Is there a safe threshold for alcohol consumption in nonalcoholic fatty liver disease?

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Dose modest alcohol consumption (MAC) help the health care? There is a mainstream that MAC may not aggravate or even reduce cardiovascular disease and all-cause mortality (1,2). Light (≤3 drink/week) or moderate (>3 to ≤14 drinks/week for men or >3 to ≤7 drinks/week for women) alcohol consumption were reducing risk of mortality for all causes and cardiovascular disease (2). In 2018, combined analysis of 599,912 current drinkers in 83 prospective studies of high income countries, showed alcohol consumption was positive and curvilinear association with all-cause mortality and roughly linearly associated with a cardiovascular disease other than myocardial infarction (1). They recommend the threshold for lowest risk of all-cause mortality was 100 g/week.

Is there any safe threshold for alcohol consumption at nonalcoholic fatty liver disease (NAFLD)? There are evidences of a protective effect of MAC on prevalence and development of hepatic steatosis (3-5). Fibrosis is more important in the prognosis of patients, however, there are few studies about the effect on development and risk of hepatic fibrosis of MAC. In this study of Chang et al. (6), the risk of hepatic steatosis in light (1–9.9 g/day) and moderate drinkers (10–29.9 g/day for men and 10–19.9 g/day for women) was lower than that of nondrinkers with hazard ratio (HR) 0.93 and 0.90, respectively, as previous studies. Especially, the risk of hepatic steatosis is reduced in obese subjects, although the protective effect is lost in non-obese subjects. However, development of hepatic steatosis plus intermediate/high fibrosis score of fibrosis-4 index (FIB-4) was higher in light and moderate drinkers than that of nondrinkers with HR were 1.15 and 1.49, respectively, and the association was stronger in non-obese subjects.

There were some cross-sectional studies suggested the protective effect of MAC for nonalcoholic steatohepatitis (NASH) (7-9). Mitchell et al., studied with 187 subjects biopsy-confirmed NAFLD and showed modest consumption (<70 g/week) in a non-binge pattern was associated with lower fibrosis scores compared to nondrinkers (OR: 0.33; 95% CI: 0.14–0.78, P=0.01) (7). In similar vein, in a meta-analysis of 882 subjects with biopsy-proven NAFLD, MAC (<40 g/day of alcohol) was found to have a significant protective effect on the development of NASH in both fixed and random models (OR 0.501; 95% CI: 0.340–0.740, P<0.001) (8). Also, the histopathologic feature was significantly better in the MAC (<20 g/day) than non-drinker at ballooning score (OR: 0.575; 95% CI: 0.364–0.907, P=0.017) and fibrosis scores (OR: 0.707; 95% CI: 0.512–0.977, P=0.035) in the study of 178 NAFLD subjects (9). However, it is easy to be contaminated by bias such as the reflection of recent alcohol consumption and underestimation of alcohol consumption in these cross-sectional studies. And there may be limited by ambiguous temporal and reverse causality between exposure and consequences. Additionally, they did not adjust co-morbidity including obesity and diabetes or competing subject factors including socioeconomic class, education, diet and physical activity. Therefore, it has emerged a need for large-scale, longitudinal cohort study in an effort to overcome some of these cross-sectional studies.

At a cohort study with 5,437 subjects received the health checkup program repeatedly for 10 years in Japan, new onset of NAFLD diagnosed by US was significantly repressed in healthy men who consume light to moderate alcohol consumption (40–140 and 140–280 g/week) after adjusting age, BMI, smoking states and physical activities (HR: 0.72; 95% CI: 0.60–0.86, P<0.001 and HR: 0.69; 95% CI: 0.57–0.82, P<0.001 in light and moderate alcohol...
consumption, respectively), but not in women (3). However, the meaning of this has dimmed by absence of other compounders including smoking, insulin resistance, high-sensitive C-reactive protein, and socioeconomic status and the lack of evidence of MAC to fibrosis.

In the current issue, it showed some protective effect of MAC on NAFLD in the obese (defined as BMI ≥25 Kg/m²), but not in the non-obese subject. And it revealed a consistently adverse effect of MAC on noninvasive liver fibrosis score. In the prior study conducted in the same research group with 58,927 middle aged subjects diagnosed NAFLD by US and low fibrosis score, also showed that the HR of noninvasive fibrosis marker was significantly worse in light and moderate drinkers compared with non-drinkers after adjustment of compounding factors (10). A harmful effect of MAC was reobserved in a paired biopsy study of Ajmera et al. (11), in 168 subjects with MAC (<20 g/day with non-binge pattern) out of 285 had lower proportion of definitive NASH compared with nondrinker (57% vs. 74%, P=0.01) at baseline. However, MAC had a lower reduction of steatosis grade (0.30 vs. 0.40, P=0.04), and improvement of NASH (adjusted OR: 0.32; 95% CI: 0.11–0.92, P=0.04) compared with non-drinker group during the follow-up of a period of 46±26 months. In particular, they also evaluated the association between change in drinking status and change in histology. The rate of improvement of NASH was highest in the consistent nondrinker and the next highest at modest drinkers who became nondrinkers (11).

It has been already known that heavy alcohol drinking and binge drinking is detrimental effect at health care of NAFLD, but there's still a debate about MAC. However, this large cohort study by Chang et al., has a strength about the evaluation of many of the possible compounding factors with repeated measures of alcohol consumption and other covariates. However, this study also has limitations in the absence of gold standard for the diagnosis of fatty liver and fibrosis which were evaluated by ultrasonography and noninvasive fibrosis marker. In practice, there are ethical and practical problems with conducting invasive biopsies on subjects, therefore, transient elastography or magnetic resonance elastography may be considered as alternatives. Also, there might be selection bias because the subjects with checkups once a year or once every 2 years were relatively healthy and may be concerned about health care.

Regardless of the impact of MAC has on NAFLD and NASH, studies have shown that MAC increases the incidence of liver cancer and lowers overall survival. Even small amounts of alcohol need to be careful, and it is important, ‘as low as possible’. In particular, the harmful effects of alcohol may be significant in female and non-obese group, the personalization of alcohol consumption is required.

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**Footnote**

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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