Review Article

Addiction and Liver Disease

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Abstract

Drug induced liver disease is a global problem. The aims of the study are to know the recreational drugs causing harmful effect on liver, epidemiology of addiction; pathophysiology and their consequences.

The major findings published to date concerning different agents causing addiction and liver disease, their implications with regard to understanding disease mechanisms and their amplitude or spectrum are described.

Addiction not only invites lot of sufferings to the family and the country, but also responsible for different types of liver disease including fatty liver, hepatitis and liver failure; responsible for mortality and morbidity. Among the addiction causing substances alcohol playing the main role for liver disease worldwide. Indirect effects of addiction on liver are hepatitis B, hepatitis C and their complication, mainly due to contamination of sharing needle. Majority of people in Bangladesh are life long abstainer.

Excessive alcohol beverages and other substances like heroin, amphetamine are not harmless, rather they can cause serious liver diseases. There are some differences in prevalence of addiction and liver diseases among countries. Intravenous drug users are affected both directly and indirectly due to contaminated needle sharing .

Introduction

The liver is an important organ in the human body. It is the largest gland and plays a key role in the removal of toxins and lipophyllic materials from the plasma. When this liver is exposed to toxic substances particularly due addiction such as alcohol with an excess, it becomes sick.

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Addiction is a global problem which is a compulsive act causes harm to the person and those around them and over which the person no longer has control. For an example a person who constantly drinks excess alcohol in spite of the fact that it is hurting his family and career. An addict may deny it, rather state they are, "just enjoy". Addiction is the continued use of a mood altering substance or behaviour despite adverse dependency consequences[1], or a neurological impairment leading to such behaviors[2].
The American Society of Addiction Medicine (ASAM) has published a definition of addiction highlighting that addiction is a chronic brain disorder and not simply a behavioral problem involving too much alcohol, drugs. ASAM has taken an official position that addiction is not solely related to problematic substance use[3].

Characteristics of addiction:
(a). Inability to consistently abstain; (b). impairment in behavioural control; (c). craving; or increased "hunger" for drugs or rewarding experiences; (d). diminished recognition of significant problems with one's behaviors and interpersonal relationships; (e) a dysfunctional emotional response[4].

List of Addictions to Substances:

Substance use disorders in the DSM-IV-TR provide a list of addictions relating to the following substance:

- Alcohol
- Tobacco
- Opioids (like heroin)
- Prescription drugs (sedatives, hypnotics, or anxiolytics like sleeping pills and tranquilizers)
- Cocaine
- Cannabis (marijuana)
- Amphetamines (like methamphetamine, known as meth)
- Hallucinogens
- Inhalants
- Phencyclidine (known as PCP or Angeldust)
- Other unspecified substances[5]

Type of addiction causing liver disease:
Alcohol:
Among the substances causing addiction, alcohol is the most important one causing liver disease worldwide. Alcohol dependence is a powerful mechanism sustaining alcohol consumption and thus impacting on both chronic and acute consequences of alcohol, though it is also a consequence of drinking itself [6].

The clinical history which may suggest alcohol abuse or alcohol dependence includes the pattern, type, and amount of alcohol ingested, as well as evidence of social or psychological consequences of alcohol abuse[7]. Alcoholic liver disease ranging from fatty liver to hepatic inflammation and necrosis (alcoholic hepatitis) to progressive fibrosis (alcoholic cirrhosis)[8]. Alcohol causes 1.8 million deaths (3.2% of total) and a loss of 58.3 million (4% of total) of Disability-Adjusted Life Years[9].

Overall there is a causal relationship between alcohol consumption and more than 60 types of disease and injury. Alcohol is estimated to cause about 20-30% of oesophageal cancer, liver cancer, cirrhosis of the liver worldwide[10].

Prevalence of alcohol addiction:

Alcohol consumption and addiction is prevalent worldwide, but quality varies in different parts, as well as urban and rural areas. The true prevalence is unknown, but histologic studies of patients with ALD suggest that alcoholic hepatitis may be present in as many as 10%-35% of hospitalized alcoholic patients[11,12,13]. The World Health Organization (WHO) estimates about 2 billion people worldwide who consume alcoholic beverages and 76.3 million with diagnosable alcohol use disorders[9].

In the 1993 National Household Survey, 21.7% of Asian American and Pacific Islanders had smoked cigarettes, 53.2% had used alcohol[14]. Asian Pacific Islanders had the lowest percentages of alcohol dependence (1.8%), need for drug treatment(1.7%), and heavy alcohol use(0.9%.)[15,16].

Total lifetime abstainers in Bangladesh as measured by the 2003 World Health Survey is estimated to be 94% of the total population; 87.4% of male Bangladeshis are abstainers and likewise, 99.7% of female Bangladeshis are abstainers[17].

Approximately 7.4% of adult Americans were estimated to meet DSM-IV criteria for the diagnosis of alcohol abuse and/or alcohol dependence in 1994[18]; Alcohol is commonly used in USA and approximately two-thirds of adult Americans drink some alcohol [19].

Another more recent data suggest 4.65% meet criteria for alcohol abuse and 3.81% for alcohol dependence[20]. However, geographic variability exists in the patterns of alcohol intake throughout the world[21] The majority drink small or moderate amounts and do so without evidence of clinical disease [22,23,24] A subgroup of drinkers, however, drink excessively, develop physical tolerance and withdrawal, and are diagnosed with alcohol dependence[25]. In Australia, prevalence of DSM-IV alcohol abuse and dependence by gender: Harmful use in males- 4.3%, dependence 5.2%, whereas in females it is 1.8.[26]

Alcohol is also commonly consumed in Australia; 83% of the population in the 2007 Drug Strategy Household Survey aged over 14 years reported drinking alcohol in the previous 12 months[27].

Spectrum of alcoholic liver disease:

Alcohol is responsible for significant disability as well as it kills many people in the world. The most prevalent types of alcoholic liver disease are fatty liver, alcoholic hepatitis, and cirrhosis. Fatty liver may be a less problematic and reversible if abstinence is maintained. Often, as people continue to drink heavily, they progress from fatty liver to hepatitis to cirrhosis. The disorders can also occur together, however, and liver biopsies can show signs of all three in some people[28]. Furthermore, sustained excessive alcohol intake may be the cause of the progression of other liver diseases, such as virus-related chronic hepatitis, also increasing the risk of hepatocellular carcinoma[21,29,30].

Although not invariable, fatty liver develops in about 90% of individuals who drink more than 60 g/day of alcohol[31]. According to another study report, about 20 percent of alcoholics and heavy drinkers develop fatty liver, or steatosis. In many cases there are no clinical symptoms except for an enlarged liver (hepatomegaly). Fatty liver can be reversed if alcohol consumption is stopped or significantly reduced [32].

These are not necessarily distinct stages of evolution of disease, but rather, multiple stages that may be present simultaneously in a given individual[33,34]. However, alcohol dependency per se is not always a pre-requirement for ALD development[35]. In fact, some patients develop ALD, particularly, cirrhosis, without a history of dependence. Moreover, the severity of disease does not always correlate with the amount of alcohol intake, and environmental and genetic factors likely play a crucial role in ALD development [36,37].

Daily ethanol consumption exceeding 40-80 g/day for males and 20-40 g/day for females for 10-12 years will almost certainly lead to ALD[38,39,40]. It is shown that women have been found to be twice as sensitive to alcohol-mediated hepatotoxicity and may develop more severe ALD at lower doses and with shorter duration of alcohol consumption than men[41].

Likewise, heavy drinking in combination with hepatitis B or C substantially increases the risk of liver cirrhosis, compared with the risk associated with heavy drinking alone[42]. For example, people with alcohol-related cirrhosis are at much higher risk for the development of liver cancer[43].

Liver cirrhosis is an irreversible condition which is a long term effect of alcohol consumption and this cirrhosis is a major cause of death in the United States [44, 45]. In 2000, it was the 12th leading cause of death, accounting for 1.1 percent of all deaths[32]. In 2003, 44% of all deaths from liver disease were attributed to alcohol[46]. In Europe alone, alcohol consumption was responsible for over 55 000 deaths among young people aged 15-29 years in 1999[47].

Mortality studies have demonstrated that heavy drinkers and alcoholics die from cirrhosis at a much higher rate than the general population[40,48,49,50]. Alcohol has consistently been related to the risk of malignancy like cancer of the mouth (lip, tongue), pharynx, larynx, hypopharynx, oesophagus and liver[51-54].

Pathophysiology of alcohol toxicity:

Liver disease in the alcoholic is due not only to malnutrition but also to ethanol's hepatotoxicity linked to its metabolism by means of the alcohol dehydrogenase and cytochrome P450 2E1 (CYP2E1) pathways and the resulting production of toxic acetaldehyde. In addition, alcohol dehydrogenase-mediated ethanol metabolism generates the reduced form of nicotinamide adenine dinucleotide (NADH), promotes steatosis by stimulating the synthesis of fatty acids and opposing their oxidation. Steatosis is also promoted by excess dietary lipids and can be attenuated by their replacement with medium-chain triglycerides[55].

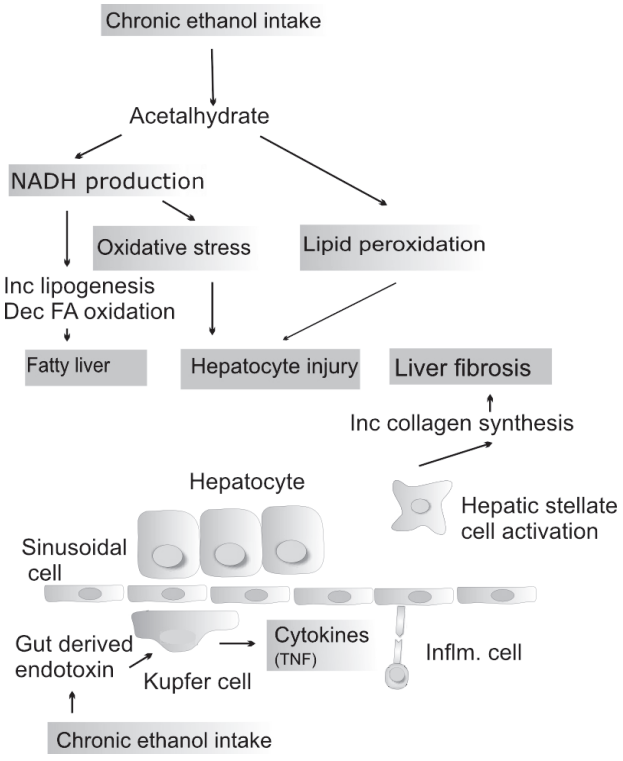

Figure: Pathogenesis of alcohol induced liver injury[56]

According to reports, genetic predisposition to ALD has clearly emerged. Family, twin and adoption studies have convincingly shown that genetic determinants play an important role in the development of alcohol dependence and alcohol-related disorders with heritability estimates in the range of 50-60%[57-66].

Alcohol also affects the energy production. The rate of ATP synthesis in liver cells exposed to ethanol is typically reduced[67]. Chronic alcohol consumption depresses the activity of all mitochondrial complexes, except complex II, as several abnormalities in mitochondrial respiratory chain have been described in experimental models of chronic ethanol intoxication[68,69]. Alcohol consumption causes free radical generation that damages DNA[70], which is repaired by the base excision-repair pathway involving DNA ligase III, DNA polymerase b and poly(ADPribose) polymerase.

Liver has tremendous power of repairing the damage. Reduced repair of DNA lesions represents an important risk factor for the development of ALD. Many of polymorphisms in several DNA repair genes have been identified[71,72,73].

Alcohol consumption can impair the immune response. Alcohol intake increases the intestinal permeability to a variety of substances that include bacterial endotoxins such as lipopolysaccharide[74]. Lipopolysaccharide 'sensitises' Kupffer cells by binding with the CD14 receptor. This bond activates the nuclear factor kappa B (NF-jB) which, in turn, causes exaggerated transcription of pro-inflammatory cytokines such as TNF-a, IL-6 and transforming growth factor beta (TGF-b)[74,75,76].

The risk factors for alcoholic liver disease(ALD):

Quantity : Alcohol consumption of 60-80g per day (about 75-100 ml/day) for 20 years or more in men, or 20g/day (about 25 ml/day) for women significantly increases the risk of hepatitis and fibrosis by 7 to 47%[7,21].

Drinking pattern: drinking of alcohol outside of meal times increases up to 2.7 times the risk of alcoholic liver disease[77].

Female gender: Females are as twice as men susceptible to alcohol related liver disease, and may develop alcoholic liver disease with shorter durations and doses of chronic consumption. The lesser amount of alcohol dehydrogenase secreted in the gut, higher proportion of body fat in women, and changes in fat absorption due to the menstrual cycle may explain this phenomenon[77]. Hepatitis C infection: a concomitant hepatitis C infection significantly accelerates the process of liver injury[77].

Genetic factors: genetic factors predispose both to alcoholism and to alcoholic liver disease. Monozygotic twins are more likely to be alcoholics and to develop liver cirrhosis than dizygotic twins. Polymorphisms in the enzymes involved in the metabolism of alcohol, such as ADH, ALDH, CYP4502E1, mitochondrial dysfunction, and cytokine polymorphism may partly explain this genetic component. However, no specific polymorphisms have currently been firmly linked to alcoholic liver disease[57,66].

Iron overload (hemochromatosis):Iron plays a role in the genesis of ALD[37,78]

Dietary factor: Malnutrition like vitamin A and E deficiencies may worsen alcohol-induced liver damage by preventing regeneration of hepatocytes. This is particularly a concern as alcoholics are usually malnourished because of a poor diet, anorexia, and encephalopathy[77].

Nutritional effect of alcohol:

Although previously thought that alcoholic liver disease was attributed exclusively to dietary deficiencies, but clinical studies have now established alcohol's hepatotoxicity[79]. Despite an adequate diet, it can contribute to the entire spectrum of liver diseases, mainly by generating oxidative stress through its microsomal metabolism via cytochrome P4502E1 (CYP2E1). It also interferes with nutrient activation, resulting in changes in nutritional requirements[79]. Nutritional deficiencies coupled with alcohol consumption can favour the development of ALD. It is also found that malnutrition is common in alcoholics[80].

Amphetamines:

Amphetamine is one of the most important substance causing addiction. The use of "ecstasy" or Methylenedioxymethamphetamine (MDMA) as a recreational drug is increasing in Europe since the 1980's. Aside intended psychological effects the use of ecstasy can be followed by symptoms of intoxication; complications include toxic hepatic damage up to acute hepatic failure[81].

The "ecstasy"-induced hepatotoxicity can occur dose-independently with a symptom-free period from days to weeks after ingestion, although etiopathology is not yet fully understood[81]. Although various estimates have been given on the extent of current illicit MDMA use in the United States and western Europe, the exact prevalence remains unknown. According to the 2004 National Drug Use and Health, more than 11 million persons aged 12 years and older have reported using MDMA at least once in their lifetimes[82].

Drug Abuse Warning Network (DAWN) data have shown a steady increase in emergency department (ED) visits from MDMA abuse. The DAWN estimates have shown a greater than 800% increase since 1995 from 421 ED visits to 4,026 in 2002 and another 167% increase in 2005 with 10,752 ED visits. These are collected from hospitals in major metropolitan areas throughout the United States and reflect trends of drug abuse and not national numbers[83].

According to a 1993 National Institute on Drug Abuse survey, 2% of all US college students admitted to taking MDMA in the previous 12 months. Study of Stanford University undergraduate students reported that 39% had taken MDMA at least once in their lives. But another data from Tulane University survey of more than 1200 students shows 24% had used MDMA[84].

Although direct toxic effect of MDMA to the liver is unclear, hepatitis and liver failure have been reported. It is interesting that a subset of the population may be at risk for liver toxicity. These patients are missing a liver enzyme called CYP2D6, which is necessary to metabolize MDMA. It is deficient or totally absent in 5-10% of whites and African Americans and in 1-2% of Asians[85].

Hepatotoxicity ranges from asymptomatic liver injury with abnormal liver function tests to fulminant acute hepatic failure. Different patterns of liver injury including benign lesions, viral hepatitis, extensive or focal hepatic necrosis, total loss of liver parenchyma and function with accompanying encephalopathy, cerebral edema, and multiorgan system failure are evidenced[85]. High doses of amphetamines can be associated with liver injury and distinctive forms of liver injury which has been most commonly associated with MDMA: "ecstasy")[86].

Although amphetamine has not been invariably associated with serum aminotransferase elevations, there have been several case reports of clinically apparent acute liver injury attributed to the amphetamines; particularly MDMA has been implicated in a large number of cases of acute liver injury which can be severe and lead to acute liver failure and death[86].

As mentioned before that the onset of ecstasy-associated hepatitis is generally 3 to 14 days after ingestion and abrupt onset with fatigue, weakness, jaundice and confusion. The pattern of serum enzyme elevations is typically hepatocellular and ALT and AST values may be markedly increased with similar increases in lactic dehydrogenase. There is often an early presentation with acute liver failure and prolongation of the prothrombin time and other organ injury is often present[86]

The clinical course and early histological features of ecstasy-induced hepatitis are similar to the patterns that occur with ischemic hepatitis and liver injury due to hyperthermia[85]. In grade III or IV hepatic encephalopathy induced by MDMA, without a liver transplant, the mortality rate is more than 50%. The timing of ingestion and onset of symptoms, as well as doses, do not seem to correlate with the clinical severity, and recurrence can also occur due to chronic use. Chronic use of MDMA leads to fibrotic changes that are related to an increase of collagen I production by the stellate cells[85].

Amphetamines undergo extensive hepatic metabolism largely by the hepatic P450 system (CYP 2D6) and generation of a toxic metabolite may cause of hepatic injury with high doses. In cases of hyperacute liver failure due to ecstasy and to intravenous amphetamine, hyperthermia, shock and ischemia may account for the early liver injury[86].

Addiction and viral hepatitis:

Intravenous drug addiction by sharing of contaminated needle is very much important risk factor for the development of liver disease, particularly hepatitis B and hepatitis C. Globally, 90% of new hepatitis C infections are attributed to injection drug use[87]. Among them ~90% in Australia, ~72% in Canada, and ~54% in the United States are contracted through injection drug use as the major risk factor for HCV infection[88 -92].

HBV and HCV infections are also acquired relatively rapidly among IDUs. Within 5 years of beginning injection drug use, 50%-70% of IDUs become infected with HBV. Between 50%-80% of IDUs become infected with HCV within 5 years of beginning injection drug use; it is usually the first bloodborne virus they acquire[92]. Among the countries in Asia HBV prevalence was 6.5% detected amongst Kabul IDUs[93]

Morphine and it`s derivatives addiction:

Heroin is a derivative of morphine. Heroin, diacetylmorphine, is produced through morphine acetylation at loci 3 and 6. Wright synthesized it in 1874, the event that was warmly welcomed by the medical profession due to the fact that heroin could be used as a possible substitute for morphine and codeine[94].

In 1895, the German drug company Bayer marketed diacetylmorphine as an over-the-counter drug under the trademark name Heroin[95]. Heroin is a highly addictive drug, and its use is a serious problem in America. Current estimates suggest that nearly 600,000 people need treatment for heroin addiction[96].

Estimated worldwide prevalence of current opioid use in 2009 was between 0.3% and 0.5%, equating to 21 to 35 million people, including nearly 18 million people (5.9% of the population) in the United States[97]. In Asia, heroin addiction spread first to the populations of capital cities and then to other cities and towns and even to the hill tribes in Thailand have revealed. Most recent studies have shown that heroin abuse has spread further in Asia, both socially and geographically, involving such countries as India and Sri Lanka[98].

An estimated 4.1 million people (1.6%) in the United States have used heroin at least once in their lives, and at least 359,000 are believed to be addicted to the drug[99,100]

Substantial regional differences in abuse patterns exist. In the majority of Europe, Africa, and Asia, heroin is the most prevalent illegally consumed opioid. However, some African and Asian nations have reported a surge in prescription opioid abuse in the last decade[97,101]

Traditional opium-cultivating countries and their neighbors contain the majority of raw opium users. Although comprising less than 5% of the world population, Americans consume roughly 80% of the global opioid supply[102].

Intravenous (i.v.) heroin intake leads to significant morphological changes in the liver tissue (vesicular changes, fat changes, chronic hepatitis, cirrhosis). The intensity of these changes increases with duration of heroin usage[103].

Hepatocyte is the main locus of the bio-transformational systems which, through the action of the enzymes, enable the removal of the metabolites of these compounds from the organism. During these processes, ultrastructural hepatocyte changes and toxic liver damage occur, and intravenous intake of heroin leads to severe hepatic tissue infections (hepatitis, AIDS). The effects of heroin intake are most pronounced in the liver[103].

The morphologic changes in the liver tissue are associated with its function

disturbances, which results in the altered metabolism of heroin and other toxins taken simultaneously (alcohol, drugs) and, if these substances are abused, leads to the effects that are often surprising[104-106].

The functional disorder of the liver increases hemato-encephalic barrier permeability, thus enabling neuroactive substances to reach the brain cells in enormous amounts[107,108].

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