Alcohol's Effect on Other Chronic Liver Diseases

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KEYWORDS

• Alcohol • Autoimmune hepatitis • Fatty liver disease • Hepatitis B • Hepatitis C • Hemochromatosis • Fibrosis • Cirrhosis

KEY POINTS

- Alcohol consumption synergistically exacerbates liver injury in several major nonalcoholic chronic liver diseases.
- Alcohol's synergistic injury results in increased hepatic inflammation and accelerated rates of fibrosis.
- Alcohol also increases the risks of developing cirrhosis, liver cancer, and death.
- There does not seem to be a safe level of alcohol consumption in chronic liver diseases.

ALCOHOL AND FATTY LIVER DISEASE

Nonalcoholic fatty liver disease (NAFLD) is increasingly recognized as the downstream hepatic consequence of the metabolic syndrome. Well-known risk factors for NAFLD include obesity (especially with increased waist circumference), insulin resistance (with either elevated fasting glucose or frank type 2 diabetes), and hypertriglyceridemia, and these risk factors are also strongly associated with the development of metabolic syndrome.[1] Other risk factors for the metabolic syndrome such as hyperlipidemia and hypertension may also prompt suspicion for NAFLD; therefore, metabolic syndrome is a strong predictor for the development of NAFLD.[2] The absence of excessive alcohol consumption is a necessary prerequisite for the diagnosis of NAFLD from alcoholic liver disease, because the 2 conditions may be histologically indistinguishable[3]; however, recent studies indicate that alcohol may play a role in both the progression and pathogenesis of NAFLD, as reviewed later.

Most patients with NAFLD have hepatic steatosis in the absence of necroinflammatory features or fibrosis; however, a significant minority may have nonalcoholic steatohepatitis (NASH), which is characterized by hepatocellular inflammation, injury,

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and fibrosis.[4] Prolonged duration of NASH may ultimately lead to cirrhosis and many cases of "cryptogenic cirrhosis."[5] Obesity-related insulin resistance is one of the main pathogenic factors responsible for this progression, as hyperinsulinemia has been shown to increase the levels of free fatty acids and cholesterol[6] within the liver, resulting in cytotoxicity and oxidative stress, which then promote hepatic stellate cell activation and fibrosis.[7]

Like with other chronic liver diseases, alcohol seems to be an important risk factor for progressive fibrosis in NASH. One recent experimental animal model confirmed this effect by randomizing mice between a regular diet, a NASH-inducing high-fat diet, a regular diet with alcohol-laced drinking water (up to a concentration of 5%), and a combined high-fat and alcohol diet. The NASH-inducing high-fat diet significantly induced hepatic triglyceride accumulation and the expression of proinflammatory and profibrogenic genes compared with alcohol alone. However, in mice given a combined high-fat and alcohol diet, both proinflammatory and profibrogenic gene expressions were even more significantly elevated than with either diet alone, and there was a further marked induction of hepatic fibrosis.[8] Another recent study in rats also showed that moderate alcohol consumption, along with a high-fat diet, led to significantly more hepatic inflammation and cellular apoptosis, compared with a high-fat diet alone.[9] In humans, moderate alcohol consumption has also been associated with the progression of hepatic fibrosis in NAFLD.[10] On the other hand, light-to-moderate alcohol use has also been shown to decrease insulin resistance and the risks of both metabolic syndrome[11] and cardiovascular mortality.[12] Because the risk factors for NAFLD overlap with those of cardiovascular disease, patients may end up receiving contradictory recommendations[13] from different health care providers.

Recent studies have attempted to clarify whether there may be an optimal concentration of alcohol use in NAFLD patients. In a study of 132 morbidly obese Brazilian patients, light-to-moderate alcohol consumption (defined as between <20 g/d and 40 g/d) did not have an impact on the severity of steatosis and steatohepatitis,[14] although light-to-moderate alcohol consumption caused a decrease in insulin resistance in these patients. Several Japanese cohort studies have further examined whether alcohol consumption may actually be protective against NAFLD. In a large Japanese cohort of 4957 men and 2155 women, alcohol consumption was inversely associated with a lower prevalence of fatty liver compared with nondrinkers in both men (28% vs 40%) and women (10% vs 16%). Furthermore, light alcohol consumption (defined as <20 g/d for only 1–3 days per week) was associated with a lower prevalence of NAFLD with an odds ratio of 0.47, suggesting a protective effect against the development of NAFLD.[15] Two other large Japanese cohort studies have also examined whether this potential protective effect held true across broader categories of alcohol consumption, including moderate and heavy drinking. In 2009, Gunji and colleagues[16] found in 5599 Japanese men that both light (40–140 g/wk) and moderate (140–280 g/wk) alcohol consumption were significantly associated with a reduction in the risk of developing NAFLD (odds ratios of 0.824 and 0.754, respectively). In 2011, Hiramine and colleagues[17] found in 9886 Japanese men that the prevalence of fatty liver disease followed a U-shaped distribution across several categories of alcohol use among 44.7% of nondrinkers, 39.3% of light drinkers (<20 g/d), 35.9% of moderate drinkers (20–59 g/d), and 40.1% of heavy drinkers (>60 g/d). The prevalence of NAFLD was inversely associated with alcohol consumption, with odds ratios of 0.71 in light drinkers, 0.55 in moderate drinkers, and 0.44 in heavy drinkers. NAFLD prevalence was also inversely associated with the frequency of alcohol consumption (>21 d/mo) but not necessarily volume consumed, with an odds ratio of 0.62. In another large 2012 cohort study of 18,571 Japanese men and women, Hamaguchi