REVIEW

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Diabetes medications and risk of HCC

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Abstract

Type 2 diabetes mellitus is a recognized risk factor for HCC in patients with liver disease, independent from the etiology of their liver disease. Hence, prevention and treatment of type 2 diabetes mellitus and its underlying cause, insulin resistance, should be considered a treatment target for patients with liver disease. The drug armamentarium for diabetes is wide and consists of agents with insulin-sensitizing activity, agents that stimulate insulin secretion, insulin itself, and agents that reduce gastrointestinal and urinary glucose absorption. From an endocrinology perspective, the main goal of treatment is the achievement of euglycemia; however, in patients at risk of, or with known underlying liver disease, the choice of diabetic medication as it relates to potential hepatic carcinogenesis remains complex and should be carefully considered. In the last decade, increasing evidence has suggested that metformin may reduce the risk of HCC, whereas evidence for other classes of diabetic medications, particularly some of the newer agents including the sodium glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists, is fewer and often inconsistent. In this review, we aim to summarize the current evidence on the potential effects of the most widely used diabetic agents on liver cancer tumorigenesis.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a well-established, independent risk factor for both NAFLD and HCC.[1,2] It has been shown that the risk of developing HCC is 2.5–4-fold higher in patients with T2DM, independently of the presence of cirrhosis or of the etiology of the underlying liver disease.[3–8] Additionally, the risk of HCC appears to be higher in patients with long-standing and poorly controlled diabetes.[9,10] Given these clear associations, it is of utmost importance that hepatologists and primary care providers both screen for and ensure appropriate management of diabetes to prevent the development of liver disease

and mitigate risk factors for HCC development and/or recurrence.

The precise pathophysiologic mechanisms behind the association between T2DM and HCC are not completely understood, and in-depth discussion of the putative mechanisms at the basis of this association goes beyond the aims of this manuscript, although some hypotheses postulated to explain this association are reported here in order to provide an introduction to the potential role of T2DM medications on this relationship. Briefly, insulin resistance (IR) and activation of the insulin receptor and insulin-like growth factor 1 (IGF-1) signaling pathways are among the main determinants in the initiation and progression of hepatocarcinogenesis.[11–13] In fact, it has been shown that hepatoma cells overexpress IGF-1 and insulin receptor substrate-1, suggesting its importance in HCC development.[14] To this point, data from the Human Protein Atlas demonstrate that high expression of the IGF-1 receptor predicts poorer survival in patients with liver cancer.[15] IR has a variety of metabolic and molecular effects that cause inflammation, oxidative stress with resultant DNA damage, and stimulation of cellular pathways that play a role in cellular growth and proliferation, all leading to potential HCC development. Additionally, IR leads to a systemic redistribution of substrate that is predicted to be permissive for tumor growth: Insulin-resistant skeletal muscle and liver fail to take up glucose in response to insulin, but there is little evidence that insulin resistance develops in tumor cells. Therefore, insulin resistance redistributes glucose toward the tumor, where it has been known for a century to accelerate pathology.[16] Finally, IR also leads to changes in visceral adipose tissue, including increased fatty acid oxidation and liberation along with changes in the inflammatory and adipokine secretory profile, resulting in increased levels of TNF-alpha, IL-6 and leptin, which further result in states of hepatic inflammation and fibrosis, perpetuate insulin resistance, and result in tumorigenesis.[17]

In the hepatocytes, IR also results in steatosis through alterations in lipoprotein metabolism. In one study by Bugianesi et al., patients with NAFLD and IR had increased *de novo* hepatic lipogenesis of up to 25% compared with 5% in control subjects.[18] The resultant hepatic steatosis results in the activation of the mammalian target of rapamycin (mTOR)/NF-kB pathway, which inhibits the expression of the tumor suppressor phosphatase and tensin homologue in hepatocytes.[19,20] Moreover, hepatic IR alters glucose metabolism by enhancing hepatic gluconeogenesis and glycogenolysis, which lead to hyperglycemia, glucose intolerance, and, when glucolipotoxicity damages the pancreatic beta-cell sufficiently to render beta-cell insulin secretion unable to match increasing demand for insulin resulting from IR, results in diabetes.[21,22] These alterations in lipid and glucose metabolism stimulate microsomal peroxidases and cause mitochondrial

damage and excess production of reactive oxygen species (ROS). The consequences of such oxidative stress include increased inflammatory cytokine release, direct DNA damage, mitochondrial dysfunction, mutations in the p53 onco-suppressor gene and the activation and suppression of genes involved in antioxidant pathways, cellular proliferation, and metabolism.[2,23,24] Additionally, as insulin is an important mitogen, the state of hyperinsulinemia resulting from IR results in the up-regulation and/or cross-activation of multiple growth factor receptors (e.g., IGF-1), which play a key role in cellular proliferation and inhibition of apoptosis. Indeed, IGF-1 and its receptor (IGF-1R) signaling are known to regulate stem cell pluripotency and differentiation to trigger cell proliferation, organ development, and tissue regeneration during embryonic development. Thus, an unbalanced IGF/IGF-1R signaling can promote cancer-cell proliferation and activate cancer reprogramming in tumor tissues, especially in the liver.[25] Insulin receptor substrate-1 (IRS-1) activity is also increased as a result of insulin receptor and IGF-1 signaling, and this results in the activation of multiple cytokine pathways including phosphoinositide-3-kinase/AKT/mTOR and mitogen-activated protein kinases, which modify cell cycle and thus cellular proliferation. Additionally, IRS-1 may play a role in preventing TGF-β–mediated apoptosis.[26–28] Finally, insulin also increases hepatic growth hormone receptor levels and down-regulates IGF-1 binding protein, resulting in increased bioavailability of IGF-1 and further potentiating its tumorigenic effects.[29]

In summary, through the intricate and synergistic effects of insulin resistance and resultant hepatic steatosis, there is increased production of ROS leading to subsequent DNA damage and alterations in cytokine and adipokine production, which affect various cellular pathways involved in cell proliferation, anti-apoptosis and inflammation, all leading to a pro-carcinogenic environment.

T2DM medications and HCC

Given the increased risk of HCC in patients with T2DM and the potential hepatoprotective features of some anti-diabetic agents (Fig. 1), recent research has focused on the effects of anti-diabetic therapy on the incidence and outcome of HCC.

Metformin

Metformin was first identified as a potential hepatoprotective medication in 2005 when it was shown to reduce the risk of cancer in patients with diabetes.[30] Since that time, several studies have demonstrated its potential preventative role against HCC development.[31–34] As an example, a metanalysis by
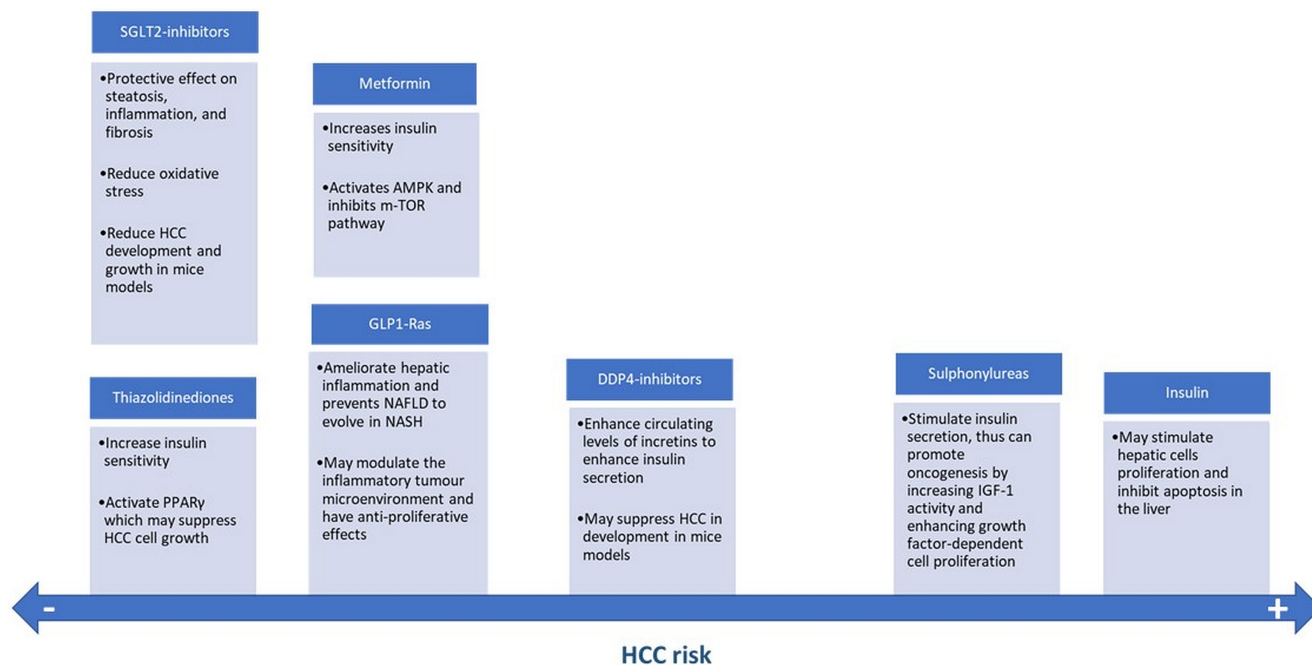
FIGURE 1 Postulated mechanisms by which the mostly used anti-diabetic medications may favor or prevent hepatocarcinogenesis. Metformin, TZDs, SGLT2 inhibitors, GLP1-Ras, and DDP4-inhibitors may protect from HCC development and growth, whereas sulphonylureas and insulin favor HCC development

Zhang et al. including three cohort studies and four case-control studies with more than 16,000 diabetic subjects, showed that metformin treatment was associated with a 76% reduced risk of HCC (relative risk [RR] 0.24, 95% CI 0.13–0.46, $p < 0.001$).[32] Importantly, the protective effect of metformin remained significant after adjusting for other risk factors such as the etiology of liver disease.[32] In the same year, another metanalysis by Singh et al. showed similar results, with an overall 50% reduced risk of incident HCC among metformin-treated patients (adjusted OR [aOR] 0.50, 95% CI 0.34–0.73, $p < 0.05$).[31] Consistent with the results by Zhang et al., when restricting the analysis to studies that adjusted for the effect of other anti-diabetic medications, the chemo-preventive effect of metformin was still significant and relevant (aOR 0.78, 95% CI 0.75–0.83, $p < 0.05$). Likewise, in a subgroup analysis of studies that adjusted for duration and/or severity of T2DM, the chemo-preventive effect of metformin still persisted.[31] These findings were recently confirmed in a study showing that metformin use was associated with a significantly decreased risk of HCC in T2DM (OR 0.59, 95% CI 0.51–0.68, $p < 0.001$).[34] Additionally, this study indicated that metformin use was associated with a decreased all-cause mortality in diabetic patients with HCC (HR 0.74, 95% CI 0.66–0.83, $p = 0.037$).[34] This finding is in accordance with those from a previous report showing a reduced overall mortality risk among metformin users (HR 0.68, 95% CI 0.61–0.75).[35]

Metformin has multiple potential mechanisms by which it may inhibit HCC development and growth. First, metformin reduces hepatic glucose production, thus indirectly reducing circulating insulin levels and mitigating effects of hyperinsulinemia on cell cycle and inflammation.[36] Additionally, the anti-neoplastic effect of metformin may be mediated by activation of adenosine monophosphate–activated protein kinase (AMPK), which has various downstream effects including inhibition of mTOR pathway, which plays a key role in proliferation through control of the cell cycle, activation of the immune system, alterations in cancer stem cell activation, along with anti-angiogenic effects.[36] Moreover, compared with exogenous insulin and insulin secretagogues, which raise plasma insulin levels and promote body weight gain, metformin has the benefit of stimulating moderate weight loss through the activation of AMPK.[36] This latter effect is of particular importance in patients with concomitant obesity and NAFLD, as weight loss is the key treatment target for the achievement of metabolic control, regression of steatosis and steatohepatitis, and, secondarily, for the reduction of HCC development.[37,38] Finally, metformin use has further immune-biologic effects, as it can lead to positive changes in the gut microbiome that can affect glucose metabolism—a finding that appears to be mediated by the effect(s) of the drug on short-chain fatty acid–producing bacteria, especially butyrate-producing *taxa*, and by the increase in *Akkermansia muciniphila*, which improves antitumor immune CD8+ T-cell infiltration and activity.[39] Moreover, metformin use is associated with an improvement in liver biochemistry and histology in patients with NAFLD, a finding that may explain its favorable influence on the prognosis of patients with advanced liver disease and T2DM.[40–44]

Statins are frequently prescribed in patients with T2DM, as dyslipidemia is a common comorbidity and known element of the metabolic syndrome. Statin co-utilization has been hypothesized to confound the prior evidence for metformin as a chemo-preventive agent for HCC in population-level studies. For example, in the aforementioned retrospective cohort study by Kaplan et al., no demonstrable impact of metformin on HCC or hepatic decompensation was shown after adjusting for concomitant statin use.[35] We could argue that dual treatment with metformin and statins may play synergistically in the HCC risk reduction, as shown by a study by Tseng et al., which enrolled 21,900 ever-users and a matched-pair cohort of 21,900 never-users of metformin.[45] The results confirmed the chemo-preventive role of metformin, and the subanalysis assessing concomitant treatment with statins showed a potential protective synergistic effect. Indeed, metformin had a protective effect independently from the concomitant treatment with statins, but the group under the dual treatment showed the lowest risk of HCC (HR 0.46, 95% CI 0.39–0.54, p < 0.0001 vs. metformin-only treatment: HR 0.66, 95% CI 0.59–0.74, p < 0.0001).[45] Additionally, another recent study did demonstrate an anti-neoplastic effect of metformin independent from statin use.[46]

Metformin has not only been associated with a reduced risk of HCC and mortality, but it has also been shown to prolong overall survival (OS) among patients with cirrhosis.[44,47,48] A retrospective study conducted at the Mayo Clinic of 250 patients with diabetes and cirrhosis taking metformin at the initial visit showed that patients who continued metformin during the observation period had a significantly longer median survival than those who discontinued metformin (11.8 vs. 5.6 years in the overall cohort, p < 0.0001; 11.8 vs. 6.0 years for Child-Pugh class A patients, p = 0.006; and 7.7 vs. 3.5 years for class B/C patients, p = 0.04), even after adjusting for other variables (HR 0.43, 95% CI 0.24–0.78, p = 0.005).[44] Notably, the administration of metformin was safe, as no adverse reactions were reported and none of the patients developed metformin-associated lactic acidosis during follow-up. These results were confirmed in a nested case-control study by Bosetti et al. and in a recently published Thai study of 1061 patients with cirrhosis followed up for at least 5 years.[47,48] In this latter study, the outcomes of 719 metformin users were compared with those of 342 metformin never-users: Consistent with previous results, metformin-exposed patients had a significantly lower risk of developing HCC (HR 0.48, 95% CI 0.36–0.61, p < 0.001), and the median survival of metformin users was almost twice that of metformin never-users (6.9 and 3.88 years, respectively; p = 0.003).[47] The small numbers for the subgroup analysis between each Barcelona Clinic Liver Cancer (BCLC) stage of disease did not allow us to investigate whether metformin could give a survival advantage in each HCC stage group.[47]

Evidence regarding the potential effects of metformin in patients with HCC has been shown by a prior meta-analysis, which revealed that metformin significantly prolonged the survival of diabetic patients with HCC who were treated with curative intent, whereas it had no effect in patients with more advanced stages of cancer.[49] Consistent with this finding, Seo et al. found a significantly lower risk for HCC-specific mortality (HR 0.38, 95% CI 0.30–0.49) and for retreatment events (HR 0.41, 95% CI 0.33–0.52) among metformin-treated patients.[50] Finally, a recent multicenter study reported that diabetic patients with HCC on metformin treatment had a significantly longer median OS than those who were not treated with metformin (22 vs. 15 months, p = 0.019), and that this effect was more relevant among patients with potentially curative stages of HCC.[51] A unique finding is the potential negative impact on survival that metformin may have when used in combination with sorafenib, a well-known tyrosine kinase inhibitor used in the treatment of HCC. Schulte et al. demonstrated that co-treatment with metformin tended to have a negative impact on survival in patients treated with sorafenib (7 vs. 11 months, p = 0.088).[51] This finding may be explained by the potential of metformin to confer resistance to sorafenib, as was previously shown by Casadei Gardini et al. in their study of 279 patients, in which 19% were on metformin therapy and 12% were on insulin therapy; for patients with HCC on metformin, the use of sorafenib was associated with poor progression-free survival (PFS) and OS: 1.9 and 6.6 months, respectively, compared with 3.7 and 10.8 months, respectively, for patients without T2DM, and 8.4 and 16.6 months, respectively, for patients on insulin (p < 0.0001).[52] The analysis from the biopsy samples suggested that tumors that developed during chronic treatment with metformin had intrinsic mechanisms of resistance to metformin, which may have led to resistance to sorafenib.[52] Conversely, Chung et al. found there was no difference in PFS and OS among metformin-treated and non-metformin-users receiving sorafenib for HCC recurrence after hepatic resection, although the study included a low number of patients—a fact that could have prevented the results from showing a true effect of metformin.[53] Additionally, there is also evidence for a positive effect of metformin in patients undergoing sorafenib treatment[54]; thus, given the inconsistencies in available studies, it remains unclear as to the true effects of metformin in sorafenib users.

With regard to the potential effects of metformin on the outcomes of patients treated with immune checkpoint inhibitor (ICI)–based therapies, which currently represent the first-line systemic treatment option for patients with advanced HCC, data on primary liver cancer are still scanty, but the evidence emerging from studies on other cancer types are intriguing. Indeed, recent

literature has shown that some concomitant medications, such as proton-pump inhibitors, antibiotics and corticosteroids, may negatively impact the response to these drugs—not because of pharmacodynamics and pharmacokinetic interactions, but through immune-modulatory effects, not only systemically and within the tumor microenvironment, but also through the modulation of the gut microbiome.[55–58] Interestingly, changes in gut microbiome driven by medications appear to play a pivotal role in the response to ICIs. Specifically, a decreased concentration of *Akkermansia muciniphila* may reduce the effectiveness of immunotherapy. Metformin increases *Akkermansia muciniphila* concentration in the gut, which improves antitumor immune CD8+ T-cell infiltration and activity; this finding might explain the recent evidence of a prolonged OS, PFR, and response rate among patients with non–small-cell lung cancer treated with metformin.[59] However, evidence of an absence of association between metformin use and response to ICIs has been presented as well[60]; hence, until further evidence regarding the eventual role of metformin in response to immunotherapy is available, definite conclusions cannot be drawn.

Overall, although evidence suggests that metformin could decrease the risk of HCC in diabetic patients, the magnitude and severity of liver disease, concomitant treatment with statins, use of sorafenib, and duration of diabetes all remain potentially confounding factors that have limited consistent findings in various studies. Moreover, even if recent studies suggest that metformin could worsen the prognosis of patients treated with sorafenib, more consistent evidence from large populations are needed to draw definite conclusions and further elaborate the underlying cellular mechanisms responsible for these findings. Notably, given the changing paradigm in systemic therapies, further studies assessing the effects of metformin on patients undergoing treatment with immunotherapy and/or other tyrosine kinase inhibitors are still needed.[61]

Thiazolidinediones

Thiazolidinediones (TZDs) improve glycemic control by activating peroxisome proliferator–activated receptor gamma (PPARγ), leading to insulin sensitization and enhanced glucose metabolism. Expression of PPARγ has been shown to suppress HCC cell growth in mice and *in vitro* models.[62] TZDs may be advantageous for patients at risk for HCC, as they not only increase insulin sensitivity, but they have demonstrated anti-tumorigenic effects via cell cycle arrest, induction of apoptosis, inhibition of cell invasion, along with stimulation of anti-angiogenic and pro-differentiation pathways.[63]

The potential effects of TZDs on HCC incidence have been investigated by several retrospective and metan-alytical studies with contrasting results. A nationwide case-control study that was run in Taiwan included a total 606,583 patients with T2DM, without a history of cancer.[64] Patients with incident cancer of liver, colon, lung, and urinary bladder were included, as cases and up to four age-matched and sex-matched controls were selected by risk-set sampling. A significantly lower risk of liver cancer incidence was found for any use of rosiglitazone (OR 0.73, 95% CI 0.65–0.81) or pioglitazone (OR 0.83, 95% CI 0.72–0.95), and the protective effects were stronger for higher cumulative dosage and longer duration.[52] These results are consistent with those found by other retrospective studies, mostly conducted in Asia, which showed a reduced risk for HCC among TZD-treated diabetics as compared with non-TZD users.[65–69] Interestingly, in a recent study the use of pioglitazone was also found to reduce the risk of HCC recurrence in a cohort of overweight patients treated for HCV infection. This study was important, as it shed light on some of the mechanisms in which pioglitazone may reduce the risk of HCC recurrence, with overweight status being an important factor. Excess adiposity is a risk factor for IR, and as previously described, increased levels of insulin is associated with increased HCC risk, given its growth-promoting effects. The authors of this study hypothesized that pioglitazone may suppress HCC recurrence through improvement of IR, as supported by the finding of a reduced homeostasis model assessment–IR score, as well as reduced serum insulin levels, in patients treated on the drug—a finding that has also been confirmed by other reports.[67,68,70,71] With regard to the meta-analytic evidence, in 2013 two studies reported TZD use to be associated with a significantly decreased incidence of HCC.[72,73] However, another metanalysis in the same year did not identify a significant protective association, although notably there was significant heterogeneity across studies.[31] More recently, a systematic review/meta-analysis including seven studies, 280,567 participants, and 19,242 HCC cases found that TZDs use was associated with an overall reduced HCC risk (aOR 0.92, 95% CI 0.86–0.97, I^2 = 43%), which was confirmed only among Asian subjects (aOR 0.90, 95% CI 0.83–0.97), but not in Western subjects (aOR 0.95, 95% CI 0.87–1.04).[73] Potential theories as to the lack of protection in Western subjects was hypothesized to be due to genetic polymorphisms, which may affect TZD alterations on insulin sensitivity and also on drug metabolism.

Conversely, other studies have demonstrated that TZDs may not be associated with a reduced risk of HCC and may in fact be associated with increased cardiovascular adverse events in patients with cirrhosis.[74] For example, a study compared the risks for all-cause mortality, major adverse cardiovascular events, and hepatic outcomes in 1705 patients with T2DM and cirrhosis based on TZD use. For the patients on TZD, the aHRs (95% CIs) for stroke, ischemic heart disease, and heart failure were 1.81 (1.28–2.55), 1.59 (1.03–2.44),

and 2.09 (1.22–3.60), respectively. Conversely, all-cause mortality, HCC, decompensated cirrhosis, and hepatic failure risks did not differ significantly between TZD users and nonusers. Therefore, given the lack of hepatic benefit with TZD use, the authors expressed caution in prescribing TZDs to patients with T2DM and cirrhosis, given the higher risk of major adverse cardiovascular complications.[74] It is worth noting, however, that because TZDs are at best second-line for T2DM, there is a risk of bias in observational studies, because patients treated with TZDs will be the ones who have not achieved adequate glycemic control with first-line therapy. In addition, socioeconomic factors may play a role, as TZD are far cheaper than sodium glucose cotransporter 2 (SGLT2), glucagon-like peptide-1 (GLP1), and dipeptidyl peptidase-4 (DPP-4) modulating drugs.

Overall, there is insufficient evidence to recommend against or in favor of the use of TZDs in patients with comorbid T2DM and cirrhosis, as the potential benefit on liver-related outcomes has yet to be consistently demonstrated. Moreover, because there is evidence of increased cardiovascular complications in patients with cirrhosis treated with TZDs, these drugs should be prescribed with caution in subjects who have significant risk factors for, or history of, cardiovascular disease. Note, however, that the American Association for the Study of Liver Disease (AASLD) currently recommends the use of TZDs to treat patients with biopsy-proven NASH, which is a common complication in patients with T2DM.[75]

Sulfonylureas

Sulfonylureas, which are insulin secretagogues, have been associated with an increased risk of HCC. Sulfonylureas stimulate insulin secretion by closing ATP-sensitive potassium channels in pancreatic β cells. By increasing insulin secretion, and exogenous insulin itself, this drug class can promote oncogenesis either directly or indirectly by increasing IGF-1 activity, resulting in abnormal stimulation of multiple cellular signaling cascades, enhancing growth factor–dependent cell proliferation, and affecting cell metabolism.[76]

The available evidence suggests that sulfonylureas significantly increase the risk of HCC.[48,69,77–79] Lee et al. documented an almost 2-fold increased risk of HCC for sulfonylurea users, with the risk being higher for those taking glimepiride as opposed to gliclazide.[77,78] These results are in accordance with those from Bosetti et al., who found an increased HCC risk (OR 1.39, 95% CI 0.98–1.99) in patients treated with this drug class,[48] but slightly in contrast to those from the Kawaguchi et al. nested case-control study that showed an even higher risk for HCC development in patients treated with second-generation sulfonylureas

(gliclazide, glibenclamide), as the OR was 6.831, with a 95% CI between 1.954 and 23.881 (p < 0.0026).[79] At odds with the finding by Lee et al., this association was not observed with the third-generation sulfonylurea glimepiride. However, the baseline characteristics of the included subjects differ between the two studies: Indeed, Lee et al. included and monitored T2DM patients of whom only a minority had comorbid liver diseases, whereas the cohort of Kawaguchi et al. was made up of patients with T2DM and concomitant HCV infection, and a high prevalence of cirrhosis. Therefore, we feel that these results are not directly comparable. Interestingly, in the stratified analyses of the cohort by Kawaguchi et al., the impact of sulfonylureas was more evident in patients without cirrhosis than in those with cirrhosis. Severity of liver fibrosis was the strongest risk factor for hepatocarcinogenesis; therefore, in patients with cirrhosis, the authors suggested the potential carcinogenic activity of exogenous insulin, and a second-generation sulfonylureas was less evident in comparison to the carcinogenic mechanisms seen in cirrhosis. The carcinogenic risk of different classes of sulfonylureas demonstrated inconsistent results in studies, but it is worth nothing that glimepiride may lead to reduced ability to stimulate insulin secretion, and gliclazide may act as a potential free-radical scavenger and aid in DNA repair.[80,81] The clear effect of sulfonylureas to increase HCC risk further confirms the role of insulin as a carcinogenic factor in those at risk for HCC.

Insulin

As described previously, insulin is a potent mitogen associated with up-regulation of various growth factors that lead to stimulation of cytokine pathways related to cell proliferation and inhibition of apoptosis.[82] In the past decade, increasing evidence has shown a higher risk of HCC incidence in diabetic patients treated with insulin. Indeed, high fasting serum insulin levels (> 6.10 µU/ml) have been associated with a 2.36-fold risk of HCC when compared with low fasting insulin levels (< 2.75 µU/ml).[83]

In 2013, Schlesinger et al. conducted a prospective analysis among 363,426 EPIC-cohort study participants with self-reported diabetes.[84] During 8.5 years of follow-up, 176 HCC cases were identified. Independent from other factors including body mass index and waist-to-height ratio, diabetes was associated with a higher risk of HCC (RR 2.17, 95% CI 1.36–3.47), and treatment with insulin conferred the highest risk of HCC (RR 5.25, 95% CI 2.93–9.44), whereas no association was observed for participants without insulin treatment.[84] Unfortunately, important factors including other medications used other than insulin and status of cirrhosis were not available, which could have confounded the results. Similar results were found by

Bosetti et al., who analyzed the role of various antidiabetic drugs on HCC risk in a large population-based study from Italy.[48] Increased risks of HCC were found with the use of insulin (OR 3.73, 95% CI 2.52–5.51), with a higher risk associated with longer treatment duration (OR 2.52 for < 1 year, 5.41 for 1–2 years, and 6.01 for ≥ 2 years; p < 0.001), and sulfonylureas (OR 1.39, 95% CI 0.98–1.99).[48] Similarly, a recent study showed a 2-fold increased risk of HCC for patients treated with insulin (aOR 1.9, 95% CI: 0.8–4.6).[69] These results are in accordance with those from the metanalysis by Singh et al., who found an increased risk of HCC for insulin users (OR 2.61, 95% CI 1.46–4.65).[31]

Interestingly, an association has also been found between survival of patients with advanced HCC who are concurrently treated with insulin and sorafenib. Among 279 patients consecutively treated with sorafenib, the use of sorafenib in patients undergoing chronic treatment with metformin was associated with a median PFS of 1.9 months (95% CI 1.8–2.3) compared with 8.5 months (95% CI 5.3–11.4) for those on insulin (p < 0.0001).[52] Metformin *plus* sorafenib–treated patients showed a median OS of 6.6 months (95% CI 4.6–8.7) compared to 16.6 months (95% CI 14.5–25.5) for the insulin group (p < 0.0001). The effect of metformin on clinical outcomes was also investigated in relation to the objective response rate. Patients treated chronically with metformin and sorafenib showed a higher percentage of progression at the first CT scan re-evaluation than those treated with insulin or the non-diabetic group (75.8% vs. 14.7% vs. 38.8%, respectively). The risk of progression was higher in those taking metformin+ sorafenib than in the insulin *plus* sorafenib group (HR 2.91, 95% CI 1.84–4.6).[52] Similar results were observed for survival (HR 2.74, 95% CI 1.69–4.43, p < 0.0001). However, these results may not reflect a potential advantage for insulin users, but may rather be explained by the hypothetical resistance to sorafenib in metformin-treated patients, as the survival of patients treated with metformin was similar to the survival of BCLC C untreated patients and to the control arm of the sorafenib registration study.[52,85,86]

DPP-4 inhibitors

DPP-4 inhibitors work by increasing circulating levels of incretins, such as GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), to enhance insulin secretion and inhibit glucagon secretion. The potential role of these drugs in HCC development has not been investigated so far. To the best of our knowledge, only one clinical study has been published considering the hepatic outcomes of DDP-4 inhibitors.[87] This study evaluated the risks of mortality, cardiovascular events, and hepatic outcomes between DPP-4 inhibitor users and nonusers with comorbid diabetes and compensated

cirrhosis. The incidence rate of decompensated cirrhosis during follow-up was 2.20 and 1.53 per 100 patient-years (aHR 1.35, 95% CI 1.03–1.77, p < 0.05) for DPP-4 inhibitor users and nonusers, respectively. The aHRs (95%CI) of variceal bleeding and hepatic failure were 1.67 (1.11–2.52) and 1.35 (1.02–1.79), respectively, for DPP-4 inhibitor users over nonusers (p < 0.05).[87] The risk of all-cause mortality, HCC, and major cardiovascular events between DPP-4 inhibitor users and nonusers were not statistically different. Possible explanations for the higher risk of decompensating events rely on the findings from animal studies showing that DPP-4 inhibitors can elevate GLP-1 and GIP levels in splanchnic and portal circulation, which can promote nitric-oxide production and accelerate portal vein inflow.[88] One pharmacovigilance study found that DPP-4 inhibitors were associated with a higher risk of gastrointestinal venous thromboembolism,[89] which may then increase portal pressure and result in complications such as variceal bleeding. However, a meta-analysis of DPP-4 inhibitors did not indicate a risk of hepatic injury,[90] and a prospective study investigating the efficacy and safety of sitagliptin in 122 diabetic patients with chronic liver disease (including 19 patients with cirrhosis) suggested that sitagliptin can be safely administered.[91]

In vivo and *in vitro* studies have suggested that DDP-4 inhibition may prevent HCC development in mice both indirectly in a glucose metabolism–independent manner by suppressing NASH development and directly by suppressing HCC development through the activated infiltration of lymphocytes into the tumor, although evidence is still scarce and further data are needed before understanding the potential carcinogenic effects of this medication in humans.[92,93]

SGLT2 inhibitors

SGLT2 inhibitors are a new class of oral hypoglycemic agents that work by decreasing glucose reabsorption in the renal proximal tubules, leading to increased urinary glucose excretion and reduced blood glucose levels as a result of the decreased glucose area under the curve (i.e., decreased glucose load presented over the course of the day).

Various animal models of NAFLD treated with SGLT2 inhibitors have demonstrated a protective effect on steatosis, inflammation, and fibrosis.[94–99] To date, there are no clinical data on whether these drugs might protect from—or favor—carcinogenesis in patients with cirrhosis. However, in an experimental mouse model of NASH, canaglifozin altered glutathione metabolism and reduced oxidative stress in adipose tissue; moreover, it inhibited the development of hepatic fibrosis and HCC.[100] Another study showed that in a mouse model of diabetes and NASH-related HCC, canagliflozin had anti-steatotic and anti-inflammatory

TABLE 1 Clinical studies on the impact of anti-diabetic medications on the risk of HCC

Reference	Study design	Anti-diabetic medication	Study population	No. of patients (HCC incidence: n; %)	Patients with cirrhosis (%)	Results
Singh, 2013[31]	Metanalysis of RCTs and observational studies	Metformin SUs TZDs Insulin	Patients with T2DM	334,307 (22,650; 6.8%)	NR	Metformin reduced by 50% HCC incidence (OR = 0.50, 95% CI 0.34–0.73); sulfonylurea increased HCC risk by 62% (OR = 1.62, 95% CI 1.16–2.24); insulin use increased the risk by 161% (OR = 2.61, 95% CI 1.46–4.65); TZDs did not modify the risk of HCC (OR = 0.54, 95% CI 0.28–1.02)
Zhang, 2013[32]	Metanalysis of observational studies	Metformin	Patients with T2DM	16,739 (752; 3.4%)	NR	Metformin significantly reduced the risk of HCC (RR = 0.24, 95% CI 0.13–0.46, $p < 0.001$)
Li, 2021[34]	Metanalysis of observational studies	Metformin	Patients with T2DM	1,452,265 (NR)	NR	Metformin decreases the HCC risk with a random effects model (OR/RR = 0.59, 95% CI 0.51–0.68, $p < 0.001$) and decreases all-cause mortality of HCC in T2DM with a random effects model (HR = 0.74, 95% CI 0.66–0.83, I^2 = 49.6%, $p = 0.037$)
Donadon, 2010[112]	Retrospective case-control study	Metformin	HCC cases compared to matched patients with cirrhosis and controls (general population)	610 HCC cases 618 matched patients with cirrhosis 1696 controls	—	Metformin, compared with SUs or insulin therapy, was associated with a significant reduction of the risk for HCC vs. controls and vs. liver cirrhosis cases (OR = 0.15, 95% CI 0.04–0.50, $p = 0.005$; and OR = 0.16, 95% CI 0.06–0.46, $p = 0.0006$, respectively)
Kaplan, 2021[35]	Retrospective cohort study	Metformin	Subjects with liver cirrhosis (58.2% with comorbid T2DM: 53.8% before the diagnosis of cirrhosis and 4.8% following the diagnosis of cirrhosis)	74,984 (NR)	100%	Metformin was not associated with reduced HCC after adjustment for concomitant statin exposure; for patients with diabetes before diagnosis of cirrhosis but no before metformin exposure, metformin was associated with reduced mortality (HR = 0.72 95% CI 0.35–0.97) but not with reduced HCC or hepatic decompensation ($p < 0.05$)
Bosetti, 2015[48]	Retrospective case-control study	Metformin SUs TZDs Insulin Alpha-glucosidase inhibitors Incretins Repaglinide	Subjects with T2DM with an HCC diagnosis compared to controls with T2DM only	190 T2DM subjects with HCC; 3772 controls	NR	Increased risks of HCC were found for use of insulin (OR = 3.73, 95% CI 2.52–5.51), SUs (OR = 1.39, 95% CI 0.98–1.99), and repaglinide (OR = 2.12, 95% CI 1.38–3.26), whereas a reduced risk was found for use of metformin (OR = 0.57, 95% CI 0.41–0.79)

TABLE 1 (Continued)

Reference	Study design	Anti-diabetic medication	Study population	No. of patients (HCC incidence: n; %)	Patients with cirrhosis (%)	Results
Tseng, 2018[45]	Retrospective cohort study	Metformin	Patients with T2DM treated with metformin and matched metformin never-users	Among 21,900 metformin ever-users: 462 (2.11%); among 21,900 metformin never users: 619 (2.83%)	Among metformin ever-users: 3.3%; among metformin never-users: 5.1%	Decreased risk for HCC in metformin ever-users: HR = 0.45 (95% CI 0.41–0.49), $p < 0.001$; the risk remained significantly decreased also in the subanalysis considering only subjects with cirrhosis (HR = 0.51, 95% CI 0.43–0.60)
Tangjarusritaratorn, 2021[47]	Retrospective cohort study	Metformin	1061 patients with T2DM with cirrhosis	Among 719 metformin users: 125 (17.4%); among 342 metformin never-users: 128 (37.4%)	100%	Metformin exposure was associated with a decreased incidence of HCC, with a HR of 0.48 (95% CI 0.36–0.62, $p < 0.001$)
Vilar-Gomez, 2019[113]	Retrospective cohort study	Metformin	191 patients with T2DM with NASH and advanced liver fibrosis	Among 110 metformin ever-users: 7 (6%); among 81 metformin never-users: 21 (26%)	Among metformin ever-users: 85%; among metformin never-users: 88%	The 10-year cumulative incidence of HCC was significantly lower in metformin users (12%, 95% CI 7–18) as compared with nonusers (40%, 95% CI 35–48), which corresponds with a subhazard ratio = 0.25 (95% CI 0.11–0.58; ($p < 0.01$)
Vilar-Gomez, 2021[46]	Retrospective cohort study	Metformin	Patients with biopsy-proven NASH with Child–Pugh A cirrhosis	299 (39; 13%)	100%	Metformin use was associated with a significant reduction in risk of HCC (aHR = 0.78; 95% CI 0.69–0.96); metformin significantly reduced the risk of hepatic decompensation and HCC only in subjects with HbA1c levels > 7.0% (aHR = 0.97, 95% CI 0.95–0.99; and aHR = 0.67, 95% CI 0.43–0.94, respectively)
Chang, 2012[64]	Retrospective case-control study	TZDs SUs Metformin	Patients with T2DM	606,583 (10,741; 1.7%)	NR	A significantly decreased risk of HCC was found for any use of rosiglitazone (OR 0.73, 95% CI 0.65–0.81) and pioglitazone (OR 0.83, 95% CI 0.72–0.95) and for metformin (OR = 0.77, 95% CI 0.69–0.85), in contrast to the aORs = 2.35 (95% CI 2.21–2.49) for short-acting insulin and 1.05 (95% CI 0.93–1.18) for sulfonylurea

TABLE 1 (Continued)

Reference	Study design	Anti-diabetic medication	Study population	No. of patients (HCC incidence: *n*; %)	Patients with cirrhosis (%)	Results
Huang, 2017[65]	Retrospective population-based cohort study	TZDs	76,349 patients with T2DM (TDZ users and TDZ ever-users)	Among 3026 TZD users: 46 (1.5%); among 12,104 TZD never-users: 200 (1.6%)	Among TZD users: 2973 (98.25%); among TZD never-users: 11,784 (97.36%)	Patients in the TZD cohort had a 0.53-fold lower risk of cancer compared with the risk for patients in the non-TZD cohort (aHR = 0.53, 95% CI 0.38–0.77)
Lai, 2020[66]	Retrospective population-based case-control study	TZDs	23,580 subjects with T2DM with newly diagnosed HCC and 23,580 matched controls	—	NR	A negative association was found between HCC and every 1-year increase of cumulative duration of TZDs use (aOR = 0.94, 95% CI 0.92–0.97)
Yip, 2020[67]	Retrospective cohort study	TZDs	Diabetic patients with chronic hepatitis B	28,999 (2655; 9.2%)	5261 (18.1%)	At univariate analysis, TZDs protected from HCC incidence (HR = 0.38, 95% CI 0.20–0.71, $p < 0.002$) but not in the multivariate analysis (HR = 0.57, 95% CI 0.28–1.14, $p = 0.111$)
Hassan, 2010[69]	Retrospective case-control study	Metformin SUs TZDs Insulin	420 patients with HCC and T2DM	—	NR	The aORs (95%CI) were 0.3 (0.2–0.6), 0.3 (0.1–0.7), 7.1 (2.9–16.9), 1.9 (0.8–4.6), and 7.8 (1.5–40.0) for those treated with biguanides, TZDs, SUs, insulin, and dietary control, respectively ($p < 0.05$ for all except insulin [$p = 0.1$])
Yen, 2021[74]	Retrospective cohort study	TZDs	1705 TZD users and 1705 matched TZD-nonusers, with cirrhosis	Among TZD users: 147 (8.6%); among TZD nonusers: 170 (9.9%)	100%	The HCC risk did not differ significantly between TZD users and non-users (aHR = 0.85, 95% CI 0.68–1.06, $p = 0.15$)
Wang, 2013[72]	Metanalysis including 1 RCT, 2 case control, and 2 cohort studies	TZDs	900,522 patients with T2DM	—	NR	TZDs were associated with a significantly lower risk HCC (HR = 0.73; 95% CI 0.63–0.85, $p < 0.005$)

TABLE 1 (Continued)

Reference	Study design	Anti-diabetic medication	Study population	No. of patients (HCC incidence: n; %)	Patients with cirrhosis (%)	Results
Arvind, 2021[73]	Metanalysis of observational studies	TZDs Meglitinides SUs Alpha-glucosidase inhibitors	562,360 patients with T2DM	—	—	TZDs were associated with reduced HCC risk (aOR = 0.92, 95% CI 0.86–0.97, I^2 = 43%); alpha-glucosidase inhibitors were associated with increased HCC incidence (aOR = 1.08; 95% CI 1.02–1.14, I^2 = 21%); SUs were associated with increased HCC risk (aOR = 1.06, 95%CI 1.02 –1.11, I^2 = 75%); meglitinide use was not associated with HCC incidence (aOR = 1.19; 95% CI 0.89–1.60, I^2 = 72%)
Lee, 2019[77]	Nationwide nested case-control study	SUs Metformin Insulin Glinide TZDs DDP4 inhibitors	241 HCC cases and 1205 matched controls	—	Cases: 96 (39.8%); controls: 19 (1.6%)	SUs and glinide use were significantly higher in the HCC group (OR = 1.84 [95% CI 1.19–2.86] and OR = 2.00 [95% CI 1.29–3.08], respectively) than in the control group, whereas metformin use was lower in the HCC group than in the control group (OR = 0.59, 95% CI 0.43–0.81)
Kawaguchi, 2010[79]	Nested case-control study	SUs Insulin Alpha-glucosidase inhibitors Glinide Metformin TZDs	138 HCC cases and 102 non-HCC controls; all patients had T2DM and HCV	—	Cases: 101 (73.2%); controls: 34 (33%)	Insulin and a second-generation SUs were significantly associated with an incidence of HCC (OR = 2.969, 95% CI 1.293–6.819, p < 0.0103; and OR = 6.831, 95% CI 1.954–23.881, p < 0.0026, respectively); in stratified analyses, the impact of these antidiabetic agents was more evident in patients without cirrhosis than in those with cirrhosis; there were no significant differences in the use of a third-generation SU, a-glucosidase inhibitor, glinide, metformin or TZDs between HCC and non-HCC groups
Schlesinger, 2013[84]	Observational prospective study	Insulin	Patients with T2DM	363,426 (176; 0.04%)	—	The risk for HCC was particularly higher in participants treated with insulin (RR = 6.19, 95% CI 3.50–10.98, p < 0.05)
Yen, 2021[87]	Observational case control study	DDP4-inhibitors	2828 propensity score–matched DPP-4 inhibitor users and nonusers from a cohort of T2DM with compensated liver cirrhosis	—	100%	The risk of HCC was not statistically different between DDP4 inhibitors users and non-users; DDP4-inhibitor users had higher risks of decompensated cirrhosis (aHR = 1.35, 95% CI 1.03–1.77) and hepatic failure (aHR = 1.35, 95% CI 1.02–1.79) and of variceal bleeding (aHR = 1.67, 95% CI 1.11–2.52)

Abbreviations: NR, not reported; RCT, randomized controlled trial; RR, relative risk; SU, sulphonylureas.

effects that attenuated the development of NASH and prevented the development of HCC, partly due to the induction of cell cycle arrest and/or apoptosis, as well as the reduction of tumor growth through the direct inhibition of SGLT2 in tumor cells.[101] Using multi-omic analysis of metabolomics, canaglifozin has been found to alter mitochondrial oxidative phosphorylation metabolism, fatty acid metabolism, and purine and pyrimidine metabolism, resulting in metabolic reprogramming of HCC cell lines and suppression of HCC cell proliferation.[102] Additionally, *in vitro* studies have demonstrated that canaglifozin suppresses human HCC cell growth by inducing cell cycle arrest and apoptosis.[103] Finally, canaglifozin may reduce the human HCC xenograft tumor burden, independent from glycemic status (*in vivo*), and attenuate the proangiogenic activities of human HCC cells[103]—an effect that is potentiated with the combination of canaglifozin and tenegliptin, a DDP-4 inhibitor.[104] Again, due to lack of clinical data, recommendations on this class of medication for use in patients with T2DM with liver disease cannot yet be made.

GLP-1RAs

GLP-1RAs constitute an anti-diabetic class that acts as insulin secretagogues and reduce postprandial glucose levels in patients with T2DM. Additionally, GLP-1, which is an intestinal peptide made by gut neuroendocrine cells, has been shown to stimulate pancreatic beta cell proliferation, inhibit glucagon secretion, increase satiety through alterations in the hypothalamic signaling pathways, and delay gastric emptying.[105] Recently, several animal and human studies have emphasized the role of GLP-1RAs in ameliorating liver fat accumulation, alleviating the inflammatory environment and preventing NAFLD progression to NASH.[106] Intuitively, the amelioration of hepatic inflammation and the prevention of NASH should also help indirectly to reduce the risk of HCC development, given our knowledge that NASH portends a higher risk of HCC compared with NAFLD,[107] but to date, there is no clinical evidence on whether GLP1-RAs might prevent HCC occurrence. *In vitro* and *in vivo* studies have shown that liraglutide and exenatide, despite being insulin secretagogues, may possess antitumor efficacy by modulating the inflammatory microenvironment of HCC and inducing autophagy and senescence, although evidence of an effect in patients with liver disease at risk of HCC is still lacking.[108,109]

CONCLUSIONS

The bidirectional relationship between diabetes and chronic liver diseases is well established. Indeed,

advanced liver disease may favor the onset of T2DM, while T2DM is a recognized risk factor for cirrhosis and its complications, including HCC.[6,8,9,110] Several preclinical and clinical studies have shown that diabetic medications may influence the risk of HCC development, as summarized in Table 1. Most available clinical data have evaluated the effects of metformin, TZD, sulfonylureas and insulin, whereas data on the more novel glucose-lowering agents (i.e., DDP-4 inhibitors, SGLT-2-inhibitors, and GLP1-RAs) are preliminary and lack large clinical studies. Notably, to date there are still no large multicenter randomized clinical trials for any class of diabetic medications. Metformin is the first-line treatment option for T2DM.[111] Considering that metformin has consistently been reported to reduce the risk of HCC in diabetic patients while also potentially improving the prognosis of patients with an established HCC diagnosis at early stages, this drug can be considered the first-line option for patients with advanced liver disease.[31,32,34,35,45–51,112,113] Moreover, the available evidence suggests that metformin can be safely administered in well-selected patients with T2DM and cirrhosis, with limited risk of lactic acidosis.[114–116] However, due to the reported cases of this complication, and to the frequent incidence of renal impairment in patients with chronic liver disease, it seems reasonable to implement caution while prescribing metformin in patients with decompensated liver disease, particularly considering the recent addition of numerous effective therapeutic options to the anti-diabetes arsenal. Additionally, given the potential for metformin to induce resistance to sorafenib and portend a worse survival in patients co-treated with these medications, caution again must be implemented when considering use in patients with advanced HCC under consideration of sorafenib treatment.[51–54,117] Evidence regarding the effects of metformin when used in combination with other systemic therapies, including other tyrosine-kinase inhibitors or ICIs, is still needed. Although data obtained in other oncological settings do not appear to support a positive effect of concomitant metformin and ICI treatment, there is still no solid evidence in patients with HCC.[61]

With regard to TZDs, most studies suggest this class of medication appears to protect from HCC development, although we acknowledge the inconsistency of these results. Hence, in light of the paucity of data regarding its potential chemo-preventive role and advantage on liver-related events, along with the concern for increased cardiovascular events in patients with cirrhosis, it appears premature to recommend the preferential treatment with these drugs in patients with comorbid cirrhosis and diabetes.[31,48,64–69,72–74] Again, for patients with biopsy-proven NASH, which is a common complication in patients with diabetes, the use of the TZD pioglitazone is recommended by the AASLD, given the evidence that suggests it induces regression of fibrosis in this class of patients.[75,118–123]

Unlike metformin and TZDs, sulfonylureas have consistently been reported to significantly increase the risk of HCC, especially for patients treated with second-generation sulfonylureas.[48,69,77–79] The effects of sulfonylureas on HCC were more evident in patients without cirrhosis; this finding was similar to those on TZDs and may find an explanation in the increased intrinsic tumorigenic mechanisms found in cirrhosis. Due to the potential tumorigenic effect of this drug class, together with a high risk of inducing hypoglycemia, one could argue that sulfonylureas might not be the best treatment option for patients with advanced liver disease. As suggested by Chung et al., who proposed a treatment algorithm for patients with comorbid T2DM and chronic liver disease, GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT-2 inhibitors may be preferred, even in patients with mild-to-moderate hepatic impairment, given their low risk of hypoglycemia and the potential protective effect on HCC development.[92,93,100,101,103,108,109,124] However, because safety data on subgroups of patients with chronic liver disease are scarce, caution and monitoring of liver function tests should be taken, especially in patients treated with DDP4 inhibitors, given the potential risk of hepatic decompensation.[89,90] Data on the potential effects of alpha-glucosidase inhibitors are poor and controversial[48,73,123]; therefore, their potential role as preventive treatments for HCC needs further investigation. With regard to insulin, clinical evidence has consistently shown an increased risk of HCC among insulin-treated patients as compared with cohorts treated with other anti-diabetic medications.[31,48,69,84] The risk seems to rise for longer treatment duration; however, whether this is reflective of a more severe course of diabetes with a secondarily inherent higher carcinogenic effect, or of a true independent higher pro-neoplastic activity of the medication itself, remains unclear.

It is worth emphasizing that most of the studies assessing the effects of various diabetic medications on HCC incidence did not adjust for the same confounders (i.e., cirrhosis, diabetes duration and severity, etiology of liver disease, and nature of comparator group) and for the degree of metabolic control of diabetes. As the presence of diabetes may predict more severe liver dysfunction, treatment of diabetes (and treatment with some drugs) may just represent a proxy of more advanced liver disease, and most studies have not truly adjusted for the competing mortality related to liver failure. Moreover, most diabetic patients were on multiple glucose-lowering agents simultaneously; hence, the nature of the control group for each drug consisted of patients treated with multiple diabetic medications, each one with an inherent cancer-modifying effect. Diabetes duration and severity may increase the risk of HCC, and the prescription of multiple antidiabetic agents and insulin is reflective of more severe glycemic impairment. Finally, although some studies tried to adjust their analyses for co-prescription of other drugs with a putative effect on HCC development such as statins, it is difficult to truly rule out the potential effect attributable to the use of diabetic medications alone. Thus, notwithstanding the increasing evidence in this field, it is difficult to interpret whether the risk modification for any one agent is real or confounded by diabetes severity, exposure to different glucose-lowering medications, or various of other medications commonly used in patients affected by the metabolic syndrome. However, based on the current evidence, we could argue that metformin may be considered the first-line treatment option for patients with advanced compensated chronic liver disease, and that in case of unsatisfactory glycemic control, it would be prudent to avoid sulfonylureas and insulin in favor of newer glucose-lowering drugs such as TZDs, SGLT-2 inhibitors, DDP4-inhibitors and GLP1-RAs, particularly in light of the data supporting their potential protective effect against HCC development. However, in the case of the selection of SGLT-2 inhibitors, special attention should be paid to the potential occurrence of urinary tract infections, which are a common complication of these drugs due to their intrinsic mechanism of action that causes glycosuria, and that actually represent one the most frequent infections in patients with cirrhosis.[125] GLP1-RAs may be preferred in patients needing to lose weight, as these drugs favor weight loss, whereas TZDs should be avoided in patients at high risk of cardiovascular events. Conversely, in the case of patients with decompensated liver disease, insulin remains the safest option, as consistent evidence has shown its efficacy and safety in this subpopulation, and these patients are often candidates to liver transplantation independently of the presence of HCC, thus decreasing the potential HCC risks associated with long-term treatment. With regard to non-insulin agents, until specific guidelines are created, use of these classes of drugs may be considered in compensated and mildly decompensated cirrhosis (i.e., Child-Pugh class A or B), with the recommendation of caution and strict monitoring of liver and renal function tests, whereas all of them should be avoided in cases of severely decompensated cirrhosis (i.e., Child-Pugh class C or score > 9), in which insulin is the sole safe treatment option.[126]

In a context of an increasing prevalence of diabetes and of metabolic-associated liver disease, further well-designed, large randomized controlled trials are needed to understand how to optimize the diabetes treatment in patients with cirrhosis, to prevent cardiovascular, hepatologic, and malignant complications.

FUTURE PERSPECTIVES

Due to the progressive, dramatic decrease in patients affected by chronic viral hepatitis as the etiologic agent of liver disease and HCC, at least in the Western world, the

burden of patients with NAFLD and HCC is expected to proportionally rise in the near future.[127] Surveillance for HCC in patients with NAFLD may be hampered by the high prevalence of the disease in the general population, thus making the surveillance not cost-effective.[37] However, the presence of diabetes has consistently been associated with a clinically relevant increase in the risk of HCC in patients without cirrhosis with NAFLD, thus helping narrowing down the population who may need to undergo surveillance.[128] How use of (certain) diabetes medications might affect this risk and further help restrict surveillance to limited subgroups of patients is yet unknown, although it is likely that that the evaluation of large prescription databases might help to provide indications on this issue in the future.

Currently, HCC represents the most common indication for liver transplantation in the United States, and NASH represents the fastest cause for advanced liver disease and HCC.[129,130] Between 10% and 15% of patients undergoing liver transplantation are affected by T2DM, and the 5-year cumulative incidence of post-transplant diabetes may be as high as 35%.[131] Given that metformin is considered the anti-diabetic treatment of choice following liver transplantation,[132] analysis of a large transplant database may help to identify whether, and how, anti-diabetic treatment might modulate HCC recurrence, as hypothesized in a study performed in patients with viral etiology of disease.[133]

Finally, given the rapidly emerging landscape of HCC treatment with ICIs and the recent hypothesis that patients with NAFLD and HCC may be inherently "resistant" to these highly effective drugs due to aberrant T-cell activation,[134] it may be of interest to assess whether the use of diabetes medications might counteract, or modulate, this negative effect, as the use of metformin might promote intratumoral T-cell infiltration, and there is experimental evidence that metformin may reverse the reduced intrahepatic T-cell density determined by a high-fat diet in a NAFLD/NASH-HCC zebrafish model.[135,136]

All in all, we feel that—due to the rapid changing landscape of chronic liver disease etiology and to the high prevalence of T2DM in these patients—it is likely that in the future we will witness an exponential increase in the knowledge regarding not only the modulating effect(s) potentially exerted by diabetes medicine on the risk of HCC, but also on how use of anti-diabetic drugs might help focus interventions, and how their use might possibly help enhance the effects of anti-tumoral therapies.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Maria Corina Plaz Torres: conception and design, drafting the article, preparation, creation of the published work, specifically writing the initial draft, final approval of the version to be published. Ariel Jaffe: conception and design, drafting the article, revising the article for intellectual content, final approval of the version to be published. Rachel Perry: drafting the article, revising the article for intellectual content, final approval of the version to be published. Elisa Marabotto: drafting the article, revising the article for intellectual content, final approval of the version to be published. Mario Strazzabosco: conception and design, revising the article for intellectual content, supervision, final approval of the version to be published. Edoardo G. Giannini: conception and design, revising the article for intellectual content, supervision, final approval of the version to be published.

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