Editorial

Diabetes and hepatocellular carcinoma risks in patients with nonalcoholic steatohepatitis related cirrhosis

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Hepatocellular carcinoma (HCC) oncogenesis in the absence of alcoholic liver disease and chronic viral hepatitis has aroused growing clinical concern in clinical practice. In the era of remarkable advances of viral hepatitis treatment, nonalcoholic steatohepatitis (NASH) has become an emerging cause of HCC (1,2). Diabetes is a major risk factor of NASH and nonalcoholic fatty liver disease (3). With the increasing burden of diabetes globally, diabetes has also been recognized for contributing to cirrhosis, HCC development, and deaths from HCC (4-6). Nonetheless, the role of diabetes in the progression of NASH-related cirrhosis to HCC is unclear.

To investigate the link between risk of HCC and diabetes among patients with NASH-related cirrhosis, Yang *et al*. launched a retrospective cohort study among patients with NASH-related cirrhosis at Mayo Clinic Rochester from 2006 to 2015 (7). Among 354 participants with NASH-related cirrhosis, 30 developed liver cancer during a median period of 47 months. Diabetes was related to an increased HCC risk (adjusted HR, 4.2; 95% CI: 1.2 to 14.2). In addition, low serum albumin (adjusted HR, 2.1; 95% CI: 1.5 to 2.9) was also positively related to HCC risks. HCC development was not associated with body mass index, hyperlipidemia, and hypertension. They also obtained a registry database of 6,630 adult liver transplant registrants with NASH-related cirrhosis from 2004 to 2017 for external validation. During a median period of 21 months, 291 subjects progressed to HCC. Diabetes was also positively related to HCC risks (adjusted HR, 1.3; 95% CI: 1.0 to 1.7).

In line with a cohort study linking diabetes to liver cancer in patients who had neither chronic viral hepatitis nor cirrhosis (5), Yang *et al*. further highlighted the contribution of diabetes to the progression from NASH-related cirrhosis to HCC. However, anti-diabetic medications were not linked to HCC occurrence in this study among participants with diabetes. Nevertheless, to explore the association of anti-diabetic medications with HCC occurrence, restricting the analysis to newly diagnosed diabetes participants on any antidiabetic agents would be more appropriate. A recent nationwide population-based study from 2003 to 2013 in a HCC-endemic area observed that any use of all insulin analogues was no more related to HCC incidence after exclusion of chronic viral hepatitis and concluded that chronic viral hepatitis might amplify the impact of premixed insulin analogues during liver cancer development (8).

A practical concern is that a substantial number of NASH-related HCCs arise in patients without cirrhosis (9-12). The characteristic features of NASH might appear in patients with early cirrhosis but disappear at late stages of cirrhosis (9). This partially explains why dyslipidemia and obesity were not related to HCC risks among patients with NASH-related cirrhosis, as shown by Yang *et al*. (7).

The association between dyslipidemia and the progression of NASH-related cirrhosis to liver cancer might also be affected by the protective effects of lipid-lowering drugs on HCC oncogenesis (13), although many clinicians feared to prescribe lipid-lowering drugs among patients with cirrhosis and led to confounding by contraindication. However, this study did not estimate the association of lipid-lowering drugs with HCC occurrence. Another issue is the potential contribution of occult hepatitis B virus infection to HCC development, but its impact was obscure and difficult to be measured without liver tissues in this study (14). A recent hospital-based analysis of 90 patients with HCC and negative hepatitis B surface antigen reported that 70% of these patients had occult hepatitis B virus infection (15).

In conclusion, Yang *et al.* conducted a retrospective cohort study to elucidate a positive association between diabetes and HCC risks in patients with NASH-related cirrhosis. It implies we should arrange liver cancer surveillance for high-risk individuals including the elderly, diabetes patients, and those with a low serum albumin level. Next, clinicians will wonder whether DM prevention or choosing certain anti-diabetic medications in NASH-related cirrhosis patients results in reduced HCC risks in the future.

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Footnote

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