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Hepatotoxicity and Functional anatomy of the liver: An overview

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Abstract: The liver is the second-largest organ in the human body. Traditionally, the anatomy of the liver has been described on the basis of its external appearance/gross anatomy. However, with the increase in surgical procedures, for example resection and transplant, the need for a more functional description of the liver based on its vascular and biliary architecture evolved. Different models of functional anatomy of the liver have been described in the literature in the past, but Couinaud's model of functional anatomy of the liver is the most popular. The liver has dual vascular supply, with most of its supply coming from the portal vein and the remainder through the hepatic artery. In this article, we outline the functional anatomy of the liver along with its blood supply.

Keywords: Liver, Anatomy, Hepatotoxicity, Detoxification, Blood supply

Introduction: Liver is a largest gland of the body, weighing between 1 to 2.5 kg situated in the right upper quadrant of the abdomen, just below the diaphragm. Its upper and anterior surfaces are smooth and curved to fit the under surface of the diaphragm; while posterior surface is irregular in outline.[1-3]

A thick capsule of connective tissue called Glisson's capsule covers the entire surface of the liver. The liver is multi-lobed organ i.e., it has 4 distinct lobes, divided into a

large right lobe and a smaller, wedge-shaped left lobe, the other two, the caudate and quadrate lobes (Figure 1).

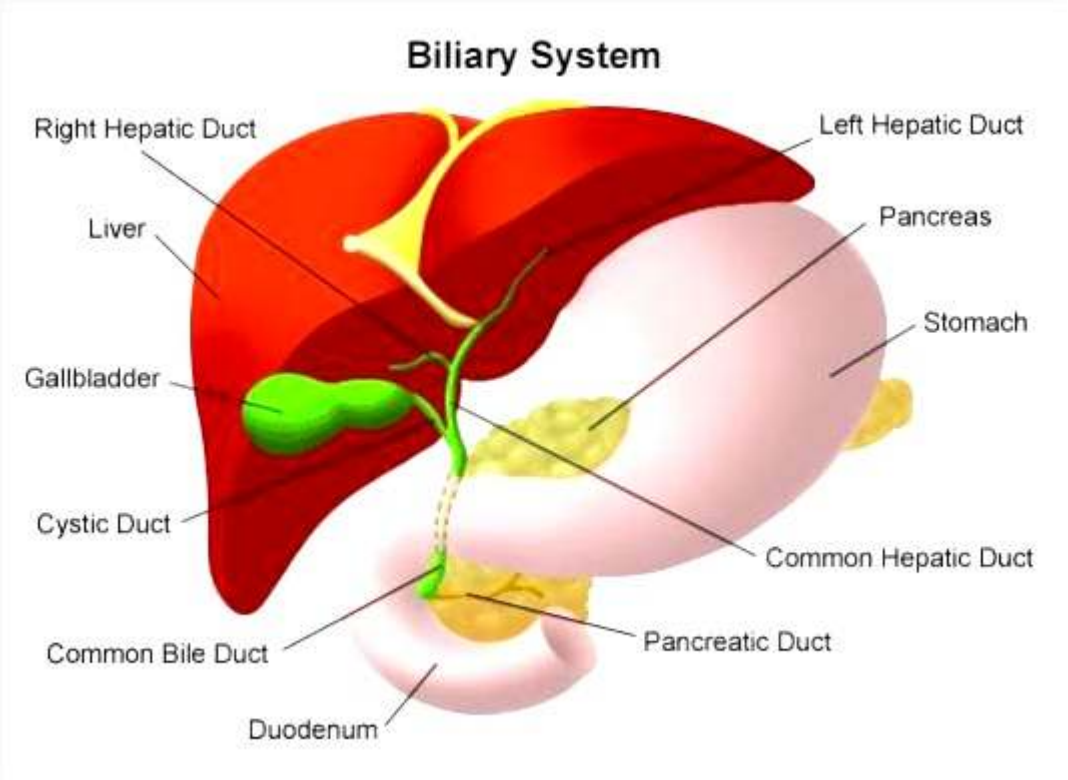

Figure: 1 Anatomy of Liver

These hepatic lobules are the functioning units of the liver, which is a cylindrical structure several millimetres in length and 0.8 to 2 millimetres in diameter, each of them have approximately 1 million lobules that consist of a hexagonal row of hepatic cells called "**hepatocytes**". They secrete bile into the bile channels and also perform a variety of metabolic functions.[4]

Between each row of hepatocytes are small cavities called "sinusoids" and each sinusoid is lined with Kupffer cells, phagocytic cells that remove amino acids, nutrients, sugar, old red blood cells, bacteria and debris from the blood that flows through the sinusoids. The main functions of the sinusoids are to destroy old or defective red blood cells, to remove bacteria and foreign particles from

the blood and to detoxify toxins and other harmful substances. [4]

Hepatic arterioles are also present in the interlobular septa. These arterioles supply arterial blood to the septal tissues between the adjacent lobules and many of the small arterioles also empty directly into the hepatic sinusoids, most frequently emptying into those located about one third the distances from the interlobular septa. [4]

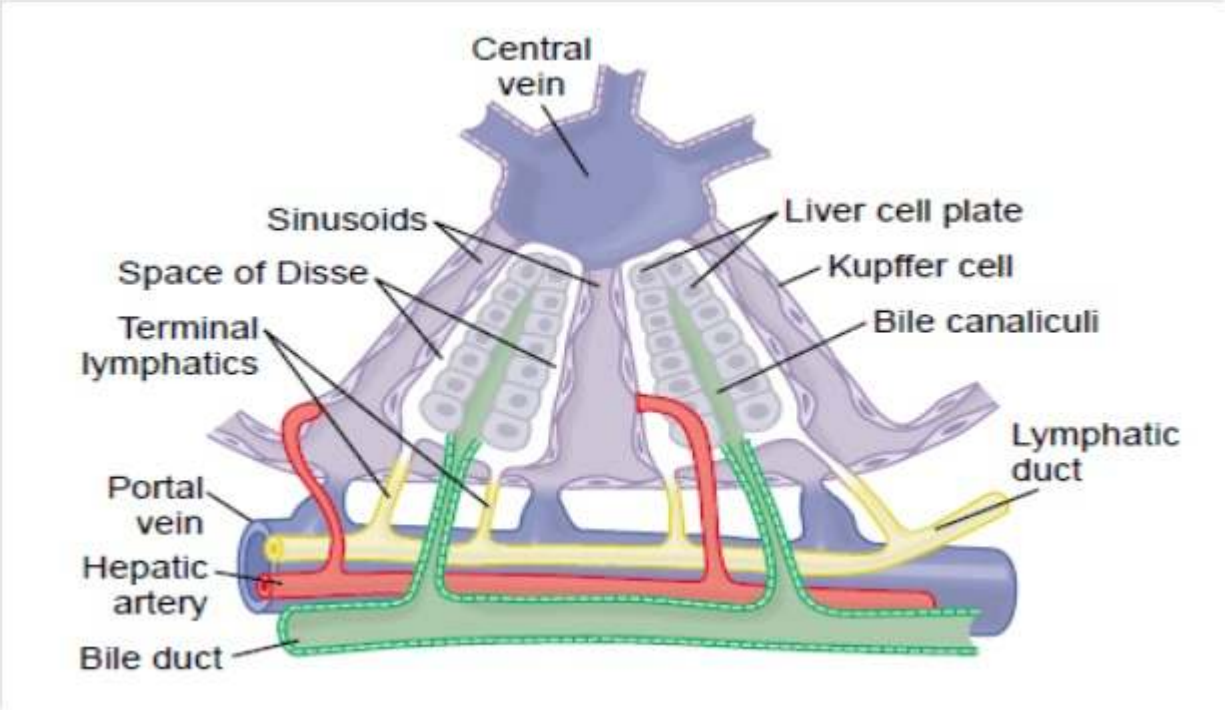

Figure: 2 Basic structure of a liver lobule

In addition to the hepatic cells, the venous sinusoids are lined by two other types of cell: (1) typical endothelial cells and (2) large Kupffer cells (also called reticuloendothelial cells), which are resident macrophages that line the sinusoids and are capable of phagocytosizing bacteria and other foreign matters in the hepatic sinus blood (Figure 2). [4]

Blood Supply to the Liver:

The liver receives blood from two sources. From the hepatic artery it obtains oxygenated blood, and from the hepatic portal vein it receives deoxygenated blood containing newly absorbed nutrients, drugs, and possibly microbes and toxins from the gastrointestinal tract. Branches of both the

hepatic artery and the hepatic portal vein carry blood into liver sinusoids, where oxygen, most of the nutrients, and certain toxic substances are taken up by the hepatocytes. Products manufactured by the hepatocytes and nutrients needed by other cells are secreted back into the blood, which then drains into the central vein and eventually passes into a hepatic vein.[5]

The blood flow to the liver is 1350 ml/min (27% of the cardiac output) on average. The hepatic artery supplies the liver with 300 ml/min of oxygenated blood from the aorta. The remaining 1050 ml/min of blood flow is delivered by the hepatic portal vein. This blood comes directly from the digestive tract. It is low in oxygen but contains a high concentration of nutrients absorbed from the intestines[6]

Functions of the Liver: [1, 2, 4, 7]

The liver is responsible for important functions which include:

1. It produces and secretes bile (stored in the gallbladder until needed) that is used to break down and digest fatty acids.
2. It produces prothrombin and fibrinogen, both blood-clotting factors.
3. It converts sugar into glycogen, which it stores until the muscles need energy and it is secreted into the blood stream as glucose.
4. It synthesizes proteins and cholesterol and converts carbohydrates and proteins into fats, which are stored for later use.
5. It produces blood proteins and enzymes needed for digestion and other bodily functions.
6. It produces urea, while breaking down proteins, which it synthesizes from carbon dioxide and ammonia. It is eventually excreted by the kidneys.
7. Liver also stores critical trace elements such as iron and copper, as well as vitamins A, D, and B12.
8. Uptake of nutrients supplied by the intestines via the portal vein.
9. The liver is also responsible for detoxifying the body of poisonous substances.

The Metabolism of Drugs and Xenobiotics (Detoxification): [8, 9]

Hepatocytes play an extremely important role in the metabolism of drugs and xenobiotics—compounds that are foreign to the body, some of which are toxic. Most drugs and xenobiotics are introduced into the body with food. The more hydrophobic (nonpolar, lipid-soluble) a substance is, the more likely it will be reabsorbed. Many drugs and metabolites are hydrophobic, and the liver converts them into hydrophilic compounds.

Two reactions catalyzed by different enzyme systems, are involved in the conversion of xenobiotics and drugs into hydrophilic compounds.

- Phase I reaction
- Phase II reaction

Phase I Reaction:

In phase I reactions, the parent compound is biotransformed into more polar compounds by the introduction of one or more polar groups. The common polar groups are hydroxyl (OH) and carboxyl (COOH). Most phase I reactions involve oxidation of the parent compound. The enzymes involved are mostly located in the smooth ER; some are located in the cytoplasm.

The enzymes involved in phase I reactions of drug biotransformation are present as an enzyme complex composed of the NADPH-cytochrome P450 reductase and a series of hemoproteins called cytochrome P450.

Phase II Reaction:

In phase II reactions, the phase I reaction products undergo conjugation with several compounds to render them more hydrophilic. Glucuronic acid is the substance most commonly used for conjugation, and the enzymes involved are the glucuronyltransferases. Other molecules used in conjugation are glycine, taurine, and sulfates.

Disease of Liver: [2, 5, 10, 11]

Various liver diseases include jaundice, viral hepatitis of different types i.e. Hepatitis A, B, C, D & E, cirrhosis and Hepatocellular carcinoma.

Besides, there also occurs various clinical syndromes due to the irregular metabolic disorders i.e. hepatic encephalopathy, ascites, cholestasis, autoimmune hepatitis,

inherited metabolic disease, necrosis,fibrosis and cholangitis.

Hepatotoxicity: [2, 5, 12. 13]

Hepatotoxicity is a general term for liver damage. Toxic liver injury produced by drugs and chemicals may virtually mimic any form of naturally occurring liver diseases. In fact, any patient presenting liver disease or unexplained jaundice is thoroughly questioned about history of drug intake or exposure to chemicals. Hepatotoxicity from drugs and chemicals is the commonest form of iatrogenic disease. Severity of hepatotoxicity is greatly increased if the drug is continued after the symptoms develop.

There are several specific conditions that all fall within the general category of hepatotoxicity. These conditions include

a) Hepatitis—inflammation of the liver
b) Hepatic necrosis—death of liver cells
c) Hepatic steatosis—too much fat in the liver; may be associated with life-threatening conditions called lactic acidosis.

Symptoms of Hepatotoxicity-[13]

The first sign of damage to the liver is an increase in liver enzyme levels in the blood. When the liver is damaged, its enzymes are released into the bloodstream, where the levels can be measured by blood tests. These are called liver function tests (LFTs).

The signs and symptoms of Hepatotoxicity vary depending on how badly the liver is damaged. Symptoms of liver damage include: Nausea, Vomiting, Abdominal pain, Loss of appetite, Diarrhea, Feeling tired or weak, Jaundice (yellowing of the skin and eyes) and Hepatomegaly (liver enlargement).

Hepatotoxins:

There are literally thousands of chemicals and drugs that could be toxic to the liver. These chemicals and drugs are classified as given in table no 1.4.

Many drugs undergo chemical change in the liver before secretion in bile or other organs. They may damage the liver cells in their original form or while in various intermediate stages. Some substance always causes liver damage (predictably toxic)

while others only do so when hypersensitivity to normal doses develops (unpredictably toxic). In both types, the extent of the damage depends on the size of the dose and the duration of exposure.[2, 14]

Among the various inorganic compounds producing hepatotoxicity are arsenic, phosphorus, copper and iron. Organic agents include certain naturally occurring plant toxins such as pyrrolizidine alkaloids, mycotoxins and bacterial toxins. The synthetic group of organic compounds are a large number of medicinal agents. In general, drug reactions affecting the liver are divided into two main classes: - [3, 15]

1. Direct or predictable Reactions and
2. Indirect or unpredictable or idiosyncratic Reactions

Direct or predictable Reactions:

When the drug or one of its metabolites is either directly toxic to the liver or it lowers the host immune defense mechanism. The adverse effects occur in most individuals who consume them and their hepatotoxicity is dose dependent.

Indirect or unpredictable or idiosyncratic Reactions:

Most drugs cause liver injury infrequently. These reactions considered idiosyncratic, occur at therapeutic doses with a pattern that is consistent for each drug and for class class. Idiosyncratic reactions are characterized by a variable delay or latency period ranging from 5 to 90 days from the initial ingestion of the drug, and are frequently fatal if the drug is continued once the reaction has begun.

When the drug or one of its metabolites acts as a hapten and induces hypersensitivity in the host. In many instances, drug hepatotoxicity is associated with appearance of autoantibodies to liver, kidney microsomes (i.e. anti-LKM^2) directed against cytochrome P-450 enzyme. The hepatotoxicity by all individuals and the effects are usually not dose related.

Class of Hepatotoxins

Category of agent	Examples
Direct or predictable	1. Chloroform 2. Tetracyclines 3. Cytotoxic drugs 4. Anabolic steroids 5. Alcohol 6. Paracetamol (Acetamenophen) 7. Some fungi
Indirect or unpredictable or idiosyncratic	1. Phenothiazine compounds 2. Methyldopa 3. Indometacin 4. Chlorpropamide 5. Halothans 6. Thiouracil 7. Sulphonamide

Diagnosis and Management of Drug-Induced Liver Injury:[16]

There is no single test including liver biopsy that can be used to diagnose drug-related hepatotoxicity. Other causes of liver injury must first be considered with the use of a combination of serologic tests, imaging studies and clues from the patient's history.

Various technique employed for the diagnosis of liver injuries include computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total iron-binding capacity (TIBC) and alpha1-antitrypsin (A1AT) (Figure 3).[17]

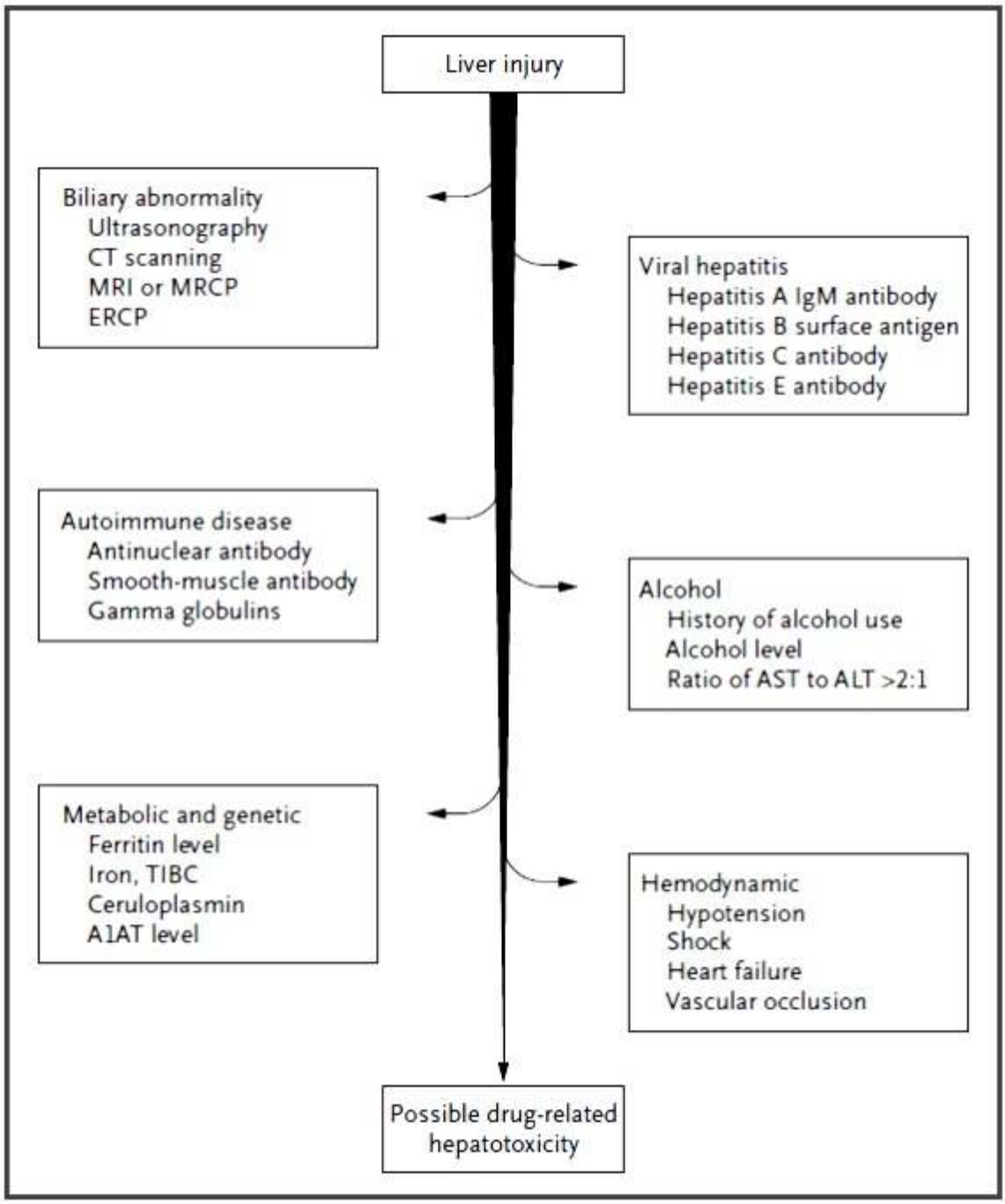

Figure: 3 Diagnosis of Drug-Related Hepatotoxicity

The following way diagnosis and management of drug-induced liver injury can be done.

1. Taking a careful drug history, including over-the-counter and alternative complementary medicine remedies.
2. In patients with hepatitis a viral aetiology should be excluded.
3. Cholestatic lesions, which may resolve only slowly on drug withdrawal, have to be differentiated from other causes of obstructive jaundice, both intrahepatic and extrahepatic.
4. Underlying liver disease can cause diagnostic confusion, e.g. the alcoholic patient receiving ant tuberculosis drugs. It is wise to measure liver function tests before starting treatment with any drug which has documented hepatotoxic potential.
5. Liver biopsy is of only limited use in diagnosis, although certain features, e.g. eosinophil infiltration, may provide a pointer to drug induced liver disease.
6. Diagnostic challenge is extremely dangerous for hepatic reactions because it may precipitate fulminant hepatic failure; the procedure is safer for cholestatic reactions.
7. Monitoring liver function tests in the early weeks of therapy is useful in detecting an impending reaction to some drugs e.g. isoniazid. Minor abnormalities (serum transaminases less than twice normal) are often self-limiting and progress can be monitored.

Conclusion:

According to World Health Organization (WHO), about 18,000 people die every year due to liver diseases. The common ailments of liver are cirrhosis, cholestasis, hepatitis, portal hypertension, hepatic encephalopathy, fulminant hepatic failure and certain tumors like hepatoma. It is estimated that two billion people around the world are infected with hepatitis B. About 350 million of these have the chronic form of the disease.

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