

Review Article

Emerging Roles of Antidiabetic Drugs beyond Glucose Control: Beneficial Effects on Hepatitis and Hepatocellular Carcinoma

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Abstract

Insulin resistance and hyperglycemia in type 2 diabetes mellitus (T2DM) are both correlated with hepatitis and hepatocyte carcinoma. Thiazolidinediones and biguanides, belong to insulin sensitizers, are front-line antidiabetic drugs. DPP-4 inhibitors, a member of incretin-based products, are novel target in the treatment of T2DM. These drugs are widely used to treat T2DM by improving insulin actions and regulating glucose homeostasis. In addition to their antidiabetic roles, increased incidences have been recently reported to treat hepatitis and hepatocellular carcinoma. These underappreciated effects indicate that antidiabetic agents could be re-purposed therapeutic strategies for treatments of liver diseases in patients with diabetes.

ABBREVIATIONS

T2DM: Type 2 Diabetes Mellitus; TZD: Thiazolidinediones; Ppar γ : Peroxisome Proliferator-Activated Receptor Gamma; AMPK: Activates Adenosine Monophosphate Kinase; SVR: Sustained Virological Response; MTOR: Mammalian Target of Rapamycin; HCC: Hepatocellular Carcinoma; HCV: Hepatitis C Virus; HBV: Hepatitis B Virus; Camp: Cyclin Adenosine Monophosphate; GLP-1: Glucagon-Like Peptide 1; DPP-4: Dipeptidyl Peptidase-4

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease, accounting for almost 90% of diabetic cases worldwide with rapidly increasing prevalence. By 2025, the population of T2DM patients is expected to reach 270 million, doubling the number of diabetic cases in 1995 [1,2]. The disease is characterized by high blood glucose levels, which arise from impaired insulin secretion and decreased insulin action. The pathogenesis of T2DM is complex, involving genetic and, more importantly, environmental factors [3]. T2DM also leads to a series of complications, including diseases of the eye, the nervous system, the kidney, the cardiovascular system, and the liver.

As the major site of glucose regulation, the liver plays an essential role in metabolism. Shortly after food ingestion, blood glucose levels rise. Elevated blood glucose levels give rise to increased circulating insulin levels, which in turn inhibit

endogenous glucose production and stabilize postprandial glucose levels. Several hours after food ingestion, blood glucose levels decrease. When blood glucose levels are low, liver glycogen is broken down, and endogenous glucose is released into the blood, maintaining normal glucose concentrations. In this way, a healthy liver is able to maintain glucose homeostasis [4] impaired liver function is required for the pathogenesis of T2DM. As a result, liver diseases such as hepatitis often co-occur with T2DM. Hepatitis results from impaired liver function and lead to increasing liver damage and ultimately death. T2DM patients are in the higher risk of hepatitis virus infection. Chronic hepatitis virus infection together with T2DM, contribute to a gradual development of hepatocellular carcinoma (HCC).

The increased prevalence of T2DM encouraged the development of new therapeutic strategies. The purpose of these strategies is mainly focusing on safely reducing and maintaining normal glucose homeostasis in T2DM and preventing complications. Several oral antidiabetic agents, like insulin sensitizers and incretin-based products, are used worldwide. Insulin sensitizers lower blood glucose by increasing insulin sensitivity in peripheral tissues, such as the liver and the muscle. Incretin-based drugs maintain glucose homeostasis through incretin-induced insulin secretion, decreasing excessive blood glucose by promoting peripheral insulin actions while improving pancreatic islet- β cell functions at the same time. The decreased insulin secretion and increased blood glucose in T2DM patients contribute to the pathogenesis of hepatitis and

HCC. Hepatitis infection and HCC occurrence result in high risks of T2DM development. The interrelationship between T2DM and hepatitis/HCC brought out different treatment strategies for patients with high risks of both T2DM and liver diseases. In fact, beyond antidiabetic roles, insulin sensitizers and incretin-based drugs are suggested to have beneficial effects on treatment of hepatitis and hepatocellular carcinoma.

Insulin sensitizer: thiazolidinediones

Thiazolidinediones (TZDs) is a group of oral insulin sensitizers that improves glycemic control by increasing insulin sensitivity. Adipose tissue is an essential organ involved in insulin sensitizing. Decreased insulin sensitivity mainly results from imbalanced adipogenesis-induced circulating free fatty acids, inhibited adipocytes development, and decreased adipocyte cytokine secretion. Peroxisome proliferator-activated receptor gamma (PPAR γ) activation stimulates adipocyte development, reduces circulating free fatty acids, and increases cytokine secretion. TZDs are synthetic ligands for PPAR γ , thereby boosting insulin sensitivity [5]. In addition to their effects on insulin-sensitivity, TZDs were reported to have beneficial effects on liver cancer.

It was hypothesized that TZDs can activate tumor suppression pathways [6]. In a hospital based case-control study, the HCC incidence was examined among long-term diabetic patients with different antidiabetic drugs treatment. Diabetic patients receiving TZDs showed around 70% less risk of HCC development, compared with insulin and sulfonylurea's [7]. The similar effect of TZDs was also observed in a population based cohort study, in which HCC risk was determined among diabetic patients with cirrhosis and hepatitis. TZDs treatment showed 44% reduction of HCC risk [7,8]. In several meta-analysis studies comprising around 900,000 patients with T2DM, TZDs treatment is associated with decreased HCC incidences [9]. In HCV patients, TZDs inhibit HCC recurrence by improving insulin sensitivity and increasing the adipocytokine level [10]. The association between TZDs and hepatocellular carcinogenesis suggests that TZD could perform as a therapeutic target to against HCC occurrence and progression.

Insulin sensitizer: biguanides

The liver plays an essential role in the maintenance of glucose homeostasis through the tight control of hepatic glucose production. Biguanides is another group of oral insulin sensitizers that decrease insulin resistance by inhibiting liver glucose production. The tight control of normal liver glucose production is necessary for the maintenance of glucose homeostasis. Metformin, a commonly used biguanide drug for T2DM treatment, exerts its hypoglycemic effect by inhibiting gluconeogenesis and glycogenolysis in liver cells, the two main pathways that produce glucose [11]. Metformin also activates adenosine monophosphate kinase (AMPK), which subsequently constrains liver glucose release and boosts glucose uptake in peripheral tissues [12].

Although no clinical studies about metformin treatment on patients with hepatitis B virus (HBV) were performed, one *in vitro* study using human hepatocellular carcinoma line reported that metformin synergistically cooperated with anti-HBV drugs,

such as lamivudine and interferon α -2b. In these examples, metformin suppressed hepatitis B surface antigen expression and HBV replication [13]. In addition, a small, randomized control trial showed combined treatment with metformin together with interferon-based therapy in patients with both hepatitis C virus (HCV) and diabetes attained better sustained virological response (SVR) success, a standard for a curative treatment [14], suggesting metformin helps improving HCV treatment response in diabetic patients, therefore ameliorates HCV-triggered liver damage.

The increased risk of hepatocellular carcinoma has been noticed in patients with combined diabetes and chronic HCV infection [15]. Metformin treatment showed delayed HCC development in diabetic patients with HCC [16]. Additions to ameliorating endogenous hyperinsulinemia, metformin lower the risk of hepatocyte carcinogenesis by insulin-independently activation of AMPK, which subsequently inhibits the mammalian target of rapamycin (mTOR), one of HCC therapeutic targets [17,18].

As a front-line antidiabetic agent, metformin is a well-tolerated drug with a low-cost price. Transient gastrointestinal distress and rare cases of severe lactic acidosis might be the only side effect of metformin [19]. Effects of metformin on the progression of hepatitis and the onset of hepatocellular carcinogenesis appealed interests of metformin being an anti-hepatitis and anti-cancer agent. More studies about the translation from preclinical findings to clinical trials would be helpful to plan the way forward.

Incretin-based agent: DPP-4 inhibitors

Glucagon-like peptide 1 (GLP-1) is an incretin hormone secreted in a food ingestion dependent manner. Cyclin adenosine monophosphate (cAMP) and calcium signaling are two central intracellular pathways that regulate islet insulin secretion. GLP-1 triggers postprandial insulin secretion through the rapid increase of pancreatic islet β cell intracellular cAMP and calcium level [20]. GLP-1 also exerts trophic effects on pancreatic islets via improving the β cell s proliferation and differentiation, while decreasing apoptosis [21]. Dipeptidyl peptidase-4 (DPP-4) is a ubiquitously expressed serine peptidase that metabolizes and inactivates GLP-1 by cleaving oligopeptides from the N-terminal of GLP-1. Fasting DPP-4 activity increases in type 2 diabetes [22], which leads to retarded GLP-1 functions. Impaired GLP-1 actions decrease postprandial insulin secretion, contributes to hyperinsulinemia, insulin resistance, obesity, and eventually T2DM [23]. The inhibition of DPP-4 activity is a therapeutic strategy for T2DM.

In addition to its conventional role in glycemic control, DPP-4 is also suggested to be a regulator in liver diseases. In HCV infected patients, increased DPP-4 level was reported in serum, liver, and ileum [24]. HCV infected CD8+ T-cells locate in the liver portal and periportal areas, which may be responsible for the increased DPP-4 activity independent of glucose metabolism [25-27], while the abolishment of HCV by interferon-based treatment reduces the serum DPP-4 [28]. These findings suggested a direct role of DPP-4 in hepatitis infection.

Increased DPP-4 level was also observed in liver specimens and serum from animal models and patients with HCC [29,30].

DPP-4 inhibitor treatment was reported to spontaneously regressed HCC condition in a patient with chronic HCV infection [31], potentially due to the improvement of HCV infected immune system [24].

Growing studies are showing that DPP-4 sub serves many roles addition to glycemic control. The potentials of combination with other antidiabetic drugs including metformin and TZDs indicate the more diverse therapeutic strategies that DPP-4 inhibitors may have. More studies based on long-term DPP-4 inhibitors administration on hepatitis progression and hepatocyte carcinogenesis are required.

SUMMARY

Antidiabetic agents like TZD, bioguanides, and DPP-4 inhibitors have emerged multifunctional effects on hepatitis and hepatocellular carcinoma addition to their roles in glycemic control. More basic and clinical studies are needed to focus on the safety and effectiveness of these oral antidiabetic medications on liver diseases.

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