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Review Article

Antidiabetic Drugs: Their Hepatoprotective and Hepatocarcinogenic Effect

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Abstract

Hepatocellular carcinoma (HCC) is a major cause of cancer-related death worldwide. Diabetes mellitus (DM), with insulin resistance, is an established independent risk factor for HCC, as reported in multiple observational studies and subsequent meta-analyses.

Current evidence suggests that there may be interplay between obesity, DM, and tumorigenesis, with insulin resistance and hyperinsulinemia playing critical roles.

Given the significant link of DM with the risk of HCC, the use of antidiabetic medications may modify DM and reduce the risk of cancer as shown in recent research. So, the aim of this review is to illustrate the hepatocarcinogenic and hepatoprotective effects of antidiabetic medications on HCC.

Keywords: Antidiabetic Drugs; Hepatoprotective; Hepatocarcinogenic

Introduction

The occurrence of hepatocellular carcinoma (HCC) is two to three times higher in patients with diabetes mellitus (DM), the prevalence of which is increasing sharply worldwide.

The underlying biological mechanisms linking T2DM and HCC are complex and difficult to elucidate, but the existence of close inter-connections among T2DM, obesity and nonalcoholic fatty liver disease (NAFLD) induces hepatic/systemic insulin resistance and causes the release of multiple pro-inflammatory cytokines, vasoactive factors and pro-oxidant molecules, which are all potentially implicated in the development and progression of HCC [1].

In addition, the type and dosage of antidiabetic medication used appears to affect the risk of HCC [2].

The purpose of this review was to discuss the potential effect of antidiabetic medicines on HCC risk.

Diabetes and hepatocellular carcinoma

Currently, the estimated global prevalence of T2DM is approximately 9% worldwide, with a worrying tendency to increase sharply in the next years. HCC represents the commonest form of primary liver cancer [3].

An early description of the existence of an association between T2DM and HCC has been reported approximately 30 years ago. Notably, the presence of obesity and hepatic steatosis (along with T2DM) were also found to be independent predictors of incident HCC [4].

Although the precise biological mechanisms underlying the link between DM and HCC are not completely understood, the following

factors may be involved in the neoplastic process: endogenous hyperinsulinemia (insulin resistance), exogenous hyperinsulinemia (treatment with insulin or secretagogues), hyperglycemia, and/or chronic inflammation [5].

Hyperinsulinemia increases Insulin-like growth factor 1 (IGF-1), which in turn can stimulate liver cell proliferation. Furthermore, insulin resistance is independently associated with the progression of liver fibrosis, which is a risk factor for HCC.

Type 2 diabetes mellitus (T2DM) is associated with central obesity, which promotes carcinogenesis through the secretion of pro-inflammatory cytokines by visceral adipose tissue. Obesity is often associated with liver cirrhosis and liver fibrosis progression, a primary risk factor for HCC. Numerous case reports and case reviews indicate DM appears to be a risk factor for NASH, which is a cause of cryptogenic HCC, and DM is an independent risk factor for HCC in patients with NASH [6].

Chronic inflammation associated with DM may promote the development of HCC through the action of proinflammatory cytokines that regulate the apoptotic regulators Bcl-2 and Bax suggesting their potential as apoptotic and inflammatory markers for HCC [7].

Antidiabetic medication and risk of HCC

Results of *in vitro* and *in vivo* preclinical studies have suggested that antidiabetic drugs influence the development of multiple cancers. we reviewed the effect of conventional antidiabetic drugs on the risk of HCC in patients with DM

Metformin

As an insulin-sensitizing drug, metformin improves insulin sensitivity, reducing plasma levels of this hormone, inhibiting hepatic gluconeogenesis and reducing glycogenolysis. In addition, it also increases insulin-stimulated glucose uptake into skeletal muscles, suppresses oxidation of fatty acids, and reduces triglyceride levels in patients with hypertriglyceridemia. All these effects can contribute to reduce hyperinsulinemia, improve hepatic insulin resistance, reduce steatosis, improve liver enzymes and reduce body weight [8].

Metformin treatment has been independently associated with decreasing the occurrence of HCC and liver-related deaths. These observations are according to a case–control study, which reported an 85% reduction in the chance of developing HCC in cirrhotic patients receiving metformin compared to patients using exogenous insulin and insulin secretagogues [9].

The direct mechanism generated by metformin is the reduction of plasma insulin levels. Among the indirect mechanisms of inhibition of carcinogenesis is the induction of cellular apoptosis, the stimulation of the immune system, and the activation of AMPK. When in high intracellular concentrations in the liver, metformin can prevent protein synthesis, cellular proliferation and angiogenesis through the activation of the AMP-activated protein kinase (AMPK pathway). AMPK is a key mediator of the tumor suppressor liver kinase B1 (LKB1), working as a cellular energy sensor, being essential for the metabolic processes and can be suppressed in cancerous cells containing LKB1 function loss mutations or in cancers associated with the metabolic syndrome [10].

Thiazolidinediones

Thiazolidinediones (TZDs) are peroxisome proliferator-activated receptor gamma (PPARγ) agonists that lower insulin resistance without directly affecting insulin secretion. Although the risk of HCC in patients using TZDs is unclear, results of several studies indicate that TZDs may exert a beneficial effect [11].

In the meta-analysis of 119 studies use of glitazones was associated with significant reduction of overall cancer risk [12]. A population-based retrospective cohort study in Taiwan suggested that the use of TZDs may be associated with a decreased risk of HCC development among DM patients and they concluded that TZDs may play a role in the chemoprevention of liver cancer [13].

TZDs as PPARγ agonists increase insulin sensitivity and trigger cell cycle arrest, apoptosis, as well as anti-proliferative, anti-angiogenic, and pro-differentiation pathways, thus contributing to the down-regulation of carcinogenesis [14].

Incretin based therapy

GLP1 is an incretin hormone which stimulates insulin secretion after an oral glucose load. GLP1 receptor agonists and DPP4 inhibitors act through GLP1 or its receptor with effective results in Type 2 Diabetes. Not only do they improve insulin sensitivity, decrease glucagon production and increase satiety, they also decrease free fatty acid concentration and indirectly reduce hepatic steatosis and inflammation [15]. Moreover, GLP1 is known to have trophic ef-

fects mediated by G protein coupled receptor which help decrease B cell apoptosis and increase their proliferation, differentiation and survival through the activation of signaling pathways as PI3K and ERK 1/2. [16]. These trophic changes have elicited concerns as to whether GLP1 would cause malignant transformation of tissues with prolonged use.

GLP1 receptors were discovered in parts of the brain, pituitary, thyroid, lungs, pancreas, small intestine and others. They have also been found in some malignant neoplasms as breast cancer and colon cancer. Thus, much research was conducted to investigate the role of GLP1 in carcinogenesis. While may researches deny the presence of GLP1 receptors on hepatocytes, a study by Gupta., *et al*. in 2010 demonstrated the presence of GLP1R on hepatocytes and provided an explanation as to why GLP1 could be beneficial in the treatment of NAFLD [17].

A multitude of published research addressed the effect of GLP1 based therapy and cancers. Several meta-analyses carefully selected data from these studies and provided relatively unbiased conclusions.

In a meta-analysis encompassing 37 eligible trials by Cao., *et al*. they found no evidence to suggest an increased risk of cancer with GLP1 based therapy [18].

Another meta-analysis utilizing data from 34 relevant articles compared the incidence of malignant neoplasms in cases on GLP1 RA therapy with cases on placebo or other interventions. They found no increase in the risk of neoplasia with the use of GLP1-R agonists and concluded that they can be used without concern of cancer risk in patients with type II diabetes [19]. Furthermore, a network meta-analysis reviewing the effect of DPP4 inhibitors on malignant tumors in type II diabetics concluded that there is no evidence to support an association between this class of drugs and carcinogenesis [20].

On the other hand, Zhou., *et al*. 2017 investigated the *in vivo* effect of Exendin4 in mouse models with features of obesity and hepatocellular carcinoma. They found that Exendin4 not only improved obesity, inflammation and fibrosis but also inhibits HCC development through suppressing cell proliferation and inducing apoptosis selectively in tumor cell only [21]. In a similar study by Kojima., *et al*. they found that liraglutide suppressed hepatocarcinogenesis and ameliorated hepatocyte ballooning, inflammation and steatosis in mice with induced diabetes and NASH [22]. Both studies recommend GLP1 based therapies as protective agents against hepatocarcinogenesis in obese and diabetic patients.

In conclusion, even if there is a suspicion of increased risk for the development of specific types of malignancies with incretin-based therapy, this should not be taken as an indication for tumor promoting potential in general [23].

SGLT2 inhibitors

NASH is associated with an increased risk of cirrhosis and HCC, and has emerged as a major risk factor for HCC. Patients with type 2 diabetes are susceptible to developing severe NASH, and also have a higher risk of NASH progressing to cirrhosis and/or HCC when compared with non-diabetic persons [24].

Several studies have examined the impact of sodium-glucose co-transporter 2 (SGLT2) inhibitors on the occurrence of non-alcoholic fatty liver disease (NAFLD) and/or NASH in rodent models and humans.

Overall, the studies are consistent in showing a significant reduction in alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transpeptidase, particularly among patients with confirmed NAFLD and high liver enzymes at baseline. Imaging, biomarkers of hepatic steatosis, including controlled attenuation parameter by transient elastography, magnetic resonance imaging proton density fat fraction, and proton magnetic resonance spectroscopy, also improved during SGLT2 inhibitor treatment. On average, liver fat content by magnetic resonance imaging decreased by 3%–10% after 3–12 months of treatment [25,26].

At present, only 2 small single-arm studies have tested the efficacy of 24 weeks of SGLT2 inhibitor treatment on liver histology in patients with type 2 diabetes and NASH. In the first study from Japan, of 9 patients receiving canagliflozin, 7 had improvements in histologic steatosis, 3 had improvements in lobular inflammation, 2 had improvements in hepatocyte ballooning, and 3 had improvements in fibrosis [25]. In the second study from Malaysia, of 9 patients receiving empagliflozin, 6 had improvements in histologic steatosis, 2 had improvements in lobular inflammation, 7 had improvements in hepatocyte ballooning, and 4 had improvements in fibrosis [27].

Canagliflozin showed anti-steatotic and anti-inflammatory effects that attenuated the development of NASH in a mouse model of diabetes/NASH/HCC, and prevented the progression of NASH to HCC, partly due to the induction of cell cycle arrest and/or apoptosis, or the reduction of tumor growth through the direct inhibition of SGLT2 in tumor cells [28].

One study investigated the effects of CANA on proliferation and metabolic reprograming of HCC cell lines using multi-omics analysis of metabolomics and absolute quantification proteomics (iMPAQT). CANA suppressed the proliferation of HCC cells through alterations in mitochondrial oxidative phosphorylation metabolism, fatty acid metabolism, and purine and pyrimidine metabolism. Thus, CANA may suppress the proliferation of HCC by regulating metabolic reprograming [29].

According to several large-scale genetic studies, aberrant activation of WNT/β-catenin-related signaling is one of the most common genetic predispositions in the HCC population, which makes WNT/β-catenin signaling an attractive target for designing novel anti-HCC treatments. CANA treatment significantly downregulated the expression of β-catenin in HCC cells. It was shown to delay tumor growth and improved the survival of HCC bearing mice [30].

A case report of Spontaneous regression of hepatocellular carcinoma in a patient admitted to the hospital for treatment of diagnosed recurrent HCC ten weeks after the initiation of SGLT2i treatment, the hypervascular tumor had disappeared, and the elevated serum α-fetoprotein level had decreased to normal limits, indicating spontaneous regression of HCC. In addition, an angiogenesis array analysis revealed downregulated protein expression of matrix metalloproteinase8, angiopoietin-1/2, platelet-derived growth factor-AA, and prolactin at 10 weeks after SGLT2i treatment. Their findings suggest that SGLT2i treatment could cause regression of HCC through downregulation of angiogenesis-related cytokines [31].

Sulfonylureas

Sulfonylureas are antidiabetic medications that bind to and inhibit ATP sensitive potassium channels on the pancreatic Beta cells allowing insulin release, an action not related to or limited by the blood glucose level. Studies suggest that hyperinsulinemia, whether endogenous or exogenous, is associated with an increased risk of Hepatocellular carcinoma in diabetic patients. Insulin hormone acts either directly or indirectly through stimulation of post receptor signaling pathways, as the mTOR/MAPK pathway [32].

Sulfonylureas available in most areas of the world are either second or third generation medications. These differ in their duration of action and their binding sites on the Sulfonylurea cell receptors. There are two types of receptors, SUR1 and SUR2; SUR1 is expressed on the Beta cells of the pancreas while SUR2 can be found on the heart, smooth and skeletal muscle cells. Gliclazide binds mainly to SUR1 and Glibenclamide, Glimepiride, Repaglinide and Meglitinide block both receptors [33]. Sulfonylureas were found to affect the risk of HCC in diabetic patients independent of other risk factors; a meta-analysis by Singh., *et al*. showed a 62% increased incident of HCC in patients using Sulfonylureas [34]. In a study conducted by Hassan., *et al*. the authors reported that the use of Sulfonylureas resulted in a 7-fold increase in HCC risk among diabetics [35]. Similarly, Bosetti., *et al*. conclude that sulfonylureas lead to increased risk of HCC among its users [36].

However, not all Sulfonylureas are implicated in the risk of hepatocarcinogenesis. A study by Kawaguchi., *et al*. found that second generation but not third generation (Glimepiride) are significant variables associated with incidence of HCC., the authors suggested that third generation SU improve hyperinsulinemia through extra pancreatic effects [37]. In a study by Lee., *et al*. the authors showed that SU increases incident HCC by 1.7 folds. But contrary to Kawaguchi., *et al*. they found that the use of Glimepiride increased the risk for hepatic cancer with no similar association found with Gliclazide. Moreover, they reported that a significant lower risk for HCC by 0.3-fold was found in those patients treated with Gliclazide for a duration more than two years. They explained their findings by highlighting the free radicle scavenging property of the drug and its ability to upregulate the antioxidant enzymes [38]. Similarly, Monami., *et al*. also shed light on the significant reduction in the risk of cancer with the use of gliclazide [39]. There are no studies confirming the underlying mechanisms besides hyperinsulinemia for the increased risk for HCC with the use of SU, nor are there clear and collective data to establish the superiority on one SU over the others. Large scale randomized control trials are needed to provide evidence-based results which can be translated into guideline clinical practice for the use of Sulfonylureas in patients with chronic liver disease or those with other risk factors for HCC.

Insulin and hepatocellular carcinoma

Insulin is known for its capability to stimulate the proliferation of many cell types and in particular malignant cells. Yet, there is no evidence to indicate that insulin has mutagenic properties and can induce malignancy; it is rather considered to have a mitogenic effect on cells. There is no evidence that insulin regulates or affects the expression of established oncogenes [40]. This means insulin may promote the growth of transformed cells and aid in overcoming immune surveillance mechanisms, so affect the lifetime incidence of cancer [41].

Hyperinsulinemia whether endogenous or exogenous influences the neoplastic process by direct and indirect mechanisms [42]. Insulin binds to receptors on the surface of target cells. There are two types of insulin receptor (IR) isoforms, A and B. *in vitro* studies suggest that IR-B is the specific receptor for Insulin and is responsible for the metabolic effect of insulin whereas IR-A is which is expressed mainly in fetal tissue has a strong effect on mitogenesis and bind with high affinity to IGF [43]. Cancer cells require insulin binding for optimal cell growth. Insulin receptors are overexpressed in malignant cells particularly the isoform A which is predominant especially breast, pancreatic and lung cancers and when stimulated by insulin was found to promote cancer cell proliferation and metastasis [44].

After insulin binds to its receptors (IR, and to a lesser extent IGF) it induces phosphorylation of insulin receptor substrate 1 and 2 that activate the phosphatidyl inositol 3 kinase (PI3K) which then activates the AKT/mTOR pathway. PI3K further stimulates the MAPK/ERK pathway; both these signaling pathways promote proliferation as well as glucose utilization by cells [45].

Hyperinsulinemia can further influence carcinogenesis indirectly by affecting the level of IGF1. Insulin decreases the production of IGF! Binding protein 1 and 2 by the liver resulting in increased levels of free IGF1. IGF1 has more mitogenic and antiapoptotic activities than insulin and is a growth stimulator in tissues that express insulin and IGF receptors whether premalignant or malignant [46].

In addition, insulin was found to be associated with lipid peroxidation, increased oxidative stress and the generation of reactive oxidative species which could affect DNA mutation. It has also been suggested that lipid peroxidation may upregulate the peroxidation of proinflammatory cytokines which are involved in P53 tumor suppressor gene mutation [35].

In diabetes, both type 1 and 2, chronic hyperinsulinemia is present whether due to administration of large doses of exogenous insulin used to achieve and maintain proper glycemic control or due to insulin resistance and increased endogenous insulin. In either case, exposure to circulating insulin levels is very high for many years [42].

To assess the significance of these findings on clinical outcomes, epidemiological surveys were performed and some actually verified a significant relationship between insulin therapy and increased risk of malignancy. In a meta-analysis by Karlstad., *et al*. insulin therapy was associated with an increased risk of cancer in the pancreas, liver, kidney, stomach and the lungs [47]. Even though Randomized controlled trials provide the best evidence on which to build clinical guidelines, very few RCT are present that shed light on the incidence of cancer or cancer related mortality with the use of insulin. Of these, is the time honored UKPDS trial which reports similar incidence of cancer related mortality in insulin versus conventionally treated patients [48]. More recently. a study of Insulin Glargine as compared to oral therapy reports similar results in cancer incidence and cancer related mortality between the two studied groups [49].

There are several formulations of insulin available; studies demonstrated that modification in the insulin structure may increase the mitogenic properties of insulin. Insulin glargine was found to stimulate the IGF1 receptor with more potency than insulin which could impact a greater risk of malignancy than human insulin [50]. In an analysis comparing insulin glargine to human insulin, they found an increased risk of malignancy; no similar risk was found with insulin detemir [51]. On the other hand, a multicenter observational study by But A., *et al*. found no significant difference between commonly used exogenous insulins with respect to cancer risk [52].

Several animal studies have addressed the role of insulin in hepatocarcinogenesis. Sukarai., *et al*. reports that insulin receptor substrates 1 (IRS1), responsible for transducing insulin signal in the liver, is upregulated in human HCC and a significant relationship has been found between the IRS1 expression level and the size of the tumor as well as patient survival [53]. In another study by

Baba., *et al*. they found insulin therapy to promote the progression of liver cancer despite the improvement of hypoglycemia and suggested that hyperinsulinemia rather than hyperglycemia through activation of signaling pathways accelerate tumor progression [54].

Numerous studies addressed the relationship between the risk of hepatocellular carcinoma and insulin therapy. Most of them consistently reported that insulin therapy was associated with the increased risk of HCC in comparison to patients with diabetes and chronic liver disease or diabetes alone [35,32].

Conclusion

Type 2 diabetes mellitus has been associated with hepatocellular carcinoma (HCC). However, the relationship between type 2 diabetes mellitus and the underlying liver cirrhosis, and the effects of antidiabetic therapy on HCC risk have not yet been fully evaluated. Studies are needed to elucidate the possible effects of antidiabetic drug type/dosage and duration of DM on the risk of HCC and to better understand the relationship between DM and HCC with different etiologies.

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