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CONTEMPORARY APPROACHES TO TREATING ALCOHOLIC LIVER DISEASE

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ABSTRACT
Alcoholic liver disease (ALD) is a spectrum of liver damage caused by the excessive consumption of alcohol, leading to conditions such as fatty liver. Excessive alcohol use results in various hepatic diseases, the most common being fibrosis/cirrhosis, hepatitis, and fatty liver (steatosis). ALD is the leading cause of alcohol-related deaths among adults worldwide. Factors influencing the progression of the disease include ethnicity, gender, age, viral hepatitis, genetic variations, smoking, and obesity. Corticosteroid treatment, particularly prednisolone, is the most commonly prescribed therapy for adults with ALD due to its ability to reduce the immune response and pro-inflammatory cytokine response. Liv-52, a herbal formulation widely used in Indian traditional medicine, is another treatment option. For patients with end-stage liver failure, liver transplantation remains the preferred therapy.

KEY WORDS: Alcoholic Liver Disease, Mechanism, risk factor, Clinical Management, Treatment.

INTRODUCTION
Alcoholic liver disease (ALD) encompasses a range of liver damage caused by excessive alcohol consumption, including acute or chronic liver malfunction, alcohol-associated cirrhosis, alcohol-related hepatitis, and hepatic steatosis. Globally, ALD is the most common cause of alcohol-related deaths in adults. Excessive alcohol intake can lead to addictive behavior affecting people of all ages, genders, races, and economic backgrounds, potentially resulting in ALD[1]. Approximately 40% of deaths in patients with liver cirrhosis and 28% of all-cause liver disease mortality are attributed to ALD. Milder forms of ALD often go unrecognized and asymptomatic, making it difficult to determine the true incidence of the condition. Patients with ALD are rarely identified in the early stages compared to those with nonalcoholic fatty liver disease or viral infections[2].

Recent research indicates that in 2016, alcohol use was ranked seventh for both disability-adjusted life years and mortality, accounting for 2.2% of age-standardized deaths in females and 6.8% in males[3]. Approximately 2% to 3% of ALD cases progress to hepatocellular

carcinoma. While some ALD manifestations are reversible with alcohol abstinence, severe conditions have a poor prognosis. Alcohol-related morbidity contributes significantly to disability-adjusted life years globally, comparable to tobacco-related illnesses. In 2010, thousands died specifically from alcohol-related hepatocellular carcinoma (HCC), with nearly half of all liver cirrhosis fatalities worldwide attributed to alcoholic liver cirrhosis. Clinical manifestations of ALD range from asymptomatic to end-stage disease with symptoms like jaundice, hypertension, and encephalopathy. Patients may experience various digestive symptoms but often delay seeking medical attention until the condition becomes severe. Effective treatment for ALD includes psychosocial interventions combined with pharmacological and medical therapies[4].

NEED FOR UNDERTAKING TREATMENT OF LIVER DAMAGE CAUSED BY ALCOHOL

HEALTH PRESERVATION: The primary goal of therapy is to prevent further liver damage while maintaining liver function. Early treatment of ALD can help stop or delay the onset of severe complications such as liver failure and cirrhosis[5].

ENHANCEMENT OF QUALITY OF LIFE: Symptoms of ALD, including fatigue, jaundice, abdominal pain, and cognitive impairment, can significantly reduce one's quality of life. Treatment aims to alleviate these symptoms and improve overall health[6].

REDUCTION OF MORTALITY RISK: Advanced stages of ALD, such as cirrhosis and liver failure, carry a high risk of death. Prompt treatment can reduce the mortality risk associated with these complications[7].

RECURRENCE PREVENTION: Besides addressing current symptoms, treatment helps patients adopt healthier habits and lifestyles to prevent further liver damage[8].

HANDLING COMPLICATIONS: ALD can lead to various complications like ascites, hepatic encephalopathy, and portal hypertension. Treatment focuses on managing these issues to minimize their impact on health and improve outcomes[9].

PSYCHOSOCIAL ASSISTANCE: Addressing the emotional and social aspects of living with chronic liver disease is vital. Psychosocial support, including support groups, therapy, and educational programs, plays a crucial role in helping individuals manage the challenges of ALD and maintain sobriety[10]

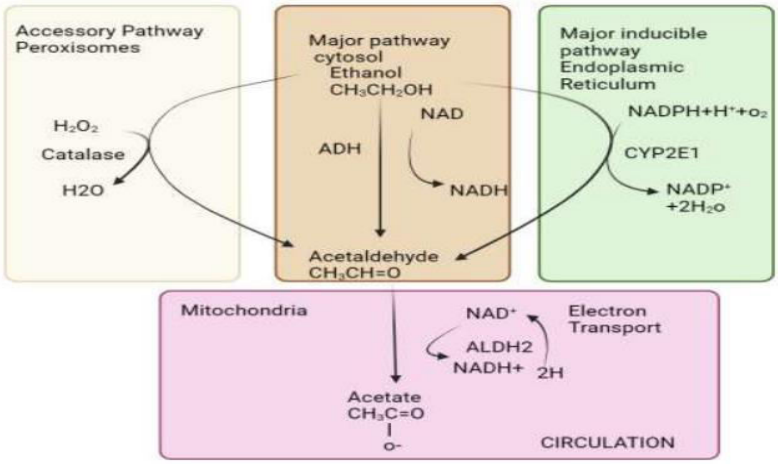

Fig 1: liver's major and minor ethanol-oxidizing mechanisms

ALCOHOL CONSUMPTION, DRINKING HABITS, AND ALCOHOL-RELATED LIVER INJURY

There is a clear link between per capita alcohol consumption and alcohol-related mortality, though not everyone who drinks heavily develops alcohol-related dementia. In the Dionysus cohort study, a survey of alcohol consumption was conducted with 6,534 Italians. Awkward et al. made three significant contributions: first, they found that daily drinking was most strongly associated with hepatic cirrhosis vulnerability; second, recent drinking (within the past several years) was more impactful than earlier drinking over a lifetime; third, wine, compared to beer or spirits, might be linked to a decreased risk at equivalent alcohol levels. Individuals prone to ALD often start drinking alcohol at a young age and increase their intake over time. In the UK, regular heavy drinking has been associated with higher risks of alcohol-related liver damage compared to binge drinking or infrequent drinking[11].

HEPATIC ALCOHOLIC METABOLISM

Ethanol, or beverage alcohol, is primarily metabolized in the main liver cells, which constitute 70-80% of the liver's mass. These cells contain high levels of key ethanol-processing enzymes such as alcohol dehydrogenase (ADH) and cytochrome P450 2E1 (CYP2E1). Additionally, hepatocytes have high levels of catalase in peroxisomes, which typically detoxifies hydrogen peroxide to water and oxygen. In the presence of ethanol, catalase also helps metabolize ethanol by using hydrogen peroxide to convert it into acetaldehyde. While this pathway is minor in the liver's ethanol metabolism, it plays a more significant role in ethanol oxidation in the brain[12].

Alcohol consumed is absorbed by the stomach and intestines. Less than 10% of this alcohol is expelled through breath, sweat, and urine, indicating that over 90% travels through the body via the portal vein to the liver. The liver is crucial in alcohol metabolism due to its high concentration of alcohol-breaking enzymes. The liver employs both oxidative and non-oxidative processes to metabolize alcohol. The primary mechanism is the oxidative route, which involves two steps: first, alcohol is oxidized to acetaldehyde by ADH; second, in cases of heavy alcohol consumption, CYP2E1 levels increase, leading to the production of acetaldehyde and reactive oxygen species (ROS).

CYP2E1 is another crucial liver enzyme responsible for catalyzing the oxidation of ethanol into acetaldehyde. CYP2E1 has a greater binding affinity for ethanol and reaches half-saturation at ethanol concentrations between 46 and 92 milligrams per deciliter, but it is less efficient than ADH.

Long-term alcohol consumption leads to an increase in hepatocellular levels of CYP2E1. Ethanol directly interacts with the CYP2E1 protein, causing a conformational change that makes it resistant to degradation by the proteasome-ubiquitin system and results in the aggregation of CYP2E1 molecules. The induction of CYP2E1 has significant effects on heavy drinkers. First, as more ethanol is oxidized by CYP2E1, individuals develop "metabolic tolerance," requiring higher alcohol consumption to achieve the same level of intoxication. Furthermore, the increased CYP2E1-induced alcohol metabolism puts liver cells at risk for metabolic damage by increasing the production of acetaldehyde and additional reactive oxygen species (ROS), including superoxide anions (O2−), hydroxyl radicals (√OH), and hydroxyethyl radicals (free-radical forms of ethanol).

Over time, the production of these reactive substances results in oxidative stress among heavy drinkers, as ROS generation surpasses the liver's antioxidant capacity. Animal studies have shown that long-term ethanol consumption reduces the activities and/or levels of various antioxidant enzymes, leading to increased oxidative stress in hepatic cells. Lipid peroxides, generated when ROS react with unsaturated fats and proteins, exacerbate this stress. These peroxides can then interact with proteins and acetaldehyde to form larger adducts, such as malondialdehyde-acetaldehyde adducts, which can trigger an immune response. Additionally, due to CYP2E1's broad substrate specificity, elevated levels of this enzyme can convert other substances, such as acetaminophen, into more toxic compounds.

Alcohol has significant impacts on liver cells, which are responsible for removing harmful substances like alcohol from the blood. However, the liver's capacity to process alcohol is limited, and excessive consumption can lead to damage or changes in liver cells over time. These modifications include:

1. Accumulation of fat in liver cells, known as fatty liver.
2. Alcohol-induced hepatitis.
3. Severe scarring of the liver, known as cirrhosis.
4. Increased risk of liver cancer or death due to extensive liver damage.

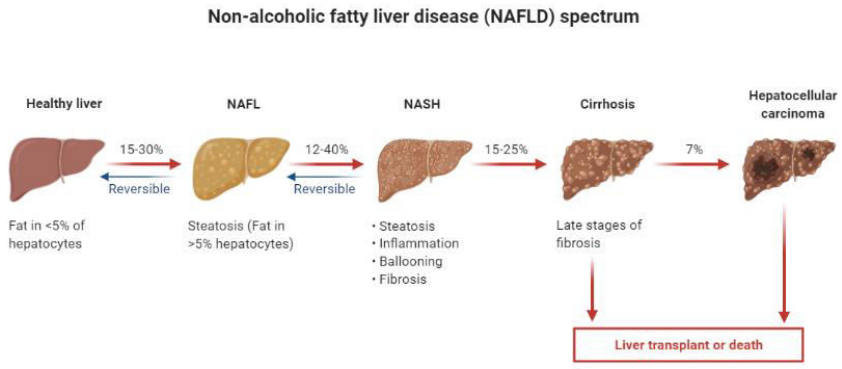

Fig 2: Alcoholic liver disease spectrum

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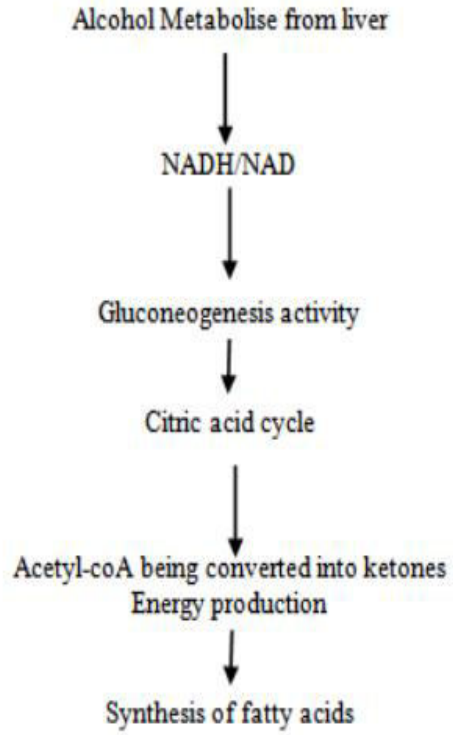
Alcohol is primarily metabolized in the liver and, to a lesser extent, throughout the digestive system. Liver metabolism of alcohol involves two main pathways: the alcohol dehydrogenase pathway and the cytochrome P-450 2E1 (CYP2E1) pathway. These pathways result in an increased ratio of NADH/NAD, which has significant effects on carbohydrate and lipid metabolism.

The metabolic consequences include a decrease in gluconeogenesis activity and the redirection of substrates through the citric acid cycle, leading to the conversion of acetyl-CoA into ketones for energy production and the synthesis of fatty acids. Alcohol dehydrogenase converts alcohol into acetaldehyde, which is then further metabolized to acetate. These processes also generate NADH.

For many years, the metabolic explanation for alcoholic fatty liver has been widely accepted but was insufficient to explain why fatty liver develops rapidly following acute ethanol intake. Additionally, the extent of liver redox potential changes observed in vivo after prolonged ethanol consumption is notable but relatively mild. As a result, the metabolic theory alone could not account for all the alterations in hepatic lipids observed after ethanol use. Further investigations into cell signaling mechanisms and the discovery of specific transcription factors have provided additional insights into the mechanisms underlying alcohol-induced steatosis.



CONCLUSION:

The fundamental approach to managing ALD revolves around complete abstinence from alcohol, which is crucial for preventing further liver damage and facilitating potential recovery. Proper nutrition plays a vital role, and ALD patients may benefit from dietary

supplements. Corticosteroids like prednisolone may be prescribed for severe cases of alcoholic hepatitis, although their effectiveness is debated, and they come with significant side effects. In cases of end-stage liver disease or failure to respond to medical therapy, liver transplantation may be considered as a lifesaving option.

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