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Progress in the Study of the Hepatoprotective Effect of SGLT2i on NAFLD Patients with T2DM

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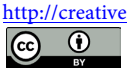

Abstract

In recent years, the progress of NAFLD has become an important health problem, and the prevention or delay of progress in NAFLD is a major key point. Whether or not to combine T2MD, people are interested in the mechanisms and efficacy of SGLT2i for NAFLD. In this review, we summarized the current clinical research on SGLT2i for the combination of T2MD's NAFLD patients, and the latest evidence of external or animal experiments. These evidences will help us to more accurately understand the protective effects of SGLT2i in NAFLD. Lifestyle changes are still essential to prevent and treat NAFLD, and for all kinds of drugs that treat NAFLD in clinical trials, SGLT2i may be one of the promising treatments.

Keywords

Sodium-Glucose Cotransporter-2 Inhibitors, Non-Alcoholic Fatty Liver Disease, Diabetes Mellitus

1. Background

Non-alcoholic fatty liver disease (NAFLD) is a common chronic liver condition characterized by extensive liver damage, ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis [1]. It is a liver disease that causes hepatocyte steatosis after excluding other risk factors such as viral infection, heavy drinking, and drug damage. The pathogenesis of NAFLD is still unclear, and most experts recognize the "multiple hit theory". It is the combined result of chronic inflammation, oxidative stress, intestinal microecology and genetic factors under the influence of high-fat diet, obesity and insulin resistance

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[2]. NAFLD patients are often accompanied by obesity and different degrees of metabolic disorders, blood lipid and body mass index are often higher, and obesity is one of the main causes of insulin resistance. The accumulation of excess free fatty acids in obese people and synthesis of triacylglycerol in the liver will form a chronic inflammation, leading to hypoxia of liver fat cells. Meanwhile, this inflammation will activate macrophages, and then produce a variety of inflammatory factors to act on insulin target cells, resulting in phosphorylation of insulin receptor substrates mediated by signaling pathways, thus inhibiting insulin signal transduction. Causing insulin resistance [3]. Recent data indicates that approximately one-third of adults [4] are affected by NAFLD, making it one of the most prevalent non-communicable diseases. Its development and progression are closely associated with metabolic dysregulation and insulin resistance.

Type 2 diabetes (T2DM) is a recognized risk factor for chronic liver diseases, and patients with diabetes may progress to complications such as cirrhosis. NAFLD represents the hepatic manifestation of metabolic syndrome and is a common complication of T2DM [5]. A study evaluating the prevalence of elevated liver enzymes and diabetes-related complications in T2D patients found that elevated liver enzymes are common in T2D patients and significantly correlated with a higher prevalence of clinical complications [6]. Currently, effective pharmacological treatments for NAFLD are lacking. Sodium-glucose co-transporter 2 (SGLT-2) inhibitors are a recent class of anti-diabetic drugs [7]. They prevent the reabsorption of glucose in the proximal renal tubules, thereby lowering blood glucose levels [8]. Diabetes drugs such as empagliflozin and some glucagon-like peptide-1 receptor agonists have been shown to improve liver histology and metabolic health. The effects of SGLT-2 inhibitors and insulin on hepatic steatosis remain unclear [9]. A study investigating the impact of SGLT2 inhibitors on non-diabetic patients with NAFLD suggested that 12 weeks of SGLT2i treatment did not improve hepatic steatosis in patients without T2D [10]. However, a significant body of research indicates that SGLT2 inhibitors have hepatoprotective effects in patients with T2DM and NAFLD.

SGLT-2 inhibits the renal reabsorption of glucose, increases glucose excretion in urine, lowers blood glucose levels, and improves insulin resistance [11]. SGLT-2 inhibitors also exert various metabolic effects, such as weight reduction, blood pressure reduction, and improvement in lipid profiles [12]. The main drugs of SGLT-2i are canagliflozin, empagliflozin, dapagliflozin, Ipragliflozin and so on.

2. Clinical Studies on the Hepatoprotective Effects of SGLT-2 Inhibitors (Table 1)

2.1. Effects of SGLT-2 Inhibitors on Hepatic Fat Accumulation

A clinical study involving 156 patients showed that treatment with SGLT-2 inhibitors not only improved blood glucose control in patients with non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes (T2D), but also significantly

Table 1. The results of some clinical trials and studies on SGLT2-I phase.

The experiment involves drugs.	The observed indicators.	research results
Canagliflozin	IHTG, HbA1c, weight	HbA1c↓, weight↓, IHTG↓ [15]
Dapagliflozin	BM, IHTG, Plasma amino acid concentration	BM↓, IHTG↓, There was little difference in the change of AAs among the groups. [16]
Dapagliflozin, Canagliflozin	Liver fat content, Subcutaneous and visceral fat mass, Body fat/weight ratio, Skeletal muscle mass/weight ratio, liver enzyme	Liver fat content↓, Subcutaneous and visceral fat mass↓, Body fat/weight ratio↓, Skeletal muscle mass/weight ratio↑, liver enzyme (AST, ALT, γ-GGT) ↓ [14]
Canagliflozin	Histological evaluation, insulin resistance, serum ferritin	After 5 years, histology showed improvements in 50%, no change in 17%, and deterioration in 33%. Scores for steatosis, lobular inflammation, ballooning, and fibrosis stages decreased by 67%, 33%, 0%, and 33% respectively. insulin resistance↓, serum ferritin↓ [26]
Canagliflozin	Incidence of hepatocyte steatosis, BMI, waistline, fasting blood-glucose, γ-GGT, ferroprotein, Type IV Collagen 7S, Histopathological findings	Incidence of hepatocyte steatosis↓, BMI↓, waistline↓, fasting blood-glucose↓, γ-GGT↓, ferroprotein↓, Type IV Collagen 7S↓, The histopathology of the tissues improved, and there was enhancement in the results of transient elastography (liver stiffness measurement). [19]
Empagliflozin	body mass index, Liver biopsy was repeated at the end of treatment	body mass index↓, waistline↓, systolic pressure↓, diastolic pressure↓, fasting blood-glucose↓, total cholesterol↓, γ-GGT↓, Volume liver fat fraction↓ Steatosis, ballooning and fibrosis were improved [20]
Ipragliflozin	HbA1c, BMI	HbA1c↓, BMI↓ [21]

reduced patients' visceral fat area (VFA) and body weight. [13]. SGLT-2 inhibitors can reduce liver fat content, and reduce fat mass mainly by reducing visceral fat to achieve body weight loss. [14] A study involving canagliflozin showed that it improved liver insulin sensitivity, regulated metabolism, and reduced hepatic accumulation of triglycerides (IHTG), resulting in greater weight loss in the canagliflozin group compared to the placebo group. [15] dapagliflozin also reduces body weight primarily by reducing fat mass [16]. Another study involving 49 patients who completed the trial showed significant reductions in body weight and visceral fat area (VFA) in the empagliflozin group compared to the control group. And serum HMW adiponectin was significantly increased in the empagliflozin group, and the changes of plasma PAI-1 were positively correlated with the changes of body weight and leptin [17]. In addition, SGLT-2 inhibitors play a beneficial role in lipid regulation, which can increase the content of high-density lipoprotein and decrease the content of low-density lipoprotein [18]. These clinical studies have shown that SGLT-2 inhibitors can reduce the accumulation of body fat, and weight loss has a positive effect on the delay and regression of liver steatosis and fibrosis in patients with NAFLD. Therefore, SGLT-2 inhibitors are a suitable choice for patients with type 2 diabetes complicated with NAFLD.

2.2. Effects of SGLT-2 Inhibitors on Liver Inflammation and Fibrosis

Twenty-four weeks of SGLT-2 inhibitor treatment showed improvements in both the fibrosis stage marker type IV collagen 7S and liver hardness measure-

ments [19]. Treatment with empagliflozin 25 mg for 24 weeks compared with placebo increased the risk of steatosis (67% vs. 26%, p = 0.025), ballooning (78% vs. 34%, p = 0.024) and fibrosis (44% vs. 6%, respectively). p = 0.008) has significantly greater improvement [20]. A multicenter, randomized, controlled trial comparing patients with type 2 diabetes with NAFLD. Results showed that long-term Ipragliflozin therapy (50 mg/day for 72 weeks) could improve liver fibrosis in NAFLD patients [21]. A study has shown that SGLT2-Is has a good effect on improving FIB-4 index in NAFLD patients with T2DM, especially in patients with moderate and high-risk advanced fibrosis, and this anti-fibrosis effect is long-term sustained [22]. After 6 months of SGLT-2i treatment, results reported reductions in FLI and APRI as well as FibroScan outcomes, and serum HNE- and mda protein adductions were significantly reduced in SGLT2-I patients compared to other patients, and were associated with liver steatosis and fibrosis scores. SGLT2-I treatment in patients with T2D and NAFLD was associated with improvements in markers of liver steatosis and fibrosis, as well as circulatory pro-inflammatory and REDOX status, rather than just optimizing blood glucose control [23].

2.3. Effects of SGLT-2 Inhibitors on Liver Enzymology

At 12 weeks, the serum GGT level in the empagliflozin group was significantly decreased, while the control group was unchanged [17]. At 24 weeks, SGLT-2I treatment significantly reduced BMI, waist circumference, fasting blood glucose, and markers of liver dysfunction (γ-glutamyl transpeptidase, ferritin) [19]. A study of 765 patients showed that alanine aminotransferase (ALT) levels decreased more in the SGLT2i group at 3, 6, and 12 months. In multivariate logistic regression models, the addition of SGLT-2 was an independent predictor of ALT improvement (odds ratio 1.91; P = 0.016). Compared with other oral hypoglycemic agents, SGLT-2-is is more effective in weight loss and ALT improvement in T2DM patients with NAFLD [24]. A meta-analysis of 6 trials including 309 patients showed that SGLT-2 inhibitors significantly reduced alanine aminotransferase and liver fat, with associated weight loss, and may have a positive effect on fatty liver in type 2 diabetes patients [25].

3. Mechanistic Studies on the Hepatoprotective Effects of SGLT-2 Inhibitors

In some animal studies, it has been demonstrated that SGLT-2 inhibitors can promote fat breakdown, ketogenesis, mitochondrial biogenesis, and autophagy, while simultaneously attenuating the renin-angiotensin-aldosterone system, lipid synthesis, endoplasmic reticulum stress, oxidative stress, cell apoptosis, and fibrosis [8].

SGLT2 inhibitors regulate glucose metabolism and insulin related adipokine secretion. A novel SGLT-2 inhibitor, NGI001, increased phosphorylation of its main downstream target, acetyl-CoA carboxylase, in human hepatocyte HuS-E/2

cells by increasing AMPK phosphorylation, a cascade that ultimately led to down-regulation of downstream fatty acid synthesis-related molecules and up-regulation of downstream β-oxygenation-related molecules [27]. SGLT-2 inhibitors can improve intracellular fat deposition, inhibit liver lipid accumulation, and regulate lipid metabolism. NGI001 reduced gene and protein expression of SGLT-1 and SGLT-2 and glucose uptake in oleic acid-treated HuS-E/2 cells. In addition, NGI001 supplementation inhibited liver lipid accumulation and inflammation. Ipragliflozin improves NASH by reducing insulin resistance and lipotoxicity in NASH model mice, and has therapeutic effects on T2DM associated with NASH [28]. Empagliflozin reduced neutral triacylglycerol and lipotoxic diacylglycerol in the liver of non-obese prediabetic rats, along with significant changes in the expression of lipogenic enzymes (Scd-1, Fas) and transcription factors (Srebp1, Pparγ). Reduced level of fetal hormone a circulation improved lipid metabolism and insulin resistance in liver and peripheral tissues. Reduce the symptoms of NAFLD in the early stages of the disease and before the onset of diabetes [29]. The increase of cytochrome P450 protein genes Cyp2e1 and Cyp4a, as well as Nrf2, contributed to the improvement of liver lipid metabolism after Empagliflozin administration. One study showed that phloridzin treatment restored: insulinemia; Liver expression of phosphoenolpyruvate carboxykinase (PEPCK), glucose-6-phosphatase (G6Pase) and glucose transporter 2 (Slc2a2 gene); The binding activity of hepatic nuclear factor 1A/4A/3b in Slc2a2; Endogenous glucose production; Liver weight, plasma transaminase concentrations, and markers of liver inflammation, and induced histological signals in nonalcoholic steatohepatitis (NASH). Phloridzin treatment partially restored plasma aminotransferase concentrations, and some markers of liver inflammation remained unchanged [30]. The development of NAFLD was mitigated by the reduction of genes associated with liver adipogenesis. After treatment with Empagliflozin, the mice experienced a 4% increase in energy expenditure, a 5% decrease in body weight, and improvements in glucose tolerance, insulin sensitivity, and insulin resistance. According to protein expression, the expression of Pparα was greater in the HF-EMPA group, while the expression of lipogenic genes Fas, Srebp1c, and Pparγ was reduced [31].

SGLT-2 inhibitors significantly enhance autophagy of liver macrophages through AMPK/mTOR signaling pathway and alleviate liver injury. Empagliflozin significantly enhanced autophagy of liver macrophages through AMPK/mTOR signaling pathway to inhibit the expression level of IL-17/IL-23 axis related molecules. Inhibition of IL-17/IL-23 axis activity can alleviate liver injury in T2DM mice with NAFLD [32]. Empagliflozin promotes autophagy, reduces ER stress and inhibits hepatocyte apoptosis to slow the progression of NAFLD in mice. Autophagy was activated by increasing AMPK phosphorylation, decreasing mTOR and increasing LC3B expression. Empagliflozin increased the ratio of Bcl2/Bax, inhibited CASPASE-8 cleavage, and reduced hepatocyte apoptosis [31]. SGLT-2 inhibitors play a liver protective role by reducing endoplasmic reticulum stress and delaying liver disease progression. After 5 weeks of treatment,

the expression of endoplasmic reticulum stress molecules Grp78, Ire1*α*, Xbp1, Elf2*α*, Atf4, Atf6, Chop, P62 (Sqstm1) and Grp94 were significantly decreased [31]. Empagliflozin decreased the expression of ER stress-related genes, and HF-EMPA showed a decrease in ER stress-related genes Chop, Atf4 and Gadd45 [33]. A model study using genetically obese melanocortin 4 receptor deficient mice has shown that glucose cotransporter 2 inhibitors prevent the development of the NAS-like liver phenotype and the progression of liver tumors [34].

4. Discussion

A meta-study showed existing evidence related to sodium-glucose cotransporter-2 inhibitors: SGLT2i is a hypoglycemic drug that improves NAFLD in patients with type 2 diabetes [35]. Many randomized controlled trials have studied the effects of various anti-hyperglycemic drugs on NAFLD patients with and without type 2 diabetes mellitus (T2DM). Both hyperglycemic T2DM and insulin resistance are closely related to liver disease and progression. Like most other anti-hyperglycemic drugs, SGLT-2i can also improve the level of serum liver enzymes [36]. A study comparing the possible effects of three oral hypoglycemic drugs on NAFLD in patients with type 2 diabetes by looking at changes in liver and spleen ratio on abdominal computed tomography showed that dapagliflozin, pioglitazone, and glimepiride had similar effects on hyperglycemia. Only dapagliflozin and pioglitazone significantly increased the hepato-spleen ratio, and NAFLD was improved in type 2 diabetes patients with reduced visceral area and weight loss. Moreover, dapagliflozin showed the same beneficial effect as pioglitazone in exerting protective effect on NAFLD in type 2 diabetes patients [37]. A meta-analysis investigated the effect of canagliflozin on fatty liver index in T2DM patients. It has been shown that canagliflozin reduces serum alanine aminotransferase concentration, aspartate aminotransferase, *γ*-GGT and triglyceride, and it is believed that canagliflozin has a protective effect on fatty liver in T2DM patients [38]. Another meta-analysis also showed that SGLT-2 inhibitor treatment was associated with reduced hepatic steatosis, and that SGLT-2 inhibitor treatment induced decreased serum alanine and aspartate aminotransferase and increased plasma total bilirubin, suggesting that SGLT-2 inhibitor treatment improved liver structure and function in T2D patients. It may be a promising pharmacological approach for the treatment of NAFLD [39]. A meta-analysis showed that the use of SGLT2-i improved non-invasive markers of steatosis and even fibrosis in T2DM patients. It is also believed that SGLT2-i drugs may be the first choice for patients diagnosed with T2DM and NAFLD/NASH [40].

Although SGLT-2 inhibitors play a vital role in the treatment of NAFLD, there are still some cases where caution is warranted. A study investigating the effects of SGLT-2 inhibition on cirrhotic rats and hepatocirrhosis showed that inhibition of SGLT-2 by empagliflozin did not improve portal hypertension and liver inflammation in cirrhotic rats. Instead, it aggravated hepatic encephalopathy, possibly by an increase in portal-systemic shunt associated with up-regulation of

VEGF. Therefore, in view of the development of hepatic encephalopathy, patients with cirrhosis should be cautious about using empagliflozin. [41] Animal trials have shown that SGLT-2i has the risk of aggravating hepatic encephalopathy, and SGLT-2i is not necessarily a safe and effective hypoglycemic drug for T2MD patients with advanced NAFLD progression to cirrhosis complicated with hepatic encephalopathy. In a meta-analysis, it was noted that SGLT-2 inhibitors reduced hospitalizations for heart failure more than GLP-1 receptor agonists. In patients with type 2 diabetes, SGLT-2 inhibitors and GLP-1 receptor agonists reduced cardiovascular and renal outcomes, but there was high quality evidence that SGLT-2 inhibitors caused genital infections [42]. Therefore, the use of SGLT-2i should be avoided in patients with evidence of related genitourinary system infection, and attention should be paid to the infection status and health care of patients taking the drug. A meta-analysis involving 59,692 patients showed that SGLT-2 inhibitors significantly increased the risk of diabetic ketoacidosis, genital infection, and blood volume deficiency. They showed an increased risk of fractures, amputations, and urinary tract infections [43]. The effect of SGLT-2is on fracture is controversial, and bone mineral density (BMD) and fracture risk assessment should be considered in patients at high risk of fracture [44]. When selecting SGLT-2 inhibitors, we should not only see its beneficial effects, but also consider its contraindications. Comprehensive evaluation should be carried out after understanding the patient's condition, especially when the patient has hepatic encephalopathy, urogenital tract infection, diabetic ketoacidosis, fracture and other conditions, the use of SGLT-2i may aggravate the patient's condition. Causing more harm than good.

5. Conclusion

There is now more clinical evidence showing that SGLT-2 inhibitors play an effective role in liver protection in patients with T2MD. The guidelines of the Japanese Society of Hepatology suggest that SGLT2-Is is one of the effective methods for the treatment of NAFLD complicated T2DM [45]. SGLT2-Is may be a first choices hypoglycemic agent for NAFLD patients with T2MD. It can play a protective role in liver by reducing liver fat accumulation, inhibiting liver inflammation, slowing the progression of liver fibrosis, reducing liver enzymes, and regulating glucose and lipid metabolism. It is safe and effective for most NAFLD patients with T2MD. Caution should be exercised in NAFLD patients with hepatic encephalopathy, urogenital tract infection, diabetic ketoacidosis, or fracture. We look forward to more evidence from animal experiments and clinical studies in the future to help us more comprehensively understand the internal mechanism of SGLT2i's liver protective effect, and more evidence to help evaluate the pros and cons of medication in patients with comorbidities. In order to guide the clinical effective selection of the most favorable treatment plan for the individual situation of patients. At present, SGLT2-Is provides an effective treatment option for NAFLD patients with type 2 diabetes.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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