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LIVER DISORDERS

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ABSTRACT
The liver is a vital organ present in vertebrates and some other animals. It has a wide range of functions, including detoxification, protein synthesis, and production of biochemicals necessary for digestion. The liver is a reddish brown organ with four lobes of unequal size and shape. A human liver normally weighs 1.4–1.6 kg (3.1–3.5 lb), and is a soft, pinkish-brown, triangular organ. It is both the largest internal organ (the skin being the largest organ overall) and the largest gland in the human body. The liver supports almost every organ in the body and is vital for survival. Because of its strategic location and multidimensional functions, the liver is also prone to many diseases. Liver disease (also called hepatic disease) is a broad term describing any single number of diseases affecting the liver. Many are accompanied by jaundice caused by increased levels of bilirubin in the system. The bilirubin results from the breakup of the hemoglobin of dead red blood cells; normally, the liver removes bilirubin from the blood and excretes it through bile.
KEYWORDS: Liver disorders, Hepatic injury, Liver cirrhosis

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INTRODUCTION

The liver is the largest organ of the body, weighing 1 to 1.5 kg and representing 1.5 to 2.5% of the lean body mass. The size and shape of the liver vary and generally match the general body shape – long and lean or squat and square. The liver is located in the right upper quadrant of the abdomen under the right lower rib cage against the diaphragm and projects for variable extent into the left upper quadrant. It receives a dual blood supply; approximately 20% of the blood flow is oxygen rich blood from the hepatic artery, and 80% is nutrient rich blood from the portal vein arising from the stomach, intestines, and spleen. The majority of cells in liver are hepatocytes, which constitute two –thirds of the mass of liver. The remaining cell types are kupffer cells (members of reticuloendothelial system), stellate cells, endothelial cells and blood vessels, bile ductular cells, and supporting structures.Liver cells synthesize albumin, clotting factors including fibrinogen, some complement components, 1- antitrypsin etc., and remove from the body many waste products and potentially toxic substances. Liver cells are also involved in the metabolism of many drugs. Extensive disease of the liver therefore affects many vital functions and has profound effects on the body[1]

Liver injury and its manifestations tend to follow characteristic patterns, which are as follows:

A) Hepatic Injury: - From a morphological stand point the liver is an inherently simple organ, with a limited repertoire of responses to injurious events. Regardless of cause, five general responses are seen:

(i) Inflammation: - Injury to hepatocytes associated with an influx of acute or chronic inflammatory cells into the liver is termed hepatitis. Attack of viable antigen expressing liver cells by sensitized T cells is a common cause of liver damage. Inflammation may be limited to portal tracts or may spill over into the parenchyma. Foreign bodies, organisms, and a variety of drugs may incite a granulomatous reaction[2]

(ii) Degeneration: - Damage from toxic or immunologic insult may cause hepatocytes to take on a swollen, edematous appearance (ballooning degeneration) with irregularly clumped cytoplasm and large clear spaces. Alternatively, retained biliary material may impart a diffuse, foamy, swollen appearance to the hepatocyte (foamy degeneration). Accumulation of fat droplets within hepatocytes is known as steatosis.

Macrovesicularsteatosis appears in alcoholic liver disease, Reye's syndrome, and acute fatty liver of pregnancy. Macrovesicularsteatosis may be seen in the alcoholic liver or in the livers of obese or diabetic individuals.[2]

(iii) Cell death: - Virtually any significant insult to the liver may cause hepatocyte destruction. In the setting of ischemia and a number of drug and toxic reactions, hepatocyte necrosis is distributed immediately around the central vein (centrilobular necrosis). In immunologically mediated hepatocyte death, apoptosis may be limited to scattered cells with in the hepatic parenchyma or to the interface between the periportal parenchyma and inflamed portal tracts (interface hepatitis). With more severe inflammatory or toxic injury, apoptosis or necrosis of contiguous hepatocytes may span adjacent lobules in a portal-to-portal, portal-to-central, or central-to-central fashion (bridging necrosis). Destruction of entire lobules (sub massive necrosis) or most of the liver parenchyma (massive necrosis) is usually accompanied by hepatic failure.[1]

(iv) Fibrosis: - Fibrous tissue is formed in response to inflammation or direct toxic insult to the liver. In the initial stages, fibrosis may develop within or around portal tracts or the central vein or may be deposited directly within the sinusoids. Fibrosis is generally considered as an irreversible consequence of hepatic damage but there is a growing evidence that cessation of hepatic injury in some settings can lead to reversal of fibrosis.[3]

(v) Cirrhosis :- With continuing fibrosis and parenchymal injury, the liver is subdivided into nodules of regenerating hepatocytes surrounded by scar tissue, termed cirrhosis.[4, 5]

B) Jaundice And Cholestasis:- Jaundice, a yellow discoloration of skin an sclerae (icterus) occurs when systemic retention of bilirubin leads to elevated serum levels above 2.0mg the normal in the adult being less than 1.2mg/dl. Cholestasis, on the other hand, is defined as systemic retention of not only bilirubin but also other solutes eliminated in bile (particularly bile salts and cholesterol).[6, 7] (**Table 1**)

(C) Hepatic Failure: - The most severe clinical consequence of liver disease is hepatic failure. This may be the result of sudden and massive hepatic destruction. More often, it is the end point of progressive damage to the liver, either by insidious destruction of hepatocytes or by repetitive discrete waves of parenchymal damage. The morphological alterations that cause liver failure fall into three categories viz. Massive hepatic necrosis, chronic liver disease, and hepatic dysfunction without overt necrosis.

Massive hepatic necrosis is most often caused by fulminant, viral hepatitis. Acetaminophen, Halothane, Antituberculosis drugs (Rifampin, Isoniazid), Chemicals such as carbon-tetrachloride, and mushroom poisoning (Amanita phalloides).[4]

D) Cirrhosis: - It is among the top 10 causes of death in the western world. Although largely the result of alcohol abuse and other major contributors include chronic hepatitis, biliary disease, and iron overload. There is no satisfactory classification of cirrhosis but the following is the approximate frequency of etiologic categories in the western world:-

1. Alcoholic liver disease, 60% to 70%
2. Viral hepatitis, 10%
3. Biliary diseases, 5% to10%
4. Hereditary hemochromatosis, 5%
5. Wilson's disease, rare
6. α_1– Antitrypsin deficiency, rare

The three major pathologic mechanisms that combine to create cirrhosis are hepatocellular death, regeneration, and progressive fibrosis.[4, 5]

E) Portal Hypertension: - Increased resistance to portal blood flow may develop in a variety of circumstances, which can be divided into prehepatic, intrahepatic, and post hepatic causes. The major prehepatic conditions are occlusive thrombosis and narrowing of portal vein before it ramifies within the liver. The major post hepatic causes are severe right sided heart failure, constrictive pericarditis, and hepatic vein outflow obstruction.[8]

LIVER DISEASES

There are many causes of the liver diseases. Different Liver diseases and their causes are summarised in **Table 2**.

Liver diseases generally present clinically in a few distinct patterns, usually classified as either hepatocellular or cholestatic (obstructive). In hepatocellular diseases (such as viral hepatitis or alcoholic liver disease), features of liver injury, inflammation, and necrosis predominate. In cholestatic diseases (such as gall stone or malignant obstruction, primary biliary cirrhosis, many drug –induced liver diseases), features of inhibition of bile flow predominate.[3]

Investigation of Liver Diseases

The commonly used investigations for liver disease includes:-

- Analysis of serum concentrations of bilirubin, hepatic enzymes, albumin, clotting factors, etc.
- Immunological testing for auto-antibodies.

• Liver biopsy
• Imaging techniques

Bilirubin: - Bilirubin pigment is a breakdown product of the haem moiety of haemoglobin. It is produced at sites of red cell destruction (e.g. spleen) and circulates in the blood in an unconjugated water-insoluble form bound to albumin. In the liver it is conjugated to glucuronic acid by the enzyme glucuronyltransferase. Conjugated bilirubin is water –soluble and can therefore appear in the urine if the outflow of bile from the liver is interrupted. Bilirubin is converted by bacteria in the intestine to faecal urobilinogen (stercobilinogen), some of which is absorbed and then excreted, mostly in the bile to complete its enterohepatic circulation or, in only trace amounts normally, by the kidneys to appear in the urine as urobilinogen. Stercobilinogen is oxidised to stercobilin (faecal urobilin), the principal faecal pigment.

In early or recovering viral hepatitis, impaired biliary excretion results in pre-formed stercobilinogen appearing in the urine in excess as urobilinogen; this is one sensitive marker of early liver injury. In well-established Bellary obstruction, the urinary urobilinogen concentration falls, because the cessation of biliary excretion into the gut result in sustained absence of synthesis of focal urobilinogen[9] (**Figure 1**)

Enzymes: - In liver cell injury, damage to the membranes of cells and organelles allows intracellular enzymes to leak into the blood. Examples include ALT, AST and - GT. Their diagnostic usefulness is summarized in table 3. The enzyme alkaline phosphatase is normally present in bile. Obstruction to the flow of bile causes regurgitation of alkaline phosphatase into the blood, resulting in increased serum concentrations.[10](**Table 3**).

Albumin: - Albumin is a major serum protein synthesized by the liver cells. Albumin is not an early marker of liver disease due to its long half-life in comparison to clotting factor. In chronic liver disease, such as cirrhosis, a low serum albumin concentration is an important manifestation of liver failure, which results in peripheral oedema and contributes to the presence of ascites, due to a reduction in plasma oncotic pressure.[9]

Clotting factors: - Liver cells synthesize the vitamin K-dependent clotting factors, deficiency of which results in a bleeding tendency. This can be detected in the laboratory by measuring the prothrombin time.[11]

Immunology: - Although insignificant amounts of immunoglobulins are synthesized in the liver, immunological abnormalities often accompany liver disease and are useful diagnostic markers. Examples include:

• Anti-mitochondrial antibodies found in primary biliary cirrhosis
• Anti-nuclear antibodies and anti-smooth muscle antibodies found in autoimmune hepatitis.

Polyclonal immunoglobulin elevations also occur say for example raised IgG in autoimmune hepatitis, raised IgM in primary biliary cirrhosis, and raised IgA in alcoholic cirrhosis.

Biopsy: - The two common types of live biopsy are:
• Wedge biopsies, taken during the course of an abdominal operation
• Needle biopsies, which are done percutaneously under local anaesthesia.

Most liver diseases produce diffuse abnormalities in the organ and a biopsy from any part of it will therefore be representative.[12]

Imaging: - Techniques used to visualize the liver and detect lesions within it includes Cholangiography to visualise the biliary system, Scintigraphy after the injection of 99m Tc-labeled colloids, which are taken up by the phagocytic Kupffer cells, Ultrasound, Computed axial tomography (CAT), and Magnetic resonance imaging (MRI).

CONCLUSION

The outlook for the hepatic patient has never been more positive.The new approach to educating patients and giving them responsibility for self-monitoring should also produce positive results and decrease complications. The new imaging techniques provide a much needed tool for the diagnosis of the hepatic injury which results in the better and on time treatment of the disorder. More new techniques are required to be developed to treat different liver disorders efficiently and conveniently. The disorders like cirrhosis, hepatitis and other liver diseases should be carefully monitored and the agents causing these disorders must be kept in check.

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Table 1: Causes of jaundice[2]

Sl. No.	Causes of Jaundice
I.	Predominantly Unconjugated Hyperbilirubinemia
a.	Excess production of bilirubin Hemolytic anemia, Resorption of blood from internal hemorrhage (e.g., alimentary tract bleeding, hematomas), Ineffective erythropoiesis syndromes (e.g., pernicious anemia, thalassemia), Reduced hepatic uptake, Drug interference with membrane carrier systems Some cases of Gilbert syndrome
b.	Impaired bilirubin conjugation, Physiologic jaundice of the newborn, Breast milk jaundice Genetic deficiency of bilirubin (Crigler –Najjar syndromes types I and II) Gilbert syndrome
c.	Diffuse hepatocellular disease (e.g., viral or drug –induced hepatitis, cirrhosis)
II.	Predominantly Conjugated Hyperbilirubinemia
a.	Decreased hepatic excretion of bilirubin glucuronides
b.	Deficiency in canalicular membrane transporters (Dubin-Johnson syndrome, Rotor syndrome), Drug-induced canalicular membrane dysfunction (e.g., oral contraceptives, cyclosporine), Hepatocellular damage or toxicity (e.g., viral or drug-induced hepatitis, total parenteral nutrition, systemic infection), Decreased intrahepatic bile flow, Impaired bile flow through bile canaliculi (e.g., drug-induced microfilament dysfunction)
c.	Inflammatory destruction of intrahepatic bile ducts (e.g., primary biliary cirrhosis, primary sclerosing cholangitis graft-versus host disease, liver transplantation), Extra hepatic biliary obstruction, Gallstone obstruction of biliary tree, Carcinomas of head of pancreas, extrahepatic bile ducts, ampulla of Vater, Extra hepatic biliary atresia, Biliary strictures and choledochal cysts Primary sclerosing cholangitis (extra hepatic)

Table 2: Causes of Liver diseases[13-20]

Sl. No	Liver Diseases
1.	Inherited hyperbilirubinemia Gilbert's syndrome Crigler –Najjar syndrome, types I and II Dubin – Johnson syndrome Rotor syndrome
2.	Viral hepatitis Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, Hepatitis E Others (mononucleosis, herpes, adenovirus hepatitis) Cryptogenic hepatitis
3.	Immune and autoimmune liver diseases Primary biliary cirrhosis, Autoimmune hepatitis, Sclerosing cholangitis, Overlap syndromes, Graft –vs-host disease, Allograft rejection
4.	Genetic liver diseases α_1 -Antitrypsin deficiency, Hemochromatosis, Wilson's disease, Benign recurrent intrahepatic cholestasis (BRIC), Familial intrahepatic cholestasis (FIC), types I-III Others (galactosemia, tyrosinemia, cystic fibrosis, Newman-Pick disease, Gaucher's disease)
5.	Alcoholic liver disease Acute fatty liver, Acute alcoholic hepatitis, Laennec's cirrhosis

6.	Nonalcoholic fatty liver Steatosis, Steatohepatitis, Acute fatty liver of pregnancy
7.	Liver involvement in systemic diseases Sarcoidosis, Amyloidosis, Glycogen storage diseases Celiac disease Tuberculosis Myobacteriumaviumintracellulare
8.	Cholestatic syndromes Benign postoperative cholestasis, Jaundice of sepsis, Total parenteral nutrition (TPN) induced jaundice , Cholestasis of pregnancy, Cholangitis and cholecystitis Extrahepaticbillary obstruction (stone, stricture, cancer), Biliary atresia, Caroli's disease, Cryptosporidiosis
9.	Drug induced liver disease Hepatocellular patterns (isoniazid, acetaminophen) Cholestatic patterns (methyltestosterone) Mixed patterns (sulfonamides, phenytoin) Micro-and macrovesicularsteatosis (methotrexate, fialuridine)
10.	Vascular injury Venoocclusive disease Budd-Chiari syndrome Ischemic hepatitis Passive congestion Portal vein thrombosis Nodular regenerative hyperplasia
11.	Mass lesions Hepatocellular carcinoma Cholangiocarcinoma Adenoma Focal nodular hyperplasia Metastatic tumors Abscess Cysts

Table 3: The diagnostic usefulness of Serum analyses in Liver disease[10]

Diagnostic usefulness of serum analyses in liver disease		
Test	**Deviation from normal**	**Interpretation**
Albumin * Normal 35-50g/l	↓	Liver failure
Prothrombin time * Normal <15s	↑	Liver failure
Alanine aminotransferase (ALT) * Normal <40IU/I	↑	Hepatocellular injury
Aspartate aminotransferase (AST) * Normal <40IU/I	↑	Hepatocellular injury
γ-Glutamyltransferase (γ-GT) * Normal <50 IU/I	↑	Hepatocellular injury (centrilobular)
Alkaline phosphatase * Normal <100 IU/I	↑	Biliary obstruction Hepatic metastases
Bilirubin * Normal 5-12 µmol/I	↑	Hepatocellular injury Biliary obstruction Liver failure Congenital hyperbilirubinaemia Hemolysis

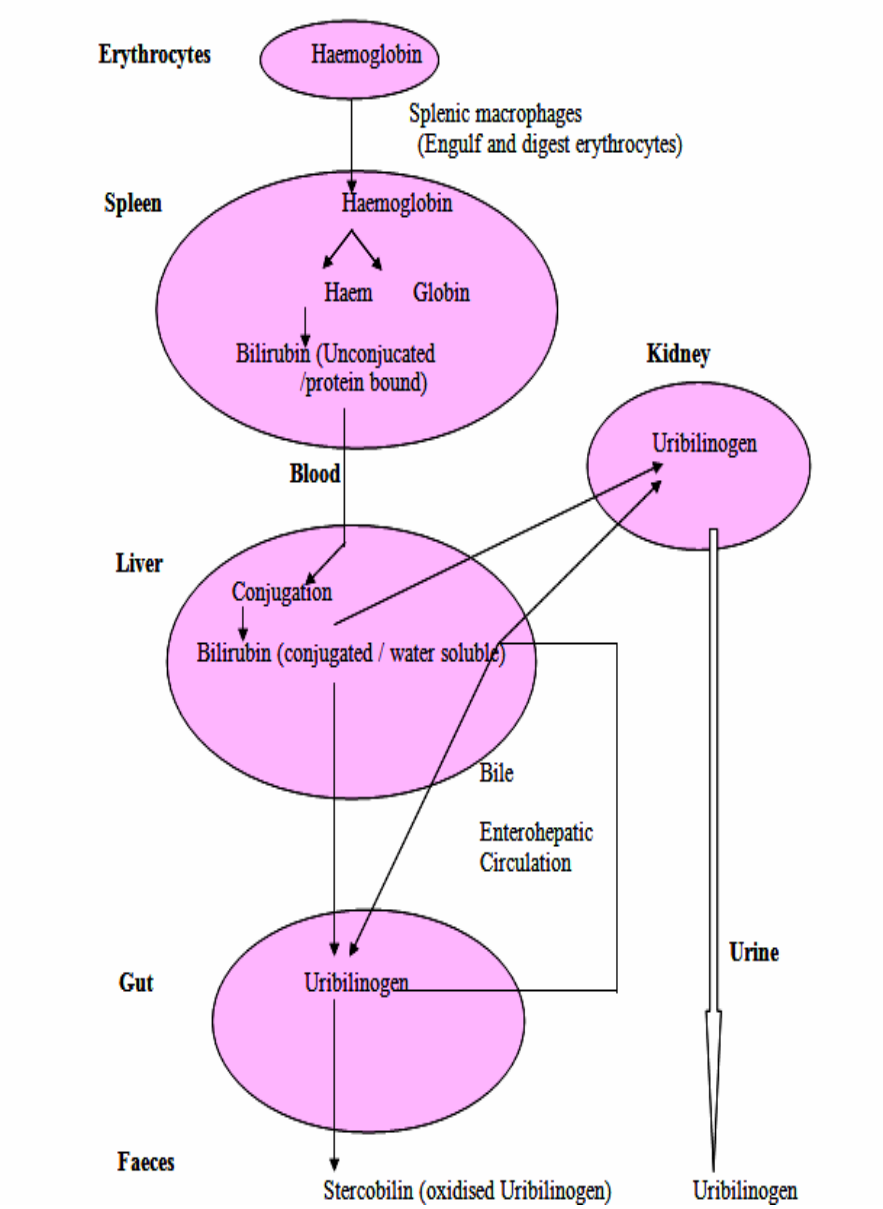

Figure 1: The simplified pathway of Bilirubin Metabolism