

MANUSCRIPT EDITING SAMPLE WORK

**ALCOHOL-RELATED LIVER DISEASE:
CLINICAL BURDEN, PATHOPHYSIOLOGY,
AND MANAGEMENT STRATEGIES**

Alcohol-Related Liver Disease: Clinical Burden, Pathophysiology, and Management Strategies

Abstract

Worldwide, alcohol-related liver disease (ALD) is one of the leading causes of morbidity and mortality. It represents many liver-related deaths and disability. The spectrum of ALD includes simple steatosis, alcoholic hepatitis, Fibrosis, Cirrhosis, and Hepatocellular Carcinoma. The progression of the disease is affected by the quantity and the pattern of alcohol consumption, genetic predisposition, coexisting conditions, and social environmental factors. The early diagnosis of ALD as well as intervention to treat alcohol use disorder (AUD) and effective treatment significantly reduce the chance of disease progression and enhance outcomes. Effective public health policies such as taxation, minimum unit pricing for alcohol, and limiting the supply of alcohol must be developed to alleviate the burden of ALD on a population. Improving our knowledge of the epidemiology, pathophysiology, clinical presentation and diagnosis, and treatment of ALD as well as describing the challenges and future research directions are the primary objectives of this review.

1. Introduction

An excessive amount of alcohol consumption is one of the most common preventable causes of premature death **around the world**[TS1] . [1,2] **Alcohol use** [TS2] leads to 5.3% of all premature deaths, as well as 5.1% of lost productive years due to disability (or Disability-Adjusted Life Years, or DALYs). Most alcohol use occurs among the young economically productive population (ages 15 to 44); these are the most economically productive people in society. Besides liver disease and liver damage caused by excessive alcohol consumption, many alcohol-related health conditions include heart disease, certain cancers, injuries, and mental illness.[2] Alcohol-induced liver disease (ALD) is still one of the primary causes of cirrhosis in Europe, North America, and Latin America.

Comments :

Consider shortening “around the world” to “worldwide” for conciseness.

Comments :

“Alcohol use” should be corrected to “alcohol addiction” for accuracy.

[3] In contrast, viral hepatitis is the leading cause of cirrhosis in Southeast Asia, Africa, and the Eastern Mediterranean (areas with significant numbers of liver disease cases). ALD is still one of the diseases that has been least studied in terms of the associated morbidity and mortality and therefore requires urgent attention to clinical and public health interventions that will help prevent ALD through early intervention, treatment, and supportive care services.[4].

2. Etiology

ALD is a complex disorder that has a multitude of risk factors influencing its course. It is influenced by numerous behavioral, environmental, and genetic factors.[5] The primary risk factor for the development of ALD is chronic and excessive alcohol use, which is directly related to the quantity and the pattern of alcohol consumption. Daily use leads to continuously elevated levels of acetaldehyde **around the hepatocytes**[TS1] , which activates cytochrome P450 2E1 and leads to the production of reactive oxygen species (ROS), ultimately resulting in oxidative stress.[6] **On the other hand**[TS2] , both binge drinking and heavy episodic drinking could worsen liver damage.[7]

Obesity, insulin resistance, type 2 diabetes, and hepatitis are additional environmental factors that increase the likelihood of developing ALD. [8] In addition, lifestyle choices such as smoking and poor dietary habits can also make ALD worse. In addition to these factors, there is evidence that people carry certain genetic variations that may make them more or less susceptible to developing fibrosis and/or cirrhosis, as well as that genetic predisposition and epigenetic regulation may also create heterogeneity in the overall disease.[9,10,11] The interaction of these factors may explain why not all people who are heavy drinkers develop advanced liver disease.

Comments :

Revise "around the hepatocytes" to "within hepatocytes" to improve anatomical accuracy

Comments :

Use "Additionally" instead of "On the other hand" for logical flow

3. Pathophysiology

The pathophysiology of Alcoholic Liver Disease (ALD) is very comprehensive and broad, with many intricate details involved, including: Ethanol metabolism and oxidative stress; Immune system dysfunction caused by Alcohol, including Interleukin-6 and TNF-alpha; Fibrotic response of the liver cells through stellate cell activation; Kupffer cells (i.e. macrophages that are activated by Alcohol); and neutrophil response to Alcoholic hepatitis. Ethanol is broken down to Acetaldehyde, a **Hepatotoxin intermediate**[TS1] , through the action of alcohol dehydrogenase (ADH), Acetaldehyde on action of cytochrome P450 2E1 generates ROS. This hepatotoxin causes an inflammatory response, which causes stellate cell activation leading to Extra Cellular Matrix deposition and fibrosis. The chronic influx of alcohol results in the **activation of Kupffer cells**[TS2] . When combined with neutrophil infiltration it leads to hepatocyte injury and development of alcoholic hepatitis, these processes invariably lead to the development of cirrhosis and portal hypertension, and thus the increased risk of hepatocellular carcinoma. [12,13]

4. Clinical Spectrum

ALD develops through a continuum, starting with asymptomatic steatosis that affects approximately 90-95% of those who are heavy drinkers and resolves with abstinence. Alcoholic hepatitis (AH) is an acute inflammatory illness with symptoms including jaundice, hepatomegaly, elevation in transaminase levels, and systemic inflammation; with severe cases associated with a three-month mortality rate of 30-40%. Chronic disease results in Fibrosis, cirrhosis, and complications of ascites, variceal bleeding, hepatic encephalopathy, and **HCC**[TS1] . Additionally, the presence of metabolic dysfunction can speed up the advancement of ALD, which has recently been **labelled as MetALD** [TS2] where metabolic dysfunction and alcohol are both causes of liver disease.

Comments :

Convert 'Hepatotoxin intermediate' to 'Hepatotoxic intermediate' to match standard scientific terminology

Comments :

consider specifying "resident liver macrophages (Kupffer cells)" for clarity for readers unfamiliar with the term

Comments :

consider adding the full form of "HCC" for clarity for readers unfamiliar with the abbreviation.

Comments :

Revise "labelled as MetALD" to "termed MetALD" for clearer expression and to emphasize the conceptual definition.

5. Diagnosis

ALD must be diagnosed at the earliest time possible to provide effective treatment and prevent the severe complications associated with advanced liver disease. A multifactorial approach is encouraged to diagnose ALD that includes a thorough clinical history or assessment and physical examination[TS1] of a patient, laboratory testing, imaging techniques, and, when appropriate, a liver biopsy.

- The patient's alcohol consumption history should include an accurate record of how much alcohol the patient has consumed over what period of time as well as how often the patient consumes alcohol.
- During the physical examination, physical signs of ALD can be seen such as jaundice, hepatomegaly, spider angiomas, palmar erythema, and signs of portal hypertension.
- The laboratory results for ALD generally show an elevated AST-to-ALT ratio > 2:1, elevated GGT levels, and macrocytosis.[12]
- The use of imaging methods, such as ultrasound, CT, MRI, and transient elastography, are helpful in assessing for the presence of steatosis, fibrosis, and cirrhosis of the liver; however, liver biopsy would still provide the most accurate information regarding the diagnosis of alcoholic hepatitis and the assessment of hepatic fibrosis in any atypical or severe cases.
- A validated screening tool (AUDIT, AUDIT-C, or CAGE) can be used to screen for AUD, which must meet DSM-5 criteria for diagnosis. A high number of patients diagnosed with ALD have not been diagnosed until late stage[TS2], indicating a need for the development and implementation of systematic early screening programs for AUD, especially in those at high risk of developing alcohol-related liver disease (ARLD) due to excessive drinking.[4]

Comments :

Revise "includes a thorough clinical history or assessment and physical examination " to "including clinical history, physical examination" for conciseness and clarity

Comments :

Revise "have not been diagnosed until late stage" to "are often diagnosed at a later stage" for smoother flow; consider splitting the sentence for clarity

6. Management

6.1 Life-style Modification

Alcohol abstinence is the cornerstone of ALD management across all disease stages. Complete cessation is the best way to halt the disease process and to reverse steatosis and fibrosis **at an early point**[TS1] . All patients with ALD may require supplementing their diets with Thiamine, Folate, Zink, and Protein supplements, particularly if they are malnourished.[12]

6.2 Pharmacotherapy

Currently, [TS2] three drugs are approved by the FDA to treat alcohol use disorder (AUD): disulfiram, acamprosate, and naltrexone. Disulfiram has been studied as a deterrent; when taken, disulfiram results in the accumulation of acetaldehyde (toxic) from the alcohol consumed. Acamprosate works on decreasing cravings for alcohol and naltrexone, an opioid antagonist, has been shown to lower the rate of relapse. Gabapentin, Baclofen and Topiramate have been studied for off label use, and there is significant variability in results. The use of pharmacotherapy decreases alcohol consumption and decreases the chance of decompensation of the liver, resulting in a longer life for patients with cirrhosis. Despite this evidence, these agents are under-utilized; the treatment rate is very low. Baclofen has been shown in randomized, controlled clinical trials in patients with cirrhosis to be an effective option for maintaining abstinence from alcohol with minimal hepatic toxicities.[13]

6.3 Management of Alcoholic Hepatitis

Patients with severe acute alcoholic hepatitis (AAH) will need a complete formal assessment, usually done through Maddrey's discriminant function or MELD scoring before proceeding. Supportive care is an integral component of primary management of AAH. Corticosteroids (prednisolone preferred) are effective in the treatment of AAH and significantly decrease [TS1] short-term mortality from AAH. As well, patients who do not incrementally respond to traditional medical therapies may benefit from Liver transplantation although strict selection criteria are applied. [14,15]

Comments :

consider revising "at an early point" to "in the early stages" for clarity.

Comments :

Remove " Currently, " for Conciseness

Comments :

Revise "treatment of AAH and significantly decrease short-term mortality from AAH" to " treating AAH and significantly reduce short-term mortality" to avoid repetition and improve readability

6.4 Management of Cirrhosis and Complications

Management of Cirrhosis include management of portal hypertension (by means of beta-blockers or endoscopic ligation)[TS1] , management of ascites (by means of sodium restriction and/or diuretics) and management of hepatic encephalopathy (usually by lactulose and/or rifaximin). In cirrhosis patients, ultrasound and alpha-fetoprotein should be performed every 6 months to assess for (HCC. A multidisciplinary team approach to cirrhosis management that incorporates all aspects of AAH (hepatology, addiction medicine, nutrition and mental health) is recommended.[Z]

7.Public Health and Prevention

To successfully alleviate the population burden associated with ALD, there must be a comprehensive public health strategy. The World Health Organization (WHO) has established the SAFER initiative promoting evidence-based methods for reducing alcohol consumption through restricting availability of alcohol, this includes; [TS1] Strengthening enforcement of drunk driving laws, improving access to screening and treatment for AUD, banning advertising of alcoholic beverages, and Increasing tax rates on alcohol or establishing a minimum unit price for alcohol. Research shows that all these interventions have proven to [TS2] produce significant reductions in alcohol use and alcohol-related deaths.

The COVID-19 pandemic has further revealed how vulnerable individuals with AUD are and how much we need to focus on improving prevention and early intervention, along with creating a solid and effective public health infrastructure in our communities to reduce alcohol-related harm.

Comments :

Change 'include management of' and 'by means of' to 'includes management of' and 'using' to correct subject-verb agreement and to streamline clinical language

Comments :

revise semicolon after "includes" to a colon for proper punctuation; consider converting the list to bullet points or parallel structure to improve readability and visual clarity

Comments :

revise "have proven to produce" to "significantly reduce" for a stronger active voice

8.Future Directions

The research agenda for alcohol-related disorders includes determining how alcohol-related liver disease progresses; assessing long-term effects of ALD pharmacological treatment; and, most importantly, optimizing population-based approaches to managing these disorders. High-risk individuals may be identified through the integration of **genetic and epigenetic data**[TS1] into the context of precision medicine. The establishment of integrated care models that connect primary care, hepatology, and addiction treatment programs can assist with early intervention, enhancing patients' compliance with treatments, as well as elimination or reduction of complications.

9.Conclusion

Liver disease caused by alcohol is completely preventable yet is becoming a **growingly common** [TS1] cause of morbidity and mortality all over the globe. There are multiple factors involved in the development and progression of liver disease due to alcohol, including behavioural issues, genetics, and metabolic issues. The sooner the disease can be diagnosed and treated, the better would be the outcome for the patient. Public health efforts to decrease the overall burden of society from alcohol-related liver disease, including taxes, advertising restrictions, and minimum unit prices for alcohol, are essential in this regard. Strengthening research, resource allocation, and integrated care approaches is vital to address the growing global challenge posed by ALD.

Comments :

consider specifying "genetic and epigenetic markers" instead of "data" to increase scientific precision

Comments :

revise "growingly common" to "increasingly common" to align with standard epidemiological language