The Detoxication Function of the Liver

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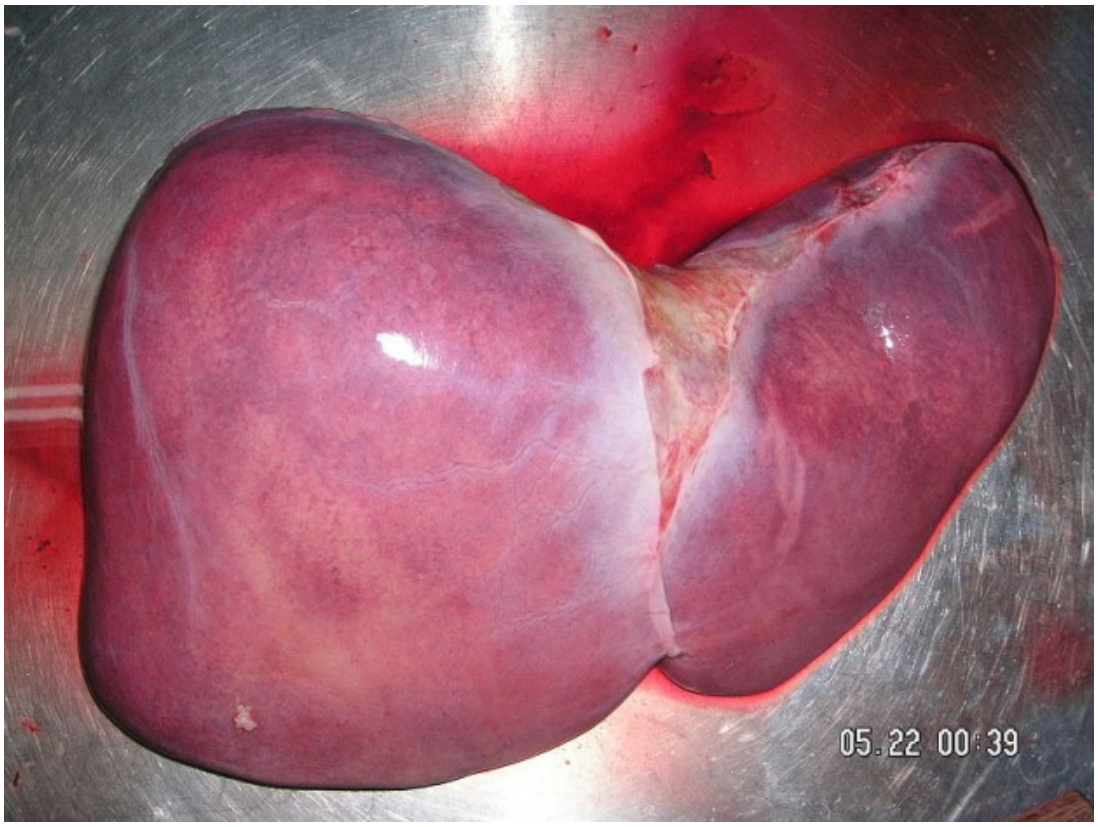
The liver, the central organ of our bodies' metabolism, is crucial in the detoxication of the body. This article will inform you of the more detailed processes and will provide you with information that will help you in your medical exam.



Roles of the Liver

The liver is the central organ of metabolism in the adult human body. Its tasks include the production of blood proteins (albumin, coagulation factors), bile, and antigens, storage of vitamins, synthesis of the starting products for hormone production, storage of glycogen as an energy reserve, decomposition of red blood cells, production of hormones, and removal of toxic endogenous (ammonia) and exogenous (e.g., medications) substances.

The liver acts as an accessory digestive gland and produces bile which aids in breaking down fat.

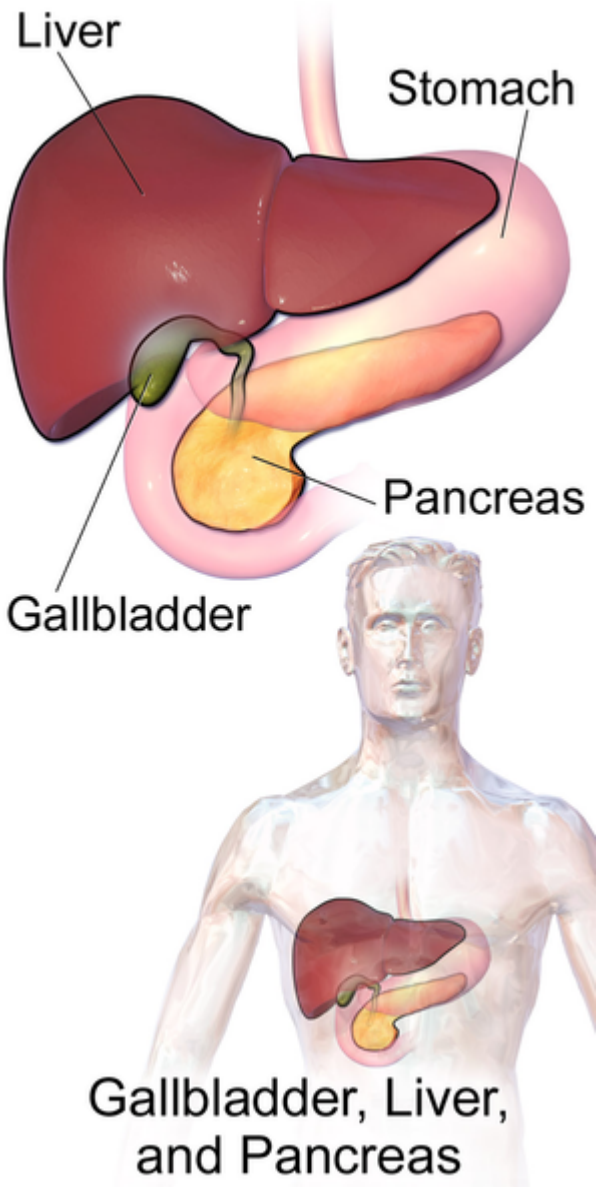


Image: Gallbladder-Liver-Pancreas location. By: Blausen. License: CC BY 3.0

All nutrients resorbed from the intestine into the blood pass through the portal vein (portal circulation) to the liver, where they are either removed or returned to the blood if necessary.

Byproducts formed in the liver can be expelled in 2 ways:

- Expulsion via the kidney: Water-soluble products (medications, alcohol) are delivered by the liver cells to the **liver sinusoids.** From there, they pass into the bloodstream to the kidney and are then expelled with urine.
- Expulsion via the gall bladder: As the largest exocrine gland, the liver produces about 600–800 mL of bile per day. Non-water-soluble substances pass through the bile capillaries in the intestine and are expelled with stool.

Shape and Structure of the Liver

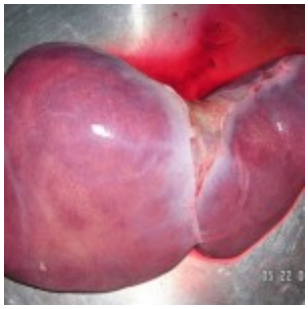


Image: Human liver. By: Suseno.
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The dark red liver is located in the upper right abdomen, weighs approx. 1.5–2 kg (3.3–4.4 lb), and is soft.

Symptoms: Because of its consistency, the liver is prone to rupture in an accident, and the rupture may be accompanied by intra-abdominal bleeding (blunt abdominal trauma).

Neighboring organs leave characteristic impressions on its surface.

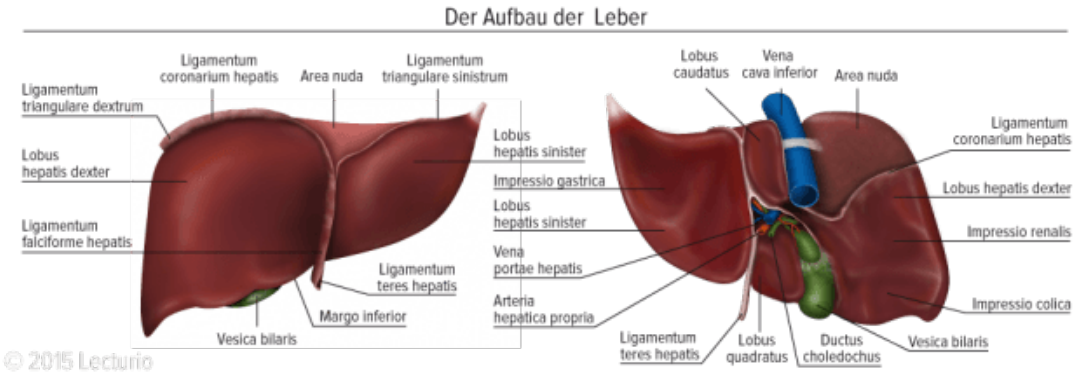

Image: Structure of the liver. By: Lecturio

There are 2 different surfaces of the liver. One is the **diaphragmatic surface** which faces and coalesces with the diaphragm, and the other is the **visceral surface** facing the abdominal organs. Ventrally, the diaphragmatic surface passes into the visceral surface along the **inferior margin**. Because of its coalescence with the diaphragm, the liver moves during respiration, moving caudally during inspiration. The non-coalesced surface is covered by the **visceral peritoneum,** and its position is thus **intraperitoneal**.

A shell of conjunctive tissue, the **fibrous capsule** or **Glisson's triad**, surrounds the entire organ. It is connected to the peritoneum by **subserosa**. Septa protruding inward from the shell divide the liver into its 4 morphologically distinct lobes: **right lobe** (largest lobe), **left lobe**, **quadrate lobe** (ventral), and **caudate lobe** (dorsal).

Furthermore, the division into 8 macroscopically identical segments is of clinical relevance (Couinaud classification system). It stems from the arrangement of blood vessels and biliary ducts and allows for a clear demarcation into other segments for the resection of individual segments.

The Couinaud classification system divides the liver into 8 segments, with each of the segments having its own independent vascular inflow, outflow, and biliary drainage. The classification makes use of the vascular supply to determine the separation of each functional unit.

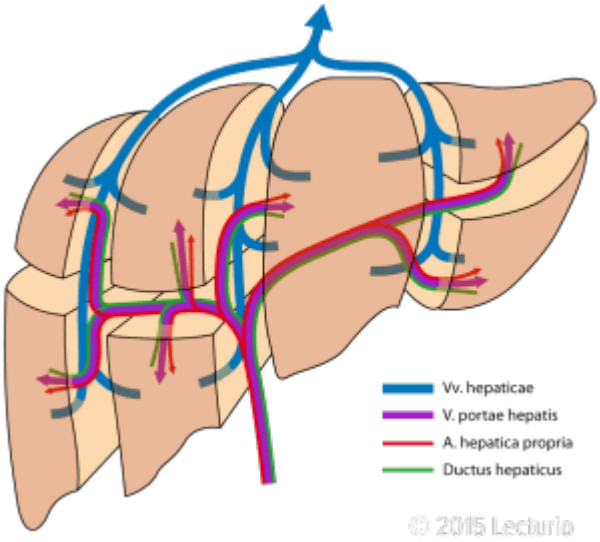

Image: Segments of the liver. By: Lecturio

The following structures always run together (triad), from the beginning of the macroscopically dominant liver portal (**porta hepatis**) down to the smallest units of the liver:

- Arterial vessels (oxygen-rich, **proper hepatic artery** and branches)
- Portal venous vessels (nutrient-rich, **hepatic portal vein** and branches)
- Biliary ducts (**the right and left hepatic ducts** and their branches merge into the **common hepatic duct**)

The efferent **hepatic veins** run independently from the triad.

Fine Structure of the Liver

The smallest, most sparse conjunctive tissue divides the liver parenchyma into lobes (**hepatic lobes**). These are polyhedral and are arranged around a central vein. Multiple adjacent lobes form periportal areas at their point of contact, or conjunctive tissue gussets, into which flow the aforementioned incoming vessels and outgoing biliary ducts.

Considering the function of the parenchyma, there are 3 different entities: **central vein lobule**, **portal vein lobule** (also periportal/portal lobule), and **liver acinus.**

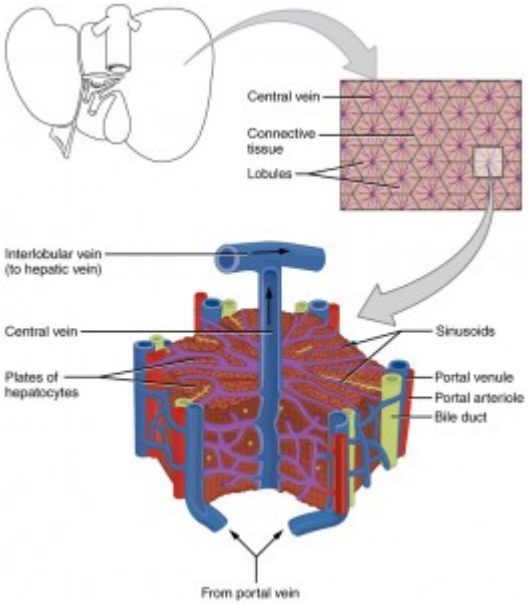

Image: Microscopic anatomy of the liver. By: Phil Schatz.
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Central vein lobule

In the center of the liver is a **central vein**, around which trabeculae radiate, arranged by hepatocytes and liver sinusoids. Liver sinusoids are extended spaces between the liver cell trabeculae with a fenestrated endothelium, into which blood flows from the portal vein and **proper hepatic artery** toward the **central vein**. The entire exchange of blood and hepatocytes occurs over a stretch of 0.5 mm. The fenestrated endothelium is separated from the adjacent liver parenchyma by a plasma-filled space (**perisinusoidal space** or **space of Disse**).

Portal vein lobule

As the name itself implies, the portal vein lobule is concerned with structures in the periportal region. Central veins form the corners, and the bile passes in the central outlet. Three or more central vein lobules form one portal vein lobule.

Liver acinus

The division into the liver acinus stems from different metabolic zones. The shape of an acinus is rhombic, and 2 periportal areas and 2 central veins form each corner of the rhombus.

Liver Cell Types

Liver cells (hepatocytes)

Arranged around the central vein in a stellate pattern, these large cells have many cellular organelles and often have multiple nuclei due to their metabolic activity. Their tasks include the production of bile, breakdown of hormones, and regulation of the acid-base balance. They form a one- to multi-layered epithelium. The basolateral surface facing the space of Disse shows a trimming of microvilli. Opposite this is the apical or

biliary cellular pole. Two opposing apical membranes of the hepatocytes border the bile capillaries.

Kupffer cells

These **phagocytosing scavenger cells** are part of the **mononuclear phagocyte system** of the immune system and are antigen-presenting macrophages. They may gather, store, and break down cell debris, foreign substances, obsolete erythrocytes, and bacteria from the portal vein blood. They also lie atop the sinus endothelium and their cell bodies bulge into the sinusoidal lumen.

Ito cells **(hepatic stellate cells or perisinusoidal cells)**

These fat-storing stellate cells are located in the space of Disse and store vitamin A. After increased vitamin A intake, the cells proliferate. Ito cells play an important role in the **pathogenesis of liver cirrhosis** and are believed to be responsible for the increased collagen production.

Pit cells

These **natural killer (NK) cells** are liver-specific lymphocytes and stick to endothelial cells.

Detoxication of Organic Exogenous Substances: Biotransformation

Note: Substances taken in from the environment, which cannot find immediate use as nutrients, are expelled or metabolized by the organism if possible. The metabolism of such substances is referred to as **biotransformation**.

Most biotransformation reactions occur in the liver and include enzymatically catalyzed reactions that aim to make endogenous or exogenous substances water-soluble in order to expel them. Generally, an inactivation of active or toxic substrates occurs, with the objective of rendering them harmless.

However, there are also substances that are converted into toxic substances by this reaction, and these substances can harm the body. The most well-known example of this is benzopyrene, which is contained in the tobacco smoke of cigarettes. It is also found in charcoal-grilled meat. The biotransformation reaction with the cytochrome P450 enzyme results in the ultimately **cancerogenic diol epoxide**, which reacts with guanine in the DNA, resulting in permanent damage to the organism.

Biotransformation encompasses 2 successive reaction types: A **phase I reaction (conversion reaction)** and a **phase II reaction (formation of conjugates)**. Each process aims at transforming the toxic substances into non-harmful and easily removable compounds.

Phase I reaction

This reaction is also called a conversion or functionalization reaction. **Oxidation, reduction, and hydrolysis reactions** are attached to the starting compound of

functional groups. The monooxygenases involved in the oxidation reactions bind oxygen and transfer 1 of the 2 oxygen atoms to the respective starting substrate.

The second atom is released upon the formation of water. Because of their parallel reaction behavior or their reaction with both the oxygen and substrate, **monooxygenases** are also referred to as **mixed-function oxygenases**. Most monooxygenases are cytochrome P450 enzymes (CYP) that vary from one another in their substrate specificity.

Other enzymes of the phase I reaction are:

Catalysis of oxidations	Catalysis of reductions	Catalysis of hydrolysis
Monoamine oxidases and monooxygenases containing FAD	Cytochrome P450 enzymes	Esterases
Xanthin oxidase		Epoxide hydrolases, sometimes associated with cytochrome P450
Aldehyde dehydrogenase		
Alcohol dehydrogenase		

The side effect of the first phase of the detoxification process is the production of free radicals, which attach to the cellular elements and lead to its damage. It is worth noting that both phases make use of a vital antioxidant, glutathione, which neutralizes the free radicals. In the event that many free radicals are produced in the first phase, glutathione may be exhausted. This leads to an imbalance in the activities in both phases resulting in a build-up of toxic reactions in the body.

Phase II reaction

With this biotransformation, also known as a **conjugation reaction**, substrates are bound to additional chemical groups. Substrates are both endogenous (steroid hormones, bilirubin, bile pigments) and exogenous substances (medications, alkaloids, preservatives, environmental toxins). Phase II reactions are distinctive in that the transferred groups were previously activated by binding to a coenzyme. They thus exhibit high **group-transfer potential**. A lot of energy is released during the split of the bonding phase, which is utilized during energy coupling for the transfer in the biotransformation reaction. **Transferases** are involved in all phase II reactions.

Conjugation with glucuronic acids:

The transfer of glucuronic acids occurs through **UDP glucuronic acid** to the OH, COOH, NH_2, and SH groups of endogenous or exogenous substances. The resulting **glucuronides** are expelled through the gall bladder.

Conjugation with glutathione:

Glutathione is a natural form of protection for cells against oxygen radicals. It is made from the **tripeptide Glu-Cys-Gly**. The transfer to the substrate is catalyzed by the enzyme **glutathione S-transferase (GST)**. In more precise terms, the conjugation is facilitated by the SH group of the central cysteine. After the split of glutamine and glycine, the remaining amino group of cysteine is acetylated, and mercapturic acid is formed, which is in turn expelled through the kidneys.

Conjugation with acetyl groups:

This transfer occurs with amino groups and is catalyzed by **N-acetyltransferase**. An

inactivation of sulfonamides occurs in this manner, and the important tuberculostatic, **isoniazid (INH)**, is of significance.

Conjugation with methyl groups:

S-adenosylmethionine is involved. The transfer takes place from methyl groups to N, O, and S atoms.

Conjugation with sulfate groups:

The sulfate group is separated from **3′-phosphoadenosine-5′-phosphosulfate (PAPS)** and transferred to amino and OH groups.

Optimization of the detoxification process

Phase 1:

- Sufficient intake of vitamin B and amino acids is required to optimize this process

Phase 2:

This process requires the sufficient intake of amino acids such as cysteine and methionine, as well as the intake of N-acetylcysteine.

- To aid in the optimization of the entire detoxification process (phases 1 and 2), minerals such as copper and manganese, vitamins such as vitamin C and vitamin B12, as well as milk thistle, are required.

Decomposition of Ethanol

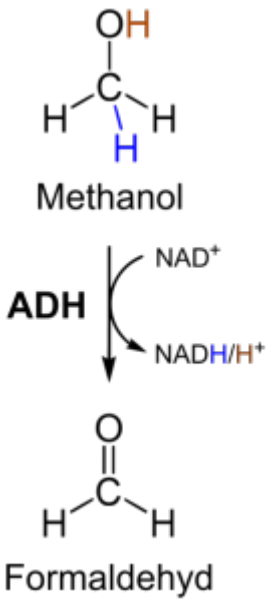

Image: Oxidation of methanol to formaldehyde by alcohol dehydrogenase (ADH). By: Yikrazuul. License: Public Domain

In many industrialized countries, a large percentage of all diseases are attributed to alcohol abuse. Thousands of people die annually from alcohol-related causes. The role

played by ethanol in energy metabolism is significant. A person could consume an amount of ethanol per month that comprises 5% of all consumed energy sources.

Ethanol, in the form of alcohol, is broken down in the liver to **acetyl-CoA**. This process occurs in 3 steps. First, the ethanol in the cytosol is oxidized to **acetaldehyde** by alcohol dehydrogenase. In turn, the acetaldehyde is oxidized to **acetate** by aldehyde hydrogenase.

Alcohol/aldehyde dehydrogenase requires **NAD+ as an oxidant**. The oxidation of ethanol takes place in the peroxisomes and is catalyzed by peroxidases. Oxidation with hydrogen peroxide (H_2O_2) occurs, which is reduced to H_2O. Acetate is formed from this ethanol.

With frequent or chronic consumption of alcohol, as is the case with alcoholics, an **inducible microsomal ethanol oxidase (MEOS)** is also found in the endoplasmic reticulum. This system drives one method of ethanol metabolism in the liver independent of alcohol dehydrogenase (ADH); this was discovered by **Lieber and DeCarli in 1968**. MEOS is a member of the **cytochrome P450 family** and the monooxygenases. This enzyme takes on an oxygen molecule and transfers one of the atoms to the substrate, and the other oxygen atom is converted to water by accepting 2 protons. The formation of acetic acid is catalyzed in this manner.

The conversion of other substrates can be decreased or deferred to toxic metabolites through the activity of MEOS and the induced cytochromes. One example is the detrimental effect of some medications in alcoholics, in whom the side effects of a medication can be amplified.

Furthermore, it has been determined that MEOS exhibits a sort of retention or memory function. This is because, after activation upon the first small sip of alcohol after withdrawal therapy, MEOS is regenerated and metabolizes ethanol very quickly. The pressure to drink more is thus increased and commonly results in relapse.

Alcohol Dehydrogenase

Alcohol dehydrogenase (ADH) is an **oxidoreductase** and is located in the human body in both the liver and stomach. ADH catalyzes both the reaction of ethanol to an aldehyde, as is the case in the breakdown of alcohol, as well as the reverse reaction of acetaldehyde into ethanol, as occurs in the last step of alcoholic fermentation by yeast.

As with all enzymatically catalyzed reactions, the enzyme remains unchanged by the reaction. Depending on how much ADH is present in the body, one can conclude the amount of alcohol the individual can tolerate. This varies from person to person. Usually, people from East Asian countries as well as indigenous peoples are more sensitive to ethanol than Europeans, because of their less effective form of ADH.

It is assumed that, regardless of the country of origin, at least 6 slightly different types of ADH coexist in the body. They all share the same structure, consisting of a **dimer of 2 polypeptide chains**, where each subunit contains 2 zinc ions essential for enzyme function. The **zinc ion is localized in the active center,** and its function is to stabilize the hydroxyl groups of ethanol. The cofactor NAD is involved in the oxidation of ethanol to acetaldehyde: $\mathbf{C_2H_5OH + NAD \rightarrow NADH+ + H+}$

ADH is also responsible for other alcoholic substances that are not initially toxic. For instance, it oxidizes methanol into the significantly more toxic methanal (formaldehyde),

and ethylene glycol to glycolic or oxalic acid. This type of poisoning is treated by administering ethanol. As long as the ethanol is broken down in the liver, methanol is expelled through the kidneys and no poisoning will occur.

The presence of ADH has also been verified in insects, such as the fruit fly. However, this enzyme is not bound to a metal ion and is not related to human ADH.

Consequences of Alcohol Consumption

Regular consumption of alcohol is considered to have preventative effects. A half-liter of beer or wine per day is said to decrease the risk of arteriosclerosis. Excessive consumption of alcohol, however, is dangerous. The breakdown of ethanol in the liver results in the overproduction of NADH and acetyl-CoA.

NADH inhibits the citric acid cycle, and acetyl-CoA increases the synthesis of **triacylglycerol (TAG)** and fatty acids. This results in the formation of a **fatty liver**. To protect itself, the liver produces more and more conjunctive tissue. This progresses into an advanced state of **liver cirrhosis**.

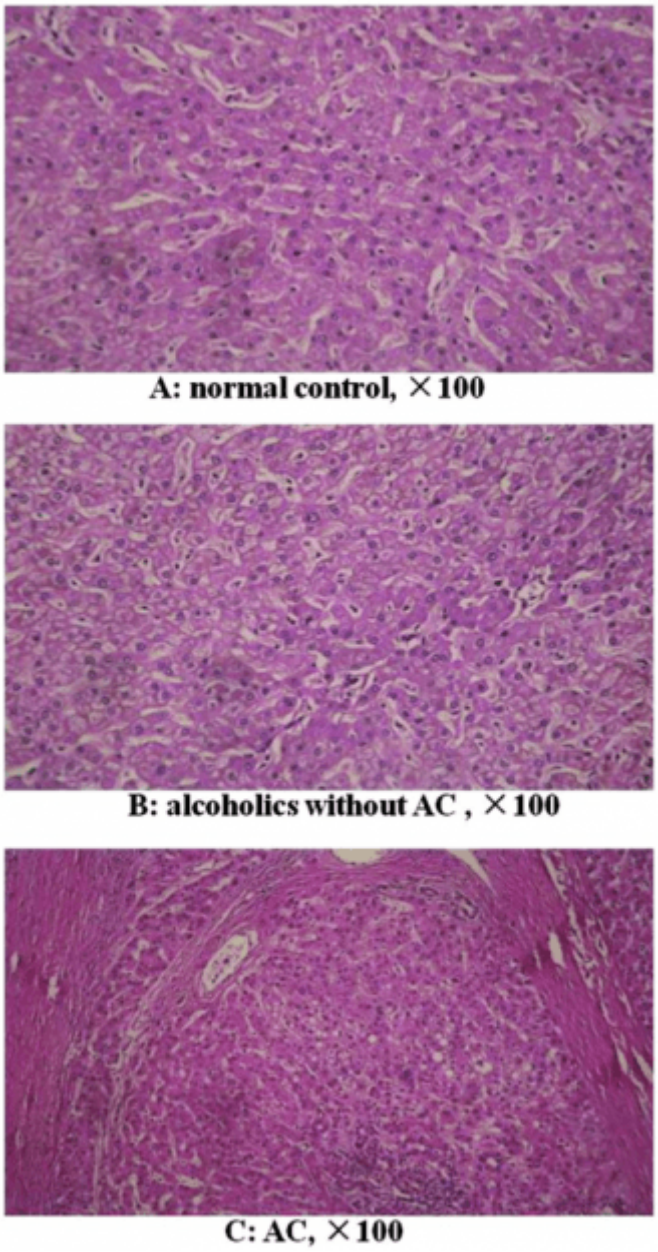

Image: Analysis of mitochondrial transcription factor A SNPs in alcoholic cirrhosis. By: Openi. License: CC BY 3.0

The growth of conjunctive tissue in the liver makes continuous, uninterrupted blood flow impossible. This leads to clotting in the portal vein. In an attempt to establish other routes to the heart, severe widening of the vessels occurs, resulting in varicose veins. However, these vessels are not designed for the additional blood and are exposed to a high risk of collapsing (**variceal hemorrhage**). Bilirubin, a byproduct of hemoglobin, is now increasingly transported in the blood, causing the skin and the underlying vessels to appear yellow (**jaundice = icterus**).

Note: For a healthy liver, the diet should consist of the following:

1. Fruits
2. Fiber
3. Water
4. Vegetables

Moreover, **alcohol** and **processed foods should be avoided**.

References

Notes