Viewpoint

Alcohol consumption in non-alcoholic fatty liver disease—harmful or beneficial?

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Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease with an estimated global prevalence of 25%. Approximately 5% of NAFLD patients have cirrhosis and currently NAFLD is the second most common etiology among adults awaiting liver transplant in the United States. In the Western world alcohol overconsumption is the leading cause for advanced decompensated liver disease but whether moderate alcohol consumption, compatible with the diagnosis of NAFLD, plays a role for development of liver-related complications in NAFLD is disputed. Although NAFLD entails a clinically significant risk for encountering complications of advanced liver disease, cardiovascular disease (CVD) is the leading cause of mortality and morbidity among subjects with NAFLD. NAFLD and CVD share many common risk factors, for instance components of the metabolic syndrome. It has been reported that modest alcohol consumption is associated with beneficial effects on risk of metabolic syndrome and insulin resistance, which are crucial for the development and progression of NAFLD.

Studies on effects of alcohol in NAFLD have assessed four different aspects: (I) effects of alcohol on prevalence or incidence of NAFLD; (II) effects of alcohol on the severity of established NAFLD; (III) association of alcohol consumption with hepatocellular carcinoma in NAFLD; and (IV) association of alcohol consumption with mortality in subjects with NAFLD.

Regarding the first aspect a recent meta-analysis of mainly cross-sectional studies concluded that moderate alcohol consumption was associated with a 23% reduction in prevalence of steatosis (1). In a prospective Japanese study of subjects without liver disease at baseline drinking alcohol was associated with reduced incidence of steatosis diagnosed by ultrasonography (2). Moreover, moderate alcohol consumption did not induce hepatic steatosis in healthy individuals when hepatic triglyceride content was measured prospectively with proton magnetic resonance spectroscopy in a randomized study (3).

To assess the second aspect Chang *et al.* have studied the impact of moderate alcohol consumption on non-invasive hepatic fibrosis indices in a large cohort of Korean adults with NAFLD and low fibrosis scores who were followed for a median of 8.3 years (4). They found that moderate alcohol consumption was associated with aggravation of non-invasive markers of fibrosis. The rationale for the study is relevant since fibrosis stage is the best predictor of future liver-related morbidity and overall mortality in NAFLD. Thus, their study may indicate that modest alcohol consumption is detrimental in subjects with NAFLD. However, a major weakness of using non-invasive fibrosis markers is that, although they are excellent in ruling out significant fibrosis, their ability to confirm advanced fibrosis is limited when liver biopsy is used as the reference method. Thus, worsening of fibrosis indices does not necessarily imply that liver fibrosis has progressed during follow-up.

Liver biopsy is still considered the gold standard for assessing severity of NAFLD. In a cross-sectional study of subjects with biopsy-proven NAFLD modest alcohol consumption was associated with 34% less hepatocellular ballooning and 44% lower risk of liver fibrosis compared

with nondrinkers (5). Another report from the same group confirmed a beneficial effect on fibrosis stage in modest consumers compared to alcohol abstainers (6). Similar results were shown in a Swedish study of 120 subjects with histopathologically confirmed NAFLD in which a maximum of 13 drinks per week was associated with lower fibrosis stage (7). However, increased levels of phosphatidyl ethanol in blood (a biomarker of alcohol consumption) were associated with higher stages of fibrosis. This may indicate that more pronounced alcohol consumption, contrary to modest consumption, is harmful in NAFLD or that assessment of alcohol consumption through questionnaires is prone to error. In another histopathological study from Sweden (8), 71 NAFLD patients were followed for an average of almost 14 years and it was shown that heavy episodic drinking was associated with increased risk of progression of fibrosis. Further evidence for a potentially harmful effect of moderate alcohol consumption on the deterioration of NAFLD comes from a recently published longitudinal study (9), in which it was concluded that NAFLD patients with moderate alcohol consumption was less likely to experience spontaneous improvement in liver histology.

Regarding the third aspect, there is increasing evidence to suggest an additive, or even a synergistic, effect between alcohol consumption and BMI for the development of HCC (10). In a recent Japanese study of 301 patients with histopathologically diagnosed NAFLD, patients with modest drinking had significantly higher risk of developing HCC compared with nondrinkers (11).

Results on the fourth aspect, i.e. the effect of alcohol consumption on survival in subjects with NAFLD have been conflicting (2,5). Recently, 4,568 subjects with NAFLD from the National Health and Nutrition Examination Survey were evaluated. Daily consumption of 7 to 21 g alcohol decreased the risk of overall mortality by 41% compared with not drinking (12). Since NAFLD patients are more likely to die from CVD than liver disease these results are in accordance with previous studies showing that modest alcohol consumption is associated with decreased risk of CVD mortality (13). However, a major weakness of the aforementioned study (12) is that the diagnosis of NAFLD was based on a biochemical model and not on imaging or histology.

In summary, most studies indicate that modest alcohol consumption is associated with decreased risk for development of fatty liver disease and moderate drinking may be associated with increased survival in NAFLD patients. Emerging evidence indicates an additive risk of BMI and alcohol for the development of HCC in NAFLD. There are conflicting results regarding the role of alcohol for fibrosis progression in established NAFLD. The paper by Chang *et al*. proposes that modest alcohol consumption can aggravate fibrosis in NAFLD. Unfortunately, liver fibrosis was assessed indirectly with non-invasive fibrosis indices, which have limited ability to detect significant fibrosis. Thus, further studies are needed before well founded advice can be given to NAFLD patients regarding modest alcohol consumption. Ideally, these studies should longitudinally evaluate fibrosis stage histopathologically or, in larger cohorts, with elastography and include direct biomarkers as an objective marker of alcohol consumption.

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None

Footnote

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

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