ALCOHOLIC LIVER DISEASE UNVEILED: EPIDEMIOLOGY, CAUSES, MECHANISMS, AND LIFELONG IMPACT

AKHIL AKKENAPALLY, RITHIKA SHATRASHI, KEERTHIJA REDDY KOMMIDI, MAHESH AVULA, TEJASRI MAHALAXMI PANALA, SREEJA DODDA, NARENDER BOGGULA*

Omega College of Pharmacy, Edulabad, Ghatkesar, Hyderabad, Telangana, India.

Corresponding author:

Dr. NARENDER BOGGULA

Associate Professor,

Omega College of Pharmacy,

Edulabad, Ghatkesar, Hyderabad, Telangana, India - 501 301.

E-Mail: drnarenderboggula@gmail.com

Mobile: +91 9666 55 2211

ABSTRACT

Alcoholic liver disease (ALD) is a major global health concern caused by chronic excessive alcohol consumption, manifesting as a spectrum of disorders from steatosis to alcoholic hepatitis, fibrosis, and cirrhosis. This article provides an overview of ALD, addressing its epidemiology, etiology, pathophysiology, and consequences. Epidemiologically, alcohol affects millions worldwide, with prevalence tied to alcohol consumption patterns, peaking in regions like Eastern Europe and among men aged 40-60, though women are more susceptible at lower doses. Etiologically, ALD results from prolonged heavy drinking, modulated by genetic polymorphisms (e.g., ALDH2, PNPLA3), gender, malnutrition, and comorbidities like hepatitis C. The pathophysiology involves a cascade of alcohol metabolism-induced oxidative stress, acetaldehyde toxicity, and inflammation, progressing from reversible steatosis to severe alcoholic hepatitis and irreversible cirrhosis. Key mechanisms include reactive oxygen species generation, cytokine-mediated inflammation via gut-liver axis disruption, and hepatic stellate cell activation driving fibrogenesis. The consequences are profound, encompassing liver-related complications (e.g., portal hypertension, hepatocellular carcinoma), systemic effects (e.g., infections, cardiovascular disease), and significant economic and social burdens due to healthcare costs and reduced quality of life. Early stages of ALD are reversible with abstinence, but advanced disease requires complex interventions like transplantation. This article underscores the need for public health strategies to reduce harmful alcohol use, enhance screening, and improve access to addiction treatment to mitigate alcohol's impact. By elucidating the multifaceted nature of ALD, we aim to inform prevention and management efforts.

Key words: Alcoholic liver disease, portal hypertension, cytokine-mediated inflammation, hepatocellular carcinoma.

INTRODUCTION

Excessive alcohol consumption is a global healthcare problem with enormous social, economic, and clinical consequences, accounting for 3.3 million deaths in 2012. Excessive drinking over decades damages nearly every organ in the body. However, the liver sustains the earliest and the greatest degree of tissue injury from excessive drinking because it is the primary site of ethanol metabolism. Alcoholic liver disease (ALD) encompasses a spectrum of liver disorders caused by excessive alcohol consumption, ranging from steatosis (fatty liver) to alcoholic hepatitis, fibrosis, which is a major cause of liver-related morbidity and mortality worldwide, and ALD represents a significant public health challenge. The liver, a vital organ for metabolism, detoxification, and nutrient storage, is particularly vulnerable to alcohol's toxic effects of alcohol. Chronic alcohol use disrupts hepatic function, leading to progressive damage that can culminate in life-threatening complications, such as liver failure or hepatocellular carcinoma.

ALD's impact extends beyond the individual, straining healthcare systems and economies due to its association with hospitalizations, long-term care, and reduced productivity. Despite its preventability, alcohol

remains prevalent due to social, cultural, and behavioural factors surrounding alcohol use. This article explores ALD through its epidemiology, etiology, pathophysiology, and consequences, with a detailed examination of disease progression in the pathophysiology section. By understanding these aspects, we aim to highlight the importance of prevention, early diagnosis, and intervention in mitigating ALS's burden [1,2].

Epidemiology

Alcohol is a global health issue, with prevalence varying by region, alcohol consumption patterns, and socioeconomic factors. According to the World Health Organization (WHO), harmful alcohol use contributes to approximately 5.3% of global deaths, with liver disease accounting for a significant portion. In 2020, the WHO estimated that alcohol-related liver diseases caused over 400,000 deaths annually, with alcohol being a leading contributor.

The prevalence of alcohol correlates closely with per capita alcohol consumption. In high-income countries like the United States and European nations, where alcohol consumption is widespread, alcohol is a major cause of liver disease. In the U.S., approximately 30% of adults engage in heavy drinking (defined as 14 drinks/week for men or >7 drinks/week for women), and alcohol abuse affects 10-20% of chronic heavy drinkers. Men are disproportionately affected due to higher alcohol consumption rates, though women are more susceptible to liver damage at lower doses due to physiological differences in alcohol metabolism.

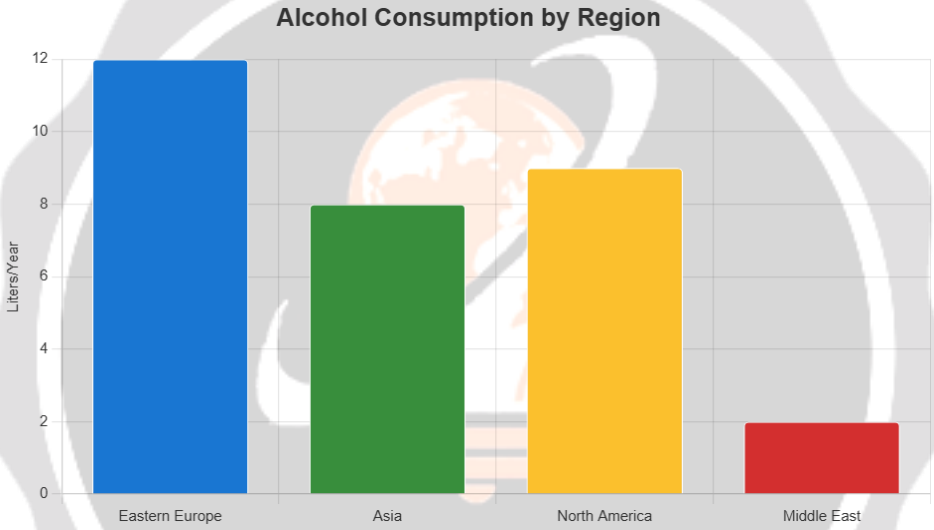

Figure 1: Alcohol consumption by region

Geographically, Eastern Europe and parts of Asia report higher alcohol prevalence due to cultural drinking norms, while lower rates are observed in regions with religious or legal restrictions on alcohol, such as parts of the Middle East. Socioeconomic factors, including poverty and lack of healthcare access, exacerbate ALS's burden, as delayed diagnosis and treatment worsen outcomes. Age also plays a role, with peak incidence occurring in adults aged 40-60, reflecting cumulative alcohol exposure.

Epidemiological data on ALD are limited by underdiagnosis, as early stages (e.g., steatosis) are often asymptomatic. Autopsy studies suggest that up to 70% of heavy drinkers have some degree of liver steatosis, but only 20-30% progress to severe forms like cirrhosis. These statistics underscore the need for improved screening and public health interventions to address the global impact of ALD [3-6].

Etiology

The primary cause of alcoholism is chronic, excessive alcohol consumption, defined as >30 grams/day (approximately 2-3 standard drinks) for men and >20 grams/day for women over several years. However, not all heavy drinkers develop alcoholism, indicating a multifactorial etiology involving genetic, environmental, and behavioural factors.

Quantity and duration of the patient's alcohol intake are the highest risk factors for the development of liver disease. The beverage type plays a minimal role. Women are more susceptible than men. Obesity and high-fat diet also increase the risk of alcoholic liver disease. Concurrent hepatitis C infection is associated with younger age of onset, more advanced histological damage, and decreased survival. Patatin-like phospholipase domain-containing protein 3 (PNPLAP3) is associated with alcoholic liver cirrhosis [7,8].

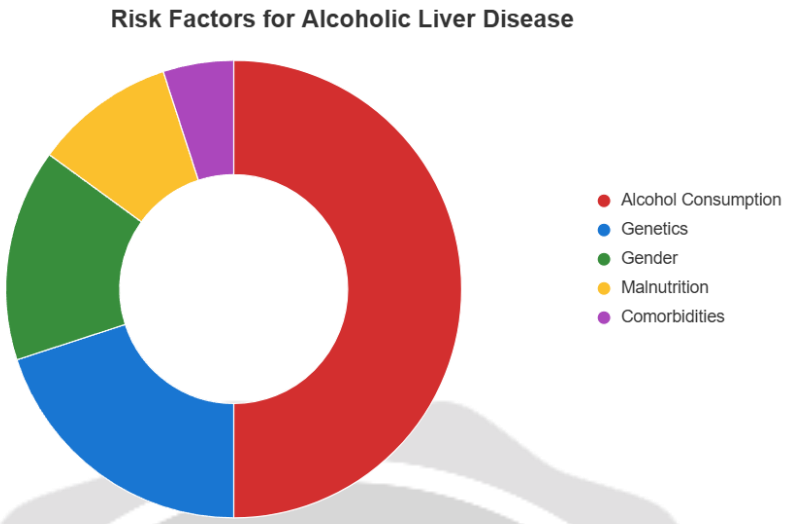

Figure 2: Risk factors for ALD

Alcohol consumption patterns

The quantity, frequency, and duration of alcohol intake are critical determinants. Binge drinking (consuming ≥5 drinks in one sitting for men or ≥4 for women) increases risk, as does continuous heavy drinking over decades. The type of alcohol (e.g., beer, wine, spirits) is less significant than total ethanol intake.

Genetic factors

Genetic predisposition influences ALD susceptibility. Polymorphisms in genes encoding alcohol-metabolizing enzymes, such as ALDH2 (aldehyde dehydrogenase 2), are associated with increased acetaldehyde accumulation, a toxic alcohol metabolite that exacerbates liver damage. Variants in the PNPLA3 and TM6SF2 genes are also linked to higher risks of steatosis and fibrosis in ALD.

Gender and physiological factors

Women are more vulnerable to alcohol due to lower body water content, reduced gastric alcohol dehydrogenase activity, and hormonal influences that enhance alcohol's hepatotoxicity. This results in faster progression to severe alcoholism at lower alcohol doses compared to men.

Environmental and lifestyle factors

Malnutrition, common in chronic alcoholics, exacerbates ALD by depleting antioxidants (e.g., glutathione) and impairing liver repair. Coexisting liver diseases, such as hepatitis C, synergistically worsen ALD outcomes. Obesity and metabolic syndrome also amplify steatosis and inflammation, accelerating the progression.

Socioeconomic and behavioural factors

Poverty, mental health disorders, and social stressors contribute to sustained heavy drinking, increasing the risk. Lack of access to healthcare delays diagnosis, allowing subclinical damage to progress [9-12].

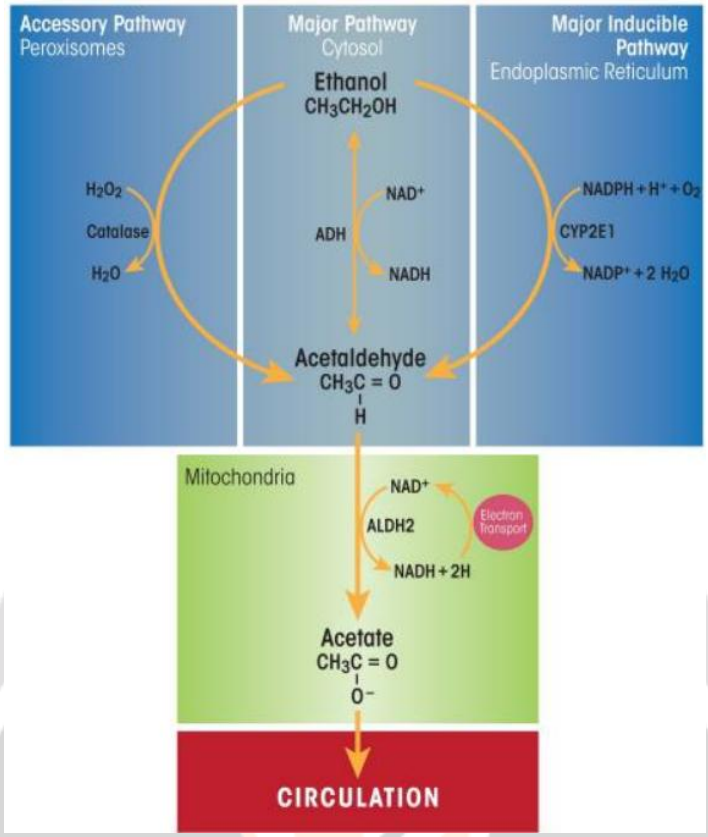

Figure 3: Major and minor ethanol-oxidizing pathways in the liver. Ethanol (i.e., ethyl alcohol) is oxidized principally in hepatocytes of the liver. (Middle panel) Alcohol dehydrogenase (ADH), a major enzyme in the cytosol, and aldehyde dehydrogenase 2 (ALDH2), which is located in the mitochondria, catalyze sequential oxidations that convert ethanol to acetate, producing two mole equivalents of reduced nicotinamide adenine dinucleotide (NADH). (Right panel) Cytochrome P450 2E1 (CYP2E1) is a major inducible oxidoreductase in the endoplasmic reticulum that oxidizes ethanol, in the presence of molecular oxygen (O_2), to acetaldehyde and converts reduced NAD phosphate (NADPH) to its oxidized form, generating water. (Left panel) Peroxisomal catalase is a minor hepatic pathway of ethanol oxidation that uses hydrogen peroxide (H_2O_2) to oxidize ethanol to acetaldehyde and water.

Pathophysiology

The pathophysiology of alcohol involves a complex interplay of alcohol metabolism, oxidative stress, inflammation, and fibrogenesis, leading to progressive liver damage. ALD develops through distinct stages. Each has its specific mechanism.

Steatosis → Alcoholic Hepatitis → Fibrosis → Cirrhosis

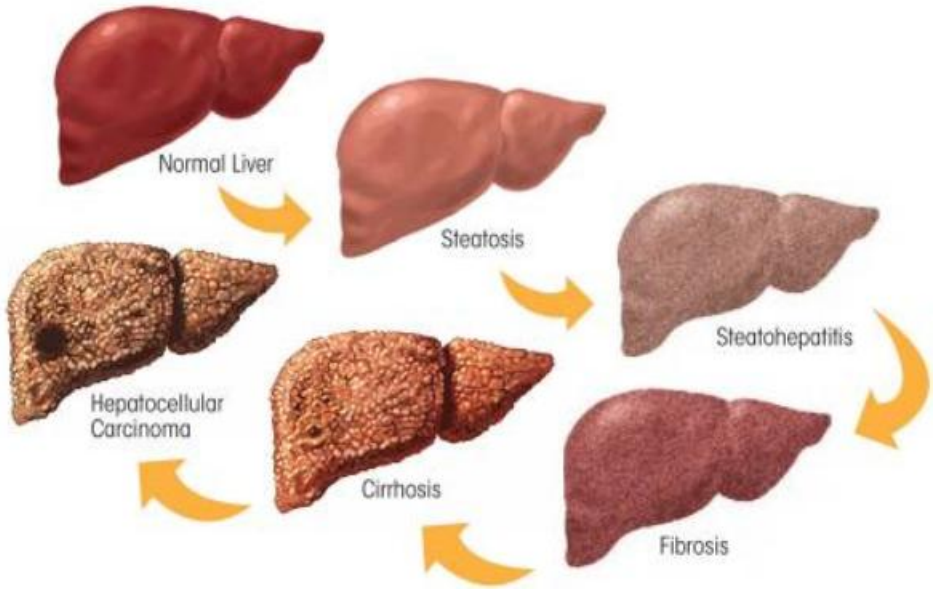

Figure 4: Spectrum of alcoholic liver disease. Heavy ethanol consumption produces a wide spectrum of hepatic lesions. Fatty liver (i.e., steatosis) is the earliest, most common response that develops in more than 90 percent of problem drinkers who consume 4 to 5 standard drinks per day. With continued drinking, alcoholic liver disease can proceed to liver inflammation (i.e., steatohepatitis), fibrosis, cirrhosis, and even liver cancer (i.e., hepatocellular carcinoma).

Alcohol metabolism and hepatotoxicity

Alcohol is metabolized primarily in the liver via dehydrogenase (ADH) and cytochrome P450 2E1 (CYP2E1). ADH converts ethanol to acetaldehyde, a highly reactive and toxic compound, which is then oxidized to acetate by aldehyde dehydrogenase (ALDH). Chronic alcohol consumption upregulates CYP2E1, increasing acetaldehyde production and generating reactive oxygen species (ROS). These ROS cause oxidative stress, damaging hepatocytes and mitochondrial membranes.

Acetaldehyde also forms adducts with proteins and DNA, impairing cellular function and triggering immune responses. Mitochondrial dysfunction reduces ATP production and fatty acid oxidation, leading to lipid accumulation in hepatocytes (steatosis), the earliest stage of ALD.

Steatosis (fatty liver)

Steatosis, observed in 90% of heavy drinkers, is characterized by triglyceride accumulation in hepatocytes. This results from:

- ✓ Increased lipogenesis: alcohol upregulates sterol regulatory element-binding protein 1C (SREBP-1C), promoting fatty acid synthesis.
- ✓ Impaired fatty acid oxidation: alcohol inhibits peroxisome proliferator-activated receptor-alpha (PPARα), reducing mitochondrial β-oxidation.
- ✓ Enhanced lipid uptake: alcohol increases hepatic uptake of circulating free fatty acids.
- ✓ Steatosis is reversible with abstinence but sets the stage for further damage if drinking continues.

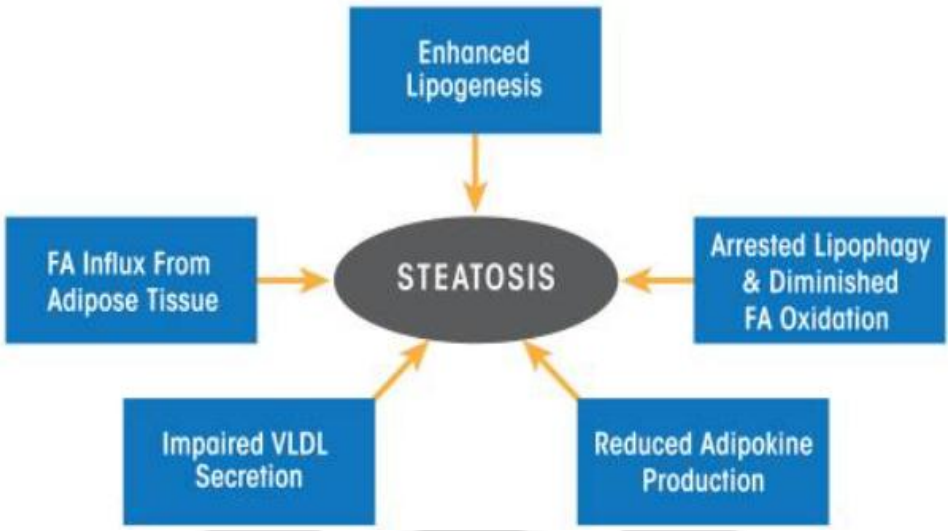

Figure 5: Hepatic and extrahepatic mechanisms that contribute to the development of alcoholic fatty liver (i.e., steatosis)

Alcoholic hepatitis

In 20-40% of heavy drinkers, steatosis progresses to alcoholic hepatitis, an inflammatory condition marked by hepatocyte injury and necrosis. Key mechanisms include:

- Oxidative stress: ROS and acetaldehyde damage hepatocytes, triggering apoptosis and necrosis.
- Inflammatory cytokines: alcohol disrupts gut barrier integrity, increasing gut-derived lipopolysaccharide (LPS) translocation. LPS activates Kupffer cells (hepatic macrophages) via Toll-like receptor 4 (TLR4), releasing pro-inflammatory cytokines (e.g., TNF-α, IL-6). These cytokines amplify inflammation and recruit neutrophils, causing further tissue damage.
- Endoplasmic reticulum (ER) stress: alcohol-induced protein misfolding in the ER activates the unfolded protein response, contributing to hepatocyte death.

Alcoholic hepatitis ranges from mild to severe, with severe cases presenting with jaundice, coagulation abnormalities, and high mortality (up to 40% in 6 months without treatment).

Fibrosis and cirrhosis

Chronic inflammation drives fibrosis, characterized by excessive extracellular matrix deposition. Activated hepatic stellate cells (HSCS) are central to this process and are stimulated by:

- TGF-β signaling: Transforming growth factor-beta (TGF-β), released by inflamed hepatocytes and Kupffer cells, activates HSCs.
- Oxidative stress: ROS further stimulates HSCs, perpetuating.
- Fibrosis progresses to cirrhosis in 10-20% of ALD patients, marked by nodular regeneration and loss of normal liver architecture. Cirrhosis impairs liver function, leading to portal hypertension, synthetic dysfunction (e.g., reduced albumin, clotting factors), and an increased risk of hepatocellular carcinoma (HCC) [2,13-16].

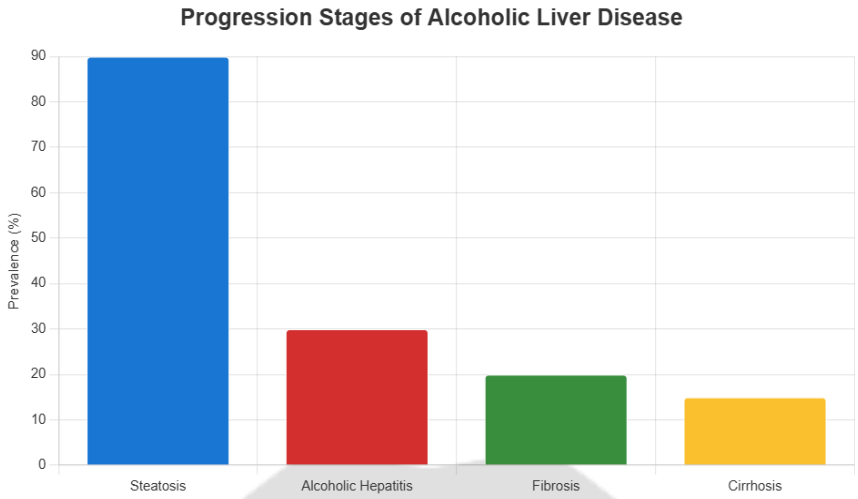

Figure 6: Progression stages of ALD

Consequences

ALD's consequences are profound, affecting individuals, healthcare systems, and society. These can be categorized into clinical, economic, and social impacts.

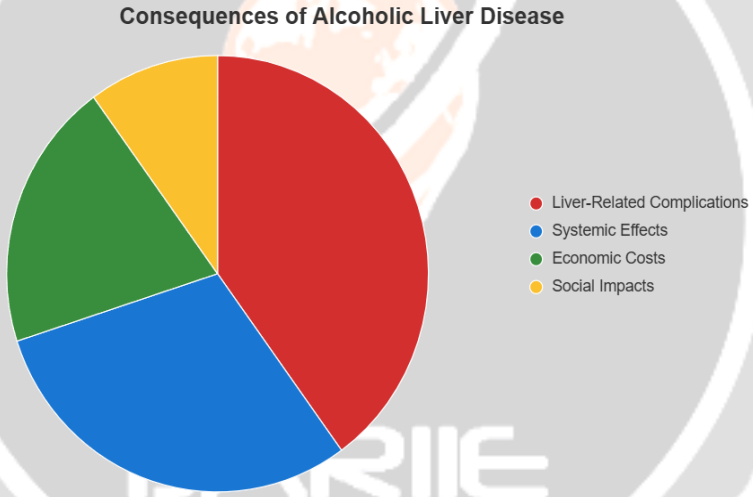

Figure 7: Consequences of ALD

Clinical consequences

Liver-related complications: cirrhosis leads to portal hypertension, causing variceal bleeding, ascites, and hepatic encephalopathy. Severe alcoholic hepatitis has a high short-term mortality rate. HCC, a late complication, develops in 1-2% of cirrhotic ALD patients annually.

- Systemic effects: Aldosterone increases the risks of infections (e.g., pneumonia, sepsis) due to immune suppression, cardiovascular disease, and acute kidney injury (e.g., hepatorenal syndrome).
- Mortality: ALD is a leading cause of liver-related death, with a 5-year survival rate of < 50% in decompensated cirrhosis.

Economic consequences

Ald imposes significant costs through hospitalizations, liver transplantation, and long-term care. In the U.S., alcohol-related liver diseases account for billions in annual healthcare expenditure. Lost productivity due to disability or premature death further amplifies the economic burdens.

Social consequences

Alcohol affects families and communities through increased healthcare dependency, reduced workforce participation, and stigma associated with alcoholism. Alcohol dependence often coexists with mental health disorders, exacerbating social isolation and reducing the quality of life.

Preventive and therapeutic challenges

The reversibility of early ALD (steatosis, mild hepatitis) with abstinence highlights the importance of early intervention. However, advanced stages require complex management, including corticosteroids for severe alcoholic hepatitis, liver transplantation for end-stage disease, and addressing alcohol dependence through behavioural therapy. Barriers to care such as limited access to addiction treatment [16-18].

Unconventional and herbal remedies

Patients often turn to natural and herbal therapies based on their potential for hepatoprotection. A U.S. survey revealed that 41 percent of patients with liver disease used some form of complementary and alternative medicine. An extract of milk-thistle seeds (silymarin) and garlic were reported as the most commonly used herbs for liver disease, followed by ginseng, green tea, gingko, echinacea, and St. John's wort. Other natural medicines, including betaine, curcumin, fenugreek seed polyphenol, LIV-52, vitamin E, and vitamin C, have shown efficacy in experimental models of alcoholic liver injury but must pass the rigors of large randomized, controlled clinical trials [2,3,19].

CONCLUSION

Alcoholic liver disease is a preventable yet devastating condition driven by chronic alcohol consumption and modulated by genetic, environmental, and lifestyle factors. Its epidemiology reflects global drinking patterns, with a significant prevalence in regions with high alcohol use. The etiology underscores the interplay of alcohol dose, genetics, and comorbidities, while the pathophysiology reveals a cascade of metabolic, inflammatory, and fibrotic processes culminating in severe liver damage. The consequences of alcohol-clinical, economic, and social-highlight the urgent need for public health strategies to reduce harmful alcohol use, improve screening, and enhance access to treatment. By addressing the root causes of AD and promoting early intervention, we can mitigate its profound impact on individuals and society.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Competing interest statement

All authors declare that there is no conflict of interests regarding publication of this paper.

Ethical approval

Not required.

Source of support

Nil.

REFERENCES

1. Hussen N, Zhu L, Tetangco E, Ellison S. Hepatoptosis in a Patient with Alcoholic Hepatitis. Am J Gastroenterol. 2018; 113(11):1581.
2. Osna NA, Donohue TM Jr, Kharbanda KK. Alcoholic Liver Disease: Pathogenesis and Current Management. Alcohol Res. 2017; 38(2):147-161.
3. Lazo M, Mitchell MC. Epidemiology and Natural History of Alcoholic Liver Disease. Clinical Liver Disease. 2014; 7(4):81–85.
4. Louvet A, Mathurin P. Alcoholic Liver Disease: Mechanisms of Injury and Targeted Treatment. Nature Reviews Gastroenterology & Hepatology. 2015; 12(4):231–242.
5. Gao B, Bataller R. Alcoholic Liver Disease: Pathogenesis and New Therapeutic Targets. Gastroenterology. 2011; 141(5):1572–1585.
6. Rani Samyuktha Velamakanni, Sai Kishore Pittla, Srikanth Reddy Anugu, Raj Kiran Sriramula, Mounika Tejaswi Gorle, Narender Boggula. Efficacy of anti-hypertensives in prolonging diabetic nephropathy. International Journal of Research in Pharmacy and Chemistry. 2018; 8(3):422-436.
7. Lieber CS. Alcoholic Fatty Liver: Its Pathogenesis and Mechanism of Progression to Inflammation and Fibrosis. Alcohol. 2004; 34(1):9–19.

8. Seitz HK, Bataller R, Cortez-Pinto H, Gao B, Gual A, Lackner C, Mathurin P, Mueller S, Szabo G, Tsukamoto H. Alcoholic Liver Disease. Nature Reviews Disease Primers. 2018; 4(1):16.
9. Stickel F, Datz C, Hampe J, Bataller R. Pathophysiology and Management of Alcoholic Liver Disease: Update 2016. Gut And Liver. 2017; 11(2):173–188.
10. Sampath Kumar Ch, Sai Krishna M, Prashanth N, Narender Boggula, Rani Samyuktha Velamakanni. Clinicopathological Study and Management of Liver Abscess in a Tertiary Care Hospital. Indo American Journal of Pharmaceutical Sciences. 2018; 05(06):5996-6009.
11. Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global Burden of Disease and Injury and Economic Cost Attributable to Alcohol Use and Alcohol-Use Disorders. The Lancet. 2009; 373(9682):2223–2233.
12. Haflidadottir S, Jonasson JG, Norland H, Einarsdottir SO, Kleiner DE, Lund SH, Björnsson ES. Long-term follow-up and liver-related death rate in patients with non-alcoholic and alcoholic related fatty liver disease. BMC Gastroenterol. 2014; 14:166.
13. Addolorato G, Mirijello A, Barrio P, Gual A. Treatment of alcohol use disorders in patients with alcoholic liver disease. Journal of Hepatology. 2016;65(3):618–630.
14. Ambade A, Mandrekar P. Oxidative stress and inflammation: Essential partners in alcoholic liver disease. International Journal of Hepatology. 2012; 2012;853175.
15. Halsted CH. Nutrition and alcoholic liver disease. Seminars in Liver Disease. 2004; 24(3):289–304.
16. Torruellas C, French SW, Medici V. Diagnosis of alcoholic liver disease. World J Gastroenterol. 2014; 20(33):11684-11699.
17. Edula RG, Muthukuru S, Moroianu S, Wang Y, Lingiah V, Fung P, Pyrsopoulos NT. CA-125 Significance in Cirrhosis and Correlation with Disease Severity and Portal Hypertension: A Retrospective Study. J Clin Transl Hepatol. 2018; 6(3):241-246.
18. Mathurin P, Bataller R. Trends in the management and burden of alcoholic liver disease. J Hepatol. 2015; 62(1 Suppl):S38-46.
19. Kim MS, Ong M, Qu X. Optimal management for alcoholic liver disease: Conventional medications, natural therapy or combination? World Journal of Gastroenterology. 2016; 22(1):8–23.