe cases, there are hypercalcemia and increased excretion of hydroxyproline.
- Pregnancy.
- Osteoporosis.

2. Liver disease:

- Hepatic congestion due to heart disease.
- Increased synthesis of ALP in liver as in Diabetes Mellitus (44% of diabetic patients have 40% increase of ALP) and parenteral hyperalimentation of glucose.
- Acute hepatitis (viral, toxic, alcoholic).
- Acute fatty liver.
- Cirrhosis.
- Carcinoma of head of pancreas.
- Drug cholestatic hepatitis.
- Primary or metastatic carcinoma.
Liver Function Tests

ALP decreases in:

- Excess vitamin D ingestion.
- Congenital hypophosphatasia.
- Hypothyroidism, cretinism.
- Pernicious anemia in one-third of patients.
- Malnutrition.
- Scurvy.
- Zinc deficiency.
- Postmenopausal women with osteoporosis taking estrogen replacement therapy.
- Therapeutic agents e.g. corticosteroids.