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Review Article

Diabetes and Risk of Hepatocellular Carcinoma in Cirrhosis Patients with Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the world. NAFLD is a hepatic manifestation of insulin resistance, the core pathophysiology of diabetes. Multiple clinical studies show that diabetes increases the risk of liver disease progression and cirrhosis development in patients with NAFLD. Diabetes has causal associations with many different cancers, including hepatocellular carcinoma (HCC). More recent studies demonstrate that diabetes increases the risk of HCC in patients with underlying NAFLD cirrhosis, confirming the direct hepatocarcinogenic effect of diabetes among cirrhosis patients. Diabetes promotes hepatocarcinogenesis via the activation of inflammatory cascades producing reactive oxygen species and proinflammatory cytokines, leading to genomic instability, cellular proliferation, and inhibition of apoptosis. Given the global increase in the burden of NAFLD and HCC, high-risk patients such as older diabetic individuals should be carefully monitored for HCC development. Future larger studies should explore whether the effect of diabetes on HCC risk in NAFLD cirrhosis is modifiable by the type of antidiabetic medication and the effectiveness of diabetes control.
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Key Words: Cirrhosis; Diabetes mellitus; Hepatocellular carcinoma; Non-alcoholic fatty liver disease

INTRODUCTION

Hepatocellular carcinoma (HCC) comprises approximately 80% of primary liver cancer cases[1] and leads to the fourth most common cancer-related death worldwide.[2] Although new advances in systemic therapy, such as targeted therapies[3] and immune checkpoint inhibitors,[4] have substantially improved the clinical outcomes of patients with advanced HCC, early diagnosis is still essential since patients with early-stage HCC can potentially undergo curative-intent treatment.[5] As such, identifying risk factors of HCC and implementing surveillance among at-risk patients play a crucial role in early-stage cancer detection and improving the prognosis of patients with HCC. The main risk factors for HCC include chronic hepatitis B virus, hepatitis C virus infection, heavy alcohol consumption, nonalcoholic fatty liver disease (NAFLD), aflatoxin,[6] smoking, and type 2 diabetes with variation in the proportion of each risk factor by regions.[7,8] These risk factors can result in cirrhosis, the strongest risk factor for HCC development.[9,10]

NAFLD includes a spectrum of diseases, such as simple hepatic steatosis and nonalcoholic steatohepatitis (NASH).[11] A meta-analysis by Le *et al.*[12] including 245 studies of approximately 5.4 million individuals reported that the global prevalence of NAFLD was 29.8%, with South America and North America having the highest prevalence (35.7% and 35.3%, respectively). Risk factors for NAFLD-related HCC include diabetes, obesity, metabolic syndrome, smoking, gut microbiome and bile acids, eth-

nicity, and genetics.[13,14] Of note, diabetes is associated with higher rates of advanced fibrosis in patients with NASH[15,16] and is the most significant population-attributable fraction of risk factors for HCC in the United States.[17]

In this review, we will discuss the role of diabetes on the risk of HCC in patients with cirrhosis and NAFLD. We will also summarize risk stratification, prediction models, and potential preventive strategies for these patients.

EPIDEMIOLOGY OF NAFLD-ASSOCIATED HCC

NAFLD can account for up to 38% of the HCC burden in some regions and is the most rapidly growing cause of HCC worldwide.[7,18] Karim *et al.*[19] identified 5,098 HCC patients in the United States from the Surveillance, Epidemiology and End Results–Medicare database and reported that NAFLD was the leading cause of HCC (35.6%). The authors also found that NAFLD was associated with lower surveillance receipt (adjusted odds ratio [aOR], 0.31) and more unrecognized cirrhosis at HCC diagnosis (aOR, 4.42). Dyson *et al.*[20] reported that the proportion of NAFLD-associated HCC increased from <10% in 2000 to 35% in 2010, and the proportion might be substantially higher because only patients with histologic or radiological evidence were considered to define NAFLD, while half the HCC patients with no known chronic liver disease had at least one metabolic risk factor. Estes *et al.*[21] projected that the incidence of NAFLD-associated HCC in the United Kingdom would increase by 88% from 2016 to 2030, and the incidence would be the highest in Germany in 2030. Similarly, the incidence of NAFLD-related HCC by 2030 is projected to rise by 82%, 117%, and 122% from 2016 in China, France, and the United States, respectively.[7] Rising rates of obesity may contribute to the increasing incidence of diabetes and NAFLD as well as NAFLD-related HCC. A United States-based study by Lee *et al.*[22] demonstrated a moderate, positive correlation between the temporal trend of HCC incidence rates and obesity prevalence among different states. In addition, state-level physical activity was inversely associated with the trend of HCC incidence rates, which suggested that NAFLD may have a significant impact on the ongoing rise in HCC incidences in some states.

A meta-analysis including 18 studies with 470,404 patients showed that the incidence of HCC in patients with NAFLD was 0.03 per 100 person-years, compared to 3.78 per 100 person-years in those with cirrhosis.[23] In contrast to viral hepatitis-related and alcohol-related HCC, which typically occurs in the setting of underlying cirrhosis, NAFLD-associated HCC can develop without cirrhosis.[24] A recent U.S. population-based study showed that only 57.9% of patients with NAFLD-related HCC had confirmed cirrhosis,[19] and a meta-analysis including 61 studies demonstrated that 38.5% of patients with NAFLD-related HCC did not have cirrhosis.[25] Rates of NAFLD-related HCC were estimated at 0.01 to 0.08 per 100 person-years in patients with non-cirrhotic liver.[13] The absence of cirrhosis often leads to late detection of HCC in NAFLD patients as cancers are often diagnosed when patients develop cancer-related symptoms in the absence of a surveillance program.

DIABETES AS A RISK FACTOR FOR HCC

Multiple studies confirmed diabetes as a risk factor for HCC. El-Serag *et al.*[26] published a prospective cohort study, including 173,643 diabetic patients and 650,620 non-diabetic patients, and reported that diabetes was significantly associated with NAFLD (hazard ratio [HR], 1.98) and HCC (HR, 2.16). They also found that diabetic patients with more than 10 years of follow-up carried the highest risk. Hassan *et al.*[27] conducted a hospital-based case-control study comparing 420 HCC patients with 1,104 healthy controls and found that diabetes was more prevalent in HCC patients (aOR, 4.2). Compared to patients with a diabetes duration of 2 to 5 years, patients with a diabetes duration of 6 to 10 years and more than 10 years had an OR of 1.8 and 2.2 for HCC, respectively. This suggests that the duration of diabetes is associated with the risk of HCC development.

A systematic review by El-Serag *et al.*[28] exhibited that type 2 diabetes was associated with an approximately 2.5-fold increase in the risk for HCC. In addition, the risk estimate from 13 case-control studies indicated a 2.5-fold increased odds of diabetes in patients with HCC compared to controls without diabetes. Kanwal *et al.*[29] conducted a study of 271,906 NAFLD patients from 130 facilities in the Veterans Administration with a mean follow-up of 9 years. They observed a stepwise increase in the risk of developing cirrhosis or HCC with each additional metabolic trait (i.e., obesity, diabetes, hypertension, and dyslipidemia), and diabetes had an adjusted HR of 2.77 and 1.31 for developing HCC and cirrhosis, respectively.[29] Moreover, NAFLD is associated with an approximately 2-fold risk of diabetes, independent of obesity and other metabolic traits. The risk of diabetes is also correlated with the severity of NAFLD.[30]

Studies showed that the prevalence of diabetes increased with liver disease progression and cirrhosis development.[31,32] Diabetes also accelerates fibrosis progression in NASH patients.[15] More recently, several studies investi-

gated the association between diabetes and HCC in NASH cirrhosis patients to determine if diabetes has a direct carcinogenic effect independent of liver disease progression. In this study, diabetic patients had an increased risk of developing HCC in a Mayo Clinic Rochester cohort (n=354 patients with NASH cirrhosis; HR, 4.2) and a United Network for Organ Sharing cohort (n=6,630 NASH registrants; HR, 1.3) in multivariable analyses.[33] Similar results were seen in a nationwide study involving 130 Veterans Administration facilities by Kanwal *et al.*[34] suggesting a 1.5-fold increased risk of HCC among NAFLD cirrhosis patients with diabetes compared to those without diabetes.

DIABETES AND HEPATOCARCINOGENESIS

Diabetes mellitus, type 2, is characterized by hyperglycemia, hyperinsulinemia, and insulin resistance, which can contribute to hepatocarcinogenesis (Fig. 1).[35] Hyperglycemia initiates modification in cell vasculature and causes endothelial cell debilitation, resulting in increased growth factor production, upregulation of inflammatory genes, excessive generation of reactive oxygen species (ROS), increased oxidative stress, and enhanced cell permeability. Vascular endothelial growth factor in response to endothelial damage stimulates the proliferation of liver cells and the development of HCC.[36] ROS can interact with lipids and amino acids and damage DNA.[37] For example, ROS may induce mutations in TP53, which is a tumor suppressor gene.[38] Hyperinsulinemia leads to *de novo* lipogenesis and consequently lipid accumulation within the liver.[39] Adipocytes excrete adipokines and leptin that promote insulin resistance.[40,41] Cytokines produced by the liver, infiltrating immune cells, and adipocytes, such as tumor necrosis factor α, interleukin 6, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), due to chronic lipid accumulation and lipotoxicity can also lead to insulin resistance, which further accelerates the defects in insulin signaling in pancreatic β cells.[42,43] In addition, adipocytes produce adiponectin, a peptide hormone that enhances insulin reaction, decreases triglyceride synthesis, and stimulates β oxidation in favor of lipid clearance in skeletal muscle and liver.[44] Clinically, the leptin to adiponectin ratio can be used to measure insulin resistance, with lower values associated with higher insulin sensitivity and lower cardiovascular risks.[45] Hyperinsulinemia also involves upregulation of the insulin growth factor (IGF) pathway as the consequence of overexpressed IGF-1 and aberrantly expressed fetal IGF-2.[46] IGF-1 then activates protein kinase B/mammalian target of rapamycin (AKT/

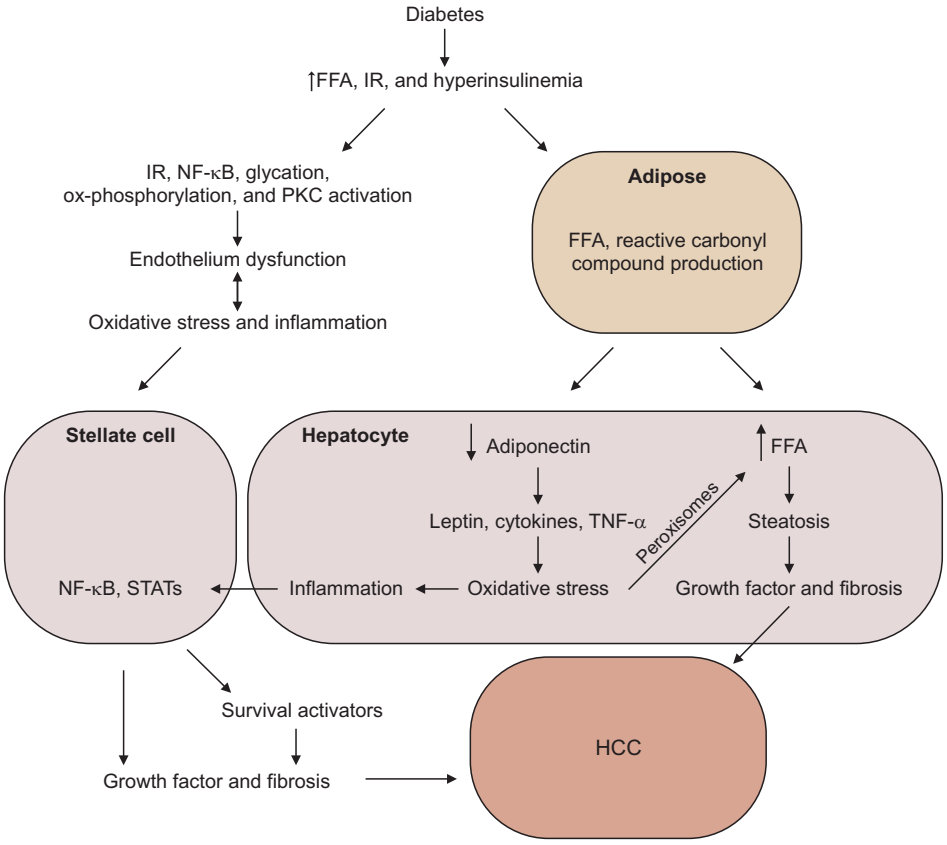

Fig. 1. Brief illustration of hepatocarcinogenesis in diabetes. Diabetes enhances the production of FFA, insulin secretion, and IR. These lead to increased reactive oxygen species, inflammation, and oxidative stress in adipocytes and hepatocytes. Impaired PKC, NF-κB, STAT, leptin, and TNF-α cascades due to diabetes also accelerate fibrosis by stellate cells and contribute to hepatocarcinogenesis.
FFA, free fatty acid; IR, insulin resistance; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; ox-phosphorylation, oxidative phosphorylation; PKC, protein kinase C; STAT, signal transducer and activator of transcription protein; TNF-α, tumor necrosis factor α; HCC, hepatocellular carcinoma.

mTOR) and mitogen-activated protein kinase (MAPK) pathways, which inhibit apoptosis and enhance cell proliferation.[47] Activation of the IGF pathway has been observed in a subset of human HCC.[46] Besides, the production of free fatty acids also activates c-Jun N-terminal kinase 1 (JNK1) that inhibits cell apoptosis.[48]

Fujii *et al.*[49] developed a murine model and proposed that NASH-based fibrosis might be a pivotal link to diabetes and HCC. They exposed neonatal mice to low-dose streptozotocin, and the mice developed liver steatosis with diabetes after 1 week of a high-fat diet. Liver biopsy displayed increased lobular inflammation and foam cell-like macrophages, consistent with NASH pathology. In parallel, fibroblasts accumulated to form chicken-wired fibrosis, and all of these mice developed HCC later. Interestingly, mice with diabetes alone but without NASH-based fibrosis never developed HCC.[49] More biological studies are still necessary to comprehensively determine the pathophysiological role of diabetes in cirrhosis and NAFLD-associated HCC.

RISK STRATIFICATION, PREDICTION MODELS, AND GENETIC RISK SCORES

HCC risk stratification of non-cirrhotic NAFLD and early recognition of cirrhosis among patients with NAFLD will be critical to increase surveillance implementation and earlier detection of HCC eventually leading to utilization of curative-intent treatment and improved survival.[19] Cirrhotic patients of any etiology are recommended to undergo semiannual HCC surveillance based on the American Association for the Study of Liver Diseases or the European Association for the Study of the Liver guideline. However, the risks are still heterogeneous across all cirrhotic and non-cirrhotic patients. Thus, several prediction models considering different etiologies were used for better risk stratification, especially for cirrhotic NAFLD patients (e.g., ADRESS-HCC,[50] THRI score,[51] and APAC score[52]). The ADRESS-HCC represented the first model derived from 34,932 cirrhotic patients, and the primary etiology of cirrhosis (NASH, hepatitis C virus, alcohol, hepatitis B virus, others) was associated with 1-year HCC risk. The ADRESS-HCC model could differentiate whether the cirrhotic patients would develop HCC with a C-index of around 0.7.[50] The primary etiology of cirrhosis in the THRI score included steatohepatitis, viral hepatitis, primary biliary cirrhosis, and autoimmune hepatitis. The THRI model could predict 10-year cumulative HCC incidence, with 3%, 10%, and 32% for scores <120, 120 to 240, and >240, respectively.[51] The APAC score was based on serum sPDGFRβ (soluble platelet-derived growth factor receptor β), age, serum alpha-fetoprotein (AFP), and creatinine and categorized the etiology of cirrhosis into NAFLD, viral hepatitis, and alcohol. The APAC score could predict HCC with an area under the curve (AUC) of 0.95. The AUC was also around 0.95 in a sub-analysis of NAFLD-associated cirrhosis.[52] Most recently, a study reported prognostic liver signature (PLS)–NAFLD, which predicted incident HCC over up to 15 years of longitudinal observation.[53] Four-protein secretome signature, PLSec-NAFLD, showed excellent risk stratification among NAFLD and cirrhosis (HCC incidence rates at 15 years were 37.6% and 0% in high- and low-risk patients, respectively).[53]

In non-cirrhotic NAFLD patients, HCC screening by ultrasonography and serum AFP levels could be considered in the presence of advanced fibrosis (F3).[7] Besides, ethnicity and genetics may play an essential role on risk stratification in this population. For example, Hispanics have higher rates of NAFLD-associated HCC in the United States, possibly due to their higher rates of metabolic syndromes.[34,54,55] The PNPLA3 single-nucleotide polymorphisms (SNPs) are strongly linked to HCC.[7] Genome-wide association studies (GWAS) have also uncovered SNPs of many other genes that contribute to NAFLD-associated HCC, including TM6SF2, MBOAT7, GCKR, HSD17B13, etc.[13] Therefore, researchers built polygenic risk score (PRS) models, which consider effects of different SNPs at different genes, combined with clinical features to predict risks on developing HCC.[56-59] For example, Bianco *et al.*[56] developed two PRS models considering four (PNPLA3, TM6SF2, MBOAT7, and GCKR) or five (adjusted for the rs72613567 HSD17B13) genetic variants in Italian and the U.K. cohorts. These two models could predict HCC in NAFLD patients with or without cirrhosis, with an AUC of around 0.65. Gellert-Kristensen *et al.*[57] established a PRS model based on PNPLA3, TM6SF2, and HSD17B13 in United Kingdom and Danish cohorts. This model demonstrated up to a 12-fold and a 29-fold higher risk of cirrhosis and HCC, respectively. Pelusi *et al.*[58] and Donati *et al.*[59] also demonstrated PRS models with outstanding AUC (>0.9), but these require further careful validation. Despite these potential PRS models, risk stratification without genetic input is more likely feasible in the clinical setting since GWAS is currently not applicable to each individual. For instance, the GALAD score considers gender, age, AFP, AFP isoform L3 (AFP-L3), and des-gamma-carboxy prothrombin and has been used in many studies.[60] In a German cohort with 356 NAFLD patients, the GALAD score could identify HCC patients with an AUC of 0.96. Notably, the AUC for detecting HCC based on the GALAD score in NASH patients without cirrhosis was 0.98.[60] Liver en-

zymes, platelets number, serum albumin levels, and presence of diabetes were also proposed as variables in some risk stratification models.[61]

Researchers have extensively developed liquid biopsy, including circulating tumor DNA,[62] circulating tumor cells,[63] and extracellular vesicles,[64] for HCC biomarkers. For example, Kalinich *et al.*[65] utilized digital polymerase chain reaction (dPCR) to quantify RNA expression of 10 HCC-relevant genes in purified circulating tumor cells and yield genetic scores that had values in screening high-risk patients. Sun *et al.*[66] also detected the same 10-gene expression by dPCR in purified HCC extracellular vesicles that could aid with early diagnosis of HCC. The dPCR can quantify tiny amounts of DNA or RNA, as sensitive as one copy per cell, which is a huge advance in the early diagnosis of malignancy at a low cost. The combination of the cutting-edge dPCR system and liquid biopsy may allow these blood-based, noninvasive biomarkers to hold great potential for early diagnosis of HCC, particularly in patients with non-cirrhotic NAFLD.

POTENTIAL PREVENTIVE STRATEGIES

Given the strong association of obesity with insulin resistance, diabetes, and HCC,[67-69] encouraging physical activity to control weight and other major metabolic traits is a rational and cost-effective way to prevent the development of HCC. Smoking cessation should be encouraged for HCC prevention with the evidence from a meta-analysis demonstrating a pooled OR of 1.55 and 1.39 for HCC in current and former smokers, respectively.[70]

Although life modifications are cost-effective and the first step for diabetes management, most patients still require antihyperglycemic agents. Metformin, a biguanide, has long been the first-line medication for managing diabetes. In addition, metformin can inhibit mitochondrial respiration with decreased adenosine triphosphate (ATP) production. Reduced ATP production activates the adenosine monophosphate-activated protein kinase signaling pathway, resulting in mTOR pathway inactivation and subsequent inhibition of cancer cell proliferation (Fig. 2).[71] Metformin also regulates the glucose metabolic intermediate to influence *de novo* lipid biosynthesis.[72] Other antitumor mechanisms of metformin include epigenetic modification, immunoregulation via the NF-κB pathway, and regulation of autophagy.[73] Clinically, metformin can help lose weight and increase insulin sensitivity.[74]

Chen *et al.*[75] conducted a nationwide case-control study, recruiting 97,430 HCC patients and 194,860 match controls, and found that each incremental year increase in metformin use led to a 7% reduction in the risk of HCC

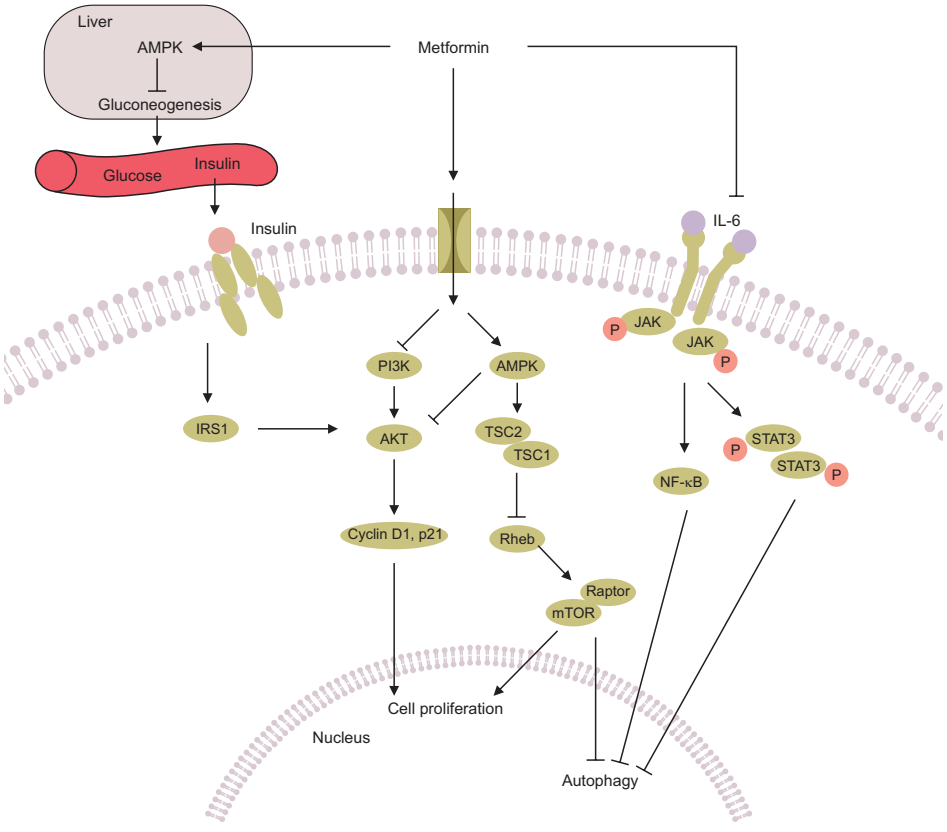

Fig. 2. Possible mechanisms of protective effects against hepatocellular carcinoma by metformin. Metformin may inhibit cell proliferation via AMPK and PI3K pathways. Metformin is also an autophagy inducer that can prohibit carcinogenesis by inhibiting IL-6. Arrows denote facilitation and blunt arrows denote inhibition.
AMPK, adenosine monophosphate (AMP)-activated protein kinase; IL-6, interleukin 6; IRS1, insulin receptor substrate 1; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B (also known as PKB); JAK, Janus kinase; TSC, tuberous sclerosis complex; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; STAT, signal transducer and activator of transcription protein; Rheb, Ras homolog enriched in brain; mTOR, mammalian target of rapamycin.

(aOR, 0.93), for diabetic patients, indicating a strong dose-dependent relation. A meta-analysis by Singh *et al.*[76] including 10 studies of 22,650 HCC cases in 334,307 patients with type 2 diabetes showed that metformin use was associated with decreased risk of HCC with an OR of 0.50. Interestingly, sulfonylurea and insulin use was significantly associated with an increased HCC risk (OR of 1.62 and 2.61, respectively). Kramer *et al.*[77] assembled a retrospective cohort of 85,936 patients with NAFLD and diabetes from 130 Veterans Administration facilities. They reported that, in landmark multivariate Cox proportional hazards models, metformin use was associated with an HR of 0.80 for developing HCC. The use of insulin alone or sulfonylureas alone was not significantly associated with the risk of HCC compared with no antihyperglycemic agent use.[77] Still, insulin in combination with other oral antihyperglycemic agents was associated with a 1.6- to 1.7-fold higher risk of developing HCC. More importantly, patients with adequate glycemic control were associated with an HR of 0.69 for developing HCC.[77] In a subgroup analysis of patients who received at least one diabetes medication, the use of insulin or sulfonylureas was associated with a 44% and 31% higher risk of HCC compared to metformin, respectively.[77] Another systemic review by Cunha *et al.*[78] showed an OR of 0.468 for the risk of HCC in metformin users. Tseng performed a propensity score-matched study pairing 21,900 ever-users and never-users of metformin. This case-control study reported an overall HR of 0.49 for developing HCC in metformin ever-users.[79]

In recent years, sodium-glucose linked transporter-2 (SGLT2) inhibitors have attracted attention not only for their efficacy in treating hyperglycemia but also for their outstanding effects on cardiovascular and renal protection.[80,81] By inhibiting SGLT2 in the kidney, the inhibitors lead to glycosuria, resulting in decreased serum glucose, caloric deficit, and thus weight loss.[82] Researchers have also observed the potential of SGLT2 inhibitors against HCC and other malignancies due to the established correlation between hyperglycemia and HCC. For example, Luo *et al.*[83] reported that canagliflozin (an SGLT2 inhibitor) could decrease HIF-1α protein synthesis via the AKT/mTOR pathway, leading to reduced hypoxia-induced metastasis and angiogenesis in HCC. Many others also demonstrated consistent results of the effects of canagliflozin and other SGLT2 inhibitors on HCC cells.[82] A meta-analysis of multiple randomized controlled trials by Benedetti *et al.*[84] exhibited an overall reduced risk of cancer (not limited to HCC) in users of SGLT2 inhibitors, with a risk ratio of 0.35.

Statins inhibit the conversion of 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate. The inhibition of this pathway by statins prevents the formation of both mevalonate and its downstream product, which have several pathophysiological functions potentially involved in carcinogenesis.[85] Singh *et al.*[86] conducted a meta-analysis including 10 studies with 4,298 HCC cases in 1,459,417 patients and showed that statin use was associated with a significantly lower risk of developing HCC (aOR, 0.63). A more recent meta-analysis by Zou *et al.*[87] including 272,431 patients with NAFLD reported that statin users had a lower risk of developing HCC than nonusers (HR, 0.47). Statin initiation was still associated with a lower risk of HCC after adjusting for fibrosis-4 index score (HR, 0.49). They also showed that statin had a protective effect against HCC in patients with NAFLD in a dose-dependent manner.[87] Aspirin, a cyclooxygenase (COX) inhibitor, was also proposed to have a protective effect against HCC because chronic inflammation could trigger the COX-2 signaling pathway, resulting in decreased apoptosis, increased cell proliferation, and angiogenesis.[88,89] A pooled analysis of two prospective cohort studies in the United States involving 133,371 healthcare professionals reported that regular use of at least 650 mg of aspirin a week was associated with a 50% reduction in HCC risk (adjusted HR, 0.51).[90] However, the chemopreventive effect of these medications has not been rigorously evaluated in the context of NASH and requires further evaluation in prospective studies.

CONCLUSIONS

Diabetes is an important risk factor for HCC development in patients with NAFLD. Diabetes also increases the risk of developing HCC in patients with NAFLD cirrhosis. Hepatocarcinogenic effects of diabetes include increased ROS production, endothelial damage, release of proinflammatory cytokines, and activation of the IGF pathway. Based on a murine model, NAFLD fibrosis may serve as a pivotal link between diabetes and HCC development. Several HCC risk stratification models were proposed, and it will be useful to determine surveillance strategies for the early detection of HCC in these patients. Since diabetes is a potentially modifiable risk factor, researchers have established preventive strategies focused on diabetes and relevant metabolic traits including physical activity (or exercise) and chemoprevention using metformin, SGLT2 inhibitors, statin, and aspirin. More biological studies are required to delineate the pathophysiological role of diabetes in patients with cirrhosis and refine risk stratification and prevention of NAFLD-associated HCC with new therapeutics.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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