Review Article

Effect of chronic alcohol consumption on the development and progression of non-alcoholic fatty liver disease (NAFLD)

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Abstract: A number of epidemiologic studies show a protective effect of light to moderate daily alcohol consumption on the development of non-alcoholic fatty liver disease (NAFLD). Although these small amounts of ethanol may prevent fatty liver, they may also be a risk factor for other diseases such as breast and colon cancer. Those individuals who have underlying hepatic steatosis or non-alcoholic steatohepatitis (NASH) should not use ethanol chronically since the data available at present do not support a beneficial effect of alcohol in this situation. Especially overweight and obese individuals may be more susceptible towards alcohol even at moderate doses. Animal experiments show a negative effect of ethanol on liver histology in either dietary or genetic NASH models. In addition, patients with NASH reveal a significant increased risk for hepatocellular cancer (HCC) even with social alcohol consumption. Thus, subjects with underlying NASH should abstain from alcohol at any amounts.

Keywords: Alcohol; non-alcoholic fatty liver disease (NAFLD); non-alcoholic steatohepatitis (NASH)

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Introduction

Sufficient evidence has been accumulated that alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) share at least some pathogenetic mechanisms in their development (1-3). This is especially true for the progression of fatty liver to hepatic inflammation with the involvement of gut derived endotoxins, cytokine secretion from Kupffer cells and oxidative stress. Both diseases start with simple fatty liver, progress with inflammatory reaction to alcoholic steatohepatitis (ASH)/non-alcoholic steatohepatitis (NASH), and end up with cirrhosis of the liver and hepatocellular cancer (HCC). Also both entities have similar pattern of liver injury and may be indistinguishable on liver biopsy (4).

However, the cause of the development of fatty liver in ALD and NAFLD is different. In ALD a major reason for hepatic fat accumulation is a change in the metabolism of triglycerides and fatty acids primarily due to the change in the redox state of the hepatocyte following ethanol oxidation with increased triglyceride synthesis and decreased ß-oxidation of fatty acids (5). In NAFLD the metabolic syndrome with hyperinsulinemia and high circulating levels of free fatty acids are the predominant reason for hepatocellular fat accumulation (3,6). This metabolic syndrome is characterized by obesity, diabetes mellitus (DM), hypertension and disturbances in fat metabolism.

Interestingly it has been shown that moderate alcohol ingestion has a beneficial effect on peripheral insulin resistance and thus a positive effect in patients with type II DM (7).

In the last years a number of epidemiologic publications occurred in which the effect of moderate alcohol consumption on the risk to develop NASH as well as on the progression of NASH has been investigated. Furthermore, some experimental data also exist studying the same

question. The purpose of this brief review is to update the knowledge on this issue with a final recommendation based on the up to date literature.

How much ethanol results in fatty liver?

The dose threshold of alcohol for its hepatotoxic effects varies. It depends on a variety of factors including genetics, ethnicity, and gender (2). The safety levels of drinking as endorsed by the European Association for the Study of the Liver (EASL) and the American Association for the Study of the Liver (AASLD) are defined as 30 and 20 g of alcohol per day in man and woman, respectively (2,8). The Asian Pacific for the Study of the Liver (APASL) Guideline recommends less than 20 g of alcohol per day in man and 10 g of alcohol per day in women (9). Taken together, it is the acceptance that daily ethanol intake of less than two drinks in man and less than one drink in woman are considered as 'safe' and such levels should not lead to hepatic steatosis (10,11), and in fact these cut off levels are also arbitrarily used to differentiate ALD from NAFLD in most clinical trials.

However, there are other factors such as baseline body weight, which should be taken into consideration in clinical practice; especially on what we normally consider as "safety drinking". In a study by Bellentani *et al*. using a large cohort of subjects in Northern Italy (12), the authors found that subjects with underlying obesity had a higher prevalence of hepatic steatosis, as determined by ultrasonography, when compared to lean controls who consumed alcohol in the same range subjects with a daily intake of more than 60 g of alcohol and a body mass index (BMI) of over 25 kg/m^2 revealed a fatty liver in more than 90%.

It is important to note that the recommended levels of a 'safety drink' are derived when we use liver pathology as the end point. These levels of drinking in fact have been shown to have adverse effects which might lead to breast (13) and colon (14) cancers. Although these relatively small amounts of ethanol seem safe for the liver, they may be harmful for other organs and tissues. In this context major concern has been raised with respect to the alcohol related risk for breast (13) and colorectal cancer (14). Such associations are mainly extrapolated from several epidemiologic studies, which have the pitfalls with multiple potential confounding factors. At present, there are no reporting data on what the minimal threshold of alcohol consumption is deem to be safe against the risk of developing breast cancer. With respect to colon cancer it was shown that individuals with an alcohol dehydrogenase (ADH) 1C polymorphism (homozygote for the rapid ethanol metabolizing allele ADH1C*1,1) resulting in increased acetaldehyde levels have an increased cancer risk when they consume more than 30 grams of ethanol per day (14). In addition, some pre-existing conditions such as hepatitis C (15), as well as borderline hypertension (16) or some metabolic disorders (17) may deteriorate with chronic alcohol ingestion even at small amounts.

Epidemiological studies analyzing the effect of alcohol on the risk to develop NAFLD

A number of epidemiologic studies from the United States, Europe, and Japan have demonstrated that moderate alcohol consumption may have a beneficial effect on the development of NAFL, primarily through the improvement in peripheral insulin resistance.

A prospective study of 109,690 women (age 25 to 42 years) showed a nonlinear and inverse relationship between alcohol consumption and risk of type 2 DM (7). Compared with lifelong abstainers, the odds of individuals who consumed <5, <15, <30, and >30 g of ethanol per day and the risk of developing type 2 DM were 0.8, 0.67, 0.42, and 0.78, respectively. The take home message of this study is that light to moderate, but not have alcohol consumption has a protective effect against the development of DM (7).

In another study from the U.S. using the data from the Third National Health and Nutrition Examination Survey (NHANES) found a reduced prevalence of NAFLD in subjects with modest wine consumption at the maximum of 10 grams per day (18).

In a cross sectional study (n=5,599) from Japan (19), Gunji *et al*. also found an inverse association between light (40-140 g of alcohol per week) and moderate alcohol consumption (140-280 g per week) and a prevalence of hepatic steatosis, as diagnosed by ultrasound (19). The results of this study (19) are in accordance with another Japanese study (20) which showed a low prevalence of fatty liver in subjects who drank less than 20 g of ethanol on 1-3 days per week. The protective effect of light to moderate alcohol consumption on hepatic steatosis was recently confirmed in a meta-analysis involving 43,175 subjects (21).

Epidemiological data also support the protective role of moderate alcohol consumption on the liver, when using serum transaminases activity as the endpoint. In a study of 1,177 male subjects without underlying liver disease the authors found that light (70-140 g per week) to moderate (140-280 g per week) alcohol consumption was associated with lower levels of serum transaminases activity as

compared to controls (22). On the other hand, drinking alcohol in the higher range (>3 drinks per day), as expected, was associated with an elevation of ALT and AST by 8.9 and 21-fold, respectively, when controlling for covariates such as BMI (23).

Despite the pitfall in the study design of several of these epidemiological studies, existing data support the notion that light to moderate drinking might be protective against diabetes and hepatic steatosis in healthy subjects.

Effect of alcohol on subjects with a histological diagnosis of NAFLD

Besides from the above mentioned epidemiological studies, the effect of alcohol drinking on the underlying hepatic histopathology in subjects with the firm diagnosis of NAFLD has been reported. Kwon *et al*. found that regular alcohol consumption was associated with less severe fatty liver disease (24).

In a study by Cotrim *et al*. in 132 morbidity obese individuals undergoing bariatric surgery, there was no relationship between alcohol consumption and liver histopathology, however, light to moderate alcohol consumption was inversely associated with insulin resistance (25). Dixon *et al*. have shown that morbidly obese patients with moderate alcohol consumption undergoing bariatric surgery in fact had a lower prevalence of steatohepatitis, even though such findings did not persist in the multivariate analysis controlling for confounders such as diabetes or insulin resistance (26). Lastly, Dunn *et al*. reported that modest alcohol ingestion was associated with a lesser degree of severity of NASH as well as of fibrosis when 252 lifetime non-drinkers were compared to 331 modest drinkers with a normal BMI (27). Moderate drinkers had a significantly lower risk for hepatic fibrosis (ORs 0.58, 95% CI, 0.41-0.77) and ballooning of hepatocytes (ORs 0.67, 95% CI, 0.48-0.92), when compared to non-drinkers.

Despite the positive effect of moderate drinking on liver histology in NAFLD, there are some studies reporting negative outcomes. A study by Ekstedt *et al*. found an accelerated progression of fibrosis over more than years in patients with NAFLD who drank moderate amounts of alcohol (28). The findings from the population based NHANES-3 study also showed that the likelihood of hepatic injury was higher at increasing body weight even when the levels of alcohol consumption were as low as 2 drinks a day. In this report by Ruhl and Everhart, the prevalence of elevated serum transaminases activities has increased with increasing BMI for each alcohol drinking level (29).

Lastly, there was a retrospective study suggesting an increasing risk for HCC in patients with underlying NASH who consumed alcohol in moderate amounts (30).

Experimental (animal) studies analyzing the effect of alcohol on NAFLD development and progression

We have investigated the effect of a rather low intake of ethanol (16% of total calories) on the progression of a high fat diet-induced NASH model in Sprague Dawley rats (31). We found an increased number of inflammatory foci and apoptosis due to the additional intake of ethanol. These histological features were found to be associated with elevated mRNA expression of Fas/FasL and cleaved caspase 3 protein. Our data suggest that moderate alcohol intake can augment the inflammation as well as apoptosis in rodents with underlying NASH.

To further study the underlying mechanism, we next investigated the effect of alcohol using the above model on SIRT1 activity, adiponectin/ Adiponectin receptor (AdipoR) related signaling and lipid metabolism (32). Ethanol increased hepatic nuclear SIRT1 protein but decreased its deacetylation activity. SREBP-1c protein expression and FAS mRNA levels were significantly upregulated, while DGAT1/2 and CPT-l mRNA levels were downregulated in the livers of ethanol-fed rats in addition to the high fat diet. Ethanol had no effect on AipoR2 and their downstream signaling, plasma adiponectin, free fats acids, and adiponectin expression in adipose tissue. These data show that the inhibitory effect of alcohol on SIRT1 deacetylase activity exacerbated hepatic inflammation and apoptosis in rats with pre-existing NASH.

Also in a further study in mice we observed joint pathological effects of chronic alcohol administration in drinking water (up to 5%) and feeding a NASH-inducing high fat diet (33). The high fat diet induced hepatic triglyceride accumulation and expression of proinflammatory genes while the effects of alcohol alone were less pronounced. However, in combination with the high fat diet, alcohol significantly enhanced proinflammatory gene expression. Furthermore, a combination of both alcohol and high fat diet led to marked induction of hepatic fibrosis compared to isolated effects of alcohol or high fat diet alone on profibrogenic gene expression and extracellular matrix deposition in liver tissue. Moreover, endotoxin levels in

the portal circulation were significantly elevated in mice that received alcohol or a high fat diet and were further significantly increased in those animals receiving both. The high fat diet alone and in combination with alcohol resulted to a markedly increased hepatic expression of the endotoxin receptor Toll-like receptor 4 (TLR4), which is known to play a crucial role in hepatic fibrosis. Thus, the synergistic effect of alcohol and high fat diet potentially acts via enhanced TLR4 signaling.

In the study by Xu *et al*. moderate obesity induce by intragastric overfeeding of a high fat diet and alcohol intake caused synergistic steatohepatitis in an alcohol dose dependent manner (34). This was associated with increased fibrosis, induction of inducible nitric oxide synthetase, and RNS stress. Thus, nitrosative-, endoplasmic reticulum- as well as mitochondrial stress, and adiponectin resistance appear as mechanisms activated by moderate obesity and ethanol.

Finally, a genetic model for NASH, the leptin deficient, insulin resistant Zucker rats was used to study the effect of ethanol on these animals with respect to cytochrome P-4502E1 induction and the generation of carcinogenic DNA lesions (35). When lean Zucker rats received an ethanol containing Lieber DeCarli diet CYP2E1 as well as exocyclic etheno DNA-adduct increased. A further increase was observed in overweight Zucker rats and the levels of these pathological factors were further enhanced when Zucker rats received the ethanol containing diet.

Recommendation

Based on existing evidence, subjects without underlying liver disease may in fact benefit from light to moderate alcohol consumption. However, one still needs to be cautious as this level of drinking might protect against fatty liver disease, it may also increase the risk of certain cancers. For those with underlying simple steatosis or NASH, the current data do not support the use of alcohol even at light to moderate amounts. In fact, several studies, notably in animals, even showed the potential adverse of alcohol on pre-existing NASH. Thus, we believe that in clinical practice, subjects with underlying NASH should refrain from alcohol consumption of any amount.

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