



NASH, Metabolic Syndrome, and Diabetes: How Sugar and Fat Increase the Risk of Developing Advanced Liver Disease

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Accepted: 15 September 2020 / Published online: 26 September 2020
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Nonalcoholic steatohepatitis (NASH) is on track to become the leading contributor to the global burden of liver disease, in particular due to the finding that NASH is one of the commonest precursors of hepatocellular carcinoma (HCC) [1]. For example in the USA, while the percentage of total liver transplants for recipients with hepatitis C has decreased from 35.3 to 23.6%, the percentage of liver transplants for NASH has increased [2]. Retrospective reviews of two large biopsy databases reported that up to 5% of HCV patients also had NASH [3] and up to one-third of individuals with chronic HCV have type 2 diabetes, which has been associated with worsening outcomes of HCV infection [4].

In this issue of *Digestive Diseases and Sciences*, Benhammou and colleagues evaluated the effects of NAFLD risk factors including obesity and diabetes on the long-term outcomes of patients with HCV treated with direct-acting antivirals (DAAs) [5]. The authors conducted a retrospective study of 33,003 DAA treated US Veterans between 2013 and 2015. The patients were categorized using the body mass index (BMI); diabetes was identified using ICD 9/10 codes in association with hemoglobin A1c > 6.5% or having an active prescription for diabetes medications. Patients were evaluated for the development of cirrhosis, liver decompensation, or the development of HCC and death with a mean follow-up of 3 years. They found an association between the presence of diabetes and increased mortality

and liver-related adverse outcomes including HCC, even among patients without baseline cirrhosis. Patients who were obese also exhibited a higher risk of developing cirrhosis compared with normal-weight patients although surprisingly they had a lower risk of mortality and of developing HCC.

These results underscore the importance of diabetes as an independent risk factor for liver disease, and in particular, HCC development. In contrast to prior experiences with IFN-based treatments, the presence of insulin resistance or type 2 diabetes mellitus did not appear to diminish the rate of sustained virological response (SVR) to DAA treatments [6]. Conversely, while several early studies had suggested that DAA-associated SVR improves the metabolic status, two of those studies did not observe long-term glycemic control [7]. Though the current study did not examine if DAA treatment changed insulin resistance, these data are unlikely to be available in an administrative retrospective study, especially since insulin resistance is not measured in routine clinical practice. Future prospective studies should evaluate this potential association between DAA-associated SVR, changes in insulin resistance, and liver outcomes.

It is particularly worrisome that a significant number of patients with pre-existing diabetes developed HCC within a 3-year follow-up period (hazard ratio of 1.4). Generally, HCC develops on a background of cirrhosis or advanced fibrosis; in particular, the risk of HCC development among those who achieve HCV SVR and who do not have cirrhosis or advanced fibrosis is low [8]. This report suggests otherwise; that this is not necessarily the case for individuals with concomitant diabetes, and is consistent with a prior meta-analysis of 25 studies which showed that those with type 2 diabetes mellitus have an increased risk of HCC, even in the absence of pre-existing cirrhosis [9]. Since NAFLD is common among those with T2DM [9], one could speculate that the majority of those with pre-existing diabetes have concomitant NAFLD. Nevertheless, without the availability of histological data, it is unclear if those who subsequently

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developed HCC had concomitant NASH, and if they had early or advanced liver fibrosis. These data are clinically relevant since they beg the question of whether individuals who achieved HCV SVR without liver cirrhosis should continue to be monitored or undergo HCC surveillance. Future multicenter studies will be needed in order to address this question, and perhaps identify those with diabetes most likely to develop HCC.

This study reinforces the limitations of using BMI to stratify metabolic and liver disease risks, and is consistent with the current WHO definition of the metabolic syndrome where obesity is defined by the presence of truncal obesity [10]. Patients with a high BMI may include those without sarcopenia; furthermore, the presence of ascites also increases body weight. Therefore, individuals with sarcopenia could have a normal BMI. Although the waist and hip circumference measurements are currently not routinely recorded in most routine practice settings, it would be important to evaluate if they are associated with HCC development and/or overall mortality. Perhaps the most promising method of simultaneously, objectively, and noninvasively assessing sarcopenia, visceral obesity, and liver morphology is the non-contrast abdominal CT scan, that has become an effective tool in this regard [11].

Despite the short follow-up, this study adds to the current literature, highlighting the contribution of metabolic risk factors such as T2DM as key drivers of chronic liver disease, including NAFLD and HCC. Given the rising NAFLD burden in the USA, providers should be cognizant of concomitant NAFLD risk factors and the potential risk of ongoing NAFLD-associated liver disease progression in those who achieve HCV SVR.

Funding Open Access funding enabled and organized by Projekt DEAL.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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