Liver
Functions of liver:

1- **Metabolic functions and blood glucose regulation:**
   - When the glucose concentration is high in the portal vein → it is converted to glycogen (glycogenesis)
   - During fasting the systemic plasma glucose concentration is maintained by:
     1) Breakdown of glycogen (glycogenolysis)
     2) Synthesis of glucose from (glycerol, lactate and amino acids) (gluconeogenesis).
   - Fatty acids reaching the liver from fat stores may be:
     1) metabolized in the **tricarboxylic acid cycle**
     2) converted to ketones
     3) incorporated into triglycerides

2- **Synthetic functions:** Hepatocytes synthesize:
   1) Plasma proteins (albumin & globulins) except immunoglobulins and complement.
   2) Most coagulation factors.
   3) Lipoproteins, VLDL and HDL.
   4) Primary bile acids.

   The liver has a very large functional reserve

   Deficiencies in synthetic function can only be detected if liver disease is extensive

3- **Excretion and detoxification:**
   1. Amino acids, cholesterol, steroid hormones → metabolized and inactivated by conjugation with glucuronate and sulphate → excreted in the urine in water-soluble forms.
   2. Many drugs, toxins; by reticulo-endothelial Kupffer cells
   3. Bilirubin

Efficient excretion of the end-products of metabolism and of bilirubin depends on normally functioning liver cells & normal blood flow through the liver and patent biliary ducts.

Efficient detoxification depends on the **Kupffer cell function**.
### Liver disease:

<table>
<thead>
<tr>
<th>1) Hepatitis</th>
<th>2) Non-alcoholic fatty liver disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>inflammation of the liver caused by: viruses, poisons (alcohol), autoimmune hepatitis (autoimmune hepatitis) or hereditary conditions</td>
<td>Accumulation of large amount of neutral fat in liver cells usually associated with obesity</td>
</tr>
<tr>
<td>The condition can be self-limiting (healing on its own) or can progress to fibrosis (scarring) and cirrhosis</td>
<td>It is related to insulin resistance and the metabolic syndrome so→ may respond to treatments developed for other insulin-resistant states (e.g. diabetes mellitus type 2) such as weight loss, metformin and thiazolidinediones</td>
</tr>
<tr>
<td>Diagnosis is done by checking levels of Alanine transaminase (ALT)</td>
<td>May lead to hepatitis→ steato-hepatitis→ cirrhosis</td>
</tr>
<tr>
<td>Hepatitis usually with no symptoms, but if present jaundice, anorexia and malaise</td>
<td>Non-alcoholic steato-hepatitis (NASH) is the most extreme form of NAFLD→ regarded as a major cause of cirrhosis of the liver of unknown cause.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3) Fibrosis</th>
<th>4) Cirrhosis:</th>
</tr>
</thead>
<tbody>
<tr>
<td>excessive accumulation of extracellular matrix proteins including collagen that occurs in most types of chronic liver diseases</td>
<td>Consequence of chronic liver disease characterized by replacement of liver tissue by fibrosis, scar tissue and regenerative nodules leading to loss of liver function.</td>
</tr>
<tr>
<td>Replacement of healthy tissue with fibrous tissue.</td>
<td>Cirrhosis is most commonly caused by alcoholism, hepatitis B and C, and fatty liver disease, other causes or idiopathic.</td>
</tr>
<tr>
<td>Scar tissue blocks the normal blood flow through the liver, which requires the remaining healthy portions to work harder.</td>
<td>complication of cirrhosis:</td>
</tr>
<tr>
<td>If the fibrosis is treated at this stage even though there is damage to the liver→ the organ can repair itself over time.</td>
<td>1) Ascites is the most common</td>
</tr>
<tr>
<td></td>
<td>2) Hepatic encephalopathy (confusion and coma)</td>
</tr>
<tr>
<td></td>
<td>3) Bleeding from esophageal varices.</td>
</tr>
</tbody>
</table>

#### 5) Hepatocellular carcinoma (malignant hepatoma):

Most cases of HCC are secondary to→ viral hepatitis infection (hepatitis B or C) or cirrhosis.

HCC symptoms: jaundice, ascites, blood clotting abnormalities

**Diagnosis:**
- Abdominal ultrasound/CT scan
- Liver scan

- Liver enzyme tests
- Alpha fetoprotein elevation greater than 400ng/mL predicts hepatocellular carcinoma.

**Hepatocellular carcinoma develops when:**
1) Mutation to the cellular machinery causes the cell to replicate at a higher rate.
2) chronic infections of hepatitis B and/or C can aid the development of HCC by causing the body's own immune system to attack the liver cells

Late in the disease→ Metastases may develop in the lung, portal vein, periportal nodes, bone, or brain
### Types of hepatitis:
#### 1) Viral hepatitis

<table>
<thead>
<tr>
<th>Item /disease</th>
<th>Hepatitis A</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition:</strong></td>
<td>Inflammation (irritation and swelling) of the liver from hepatitis A virus (HAV).</td>
<td>Inflammation (irritation and swelling) of the liver from hepatitis B virus (HBV).</td>
<td>Inflammation (irritation and swelling) of the liver from hepatitis C virus (HCV).</td>
</tr>
<tr>
<td><strong>Mode of transmission</strong>:</td>
<td><strong>feco-oral transmission</strong></td>
<td>Blood, Saliva, Semen, vaginal fluids, other body fluids of infected person, for hepatitis B.</td>
<td>1) Blood transfusions, 2) Direct contact with blood in healthcare settings, 3) Sexual contact with an infected person, 4) Tattoo or acupuncture with unclean needles or instruments, 5) Shared needles during drug abuse.</td>
</tr>
<tr>
<td><strong>Symptoms:</strong></td>
<td>Nausea and vomiting, Loss of appetite, Jaundice (yellow discoloration of skin and sclera), Fatigue, Fever, Dark urine, Itching, Pale or clay-colored stools</td>
<td>Nausea, vomiting, Loss of appetite, Jaundice, Fatigue, Fever, Dark urine, Muscle and joint aches</td>
<td>Pain (right upper corner of the abdomen), Nausea, Vomiting, Loss of appetite, Jaundice, Fatigue, Fever, Dark urine, Itching, Pale or clay-colored stools, ascites.</td>
</tr>
<tr>
<td><strong>Diagnosis:</strong></td>
<td>Detection of HAV-specific IgM antibodies in the blood</td>
<td>Albumin level, Liver function tests</td>
<td>EIA assay to detect hepatitis C antibody, Albumin level, Liver function tests.</td>
</tr>
<tr>
<td><strong>Treatment and prevention:</strong></td>
<td>No specific treatment, balanced diet, low fat diet, avoid alcohol intake are recommended, or prevented by vaccination</td>
<td>Prevention by avoidance of such transmission or by vaccination</td>
<td>The goals of HCV treatment are to remove the virus from the blood and reduce the risk of cirrhosis and liver cancer that can result from long-term HCV infection. No vaccination can be made is avoidance of causes (ex: blood scan before transfusion).</td>
</tr>
</tbody>
</table>
2) Autoimmune Hepatitis:
Hepatitis may occur along with other autoimmune diseases including:
1) Graves disease (hyperthyroidism)
2) Inflammatory bowel disease
3) Crohn’s disease
4) Ulcerative colitis
5) Rheumatoid arthritis
6) Systemic lupus erythematosus.

3) Drug-Induced Hepatitis:
Painkillers and fever reducers that contain acetaminophen are a common cause of liver inflammation.

Acetaminophen itself isn’t toxic → but in liver it undergoes metabolism giving N-acetyl para benzoquinone imine (NABQI) → normally conjugate with GSH and excreted.

4) Acute Viral Hepatitis
Widespread inflammation of the liver that is caused by hepatitis viruses A, B, C, D, and E

Four phases of symptoms:
1) Prodromal phase
2) Preicteric phase
3) Icteric phase
4) Convalescent phase

5) Fulminant Hepatitis
Syndrome in which severe liver dysfunction is accompanied by hepatic encephalopathy

### Four Stages of Hepatic Encephalopathy (End-Stage Liver Disease)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Mild confusion, agitation, irritability, sleep disturbance, decreased attention</td>
</tr>
<tr>
<td>II</td>
<td>Lethargy, disorientation, inappropriate behavior, drowsiness</td>
</tr>
<tr>
<td>III</td>
<td>Somnolence but arousable, incomprehensible speech, confusion, aggression when awake</td>
</tr>
<tr>
<td>IV</td>
<td>Coma</td>
</tr>
</tbody>
</table>

Medical and Nutritional Management of liver disease:
**Biochemical Tests Used in Diagnosis of Different Types of Liver Injury**

**Liver function tests can be divided into 3 categories**

1) Markers of acute hepatocyte injury and death (SGPT or AST, SGOT or ALT and AP)
2) Measures of hepatocyte synthesis function (Prothrombin time and Albumin)
3) Indicators of hepatocyte catabolic activity → Ammonia

1) **Cell damage:**
Several tests called (liver function tests)

**Transaminase**

Indicate liver cell membrane damage rather than synthetic function.

Intracellular enzymes found in hepatocytes.
ALT is confined to the cytoplasm, AST which is present in cytoplasm and mitochondria → rise in plasma transaminase is a sensitive indicator of damage to cytoplasmic and/or mitochondrial membranes.

And also present in other tissues → so changes in their plasma level may reflect damage to those tissues rather than to the liver.

Elevated levels in hepatocyte injury (infection, ischemia, toxins like alcohol, CCL4, NSAIDS, some mushrooms)

If elevations in hundreds/liter → mild injury but elevation in thousands → extensive hepatic necrosis.

This test may be normal in end stage liver failure where no acute hepatocyte injury occurs.

ALT is more specific than AST
AST/ALT ratios are suggestive of etiology of hepatic injuries
Ratio > 2 is common in alcoholic hepatitis
Ratio < 1 acute or chronic viral hepatitis
In absence of alcohol use with mildly raised AST and ALT with ratio > 1 suggests underlying cirrhosis.
<table>
<thead>
<tr>
<th>Aspartate aminotransferase (AST)</th>
<th>Alanine Transaminase (ALT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>(glutamate oxaloacetate transaminase, GOT)</em></td>
<td><em>(glutamate pyruvate transaminase, GPT)</em></td>
</tr>
<tr>
<td>Present in high concentrations in cells of cardiac and skeletal muscle, liver, kidney and erythrocytes → damage to any of these tissues may increase plasma AST levels.</td>
<td>Present in high concentrations in liver and, to a lesser extent, in skeletal muscle, kidney and heart.</td>
</tr>
</tbody>
</table>

**Causes of raised plasma AST activities:**

**Artefactual:** due to in vitro release from erythrocytes if there is hemolysis or if separation of plasma from cells is delayed.

**Physiological:** during the neonatal period (about 1.5 times the upper adult reference limits).

**Marked increase** (10 to 100 times the upper adult reference limit) occurs in circulatory failure with shock and hypoxia, myocardial infarction, acute viral or toxic hepatitis.

**Moderate increase:**
- cirrhosis (may be normal, but may rise to twice the upper adult reference limit)
- cholestatic jaundice (up to 10 times the upper adult reference limit)
- malignant infiltration of the liver (may be normal, but may rise to twice the upper reference limit)
- After trauma or surgery (especially after cardiac surgery).

**Causes of raised plasma ALT activities: A marked increase:** (10 to 100 times the upper limit of the adult reference range):
- circulatory failure with shock
- hypoxia
- Acute viral or toxic hepatitis.

**Moderate increase:**
- cirrhosis (may be normal or up to twice the upper adult reference limit)
- cholestatic jaundice (up to 10 times the upper reference limit in adults)
### 2) **synthetic function:**

<table>
<thead>
<tr>
<th>Transaminase</th>
<th>Bilirubin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDH</strong></td>
<td><strong>ALKALINE PHOSPHATASE</strong></td>
</tr>
<tr>
<td>It has a limited use now because of its lack of specificity</td>
<td>Associated with Biliary obstruction and Cholestasis</td>
</tr>
<tr>
<td>LDH may become significantly elevated in haemolysis.</td>
<td>Mild to moderate elevation → all hepato-biliary diseases</td>
</tr>
<tr>
<td></td>
<td>AP &gt; 4 times → Cholestasis</td>
</tr>
<tr>
<td></td>
<td>Specificity of AP in cholestasis can be improved by GGPT</td>
</tr>
<tr>
<td></td>
<td>Isolated elevation of AP without marked hyperbilirubinemia</td>
</tr>
<tr>
<td></td>
<td>AP: Bil ratio = 1000:1 → Lymphoma, Fungal infections, Sarcoidosis, TB</td>
</tr>
<tr>
<td></td>
<td>AP is 3 to 4 times raised in children</td>
</tr>
<tr>
<td></td>
<td>AP level doubles in pregnancy</td>
</tr>
<tr>
<td><strong>ALBUMIN</strong></td>
<td><strong>PROTHROMBIN TIME</strong></td>
</tr>
<tr>
<td>Albumin level reflects liver synthetic function</td>
<td>Prolongation of PT in liver diseases reflects decreased synthesis of Vitamin K dependent coagulation factors 2, 7, 9 &amp; 10 and as such serves as a real measure of liver function</td>
</tr>
<tr>
<td>Levels are decreased in advanced cirrhosis and severe acute hepatitis.</td>
<td><strong>Vit. K deficiency</strong> can be distinguished from <strong>liver synthesis dysfunction</strong> by administration of Vit.K (10mg IM) → 30% reduction in PT within 24 hrs → Vit K. Deficiency states.</td>
</tr>
<tr>
<td>Less useful in evaluating fulminant liver disease because of its long half life (3 weeks)</td>
<td></td>
</tr>
</tbody>
</table>

### 3) **Indicators of hepatocyte catabolic activity**

**Ammonia**

It’s a metabolite of nitrogen containing products.

It’s metabolized to urea in liver via Krebs hensleit cycle (urea cycle).

Very high levels are seen in fulminant liver failure, signifying poor prognosis.
**Bilirubin Metabolism**

Derived mainly from the heme moiety of the hemoglobin molecule (iron in heme is reutilized but tetrapyrrrole ring is degraded to bilirubin)

Other sources of bilirubin include myoglobin and cytochromes.

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**Unconjugated bilirubin**

Not water-soluble, transported in the blood stream bound to albumin.

**In the liver**

it is taken up by hepatocytes → conjugation principally with glucuronic acid to form a diglucuronide → **Conjugated bilirubin**

this process is catalyzed by the enzyme (bilirubin-uridyl diphosphate glucuronyl transferase)

**ligandin** (a binding protein in liver involved in conjugation of bilirubin)

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**Conjugated bilirubin**

Water-soluble and is secreted into the biliary canaliculi eventually reaching the small intestine via the ducts of the biliary system.

Secretion into the biliary canaliculi is the rate-limiting step in bilirubin metabolism.

**In the gut**

Bilirubin is converted by bacterial action → urobilinogen (stercobilinogen) colorless compound.

Some urobilinogen is absorbed from the gut into the portal blood, hepatic uptake of this is incomplete

Small quantity reaches the systemic circulation and is excreted in the urine.

Most of the urobilinogen in the gut is oxidized in the colon to a brown pigment → urobilin excreted in the stool.
Retention of Bilirubin in plasma (Hyperbilirubinemia): Jaundice

- Jaundice → yellow discoloration of tissues due to bilirubin deposition
- Frequent feature of liver disease.
- Jaundice only becomes clinically apparent when the plasma total bilirubin concentration reaches about 2 mg/dl, twice the upper reference limit.
- It occurs when bilirubin production exceeds the hepatic capacity to excrete it.
- This may be because:

<table>
<thead>
<tr>
<th>Type</th>
<th>Pre-hepatic</th>
<th>Hepatic</th>
<th>Post-hepatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td>increased rate of bilirubin production exceeds normal excretory capacity of the liver</td>
<td>The normal load of bilirubin cannot be conjugated and/or excreted by damaged liver cells</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased hemolysis of RBC’s at a rate faster than its excretion by liver.</td>
<td>• Hepatitis: viral or drug induced.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infective erythropoiesis</td>
<td>• Drugs: rifampicin (interfere with bilirubin conjugation)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>正常 load of bilirubin cannot be conjugated and/or excreted by damaged liver cells</td>
<td>• Intrahepatic obstruction as in cirrhosis.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>• Gilbert's syndrome.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>• Poisons as Cc14, Pb, As.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>The biliary flow is obstructed, so that conjugated bilirubin cannot be excreted into the intestine and is regurgitated into the systemic circulation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased</td>
<td>• Biliary obstruction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>• Gallstone.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased</td>
<td>• Carcinoma of pancreas or biliary tree.</td>
<td></td>
</tr>
</tbody>
</table>

Total bilirubin | Increased | Increased | Increased
Unconjugated bilirubin | Increased | Increased | Normal
Conjugated bilirubin | Normal | Increased | Increased
Urinary bilirubin | Absent | Present | Present
Urinary urobilinogen | Increased | Decreased | Absent
Color of urine | Dark yellow | Cola color | Cola color
Fecal stercobilinogen | Increased | Decreased | Absent
Color of stool | Dark yellow | Light brown | Clay color

**Kernicterus:** most likely to occur in newborn particularly premature infants in whom the hepatic conjugating mechanisms are immature → elevated unconjugated bilirubin (lipid-soluble, cross BBB and damages brain cells)