

# Hepatocellular Carcinoma and Alcohol Consumption: Molecular Changes

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## Abstract

Alcohol is one of the main causes of liver disease and encourages Hepatocellular Carcinoma (HCC) and cirrhosis of the liver. Alcohol is metabolized to acetaldehyde in hepatocytes, which results in hepatic steatosis, cellular death, endoplasmic reticulum stress, peroxidation, cytokine generation, and decreased immune surveillance. Produced by gut bacteria, endotoxin and lipopolysaccharide promote the synthesis of cytokines. These alcohol metabolites cause hepatic fibrosis to develop as well as HCC to manifest. Recently, several host genetic variables involved in this process have been discovered.

**Keywords:** Hepatocellular carcinoma • Alcohol • Acetaldehyde

## Introduction

Hepatocellular Carcinoma (HCC) is a severe issue in cirrhosis and chronic liver illnesses that are brought on by chronic hepatitis B and C virus infection as well as non-alcoholic steatohepatitis. Additionally, alcohol use in both patients with and without HCV infection results in cirrhosis, hepatic steatosis, hepatic fibrosis, and HCC. Alcohol-related liver damage is a significant global health issue. Chronic hepatic inflammation and hepatic fibrosis resulting from numerous liver disorders with distinct etiologies are linked to HCC. Different etiologies of HCC are caused by a number of similar molecular pathways. The frequency of HCC in patients with alcoholic liver disorders has some recognized specific genetic causes. It is unclear what level of alcohol use leads to the development of alcoholic hepatitis. The lower limit of alcohol consumption per day for the onset of cirrhosis is between 30 g and 50 g of ethanol. But the majority of alcoholic hepatitis patients consume more than 100 g each day. Most patients with the alcoholic liver disease generally admitted to drinking heavily (more than 100 g per day) for two or more decades. An additional risk factor for cirrhosis, acute alcoholic hepatitis, and steatosis includes being overweight for at least 10 years. Weekly ethanol use of 140 g in women and 210 g in males indicates that patients with NAFLD or NASH (Nonalcoholic Steatohepatitis) do not abuse alcohol. Alcohol consumption has been linked to steatosis as well as the development of cirrhosis and/or NASH in Nonalcoholic Fatty Liver Disease (NAFLD). While moderate alcohol use is favorably correlated with the frequency of HCC in patients with chronic viral liver disorders, it is adversely correlated with the incidence of NASH and liver fibrosis. In the early stages of HCC, current treatment is beneficial. To treat HCC effectively and with precision, it is crucial to comprehend the molecular mechanism. Immune checkpoint inhibitors have been given the go-ahead to treat HCC. Immune modulators and targeted therapy molecules can be used to increase the effectiveness of the treatment. In this research, we investigated the molecular causes of alcoholic liver disease-related HCC. Understanding the molecular alterations in alcohol use and HCC is crucial. The prognosis of patients with HCC-related alcoholic liver diseases may improve as a result of these being able to detect and treat HCC linked with those diseases early.

## Alcohol metabolism and Liver injuries

**Alcohol Oxidation:** Ethanol, a component of alcohol, is mostly metabolized in the liver. Additionally, the digestive system oxidizes ethanol less slowly than the liver. By first converting to acetaldehyde in the cytoplasm of hepatocytes, Alcohol Dehydrogenase (ADH) catabolizes about 80% of the ethanol oxidation. A role in the initial pathophysiology of alcohol-induced steatosis may be played by the elevated ratio of decreased Nicotinamide Adenine Dinucleotide (NADH)/oxidized Nicotinamide Adenine Dinucleotide (NAD), which is obtained from the vitamin niacin. Chronic alcohol-induced fatty liver in rats has been shown to ameliorate with dietary nicotinic acid supplementation. The majority of the residual ethanol is converted to energy via the Microsomal Ethanol-Oxidizing System (MEOS) route. In this MEOS pathway, *cytochrome P45011E1 (CYP2E1)* functions. Although acetaminophen consumption has been linked to liver damage in alcoholics, *CYP2E1* activation by ethanol and glutathione depletion are thought to be the main contributors to vulnerability to acetaminophen hepatotoxicity. The peroxisome catalase-dependent pathway has a modest role in the metabolism of some ethanol. The conversion of ethanol to acetaldehyde in the liver may occur primarily through the ADH route. The majority of the acetaldehyde produced by ethanol is further oxidized to acetate in the liver by Aldehyde Dehydrogenases (ALDHs). Patients with an inactive type of ALDH may experience rinsing after drinking alcohol due to acetaldehyde buildup. The livers of human *CYP2E1*-transgenic mice displayed hepatotoxicity as evidenced by increased blood Alanine Aminotransferase (ALT) levels, increased hepatocyte necrosis, and decreased *CYP2E1* levels, which resulted from the *CYP2E1*-mediated activation of acetaminophen. *CYP2E1*-transgenic mice had worsened alcohol-related liver disease. *CYP2E1* may contribute to alcohol-induced steatohepatitis and exacerbate liver damage brought on by TNF. Additionally, autophagy has a protective effect against *CYP2E1*-dependent liver damage brought on by long-term ethanol exposure.

**Acetaldehyde:** Acetaldehyde may harm the liver in severe ways. Through the creation of adducts and inflammatory reactions, acetaldehyde build-up promotes the evolution of alcoholic fatty liver and other liver illnesses, such as Non-Alcoholic Fatty Liver Disease (NAFLD), viral hepatitis, and HCC. Acetaldehyde build-up makes hepatocyte cell death caused by Tumour Necrosis Factor (TNF) more susceptible. In human hepatoma HepG2 cells, acetaldehyde enhances the production of TNF- and Interleukin (IL)-8, stimulates the release of IL-1 and IL-8, increases lipid peroxidation damage, and lowers catalase activity. Chronic ethanol consumption may promote apoptosis because it potentiates TNF-induced p38 Mitogen-Activated Protein Kinase (MAPK). Kupffer cells are a significant contributor to the rise in circulating proinflammatory cytokines and are sensitised to produce TNF. In patients with prolonged alcohol use, the regulation of autophagy also plays a role in the development of steatosis and inflammation. Acetaldehyde produces neoantigens, binds to host proteins, and stresses the Endoplasmic Reticulum (ER). Acetaldehyde Dehydrogenase 2 (ALDH2) boosts the expression of Phosphorylated Eukaryotic Initiation Factor 2 (peIF2) and Glucose-Regulated Protein 78 (*GRP78*) in mice. ALDH2 induces the ER stress response and apoptosis by reducing the expression of apoptosis-related proteins such C/EBP Homologous Protein (*CHOP*), caspase 12, and caspase 9, among others. Acetaldehyde also reduces the antigen presentation on hepatocytes linked with HBV-MHC class I by inducing ER stress and Golgi fragmentation. In addition to causing cytotoxicity, ER/oxidative stress, and mitochondrial stress, ethanol, and its metabolites, acetaldehyde and fatty acid ethyl esters, also dysregulate AMP-Activated Protein Kinase (*AMPK*) signaling.

## Hepatic steatosis, oxidative stress, and peroxidation

NAFLD and NASH cause liver pathology that resembles alcoholic steatosis and alcoholic liver disease. An obvious sign of alcoholic liver damage is steatosis. Alcohol oxidation causes fat to deposit in the hepatocytes, as was previously mentioned.

Hepatic steatosis, oxidative stress, acetaldehyde-mediated toxicity, and cytokine/chemokine-induced inflammation are all symptoms of alcoholic liver disease.

In patients who consume alcohol, the elevated NADH/NAD ratio in hepatocytes impairs the mitochondrial  $\beta$ -oxidation of fatty acids and causes hepatic steatosis. Alcohol consumption can directly activate *Sterol Regulatory Element-Binding Protein 1c* (*SREBP-1c*) and inactivate the expression of *PPAR-, inducing the production of fatty acids and inhibiting the oxidation of fatty liver, which results in the development of alcoholic steatosis. Alcohol exposure suppresses AMPK as well, increasing Acetyl-CoA Carboxylase (ACC) activity while decreasing *Carnitine Palmitoyl Transferase 1* (*CPT-1*) activity, increasing fatty acid synthesis and decreasing fatty acid  $\beta$ -oxidation.*

### Immune mechanism of alcoholic liver diseases

**Endotoxin:** Rodents naturally dislike drinking alcohol, thus there is no animal model that accurately represents human alcoholic liver disease by alcohol intake. In animal models of alcoholic liver disease, portal-derived Lipopolysaccharide (LPS) plays a key role in inflammatory activation of local Kupffer cells. LPS, another name for endotoxin, is created by gut bacteria. Drinking alcohol raises the levels of endotoxins in the blood and liver, promotes Kupffer cells' release of inflammatory cytokines, and causes the liver to produce Reactive Oxygen Species (ROS), which can harm hepatocytes. ROS buildup results in structural and functional DNA alterations that affect the cell cycle and cause carcinogenesis. Oxidative stress causes lipid peroxidation products, which boost the effects of endotoxins produced by gut bacteria, as well as p53 gene alterations, which cause HCC.

In addition to creating ROS, neutrophils also create growth factors and may aid in liver healing by eliminating apoptotic or necrotic hepatocytes. In alcoholic liver disease, neutrophils are crucial in regulating bacterial infection, but the severe alcoholic liver disease is also accompanied by reduced phagocytic and bactericidal activity. As a result, neutrophils exhibit similar behaviors to Kupffer cells, which results in the attraction of neutrophils. Alcohol-induced increased gut permeability causes intestinal *CYP2E1* to encourage the transfer of gut LPS into the blood, which causes endotoxemia, liver steatosis, and steatohepatitis.

### Innate immunity and adaptive immunity

The innate and adaptive immune systems are hampered by the development of alcoholic liver disease. Activation of the complement is a factor in the onset of alcoholic liver disease. Complement Component 1q (*C1q*) binding to apoptotic cells in the liver for hepatic inflammation can activate the classical complement pathway. While *complement Component 5* (*C5*) is involved in inflammation and damage due to prolonged ethanol intake, Complement *Component 3* (*C3*) contributes to triglyceride accumulation in the liver and adipose tissues.

Both cellular and circulatory innate immune components are activated by ethanol exposure. Toll-Like Receptor-4 (TLR4)-dependent cytokine production in Kupffer cells is increased by ethanol exposure, and redox signaling dysregulation is also increased. Alcohol, on the other hand, inhibits TLR3 signaling, different innate effector molecules, and proinflammatory cytokines and chemokines, suppressing innate immune responses.

The makeup of the gut microbiota changes in alcohol-dependent individuals with increased intestinal permeability. Alcohol leads to intestinal dysbiosis, which lowers the microbiome's ability to produce saturated long-chain fatty acids and the percentage of *Lactobacillus* species.

By way of their structural components, Pathogen-Associated Molecular Patterns (PAMPs), such as the TLR4 ligand LPS, or by way of their metabolites changing the integrity of the gut mucosa, gut-associated bacteria contribute to the pathogenesis of alcoholic liver disorders. Numerous bacterial PAMPs bind to certain receptors in cells, including TLRs, to activate the innate immune systems in those cells. *Myeloid Differentiation protein-2* (*MD-2*) and *Cluster of Differentiation 14* (*CD-14*) bind LPS and, upon doing so, activate TLR4. These substances enable the activation of hepatic macrophages by gut-derived LPS.

Alcoholic liver disease develops in large part as a result of LPS-induced TNF-. Increased IL-1, TNF-, and IL-8 blood levels, increased caspase-1 and Nucleotide-Binding Oligomerization Domain-Like Receptor (NLR) family pyrin domain-containing 3 (*NLRP3*) expression, neutrophilia, and activated monocytes and macrophages in the liver are all symptoms of alcoholic liver disease. Additionally confirmed is the function of inflammasomal activation in alcoholic liver disease. Alcohol alters the innate immune system's ability to produce tissue macrophages, neutrophils, monocytes, and lymphocytes as well as eventually adaptive immunological responses. Patients with alcoholic liver disease have higher levels of circulating Immunoglobulin A (IgA). Higher levels of IgA imply a T cell-independent drive to IgA creation exists in alcoholic cirrhosis, as T cells typically govern IgA production produced by B cells. In patients with alcoholic liver disorders, liver-resident IgA-producing cells build up in the fibrotic liver and may compromise the immune system's ability to fight liver cancer. Programmed *Death Ligand 1* (*PD-L1*) and IL-10 are expressed by liver-resident IgA-producing cells, which in turn cause liver cytotoxic CD8+ T-lymphocytes to become exhausted. These circumstances stop the development of HCC and the production of a small range of T-cell receptors against tumor-associated antigens. Additionally, liver-resident IgA-producing plasmacytes and gut bacteria may inhibit CTL activation. Thus, patients with alcoholic liver disease also have decreased adaptive immune response. Since *PD-L1* inhibition causes HCC regression, understanding these mechanisms may aid in the development of future HCC treatments.

### Prevention and treatment

The most effective course of treatment for alcoholic liver problems is abstinence, or quitting drinking. When used as needed, nalmefene, an opioid antagonist and partial agonist at the receptor may help individuals with alcoholic liver illnesses avoid the development of HCC. A significant health issue is alcoholic liver damage. In this article, we covered the molecular pathways underlying alcohol-induced HCC. Along with alcohol usage, genetic and gene polymorphism factors can contribute to the development of alcoholic liver disease. In addition to them, poor socioeconomic situation and conduct may make alcoholic liver disease more likely. Alcoholic beverages cause the release of cytokines and chemokines in addition to the death of hepatocytes, which results in a reduction in protein synthesis. Finding risk-predictive biomarkers is a significant topic of HCC research. Due to the extensive follow-up necessary for the longitudinal group to track the interruption of clinical results and statistical association, the prospective evaluation has presented the most barrier. New treatment targets can be developed by comprehending the aetiology at the molecular level, including genetic and epigenetic modifiers.

### Conclusion

In the near future, it is hoped that various investigations on the creation of promising biomarkers and precision medicine would significantly improve the dismal prognosis of patients with alcoholic liver disease and HCC. Additionally, altering one's diet and drinking habits is still crucial for reducing the prevalence of alcoholic liver disease.