

Contribution of Alcohol Dependency in Liver-Related Diseases

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ABSTRACT

Worldwide, alcohol considers to be the leading cause of liver damage and generating liver-related disorders. For many decades, alcohol founds responsible for the primary aetiology of cirrhosis. In the recent studies, alcohol progressively contributing to be an common cause of liver-related diseases such as chronic liver disease, acute liver disease, cirrhosis, steatosis; either alone or in the combination with hepatitis B and C. This review focuses on the alcohol-dependent patients suffering from related liver dysfunctions', along with oxidative metabolism of alcohol and its components related to the functions of diverse isoforms of transferases. The conditions related to the alcohol-related liver-conditions as in fatty liver, alcoholic liver disease and cirrhosis. This review provides a summary from the global impending contribution of alcohol to liver disease.

Keywords – Liver, alcohol, fatty liver, alcohol metabolism, cirrhosis, transaminases.

Introduction

Alcohol is considered to be key-cause of liver diseases world-wide while alcohol triggering liver disease founds to be 2nd most common cause for liver transplantation in United States [1]. From past years, the mortality rates for alcoholic liver disease have elevated. Moreover, alcohol consumption surges the risk for liver diseases, infected by hepatitis C. Liver, the main organ, weighing about 1-1.5 kg; mainly represents 1.5-2.5 % of body mass and plays significant role in independent metabolic, excretory, and defence of the certain metabolites [3]. It has mending property to regenerate itself. Excessive heavy alcohol intake may develop serious alcoholic liver diseases. The common cause of alcoholic liver damage is mainly due to defect in the alcohol metabolism. Huge consumption of alcohol generates huge quantity of dangerous and toxic products; acetaldehyde along with highly reactive compounds such as free-radicals [2]. The alcohol & its components contributes to effect the liver, further leading to cause alcohol induce liver damage. Acute as well as heavy amount of alcohol consumption plays a vital role in developing alcohol related liver diseases, as conducted in the study by French *et al.*, (1993). The alcohol is metabolized in the liver in the presence of the enzyme Alcohol dehydrogenase (ADH). The main function of the enzyme is to convert alcohol to acetaldehyde through the oxidative process. Acetaldehyde, produced, is highly toxic compound for the body even, if present, in a very less concentration. Further, aldehyde dehydrogenase (ALDH) converts acetaldehyde to acetate, a less toxic as well as soluble compound. Acetate travels though the blood to other body parts and through other metabolic cycle that produce energy and useful molecule [1, 3].

High amount of alcohol consumption and other factors contributes to produce alcoholic liver disease. Everyone who consumes excessively alcohol will develop severe liver damage even fatty liver also reported in alcoholic population. Factors consider to determining to individual to alcohol intake include: environmental factors, gender, dose of alcohol consume, genetic [4]. Females are more susceptible to hepatotoxic effect of alcohols as compared to males who consume equal amount of alcohol to developed alcoholic liver disease. Obesity is the most significant of diet related risk factors [4, 5]. Males are prone towards the increase risk of alcoholic liver disease. There are two theories for explaining gender specific alterations in risk of alcoholic liver disease. One is Gastric ADH (alcohol dehydrogenase) it is present higher in liver and also in, stomach and intestine. Females have lower level of gastric ADH activity than men. In female, higher level of ingested alcohol reached to the liver and female is earlier onset of alcoholic disease [1, 7].

Epidemiology

Increase in the alcohol consumption shows diversity in mortality rate i.e. pattern showing stabilization, further decline till the mid of 1970. Alcohol use disorder (AUD) is considered to be inevitable disease. Recent report of WHO, indicates 3.5 million deaths (about 6.5% of global deaths) attributed to alcohol consumption, and alcohol dependency proves to be main aspect observed in 50% of cirrhosis related cases. Roughly about, 1 in 12 adults suffers from alcohol dependency related condition define as consumption which founds to > 3-4 drinks/ day in males while, for females, its about > 2-3 drinks/ day, such huge intake of alcohol being further leads to habitual pattern termed as drinking. The data provided by the National Institute of Alcoholism & Alcohol Abuse, keenly explains the cases of alcohol-addicted; as more than 5 drinks in males and >4 drinks in females consume over 2Hr period). In United States, one drink is define as a beverage comprises of 14g of alcohol, present in 12 ounce of beer or 5 ounce of wine The financial cost around 249 billion USD/ year is increasingly progressively. With an estimate of around 88,000 people (comprises of 62,000 men and 26,000 women) die due to alcohol-consumptions conditions annually, concluding alcohol to become the 4th leading inevitable cause of death in the United States.

Pathophysiology

Association between abuse of alcohol and liver disease, is still not understood. Alcohol associated with fatty liver through alcoholic hepatitis and hepatic fibrosis to establishe cirrhosis. Many of the mechanism proposed have been related to metabolism of alcohol and generation of its metabolites acetaldehyde [8]. Understanding of alcohol, metabolism, absorption, distribution is complicated because many of the biochemical changes commonly observe in alcohol-dependent patients such as hyper lipidemia, hyperurecimia and hypoglyceamia. The chemical/biological reaction of alcohol to acetaldehyde in cytosol and further metabolize of form acetate and which, finally release in the blood, with an oxidized to CO₂ and H₂O in peripheral tissue [5]. Acetate & dehydrogenase lead to produce reduced NADH and inhibit oxidation of fatty acid; further promoting accumulation of fats in the liver. An another oxidation leads to

the usage of cytochrome P450 enzyme 3E1 lead to produce reactive O₂ species; which results in the lipid peroxidation and further creating tenderness. Along with this, intestinal permeability increases and leads to endotoxemia, which cause the release tumor necrosis factor- α (TNF- α) of Kuffer cells in the liver; they leading to exhibit oxidative stress. Acetaldehyde from protein abduct, act as neo-antigen, initiating immune mediated damage to the hepatic cells. The result leads to multiple hits on liver, which further progresses in hepatocytes necrosis.

Metabolism of Alcohol

The metabolism, mainly, occurs by oxidative and non-oxidative pathway both i.e. involving the pathways comprises of ADH, cytochrome P450, and catalase enzyme. By this pathway, alcohol dehydrogenase (ADH) converts alcohol into the acetaldehyde process called oxidation. Acetaldehyde, a toxic compound, effective even at low concentration. However, aldehyde dehydrogenase (ALDH) enzyme hastily oxidize acetaldehyde to form acetate molecule. The newly formed, acetate travels through blood through other part and enter to other metabolic cycle and produce energy or useful molecule [9, 10]. Most common pathway for metabolizing the alcohol involves the presence of two enzymes i.e. alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). These enzyme helps to metabolize alcohol compound, making it easy for elimination from the body through urine. Firstly, ADH molecule is processes the conversion of alcoholic-form to acetaldehyde-form, a very lethal substance; known as carcinogen, then, further it metabolize down to another, forming less active-form called acetate, further catabolized into carbon dioxide and water.

Cytochrome P450E1 (CYP2E1): Enzyme also degrade the alcohol to form acetaldehyde. It becomes active in a condition if person consumed heavy amount of alcohol and the enzyme metabolize only a minute amount of alcohol from the body. This minute concentration of alcoholic compound is eliminated by interrelating with fatty acid to form compounds named fatty acid esterase (FAEEs). These compound has contribute to damage to hepatocellular tissues. The metabolism of alcohol occurs in some other tissue includes pancreas; which eventually cause damage to its cells and tissues. While minute amount of alcohol is processed to form acetaldehyde in gastrointestinal tract, baring these tissue to effect caused by acetaldehyde damage [11]. Furthermore, in other tissues; as brain does not contain ADH enzyme. As they consists of two important enzymatic mechanisms; comprising of enzyme cytochrome P450 and catalase.

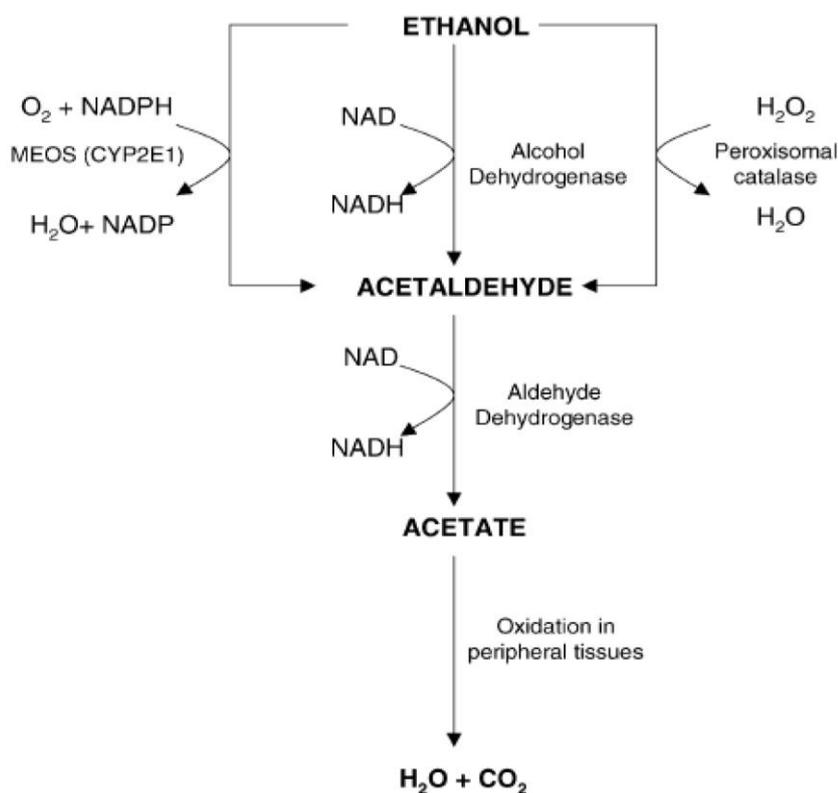


Fig. 1. Alcohol Metabolism by three consecutive pathways by oxidative mechanisms [23].

Oxidative Pathways

ADH, Cytochrome P450 2E1, and catalase all enzymes are involved in oxidative alcohol metabolism.

- ADH - The major enzyme involved in the oxidative mechanism of alcohol, highly available in the cytosol of the in the hepatocytes. Metabolism of alcohol with ADH produced acetaldehyde, a highly responsive and toxic product that contributing tissue damage. This mechanisms involves an intermediate carrier of electrons; NAD⁺ which reduces two electrons to form NADH (nicotinamide adenine dinucleotide). This reaction leaves the hepatocytes in condition; which is susceptible to injure by-product of alcohol metabolism likely by the free radicals and acetaldehyde [12].
- Cytochrome P450 iso-enzymes includes CYP2E1, 1A2, and 3A4; highly available in microsomes and endoplasmic reticulum which contributes to alcohol oxidation. CYP2E1 dependent alcohol oxidation occurs in other tissue such as brain. It produces various reactive oxygen species, H₂O₂, hydroxyl-radicals, superoxide anions which increased risk of tissue damage.
- Catalase, available in cell bodies named peroxisomes, mainly accomplished by oxidizing alcohol *in vitro*; hydrogen peroxide generating system presence named as NADPH-oxidase or the enzyme xanthine oxidase [13].

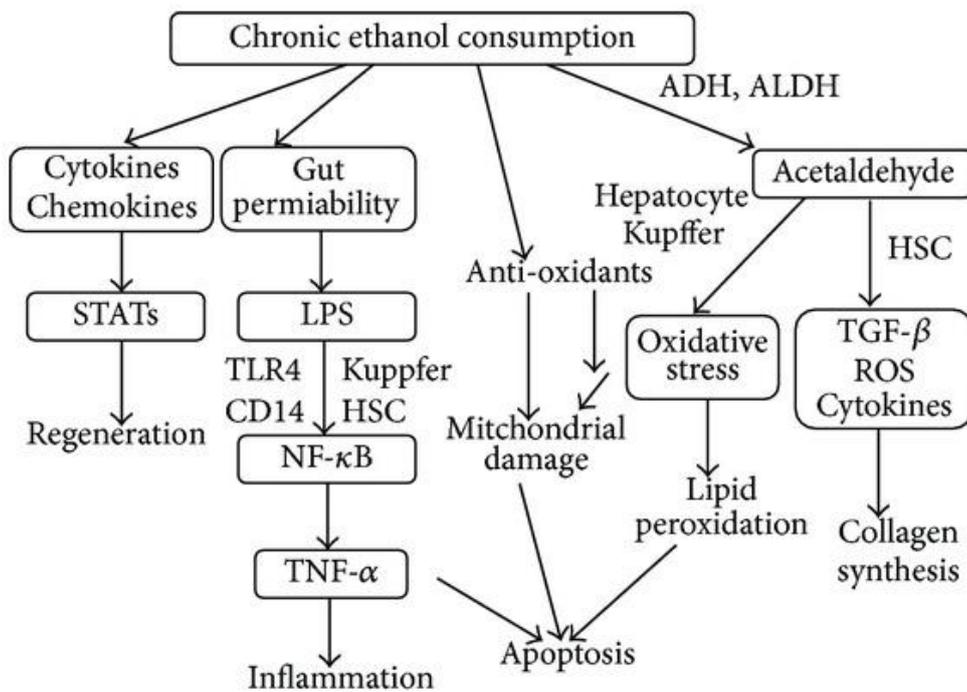


Fig. 3: The multiple mechanisms through which Alcohol can lead to fatty liver [24, 25].

- Alcoholic hepatitis - Characterized by hepatocytes inflammation. Fibrosis occurs in prominent in causing alcoholic liver disease. Alcohol consumption leads to hepatocyte necrosis (inflammation, destruction). Scar tissue replaces the healthy tissue by a process named fibrosis. Some, inflammatory cytokines (TNF α , IL6 and IL8) leads to liver injury by inducing apoptosis and necrosis. It simplifies gut-produced endotoxin absorption to the portal circulation. Kupffer's cell are phagocytosed by endotoxin stimulating releasing of TNF- α . Signs of alcoholic hepatitis comprise of fever jaundice, and abdominal pain. It occurs up to 50 % triggering apoptotic pathways through caspases activated, result is death of hepatocellular.
- Alcoholic cirrhosis- Alcoholic cirrhosis mainly diagnosed up to 15-30% liver damage of heavy drinker. The data, presented in the study of demonstrates, that fatty liver patients progresses to appear cirrhosis condition [26]. Cirrhosis is the later stage of scarring, caused by heavy alcohol consumption. Liver fibrosis may be reversible with abstinence. Acetaldehyde responsible for alcohol-induced fibrosis initiates collagen deposition in hepatic cells. The production of oxidants; from NADPH oxidase or cytochrome P-450; along with formation of acetaldehyde-protein adducts damages the cell membrane. The symptoms comprise of jaundice, liver enlargement and structural changes in liver architecture. Cirrhosis is one of the irreversible stage.

Laboratory Diagnostic

Confirm of the presence of alcohol abuse is done by blood test; indicating the occurrence of liver damage. Elevated level of GGT has been show 90 % of patient abusing alcohol (Wu et al., 1997). This rise mainly due to microsomal induction and present of liver disease. Biochemical markers related to liver damage serum aspartate transaminase activity (AST) founds to be >500 IU/litre, while ALT range >300 IU/litre. Throughout, AST/ALT ratio confirms to be above 1.5. Patient showing abnormal liver blood test may suffer

from steatosis, but can also, suffers from silent“ cirrhosis [21]. Gamma glutamyl transferase (GGT) is liver associated enzymes that are measure liver homostasis. ALT and AST indicate the concentration of hepatic enzymes; leaked in circulation; hence, marker for hepatic injury. AST, ALT, GGT, and ALP significantly rise in viral hepatitis and alcoholic liver disease [22].

Relation between alcohol consumption and AST/ALT ratio

ALT, AST and GGT are liver associated enzyme measure of liver homeostasis. ALT & AST indicates the amount of intracellular hepatic enzyme that has been leaked into the circulation and are considered as a marker for hepatocellular injury [14]. Aminotransferase is sensitive indicator for hepatocellular injury and most helpful for diagnostics. In acute hepatocellular disorder, ALT levels become higher or equal than AST in which, AST & ALT ratio $>2:1$ is progressive while $>3:1$ ratio is highly progressive comprising of alcohol related liver disease [16]. In such conditions, AST is roughly >300 U/L and ALT values are often normal. Low ALT level indicates alcohol induce deficiency of pyridoxal phosphate [17, 18]. GGT is a microsomal enzyme with tissue distribution. It is present on the cell wall of various tissues including kidney, brain, bile duct, gallbladder, spleen, pancreas, heart, and seminal vesicles [19, 20]. It involves transfer of amino acid, leukotriene metabolism and glutathione metabolism, across the cell membrane. It also elevates in pancreas and biliary tract disease that are similar to ALP in detecting the disease of biliary tract [3, 11].

Conclusion:

Alcohol induced liver damage considers to be challenging situation in recent times. Thus, it an urgent need to emphasize on its sensitivity and progressive rate of its early diagnosis to reduce the mortality rate. Various studies have suggested that huge amount of alcohol consumption leads to produce various fatal conditions which increases the death rate worldwide. To assess, the function ability of liver, it's necessary to monitor the availability as well as ability of transferases and other related enzyme for such diagnosis.

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