Journal of Diabetes & Clinical Practice

Toshiyuki, J Diabetes Clin Prac 2023, 6:1

Review Article Open Access

Diabetes Mellitus Incidence the Risk of Hepatocellular Carcinoma: A Systematic Review

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Abstract

Background: Type 2 diabetes mellitus has been proved to be a risk factor of hepatocellular carcinoma, but how diabetes affects incidence of hepatocellular carcinoma among patients with chronic hepatitis B virus infection remains controversial.

Methods: A comprehensive search of Medline and Embase was performed. Incidence of hepatocellular carcinoma in chronic hepatitis B patients was the primary outcome. Pooled HRs and 95% CIs were calculated to assess the correlation between diabetes and incidence of hepatocellular carcinoma.

Results: Five cohort studies and two case–control studies were identified, with a total of 21,842 chronic hepatitis B patients. The diabetes mellitus cohort was found to have increased incidence of hepatocellular carcinoma (pooled HR 1.77, 95% CI 1.28–2.47; fixed effect) and worse overall mortality (pooled RR 1.93, 95% CI 1.64–2.27; fixed effect) in comparison with those without diabetes. In case–control studies, hepatocellular carcinoma cases were found to have an insignificantly elevated diabetes mellitus rate in comparison with the control group.

Conclusion: Type 2 diabetes mellitus is significantly associated with increased risk of hepatocellular carcinoma among patients with chronic hepatitis B virus infection, and aggressive management of diabetes mellitus is strongly suggested.

Keywords: Type 2 diabetes mellitus; Hepatocellular carcinoma risk; HBV-infected

Introduction

Hepatocellular carcinoma (HCC) is the sixth-most common cancer worldwide, leads to nearly 1 million deaths every year, and is the third-most frequent cause of cancer-related death. The incidence of HCC is particularly high in Asia and in Africa, intermediate in southern Europe, and much lower in most developed countries. Hepatitis virus infection, mainly hepatitis B virus and hepatitis C virus, has been widely accepted as the major recognized risk factor of HCC globally, accounting for over three-quarters of primary HCC cases [1]. However, when HBV or HCV is not involved, the etiologic factor of HCC varies, of which diabetes mellitus (DM), heavy alcohol drinking, smoking, obesity, and aflatoxin are relatively important.

DM, which has been proved to be a risk factor of various kinds of malignancies, is strongly associated with nonalcoholic fatty-liver disease and many other metabolic processes. Insulin resistance was believed to play an important role in hepatocarcinogenesis in HBV patients with type 2 DM or even prediabetes. The association between DM and HCC risk was indicated to be independent of cirrhosis, though most HCC cases presented with cirrhosis. A recent systematic review demonstrated that concurrent DM is strongly associated with increased HCC risk among chronic HCV patients, but scanty evidence is available about the correlation between DM and HCC in chronic HBV (CHB) patients [2]. The clinical landscape of HCV is currently facing a great change, such that its cure would be universal for patients for whoever has access to effective therapy, which will definitely result in a decrease in HCC developments. Therefore, HBV infection, alcohol consumption, and metabolic disorders, such as DM and obesity, are supposed to be the leading etiologic factors of HCC in the coming future. There are mixed results of the few studies on the association between DM and the risk of HCC in patients with CHB. As such, we performed this meta-analysis and systematic review of the literature to achieve further understanding of the impact of DM on the risk of developing HCC in patients with CHB [3].

Epidemiological Studies Linking DM and HCC

When DM was first investigated as a risk factor in cancer related deaths, the causes of these two diseases were unknown. In 1934, a study of 10,000 diabetic patients reported an association between pancreatic cancer and DM. In 1991, a large population-based cohort study conducted by Adami et al. in Sweden reported an increased risk of both pancreatic cancer and HCC in patients with DM [4]. Subsequently, the association between DM and HCC has been observed in numerous cohort studies and case-control studies. In 2006, a meta-analysis of 13 cohort studies and 13 case-control studies conducted by El-Serag et al. found that DM is associated with an approximately 2.5- fold increased risk of HCC. In 2014, Tanaka et al. systematically reviewed epidemiologic investigations on DM and HCC among Japanese populations, 9 of the 10 relative risk (RR) estimates in the case-control studies and 17 of the 24 RR estimates in the cohort studies showed a weak to strong positive association between DM and HCC risk, indicating that the overall evidence in Japan strongly supports an increased risk of HCC among DM patients. Other studies also reported a 2- to 3-fold increased risk of HCC in patients with DM, and this association was generally observed in patients free of viral hepatitis. However, several studies conducted in Taiwan did not find an increased risk of HCC in

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Received: 03-Jan-2023, Manuscript No: jdce-23-87624, **Editor assigned:** 05-Jan-2023, PreQC No: jdce-23-87624 (PQ), **Reviewed:** 18-Jan-2023, QC No: jdce-23-87624, **Revised:** 25-Jan-2023, Manuscript No: jdce-23-87624 (R), **Published:** 31-Jan-2023, DOI: 10.4172/jdce.1000173

Citation: Toshiyuki Y (2023) Diabetes Mellitus Incidence the Risk of Hepatocellular Carcinoma: A Systematic Review. J Diabetes Clin Prac 6: 173.

patients with DM. In 2013, Chen et al. conducted a retrospective cohort study to explore risk factors for HCC in 56,231 adults and reported that DM [5], metabolic syndrome, and obesity were not risk factors for HCC, regardless of hepatitis B virus (HBV) or hepatitis C virus (HCV) status. Likewise, a case-control study conducted by Lu et al. did not nd an association between DM and HCC. In a series of 823 HCC patients and 3459 controls, El-Serag et al. found that DM increased the risk of HCC only in the presence of other risk factors such as HBV, HCV, or alcoholic cirrhosis.

A i-diabe ic Medica i a d Ri f HCC

Results of in vitro and in vivo preclinical studies have suggested that antidiabetic drugs in uence the development of multiple cancers. Epidemiological evidence indicates that metformin and thiazolidinediones (TZDs) are associated with a lower overall cancer incidence. However, insulin and insulin secretagogues are associated with higher cancer incidence and cancer-related mortality [6]. In this section, we reviewed the e ect of conventional antidiabetic drugs on the risk of HCC in patients with DM.

Me f i

e metformin is a rst-line therapy for T2DM and is o en prescribed for prediabetes and DM that is less severe or of shorter duration. Metformin can decrease blood glucose and insulin levels in these patients; however, the mechanism underlying this e ect is not entirely clear. In addition, results of several pharmacoepidemiologic studies suggest that metformin use lowers the incidence of cancers, including HCC, in patients with DM, whose risk of developing HCC is at least 2-3 times higher than individuals without DM [7]. Long-term metformin treatment appears to inhibit hepatocellular transformation, decreasing the risk of HCC to levels similar to that of nondiabetic patients. In a rat model of HCC, DePeralta et al. found that HCC incidence was decreased by 44% when metformin treatment was initiated at the rst signs of brosis but was unchanged when metformin was not initiated until the rst signs of cirrhosis. A nationwide case-control study conducted by Chen et al. found that metformin decreases the risk of HCC in patients with DM by 7% with each additional year of use. However, a cohort study conducted in the UK did not nd a lower incidence of HCC in patients receiving metformin compared with those receiving sulfonylurea. Furthermore, a meta-analysis of randomized controlled trials comparing the risk of cancer in patients receiving metformin or other antidiabetic drugs did not observe a protective e ect of metformin against HCC. e molecular mechanism underlying the antitumor activity of metformin is unclear [8]. Results of studies in breast cancer cells suggest that metformin inhibits cancer by activating AMP-activated protein kinase (AMPK), which may lead to growth inhibition, thereby decreasing protein synthesis. Other studies indicate that metformin inhibits tumorigenesis through both insulin-dependent and insulin independent mechanisms and that its e ects may be lower in patients with lower insulin levels. Results of several small-scale trials demonstrate the potential for metformin to improve liver histology and body weight in patients with NAFLD, suggesting another potential pathway by which metformin may prevent HCC. However, a more recent study did not observe a signi cant improvement in liver histology in NAFLD patients receiving metformin; thus further research evaluating liver histology in patients receiving metformin is needed.

Duration of DM and HCC Development e duration of DM prior to HCC development may play an important role in the relationship between DM and HCC. A case-control study in Canada showed that the risk of HCC was higher in individuals with a longer history of DM. Similarly, a meta-analysis by Wang et al. indicated that those with a history of DM > 10 years had the highest risk of HCC; however, this study had relatively low power because of the small number of studies included [9]. Hassan et al. reported that, compared with patients with a DM duration of 2–5 years, the risk of HCC was higher in those with a DM duration of 6–10 years or >10 years. Miele et al. also found a higher risk of HCC with longer duration of DM was higher than that of patients with duration of 5–10 years; however, this di erence was not signi cant. In our previous study, results of multivariate analysis showed that longer duration of DM did not signi cantly increase HCC risk. Taken together, most of studies which investigated positively relationship between DM duration and HCC risk suggest that duration of DM > 10 years increases the risk of HCC; however, larger studies are needed to con rm these results. Meanwhile, the severity of DM should be clari ed because patients with longer duration are likely to have more severe DM which might impact HCC development [10].

C c i

Diabetes mellitus is globally endemic, and increasing evidence from observational studies suggests that DM is a risk factor for HCC. erefore, the increasing prevalence of DM may increase the incidence of HCC. e use of metforminnce of 4sev