Lecture: 3 **Dr. Maytham Ahmed**

Liver Function Tests

The liver

The liver is the largest organ in the body, contributing about 2 per cent of the total body weight, or about 1.5 kg in the average adult human. It is reddish brown in color and has a rich blood supply 1500 ml/min from two major vessels, the hepatic artery and the portal vein. The hepatic artery, a branch of the aorta, contributes 20% of the blood supply and provides most of the oxygen requirement. The portal vein, which drains the gastrointestinal tract, transports the most recently absorbed materials from the intestines to the liver.

The basic functional unit of the liver is the **liver lobule**, which is a cylindrical structure several millimeters in length and 0.8 to 2 millimeters in diameter. The human liver contains 50,000 to 100,000 individual lobules. The liver lobule (Figure 1), is constructed around a central vein that empties into the hepatic veins and then into the vena cava. The lobule itself is composed principally of many liver cellular plates. Each hepatic plate is usually two cells thick, and between the adjacent cells lie small bile canaliculi that empty into bile ducts.

The boundary of each lobule made up of connective tissue containing a branch of the hepatic artery, portal vein and bile duct. Between the cords of the liver cells are vascular spaces, called sinusoids, that are lined by endothelial cells and Kupffer's cells. The Kupffer's cells are phagocytic macrophages capable of ingesting bacteria or other foreign material from the blood that flows through the sinusoids. Hepatocytes form 60%, Kupffer's cells 30%, endothelial cells, connective tissue and bile ducts 10% of the liver

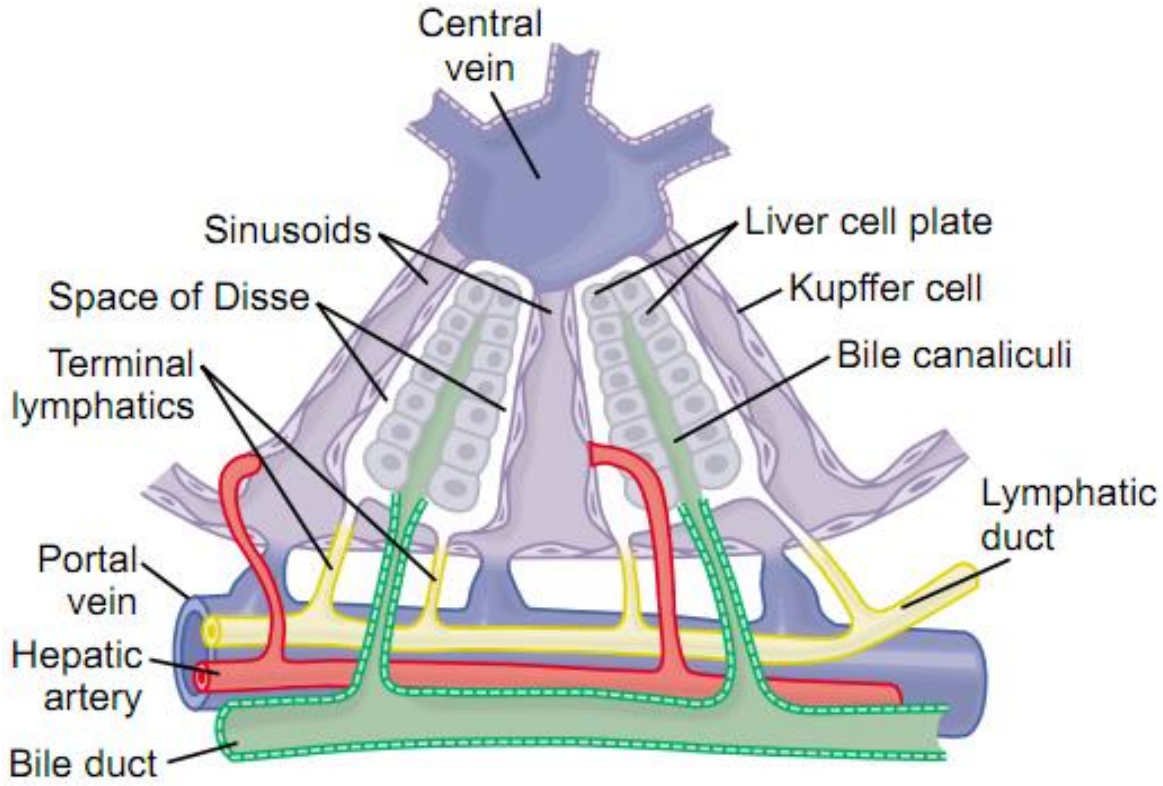

Figure (1) Basic structure of a liver lobule

Functions of liver

1. Excretory function: bile pigments, bile salts and cholesterol are excreted in bile into intestine.

2. Metabolic function: liver actively participates in carbohydrate, lipid, protein, mineral and vitamin metabolisms.

3. Hematological function: liver is also produces clotting factors like factor V, VII. Fibrinogen involved in blood coagulation is also synthesized in liver. It synthesize plasma proteins and destruction of erythrocytes.

4. Storage functions: glycogen, vitamins A, D and B_{12} and trace element iron are stored in liver.

5. Detoxification functions: Ammonia is detoxified to urea. Liver is responsible for the metabolism of xenobiotic.

6. Protective functions: kupffer cells of liver perform phagocytosis to eliminate foreign compounds.

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Liver function tests

1. Total serum bilirubin (TSB), direct (conjugated) and indirect (unconjugated) bilirubin.
2. Albumin and prothrombin time.
3. Liver enzymes include:

Alanine transaminase (ALT), Aspartate transaminase (AST), Alkaline phosphatase (ALP), γ - Glutamyl transferase (GGT) and Lactate dehydrogenase (LD).

1. Bilirubin metabolism

Reticulo-endothelial system is mainly in liver, spleen and bone marrow. About 80% of bilirubin formed from heme each day arise from red blood cells. The remaining 20% comes from red cell precursors destroyed in the bone marrow (ineffective erythropoiesis), and from other heme proteins such as myoglobin, cytochromes, catalase and peroxidase.

Hemoglobin is broken down to globin and heme. Globin go to protein pool. Heme is broken down to iron (go to iron pool) and biliverdin by heme oxygenase, then biliverdin reduced by biliverdin reductase to produce bilirubin. **Bilirubin is soluble in lipid solvents but almost insoluble in water**. These characteristics enable it to cross cell membrane readily, but special mechanisms are needed to make it water-soluble for carriage in plasma by protein-binding mainly to albumin forming indirect or unconjugated bilirubin. In this form, it does not readily enter most tissues, nor it is filtered at the glomerulus.

The bilirubin-albumin complex appears to be associated by receptors on the plasma membrane of the hepatocytes, bilirubin taken up by a specific carrier (facilitated diffusion), leaving albumin in the plasma. **Conjugation of bilirubin within the hepatocytes makes it water-soluble**. The enzyme is Bilirubin-UDP-glucuronyl transferase forms bilirubin-diglucuronide (direct or conjugated bilirubin). Then it secreted into bile and then to intestine. Bilirubin diglucuronide is degraded by bacterial

action, mainly in the colon, being deconjugated and then converted into a mixture of compounds collectively termed urobilinogen (stercobilinogen).

Urobilinogen is water soluble, mostly excreted in the feces but a small percentage (20%) is reabsorbed and then mostly re-excreted by the liver. After excretion, urobilinogen (colorless) is oxidized to stercobilin which is brown and gives stools its color. Some of the reabsorbed urobilinogen passes through the liver into the systemic circulation and is then excreted in the urine (urobilin) gives the urine its yellow color.

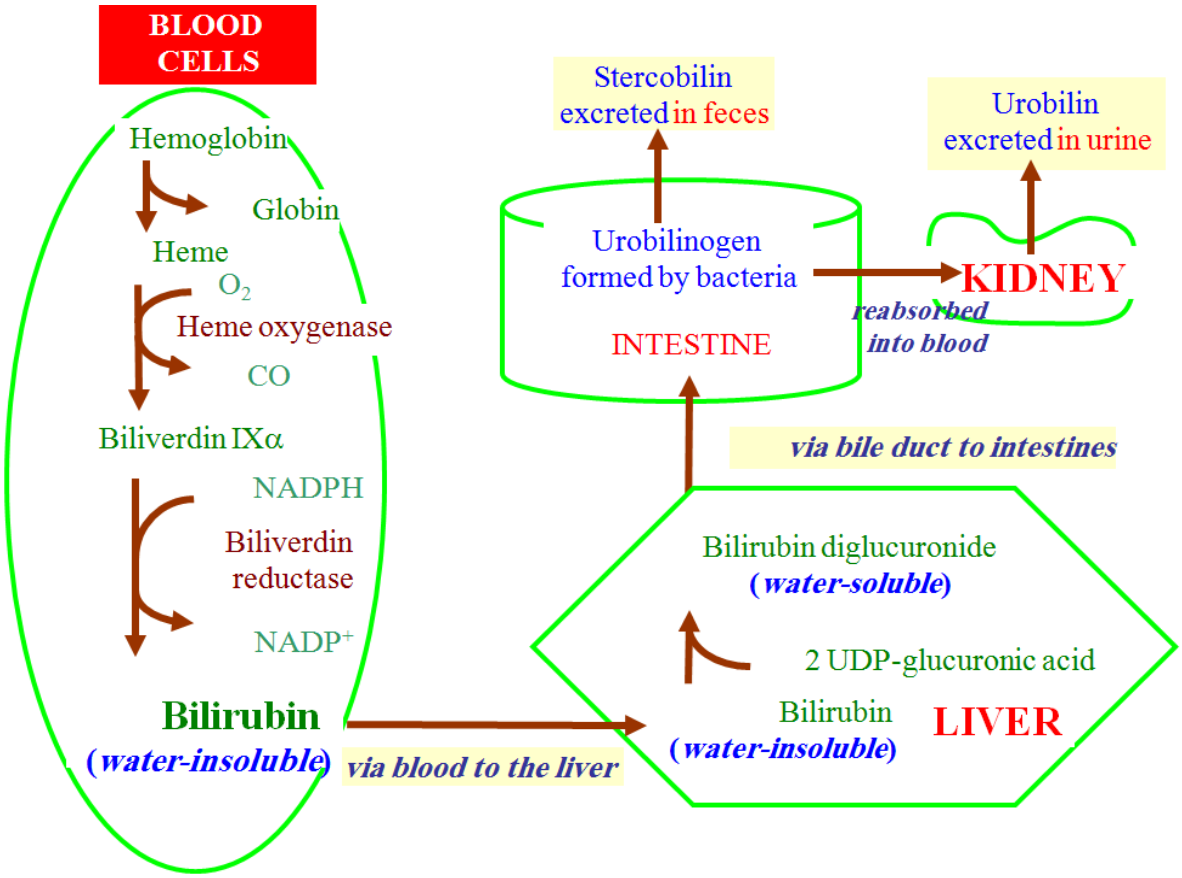

Figure (2) Bilirubin metabolism

Jaundice

Jaundice is the yellowish discoloration of the skin and sclera due to hyperbilirubinemia. **Bilirubin is a yellow pigment**, its normal plasma level is 2-17 μmol/L. Normally, more than 95% of bilirubin in the plasma is indirect (unconjugated). Jaundice becomes clinically apparent when the plasma bilirubin exceeds 50 μmol/L.

Jaundice may be classified into:

1. Pre-hepatic jaundice

The production rate of bilirubin is increased, exceeding the excretory capacity of the liver. Overproduction of bilirubin occurs in all forms of hemolytic anemia, less commonly, in conditions where there is much ineffective erythropoiesis (e.g. pernicious anemia). Indirect (unconjugated) hyperbilirubinemia may occur in pre-hepatic jaundice. Bilirubin is not excreted in urine. Urinary urobilinogen concentration is increased.

2. Hepatocellular jaundice

Hepatocellular damage due to viral hepatitis or toxins may interfere with the uptake of bilirubin, or with its conjugation or with secretion of conjugated bilirubin into bile. Both indirect (unconjugated) and direct (conjugated) hyperbilirubinemia may occur in hepatocellular jaundice. Bilirubin and excess urobilinogen are found in urine.

3.Post-hepatic (Obstructive) (Cholestatic) jaundice

It is due to impaction of gallstones in the common bile duct or carcinoma of the head of pancreas or of the biliary tree. Direct (conjugated) hyperbilirubinemia may occur in obstructive Jaundice. Bilirubin is detected in urine. It characterized by dark urine and pale stool.

Class of Jaundice	Type of Bilirubin raised	Causes
Pre-hepatic or hemolytic	Unconjugated	Abnormal red cells; antibodies; drugs and toxins; thalessemia Hemoglobinopathies (Gilbert' s, Crigler-Najjar syndrome)
Hepatic or Hepatocellular	Unconjugated and conjugated	Viral hepatitis, toxic hepatitis, intrahepatic cholestasis
Post-hepatic	Conjugated	Extrahepatic cholestasis; gallstones; tumors of the bile duct, carcinoma of pancreas

Congenital hyperbilirubinemias:

Include Gilbert's Disease (Syndrome), Crigler-Najjar Syndrome, Dubin –Johnson Syndrome and Rotor's Syndrome

2. Albumin and prothrombin time

The measurement of plasma albumin and prothrombin time may be used to assess the hepatic synthetic function.

A. Albumin

Hypoalbuminaemia is such a common finding in many severe illnesses that it is a less specific indicator of impaired synthetic capacity than a prolonged prothrombin time. However, there are many other causes of a low plasma albumin concentration that are not due to hepatic disease such as loss into urine, gut or (ascitis). Albumin has a long half-life of 20 days and levels fall slowly if no synthesis occur. Thus, serum albumin is usually normal in acute hepatitis. However, in chronic liver diseases such as cirrhosis, impaired synthesis may lead to low serum levels (i.e. a plasma albumin concentration below the lower reference limit may imply hepatic disease chronicity). Serum globulins are usually increased in cirrhosis as a reflex to decrease albumin concentration.

B. Prothrombin time

The prothrombin time may be prolonged by cholestasis, fat-soluble vitamin K cannot be absorbed normally if fat absorption is impaired due to intestinal bile salt deficiency. The abnormality is then corrected by parenteral administration of the vitamin K. A prolonged prothrombin time may also result from severe impairment of synthetic ability of clotting factors if the liver cell mass is greatly reduced; in such cases it is not corrected by parenteral administration of vitamin K.

3. Liver enzymes

A. Aspartate transaminase (AST)

Aspartate transaminase is involved in amino acid metabolism. It has widespread tissue distribution including liver, red blood cells, skeletal and cardiac muscle. **No tissue specific isoenzymes**. Cytosolic and mitochondrial enzyme.

B. Alanine transaminase (ALT)

Alanine transaminase is involved in amino acid metabolism. It is **more liver specific**. Cytosolic enzyme only.

The ALT is more specific for hepatic disease because AST may be present also in skeletal muscle and other tissues. AST is more sensitive than ALT.

A rise in plasma aminotransferase activities is a sensitive indicator of damage to cytoplasmic and/or mitochondrial membranes. Raised plasma transaminase concentrations are indicative of **hepatocyte damage**, but do not necessarily reveal its mechanism. In inflammatory or infective conditions, such as viral hepatitis, the cytoplasmic membrane sustains the main damage; leakage of cytoplasmic contents causes a relatively greater increase in plasma ALT than AST activities (acute hepatitis). In filtrative disorders in which there is damage to both mitochondrial and cytoplasmic membranes, there is a proportionally greater increase in plasma AST than ALT activity (chronic hepatitis).

C. Alkaline phosphatase (ALP)

Alkaline phosphatase has widespread tissue distribution including liver, bone, placenta and GIT. The liver isoenzyme can be identified by electrophoresis. It is located on the outside of the cell membrane (canalicular side of liver cell). It is released into plasma in **cholestasis** (obstructive) because of increased synthesis.

D. Gamma-glutamyl transpeptidase (GGT)

Gamma-glutamyl transpeptidase is **more liver specific**. It is involved in the transport of amino acids across the liver cell plasma membrane. Serum level increased by cholestasis (obstructive) or chronic ingestion of alcohol, barbiturates, phenytoin and other drugs which induce the enzyme.

E. Lactate dehydrogenase (LDH)

Lactate dehydrogenase has widespread tissue distribution including liver, red blood cells, skeletal and cardiac muscle. Tissue specific isoenzymes can be separated by electrophoresis. The LD5 isoenzyme is found in liver and skeletal muscle only.

Cirrhosis

Cirrhosis is the end result of many inflammatory and metabolic diseases involving the liver, including prolonged toxic damage, usually due to alcohol. The fibrous scar tissue distorts the hepatic architecture, and regenerating nodules of hepatocytes disrupt the blood supply, sometimes increasing the pressure in the portal vein, causing portal hypertension. Blood may be shunted from the portal into the hepatic vein, bypassing the liver. **In the early stages there may be no abnormal biochemical findings.**

During phases of active cellular destruction, the plasma AST, and sometimes ALT, activities rise. In advanced cases, the biochemical findings are mostly associated with a reduced functioning cell mass. Portal hypertension and impaired lymphatic drainage lead to fluid accumulation in the peritoneal cavity (ascites). This may be aggravated by hypoalbuminaemia (decrease synthesis of albumin), which may also cause peripheral oedema. In advanced cirrhosis, the findings of hepatocellular failure develop.

Neonatal Jaundice

- ✓ Physiologic jaundice (non-pathologic).There is **unconjugated** hyperbilirubinemia.
- ✓ Appears after 24 hours of birth. Normal full term babies may show jaundice between days 2 and 8 of life. Maximum intensity by 4th-5th day in term and 7th day in preterm.
- ✓ Plasma bilirubin level rarely exceeds 100 µmol/L.
- ✓ Transient ,clinically not detectable after 14 days.
- ✓ Can disappears without any treatment.
- ✓ Red cell destruction (increased bilirubin load), together with immature hepatic processing of bilirubin because the activity of bilirubin-UDP-glucuronyl transferase is

low at birth may cause a high plasma level of unconjugated bilirubin in the newborn infant

Non-physiologic jaundice (pathologic hyperbilirubinemia)

- ✓ There is unconjugated or conjugated hyperbilirubinemia or both.
- ✓ Appears within 24 hours of age (on the first day of life).
- ✓ Levels of bilirubin exceeding 100 mmol/L.
- ✓ Jaundice persisting after 14 days
- ✓ There are many causes including:
- ❖ Hemolytic disease: Rh and ABO incompatibility
- ❖ Infections: cytomegalovirus, malaria and bacterial infections
- ❖ G6PD deficiency
- ❖ Cirrhosis hepatitis and obstruction of common bile duct.

Bilirubin Neurotoxicity (kernicterus)

Unconjugated bilirubin is lipophilic and crosses the blood brain barrier (BBB). The BBB of infants is more permeable than adults. Unconjugated bilirubin has an affinity for the basal ganglia, hippocampus, cranial nerve nuclei. Unconjugated bilirubin interrupts metabolism in glial cells and causes apoptosis of neurons.

Treatment

- Purposes: reduce level of serum bilirubin and prevent bilirubin toxicity
- Prevention of hyperbilirubinemia: early feeds, adequate hydration
- Reduction of bilirubin levels: phototherapy, exchange transfusion
- Drugs: use of **phenobarbital** promote liver enzymes and protein synthesis