The liver (Latin: Iecur, Greek: Hepar) is the generalist among all organs - acting universally as the center of metabolism, storage unit, detoxifying- and excreting organ. The medical staff is frequently confronted with diseases such as liver cirrhosis, hepatitis, and fatty liver. Therefore, anatomical and biochemical knowledge of the liver is part of every medical student`s basic training. Read this compact overview on structure, functions, and diseases of the liver.

Location of the Liver
The liver weighs approximately 1.5 kilograms and is both the largest internal organ and the largest gland in the human body. It is located in the upper abdomen – three quarters are situated in the right and one quarter in the left upper quadrant of the abdominal cavity. Thus, the liver’s span ranges from the right hypochondriac region over the epigastric region to the left hypochondriac region.

It is fused with the lower surface of the diaphragm. That is why its upper limit is equivalent to the height of the diaphragmatic cupola and its location is breath-dependent. Hence, the liver sinks down during deep inspiration with the diaphragm. The lower limit is equivalent to the curve of the costal arch on the right side and runs upwards at a slight angle across the epigastrium to the left.

**External Shape of the Liver**

Due to the soft consistency of the liver its shape adjusts to the neighbor organs. There are two areas that blend into each other at the clearly limited **Inferior Margin**: The **Facies diaphragmatica** that lies flat against the diaphragm and is convex-shaped and the **Facies visceralis** which is facing the visceral organs. The **Porta hepatis** in conjunction with the **Ductus hepaticus communis**, the **Vena portae hepatis** and the **Arteria hepatica propria** are located in the hepatoduodenal ligament and maintain their relationship all the way to the hepatic lobule. The common path comprising these three structures is referred to as ‘portal triad’.

Macroscopically, the liver divides into four lobes. The **Ligamentum falciforme** on the front surface of the liver’s **Facies diaphragmatica**, divides the liver into a big **Lobus hepatis dexter** and a small **Lobus hepatis sinister**. In addition, the **Lobus caudatus** and the **Lobus quadratus** become apparent on the backside of the Facies visceralis. Those two lobes are divided by two sagittal incisions of the bigger lobes.
Indentations of the gallbladder (Fossa vesicae biliaris) and the inferior caval vein (Sulcus venae cavae inferioris) form the **right fissure (Fissura portalis principalis)**. Indentations of the round- and vein ligament (Fissura ligament teretis and venosi) form the **left fissure (Umbilical Fissure)**. In conjunction with the Porta hepatis that runs transverse to those fissures they form an ‘H’. The reddish brown organ is encased by a coarse **fibrous capsule (Capsula fibrosa)**.

**Liver Segments**

Besides the organization into the four lobes mentioned above, the liver can be further divided into **eight functional segments**. They are designated as functional mainly since their segmentation is not visible from the outside and the segments are mostly independent from each other. This facilitates the excision of a specific part of the liver during **liver resection**. The segments follow the common path of the portal triad (see above).

The vessels are initially distributed in two big segments, **Pars dextra**, and **Pars sinistra**, which further split into eight segments. Segments I – IV are located in the Pars sinistra, whereas segments V – VIII are located in the Pars dextra. **Segment I** is equivalent to the Lobus caudatus.

**Peritoneal Relations of the Liver**

The liver is localized intraperitoneal. It is covered by the peritoneum that gives the liver its reflecting glimmer. A part of the liver’s backside is peritoneum-free and shines roughly through the coarse fibrous capsule: the **Area nuda**. That is where the liver is associated with the diaphragm and the posterior abdominal wall. It is also the spot where the liver veins (**Venae hepaticae**) exit the liver. The peritoneum folds back on itself on the area nuda to form the **coronary ligament**, which transitions into the **right and left triangular ligaments** that connect the liver to the diaphragm.

The liver is connected to the abdominal cavity via numerous peritoneal ligaments:

- **Ligamentum hepatoduodenale:** Contains the Ductus choledochus (right), the Vena portae hepatitis (posterior) and the Arteria hepatica propria (anterior on the left). The lesser omentum (omentum minus) is formed by the Ligamentum hepatoduodenale and the Ligamentum hepatogastricum (peritoneal ligament extending between the liver and the small curvature of the stomach).

- **Ligamentum falciforme:** Is located between the Facies diaphragmatica and the abdominal wall. Contains the Ligamentum teres hepatitis and transitions into the Ligamenta triangularia and, respectively, into the Ligamentum coronarium (see above).

- **Ligamentum teres hepatitis:** (Represents the desolate umbilical vein (V.
The liver's relation to neighboring organs

The diaphragm separates the liver from the right lung and the heart. Characteristic impressions on the Facies visceralis are caused by the liver's soft consistency:

- **Impressio ösophageale**: On the upper margin of the liver's left lobe due to the esophagus.
- **Impressio gastrica**: Due to the stomach; it almost takes over the whole left lobe subsequent to the esophageal impression.
- **Impressio colica**: On the lower margin of the liver's right lobe due to the Flexura coli dextra and the transverse colon (Colon transversum).
- **Impressio duodenalis**: On the liver's right lobe due to the Pars superior of the duodenum.
- **Impressio renalis**: In the middle of the liver's right lobe due to the superior pole of the right kidney.
- **Impressio suprarenalis**: Due to the right adrenal gland; subsequent to the renal impression.

**Hint**: Knowledge about the topography of the liver yields points in the preliminary medical examination!

Microscopic anatomy of the liver
The liver lobules (Lobuli hepatis) are the smallest elements of the liver. They get separated from each other by thin strands of connective tissue. Periportal areas emerge when several lobules encounter each other. The portal triad is made of small branches of the Vena portae hepatis, the Arteria hepatica propria and the bile ducts and contains lymphatics and branches of the vagus nerve.

The liver is divided into three units: the central vein lobule, the portal vein lobule and the acinus of the liver. The central vein lobule is clearly designated morphologically, whereas the remaining units are functional.

Central vein lobule in the liver

The central vein lobule is referred to as the classic liver lobule. The central vein (Vena centralis) is located in the middle of the usually hexagonal area. It conducts blood into the Venae hepaticae and finally to the Vena cava. The edges of the lobule are marked by the portal triad (see above). Since the vessels are located between neighboring lobules they are referred to as interlobular artery and vein, as well as Ductus biliferi interlobularis.

Liver cells (hepatocytes) are radially arranged around the central vein. The sinusoids existent between the liver cells conduct mixed blood from the interlobular artery and vein from the periphery to the central vein (see above). There are also little biliary ducts (Canaliculi biliferi) between the hepatocytes, which proceed in the direction of the Ductus biliferi interlobularis and conduct bile in opposite direction to the blood flow.

Contrary to the sinusoids, the Canaliculi do not possess their own wall. That is why bile
can find its way into the bloodstream in case of bile stasis. This phenomenon can lead to jaundice (Icterus).

Portal vein lobules in the liver

The biliary tract system is essential in the portal vein lobule. The portal triad with its vessels forms the center of the triangular lobule, whereas the edges are formed by the central vein. Thus, three central vein lobules belong to one portal vein lobule.

Acinus of the liver

The acinus of the liver has a rhomboid shape. The edges are built by central veins and periportal areas that are situated across from each other. It should be considered that the blood changes its composition in this functional unit on the way from the periphery to the center of the central vein lobule.

- **Zone 1 (outer zone):** Periphery of the central vein lobule, high nutrient, and oxygen concentration
- **Zone 2 (middle zone):** Transitional zone of the central vein lobule, low nutrient, and oxygen concentration
- **Zone 3 (inner zone):** Centre of the central vein lobule, bad nutrient, and oxygen supply, especially susceptible to damage

Functional units of the liver

Sinusoids of the liver
The sinusoids are widened capillaries located between hepatocytes. They conduct oxygen-rich blood from the interlobular arteries (Arteriae interlobulares) and nutrient-rich blood from the interlobular veins (Venae interlobulares) to the central veins. The small space filled with blood plasma that lies between the discontinuous endothelium of the sinusoids and the liver parenchyma is called Disse-space.

This space is populated with vitamin A storing hepatic stellate cells. They are also called Tto cells and play an important role in the development of liver cirrhosis (see below). The endothelial cells are accompanied by macrophages, the so-called Kupffer cells. They phagocytize particles and microorganisms. Furthermore, they are involved in the degradation of aged erythrocytes, which on top of that is enhanced in asplenia. Pit cells accompany the endothelial cells as well. They function as liver-specific lymphocytes.

Parenchyma cells of the liver

The parenchyma of the liver is mainly built by polyhedral hepatocytes. Numerous organelles are found in their cytoplasm due to many metabolic processes. The cell nuclei are large and polyploidy; some cells may possess two nuclei.

A hepatocyte possesses one apical biliary pole (adjoins biliary tracts) and one basolateral blood pole (adjoins sinusoid). Endothelial cell plates are formed by aggregation of hepatocytes. They radially proceed to the central veins.

Function of the Liver

The liver as a reservoir and energy supplier

One of the liver’s most essential tasks is the storage and supply of nutrients for somatic cells. The nutrients taken up with the diet do not always match the cell’s demands. The liver has to store abundant substances and balances out deficiencies by supplying lacking nutrients.

Aside from that: The liver is involved in fetal hematopoiesis until the seventh month of pregnancy.

Carbohydrate metabolism in the liver

The liver reacts differently to food intake and fastening and is therefore involved in the regulation of blood sugar levels. If there is too much glucose in the blood, e.g. after
food intake, it becomes modified by the liver via the release of **insulin** in the pancreas and will accumulate in the liver as its storage form **glycogen**. Furthermore, the liver owns insulin-independent glucose transporters (GLUT2) through which abundant glucose find its way into hepatocytes.

During fasting periods, when there is a lack of glucose, the liver manages to convert glycogen into glucose via the hormone glucagon and releases it into the bloodstream. The storage space for glycogen in the liver is limited though. It usually does not last for longer than **24 hours** without food intake.

If the glucose reserves are depleted and despite a feeling of hunger no food intake is following, hepatocytes initiate the process of **gluconeogenesis** with the help of **glucogenic amino acids**. **Fructose** and **galactose** can also get transformed into glucose.

**Protein metabolism in the liver**

The liver provides essential components for protein metabolism: **Albumin** (maintenance of colloid osmotic pressure), proteins of the complement system (= acute phase proteins, parts of non-specific defense) and **coagulation factors (fibrinogen, prothrombin)**. Examples of impairment of the formation of these proteins are: Albumin deficiency leads to **ascites**, acute phase protein deficiency leads to an elevated susceptibility to infection and a deficiency of coagulation factors leads to unstoppable bleeding.

Due to continuous degradation and conversion of proteins and amino acids **urea** is formed as end-product of the amino acid metabolism. It gets into the kidney via blood and is excreted by urine.

The liver is able to produce glutamine with the help of transaminases. It is a matter of **glutamate oxaloacetate transaminase** (GOT=ASAT=AST) and **glutamate pyruvate transaminase** (GPT=ALAT=ALT).

In case of damages or diseases of the liver, those enzymes will be increasingly released in the bloodstream and are detectable in blood serum after taking a blood sample. **Gamma-glutamyltransferase** is another important enzyme in the amino acid metabolism. Its elevation obtains as the most critical parameter for liver and gallbladder injury.

**Cori cycle**
Fat metabolism in the liver

The liver is able to transform free fats out of the blood in its storage form, the **triglycerides**, and can release them if required. If fat reserves are depleted too fast – e.g. because of fasting or diabetes mellitus – **ketone bodies** are formed. They represent another crucial energy source besides glucose.

Another function of the liver’s fat metabolism is the **formation of bile**. Bile is needed by gut cells to take up fats. Furthermore, the liver is responsible for the formation of **cholesterol**.

Its job is also to convert the **bile’s colorant bilirubin** from its indirect into its direct water-soluble form. Bilirubin accumulates during degradation of erythrocytes in the spleen and is initially **water-insoluble**. That is why it is bound to albumin (=**indirect bilirubin**) until it reaches the liver.

There it gets separated from the protein and is taken up by liver cells. Bilirubin becomes attached to glucuronic acid (=**direct bilirubin**) to make it water-soluble and release it into the gut via bile.

**Note:** The liver stores vitamins like vitamin A and B12 as well as trace elements such as iron.

The liver as a detoxifying and excreting organ

Thanks to its **biotransformation system** the liver is able to eliminate endo- as well as exogenous toxic compounds. These mostly lipophilic substances are modified by enzymes in several steps and are getting water-soluble. In this way, they can be excreted via biliary tracts or kidney. The degradation products get into the digestive tract after resorption and then directly via the portal vein to the liver.

**First-pass effect:** When drug levels need to be maintained in a study state, they cannot be administered orally because after their gut absorption they pass through the liver that can inactivate them, rendering them ineffective and thus unreliable. Therefore, it is advisable to favor intravenous, muscular, subcutaneous, or rectal administration.

Another important task of the liver is the **degradation of ammonia**. It accumulates during bacterial decomposition of indigestible constituents in the gut and gets converted to **urea** by the liver. If the liver’s detoxifying function is restricted and not enough
ammonia is degraded, damage of the central nervous system with hepatic encephalopathy will possibly follow, which can lead to deadly hepatic coma.

Diseases of the Liver

Liver cirrhosis

The most common causes of liver cirrhosis are chronic alcohol abuse and viral hepatitis B and C. A fibrotic conversion of the lobule structure including replacement of the liver parenchyma with connecting tissue is induced by the degradation and death of liver cells with replacement with scar tissue.

The liver starts to shrink and lose its functions. Scar tissue around the Vena portal hepatis can cause a backlog of blood and portal hypertension is the result. The blood has to drain away through collateral circulation (portocaval anastomoses), which lead to esophageal varicosities and a Caput medusa (protrusion of navel vein).
Another complication of portal hypertension is **ascites**, which is defined as an accumulation of free fluid in the abdominal cavity. The synthetic ability of the liver is further reduced, which is shown by an elevated bleeding tendency because of decreased formation of coagulation factors. Neurotoxic substances (e.g. ammonia) accumulate due to malfunctioning detoxification. Hepatic encephalopathy and hepatic coma follow; these medical events can be deadly. A **liver transplantation** serves as the only life-saving therapy option when it comes to advanced liver cirrhosis.

### Fatty liver

![Image: Comparison of normal liver and fatty liver](image)

**Steatohepatitis** is defined as an accumulation of triglycerides in hepatocytes. There are two defined basic disease types: **Nonalcoholic fatty liver disease (NAFLD)** mainly caused by metabolic syndrome and diabetes mellitus type 2 and **alcoholic fatty liver disease (AFLD)**.

In case of a classic fatty liver, there are no complaints beside the enlargement of the organ. Nevertheless, in the second state, it will lead to nonalcoholic **fatty liver hepatitis (NASH)** with unspecific symptoms such as nausea and weight loss.

Icterus, pain in the right upper abdomen and fever may occur especially in case of an alcoholic **fatty liver hepatitis (ASH)**. The liver parenchyma usually appears more hyperechoic, therefore lighter, during ultrasound than the adjacent right kidney’s parenchyma. Weight normalization, optimal diabetes adjustments, exercise and **strict alcohol abstinence** are common therapy recommendations. Fatty liver and fatty liver hepatitis are still reversible whereas the third state, the **micronodular liver cirrhosis**, is irreversible.

### Hepatitis

Hepatitis is an **inflammation of the liver with** various causes, can result in liver failure or liver cirrhosis (see above). An inflammation of the liver is mostly caused by a virus infection or an autoimmune disorder.

**Viral hepatitis**
The most common virus strains causing hepatitis are virus types A-E. There are only a few cases reporting CMV, EBV and unknown hepatitis virus strain as causing factors. Hepatitis A and E get transmitted fecal-oral (contaminated water and foods). However, hepatitis B-D is transmitted parenteral (blood and sexual contact).

The prodromal stage, lasting two to seven days, is clinically defined by general symptoms like fever, fatigue and joint pain. Nausea, vomiting, and discomfort in the right upper abdomen may appear as well.

The stage of hepatic disease manifestation, lasting four to eight weeks, may follow with an anicteric (without jaundice) as well as icteric state (with icterus of sclera and skin, pruritus and dark discoloration of urine). Types B, C, and D may transition into chronic hepatitis resulting in liver cirrhosis as the final stage. Hepatitis A and E are treated symptomatically, the other types by antiviral therapy. An active immunization may be conducted prophylactically in case of an infection with hepatitis A and B.

Please note: Medical students should already get vaccinated against hepatitis A and B at the beginning of their studies!

Autoimmune hepatitis

Alterations of the immune system may lead to immune cells attacking hepatocytes, resulting in significant physical complaints. This disease is often associated with other autoimmune diseases like autoimmune thyroiditis, vasculitis or chronic inflammatory bowel diseases. Patients have to undergo lifelong immunosuppressive therapy since without this treatment the prognosis of autoimmune hepatitis would be dismal.

Hepatic encephalopathy

Hepatic encephalopathy is a complication of liver cirrhosis (see above). Neurotoxic substances such as ammonia, mercaptan, and GABA accumulate due to liver insufficiency with ensuing lack of detoxification.

The stages of hepatic encephalopathy vary from asymptomatic patients to increasing sleepiness to liver failure coma (hepatic coma) with hepatic foetor (liver breath). Triggering factors include protein rich food or gastrointestinal bleeding. This leads to an elevated intestinal ammonia production. Hepatic coma ends deadly in most cases.

Malignant liver tumors

Hepatocellular carcinoma
The hepatic carcinoma (HCC, also Liver cell carcinoma) is one of the most frequent cancerous conditions. Men are more often affected than women. The main risk for the development of an HCC is liver cirrhosis. Chronic hepatitis B or C, as well as cirrhosis caused by alcohol abuse or hemochromatosis (iron storage disease), may transition into liver cell carcinoma.

Another carcinogen is the aflatoxin of Aspergillus flavor, which is a fungus that especially grows on crop and nuts. HCC is either solitary, multicentric or diffusely infiltrating. The symptoms are nonspecific at first; e.g. pain in the right upper abdomen, icterus, cachexia and ascites. Perhaps a tumor can be palpable. Chemical analysis shows an elevation in the tumor marker alpha-fetoprotein. The therapy of choice is a partial hepatectomy.

Liver metastases

Liver metastases occur even more often than hepatocellular carcinomas. They are commonly multiple and emerge when cancer cells attain access to the vena porta. That is why organs of portal circulation (stomach, pancreas, large intestine, gall bladder) usually lead to liver metastases.

Metastases appear very variable sonographically; they can be hypo- or hyperechoic. Single metastases can be excised by performing a partial liver resection. However, palliative therapy is the only choice for advanced stages.

Echinococcosis
The **dog tapeworm** (*Echinococcus granulosus*) is the cause of **cystic echinococcosis**. Big fluid filled **cysts** are formed in the liver parenchyma. When they burst, life threatening allergic reactions may occur since foreign proteins are likely to get into the peritoneal cavity. The therapy includes the removal of the cyst.

The **fox tapeworm** (*Echinococcus multiocularis*) leads to cyst formation in the liver as well. Tough, instead of one big cyst **several small** cysts are formed. They spread like a malignant tumor. A resection is not always possible, so that it is necessary to perform chemotherapy with **albendazole**.

### Examination of the Liver

There are numerous ways and procedures to examine the liver. Some of those are listed below:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Percussion</strong></td>
<td>The lung has a sonorous, the intestines a tympanic percussion sound in contrast to the liver which possesses a damped sound. In that way the upper and lower liver border is identifiable.</td>
</tr>
<tr>
<td><strong>Liver scratch test</strong></td>
<td>The stethoscope is placed over the epigastrium. Then the patient’s skin is carefully scratched with a finger or a wooden spatula parallel to the costal arch from cranial to caudal in intervals of about one centimeter. The sound of the noise changes with reaching the liver borders.</td>
</tr>
<tr>
<td><strong>Palpation</strong></td>
<td>In a lying position and during deep inspiration. In that way, the lower liver margin slides in a caudal direction. The left hand of the examiner lies over the right costal arch, whereas the right hand lies in the epigastric angle. The lower margin of the liver is palpable with fingers 2-5 and its consistency can be assessed (soft or hard, smooth or gibbous, sharp or blunt).</td>
</tr>
<tr>
<td><strong>X-ray</strong></td>
<td>The liver is radiodense and, therefore, appears light in a radiographic image, so that it is quite possible to define its proximity to the lung. However, it is not possible to delimit it from the heart, which shows a light appearance as well. For that reason, sonography and computer tomography are used to assess the liver.</td>
</tr>
<tr>
<td><strong>Scintigraphy</strong></td>
<td>Due to its numerous metabolic processes the liver accumulates numerous substances; because of that, the organ’s widening is visible in scintigraphy.</td>
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Sonography

The liver and its vessels as well as the gall bladder are easily assessable during deep inspiration. Fatty liver, haemangioma, cyst, metastases or gallstones are diagnosable. The sizing takes place in the midclavicular line (MCL) in cranial – caudal direction (max. 14 cm).

Liver puncture

Under constant sonographic monitoring a long hypodermic needle gets pierced through the abdominal wall to stamp out an about one millimeter sized column of the parenchyma. After that, the tissue is examined microscopically.

Review Questions

The solutions can be found below the references.

1. Which liver impressions do not exist?

   A. Impressio colica
   B. Impressio suprarenalis
   C. Impressio oesophagea
   D. Impressio jejunalis
   E. Impressio gastrica

2. What is not true for the hepatoduodenal ligament?

   A. Contains the Ductus choledochus
   B. Forms the Omentum majus together with the Ligamentum hepatogastricum
   C. Contains the Arteria hepatica propria
   D. The Vena portae runs through it
   E. Is part of the Omentum minus

3. Which liver cells do not exist?

   A. Astrocytes
   B. Kupffer cells
   C. Ito cells
   D. Pit cells
   E. Hepatocytes

4. Which statement is true for a liver examination?

   A. It is not advisable to use sonography to examine the liver.
   B. Ultrasonic sizing of the liver is performed in the anterior axillary line.
   C. During a liver puncture, the liver gets punctured using X-ray monitoring.
   D. The stethoscope has to be placed over the epigastric region when performing a liver scratch test
   E. The liver should be palpated during deep expiration.

References


Correct answers: 1D, 2B, 3A, 4D

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