A Comprehensive Review On: Alcoholic Liver Disease- Pathophysiological Angles and Hazard Factors

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ABSTRACT:

Alcoholic liver infection has a known etiology however a complex and deficiently known pathogenesis. It is extremely common disease with huge morbidity and mortality, but the reason why only a few cases of heavy drinkers progress to advanced disease remains cagey. The main aim of the study is to understand the factors responsible for the progression of alcoholic liver disease. We performed an extensive literature review to identify the complex pathogenic pathway and risk factors of alcoholic liver disease. In addition to the cumulative amount of alcohol intake and alcohol consumption patterns, various factors like gender and ethnicity, genetic background, nutritional factors, energy metabolism abnormalities, oxidative stress, immunological mechanisms and hepatic co-morbid conditions play a key role in the initiation and development of alcoholic liver injury. Understanding the pathological angles and hazards factors of alcoholic liver disease should provide insight into the development of therapeutic strategies.

Keywords: Alcohol, Hazards factors, Liver, Pathophysiology,
INTRODUCTION

Alcohol consumption is well attitude and status symbol in the social area of many adult populations. Due to several factors like legal aspects, easily available and cost effective. Long term and excessive alcohol consumption leads to development of addiction that can crosses all barriers like gender, race, age, economic level and, in many patients it leads to development of alcoholic liver disease. Heavy drinking habit significantly increases the morbidity and mortality as compared to the infectious diseases. Excessive drinking over decade damage nearly every organ in the body.

Alcoholic liver disease highlights a broad spectrum of clinical illness and structural changes from development of fatty liver to liver inflammation and necrosis (alcoholic hepatitis) to progressive fibrosis (alcoholic cirrhosis). Furthermore, continuous consumption of alcohol supports the progression of other liver diseases, like virus-related chronic hepatitis, also increasing the risk of hepatocellular carcinoma. The liver sustains to the the greatest degree of tissue injury from excessive drinking because it is the primary site of ethanol metabolism.\(^1\)

According to the WHO Worldwide, 3 million deaths every year result from harmful use of alcohol, this represent 5.3 % of all deaths. Overall 5.1 % of the global burden of disease and injury is attributable to alcohol, as measured in disability-adjusted life years.

The main aim of this extensive study is that to understand the pathogenesis and risk factors for alcohol liver diseases. The literature study demonstrated that the duration and the degree of alcohol consumption increase the risk of alcoholic liver disease. However, only a in a small portion of population with heavy drinkers have clinical liver disease, suggesting other factors like environmental promote the risk of development of alcoholic liver disease.

The several steps involved in the development of hepatotoxicity. Several primary and secondary factors are interact with each other to initiate liver injury. Primary factors like genetic factor, its relationship with alcohol toxicity and alcohol leads to alteration in metabolic and immunological factors. Secondary factors like impact of nutrition, these factors potentially contribute for the development of hepatotoxicity.\(^2,3\)

EPIDEMIOLOGY OF HEPATOTOXICITY:

Generally the alcohol toxicity reported in particular group of people who are consuming the
intemperate amount of alcohol. The alcohol dependence is not the single factor responsible for the development of alcoholic liver disease, it is observed that the development of alcoholic liver disease in patient who do not have the history of dependence. Several factors also play important role in the development of alcoholic liver disease along with the higher amount of alcohol consumption, like genetic and environmental factors, malabsorption also reported in the heavy drinker due to negligence of food.\textsuperscript{4, 5}

Although the several cases of alcoholic liver disease reported, but the no set amount responsible for induction of disease is not reported. On an average 1-2 drinks per day is usually safe and consumption of more than 3 drinks per day is associated with documented adverse effects. Though the heavy drinkers have greater risk of death from non-cardiovascular causes, and develop fatty liver, but only 10-35% develop hepatitis and 8-20 % will progress to cirrhosis.\textsuperscript{6}

Low levels of alcohol intake (1-2 drinks per day for women and 2-4 drinks per day for men) are inversely associated with total mortality in both men and women.\textsuperscript{7} If daily consumption of alcohol increase more than 40-80 g/dad and 20-40 g/day for male and female respectively will leads to development of alcohol liver disease.\textsuperscript{8} Consuming alcohol with food resulted in somewhat lower risk than consuming alcohol alone. High consumption of alcohol for longer time increase the relative risk of alcohol liver disease. However the wine drinker have lower risk of liver disease as compared to beer and spirit drinker. Once the liver disease is develop, continuous consumption of alcohol is a major indicator of poor prognosis.

**PAHGENESIS**

**Gender:**

The majority of alcohol liver disease patients are male but the female patients are more susceptible to the toxic effects of alcohol, as female have greater risk of developing liver cirrhosis for small dose of alcohol consumption.\textsuperscript{9, 10} Several hypothesis have been postulated for women having higher risk as compared men, the first one is the sex difference in ethanol pharmacokinetics, following the intake of same amount of alcohol, and women have higher blood concentration as compared to the men. This can be attributed to the several reason, including a small volume of distribution due to lower total body water content because of a lower weight and higher proportion of fat.\textsuperscript{11}

In addition to that low gastric ADH level in women also leads to development of alcoholic liver disease. A fraction of alcohol ingested is metabolized by gastric ADH before systemic
circulation. This action directly decrease the systemic concentration of alcohol in the body.  

**Genetic factors:**

In some populations the alcohol consumption is high. Among all of them only few are susceptible to develop the alcohol liver disease and cirrhosis. Therefore there must be some genetic factors responsible for development of disease. Some case study reported that family twins shown genetic determinants play essential role the progress of alcohol disorders and dependence. Still the exact mechanism is not clear as it complex and difficult to identify. Genetic study reveals that the gene encoding for the enzymes that responsible for the metabolism of alcohol and acetaldehyde influence the predisposition to alcohol dependence, sensitivity to alcohol and alcoholic liver disease cirrhosis development even the result is till nonconclusive. These genes include those encoding for alcohol-dehydrogenase (ADH), aldehyde-dehydrogenase (ALDH) and C2-promoter allele of the gene coding for cytochrome CYP2E1.

**Energy metabolism:**

ATP synthesis rate is reduced in the ethanol exposed hepatocytes. Even long term exposure of ethanol to hepatocytes decrease the mitochondrial functions including decrease in cytochrome b content, decrease in activity of cytochrome oxidase, impaired functioning of proton and electron leads to impaired energy metabolism would to hepatocyte damage.

Energy metabolism is also disturbed by low oxygen level. Chronic alcohol consumption leads to increase the oxygen uptake by hepatocytes. Because to metabolize the ethanol liver required more blood supply to the central lobular area, but the oxygen supply and demand are not matched and leads to development of hypoxia, which can be responsible to tissue injury.

**Oxidative stress:**

Oxidative stress is a key factor in the development of alcohol induced liver disease. The three major hepatic system involved in the oxidation of ethanol to water and carbon dioxide, that are ethanol oxidation by microsomal enzymes present in smooth endoplasmic reticulum, alcohol dehydrogenase in cytoplasm and catalase in peroxisomal membrane. All these biochemical pathways produce a toxic by product acetaldehyde.

Ethanol increased the hepatic oxidative stress by generating reactive oxygen sepsis (ROS) and adducts. Hepatic biochemical pathway produce acetaldehyde the toxic by product of alcohol,
this acetaldehyde oxidized to acetate by aldehyde dehydrogenase. Acetaldehyde form adducts with reactive residues leads to lipid peroxidation and nucleic acid oxidation. 16 Excessive ethanol consumption leads to induction of CYP2E1 alcohol metabolizing enzyme, which contribute alcohol dehydrogenase to development of superoxide radicals via interaction of CYP2E1 with cytochrome reductase, which leads to ROS production. 17

**Role of Immunity:**

Ethanol impair the immune functions. However the exact mechanism is still unknown. As the excess alcohol consumption increase the tissue permeability to bacterial endotoxins like lipopolysaccharides. They bind the CD 14 cell and sensitize the kupffer cells which leads to transcription of pro-inflammatory cytokines like TNF-a, IL-6 and transforming the growth factors, which contribute the apoptosis and fibrosis leads to progression of liver disease. 18

**CONCLUSION**

Higher morbidity rate is observed in the population who are unhealthy by affecting various organs and systems. The pathophysiology of alcohol liver disease is quite complex which involves several factors including genetic, gender, immune and amount of alcohol consumption.

Alcohol induced liver damage involved complex mechanism and it is not completely defined. Generally accepted ethanol induces an altered redox state associated with generation of free radicals, resulting in lipid peroxidation, cell-membrane damage and depletion GSH. The metabolite of ethanol that is aldehyde involved in several toxic effects of alcohol by forming protein adducts which are responsible development of inflammatory response.

However, we are at the beginning and much more remains to be done to clarify the exact mechanisms of alcohol-induced damage. From the clear-cut understanding pathophysiology, it will result a more defined identification of risk factors for the progression of alcohol liver disease, accredit us to set preventive plans for developing therapeutic approaches.
REFERENCES:

5. (Rouault TA. Hepatic iron overload in alcoholic liver disease: why does it occur and what is its role in pathogenesis? Alcohol 2003; 30: 103–6.