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Editorial

Does obesity increase the risk of hepatocellular carcinoma in chronic hepatitis B patients?

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Many studies revealed that obesity was a risk factor for various cancers including hepatocellular carcinoma (HCC).[1] In a cohort study with a population of around 900,000, males with 35 kg/m^2 or higher body mass index (BMI) had 4.4 times as high dying risk from liver cancer as the control group with normal BMI (18.5 -24.9 kg/m^2).[2] According to a recent meta-analysis, the relative risk of liver cancer was 1.17% in overweight patients and 1.89% in obese patients compared to normal weight controls.[3] Furthermore, obesity can be a cause of metabolic syndromes including insulin resistance and type 2 diabetes as well as a broad spectrum of non-alcoholic fatty liver diseases (NAFLD) including simple steatosis, non-alcoholic steatohepatitis (NASH), and cirrhosis.[4] A population-based case control study showed that diabetes tripled the HCC risk,[5] and in another large prospective cohort study, the hazard ratio of HCC was 2.16.[6] Furthermore, the correlation between diabetes and HCC was verified through various meta-analyses.[7,8] The NAFLD which is a hepatic manifestation of metabolic syndrome was recently found to develop into cirrhosis and cause HCC, and it was regarded as the main cause of cryptogenic cirrhosis.[9-11]

Chronic hepatitis B (CHB) is one of the most important causes of HCC, accounting for around 60% in Africa and Asia and around 20% in western countries.[12] Among the patients infected by hepatitis B virus (HBV) in Asia, the incidence rate of HCC is estimated to be 0.2% per year in inactive carriers, 0.6% in chronic hepatitis without cirrhosis patients, and 3.7% in compensated cirrhosis patients.[13] It is generally known that HBV-infected subjects have around 100 times as high risk of HCC as uninfected subjects.[14] A large prospective cohort study has shown that HBV DNA titer is closely associated with HCC risk.[15] Many meta-analyses already have revealed that nucleos(t)ide analogues (NAs) decrease the occurrence of HCC in CHB patients.[16,17] A recent study on CHB patients treated with entecavir (ETV) showed that 5 year HCC incidence rate was decreased significantly by 3.7% in the ETV treated group compare to 13.7% in the historical matched untreated control group.[18]

However, unlike chronic hepatitis C (CHC), it is not clear whether obesity is associated with the development of HCC in CHB patients. In a study in Taiwan which followed up 23,820 persons for 14 years, anti-HCV seropositive people with obesity of 30 kg/m^2 or higher BMI had four times higher risk of HCC, and people with no hepatitis B virus (HBV) and hepatitis C virus (HCV) infections had twice higher risk of HCC.[19] However, obesity was not correlated with HCC risk in HBs antigen seropositive people. Dia-

Abbreviations:

BMI, body mass index; CHB, Chronic hepatitis B; CHC, chronic hepatitis C; ETV, entecavir; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NAs, nucleos(t)ide analogs

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betes was associated with HCC in all groups. Thus, HBV-related HCC risk was more correlated with diabetes (adjusted OR = 2.27, 95%CI: 1.10-4.66) than with extreme obesity (adjusted OR = 1.36, 95%CI: 0.64-2.89).[19]

This study by Lee et al. investigated the effects of obesity on HCC development in a total of 102 CHB patients who had been treated with ETV. The median follow-up duration was 45.2 (interquartile range: 36.0-58.3) months, and the 1 year, 3 years, and 5 years cumulative incidence rates of HCC were 0%, 5.3%, and 9.0%. In univariable analysis, the risk factors of HCC development were platelet count <120,000 /mm^2 (HR 5.21, *P*=0.031), HBeAg negativity (HR 5.61, *P*=0.039), and liver cirrhosis (HR 10.26, *P*=0.031). In multivariable analysis, only liver cirrhosis (HR 9.07, *P*=0.042) was a significant risk factor of HCC development. The obesity-related risk factors BMI ≥25 kg/m^2 (HR 0.90, *P*=0.894), waist circumference ≥90 cm (HR 1.10, *P*=0.912), waist-to-hip ratio ≥0.9 (HR 1.94, *P*=0.386), visceral fat area ≥100 cm^2 (HR 1.69, *P*=0.495), and hepatic steatosis (HR 0.57, *P*=0.602) had no significant correlation with HCC development. However, a few limitations of this study must be mentioned. The first is that as stated above, the number of patients was too small and the follow-up period was too short to examine the effects of obesity on HCC development in patients with CHB which is a strong risk factor of HCC development. The incident cases of HCC were only 7 (9%), the cases who had diabetes were only 4 (4%), and the cases who had metabolic syndrome were only 16 (16%). The second limitation is that a lot of cirrhosis patients were included in whom most cases of HCC developed. However, as it is well-known that metabolic factors such as obesity Only a few cases of obesity were included disappear once NAFLD patients develop cirrhosis,[20] Only a few cases of obesity were included in cirrhosis patients. However, data about this is not detailed in the results of this study. The third limitation of this study is that according to the baseline characteristics, the median BMI of enrolled patients is 23.6 ± 3.1 kg/m^2, but the numbers of patients with higher BMI more than 25 kg/m^2 or 30 kg/m^2 are not clearly stated.

In the Taiwan cohort study that was introduced above, antiviral treatment for patients with CHB is not mentioned. Therefore, the effects of obesity and similar metabolic factors on CHB patients who develop HCC in relatively younger ages than patients with CHC are estimated to be smaller. However, if serum HBV DNA continued to be negative by antiviral treatment, it would decrease the progression into cirrhosis and HCC. Thus, the effects of obesity and other metabolic factors could be increased on HCC development.

In conclusion, the authors reported that obesity had no correlation with HCC development in CHB patients unlike in CHC patients, but it is not definite. It is especially unknown about the effects of obesity or other metabolic factors on HCC development in CHB patients treated with NAs. In this retrospective study, no correlation was found between HCC development and obesity related factors in ETV treated CHB patients, but this study is insufficient for making a conclusion. A long-term cohort study of a much greater scale than those of existing studies would be required to clearly determine the correlation.

Conflicts of Interest

The author has no conflicts to disclose.

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