# Liver Functions and Liver Functions Tests

## Liver:

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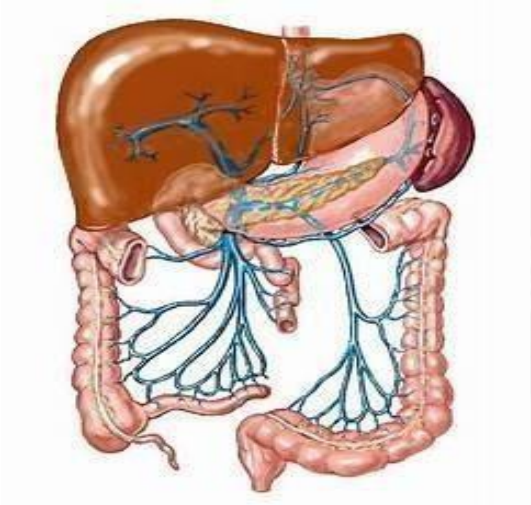
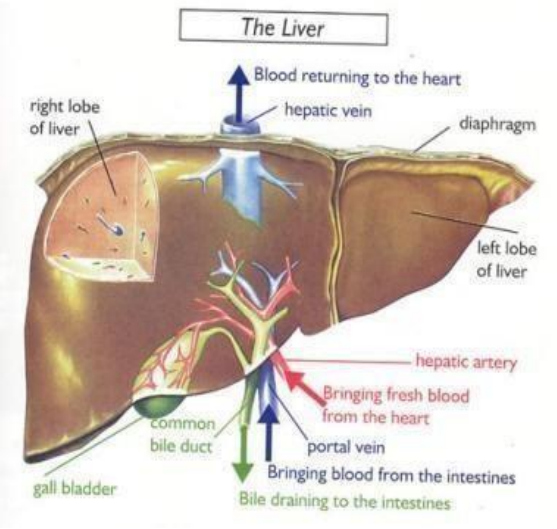





## Liver

Two main liver lobes are each made up of thousands of lobules; lobules connect to small ducts that connect to larger ducts, forming the hepatic duct. The hepatic duct transports bile, produced by the hepatocytes, to the gallbladder and duodenum.

Blood leaves the stomach and intestines, gastric and spleen, passing through the liver (hepatic portal vein), while oxygenated blood is supplied through the hepatic artery.

The liver regulates, synthesizes, stores and secretes many important proteins and nutrients, and purifies, transforms and clears toxic or unnecessary compounds from the blood. Hepatocytes are optimized for function through their contact with sinusoids (leading to and from blood vessels) and bile ducts.

A special feature of the liver is its ability to regenerate, maintaining function even in the face of moderate damage.

## Bilirubin

In adults some 250–400 mg of bilirubin is produced daily; 70–80% is derived from degradation of the haem moiety of haemoglobin, 20–25% is derived from the hepatic turnover of haem proteins, such as myoglobin, cytochromesand catalase.

Bilirubin is a potentially toxic catabolic product of haem metabolism. It is poorly soluble in water at physiologic pH, and conversion to a water-soluble form is essential for elimination by the liver and kidney.

Within the hepatocyte, the enzyme glucuronyl transferase UGT-1 covalently attaches one or two molecules of glucuronic acid to bilirubin, generating either bilirubin mono- or di-glucuronide. These glucuronic acid-attached species of bilirubin are termed "Conjugated Bilirubin" and are now water soluble.

Conjugated Bilirubin cannot be transported past the GI mucosa and so travels down the GI Tract. However, the normal GI bacterial flora convert the vast majority of conjugated bilirubin to colorless "Urobilinogen" and a small amount to brown-colored "Urobilin".

About 90% of urobilinogen is excreted along with the feces; however, about 10% is resorbed by the GI Mucosa and enters the blood stream where it is once again recaptured by hepatocytes and re-excreted in the bile.

The majority of urobilin is also excreted in the feces, giving it the characteristic brown color after converted to stercobilin; however, a small minority is resorbed by the GI mucosa and is ultimately excreted by the kidneys, giving urine its yellowish hue.

## Jaundice

Jaundice is a clinical term referring to yellowing of body tissues due to deposition of bilirubin. Because bilirubin has a high affinity for the sclera of the eye, the most sensitive indicator of Jaundice is yellowing of the sclera, termed scleral icterus, which occurs when plasma bilirubin levels are greater than 3.0mg/dl.

| Bilirubin type | Bilirubin level |
|---|---|
| Total bilirubin | 0.3–1.0 mg/dl or 5.1–17.0 mmol/l |
| Direct bilirubin | 0.1–0.3 mg/dl or 1.7–5.1 mmol/l |
| Indirect bilirubin (total bilirubin level minus direct bilirubin level) | 0.2–0.8 mg/dl or 3.4–12.0 mmol/l |

**Protein Metabolism – Nitrogen Metabolism and The Urea Cycle:**

The interconversion of amino acids, mainly through transamination reactions **catalysed by aminotransferases,** is essential to balancing the requirements for protein synthesis, while in protein catabolism the amino nitrogen must be removed in the form of ammonia (ammonium) and converted to urea for excretion by the kidneys.

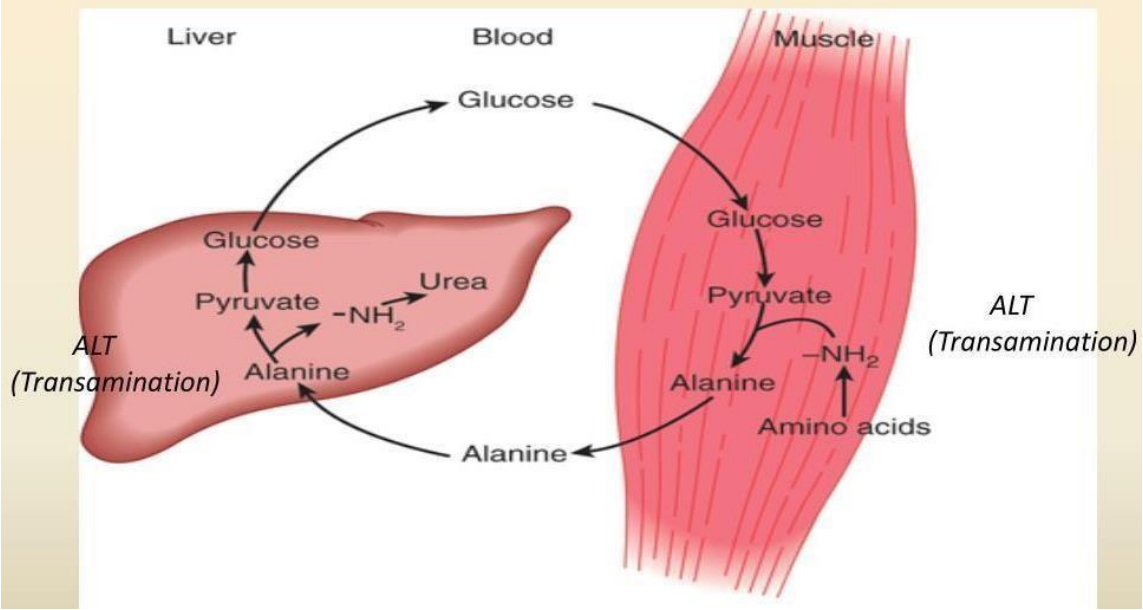
Most amino acids are **glucogenic**, meaning that their carbon skeletons (ketoacid) can be converted to glucose through gluconeogenesis.

There are specific aminotransferases for all amino acids, except threonine and lysine, and they are particularly abundant in the liver.

Alanine transaminase (ALT) and aspartate transaminase (AST) are used as clinical markers of tissue damage. ALT has an important function in the delivery of skeletal muscle carbon and nitrogen (in the form of alanine) to the liver. In skeletal muscle, pyruvate is transaminated to alanine, thus affording an additional route of nitrogen transport from muscle to liver.

In the liver, ALT transfers the ammonia to α-ketoglutarate and regenerates pyruvate. The pyruvate can then be diverted into gluconeogenesis. This process is referred to as the glucose–alanine cycle.

In peripheral tissues, two enzymes, namely glutamate dehydrogenase and glutamine synthetase, are important in the removal of reduced nitrogen, and particularly so in the brain, which is highly susceptible to free ammonia.




## The urea cycle:

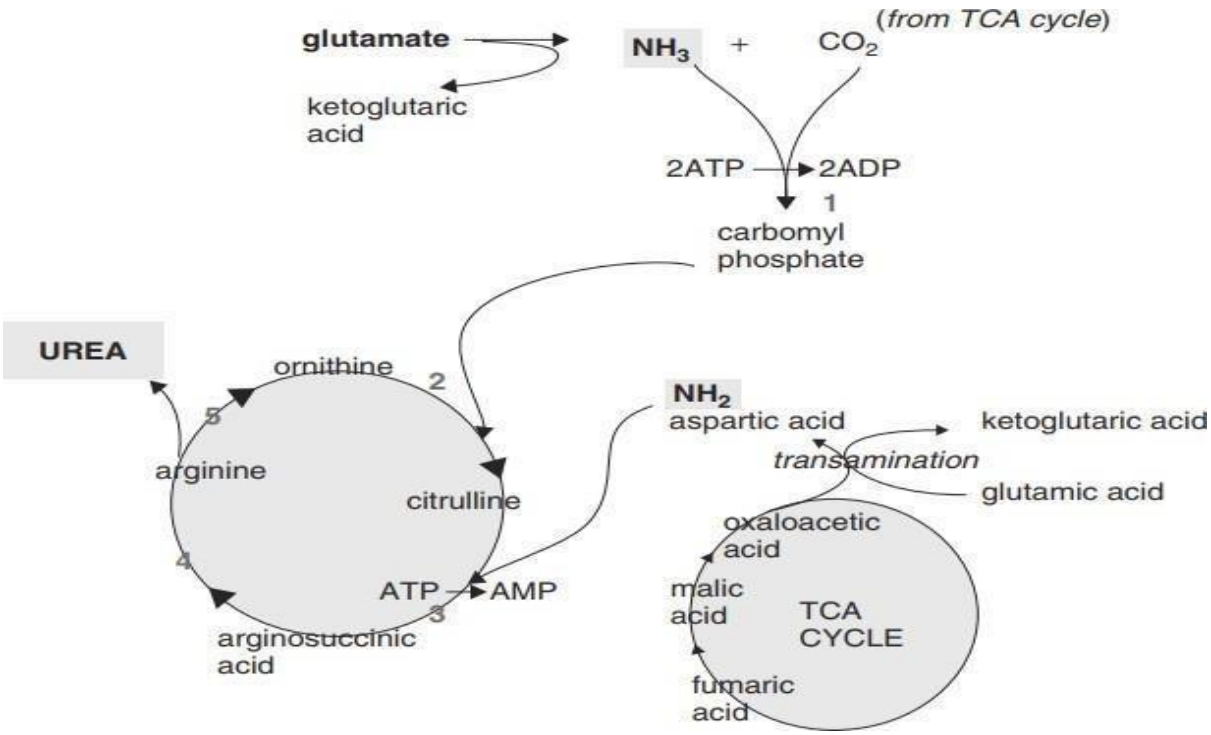
The urea cycle is responsible for the excretion of some 80% of the body's excreted nitrogen in the form of urea; this is generated in the liver.

### Regulation of the urea cycle:

The urea cycle operates only to eliminate excess nitrogen. On high-protein diets the carbon skeletons of the amino acids (keto acids) are oxidized for energy or stored as fat and glycogen, but the amino nitrogen must be excreted.

To facilitate this process, urea-cycle enzymes are closely controlled at the gene level. With long-term changes in the quantity of dietary protein, changes of 20- fold or greater in the concentration of cycle enzymes are observed.

Under conditions of starvation, enzyme levels rise as proteins are degraded and amino acid carbon skeletons are used to provide energy, thus increasing the quantity of nitrogen that must be excreted.




## Cirrhosis of the liver

Cirrhosis of the liver is the third most common cause of death, after heart disorders and cancer, among the 45–65 age group. Cirrhosis has many possible causes, sometimes more than one cause is present in the same patient. In the Western world, chronic alcoholism and hepatitis C are the most common causes.

## Liver Function Tests

**Write a short note on liver function tests.**

**Liver function tests:** They are tests done to assess the functional capacity of liver (Table 1,3).

## Functions of liver:

- Metabolism: Carbohydrates, lipids and proteins
- Excretion: Bilirubin, bile acids and bile salts
- Synthesis: Albumin, α- and β-globulins, clotting factors, cholesterol, lipoprotein
- Storage: Glycogen, vitamins (A, D, B12), etc.
- Detoxification and drug metabolism.

# Liver Functions

## Liver function tests are used to:

- Detect and diagnose liver disease
- Evaluate the severity of liver disease
- Monitor response to therapy
- Assess prognosis of liver disease.

### Table 1:(liver function tests).

| Class | Tests |
|---|---|
| Tests based on **excretory** function | Estimation of serum/urine bilirubin, bromsulfthalein |
| Tests based on **serum enzymes (indicator of liver damage/cholestasis)** | Estimation of serum alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), γ-glutamyl transferase (GGT) |
| Tests based on **synthetic** functions | Total proteins, serum albumin, globulin, albumin globulin ratio, prothrombin time |
| Tests based on **detoxification** | Hippuric acid test, blood ammonia |

### Table 2:(important liver function tests).

| Tests | Normal range | Methods | Clinical utility |
|---|---|---|---|
| Total bilirubin | 0.2–0.8 mg/dL | van den Bergh reaction | Helps in diagnosis of jaundice |
| Direct bilirubin | 0.1–0.2 mg/dL | van den Bergh reaction | ↑ in hepatic and obstructive jaundice |
| Indirect bilirubin | 0.2–0.6 mg/dL | Total bilirubin – direct bilirubin | ↑ in hemolytic jaundice |
| ALT | 5–40 U/L | Enzymatic method | ↑ in liver damage (e.g. hepatitis) |
| AST | 5–40 U/L | Enzymatic method | ↑ in liver damage (e.g. hepatitis) |
| ALP | 40–140 U/L | Enzymatic method | ↑ in obstructive jaundice |
| Total protein | 6–8 g/dL | Biuret | ↓ in cirrhosis of liver |
| Albumin | 3.5–5 g/dL | Biuret | ↓ in cirrhosis of liver |
| Globulin | 2–3.5 mg/dL | Total protein – albumin | ↑ in multiple myeloma, ↓ in HIV infection |

HIV, human immunodeficiency virus; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; ↑ = increased; ↓ = decreased.

### Table 3:(other tests with uses).

| Tests | Normal range | Clinical utility |
|---|---|---|
| γ-glutamyl transferase (GGT) | 10–50 U/L | ↑ in alcoholic hepatitis and obstructive jaundice |
| Prothrombin time | < 14 second | ↑ in hepatocellular disease |
| Plasma ammonia | 25–94 µg/dL | ↑ in severe hepatocellular disease |
| Alfa-fetoprotein (AFP) | < 15 ng/mL | ↑ in germ cell tumor, ↑ in maternal serum in neural tube defect in fetus |

↑ = increased; ↓ = decreased

# Liver Functions

## Explain the biochemical findings in blood, urine and feces in different types of jaundice.

**Definition:** Jaundice is defined as yellowish discoloration of skin, nail beds and sclera. It is caused by deposition of bilirubin, secondary to increased bilirubin levels in the blood. When bilirubin concentration is more than 1 mg/dL, the condition is called hyperbilirubinemia. At a concentration of more than 2 mg/dL, bilirubin diffuses into tissues, which then becomes yellow, leading to jaundice or icterus.

## Classification:

Jaundice is classified into three major types:

A. **Prehepatic (hemolytic):**
Due to excessive hemolysis, bilirubin production exceeds the capacity of liver toconjugate it.

B. **Hepatic:**
Impaired uptake, conjugation or excretion of bilirubin.

C. **Postherpetic (obstructive):**
Caused by an obstruction in the biliary tract (Table 4).

**Table 4: (Classification and findings in jaundice)**

| Type of jaundice | Causes | Serum bilirubin | Urine and feces | Serum ALT and AST | Serum ALP |
|---|---|---|---|---|---|
| Prehepatic [MN: MARS] | **M**alaria<br>**A**utoimmune hemolytic anemia<br>**R**h incompatibility<br>**S**ickle cell anemia | ↑ unconjugated bilirubin | • ↑ urobilinogen<br>• Bilirubin negative<br>• ↑ stercobilinogen | Normal or slight ↑ | Normal or slight ↑ |
| Hepatic | Hepatitis | ↑ conjugated and ↑ unconjugated bilirubin | • Bilirubin present (if microobstruction)<br>• ↓ urobilinogen (if microobstruction) | Markedly elevated | Normal or slight ↑ |
| Post-hepatic | Gallstones<br>Pancreatic tumor<br>Cholangiocarcinoma | ↑ conjugated bilirubin | • Urobilinogen absent<br>• Bilirubin present<br>• Clay-colored stool | Normal or slight ↑ | Markedly elevated |

↑ = increased; ↓ = decreased

## Congenital hyperbilirubinemia.

**Definition:** A group of hereditary disorders of bilirubin metabolism due to defect in uptake, conjugation or secretion of bilirubin.