Insulin Use and The Risk of Hepatocellular Carcinoma: Insights and Implications

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ABSTRACT

In recent years, the incidence of diabetes mellitus and hepatocellular carcinoma (HCC) has been increasing worldwide, in the context of an increasing prevalence of non-alcoholic fatty liver disease (NAFLD). In patients with diabetes mellitus, exogenous insulin is commonly prescribed and used in long-term settings. Recent studies suggest that insulin use may elevate the risk of HCC. A substantial body of work seeks to unpack the association between insulin use and the risk of developing HCC, although there may be conflicting evidence. Further validation is necessary to clarify the true relationship between insulin mechanisms and its hepatocarcinogenic effect. Given the burden of diabetic patients developing HCC, diabetologists and hepatologists must collaborate, particularly regarding the prevention and surveillance of HCC in diabetic patients.

Keywords*: hepatocellular carcinoma, insulin, insulin use, risk.*

INTRODUCTION

Liver cancers are the fourth most common cause of cancer-related death and rank sixth in terms of incident cases worldwide. Hepatocellular carcinoma (HCC) accounts for the majority of primary liver cancers. In most countries, Hepatitis B or C virus (HBV or HCV) infection and alcohol abuse are widely recognized as the major etiology of HCC.[1] However, in recent years, the increased prevalence of non-alcoholic fatty liver disease (NAFLD), including type 2 diabetes mellitus, amplifies the risk of liver cancer. Consequently, NAFLD soon may become a leading cause of liver cancer in the future.[2]

Several studies have established that type 2 diabetes mellitus is associated with an increased risk of HCC. In a meta-analysis, type 2 diabetes mellitus was at a 2.3-fold risk of developing HCC, which accounts for the highest risk among the 20 cancer types included in the study.[3] In a case-control observational study, diabetes is associated with more advanced lesions and poorer long-term prognosis in HCC patients.[4]

Given the increased risk of HCC in patients with diabetes, it has been suggested that anti-diabetic medication use could modify the risk. Although data on the role of anti-diabetic medication in HCC are limited, there is an indication that insulin use may increase the risk.[5] In patients with HbA1C > 9% or patients who failed to achieve their blood glucose target after being given the optimal dose of a combination of oral anti-diabetic medications, insulin is widely prescribed and often used in a long-term setting.[6] Thus, decisions concerning insulin prescribing and understanding the risk of developing HCC are substantial. Therefore, the purpose of this review is to examine the use of insulin and

its association with increased risk of HCC in diabetic patients. This review intends to inform future research and serve as a basis for potential study designs.

PHYSIOLOGICAL INSULIN SIGNALING PATHWAY

Insulin is a major anabolic hormone produced by the islet cells of the pancreas primarily for glycemia elevations. In the liver, insulin acts on hepatocytes to inhibit gluconeogenesis and stimulate glycolysis, glucose storage as glycogen, protein synthesis, and lipogenesis. Apart from its metabolic effects, insulin is also a prominent growth factor for hepatocyte division and survival.[7]

Insulin binds to insulin receptors (IR), which are expressed in all cell types in the body. IR activates its tyrosine kinase and initiates a series of signaling pathways such as Ras-MAPK, PI3K-Akt, and mTOR.[8,9] The insulin receptor substrates (IRS), acting as adaptor proteins, recruit various signaling complexes.[10] Notably, growth factor receptor-bound protein 2 (Grb2) is recruited to the binding site on IRS and phosphorylates Ras. This leads to the activation of Ras and subsequently activates the mitogen-activated protein kinase (MAPK) signaling cascade.[9] Rac1, a member of the GTPase superfamily, plays a crucial role in insulin-induced glucose uptake and glucose-induced insulin secretion.[11] IRS proteins also interact with the p85 regulatory subunit of phosphoinositide 3-kinase (PI3K), which in turn controls the activation of Akt through phosphoinositide-dependent kinase 1 (PDK1). The activation of Akt is vital for regulating metabolic enzymes, as well as facilitating cell proliferation and survival.[12] Additionally, the PI3K-Akt pathway regulates the mammalian target of the rapamycin (mTOR) pathway, which plays a central role in cell growth and metabolism.[13]

Insulin-like growth factors (IGF) are a part of the insulin-related family. These compounds (IGF-1 and IGF-2) share homologous structures with insulin although they have different origins. The production of IGF-1 is controlled mostly by the action of growth hormone in the liver. IGF is functionally related to insulin but has a much higher growth-promoting activity. Both IGFs and insulin act as ligands for their respective receptor tyrosine kinases—the IR and the insulin-like growth factor 1 receptor (IGF-1R).[8] The IR and IGF-1R are highly similar and share many overlapping signaling pathways. Activation of both receptors leads to stimulation of the major canonical signaling pathways: Ras-MAPK, PI3K-Akt, and mTOR. Disruptions in these pathways can lead to insulin resistance, which is characterized by glucose intolerance, dyslipidemia, and elevated risk of cardiovascular disease or alterations in growth.[8,14]

DIABETES MELLITUS, INSULIN, AND HEPATOCELLULAR CARCINOMA

The relationship between insulin mechanisms and its hepatocarcinogenic effects is inseparable from the underlying mechanisms of diabetes mellitus and chronic liver disease **(Figure 1)**. In patients with cirrhosis-related diabetes mellitus, insulin has a decreased ability to suppress hepatic gluconeogenesis, and hepatic insulin degradation is impaired. These mechanisms promote hyperinsulinemia, which initially compensates for insulin resistance, but eventually leads to hyperglycemia. Moreover, cirrhosis itself reduces the functional mass of hepatocytes and results in portosystemic shunting.[15]

Given that insulin resistance is a prominent characteristic of chronic liver disease that is predisposed to HCC, there is a belief that the activation of the insulin pathway due to hyperinsulinemia leads to the development of liver carcinogenesis. One possible hypothesis is that hepatic insulin resistance is partial, allowing certain pathways to retain sensitivity to higher-than-normal insulin levels. During chronic liver disease, hepatocytes that have evaded apoptosis and necrosis face significant selection pressure from factors such as inflammation, hyperglycemia, oxidative stress, and elevated levels of circulating free fatty acids, which likely contribute to cellular transformation to carcinoma cells.[15]

Ultimately, several mechanisms including hyperinsulinemia, insulin resistance, or exogenous insulin treatment, have been suggested

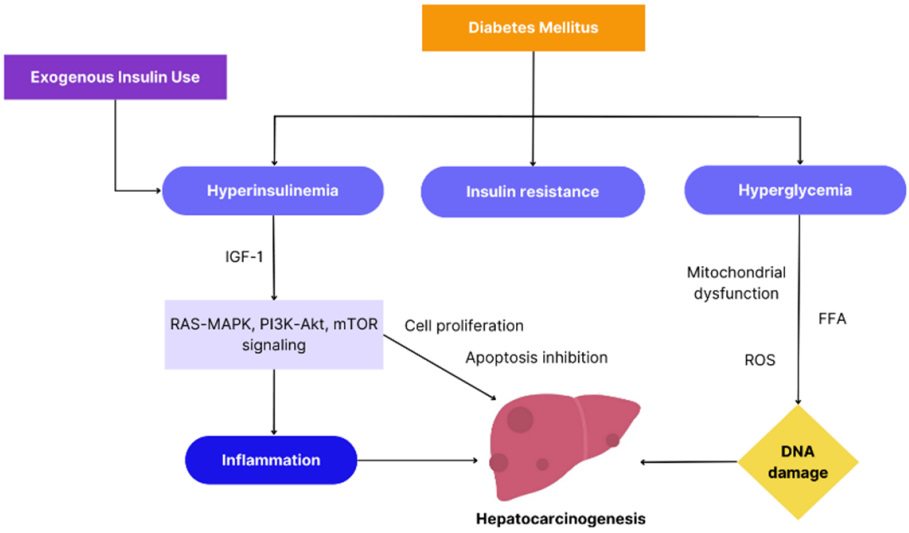

Figure 1. Pathogenic pathways that may link diabetes mellitus and insulin use to HCC development.

to explain the association between diabetes and HCC. An increase in circulating insulin levels is also seen in patients treated with exogenous insulin. Indeed, in an experimental study, exogenous insulin injection promotes colonic carcinogenesis in rats.[16] Similarly, patients with type 2 diabetes exposed to exogenous insulin have a significantly increased risk of cancer-related mortality.[17]

Insulin could be directly related to risk by promoting tumor proliferation, or it could affect risk by modulating circulating levels of growth factors and their binding proteins or by competing with their specific receptors in target tissues.[18] The insulin receptor (IR) is significantly overexpressed in 40% of the analyzed HCC tumors compared to the surrounding non-tumor tissue.[19] This overexpression is accompanied by a significant change in the relative expression of IR isoforms in approximately 70% of HCC samples. The insulin receptor substrates 1 and 2 (IRS-1 and IRS-2) are frequently overexpressed in HCC tumors compared to non-tumor liver tissue at both the mRNA and protein levels.[20,21] This overexpression is observed even in the early stages of liver carcinogenesis, where it can enhance insulin signaling. In patients with HCC, IRS-1 overexpression is associated with larger tumor size and tumor progression.[20] Moreover, insulin also activates the IGF-I receptor, known to have growth-promoting effects. Thus, reduced insulin sensitivity with compensatory hyperinsulinemia leads to an elevated level of IGF-I and stimulation of cell proliferation. The IGF-I could act as a growth stimulus in preneoplastic and neoplastic cells.[22]

STUDIES ON THE ASSOCIATION BETWEEN INSULIN USE AND RISK OF HCC IN DIABETIC PATIENTS

In the past decade, several studies have observed the elevated risk of HCC incidence in diabetic patients treated with insulin. In Shanghai, Gu et al conducted an observational cohort study in 8,774 insulin-naïve diabetes patients. The result showed that the risk of liver cancer was significantly higher in the insulin users compared to that in the non-insulin users (adjusted RR,2.84, 95% CI 1.12–7.17).[23] Similarly, a study by Kasmari also showed that insulin increased the risk of HCC compared with the general type 2 diabetes mellitus population (OR, 1.64, 95% CI 1.48-1.81).[24] Schlesinger et al conducted a prospective analysis involving 363,426 participants with self-reported diabetes. During 8.5 years of follow-up, 176 HCC cases were identified and the risk for HCC was particularly higher in participants treated with insulin (RR, 6.19, 95% CI 3.50-10.18).[25] 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. The

study reported that an increased risk of HCC was found with insulin use in diabetic patients (OR, 3.73; 95% CI, 2.52–5.51).[26] These findings were consistent with a meta-analysis by Singh et al, who found an increased risk of HCC in insulin users (OR, 2.61, 95% CI 1.46–4.65).[27]

The duration of insulin use was found to be associated with an increased risk of HCC. Bosetti et al demonstrated that the risk of HCC increased with a longer duration of insulin use (OR, 2.52 for <1 year, 5.41 for 1–2 years, and 6.01 for ≥2 years). These findings indicate that insulin plays a genuine role in the development of HCC, although the over two-fold excess risk observed for use for less than 1 year suggests that diabetic patients under insulin treatment have a higher background rate of HCC, probably related to their diabetes severity.[26]

Mannucci et al conducted a case-control study to analyze the doses of insulin and its analogs and cancer occurrence in type 2 diabetic patients. During a median follow-up of 75.9 months, 112 cancer cases were identified, including 18 hepato-gastrointestinal cancer. The study reported that incident cancer was associated with a dose of glargine ≥0.3 IU/kg/day (OR, 5.43, 95% CI 2.18–13.53). Given the possibility of an association between cancer and higher glargine doses, the study suggested that dosage should be taken into consideration when assessing the potential link between insulin and its analogs with cancer.[28]

Overall, although evidence suggests that insulin could increase the risk of HCC in diabetic patients, there may be some conflicting results from other studies **(Table 1)**. A retrospective

Table 1. Summary of clinical studies on the impact of insulin use on the risk of HCC.

Reference	Country	Study Design	Study Population	Results
Gu, et al.[23] (2013)	China	Population-based, observational cohort study	3,639 insulin-user patients, 5,135 the non-insulin user patients	Increased risks of liver cancer were found in insulin users, compared to that in the non-insulin users (adjusted RR,2.84, 95% CI 1.12–7.17)
Kasmari, et al.[24] (2017)	USA	Retrospective cohort study	2,095 diabetic and HCC patients, 5,022 diabetic patients without HCC	Insulin (OR, 1.640, 95% CI 1.48-1.81) increased the risk of HCC compared with the general type II diabetes population
Schlesinger, et al.[25] (2013)	Europe	Prospective cohort study	363,426 diabetic patients	The risk of HCC was particularly higher in patients treated with insulin (RR, 6.19, 95% CI 3.50-10.18)
Bosetti, et al.[26] (2015)	Italy	Nested case-control study	190 diabetic and HCC patients, 3,772 controls	Increased risks of HCC were found for the use of insulin (OR, 3.73, 95% CI 2.52-5.51)
Kawaguchi, et al.[35] (2010)	Japan	Nested case-control study	138 diabetic, Hepatitis C, and HCC patients, 103 controls	Use of insulin was a significant independent factor associated with HCC incident (OR, 2.969, CI 95% 1.293-6.819)
Singh, et al.[27] (2013)	USA	Meta-analysis of RCT and observational studies	334,307 patients with diabetes	Insulin use increased the risk of HCC (OR, 2.61, 95% CI 1.46-4.65)
Oliveria, et al.[29] (2008)	USA	Retrospective cohort study	191,223 patients with diabetes, 39 HCC cases	Exposure to insulin or other antidiabetic treatment was not associated with HCC risk
Simon, et al.[30] (2018)	USA	Prospective cohort study	10,110 diabetic patients, 112 HCC cases	In diabetic patients, insulin use was not significantly associated with HCC risk
Lai, et al.[31] (2012)	Taiwan	Retrospective cohort study	19,349 diabetic patients, 77,396 non-diabetic patients	There was no significant association between insulin and the risk of developing HCC
Kramer, et al.[36] (2022)	USA	Retrospective cohort study	85,963 patients with NAFLD and diabetes, 524 HCC cases	Insulin did not affect HCC risk, however, insulin in combination with other oral medications was associated with a 1.6 to 1.7-fold higher risk of HCC

cohort study among patients with type 2 diabetes was conducted using a large US population-based database. Among the 39 liver cancer cases found during follow-up, exposure to insulin and other antidiabetic regimens was not associated with an appreciable increase in HCC risk.[29] Furthermore, in a large cohort study with over 26 years of follow-up, there was a trend toward increased risk of HCC with insulin use, but this did not reach statistical significance.[30] In the Taiwanese study, there was no significant association between insulin and the risk of developing HCC.[31] The variations in findings between these studies and contradictory results reported in other studies could be attributed to differences in underlying population risk factors. In addition, the treatment duration and its impact on risk may influence the statistical analysis. However, rather than representing an association of HCC risk with the medication itself, this may serve as a marker of disease severity, as patients with more severe diabetes are typically treated with insulin.

FUTURE DIRECTIONS

Albeit further validation is needed to clarify the true relationship between insulin use and HCC risk, existing shreds of evidence suggest that insulin may have some hepatocarcinogenic effects. Considering the complex mechanism between HCC and insulin, and the burden of diabetic patients developing HCC, it is crucial to establish effective strategies for HCC surveillance in diabetic patients. The current national guidelines recommend HCC surveillance only for patients with cirrhosis or those with viral hepatitis.[32] Therefore, there is an urgent need for detecting HCC at a treatable stage in diabetic patients.

Adhering to the national guidelines, implementing routine HCC surveillance every six months through ultrasound examinations may be a reasonable approach.[32] Another method, transient elastography measurement, can be considered to evaluate liver stiffness in the population at risk. Additionally, since liver fibrosis is a major predictor of HCC in chronic liver disease, non-invasive fibrosis markers could be useful for risk stratification of HCC. Several studies have identified scoring systems to determine liver scarring and cirrhosis, such as aspartate aminotransferase (AST)-to-platelet ratio index (APRI), AST-to-ALT ratio, NAFLD fibrosis score, and fibrosis-4 (FIB-4) index.[33] A national cohort study from Japan, recruited 239 patients with T2DM who were diagnosed with non-viral HCC, with 5 years of follow-up at diabetes clinics before HCC diagnosis. The study found that the FIB-4 index was an outstanding predictor of HCC development, with an AUROC of 0.811 for predicting the 5-year HCC incidence. This result suggests that a simple calculation of the FIB-4 index in diabetes clinics can be the first step for the surveillance of HCC with non-viral etiology. Hence, future prospective studies are needed to validate the efficacy of surveillance strategies based on non-invasive methods.[34]

CONCLUSION

Understanding the complex relationship between diabetes mellitus, insulin, and HCC is challenging due to the involvement of various signaling pathways in the disease progression. Clinical studies have indicated a higher risk of HCC in patients receiving insulin treatment. However, further investigation is required to determine the specific role of insulin use and its potential carcinogenic effects. Given insulin's widespread and long-term use, collaboration between diabetologists and hepatologists is crucial for studying liver diseases in diabetic patients. This collaboration is particularly important for conducting future research to gather evidence regarding the prevention and surveillance of HCC in diabetic patients.

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