AN ALCOHOLIC LIVER DISEASE (ALD) AND ITS IMPLICATIONS

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ABSTRACT

Overindulgence in alcohol is a global health concern. Because the liver is the principal site of ethanol metabolism, excessive drinking causes the highest degree of tissue harm. Hepatic lesions resulting from prolonged and severe alcohol intake are diverse, with steatosis, hepatitis, and fibrosis/cirrhosis being the most commonly seen. The first reaction to binge drinking, steatosis is characterised by the accumulation of fat in hepatocytes. Steatosis can develop into steatohepatitis, an inflammatory form of liver disease that is more severe. Fibrosis, characterised by an excessive accumulation of extracellular matrix proteins, can arise from this stage of liver disease. Active pericellular fibrosis is the first stage of the fibrotic response. It can lead to cirrhosis, which is characterised by extensive liver scarring, changes in the blood vessels, and finally liver failure. Because a variety of disease modifiers accelerate, halt, or prevent the course of alcoholic liver disease, around 35 percent of problem drinkers have severe liver disease. For the treatment of people with alcoholic liver disease, there are currently no FDA-approved pharmaceutical or dietary therapy. Abstinence, or quitting alcohol, is a crucial component of treatment. For individuals with end-stage alcoholic liver disease, liver transplantation is still the only method that can save their lives.

KEYWORDS: Alcoholic liver disease(ALD), fatty liver, steato-hepatitis, cirrhosis.

INTRODUCTION

Drinking too much or too often can lead to major health issues that include the immune system, pancreas, liver, brain, heart, and gastrointestinal tract. Alcohol use disorder (AUD) ranks as the fifth most common cause of mortality in both the US and Europe. Each year, alcohol usage causes 3.3 million deaths worldwide, or 5.9% of all fatalities.[1,2,3]Three main classes are produced by ALD, which is linked to either increasing fibrosis or hepatic inflammation and damage.

Pure forms of each of these classes are uncommon.[4,5]These consist of cirrhosis, alcoholic hepatitis, and fatty liver. Most chronic drunks have fatty livers, which is a characteristic linked to long-term alcohol use.[6]Heavily drinking individuals are far less likely to develop alcoholic hepatitis, which has been demonstrated to be a precursor to liver cirrhosis.[7,8]The prognosis for severe alcohol-related liver damage is quite bad. At five years, more than 65% of people with alcohol-associated hepatitis who also have cirrhosis will die.[9,10,11]Although alcohol is thought to be a direct hepatotoxin, only around 20% of people with alcohol use disorders go on to develop alcohol-associated hepatitis as a result of their alcohol consumption.[12,13,14]Approximately 150 million individuals worldwide carry the hepatitis C virus (HCV), which causes an annual rise in the incidence of mortality rates.[15]Other comorbid variables, including as immunological state, inheritance, age, dietary factors, and gender, are the cause of this.[16,17,18,19]The amount and duration of alcohol use are the two main risk factors that contribute to the development of ALD. The type of beverage and consumption behaviour patterns are less important in predicting the risk.[20,21,22]

Alcohol use dose-dependently raises the risk of alcoholic liver disease (ALD), even if moderate alcohol use may be helpful for ischaemic heart disease.[23]Over the last twenty years, China and the US have seen a rise in alcohol use, while several European nations have seen a minor reduction.[24,25]ALD prevalence has also grown and is predicted to continue rising concurrently.[26]

ALD is treated with corticosteroids, and greater attention has lately been focused on antitumor necrosis factor antibodies as a result of research showing a connection between ALD and tumour necrosis factor-alpha. According to a prior study, drinking alcohol exposes people to acetaldehyde, which might have harmful consequences like tachycardia, hypotension, face flushing, and vomiting. Additionally, the larger percentage of alcohol intake demonstrated liver damage and neurotoxicity.[27]

Vitamins are important in ALD. Hepatoprotective actions of vitamin E can prevent persistent alcohol exposure-induced liver damage.[28]Vitamin C significantly reduces the invasion of neutrophils, hence alleviating liver damage caused by alcohol.[29]Vitamin B2 (riboflavin) is a member of the B vitamin family. Intestinal and hepatic inflammation can result from riboflavin deficiency ariboflavinosis. Sanches et al. discovered that riboflavin can shield mice's livers from damage brought on by ischaemia and reperfusion. According to a study, **riboflavin** influences the mitochondrial electron transport chain, which in turn influences the development of liver disease linked to parenteral feeding. In rats, riboflavin can reduce liver fibrosis via controlling the AMPK/PGC1α/HO-1 signalling pathway. Additionally, riboflavin was discovered to have a protective impact on liver cells that had been exposed to alcohol in our earlier in vitro trials. Riboflavin's anti-ALD impact in vivo and the underlying processes are yet unknown, though.[30,31,32,33,34,35]

CONSUMPTION OF ALCOHOL AND ALD

It should be remembered that 12 fluid ounces of beer, 4 ounces of wine, or 1.5 fluid ounces of distilled spirits each contain around 14 g, or 0.6 fluid ounces, of pure alcohol when assessing alcohol intake.[36]Accordingly, women appear to be at a higher risk of experiencing the same level of liver damage by taking 20–40 g of alcohol per day, but the threshold for males to acquire severe alcohol-associated liver disease is less than 60–80 g of alcohol per day for ten

years.[37,38,39,40,41,42]Women are more vulnerable to the pathophysiology of ALD than males are. Women are more likely to get advanced liver disease when they consume significantly less alcohol.[43,44,45]The gastrointestinal and hepatic metabolism of alcohol varies depending on gender, which may explain why women are more vulnerable to alcohol-induced liver damage.[46]Additionally, the activation of macrophages and liver cells due to overexpression of TNF-α mRNA in the liver results in a pro-inflammatory response and an increase in reactive oxygen species (ROS) that indicates liver damage. It has been revealed that the stimulation of ROS, IL-6, and IL-8 is the mechanism of liver damage.[47]

Quantity

• A fatty liver is produced in males by 40–80 g of ethanol per day;

• Consuming 160 g daily for 10–20 years might result in cirrhosis or hepatitis.

• Only 15% of alcohol drinkers experienceALD.

Gender: Two drinks a day are probably safe, however women are more susceptible to ALD at quantities larger than 20 g.

Virus

- Concomitant hepatitis B (HBV) and hepatitis C (HCV) infection is linked to a faster development of cirrhosis, fibrosis, and even hepatocellular cancer in ALD patients.
- One of the factors contributing to liver illness in the context of HIV infection is viral hepatitis, which interacts in a milieu influenced by alterations in cytokine expression and ongoing immunological activity.

MolecularBiology

• Gene polymorphisms linked to alcoholism, cytochrome P4502E1, and alcohol dehydrogenase may be present.

• The relationship between ALD and genetics has been shown to investigate a variety of risk factors for the onset of liver disease. Liver functions are severely damaged by the association between ALD and rs738409 gene expression, which also exacerbates liver cirrhosis. Liver fat is stored via activating lipogenic transacetylase, which is affected or mediated by PNPLA3. Increased aminotransferase levels and subsequent hepatic cell inflammation are closely linked to the buildup of lipids in the liver. GWAS analysis of the relationship between gene functions and ALD to determine the pathophysiological mechanism of the liver.[48]

DRINKING PATTERN AS A RISK FOR ALD

Heavy drinking and binge drinking are examples of high-risk drinking behaviours that have changed recently.[49]The National Institute on Alcohol Abuse and Alcoholism (NIAAA) defines binge drinking as periods of five or more drinks for males and four or more for women. This type of drinking is becoming increasingly common. According to a 2010 Centres for Disease Control survey, 1 in 6 US people, or around 38 million, binge drink. It's especially alarming when young folks engage in binge drinking. About half of college students said they had gotten drunk on a regular basis.[50]Young adult binge drinking increases the likelihood of alcohol misuse and dependency in later life, which increases the chance of developing ALD.[51]Younger women who are more likely to binge drink than drink regularly are more sensitive to the harmful consequences of alcohol since women are more prone to ALD and the gender gap in consumption is closing. It's interesting to note that high levels of

binge drinking in female mice may be influenced by female hormones, according to experimental animal models.[52]These findings are in line with earlier research that shown that reducing the amount of female hormones in mice' blood decreases their intake of alcohol.[53] Although this conclusion is debatable, epidemiological statistics point to a possible correlation between binge drinking and rising incidence of cirrhosis and cirrhosis-related mortality.[54]Acute alcohol intoxication and recurrent binge drinking have been found to worsen liver injury, including Kupffer cell activation, increased intestinal permeability, elevated cytokine production, increased oxidative stress, mitochondrial dysfunction, and hepatic apoptosis, through intra- and extrahepatic changes.[55,56,57,58]There are limits to the research looking at the pathophysiological consequences of binge drinking on the liver. To assess the extent to which this pattern of drinking exacerbates liver impairment, more research is required to determine the kind of alcohol drank during each binge and the frequency of binges.

Table 1 illustrates the varying alcohol concentrations of several alcoholic beverages, making it easier to determine how much alcohol is consumed by sipping various beverages.

Beverage type	**Serving size (fl oz)**	**ABV (%)**	**Energy (Cal)**
Beer			
Light	12	5	103
Regular			153
Malt	8–9	7	93
Table wine	5	12	121–125
Champagne	4	12	84
Sake	3.5–4.0	16	140
Fortified wine	3–4	17	Varies
Cordial, Liqueur, Aperitif	2–3	24	Varies
Distilled spirits			
Vodka, Rum, Tequila, Gin, Cognac, Brandy	1.5	40	97–98

Diagnostic tests for ALD.

- •Relation AST/ALT = 1.5 to 2
- •Elevation of GGT
- •Albumin diminished
- •Thrombin time prolongation
- •Elevation of medium corpuscular volume
- •Thrombocytopenia

INTESTINAL MICROBIOTA/ GUT MICROBIOTA

Numerous liver illnesses, such as ALD, nonalcoholic fatty liver disease (NAFLD), and hepatocellular carcinoma (HCC), are influenced by the gut flora.[59,60,61,62,63]It has been demonstrated that some substances prevent liver damage by controlling gut flora. Ganoderic acid A has been shown by LV et al. to enhance lipid metabolism and alter the makeup of the intestinal microbiota, which attenuates ALD.[64]Hippophaerhamnoides L. flavonoid extract can reduce ALD by regulating the imbalance of the gut flora.[65]

According to the previously described research, gut microbiota may present a viable treatment target for ALD. The purpose of this study is to investigate how riboflavin affects ALD and how this modification in gut microbiota homeostasis is connected.

PATHOLOGY

The liver has a very restricted ability to respond to any kind of damage. The first and most typical histologic reaction to hepatotoxic stimuli is fatty liver, which is caused by consuming alcohol in excess. Alcohol dehydrogenase is the primary enzyme involved in alcohol metabolism, and its presence really corresponds with the accumulation of fat within perivenular hepatocytes. Drinking alcohol continuously causes fat to build up across the whole hepatic lobule.[66]Stopping drinking causes the hepatic architecture and fat content inside the liver to return to normal, despite the fact that the large fatty alteration distorts the hepatocytes and accumulates macrovesicular fat.[67]

Although ALD is thought to be a completely benign process, some pathologic characteristics, such as giant mitochondria, macrovesicular fat, and perivenular fibrosis, are similar to those of nonalcoholic steatohepatitis and may indicate the development of additional chronic liver injury.[68,69]It is unclear how liver damage advances from the fatty liver stage to the alcoholic-associated hepatitis stage. Alcoholic hepatitis is primarily defined by damage to the hepatocytes, which includes patches of necrosis, ballooning degeneration, polymorphonuclear cell infiltration, and fibrotic zones that either bridge or occur in the perivenular, perisinusoidal, or Disse space.[70]

Mallory bodies may be seen in florid instances, although these are not specific nor required to make the diagnosis. Alcoholic hepatitis is a prelude to the development of cirrhosis. But if alcohol consumption is stopped, fatty liver and alcoholic hepatitis may be curable.[71]Alcoholic hepatitis is observed in half of the population with liver cirrhosis, and even complete abstinence from alcohol does not cure cirrhosis once it has started. Nonetheless, abstinence can stop the illness from getting worse.[72]

THE SPECTRUM AND CLINOCOLOGY OF ALD

1. **Alcoholic fatty liver:**

As previously noted, 90% of heavy drinkers develop alcoholic liver steatosis, the initial stage of ALD. Alcoholic steatosis patients have slightly elevated blood levels of AST, ALT, and gamma-glutamyl transferase, as well as an AST/ALT ratio of greater than 2, even if they do not exhibit any major clinical symptoms. The metabolic syndrome, which encompasses obesity, diabetes, hypertension, and hyperlipidaemia, is frequently coexisting with ALD. The advancement of ALD is influenced separately by the existence of metabolic syndrome and a

history of severe alcohol use. Hepatocyte cytosol has a considerable number of tiny and large-sized lipid droplets, according to the histology of tissues with alcoholic steatosis. The centrilobular zone (zone 3) is where these alterations start, and they then move into zones 2 and 1 (periportal zone).[73]Reversing these alterations requires abstinence for 4-6 weeks.[74]

2. **Alcoholic steatohepatitis, fibrosis, and cirrhosis:**
   Between 20% and 40% of heavy drinkers develop fibrosis and steatohepatitis after developing alcoholic steatosis. Histologically, alcoholic steatohepatitis and fibrosis is characterised by perivenular and pericellular fibrosis, cholestatic alterations, megamitochondria, hepatocyte ballooning, necrosis, and neutrophil infiltration.[75]Due to zone 3's greater cytochrome P450 2E1 (CYP2E1) expression than other zones, these pathological alterations begin there and move towards the adjacent central vein or the portal vein region (zone 1). Alcoholic steatohepatitis (AH) is a condition in which patients either show no symptoms at all (subclinical AH) or exhibit significant clinical symptoms. 8% to 20% of fibrosis patients—including those who have no symptoms—will progress to cirrhosis.In the United States, alcohol misuse accounts for 44%–48% of all cirrhosis-mediated fatalities, making it the major cause of mortality from the disease, even more so than HCV.[76]Direct acting antivirals are quite efficient in treating the hepatitis B and C virus, therefore in the near future, ALD and NAFLD will probably be the most common reasons to consider liver transplantation. Large alcohol use is linked to the development of HCC, and one important risk factor for this disease is alcoholic cirrhosis. HCC incidence during a ten-year period can range from 6.8% to 28.7%.[77,78,79,80]

3. **AH:**
   Overconsumption of ethanol (>100 g/day) might result in acute clinical syndrome (AH), a manifestation of ALD. Severe clinical signs, such as fever, jaundice, ascites, hepatic encephalopathy, gastrointestinal tract bleeding from esophageal varices, and gastro-duodenal ulcers, are prevalent in patients with severe AH. Even though AH can appear at any point during ALD, individuals with alcoholic cirrhosis (an acute-on-chronic illness) account for 40% of AH cases and 80% of severe cases. When compared to AH patients with steatosis alone, these individuals have an extremely dismal prognosis.[81]The model for end-stage liver disease (MELD) score, Maddrey's discriminant function (MDF) score, prothrombin time (PT)/international normalised ratio (INR), serum creatinine levels, and AH severity were all shown to be correlated by the American Association for the Study of Liver Diseases (AASLD) guidelines. An MDF score of >32 or a MELD score of >18 indicates severe AH. With this disease, the 1-month death rate might reach 30%–50%. Seventy percent of individuals who make it to six months will develop cirrhosis.[82,83]

   There are several histological characteristics linked to AH outcomes. Despite neutrophils being a major factor in increasing alcohol-induced liver inflammation, neutrophil accumulation was linked to improved outcomes in individuals with severe acute haemolysis.[81]The presence of proliferating hepatocytes and a reduced regenerative response were linked to a better and worse prognosis, respectively.[84,85]Furthermore, ductular responses and proliferative hepatic progenitor cells were linked to a worse outcome.[86]In severe AH patients, 123 genes were shown to be linked to survival in a recent research. Of the 123

dysregulated genes, 72 were linked to patients with alcoholic cirrhosis or non-severe AH, while 51 were linked to patients with severe AH with a bad prognosis. This study shown that whereas interleukin (IL)-33 and fibroblast growth factor (FGF) 21 were related with improved prognoses, lipocalin-2 (LCN2), interleukin 1 receptor like 1 (IL1RL1), C-X-C motif chemokine ligand (CXCL) 1, CXCL2, and keratin 19 (KRT19) were associated with worse prognoses.[87]

EXISTING AND POTENTIAL THERAPIES FOR ALD

1. ABSTINENCE AND SUPPORTIVE CARE:

For people with ALD, abstinence is the most popular prophylactic strategy. In individuals with early-stage ALD, abstinence can ameliorate liver steatosis, damage, and unfavourable outcomes. Nonetheless, abstinence does not prevent certain individuals with progressing ALD from developing cirrhosis.[88]ALD patients can only take a limited number of FDA-approved drugs (such as naltrexone and disulfiram) for AUD because they frequently produce hepatoxic effects. With less hepatotoxic side effects, baclofen and metadoxine can successfully prevent relapses in alcohol use; however, the FDA has not authorised these medications for this purpose.[89]Weight control and nutritional support (e.g., ∼2000 kcal with 1.2–1.5 g/kg/d protein and supplementation with amino acids (branched, leucine), zinc, vitamin D, thiamine, folate, cyanocobalamin, and selenium) can improve the course of ALD because obesity, sarcopenia, and malnutrition are linked to the disease.[90,91]

2. CORTICOSTEROIDS:

For many years, people with AH have been treated with corticosteroids. In AH, corticosteroids decrease TNFα production and increase IL-10 production, which lowers the risk of encephalopathy and short-term death.[92]These actions, however, have no positive long-term survival effects.[82,93]Early detection of severe AH responsive to corticosteroids is crucial, since these drugs have the potential to increase survival in the near term. After seven days of medication, the Lille model was created to assess how well severe AH patients responded to corticosteroids. In patients with severe AH, the Lille model is helpful in forecasting short-term survival. According to this model, the 6-month death rate for patients with severe AH is almost 75%, and 40% of them do not react to corticosteroids.[94]The elevated risk of infection (pneumonia, urinary tract infection, spontaneous bacterial peritonitis) brought on by corticosteroid use may be the cause of the high death rate; patients treated with corticosteroids who develop an infection have a much reduced chance of surviving than those who do not.[95]

3. N-acetylcysteine (NAC):

Antioxidant glutathione precursor NAC is frequently utilised in clinical settings to treat acute liver failure brought on by paracetamol.[96]NAC has been researched as an ALD therapy since ROS is essential to the disease's development. In contrast to corticosteroids alone, treating severe AH with NAC alone did not increase short-term survival. In contrast, there was no

discernible long-term survival advantage with combination treatment utilising NAC and corticosteroids, although it did considerably enhance 28-day survival.[97,98]

4. **Pentoxifylline:**
   Patients with severe acute lung injury have been studied for pentoxifylline, an antioxidant with an anti-TNFα action. Pentoxifylline medication alone did not significantly improve long-term survival when compared to corticosteroids, much like NAC did. Not even in conjunction with corticosteroids did pentoxifylline significantly increase survival. Pentoxifylline is therefore no longer regarded as a therapy option for severe AH.[99]

5. **Anti-TNFα antibodies:**
   One of the most important inflammatory cytokines for the development of ALD is TNFα. Anti-TNFα treatment, including chimeric monoclonal anti-TNFα antibody infliximab, is frequently used to treat inflammatory bowel disease and arthritis; it may also have potential benefits for ALD. Anti-TNFα antibody therapy for severe AH patients improved both disease severity and survival, according to clinical research.[100]Furthermore, improvements in the severity of AH were noted at 28 days in a randomised controlled pilot research with infliximab plus corticosteroids.[101]Nevertheless, among patients with acute AH, this combination unexpectedly revealed increased infection and fatality rates.[102]
6. **Liver transplantation:**
   At 25% of all liver transplant surgeries, alcoholic cirrhosis is the second most common reason for the procedure.[103]For individuals with severe AH who do not respond to corticosteroids, liver transplantation remains the most effective course of therapy. However, due to moral conundrums, a significant risk of alcohol relapse, and the 6-month abstinence requirement, the majority of AH patients are not eligible to apply for liver transplantation. According to recent reports, liver transplants that were carried out before the six months of abstinence were up for review. When compared to comparable AH patients who did not receive a liver transplant, early liver transplantation showed a higher long-term survival rate (1-3 years) and a similar survival rate to patients with alcoholic cirrhosis who had a liver transplant after 6 months of abstinence.
   Research found no differences in the rate of alcohol relapse between patients who fulfilled the 6-month abstinence requirement and those who did not. According to these research, physicians might want to reevaluate how severe AH patients are selected for early liver transplantation.[104,105,106]

CONCLUSION:

A thorough knowledge of ALD's molecular processes is necessary to generate future therapeutics that work, and translational research utilising human specimens will be essential to this effort. Consistent animal models must also be used for testing novel treatments. Regretfully, the animal models of ALD that are now available do not accurately replicate all of its characteristics, including alcoholic cirrhosis and AH. Thus, enhanced animal models are also essential for the creation of successful treatments. The current therapy approaches for ALD were established some decades ago.

While liver transplantation and corticosteroids remain the cornerstones of treatment, other therapeutic modalities have to be explored. A clinical trial is now being conducted to assess an extracorporeal human cell-based liver support system for severe acute hepatic impairment (AH) and alcohol-induced liver decompensation.

The protective effect of riboflavin against ALD was linked to intestinal microbiota homeostasis, and this protective impact was linked to the regulatory influence on inflammatory cell infiltration. For ALD, riboflavin has the potential to be a useful agent.

This approach may improve survival for patients with decompensated ALD who are unsuitable for liver transplantation and who do not respond to corticosteroids, but more prospective, randomised, controlled clinical studies in patients with lower MELD scores and age are required to assess the reproducibility of this observation. Effective anti-inflammatory medications and liver support systems may one day increase the prognosis for alcoholic cirrhosis and high-mortality acute hepatitis. The survival rate would rise much more if treatments that promote liver regeneration could be added to this mix. Recent trials on early liver transplantation have demonstrated outstanding results, which provides evidence to reevaluate the selection strategy for individuals with severe AH.

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