LIVER DISEASES

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Introduction

Liver is a dual organ having both secretory and excretory functions. It is the largest gland in the body. Liver is the second largest organ in human body, more than 5,000 separate bodily functions including helping blood to clot, cleansing the blood of toxins to converting food into nutrients to control hormone levels, fighting infections and illness, regenerating back after injury and metabolizing cholesterol, glucose, iron and controlling their levels. Most people never give their liver a thought until something goes wrong, yet, liver diseases on rise, affecting one in ten. Liver diseases can be inherited or caused by a variety of factors that damage the liver. In fact, there are many types of liver diseases that can be caused by a virus, damage from drugs or chemicals, obesity, diabetes or an attack from own immune system, when the condition is left untreated, it can become life threatening and can permanently damage the liver or the bile duct. This damage leads to malignancy and cause liver cancer.

Liver Diseases

Numerous liver diseases are accompanied by jaundice caused by augmented levels of bilirubin in the body. Bilirubin is the result of degradation of hemoglobin of dead red blood cells which are normally removed by the liver and excreted via bile. In hepatitis, inflammation of the liver, is caused by different viruses, but also some toxic substances, autoimmune diseases and inherited conditions; Liver cirrhosis is the formation of fibrous tissue in the liver to kill hepatocytes, respectively. Liver cell death can be caused by viral hepatitis, alcohol poisoning or other toxic substances; Hemochromatosis is an inherited disorder that causes iron accumulation in the body, leading to long-term liver damage; Benign tumors such as adenoma, "angioma" focal nodular hyperplasia. Liver cancer as the primary tumor or carcinoma cholangiocarcinoma

or metastasis of cancer to other parts of the digestive system; Wilson disease is an inherited disorder that causes copper accumulation in the body; Primary sclerosing cholangitis, an inflammatory autoimmune disease carries bile; Primary biliary cirrhosis, autoimmune disease of minute rage ducts; Budd-Chiari syndrome or hepatic vein obstruction; Gilbert's syndrome, a genetic disorder of bilirubin metabolism. There are also many pediatric liver diseases. Proper liver function can be verified by a number of specialized clinical studies, which measure the presence or absence of typical enzymes, metabolites or substances associated with the regular activities.

Agents Responsible for Liver Damage

- **Dietary Deficiencies**

Fatty changes in the liver, in kwashiorkor may be attributed to a low protein intake and reduced capacity to produce lipo proteins. The liver is of often grossly enlarged in children with kwashiorkor, containing 30-50 per cent, fat by weight, in the form of triglyceride. The intrahepatic accumulation of fat results due to excess delivery of fatty acids to the liver and or enhancing the lipogenesis. This is combined with the impaired lipid transport from the liver secondary to Apo protein deficiency. When protein is supplied fat clears from the liver within a short time. Fatty changes in the liver are common whenever there is a high proportion of fat in the metabolic mixture, for example, in uncontrolled diabetes, in starvation, in some cases of obesity, and when too much carbohydrate has been infused during intravenous feeding. In these cases, as in kwashiorkor, the changes are easily reversible and not followed by fibrosis

- **Infective Agents**

Virus can cause infection and damage the liver. Types A, B, C, D, E and G can cause hepatitis. Type E can be deadly during pregnancy. Hepatitis A and E virus is excreted in the stools and spread by the faecal-oral route. The patient suffers from jaundice and the liver is enlarged and tender. Recovery from a typical infection is complete and not followed by fibrosis and cirrhosis. Hepatitis B, C, D and G virus produce a disease

known as homologous serum jaundice which arises after transfusion of blood or blood products obtained from a donor who is a carrier. Improperly sterilised needles can also cause this hepatitis infection. Most patients recover. In 10 per cent of people the disease may reach a chronic stage. Types B and D can cause extreme jaundice.

- **Toxic Agents**

Alcohol: In malnourished patients consumption of alcohol produces acute liver damage and jaundice that resembles viral hepatitis. Alcohol is also known to have direct action on the lipid metabolism in the liver by enhancing fatty acid synthesis, decreasing fatty acid oxidation and producing specific stimulation to triglyceride formation. Lipids accumulate, because of the increased direct channelling of ethanol as a substrate to acetate via acetaldehyde with the subsequent conversion of acetyl CoA to fatty acids. The increased NADH/NAD ratio overwhelms the cell‘s ability to maintain redox homeostasis and contributes to this conversion. About half the increase in liver size in heavy drinkers is explained by the excess fat.

Drugs and Chemicals: Every drug that is consumed reaches the liver and its chemical nature is altered before being eliminated from the body. Drugs like paracetamol (fever) INH (TB) and oestrogen (contraceptive) may damage the liver. Workers in chemical industry like organic hydrocarbons may develop liver damage. Toxicity due to liver damage has also been observed with several commercially available herbal preparations. Excess store of iron, copper, galactose and glycogen may accumulate in the liver and in time lead to cirrhosis.

In Born Errors of Metabolism: Children with hereditary tyrosinaemia, galactosemia and hereditary fructose intolerance may develop liver damage.

1. Hepatitis

Hepatitis is an inflammation of the liver that is caused by a variety of infectious viruses and noninfectious agents leading to a range of health problems, some of which can be fatal. There are five main strains of the hepatitis virus, referred to as types A, B, C, D and E. While they all cause liver disease, they differ in important ways including modes of transmission, severity of the illness, geographical distribution and prevention methods. In particular, types B and C lead to chronic disease in hundreds of millions of people and together are the most common cause of liver cirrhosis, liver cancer and viral hepatitis-related deaths. An estimated 354 million people worldwide live with hepatitis B or C, and for most, testing and treatment remain beyond reach. Some types of hepatitis are preventable through vaccination.

1.1 Hepatitis A

Hepatitis A is an inflammation of the liver caused by the hepatitis A virus (HAV). The virus is primarily spread when an uninfected (and unvaccinated) person ingests food or water that is contaminated with the faeces of an infected person. The disease is closely associated with unsafe water or food, inadequate sanitation, poor personal hygiene and oral-anal sex. The incubation period of hepatitis A is usually 14–28 days. Symptoms of hepatitis A range from mild to severe and can include fever, malaise, loss of appetite, diarrhoea, nausea, abdominal discomfort, dark-coloured urine and jaundice (a yellowing of the eyes and skin). Not everyone who is infected will have all the symptoms (WHO).

1.2 Hepatitis B

Hepatitis B is a major global health problem. Hepatitis B is an irritation and swelling (inflammation) of the liver due to infection with the hepatitis B virus (HBV). Hepatitis B spread by contact with the blood or body fluids (such as semen, vaginal fluids, and saliva) of a person who has the virus. Symptoms of hepatitis B may not appear for up to 6 months after the time of infection. Early symptoms include loss of appetite, fatigue, low fever, muscle and joint aches, nausea and vomiting, jaundice, dark urine right upper quadrant pain and hepatomegaly. Hepatitis

B can be prevented with a safe and effective vaccine. The vaccine is usually given soon after birth with boosters a few weeks later. It offers nearly 100% protections against the virus.

1.3 Hepatitis C

Hepatitis C is a viral disease that leads to swelling (inflammation) of the liver. Hepatitis C infection is caused by the hepatitis C virus (HCV). Hepatitis C spreads by contact with the blood of someone who has hepatitis C. The following symptoms may occur with hepatitis C infection like pain in the right upper abdomen, abdominal swelling due to fluid (ascites), clay-colored or pale stools, dark urine, fatigue, fever, itching, jaundice, loss of appetite, nausea and vomiting. Globally, an estimated 50 million people have chronic hepatitis C virus infection, with about 1.0 million new infections occurring per year. WHO estimated that in 2022, approximately 242 000 people died from hepatitis C, mostly from cirrhosis and hepatocellular carcinoma (primary liver cancer). Direct-acting antiviral medicines (DAAs) can cure more than 95% of persons with hepatitis C infection, but access to diagnosis and treatment is low. There is currently no effective vaccine against hepatitis C.

1.4 Hepatitis D (Delta Agent)

Delta agent is a type of virus called hepatitis D. It causes symptoms only in people who also have a hepatitis B infection. Hepatitis D virus (HDV) is found only in people who carry the hepatitis B virus. HDV may make a recent (acute) hepatitis B infection or an existing long-term (chronic) hepatitis B liver disease which is worse. It can even cause symptoms in people who carry hepatitis B virus but who never had symptoms. Risk factors include abusing intravenous (IV) or injection drugs, being infected while pregnant (the mother can pass the virus to the baby), carrying the hepatitis B virus, men having sexual intercourse with other men, receiving many blood transfusions. Symptoms may include abdominal pain, dark colored urine, fatigue, jaundice, joint pain, loss of appetite, nausea and vomiting. HDV-HBV co-infection is considered the most severe form of chronic viral hepatitis due to more rapid progression towards hepatocellular carcinoma and liver-related death. Vaccination against hepatitis B is the only method to prevent HDV infection.

1.5 Hepatitis E

Hepatitis E is inflammation of the liver caused by the hepatitis E virus (HEV). The virus has at least 4 different types: genotypes 1, 2, 3 and 4. Genotypes 1 and 2 have been found only in humans. Genotypes 3 and 4 circulate in several animals including pigs, wild boars and deer without causing any disease, and occasionally infect humans.The virus is shed in the stools of infected persons and enters the human body through the intestine. It is transmitted mainly through contaminated drinking water. The infection is usually self-limiting and resolves within 2–6 weeks. Occasionally a serious disease known as fulminant hepatitis (acute liver failure) develops, which can be fatal.

2. Fatty Liver Disease

An increased build-up of fat in the liver. Major risk factors include obesity and type 2 diabetes, though it's also associated with excessive alcohol consumption. It usually causes no symptoms. When symptoms occur, they include fatigue, weight loss and abdominal pain. Treatment involves reducing the risk factors such as obesity through a diet and exercise programme. It is generally a benign condition, but in a minority of patients, it can progress to liver failure (cirrhosis). More than 10 million cases per year (India). There are two types of fatty liver disease. These two types can manifest alone, or they can overlap:

- Alcoholic fatty liver disease, which is caused by heavy alcohol consumption
- Non-Alcoholic fatty liver disease, which is caused by other factors.

Without management, both types of fatty liver disease can cause liver damage, leading to cirrhosis and liver failure.

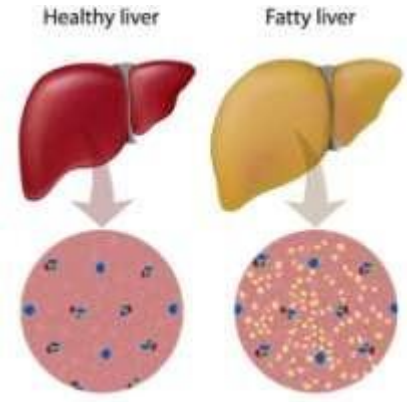

Figure 1: Fatty Liver

3. Alcohol-Related Liver Disease

Alcohol can damage or destroy liver cells. The liver breaks down alcohol so it can be removed from body. Liver can become injured or seriously damaged if drink more alcohol than it can process. There are three main types of alcohol-related liver disease: fatty liver disease, alcoholic hepatitis and alcoholic cirrhosis. Many heavy drinkers will progress from fatty liver disease to alcoholic hepatitis to alcoholic cirrhosis over time. However, some heavy drinkers may develop cirrhosis without having alcoholic hepatitis first. Others may have alcoholic hepatitis but never have symptoms. (O'Shea RS et al., 2010 and Choi G et al., 2012).

4. Auto Immune Conditions

Autoimmune conditions involve immune system mistakenly attacking healthy cells in body.

4.1 Autoimmune Hepatitis

Autoimmune hepatitis is a liver disease that happens when the body's immune system attacks the liver. This can cause swelling, irritation and damage to the liver. The exact cause of autoimmune hepatitis is unclear, but genetic and environmental factors appear to interact over time to trigger the disease. Untreated autoimmune hepatitis can lead to scarring of the liver, called cirrhosis. It can also eventually lead to liver failure. When diagnosed and treated early, however, autoimmune hepatitis often can be controlled with medicines that suppress the immune

system. A liver transplant may be an option when autoimmune hepatitis doesn't respond to medicines or liver disease becomes advanced. Common initial symptoms may include fatigue, nausea, muscle aches, or weight loss or signs of acute liver inflammation including fever, jaundice, and right upper quadrant abdominal pain. Individuals with autoimmune hepatitis often have no initial symptoms and the disease may be detected by abnormal liver function tests and increased protein levels during routine bloodwork or the observation of an abnormal-looking liver during abdominal surgery.

4.2 Primary Biliary Cirrhosis (PBC)

Primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis, is a chronic disease of the liver, presumably autoimmune in nature, that leads to progressive cholestasis through intrahepatic bile duct destruction and often end-stage liver disease (see the image below). The name change reflects the fact that cirrhosis occurs only in the late stage and therefore does not correctly identify patients with early-stage disease. PBC is most frequently a disease of women and occurs between the fourth and sixth decades of life.

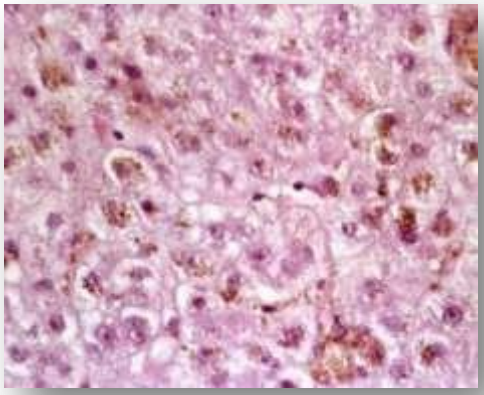

Figure 2: Primary Biliary Cholangitis (Primary Biliary Cirrhosis). This histologic picture is compatible with stage 2 primary biliary cholangitis.

4.3 Primary Sclerosing Cholangitis (PSC)

PSC is a disease that damages and blocks bile ducts inside and outside the liver. Bile is a liquid secreted by liver. Bile ducts are tubes that carry bile out of the liver to the gallbladder and small intestine. In the intestine, bile helps in break down of fat in food. In PSC, inflammation of

the bile ducts leads to scar formation and narrowing of the ducts over time. As scarring increases, the ducts become blocked. As a result, bile builds up in the liver and damages liver cells. Eventually, scar tissue can spread throughout the liver, causing cirrhosis and liver failure. In most people with primary sclerosing cholangitis, the disease progresses slowly. It can eventually lead to liver failure, repeated infections, and tumors of the bile duct or liver. A liver transplant is the only known cure for advanced primary sclerosing cholangitis, but the disease may recur in the transplanted liver in a small number of patients.

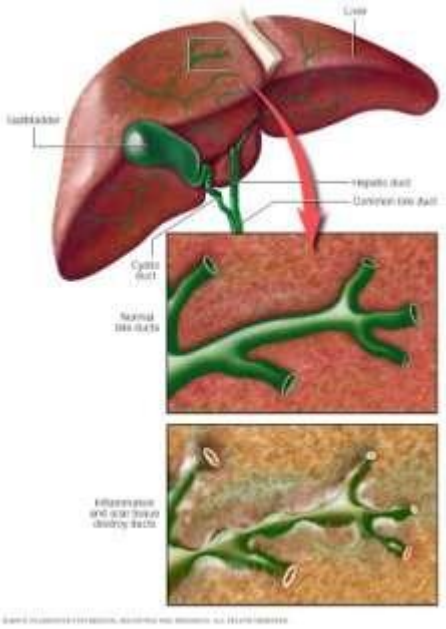

Figure 3**:** Primary Sclerosing Cholangitis (PSC)

5. Genetic Conditions

5.1 Alagille Syndrome

Alagille syndrome is sometimes an autosomal dominant disorder, meaning a person inherits it from one parent who has the disorder. In other cases, a gene mutation develops spontaneously, meaning neither parent carries a copy of the mutated gene. A child who has a

parent with Alagille syndrome has a 50 percent chance of developing the disorder. Most people with Alagille syndrome have a mutation or defect, in the Jagged1 (JAG1) gene. Mutations in the NOTCH2 gene are seen in less than 1 percent of people with Alagille syndrome. Infants with Alagille syndrome may have symptoms of liver disease and poor bile drainage from the liver in the first few weeks. These symptoms can also occur in children and adults with Alagille syndrome. (Kamath BM et al., 2007)

5.2 Alpha-1 Antitrypsin Deficiency

Alpha-1 antitrypsin deficiency (Alpha-1) is a hereditary genetic disorder which may lead to the development of lung and/or liver disease. It is the most common genetic cause of liver disease in children. Adults can also be affected by Alpha-1 and may develop lung conditions such as emphysema as well as liver problems. Fortunately, many persons diagnosed with Alpha-1 never develop any of the associated diseases.

5.3 Wilson’s Disease

Wilson‘s disease, also known as hepatolenticular degeneration and progressive lenticular degeneration, is a rare genetic disorder that causes copper poisoning in the body, especially the liver, brain and eyes. Most people with Wilson's disease are diagnosed between the ages of 5 and 35. But younger and older people can be affected too. Early diagnosis is crucial for stopping the progression of Wilson‘s disease. Treatment may involve taking medication or getting a liver transplant. Delaying or not receiving treatment can cause liver failure, brain damage, or other life threatening conditions.

6. Alcohol-Related Liver Disease

Alcohol can damage or destroy liver cells. The liver breaks down alcohol so it can be removed from body. Liver can become injured or seriously damaged if drink more alcohol than it can process. There are three main types of alcohol-related liver disease: fatty liver disease, alcoholic hepatitis and alcoholic cirrhosis. Many heavy drinkers will progress from fatty liver disease to alcoholic hepatitis to alcoholic cirrhosis over time. However, some heavy drinkers may develop cirrhosis without having alcoholic hepatitis first. Others may have alcoholic hepatitis but never have symptoms.

6.1 Fatty Liver

Fatty liver disease is the build up of extra fat in liver cells. It is the earliest stage of alcoholrelated liver disease. There are usually no symptoms. If symptoms do occur, they may include fatigue, weakness, and weight loss. Almost all heavy drinkers have fatty liver disease. However, if they stop drinking, fatty liver disease will usually go away.

6.2 Alcoholic Hepatitis

Alcoholic hepatitis causes the liver to swell and become damaged. Symptoms may include loss of appetite, nausea, vomiting, abdominal pain, fever and jaundice. Up to 35 percent of heavy drinkers develop alcoholic hepatitis. Alcoholic hepatitis can be mild or severe. If it is mild, liver damage may be reversed. If it is severe, it may occur suddenly and quickly lead to serious complications including liver failure and death.

6.3 Alcoholic Cirrhosis

Alcoholic cirrhosis is the scarring of the liver (hard scar tissue replaces soft healthy tissue). It is the most serious type of alcohol-related liver disease. Symptoms of cirrhosis are similar to those of alcoholic hepatitis. Between 10 to 20 percent of heavy drinkers affect by cirrhosis. The

damage from cirrhosis cannot be reversed and can cause liver failure. Stoping alcohol consumption can help to prevent further damage.

Figure 4: In cirrhosis, scar tissue replaces healthy liver tissue.

7. Liver Hemangioma

Liver hemangioma (he-man-jee-O-muh) is a noncancerous (benign) mass that occurs in the liver. Liver hemangioma is made up of a tangle of blood vessels. Most cases of liver hemangioma are discovered during a test or procedure for some other condition. Most people who have a liver hemangioma never experience signs and symptoms and don't need treatment. There's no evidence that an untreated liver hemangioma can lead to liver cancer.

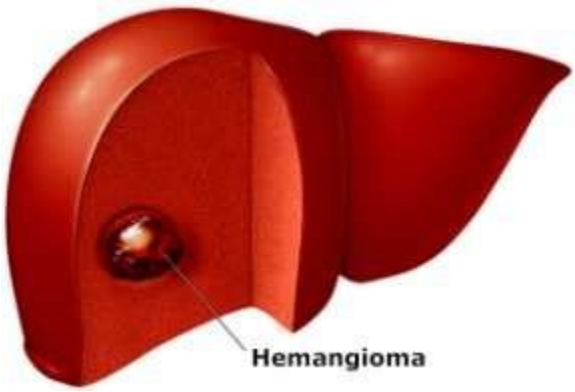

Figure 5: Liver Hemengioma

8. Nonalcoholic Steatohepatitis

Nonalcoholic steatohepatitis or NASH is a common, often ―silent‖ liver disease. It resembles alcoholic liver disease, but occurs in people who drink little or no alcohol. The major feature of NASH is fat in the liver, along with inflammation and damage. Most people with NASH feel well and are not aware that they have a liver problem. Nevertheless, NASH can be severe and can lead to cirrhosis, in which the liver is permanently damaged and scarred and no longer able to work properly. Although having fat in the liver is not normal, by itself it probably causes little harm or permanent damage. If fat is suspected based on blood test results or scans of the liver, this problem is called nonalcoholic fatty liver disease (NAFLD). If liver biopsy is performed in this case reports will show that some people have NASH while others have simple fatty liver.

9. Hepatic Encephalopathy

Hepatic encephalopathy (portosystemic encephalopathy, liver encephalopathy or hepatic coma) is deterioration of brain function that occurs because toxic substances normally removed by the liver build up in the blood and reach the brain. Hepatic encephalopathy may be triggered by bleeding in the digestive tract, an infection, failure to take drugs as prescribed, or another stress in people who have a long-standing (chronic) liver disorder. People become confused, disoriented, drowsy with changes in personality, behavior, and mood.

10. Liver Cancer

Liver cancer originates in liver cells. Symptoms are uncommon in the early stages of liver cancer. Later, symptoms may include weight loss, stomach pain, vomiting and yellowed skin.. If cancer starts elsewhere in the body but spreads to the liver, it‘s called secondary liver cancer. The most common type of liver cancer is hepatocellular carcinoma. It tends to develop as several small spots of cancer in liver, though it can also start as a single tumor. Complications of other liver diseases, especially those that aren‘t treated, may contribute to the development of liver cancer. Treatments vary but may include removal of part of the liver, transplant, chemotherapy and in some cases, radiation.

11. Chronic Liver Failure

Chronic liver disease is a progressive deterioration of liver functions. Liver functions include the production of clotting factors and other proteins, detoxification of harmful products of metabolism, and excretion of bile. This is a continuous process of inflammation, destruction, and regeneration of liver parenchyma leading to fibrosis and cirrhosis. Cirrhosis is a final stage of chronic liver disease that results in disruption of liver architecture, the formation of widespread nodules, vascular reorganization, neo-angiogenesis, and deposition of an extracellular matrix. The underlying mechanism of fibrosis and cirrhosis at a cellular level is the recruitment of stellate cells and fibroblasts that cause fibrosis, while parenchymal regeneration relies on hepatic stem cells.

Test for Liver Diseases

A number of liver function test are available to test the proper function of the liver, (serum proteins, serum albumin, bilirubin (direct and indirect), ALT, AST, GGT, ALP, PT and PTT). Imaging tests such as transient elastography, ultrasound and magnetic resonance imaging can be used to examine the liver tissue and bile ducts. Liver biopsy can be performed to examine liver tissue to distinguish between various conditions; tests such as elastography may reduce the need for biopsy in some situations (Tapper EB, Lok AS, 2017). Liver Biomarkers as well as the related in vitro diagnostic antibodies used for diagnosis being provided.

Nutritional Management in Liver Diseases

According to studies, the liver‘s ability to perform its physiological functions in the body determines the diet of patients with liver diseases. Malnutrition results from the liver‘s inability to metabolize nutrients as a result of chronic liver dysfunctions. The dietary treatment should outline daily calorie targets with a focus on high-quality protein and address any vitamin and micronutrient deficiencies, with a diet high in those nutrients or supplements.

As nutritional issues in patients with advanced liver dysfunctions are multifactorial, treating malnutrition in these patients is difficult. To improve quality of life and prevent medical complications linked to nutrition and improve nutritional status, such patients should have their

nutritional status assessed right away. All stages of chronic liver diseases are associated with the state of protein-energy malnutrition, and patients with chronic liver diseases must consume a typical diet with the addition of supplements as required. For those patients to have a positive long-term outcome, it is critical to conduct an adequate assessment and nutritional therapy, ensuring a proper macronutrient, micronutrient, and vitamin balance. Due to the vital role that the liver plays in controlling nutritional status and energy balance, patients with hepatic diseases are particularly susceptible to developing malnutrition.

Additionally, the presence of chronic liver dysfunctions may cause a decrease in appetite, which may affect the amount of nutrients consumed. Patients who have chronic liver diseases and those who are waiting for a liver transplant are almost always malnourished. Patients with cirrhosis who are malnourished have higher rates of morbidity and mortality. Furthermore, problems and overall survival rates following liver transplants are higher in individuals who are severely malnourished prior to the procedure, despite the crucial role that nutrition plays in the prognosis of persons with cirrhosis, and malnutrition frequently complicates the course of patients with the disease and has complex causes. Despite the crucial role that nutrition plays in the prognosis of those with cirrhosis, the ability to properly manage the patient‘s nutrient needs presents an additional set of challenges due to the catabolic nature of the disease process and the common occurrence of anorexia and other symptoms that lead to a poor oral intake. Malnutrition is a common complication in patients with cirrhosis and has a multifactorial etiology, and, additionally, nutritional condition prior to liver transplantation is one of the most significant factors that affect malnutrition and survival after liver transplantation.

General recommendations for people with severe liver disease include:

- Eat large amounts of carbohydrate foods. Carbohydrates should be the major source of calories in diet.
- Eat a moderate intake of fat, as prescribed by the dietitian. The increased carbohydrates and fat help prevent protein breakdown in the liver.
- Have about 1.2 to 1.5 grams of protein per kilogram of body weight. This means that a 154-pound (70-kilogram) man should eat 84 to 105 grams of protein per day. Look for non-meat

protein sources such as beans, tofu, and dairy products. Take vitamin supplements, especially B-complex vitamins.

- Many people with liver disease are deficient in vitamin D. So should take vitamin D supplements.
- Limit the amount of sodium to 2000 milligrams per day or less to reduce fluid retention.
- Eat fruits and vegetables and lean protein such as legumes, poultry, and fish. Avoid uncooked shellfish due to the risk of hepatitis A.

Conclusion

Liver diseases can be inherited or caused by a variety of factors that damage the liver (virus, drugs or chemicals, obesity, diabetes or an attack from own immune system), when the condition is left untreated, it can become life threatening and can permanently damage the liver or the bile duct. This damage can then become malignant. The liver disease prognosis depends on how quickly the condition was diagnosed and treated. In beginning stages, liver disease usually responds to treatment, but in advanced liver disease, the damage done by fibrosis, cirrhosis and liver failure cannot be reversed. This advanced stage leads to eventual death. While diagnosing liver disease, the condition causing the disease must be treated. If caught early, and are treated correctly, the damage to the liver may heal. In the middle stages of disease, treatment may work to help heal the damage, but as the disease progresses, treatments focus on managing the disease and prolonging the diagnosis.

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