The Effects of Alcohol on Other Chronic Liver Diseases

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KEYWORDS

• Alcohol • Nonalcoholic steatohepatitis (NASH) • Hepatitis B • Hepatitis C • Cirrhosis • Hepatocellular carcinoma

KEY POINTS

- Alcohol often acts in synergy with other chronic liver diseases to accelerate liver injury.
- Alcohol consumption in conjunction with other chronic liver diseases can accelerate hepatic fibrosis and increase risks of cirrhosis, hepatocellular carcinoma (HCC), and liver-related mortality.
- Modest alcohol consumption has been shown to be associated with less nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH).

Alcoholic liver disease includes a spectrum of disorders, ranging from hepatic steatosis to alcoholic hepatitis to cirrhosis. Approximately 90% of heavy drinkers (defined as >60 g of alcohol per day) have a fatty liver.[1,2] Only 30% to 35% of heavy drinkers, however, demonstrate progression to severe hepatic fibrosis and cirrhosis.[3]

The American Association for the Study of Liver Disease and European Association for the Study of the Liver define significant alcohol drinking as greater than 30 g per day in men and greater than 20 g per day in women.[4,5] The National Institute of Alcohol Abuse and Alcoholism defines binge drinking to be more than 40 g per day in women and 50 g per day in men (within 2 hours).[4]

EFFECT OF ALCOHOL ON NONALCOHOLIC FATTY LIVER DISEASE

NAFLD is increasingly recognized in the United States along with the increase in obesity and type 2 diabetes mellitus. Approximately 30% to 40% of the population in United States (80–100 million) have NAFLD.[6] NAFLD is characterized by bland steatosis, with minimal inflammation, and has a more benign course, with less than 4%

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progress to cirrhosis.[7] In 1980, Ludwig and colleagues[8] originally coined the term, *NASH*, to describe a liver disease that was histologically indistinguishable from alcoholic steatohepatitis but not associated with alcohol consumption. NASH is characterized histologically by hepatic steatosis, hepatocyte ballooning, lobular inflammation, and fibrosis.[9] Patients with NASH have an increased risk of advanced liver disease and 21% to 28% progress to cirrhosis.[7,10] NASH has also been identified as a cause of cryptogenic cirrhosis.[11] Therefore, the number of cases of end-stage liver disease or liver cancer due to NASH may be underestimated.

The pathogenesis of NASH remains complex; the central features are insulin resistance and metabolic disturbances that lead to increased hepatic steatosis and lipotoxicity from free fatty acids, along with oxidative stress.[7,12,13] This then leads to hepatocyte apoptosis, inflammation, activation of hepatic stellate cells, and subsequent fibrosis.[12] Risk factors for progressive NASH include factors associated with metabolic syndrome, such as increased waist circumference, hypertension, hyperlipidemia, type 2 diabetes mellitus or insulin resistance, and a family history of type 2 diabetes mellitus.[7,14–16] Human patatin-like phospholipase domain-containing 3 (PNPLA3) gene mutation has also been associated with the presence of NAFLD regardless of environmental factors and associated with more severe histopathology.[17,18]

Alcohol use has been associated with increased risks of NAFLD and fibrosis progression in NAFLD in both animal and clinical studies. In animal studies, mice that were fed a high-fat diet along with alcohol showed more evidence of inflammatory foci, hepatocyte apoptosis, increased profibrogenic gene expression, and hepatic fibrosis.[19,20] In the Dionysos Study, heavy drinkers (>30 g/d) had a 2.8-fold increased risk for hepatic steatosis, and the risk was even more pronounced (5.8-fold) for those who were obese and drank heavily (**Table 1**).[21] The synergy between obesity and alcohol consumption was further observed in the Rancho Bernardo Study where drinking greater than 3 alcoholic drinks per day and being obese increased risks of alanine aminotransferase (ALT) elevation by almost 8.9-fold (95% CI, 2.4–33.1).[22] In a cohort of 71 patients with biopsy-proved NAFLD, binge drinking was higher in patients with evidence of fibrosis progression than those without (47% vs 11%; $P = .003$). Although not statistically significant, there was a trend of increased weekly alcohol consumption in patients with evidence of fibrosis progression (38 g/wk vs 17 g/wk; $P = .061$) (**Table 1**).[23] Moreover, moderate to heavy alcohol intake (20–50 g/d and >50 g/d) was associated with increased risk of NAFLD in female patients (OR 3.35; $P = .002$), independent of body mass index (BMI), increased waist circumference, high-density lipoprotein, low-density lipoprotein, triglyceride, and fasting plasma glucose levels.[24]

In contrast, many clinical studies have also shown that light or modest alcohol consumption may be associated with lower rates of NAFLD, particularly in male patients or obese male patients.[25–28] Patients with biopsy-proved NAFLD had less NASH (OR 0.56; 95% CI 0.39–0.84, $P = .002$) and less fibrosis (OR 0.56; 95% CI, 0.41–0.78, $P = .0005$) if they were modest drinkers (<20 g/d) (**Table 1**).[27] In another study, only modest wine drinking (<10 g/d) and not modest beer or liquor drinking was associated with less NAFLD (**Table 1**).[29] In 1055 male patients with metabolic syndrome, modest drinking (20 g/d) was associated with less NAFLD and lower aspartate aminotransferase (AST), ALT, BMI, and waist circumference (**Table 1**).[25] In another Japanese cohort an inverse relationship was observed between amount of alcohol consumed per week and prevalence of fatty liver in male patients (**Table 1**).[28] The prevalence of NAFLD was 40% in male nondrinkers, and 24% in men who drank 7 drinks per week ($P<.001$). Alcohol consumption was associated with lower prevalence of fatty liver in men (OR 0.54; 95% CI, 0.56–0.68) but not in women (OR 0.80; 95% CI,