

## Alcohol for patients with non-alcoholic fatty liver disease: Friend or foe?

Moriya A, Iwasaki Y, Ohguchi S, Kayashima E, Mitsumune T, Taniguchi H, Ikeda F, Shiratori Y, Yamamoto K. (Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences; Junpukai Health Maintenance Center, Okayama; Department of Medicine, Miyamoto Hospital, Ibaraki, Japan.) Alcohol consumption appears to protect against non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2011;**33**:378–88.

### SUMMARY

A cross-sectional study was done to establish the association between the pattern of alcohol consumption and fatty liver in Japanese men ( $n=4957$ ) and women ( $n=2155$ ). A detailed history of alcohol consumption was obtained with the help of a questionnaire, systematic health check-up data were used for analysis, and fatty liver was diagnosed on ultrasonography. The authors found that the prevalence of fatty liver was significantly lower in drinkers than in non-drinkers (28% v. 40% in men [ $p<0.001$ ] and 10% v. 16% in women [ $p<0.001$ ]). Alcohol consumption was inversely associated with fatty liver both in men (odds ratio [OR] 0.59; 95% confidence interval [CI] 0.52–0.68) and in women (OR 0.60; 95% CI 0.45–0.80). After adjusting for several known confounding variables in multivariate analysis, alcohol consumption was found to be an independent negative predictor of fatty liver (OR 0.54; 95% CI 0.46–0.63) in men but not in women (OR 0.80; 95% CI 0.57–1.12). The prevalence of fatty liver was inversely associated with drinking frequency in men ( $p<0.001$ ): 38% (1–3 days/week), 29% (4–6 days/week), and 24% (daily drinking). The drinking frequency and not the amount of alcohol consumed was an essential factor for the inverse correlation between alcohol consumption and fatty liver in men. The inverse correlation between drinking and fatty liver was documented in men consuming up to 280 g of alcohol per week. In women, drinking <20 g on 1–3 days per week was associated with a low prevalence of fatty liver (adjusted OR 0.47; 95% CI 0.23–0.96); otherwise, there was no inverse correlation with fatty liver when the amount and/or frequency of alcohol consumption were higher than this. The inverse association between alcohol consumption and fatty liver in men was seen even in the presence of the metabolic syndrome, which is an important risk factor for non-alcoholic fatty liver disease (NAFLD). In men with the metabolic syndrome ( $n=722$ ), the prevalence of fatty liver was significantly lower in drinkers than in non-drinkers (64% v. 82%;  $p<0.001$ ). In women with the metabolic syndrome this difference was not statistically significant (57% v. 71%,  $p=0.208$ ). Based on these results, the authors concluded that alcohol consumption appears to protect against NAFLD. The authors highlight that the inverse association between alcohol consumption and fatty liver was dependent mainly on the frequency of drinking, not the amount, and also, that the association was independent of the metabolic syndrome. The less robust inverse association in women was attributed to a higher relative risk of developing an alcohol-related liver disease in women.

### COMMENT

In general, patients with NAFLD are advised to abstain from any amount of alcohol because alcohol might cause the disease to progress. However, data supporting this are lacking. The consumption of moderate amounts of alcohol is known to confer health benefits such as reduction of coronary heart disease, prevention

of development of diabetes mellitus, and elevation of high-density lipoprotein cholesterol.<sup>1–3</sup> Moderate consumption of alcohol increases the levels of adiponectin, improves insulin sensitivity, and has been found to protect against the development of non-alcoholic steatohepatitis (NASH) in severely obese people.<sup>4–6</sup> However, there are conflicting reports regarding the effect of consumption of moderate amounts of alcohol on the liver. Several studies have documented a harmful effect of alcohol on NAFLD.<sup>7–9</sup> Both alcohol and obesity are independent risk factors for liver disease, and several of the proposed mechanisms of pathogenesis of alcoholic disease and NAFLD are similar such as alteration of cytokines, oxidative stress, increased intestinal permeability, endotoxaemia, etc. Thus, the combination of obesity and alcohol, both being independent risk factors, should enhance the risk of progressive liver disease. A large prospective study has shown that obesity and alcohol act together to increase the risk for liver disease in both men and women, with effects greater than the additive effect of the two separate factors.<sup>8</sup> The results of this study are provocative, yet it adds to the body of evidence which supports a favourable effect of mild-to-moderate alcohol consumption on several metabolic variables involved in the pathogenesis of NAFLD.<sup>1–6</sup> The protective effect of alcohol consumption on NAFLD was seen in men even in the presence of the metabolic syndrome. However, the same inverse association was not observed in women with the metabolic syndrome. This can be attributed to an increased relative risk of alcohol-related liver damage in women, as pointed out by the authors. Lower gastric mucosal alcohol dehydrogenase, higher prevalence of autoantibodies, hormonal (oestrogen) effects and relatively lower body water content in women are possible explanations for the increased susceptibility of women to alcohol.<sup>10,11</sup> The other important observation was that among men with moderate alcohol consumption, drinking frequency had a more robust inverse association with NAFLD than the amount of drinking. The inverse association between drinking and developing fatty liver was documented in men consuming up to 280 g of alcohol per week. However, the authors did not evaluate the effect of type of alcoholic beverage being consumed (e.g. beer, wine or liquor) or their ingredients on the prevalence of NAFLD. This is a limitation of this study.

In another study, the protective effect of alcohol on the risk of NAFLD was seen only in wine drinkers and not in those who drank moderate amounts of beer and liquor.<sup>6</sup> In fact, the beneficial effects of alcohol have been attributed more to the non-alcohol constituents in alcoholic drinks such as oligomeric proanthocyanidins, resveratrol and other antioxidants, than to alcohol itself.<sup>12</sup> Further, a cross-sectional association study is susceptible to various biases, and thus it is difficult to draw a causal inference. Although, the authors tried to adjust for several confounders in a multivariate analysis, the results could have been affected by certain unmeasured confounders such as genetic susceptibility, type of alcoholic beverage, presence or absence of other risk factors for liver disease (e.g. viral hepatitis), diet and medications. Further, a questionnaire-based study is almost always associated with retrospective recall bias. Thus, the observed inverse association between alcohol consumption and NAFLD may be an error of judgement.

The ingestion of >60–80 g/day of alcohol for  $\geq 10$  years in men, and >20 g/day in women has been traditionally considered a risk factor for advanced liver disease. However, the least amount of alcohol consumption which is safe is not known. A study found that any level of alcohol intake was harmful in obese individuals and consumption of even 1–14 units of alcohol in a week was associated with mortality due to liver disease.<sup>13</sup> Another study

found that the odds of developing cirrhosis or non-cirrhotic chronic liver disease with a daily alcohol intake of >30 g/day were 13.7 and 23.6, respectively, when compared with non-drinkers.<sup>14</sup> Over 90% of individuals with chronic alcohol consumption develop fatty liver. Obesity is also an important risk factor for fatty liver. The prevalence of NAFLD in obese populations has been reported to vary from 30% to 100%.<sup>15</sup> Establishing the cause of fatty liver in patients with metabolic risk factors who also consume alcohol is difficult, especially when a history of alcohol consumption is ambiguous. Many of the histological and biochemical features that characterize alcoholic and non-alcoholic liver disease are similar, regardless of the initiating event. In patients with an ambiguous history of alcohol consumption, certain features can help in differentiating non-alcoholic from alcoholic liver disease.<sup>16</sup> These are younger age, AST/ALT <1, milder disease on histology, higher grade of steatosis and absence of predominantly neutrophilic infiltrate in the portal tracts.<sup>16</sup> A patient with a history of alcohol consumption >20 g/day is usually excluded from a diagnosis of NAFLD. However, this may not be true for patients with the metabolic syndrome where NAFLD may actually be the dominant cause of fatty liver. In fact, several studies on NAFLD did not exclude patients with a history of moderate alcohol consumption (up to 20–70 g/day). On the other hand, a study has documented that approximately 10% of patients classified as having NASH actually had a significant lifetime exposure to ethanol when a more structured history was obtained.<sup>17</sup> Thus, the cut-off level of alcohol ingestion for classification of 'non-alcoholic' v. 'alcoholic' liver disease in obese people remains elusive.

This association between alcohol and NAFLD is relevant for the Indian population because of a considerably larger magnitude of obesity, NAFLD and alcoholism in India. The prevalence of NAFLD in the Indian population (16.6%) is comparable to that in the West.<sup>18</sup> Furthermore, with a rising incidence of obesity and diabetes in India, the incidence of NAFLD may rise further. Based on data from the 2007 National Family Health Survey, the percentage of people who are overweight or obese in India is 12.1% men and 16% women. India is home to around 50 million people with diabetes, which is the largest number in any single country. NAFLD in India also occurs in lean subjects and hence, their host characteristics as well as mechanistic pathogenesis may be different. Alcohol is the most commonly used intoxicating substance in India with a 32% prevalence rate of ingestion among adult men.<sup>19</sup> More importantly, there are data to suggest that Indians are more susceptible to the hepatic effects of alcohol. The liver involvement appears to occur earlier and at lower consumption levels among Indians.<sup>20</sup> A study has shown that young South Asian men have a significantly higher risk of liver disease than the corresponding White population.<sup>20</sup> The possible explanations include genetic differences in the metabolism of alcohol. The liver enzyme activities are higher and acetaldehyde-mediated protein modification is more marked in Indian alcohol consumers, compared with White alcohol consumers.<sup>21</sup> Ethnic differences have also been reported for the occurrence of NAFLD: Asians and Hispanics are at greater risk for NAFLD than African-Americans, despite a similar prevalence of risk factors.<sup>21</sup> Therefore, considering ethnic differences in the effect of alcohol on liver disease and occurrence of NAFLD, including differences in the host characteristics of Indian NAFLD patients, the results of this study may not be extrapolated to the Indian population. In addition, the cross-sectional design of this study cannot demonstrate the

safety of modest alcohol consumption in subjects with pre-existing NAFLD. Further prospective studies addressing these issues in cross-cultural populations will be required before we accept this inverse association. Till that time, probably, we should discourage consumption of any amount of alcohol in patients with NAFLD.

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