

PREVALENCE AND CAUSE OF HEPATIC DISORDERS IN POPULATION OF SINDH: A REVIEW

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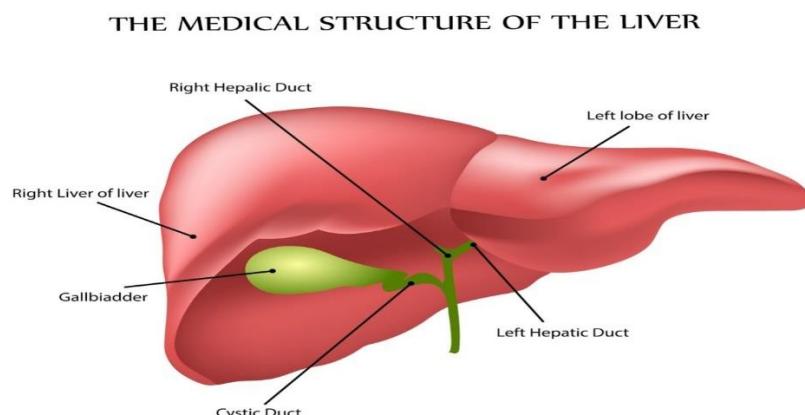
Abstract

The main metabolic functions of body are carried out by Liver. Because of its anatomical position and functional activity, it is more prone to various diseases. The influences of drugs to hepatic disorders, long observed as irrelevant, but are now widely recognized. Advances have been made over the last few years in understanding the mechanism of drug-induced hepatic disorders. Hepatitis is the main diseased condition for causing other lethal liver disorders. As hepatitis is spread by poor conditions of sanitation, hygiene, use of non-sterilized equipment's such as syringes used already by infected persons, sexual contact with infected person so the preventive measures must be taken to avoid hepatic disorders. Cleanliness determines the overall epidemiological situation in any area, but risk behavior determines an individual's chance of exposure. Chronic liver diseases are the distressing health conditions. According to a rough estimation that round about 844 million of population is affected with liver diseases of chronic type with association of death rate of 2million per year. Hepatocellular carcinoma being the most upcoming cause of death for hepatic patients is spreading rapidly. The preventive measures must be taken to overcome this consequence. Non-alcoholic fatty liver diseases are a generalized term covering lot of liver diseases that develops specifically to those individuals who either intake very limited amount of alcohol or are non-alcoholics. Chances of occurrence of Liver cancer are more as the person is aged. The ratio of male are more prone to have liver cancer than female and the patients with liver cancer is thought to have survival anticipation of about 5 years.

INTRODUCTION

Liver is the most vital organ and is categorized as main gland of the body, serving as metabolic factory. It runs >500 functions occurring in the body with the regeneration capability. Its weight is about 3.16

and 3.65 pound. It brownish-red in color [1, 2]. Because of its location and multi operative tasks it is more susceptible to countless diseases [3].



[4].

Figure 1: Structure of the Liver

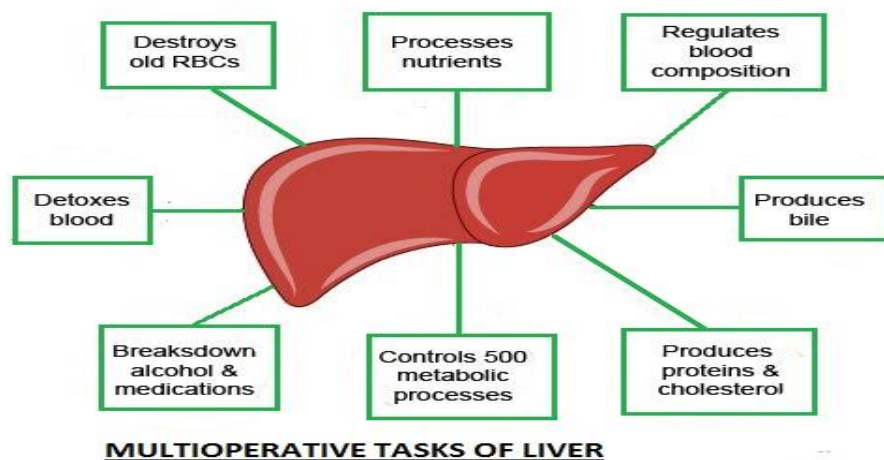


Figure 2: Multioperative tasks of the liver

Because of its location and multi operative tasks it is more susceptible to countless diseases [6]. Liver is ranked on second most number to be transplanted after kidney when it is damaged or in chronic diseased condition [7]. Whenever the hepatocytes got injured they tend to repair by themselves in some instances when this regeneration capability of hepatocytes is impaired it makes liver prone to many chronic disease which results in liver transplantation [8]. Liver transplantation can be done for the patients who are suffering from chronic liver diseases. But the chances of relapse of disease can be found in a minimal number of individuals [9].

Chronic Liver Diseases

Chronic liver diseases pose very serious and dreadful health problem all over the globe. Liver is the dynamic organ that is linked with other vital organs it runs many important body functions, if anything bad happens to the liver it affects other systems of the body as well. Chronic liver diseases are the distressing health conditions. According to a rough estimation that round about 844 million of population is affected with liver diseases of chronic type with an association of death rate of 2 million per year [10]. However, there are many several ways treatment plans are available and there are evidences as well that shows that liver diseases are not only treatable such as hepatitis C but also are avertible such as hepatitis B. There are also a lot of neglected liver

diseases in some specific population such as Viral liver disease that are more common in Asian and African countries and Latin America while ALD, NAFLD AND NASH are more prevalent in region western countries [11, 12]. In order to make our world “liver safe that is free of liver diseases” it essential to adopt some strategies like proper screening, timely treatment, avertible actions and making public aware liver diseases can help in attaining the target, and it is combined responsibility of each health care personnel [13]. Turmeric is an essential food component which can readily be used as preventive measure inflammatory along with both acute & chronic diseases [14].

CHB is about 3.6% which is about 0.5% in regions of European countries to about 8% in African countries region [15]. While CHC prevalence fluctuates in b/w 1.8% in US WHILE 5.6% in Africa while ALD is more prevalent in US and Europe that's about 12% [16]. There are about 633000 patients are being reported annually with liver cirrhosis that is CLD induced that shows prevalence of about 4.5-9% on global scale [17]. Round about 500000 Cases of Chronic hepatocellular carcinoma are reported per year alone [18]. And it serves the one of the most common cause of mortality in conjunction with cancer [19].

Liver cirrhosis

Liver cirrhosis is chronic complication of liver diseases in which the functional activity of liver is lost by the liver tissues due to the occurrence of scars in fibrous tissues [20]. Liver cirrhosis is a condition in which there is step by step reinstatement of healthy hepatocytes with the abnormal scarred hepatocytes associated with malfunctioning of liver scarring is also referred to as fibrosis. It may be due to various disease processes such as hepatitis or may be alcohol induced or due to self-repairing of liver [21].

Pathophysiology of cirrhosis

Hepatocytes repair themselves by the process of fibrosis. Fibrosis helps to repair the hepatocytes by forming scar tissues which is composed of collagen. Fibrosis tries to repair the injured tissues normally but somehow it takes the form fibro genesis which is an abnormal response towards any injury and end up

forming the scars made up of collagen. Degree of Fibrosis is different for each different etiology [22-24]. When fibrosis reaches to advanced stages it is then called as cirrhosis, where whole of hepatic vascular structure is destroyed. There will be reduced blood supply by arteries and portal veins which ultimately results in reduced exchange of nutrients, oxygen and other substances such as drugs. The situation is further worsened when there is the scarring of space of Disse and pore formation in endothelial linings takes place and this is known as sinusoidal capillarization [25]. It can cause complications like easy bruising, bleeding, loss of appetite, swollen legs, jaundice etc. [26].

Liver cirrhosis can be diagnosed by LFTs, albumin testing, CBC (to evaluate anemia), Coagulation test (to determine blood clotting time), alpha fetoprotein test (for hepatocellular carcinoma) abdominal MRI AND CT SCAN, liver biopsy, ultrasound and endoscopy [27].

In order to treat liver cirrhosis the target should be the remaining healthy cells as at present time there is no any treatment available however palliative treatment and management plans are available which can be handled by resolving the causative agent which may be alcohol, to reduce weight if patient is obese, anti-hepatitis b and C medication and vaccines, Antihypertensive, etc. [28].

According to a study report that was conducted in 2010 which states that hepatic cirrhosis is responsible for causing 31 million or 1.2% (DALY'S) and mortality rate in association with cirrhosis is about 1 million or about two percent in 2010 only [29, 30]. By the help of verbal autopsy standard of WHO 2012 hepatic cirrhosis was included as cause of mortality categorizing VA06.02 [31]. Approx. 250 million people are suffering from hepatitis; 15-45% may further be complicated for liver cirrhosis which can further lead to failure of liver and cancer of liver [32]. In western countries and Italy, the main cause of cirrhosis of liver is alcohol consumption and hepatitis c virus. Although the evidences regarding this respect have not been studied yet. But this studies is usually done by case control study [33]. Occurrence rate of Cirrhosis of liver that results due to heavy usage of alcohol has boost up to about 16.1% in contrast to Hepatitis B virus and Hepatitis C Virus and others that is about

11.9% ,14.2% and 9.8% respectively [34]. It is supposed to be that there will be the increment of three times more in the mortality in near future 2023 just because of cirrhosis [35]. Cirrhosis of liver and chronic infectious diseases of liver stood on 12th no as cause of reporting 36000 mortalities in US alone during the year 2013 which is evident from the report of centers of disease control and prevention [36].

Hepatocellular Carcinoma

It is a Tumor of hepatocytes. It is much more prevalent in the individuals who have scarring of liver cells of cirrhosis of hepatocytes or chronic alcohol users [37].

Cancer of hepatocytes responsible for 70-90% malignant tumor of the liver that is primary cancer of liver. To manage cancer of liver becomes much harder due to presence of cirrhosis and carcinoma of liver both at the same time in greater than 80% of patients. About 500,000 cases regarding carcinoma of liver is reported per year globally [38, 39]. Heavy alcohol intake in France serves a major hazardous substance for reporting of almost 69% cases related malignant tumor of liver which primary liver cancer [40]. Cancer of hepatocytes serving the sixth most frequently occurring carcinoma worldwide and therefore 626000 or 5.7% cases or carcinomas are reported each year [41]. Hepatitis B and C serves the factor of risk for the developing the cancer of liver [42]. Geographical location of Pakistan lies in south-Asia where the incidence rate of hepatitis -B and Hepatitis-C is somewhat average [43, 44]. And the cancer is responsible for 8.2million mortalities over the globe in year 2012, and from which only the liver cancer caused 745000 mortalities in year 2012 and hence ranked on number two as cause of mortalities due to cancer [45].

According to an estimate that about 7.6 % male 2.8% female/100000 population will be developing liver cancer in Pakistan [46-48], male are more prone to have liver cancer than female and the patients with liver cancer is thought to have survival expectancy of about 5 years [49], Liver cancer is more prevalent un under-developing countries in contrast to developing countries and factors of risk differs greatly from country to country [50, 51], Chances of occurrence of Liver cancer is more as the person is

aged [52], and the prevalence is greater in the individuals with age in between 65-69, it may also occurs in young people as well which is entirely dependent upon the environmental condition at the time of birth [53].

There are the following risk factors for hepatocellular carcinoma:

1. Heavy alcohol intake
2. Hepatitis due to A or B virus or due to auto-immune responses.
3. Insufficiency of alpha-1antitrypsin
4. Genetic diseases such as Wilson's disease [54].
5. Liver cirrhosis [55].

It do not show any sign and symptom until tumor reaches to advance stages or grab the size of 10cm [56]. Some of the symptoms are as follows:

- Swollen abdomen due to retention of fluid
- Easy injuring due to impaired clotting
- Urge to vomit
- Icterus
- Unexplained loss of weight
- Anorexia
- Extreme tiredness
- Liver malfunctioning etc [57].

The diagnostic measures for liver carcinoma are as follows:

- Blood testing to assess functions of liver
- Magnetic resonance imaging and computerized tomography scan
- Biopsy of liver [58].

Liver cirrhosis can be treated by surgical removal of cancerous hepatocytes, transplantation of liver may be consider in extreme cases, other options are radiofrequency ablation, cryoablations , direct injection of alcohol into cancerous hepatocytes which causes them to die, radiotherapy, chemotherapy etc. [59].

Non-Alcoholic fatty liver disease

Non-alcoholic fatty liver diseases are a generalized term covering lot of liver diseases that develops specifically to those individuals who either intake very limited amount of alcohol or are non-alcoholics. It is accumulation of fat in liver(60).NAFLD occurs when there is greater than 4.9 % fat in in the liver in an individual who either do not in take alcohol or intake in controlled limits, in women there will be

NAFLD when the fat content in liver exceeds than 19.9% and in men when it is greater than 29.9%. Other medical condition may give rise to NAFLD such as increased blood pressure (hypertension), increased level of blood glucose (Type-2 Diabetes mellitus) or increased level of triglycerides (Hypertriglyceridemia) and many others [60-62].

It generally progress in 4 stages.

STAGE 1: Steatohepatitis (fat build up in liver)

STAGE 2: NASH (NON-alcoholic steatohepatitis-associated with inflammation of liver)

STAGE 3: Fibrosis (Scarring of tissue due to Persistent inflammation)

STAGE 4: Cirrhosis (shrinkage liver, Lumpy and finally liver failure) [63].

NAFLD occurrence rate is about 23.9% worldwide [64, 65], with the evidence of higher occurrence in south America and middle East while less occurrence rate is documented from Africa [66], There about 19.9-30% of total population is suffered from NAFLD Of NORTH AMERICA [67, 68]. There about 5-19.9% of Chinese develops NAFLD [69, 70]. However keep in mind that there is no authentic worldwide accordance data of NAFLD is available till date because no any prospective study have developed yet [71-74]. According to a study that shows NAFLD prevalence in Pakistan is at rate of about 14 % [75]. Neither pathogenesis nor factors of risk are fully known of NAFLD [76]. The Sign and symptoms are dull pain in upper right region of abdomen, tiredness weakness and weightless [77]. It can be diagnosed by Liver enzyme function test, imaging techniques or histology [78].

There is no any specific treatment plan is available only symptomatic treatments are prescribed to the patients, also other options are suggested to treat the comorbid diseases such as hypertension, diabetes hypertriglyceridemia etc.Or options for way of living modification such as smoking cessation may be suggested to the patient [79].

NAFLD is limited to some extent by prevention of risk factors due to pathogenesis of disease is unknown. NAFLD is major cause of chronic liver disease in industrializes countries [80].

Hepatitis A

The virus of hepatitis A is the main significance of acute diseases of liver taking place in whole world [81]. The sign and symptoms of HAV are as under:

1. Tiredness
2. Sudden sickness and unsettled stomach
3. Stomach pain or uneasiness
4. Clay-colored bowel movements
5. Loss of hungriness
6. Joint aching
7. Staining of the skin and the whites of your eyes (jaundice)
8. Strong itching [82].

Hazardous Features for Hepatitis A are as under:

1. Contact with infectious person.
2. Living in already infected person.
3. Homosexualization.
4. Use of abused and illegal drugs [83].

Hepatitis B

It is an viral infection of liver organ. Virus caused inflammation as well as harm to liver. There are number of viruses which infected liver but most common and cause potential death are HBV & HCV [84].

Hepatitis B is blood borne infection. This is transmitted through contact of body fluids with an infected body fluid. Body fluids include blood, saliva, semen, vaginal secretions, can be contain HBV. Mechanism of transmission is not clear.

It is major reportable disease. It possesses vaccination to prevent acute hepatitis in Canadian notifiable disease surveillance system (NDSS). Standard and pegylated interferon alpha drugs block viral replications include lamivudine, adefovir, telbivudine, entecavir, tenofovir [85]. In our neighboring country China, approximately about 121 million people are the carriers of HBC Virus. Along with 301,000 individuals die per annum due to hepatitis B. To overcome this issue, the vaccination programs has been developed in china for neonates since 1990 which has markedly shown its effect in decreasing the HBV in population of china. As the route of transmission for hepatitis b is not clear yet therefore, the outcomes to decrease the incidences are not remarkable till now [86].

Hepatitis C

Hepatitis c is a type of virus like microorganism carried by blood. It is pathogen in blood [87]. It is a fifth common cause of death in U.S.A. [88]. Hepatitis c is major cause of death as compare to tuberculosis and malaria [89, 90]. Approx. 250 million people are suffering from hepatitis, 15-45% may further be complicated for liver cirrhosis which can further lead to failure of liver and cancer of liver

[91-93]. The age group between 21 to 30 showed high prevented rate for anti HCV blood reports in people of Hyderabad and Karachi. It means the more educated people the more prevention [94]. HCV is the most abundant cause for liver cirrhosis and liver failure. There are some of the causes which can lead to spread of HCV. Family history can also be the cause of it. But some of them are as under:

Table 1: Causes for the spread for HCV

Causes for the spread for HCV	Percentage of individual suffering from HCV
1. Used razors	91%
2. Used syringes	85%
3. Blood transfusion	85%

HCV is the main cause leading to cirrhosis of liver along with symptoms of decreased level of sodium, bleeding of GIT and low level of hemoglobin [96].

Nowadays, HCV affected patients are more prone to further complicated diseases thus leading to major cause of death [97].

Table 2: Virus and infected population

Virus	Infected population
Hepatitis B virus (HBV)	Approximately 370M chronic infections
hepatitis C virus (HCV)	Approximately 130M
HIV	Approximately 40M
HIV-infected persons along with, chronic HBV co-infection	Approximately 2M to 4M
HIV-infected persons along with, HCV co-infection	Approximately 4M to 5M

Following are the clinical characteristic features for Hepatitis C:

- Fatigue.
- Malaise.
- Arthralgia.
- Myalgia.
- Palmar erythema.
- Spider nevi.
- Dupuytren's contracture.
- Gynecomastia.
- Parotid enlargement.
- Temporal muscle wasting.
- Ascites.
- Hepatosplenomegaly or testicular atrophy.

Diagnostic tools for Hepatitis C Virus:

- occurrence of anti-HCV antibody along with HCV RNA in the blood.
- genotyping and quantifying HCV viral level.

- LFT'S
- Prothrombin time
- HBV as well as HIV serologies.
- Liver biopsy [90].

According to USA almost 2.8 million people are suffering from Hepatitis C Virus [100].

Hepatitis D

Hepatitis delta virus was discovered by Mario RIZZETTO as a worsened form of HEPATITIS B VIRUS complications during 1977 [101]. Hepatitis Delta Virus is a partial and malformed RNA virus that requires HbsAg in order to proceed in individuals [102]. It affects only those individuals who already have contacted Hepatitis B which results in swollen liver. It is infrequent in Australian [103]. According to observations that About 80% of pare more prone to have Cirrhosis that are affected with

HBV AND HDV simultaneously [104], that while about only 15% of patients are susceptible having cirrhosis affected with HBV only [105]. There are about three hundred and fifty million individual serves as carrier for infections with Hepatitis-B virus and from these only around 5% of individual will be having HDV infections [106]. According to an estimation that its high occurrence rate are reported from ITALY, Eastern Europe and western region of Asia which is way more higher than total global incidence even than that of middle east where it is reported as Native to this region and it is thought to be that around fifteen million peoples are affected with hepatitis Delta Virus [107]. HDV have moved from Mediterranean regions to countries that are still developing such as Pakistan, and from Pakistan Sind is facing higher incidence of HDV [108, 109]. Till now there about 8 HDV has been discovered of which type-1 genotype is reported to be more prevalent in the regions of Pakistan [110, 111].

It is an RNA virus that extends 36nm in length and contains the antigens that is specified for HDV is known as Hepatitis delta antigen denoted by HdAg. The genomic configuration of HDV consists upon 1700 nucleotides [112]. HDV belongs to communicable disease category it propagate from human to human via the body secretions such as saliva, vaginal secretion, blood etc [113].

Types of HDV infection:

1: Acute Infections: Some individual get affected with Not only the HBV but also HDV which takes the form of Co-infections. There is one plus point of acute infections which is that it will results in extermination of both the viruses.

2: Chronic Infections: Chronic infection of HDV is also known as super infections in which the person is first affected with HBV and later on with HDV which leads to development of chronic hepatitis with delta viruses.

It is associated with the presentation of:

- Increased body temperature
- darkened Urine
- Pale feces
- Jaundice
- Arthralgia
- Mayalgia
- Abdominal distress

- Anorexia etc

Antiviral proves to be less responsive towards HDV infections and HDV treatment options are still not available. One drug which peg interferon-alpha which is also have limited efficacy in only limited individuals [114]. HDV can lead to Cirrhosis and Hepatic failure [115].

It is avoidable in those individuals who have not developed HBV yet so the HBV vaccines can be a barrier against HDV more over precautionary measures should be taken such as:

- Open wounds should be guarded by dressing which resist the viral spread
- Injecting tools must be personalized
- Health care practitioner should also take precautionary while dealing with affected individuals.
- One should be safe guarded while handling the body fluid such as blood to avoid infections etc. [113]

Hepatitis E

One of major cause of viral hepatitis in many of developing countries. Transmission of HEV infection occurred due to contamination of water, food and blood transfusion. Low rate of transmission in person-person [116]. HEV cause epidemic as well as sporadic hepatitis [117]. It causes acute, entero-transmissible form of hepatitis in human as similar to cause by hepatitis A. Self -limited infection along rapid viral clearance. It can occur in more severe forms like fatal fulminant hepatitis. Chronic Hepatitis E also occurred in transplantation of recipients (solid organ) & cause fibrosis, liver cirrhosis & liver failure [118, 119].

DRUG INDUCED TOXICITY

Liver is an important metabolic and functional factory of body for food and drugs too. When the drugs are taken by oral route the go for first pass metabolism in liver. The drugs whenever, taken for prolonged period of time may cause liver toxicity by causing damage or injury to liver tissues with the help to hepatotoxins. These hepatotoxins are the type of toxic chemicals. Some examples of those drugs are as under:

1. Drugs used to treat depression.

2. Abusive Drugs
3. ACE Inhibitors.
4. Drugs used to treat epilepsy.
5. Drugs used to treat psychosis.
6. Drugs used to treat hypertension.
7. Azathioprine liver toxicity.
8. Antihypertensive.
9. Monoamine Oxidase Inhibitors.
10. Oral Contraceptives [120].

CONCLUSION

Liver diseases are fatal in nature. But they can be prevented by proper cleanliness, sanitation, hygiene particularly hand hygiene and the use of drugs causing hepatotoxicity. Along with this public awareness campaigns to native people of any region must be run to minimize occurrence of liver diseases particularly hepatitis. Vaccination and timely diagnostic measures must be taken and their importance must be spread to native people. Alcoholic taker should minimize their take for proper functioning of liver.

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