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What do we recommend our patients with NAFLD about alcohol use?

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Abstract

Patients with NAFLD are generally recommended not to consume any alcohol for the fear of worsening their underlying liver disease. Patients with NAFLD are at increased cardiovascular risk observed in patients with NAFLD and emerging studies suggest that light to moderate alcohol consumption may indeed have hepatic benefits in individuals with or at risk for NAFLD. Therefore, it is possible that current recommendation of total alcohol abstinence by individuals with NAFLD is ill-advised. In this article, authors reviewed the published literature relating to alcohol consumption and NAFLD and conclude that (a) heavy alcohol consumption has many harmful effects including those on liver and should be discouraged regardless whether an individual has NAFLD or not, (b) it is not known if cardiovascular and metabolic benefits of light to moderate alcohol consumption observed in general population are extended to those with NAFLD, (c) epidemiological and cohort studies, that suggest light to moderate drinking may have hepatic benefits, are largely are cross-sectional in nature and utilized surrogate endpoints, and (d) until further data from rigorously conducted prospective studies become available, we believe that individuals with NAFLD should avoid consuming alcohol of any type or amount.

Keywords

Alcohol drinking; Non alcoholic fatty liver disease (NAFLD)

Non-alcoholic liver disease (NAFLD) is one of the most common chronic liver diseases in the United States[1]. It's prevalence has been continuously rising over the past decade in both children and adults[2,3], and it is estimated that 17–35% of US adults may have NAFLD[4]. It consists of a spectrum of liver diseases, ranging from benign steatosis to steatohepatitis (NASH) with or without significant fibrosis, cirrhosis, and liver failure[1]. Subjects with NAFLD have higher prevalence of obesity, insulin resistance, diabetes mellitus, dyslipidemia[5] and most importantly atherosclerosis. Indeed, cardiovascular disease is the most common cause of death in these subjects[6].

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The definition of NAFLD requires that an individual must not consume significant amount of alcohol but what constitutes significant alcohol consumption for defining NAFLD remains unclear. The published literature used varying thresholds of alcohol consumption for defining NAFLD and they ranged from ≤ 1 drink (14 grams) per day to < 30 grams per day on average[6–10]. Aside from the quantity of alcohol consumed, other factors such as gender, timing (ongoing vs. remote) and the duration of alcohol consumption (short term vs. chronic) have not been routinely considered when defining the NAFLD.

Once diagnosed with NAFLD, a patient is generally recommended total or near total abstinence, presumably to avoid the harmful effects of alcohol on the underlying liver disease[11]. However, there are no studies that systematically examined the effect of various levels of alcohol consumption on the natural history of NAFLD. Three pertinent questions in this context include: (a) what is the effect of alcohol consumption on the prevalence of NAFLD in high risk population (i.e., obese or those with metabolic syndrome)?; (b) what is the effect of alcohol consumption on underlying liver disease in individuals already diagnosed with NAFLD?; and (c) is there cardiovascular benefit of alcohol consumption in individuals with NAFLD?.

The published literature suggests that the effect of alcohol on liver disease in populations at high risk for NAFLD may indeed depend on the levels of alcohol consumption (heavy vs. mild-moderate). Three cross-sectional studies suggested a synergistic effect between alcohol consumption and excess body weight[9,12]. In the Dionysos study, obese individuals who drank heavily (defined as consumption of 30 g of alcohol per day or 100 kg of alcohol over a lifetime) had significantly higher prevalence of hepatic steatosis than non-obese heavy drinker (OR 2.8, 95%CI: 1.4–7.1) and non-obese, non drinker (OR 5.8, 95%CI: 3.2–12.3)[9]. The findings from the population-based NHANES-3 study showed that the likelihood of hepatic injury was higher at increasing body weight even when the level of alcohol consumption was as low as 2 drinks a day[12]. In this report by Ruhl and Everhart, the prevalence of elevated aminotransferases levels has increased with increasing BMI for each alcohol drinking level ($p<0.05$). For example, in individuals with alcohol consumption > 2 drinks/day, the multivariate-adjusted logistic regression odds ratio for elevated serum aminotransferases increased in stepwise fashion for increasing BMI (odds ratios 1.6, 4.8, 5.4 for BMI categories < 25, 25-<30, ≥30 kg/m^2 respectively)[12]. In another paper based on elderly individuals enrolled in the Rancho Bernardo study, Loomba et al. have shown that individuals with BMI > 30 kg/m^2 and daily alcohol consumption > 3 drinks/day had towering adjusted odds ratio for elevated AST (OR 21) and ALT (OR 8.9)[13]. The mechanism for the synergistic effect is not known, but in part could be related to combined effects of alcohol and obesity on hepatic cytochrome P4502E1 and/or proinflammatory cytokines such as tumor necrotic factor alpha (TNFα)[14].

Despite of the potential interactions between alcohol drinking and liver injury, emerging data however suggest that non-heavy alcohol consumption may have paradoxical and favorable hepatic effects, presumably due to its effects on insulin sensitivity and other metabolic parameters. Suzuki et al. examined the cross-sectional relationship between alcohol consumption and hypertransaminasemia in 1,177 Japanese male subjects without HCV or HBV or other chronic liver diseases[15]. In comparison to individuals with none or minimal alcohol consumption (<70 grams per week), heavy drinkers (drinking ≥280 grams per week) had significantly higher prevalence of hypertransaminasemia, but those with light (70–139 grams per week) and moderate (140–279 grams) did not. Interestingly, in a subgroup analysis stratified by age, light alcohol consumption in the younger (≤40 years) and moderate alcohol consumption in the older (>41 years) individuals were associated with lower prevalence of hypertransaminasemia[15]. Dunn et al., examined the relationship between moderate consumption (≤7 drinks per week) of different types of alcoholic

beverages and suspected NAFLD in 11,754 adults who participated in the NHANES III participants. Moderate wine drinking, but not other types of alcohol beverages, was independently associated with lower prevalence of suspected NAFLD[16].

Two separate cross-sectional studies have reported that alcohol consumption may offer protection against the presence of fatty liver diagnosed by liver ultrasound in Japanese men. Gunji et al., have shown that light and moderate alcohol consumption was independently associated with lower prevalence of fatty liver in 5,599 Japanese men (ref). After adjusting for potential confounding variables, light (40–140 grams/week) and moderate (1–280 grams/week) alcohol consumption was inversely associated with prevalence of fatty liver (OR: 0.82, 95% CI 0.68–0.99 and OR 0.75, 95% CI 0.61–0.92, respectively) (ref). Moriya et al., examined the relationship between the prevalence of fatty liver and alcohol consumption in 4,957 Japanese men and 2.155 Japanese women (ref)[18]. After adjusting for metabolic co-variates and exercise, alcohol consumption was independently and robustly associated with lower prevalence of fatty liver in men, but not in women. Interestingly, in this study the drinking frequency rather than amount of alcohol consumed was an important factor in the protection offered by alcohol consumption against fatty liver.

The effect of alcohol consumption on liver histology in individuals firmly diagnosed with NAFLD has described in three studies. Dixon et al., have shown that morbidly obese subjects with moderate alcohol consumption undergoing bariatric surgery had lower prevalence of steatohepatitis (OR 0.35, 95% CI 0.12–1.00), but this relationship did not persist after controlling for diabetes or insulin resistance[19]. In another study of 132 morbidly obese individuals undergoing bariatric surgery, there was no relationship between alcohol consumption and liver histology, but light to moderate alcohol consumption was inversely associated with insulin resistance[20]. A recent report from the NIH funded NASH Clinical Research Network suggested that modest alcohol consumption is associated with favorable hepatic histology in NAFLD patients. After excluding NAFLD individuals with drinking ≥ 20 grams/day, binge drinkers, or those with previous heavy alcohol consumption, as identified by AUDIT questionnaire, the liver histology of 234 lifetime non-drinkers and 300 moderate drinkers with well-characterized NAFLD was compared. The odds of NASH and other histological features were analyzed using ordinal logistic regression adjusted for social, demographic, and lifestyle co-variates. Compared to lifetime non-drinkers with NAFLD, individuals with NAFLD who reported moderate alcohol consumption had significantly lower prevalence of NASH (OR 0.58, 95% CI: 0.40– 0.84, P=0.004). Moderate drinkers also significantly lower prevalence of fibrosis (OR 0.58, 95% CI 0.42–0.81, P=0.001), presence of ballooning (OR 0.67, 95% 0.48–0.94, P=0.002) and portal inflammation (OR 0.68, 95% CI 0.47 –0.99, P=0.04)[21].

The longitudinal studies examining the effect of alcohol consumption on the incidence of new fatty liver are very limited. In the study by Suzuki et al. mentioned above, there were 326 Japanese men with no evidence of hypertransaminasemia at baseline who were followed up to 5 years and moderate alcohol consumption was independently associated with lower incidence of hypertransaminasemia (adjusted OR 0.4, 95% CI 0.1–0.9, P=0.02)[15]. To our knowledge, there are no prospective or longitudinal studies that examined the effect on ongoing alcohol consumption on disease severity or natural history in patients with established NAFLD or NASH.

If light to moderate alcohol consumption indeed is hepatoprotective, is it the alcohol or some other components in the alcoholic beverages that contribute to these suggested liver protective effects? This question is difficult to answer as most published studies do not take into account the types of alcoholic beverages subjects consumed. In the study by Dunn et al., the negative relationship between alcohol consumption and biochemical evidence of

NAFLD was exclusively limited to moderate wine drinkers[16]. If this is true, then some components of wine, aside from alcohol, such as natural polyphenols may be playing a role in this phenomenon. In fact, in a mouse model of fatty liver, resveratrol improved insulin resistance and reduced the development of fatty liver[22]. The plausible mechanistic explanation may be related to the inhibition of SREBP-1c, a key transcription factor in lipogenesis, reducing oxidative damage, and amelioration of lipid peroxidation by resveratrol[22].

The benefit of light or moderate alcohol consumption may not be limited to the liver, but may also extend to cardiovascular health. Moderate alcohol drinking paradoxically relates to elevated high density lipoprotein cholesterol and lower cardiovascular disease (ref). In the analysis of 490,000 people from The Cancer Prevention Study cohort, individuals who consumed one alcoholic drink daily had a decrease in overall mortality by 20% and cardiovascular mortality by 30–40% compared with non-drinkers[25]. In another study from Europe, individuals who consumed between three and five drinks of wine daily had a decreasing risk of death from all causes, including cardiovascular and cerebrovascular events, by ~50% compared with non-wine drinkers[24]. Patients with NAFLD are heavily enriched with metabolic disorders and are at significant risk for coronary artery disease[5,6,]. These epidemiological hints do bring up the question if light to moderate alcohol consumption may in fact improve long term survival in subjects with NAFLD by reducing cardiovascular mortality.

Despite these potential benefits of light to moderate alcohol consumption, one must be aware of possible risks associated with light to moderate drinking such as breast and colon cancer[26,27]. A recent study from the Nurses' Health Study found that increasing alcohol consumption was associated with increased breast cancer risk that was significant at levels as low as 5.0 to 9.9 g per day (equivalent to 3 to 6 drinks per week)[27]. Alcohol consumption may also be associated with a wide range of social problems, including road traffic injuries and places some individuals at risk of progression to problem drinking. In light of these potential adverse effects, World Health Organization recommends that alcohol consumption should not be used as a preventive strategy for other health benefits[28].

In summary, heavy alcohol consumption has many harmful effects including those on liver and should be discouraged regardless whether an individual has NAFLD or not. However, emerging epidemiological data suggest that light to moderate drinking may have favorable effects from a liver standpoint. But most studies are cross-sectional in nature and utilized surrogates such as aminotransferases and liver imaging. Furthermore, it is not clear if cardiovascular and metabolic benefits of light to moderate alcohol consumption observed in general population are extended to those with NAFLD and NASH. There are emerging studies to suggest that even light alcohol consumption may increase the risk of cancers (e.g., breast and colon). Until further data from rigorously conducted prospective studies become available, we believe that individuals with NAFLD should avoid alcohol consumption of any type or amount.

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