Invited Editorials

Editorial: diabetes and its association with hepatocellular carcinoma in chronic hepatitis B

M. Konerman* & R. Loomba†,‡,§

*Division of Gastroenterology and Hepatology, Department of Medicine, University of Michigan, Ann Arbor, MI, USA.
†NAFLD Translational Research Unit, Division of Gastroenterology, University of California at San Diego School of Medicine, La Jolla, CA, USA.
‡Division of Gastroenterology, Department of Medicine, University of California at San Diego School of Medicine, La Jolla, CA, USA.
§Division of Epidemiology, Department of Family and Preventive Medicine, University of California at San Diego, La Jolla, CA, USA.
E-mail: roloomba@ucsd.edu

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The impact of metabolic syndrome and its complications, namely hepatic steatosis and diabetes, have appropriately become focal points of investigation within hepatology in the setting of the evolving obesity epidemic. Although there is a large body of research that has demonstrated an increased risk of hepatocellular carcinoma (HCC) in patients with diabetes, the specific disease characteristics that modify this relationship require further investigation.[1] This is particularly the case in patients with viral hepatitis, where studies have produced conflicting data in terms of the independent association of metabolic risk factors with HCC.[1–4]

In a recent issue, Fu *et al.* provide further data to support the observation of increased risk of HCC for diabetic patients with CHB.[5] Using the Taiwanese National Health Insurance Research Database, they included a random sample of 2099 patients with CHB with new-onset diabetes and 2080 age, gender and inception-point matched nondiabetic patients. After adjusting for possible contributing factors, diabetes was an independent predictor for HCC with a hazard ratio of 1.798.

This study has several strengths including a large sample-size, length of longitudinal follow-up and accounting for multiple potential confounders for competing risk for developing HCC. Several unaddressed questions remain, however, particularly those stemming from the lack of histology to address possible concomitant steatohepatitis. It is well known that diabetes is an independent risk factor and driver of steatohepatitis, and untreated steatohepatitis, along with other metabolic dysregulations associated with diabetes, have been shown to increase the risk of HCC in the setting of hepatitis B infection.[6, 7] Additionally, further detail regarding duration of diabetes and control of diabetes on the risk of HCC should also be evaluated.[2, 3, 8, 9] Lastly, the impact of antidiabetic regimen should be assessed as data has suggested decreased risk of HCC and liver-related mortality in patients on metformin.[8, 10] In this study, only 39% of diabetics were on treatment and the effect of diabetic treatment agents on HCC risk was not assessed.

Overall, this study demonstrates the importance of addressing modifiable metabolic risk factors in patients with CHB. Lifestyle interventions to prevent obesity, diabetes and other features of the metabolic syndrome should be emphasised in the care of patients with CHB. Further studies are needed to clarify the attributable risk of HCC in diabetics (such as duration and severity of steatohepatitis), as well as optimal treatment of steatohepatitis, in order to minimise the risk of incident HCC in CHB.

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Editorial: diabetes and its association with hepatocellular carcinoma in chronic hepatitis B – authors' reply

S.-C. Fu* & Y.-W. Huang*,†,‡

*Liver Center, Cathay General Hospital Medical Center, Taipei, Taiwan.
†School of Medicine, Taipei Medical University, Taipei, Taiwan.
‡Division of Gastroenterology, Department of Internal Medicine, National Taiwan University College of Medicine, Taipei, Taiwan.
E-mail: ywhuang@cgh.org.tw or yiwenhuang@ntu.edu.tw

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We thank Konerman and Loomba for the excellent editorial comments.[1] Our large population-based study in a hepatitis B virus endemic country with careful selection of newly diagnosed diabetes strongly suggests that diabetes superimposed on persistent hepatitis B infection promotes the development of hepatocellular carcinoma (HCC).[2]

Table 1 | Risk factors for hepatocellular carcinoma: Cox proportional hazard analysis in a population-based cohort of chronic hepatitis B patients with new onset diabetes

	Adjusted hazard ratio*	95% confidence interval	*P* value
Diabetes duration			
>3 years	2.067	1.144–3.734	0.016
≤3 years	0.820	0.275–2.448	0.722

*Adjusted for age, gender, hyperlipidemia, chronic hepatitis B treatment, statins therapy, cirrhosis, comorbidity index and obesity.

Previous studies disclosed the association between diabetes and HCC in hepatitis B-infected patients.[3–6] Our study provides new evidence on temporal relationship by which diabetes precedes HCC in patients with chronic hepatitis B infection could infer a causal relationship, rather than only association. Diabetes was an independent predictor for HCC with an adjusted hazard ratio (AHR) of 1.798. The risk was higher (AHR = 2.067, Table 1) among patients with the duration of diabetes of more than 3 years, which further support the causal association.

The study design, to enrol newly diagnosed diabetes, limited the potential to assess the control of diabetes including diabetic treatment on the risk of HCC. As we have shown, only 39% of diabetics were on therapy, thus lacking the power to evaluate its effect on HCC risk. The effect of diabetic control on the risk of HCC could only be assessed in a different study design, which does not exclude the pre-existing diabetes.

The effect of steatohepatitis on the risk of HCC in patients with chronic hepatitis B plus new onset diabetes is an interesting issue to be resolved. Although diabetes and its associated other metabolic dysregulations have been shown to increase HCC risk in patients with hepatitis B infection,[6, 7] the contribution of steatohepatitis in these studies in unclear. In epidemiological and database studies including huge number of patients and samples, complete histological evaluation for consistent diagnosis of steatohepatitis and its severity is a tremendous challenge. Furthermore, as the therapy of steatohepatitis is still controversial, its treatment in patients with chronic hepatitis B infection is even more challenging.