Editorial

Alcohol use in patients with non-alcoholic fatty liver: a tangled web of causality

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Wine consumption was first associated with a reduced risk of cardiovascular disease in 1979 (1); subsequent studies, including several meta-analyses, showing a J-shaped association with modest alcohol consumption (especially for wine and beer) associated with a lower rate of cardiovascular complications and all-cause mortality, compared with abstention and heavy alcohol use (2). However, controversy persists regarding whether "modest" levels of alcohol consumption (typically defined as ≤2 drinks per day for women and ≤4 drinks per day for men) can achieve health benefits without causing harms (3,4). Differences in patterns of alcohol use and differential levels of confounding across study populations are cited for reasons why benefit versus harm in a given population may vary (4). One such confounder may be the presence of non-alcoholic fatty liver (NAFL), a more prevalent condition among alcohol users now than decades ago.

Since cardiovascular disease ranks as the most common cause of death among patients with NAFL (5), determination of whether "modest" alcohol use may reduce that risk of cardiovascular complications is a high priority. Interestingly, recent studies suggest little, if any benefit. in a U.S. population-based prospective cohort of young adults followed for 20 years, cardiovascular risk factors and subclinical cardiovascular disease measures (e.g., coronary artery calcification, global longitudinal strain) were not different among patients with fatty liver (based on CT attenuation) with modest alcohol use versus abstainers (6). In another population-based study in the U.S., with ultrasound used to identify fatty liver, metabolic syndrome and excessive alcohol use (defined as more than 3 drinks per day for men and more than 1.5 drinks per day for women) were independently associated with increased mortality but with lower levels of alcohol use not interacting with metabolic risks on mortality (7). Finally, in a population-based study of young to middle-aged adults from Korea using ultrasound to detect fatty liver, NAFL plus excessive alcohol (defined as >30 and >20 grams/day for men and women, respectively) was associated with a 9% higher risk of coronary artery calcification than NAFL without excessive alcohol (8). Collectively, these studies highlight the harm of excessive alcohol use and no clear benefit from modest alcohol use.

For patients with NAFLD, potential cardiovascular benefits of alcohol use may be outweighed by harmful effects on liver health. Challenges in interpreting the literature on modest alcohol use and liver outcomes relates to the variable definitions of "modest" alcohol use. By convention, an average intake of less than 21 drinks per week for men and 14 drinks per week for women is used to exclude alcohol as contributing etiology to liver disease in patients suspected of NAFLD (9). However, it must be acknowledged that lower thresholds of alcohol use may contribute to hepatic steatosis or steatohepatitis in a given individual. Additionally, alcohol consumption is "self-reported" and measured using semi-quantitative scales, which can undermine the precision of assigning persons to categories of drinking (modest versus non-modest). Lack of details on lifetime and/or patterns of alcohol use are additional limitations of the available literature. Prospective studies are needed to overcome some of these methodologic issues and studies of liver-related outcomes would be ideally

included liver histology or liver-related outcomes such as cirrhosis and/or liver cancer. In one of the only paired biopsy studies examining NAFLD progression and alcohol use, patients who drank ≤2 (men) or ≤1 drink (women) per day had less improvement in steatosis and lower likelihood of resolution of NASH, in comparison with patients who did not drink at all (10).

In a recent publication in *Hepatology* (11), Chang and colleagues used large prospective cohort of 52,927 Korean adults with NAFL defined by ultrasound echogenicity, who were non-heavy drinkers (<30 grams per day for men, <20 grams per day for women) and had low likelihood of advanced fibrosis or cirrhosis at study entry, to evaluate the association between non-heavy alcohol use and changes in fibrosis. Three different noninvasive fibrosis scores were used: NFS (NAFLD Fibrosis Score), FIB-4, and APRI (AST to platelet ratio index). In fully-adjusted models, the rate of transition from a category of "low" to "intermediate or high" fibrosis score was 6–9% higher in light alcohol users (≤10 grams per day) and 30% higher in moderate alcohol users (10–20 for women and ≤30 for men per day) compared to abstainers. While the use of 3 different measures likely helped to delineate patterns of change, without use of liver biopsy, whether this change in score truly reflects fibrosis progression is questionable. In another study evaluating the impact of lifestyle modification where NAFLD histology was available, change in NFS or FIB-4 between patients who had fibrosis improvement *vs.* those with stabilization or worsening of fibrosis was not seen (12). Age is a component of NFS, FIB-4 and APRI, so with longitudinal follow-up, scores will increase even in the absence of other changes. Acquisition of new metabolic risk factors are also likely with aging, which would be ideally captured by use of time-varying covariate adjustment for weight, diabetes and dyslipidemia over time, in conjunction with alcohol consumption. Finally, since alcohol consumption can contribute to metabolic derangements, evaluation for interactions between alcohol and metabolic syndrome need to be considered. These points highlight the complexity of parsing out the independent effects of alcohol and metabolic derangement to liver disease progression. That said, the study by Chang and colleagues adds to the growing body of literature that call into question the benefit of alcohol in patients with pre-existing NAFLD.

Fibrosis stage has been demonstrated to be the most important predictor of overall mortality and liver-related events (13). Accurate classification of patients with advanced NAFLD is important in targeting these patients for surveillance and treatment, particularly once anti-fibrotic medications are approved and available for use in clinical practice. Use of routine laboratory tests that are readily available in clinical practice to characterize risk in patients with NAFLD and how the risk changes over time is appealing. Non-invasive tools such as NFS, FIB-4, and/or APRI still have value in the initial assessment of patients with NAFLD, but additional refinement of these indices or creation of new ones are needed to reflect sequential changes over time and with aging. Large prospective cohorts that capture cardiovascular and liver-related outcomes will be useful for the development and validation of such predictive tools.

So, what do we tell our patients about alcohol use in the setting of established NAFLD? It is difficult to ascertain a threshold of safe versus harmful levels of alcohol use in patients with NAFL and it is likely that the thresholds will be different than for persons without NAFL. Strong evidence of cardiovascular benefits of modest alcohol use in patients with NAFL is lacking and the limited prospective data on liver effects, including the study from Chang and colleagues, suggest worsening of fibrosis. For all these reasons, we should counsel alcohol abstinence as an integral part of lifestyle management.

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Footnote

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