

Protective mechanism and clinical application of SGLT2 inhibitors in patients with type 2 diabetes mellitus complicated with abnormal liver function

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ABSTRACT

Type 2 diabetes (T2DM) patients with abnormal liver function will further aggravate the complexity of the disease and affect the quality of life of patients. Sodium-glucose cotransporter protein 2 (SGLT2) inhibitors are novel hypoglycemic agents that may produce hepatoprotective effects in patients with T2DM combined with hepatic function abnormalities by improving hyperglycemic toxicity, regulating lipid metabolism, decreasing visceral adiposity, anti-inflammatory, antioxidant and other possible mechanisms. However, the exact mechanism has not been clarified and further studies are still needed. In this article, we reviewed the possible mechanisms of hepatoprotective effects of SGLT2i on patients with T2DM combined with abnormal liver function and the progress of clinical application, in order to providing reference for the rational application of SGLT2i.

KEYWORDS

SGLT2 inhibitors; Type 2 diabetes; Abnormal liver function; Protective mechanism; Clinical application

1. INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) and its complications have long been a major concern in the field of global public health, with the prevalence rising year by year, placing a heavy burden on patients and society. The liver plays a crucial role in glucose metabolism, and T2DM patients often have liver dysfunction, which further exacerbates the complexity of the condition and affects the patient's quality of life. Therefore, it is of great clinical value to study the treatment strategies of T2DM complicated with abnormal liver function.

In recent years, Sodium-glucose Cotransporter 2 inhibitor (SGLT2i), as a new type of hypoglycemic drug, has shown multiple effects in lipid regulation, weight loss, blood pressure reduction, heart failure hospitalization rate and delay the progression of diabetic nephropathy. In addition, studies have found that SGLT2i can also play a positive role in improving liver fat content [1], alleviating liver function damage, improving liver steatosis [2], improving liver structure [3] and improving the degree of liver fibrosis [4]. This article aims to review the mechanism of action and clinical application of SGLT2i in T2DM complicated with abnormal liver function, in order to provide reference for subsequent studies.

2. POTENTIAL PROTECTIVE MECHANISM OF SGLT2I AGAINST T2DM COMPLICATED WITH ABNORMAL LIVER FUNCTION

Previous studies have found that the use of SGLT2i in patients with T2DM complicated with abnormal liver function can not only effectively reduce blood sugar, but also help protect the liver. Current studies have shown that SGLT2i can produce liver protection in patients with T2DM complicated with abnormal liver function by improving hyperglycemic toxicity, regulating lipid metabolism, reducing visceral fat, anti-inflammatory, antioxidant and other possible potential mechanisms. However, the specific mechanism by which SGLT2i protects the liver in patients with T2DM complicated with abnormal liver function remains to be further studied. These potential mechanisms of action are briefly described below:

2.1. Improve the mechanism of hyperglycemic toxicity

There is a close relationship between hyperglycemia and abnormal liver function. Long-term hyperglycemic environment can cause damage to the liver, which can lead to abnormal liver function. As a new class of hypoglycemic drugs, SGLT2i mainly works by inhibiting SGLT2 in the kidney, reducing glucose reabsorption and increasing its excretion, thus effectively reducing blood glucose levels. In addition to the direct hypoglycemic effect, SGLT2i is also believed to improve hyperglycemic toxicity, which may be due to the enhancement of insulin sensitivity and the improvement of glucose metabolism, thereby reducing the glucose load and oxidative stress level of the liver, and helping to mitigate the negative effects of hyperglycemic toxicity on the liver. By protecting islet beta cell function and restoring the ability of normal tissues and organs to respond to insulin, SGLT2i can improve liver function abnormalities while treating diabetes.

Multiple studies have supported the role of SGLT2i in ameliorating hyperglycemic toxicity. For example, studies by Scherthaner et al. [5] showed that caraglipzin was more effective in reducing glycosylated hemoglobin (HbA1c) levels and body weight in the treatment of T2DM patients compared with sitagliptin. This improvement was significantly associated with increased liver function, suggesting that SGLT2i may reduce liver damage by improving blood sugar control. Another study conducted by Lee et al. [6] also found that in T2DM patients, dagaglizin and enaglizin not only improved metabolic parameters, It also significantly reduced serum alanine aminotransferase (ALT) levels, further confirming the potential of SGLT2i in improving liver function in patients with abnormal liver function. In addition, Kinoshita et al. [7] also showed that there was a close relationship between liver injury recovery and improved blood glucose control in T2DM patients after receiving SGLT2i treatment. Together, these studies support the role of SGLT2i in improving hyperglycemic toxicity and protecting liver function.

In summary, SGLT2i has a potential protective effect on liver function in T2DM patients by lowering blood glucose and improving hyperglycemic toxicity. However, the specific mechanism of action still needs further research to clarify. Future studies could focus on the effects of SGLT2i on liver metabolism, oxidative stress, and inflammatory responses to more fully understand its role in liver protection.

2.2. Mechanism of action to regulate lipid metabolism and reduce visceral fat

Obesity poses a serious threat to the physical health of T2DM patients, and the prevalence of abnormal liver function is higher in overweight and obese patients. In addition to its significant hypoglycemic effect, SGLT2i also has the effect of regulating lipid metabolism and reducing visceral fat, which may help improve insulin resistance and metabolic disorders.

Several studies have shown that SGLT2i can reduce body weight, especially the visceral and subcutaneous fat tissue, which has positive significance for the improvement of liver function. For

example, For example, Bolender et al.'s research suggests that [8] showed that daglipzin could significantly reduce body weight and total fat mass in patients with T2DM, and improve regional fat distribution. This weight loss and improved fat distribution may be related to the regulatory effects of the drug on lipid metabolism.

However, the mechanism by which SGLT2i protects the liver remains controversial. Some studies suggest that the liver protective effect of SGLT2i may be independent of its weight loss effect. For example, the study of Komiya et al. [9] found that igaglizin could improve liver dysfunction in T2DM patients, and such improvement was independent of weight change. This suggests that SGLT2i may protect the liver through other pathways, such as directly regulating lipid metabolism or reducing visceral fat.

In conclusion, SGLT2i plays a certain role in regulating lipid metabolism and reducing visceral fat, which helps to improve insulin resistance and metabolic disorders in T2DM patients. However, the specific mechanism of action still needs further study. Future studies could focus on the effects of SGLT2i on lipid metabolic pathways and combination strategies with other drugs, with a view to providing patients with more comprehensive and effective treatment options.

2.3.Mechanism of anti-inflammatory and antioxidant action

In the treatment of T2DM patients with liver dysfunction, SGLT2i has significant anti-inflammatory and antioxidant effects, providing a new treatment option for improving liver function. These drugs not only help alleviate liver inflammation and oxidative stress through their unique mechanisms of action, but also have a positive regulatory effect on lipid metabolism disorders.

Studies have shown that the liver benefits brought by SGLT2i in the treatment of T2DM patients may be closely related to its role in inhibiting liver inflammation, alleviating oxidative stress and promoting fatty acid oxidation [10]. Specifically, SGLT2i inhibits renal glucose reabsorption, reduces body weight, improves insulin resistance, and increases adiponectin production, further inducing the activation of adenylate activated protein kinase (AMPK) and enhancing skeletal muscle uptake and utilization of glucose. At the same time, SGLT2i also reduces fatty acid synthesis and promotes fatty acid oxidation in the liver by inactivating acetyl-CoA carboxylase (ACC). These effects jointly regulate fatty acid metabolism in adipose tissue, skeletal muscle and liver, and reduce fatty acid accumulation, inflammatory response and oxidative stress levels in liver, thus playing a significant liver protective role, So as to exert liver protective effects [10].

In addition, studies have shown that, some researchers have observed that SGLT2i can improve biomarkers of steatosis and fibrosis in T2DM patients, further supporting its positive role in liver protection [11]. However, the exact mechanism of the anti-inflammatory and antioxidant effects of SGLT2i has not yet been fully verified, and further research and discussion are still needed [12].

Overall, SGLT2i plays a liver protective role for patients with T2DM complicated with liver dysfunction through its unique anti-inflammatory, antioxidant, and improvement of lipid metabolism disorders. This finding provides new ideas and methods for clinical treatment, and is expected to bring greater breakthroughs in the treatment of T2DM patients with abnormal liver function.

2.4.Other mechanisms of action

In addition to known hypoglycemic effects, SGLT2i also exhibits various other mechanisms of action in the treatment of T2DM patients. Compared with DPP-IV inhibitors, SGLT2i is more effective in reducing BMI, waist circumference, and visceral fat area in T2DM patients, this discovery provides a new perspective on the potential application of SGLT2i in weight management [13].

Clinical study showed that SGLT2i after treatment there is a close relationship between body weight and liver fat loss. Notably, SGLT2i appears to be more effective in reducing liver fat content than

weight loss and visceral adipose tissue loss alone [14]. This reduction in liver fat content may be independent of weight loss, suggesting that SGLT2i may have a direct liver protective effect. Lee, etc. [15] research further support for this view, they found that subjects were treated with SGLT2i weight about 1 kg to 3 kg, this is mainly with the consumption of liver glycogen and fewer subcutaneous and visceral fat. However, other studies have pointed out that the mechanism by which SGLT2i reduces body weight and liver fat content may not be entirely dependent on weight loss, insulin resistance, inflammation and changes in skeletal muscle volume [16]. This suggests that SGLT2i may exert a protective effect on the liver through more complex mechanisms.

In addition to its effects on body weight and liver fat, SGLT2i has also been found to further improve liver fibrosis by improving liver steatosis and inflammation [17]. This finding provides new evidence for the potential use of SGLT2i in the treatment of liver disease. To sum up, SGLT2i in the treatment of patients with T2DM brought the diversity of liver protection mechanism.

In summary, SGLT2i exhibits diverse liver protective mechanisms in the treatment of T2DM patients. However, the specific protection mechanism for it is currently unclear. Future research should focus on the specific mechanism of action of SGLT2i.

3. CLINICAL APPLICATION OF SGLT2I IN T2DM COMPLICATED WITH LIVER FUNCTION ABNORMALITIES

Based on its unique mechanism of action, SGLT2i shows significant clinical potential in the treatment of T2DM complicated with liver dysfunction. SGLT2i can not only reduce blood sugar and weight, but also effectively improve liver function, providing a new treatment option for patients with T2DM complicated with abnormal liver function.

Multiple studies have confirmed that SGLT2i has significant effects in reducing liver fat content and improving liver function. The study by Arase et al. [1] showed that SGLT2i treatment can significantly reduce liver fat content in patients with T2DM complicated with non-alcoholic fatty liver disease (NAFLD). Another study conducted by Li et al. [2] further confirmed the efficacy of SGLT2i class drug canagliflozin in improving liver function in patients with T2DM. In addition, the systematic evaluation by Bica et al. [3] also pointed out that SGLT2i has a positive effect on improving liver steatosis and fibrosis in patients with NAFLD or steatohepatitis.

In terms of safety, although SGLT2i has shown good efficacy in treating T2DM with liver dysfunction, its potential risks still need to be considered. Some studies have found that SGLT2i may increase the risk of urinary and reproductive system infections in patients, while others have found that SGLT2i may not have significant advantages in improving liver function compared to other hypoglycemic drugs.

In order to better understand the mechanism of action of SGLT2i, the researchers conducted a series of explorations. Ferrannini et al. [18] found that SGLT2i inhibits proximal tubule glucose reabsorption and promotes urinary sugar excretion, thereby reducing blood sugar level, and may protect liver function by improving insulin resistance, alleviating oxidative stress and inflammatory response. In addition, SGLT2i may also improve liver health in NAFLD patients by regulating fat metabolism and reducing liver fat accumulation [9]. However, these hypotheses still need to be confirmed by further clinical studies.

In terms of clinical application, a number of studies have compared the efficacy of different SGLT2i drugs in T2DM complicated with liver dysfunction. A study by Schernthaner et al. [5] found that compared with sitagliptin, caraglizin showed greater advantages in reducing HbA1c and body weight, while also helping to improve liver function. Leiter et al. [19] also has showed that caglizin treatment could significantly reduce liver enzyme levels in T2DM patients, further confirming its efficacy in improving liver function. In addition, the retrospective clinical study of Kinoshita et al. [7] showed

that in T2DM patients, SGLT2i treatment was closely related to the improvement of liver injury, and such improvement was positively correlated with blood glucose control. These findings suggest that SGLT2i has potential clinical application in the treatment of T2DM complicated with abnormal liver function.

However, it is important to note that different SGLT2i drugs may differ in terms of efficacy and safety. Therefore, when choosing the right drug, the doctor needs to make comprehensive consideration according to the specific situation of the patient. In addition, because SGLT2i has been in clinical use for a relatively short time, its long-term efficacy and safety still need to be further evaluated.

Table 1. Comparison of the usage and dosage of three commonly used SGLT2i in clinic

	Canagliflozin	Dapagliflozin	Empagliflozin
Starting dose	100 mg	5 mg	10 mg
Highest dose	300 mg	10 mg	25 mg
Liver parameters	Can be improved	Can be improved	Can be improved
Mild to moderate liver damage	There is no need to adjust the dose	There is no need to adjust the dose	It can be used for liver injury
Severe liver damage	Not recommended	Not recommended	Not recommended
Number of doses	Once daily	Once daily	Once daily
Time of taking the medication	Taken orally before the first meal	Oral before / after meals	Oral before / after meals

Although studies have confirmed the effect of SGLT2i therapy on improving liver function in T2DM patients [20], its safety still needs attention. Research has found [21] that SGLT2i can reduce blood sugar, weight, liver enzymes, and liver fat content in patients with T2DM combined with NAFLD, and has a certain effect on improving liver fibrosis. However, it also increases the risk of urinary and reproductive system infections in patients. But it also increases the risk of genitourinary infection. Compared with T2DM patients with NAFLD who were not treated with SGLT2i, patients treated with SGLT2i were more likely to develop urinary and reproductive tract fungal infections, but not other types of infections [22]. In addition, some studies has shown that [23] that SGLT2i has little advantage compared with other hypoglycemic drugs in improving liver enzymes, liver fibrosis degree and liver fat in T2DM patients with NAFLD. Therefore, more clinical trials are needed to fully understand the efficacy and safety of SGLT2i in T2DM patients with liver dysfunction. This review will summarize the clinical application of different SGLT2i drugs in T2DM complicated with abnormal liver function, in order to provide reference for subsequent studies.

3.1. Clinical application of canagliflozin in T2DM complicated with abnormal liver function

Canagliflozin, as a type of SGLT2i drug, has good therapeutic effects on patients with T2DM and liver dysfunction. According to Seko et al. [24], canagliflozin not only effectively reduces HbA1c levels and weight loss in T2DM patients, but also significantly improves liver function. Especially in T2DM patients with impaired liver function, canagliflozin has shown good efficacy and tolerability. In addition, for patients with higher ALT values, the therapeutic effect of canagliflozin is more significant.

Other clinical studies have further confirmed the effectiveness of canagliflozin in the treatment of T2DM with liver dysfunction. After continuous use of canagliflozin for 6 months, the weight and HbA1c levels of T2DM patients with NAFLD were significantly improved [25]. After 12 months of treatment, it can further reduce liver fat content [26]. In addition, after 52 weeks of treatment, the patient's liver enzyme levels significantly decreased and showed good tolerance [27]. These research

results indicate that canagliflozin can effectively improve liver function in patients with T2DM complicated with liver dysfunction.

In summary, canagliflozin has a positive effect in the treatment of T2DM with liver dysfunction. It can not only effectively control blood sugar, reduce weight, but also significantly improve liver function. This provides a new treatment option for T2DM patients with impaired liver function.

3.2. Clinical application of dapagliflozin in T2DM complicated with abnormal liver function

Dapagliflozin is the world's first approved SGLT2i for the treatment of T2DM, and it also has positive therapeutic effects in clinical applications of T2DM combined with liver dysfunction. Several studies have shown that dapagliflozin can significantly reduce liver fat content and improve liver function indicators in patients with T2DM.

In a randomized, double-blind, placebo-controlled study of T2DM patients [28], after 8 weeks of dapagliflozin treatment, patients' liver proton density fat fraction (PDFF) and visceral adipose tissue volume were effectively reduced without adverse effects on tissue insulin sensitivity. These results suggest that dapagliflozin may improve liver function by reducing liver and visceral fat accumulation.

In another study [29], after 12 weeks of treatment in T2DM patients with NAFLD, blood glucose, body weight, visceral fat, liver fat content and liver biochemical indexes were significantly improved. These results suggest that dapagliflozin has potential application value in the treatment of T2DM with NAFLD.

In addition, other studies [30] found that the ALT concentration of patients decreased significantly after 24 weeks of use of dapagliflozin. Notably, the effect of dapagliflozin in improving ALT levels was significant even in patients with less weight loss [31]. This finding suggests that the improvement in liver function of dapagliflozin may not depend solely on its weight loss effect. This discovery provides new insights into the mechanism by which dapagliflozin improves liver function.

In order to further explore the effect of dapagliflozin on liver function and its relationship with body weight, Horibe et al. [32] conducted a clinical trial. The results suggest that in overweight T2DM patients, the effect of dapagliflozin net weight reduction may be related to the loss of fat mass. This discovery provides new insights into the mechanism by which dapagliflozin improves liver function.

In addition to monotherapy, studies have explored the effect of dapagliflozin in combination with other agents. One study [32] found that SGLT2i combined with metformin could significantly improve body weight and ALT levels in T2DM patients with NAFLD. Other studies have also confirmed [33] that dapagliflozin combined with metformin has significant efficacy and high safety in improving blood glucose control and liver function in T2DM patients with NAFLD. Compared with metformin, dapagliflozin alone may be more advantageous in the treatment of T2DM with NAFLD [34]. These results indicate that dapagliflozin has a broad application prospect in the treatment of T2DM patients with abnormal liver function.

In summary, dapagliflozin has a positive therapeutic effect in the treatment of T2DM with liver dysfunction. It can not only reduce liver fat content and improve liver function indicators, but may also play a role through various mechanisms such as reducing fat accumulation and improving insulin resistance. However, current research still has certain limitations, such as relatively small sample size and short research time. Therefore, in the future, more large-scale and high-quality clinical trials are needed to further verify the efficacy and safety of dapagliflozin in the treatment of T2DM with liver dysfunction. At the same time, it is also necessary to pay attention to the combined therapeutic effects of dapagliflozin and other drugs, as well as their application effects in different populations, in order to provide more comprehensive reference basis for clinical practice.

3.3. Clinical application of empagliflozin in T2DM complicated with abnormal liver function

Englipzin also showed significant efficacy in T2DM patients with NAFLD. A number of clinical trials have showed the positive effects of Englipzin in reducing liver fat and improving liver function [35].

A 20-week randomized controlled trial showed that liver fat content was significantly reduced and serum alanine aminotransferase (ALT) levels were improved in patients with T2DM combined with NAFLD in the englaglitzin group compared with standard therapy [35]. This indicates that englaglitzin can not only effectively control blood sugar, but also positively affect liver fat metabolism. Animal experiments have also confirmed that englaglitzin can reduce the levels of liver triacylglycerol and lipid toxic intermediates in pre-diabetic rats, thereby improving liver lipid metabolism and alleviating lipid accumulation, and is expected to delay the development of NAFLD [36].

Another randomized, double-blind, placebo-controlled Phase IV clinical trial further confirmed the efficacy of enoglizin in reducing liver fat in T2DM patients with NAFLD and found that Enoglizin reduced circulating uric acid and increased adiponectin levels, although it did not significantly alter insulin sensitivity [37]. These results suggest that Englipzin has a positive effect on improving the metabolic status of patients. In addition, a prospective cohort study found that after 6 months of continuous use of enoglizin, serum ALT, aspartate aminotransferase (AST), glutamic-pyruvic transaminase, aspartate aminotransferase (AST), Glutamic-Pyruvic transaminase, GGT), body weight and liver fat content were reduced without significant side effects [38].

A randomized, double-blind, placebo-controlled clinical trial was conducted to compare the efficacy of enaglipzin monotherapy with other agents in T2DM patients with NAFLD. The study results showed that baseline ALT levels, body weight and abdominal fat area were significantly reduced, and the degree of liver steatosis and fibrosis was improved in the Englazine group [39].

In summary, englaglizin has shown good efficacy and safety in the treatment of T2DM patients with abnormal liver function, especially NAFLD patients. Future studies can further explore its mechanism of action and the difference in efficacy in different populations.

3.4. Clinical application of other SGLT2i in T2DM complicated with abnormal liver function

In addition to the above three types of SGLT2i, other SGLT2i have also shown improvement in T2DM patients with abnormal liver function in related studies (Table 26). Studies [40] found that after 3 months of treatment with igaglipzin, the liver function of T2DM patients with abnormal liver function was significantly improved. Continuous treatment for 12 months can reduce AST and ALT levels in patients, while showing good efficacy and tolerability [41]. After 18 months of treatment, it can improve liver fibrosis in patients with T2DM combined with liver dysfunction [42], and has better therapeutic effects for T2DM patients with liver dysfunction lasting for more than 3 years [43]. Therefore, Igliflozin can also be an effective treatment option for T2DM patients [44].

Table 2. Comparison of clinical observation time and effect of different SGLT2i

Time of clinical observation	SGLT2i	Clinical efficacy
12 weeks - 52 weeks	Canagliflozi	Canagliflozin can improve liver fat content in patients with T2DM and NAFLD [26], and meta-analyses support the efficacy and safety of canagliflozin in the treatment of T2DM [27].
8 weeks - 52 weeks	Dapagliflozi	Studies [28] have shown that dapagliflozin is able to reduce liver fat in patients with T2DM, but has no effect on tissue insulin sensitivity. Phrueksotsai et al. [29] further confirmed that dapagliflozin can reduce liver fat and visceral fat. Studies have shown [31] that dapagliflozin can improve liver function abnormalities in patients with T2DM and NAFLD in South Korea. In addition, the efficacy and safety of dapagliflozin in the treatment of T2DM with NAFLD have been reported in the literature [33, 34, 45].
12 weeks - 52 weeks	Empagliflozi	In a randomized controlled trial [35], empagliflozin improved liver fat content in patients with T2DM and NAFLD. It has also been shown that empagliflozin can improve hepatic lipid metabolism independently of obesity and hyperglycemia in prediabetes models [36].

Other studies have also found that oglipzin after 52 weeks of treatment can reduce liver enzyme indexes in T2DM patients with liver dysfunction [46], without dose adjustment in patients with mild or moderate liver dysfunction [47], and is well tolerated in healthy individuals and patients with moderate liver injury [48]. Toglizin also does not require dose adjustment in the treatment of patients with moderate liver function impairment [49]. In a single-center prospective study of 55 T2DM patients with liver dysfunction, continuous treatment with luglizin for 52 weeks effectively reduced liver fat, improved liver function, alleviated liver injury, and improved liver fibrosis, while showing good tolerance [50]. In addition, liver fibrosis biomarkers M2-BP, NAFLD fibrosis score, FIB-4 index and ferritin were improved after treatment with Luseglizin in T2DM patients with hepatic insufficiency [50]. These results indicate that different SGLT2i drugs are effective in lowering blood sugar and improving liver function. These studies can provide more treatment options for T2DM patients with abnormal liver function, which is conducive to improving the quality of life and prognosis of patients.

4. CONCLUDING REMARKS

This review summarizes the potential mechanisms of action and clinical application of SGLT2i in the treatment of T2DM complicated with abnormal liver function. The potential mechanisms of SGLT2i on T2DM patients with liver dysfunction are diverse, but the specific mechanisms are not yet fully understood and further clinical research is needed to confirm. Calaglizin, daglizin, and englizin are indicated for T2DM patients with mild to moderate liver injury, but are not recommended for use in patients with severe liver injury. However, at present there are still some notable problems: first, SGLT2i improve T2DM merger of abnormal liver function of the specific mechanism is unclear [12]. Secondly, the current evidence on the improvement of SGLT2i on liver fibrosis, cirrhosis and liver cancer is insufficient [51]. Finally, liver improvement results in clinical trials based on SGLT2i are still limited [64]. Therefore, future research can explore SGLT2i protect liver specific mechanism of action; To conduct clinical studies to evaluate the efficacy of SGLT2i in T2DM patients with abnormal liver function; To analyze the therapeutic differences of different SGLT2i drugs in T2DM

patients with abnormal liver function. Pay attention to the liver protective effects of SGLT2i in different populations and stages of the disease, in order to provide more optimized treatment plans, improve patient quality of life, and reduce the risk of complications.

REFERENCES

- [1] Arase Y, Shiraishi K, Anzai K, Sato H, Teramura E, Tsuruya K, Hirose S, Deguchi R, Toyoda M, Mine T, Kagawa T. Effect of Sodium Glucose Co-Transporter 2 Inhibitors on Liver Fat Mass and Body Composition in Patients with Nonalcoholic Fatty Liver Disease and Type 2 Diabetes Mellitus [J]. *Clinical drug investigation*, 2019, 39(7): 631-641.
- [2] Li B, Wang Y, Ye Z, Yang H, Cui X, Wang Z, Liu L. Effects of Canagliflozin on Fatty Liver Indexes in Patients with Type 2 Diabetes: A Meta-analysis of Randomized Controlled Trials [J]. *Journal of pharmacy & pharmaceutical sciences: a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques*, 2018, 21(1): 222-235.
- [3] Bica I C, Stoica R A, Salmen T, Janež A, Volčanšek Š, Popovic D, Muzurovic E, Rizzo M, Stoian A P. The Effects of Sodium-Glucose Cotransporter 2-Inhibitors on Steatosis and Fibrosis in Patients with Non-Alcoholic Fatty Liver Disease or Steatohepatitis and Type 2 Diabetes: A Systematic Review of Randomized Controlled Trials [J]. *Medicina (Kaunas, Lithuania)*, 2023, 59(6).
- [4] Wong C, Yaow C Y L, Ng C H, Chin Y H, Low Y F, Lim A Y L, Muthiah M D, Khoo C M. Sodium-Glucose Co-Transporter 2 Inhibitors for Non-Alcoholic Fatty Liver Disease in Asian Patients With Type 2 Diabetes: A Meta-Analysis [J]. *Frontiers in endocrinology*, 2020, 11: 609135.
- [5] Scherthaner G, Lavalle-González F J, Davidson J A, Jodon H, Vijapurkar U, Qiu R, Canovatchel W. Canagliflozin provides greater attainment of both HbA1c and body weight reduction versus sitagliptin in patients with type 2 diabetes [J]. *Postgraduate medicine*, 2016, 128(8): 725-730.
- [6] Lee P C H, Gu Y, Yeung M Y, Fong C H Y, Woo Y C, Chow W S, Tan K, Lam K S L. Dapagliflozin and Empagliflozin Ameliorate Hepatic Dysfunction Among Chinese Subjects with Diabetes in Part Through Glycemic Improvement: A Single-Center, Retrospective, Observational Study [J]. *Diabetes therapy: research, treatment and education of diabetes and related disorders*, 2018, 9(1): 285-295.
- [7] Kinoshita T, Shimoda M, Sanada J, Fushimi Y, Hirata Y, Irie S, Obata A, Kimura T, Hirukawa H, Kohara K, Tatsumi F, Kamei S, Nakanishi S, Mune T, Kaku K, Kaneto H. There is a Close Association Between the Recovery of Liver Injury and Glycemic Control after SGLT2 Inhibitor Treatment in Japanese Subjects with Type 2 Diabetes: A Retrospective Clinical Study [J]. *Diabetes therapy: research, treatment and education of diabetes and related disorders*, 2018, 9(4): 1569-1580.
- [8] Bolinder J, Ljunggren Ö, Kullberg J, Johansson L, Wilding J, Langkilde A M, Sugg J, Parikh S. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin [J]. *The Journal of clinical endocrinology and metabolism*, 2012, 97(3): 1020-1031.
- [9] Komiya C, Tsuchiya K, Shiba K, Miyachi Y, Furuke S, Shimazu N, Yamaguchi S, Kanno K, Ogawa Y. Ipragliflozin Improves Hepatic Steatosis in Obese Mice and Liver Dysfunction in Type 2 Diabetic Patients Irrespective of Body Weight Reduction [J]. *PloS one*, 2016, 11(3): e0151511.
- [10] Yanai H, Hakoshima M, Katsuyama H. The Possible Mechanisms for Improvement of Liver Function due to Sodium-Glucose Cotransporter-2 Inhibitors [J]. *Journal of clinical medicine research*, 2019, 11(11): 769-772.
- [11] Colosimo S, Ravaioli F, Petroni M L, Brodosi L, Marchignoli F, Barbanti F A, Sasdelli A S, Marchesini G, Pironi L. Effects of antidiabetic agents on steatosis and fibrosis biomarkers in type 2 diabetes: A real-world data analysis [J]. *Liver international: official journal of the International Association for the Study of the Liver*, 2021, 41(4): 731-742.
- [12] Bonnet F, Scheen A J. Effects of SGLT2 inhibitors on systemic and tissue low-grade inflammation: The potential contribution to diabetes complications and cardiovascular disease [J]. *Diabetes & metabolism*, 2018, 44(6): 457-464.
- [13] WU Jiaojiao. Effect of SGLT-2 inhibitors on visceral fat area in patients with T2DM [D], 2022
- [14] Koutoukidis D A, Astbury N M, Tudor K E, Morris E, Henry J A, Noreik M, Jebb S A, Aveyard P. Association of Weight Loss Interventions With Changes in Biomarkers of Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-analysis [J]. *JAMA internal medicine*, 2019, 179(9): 1262-1271.
- [15] Lee P C, Ganguly S, Goh S Y. Weight loss associated with sodium-glucose cotransporter-2 inhibition: a review of evidence and underlying mechanisms [J]. *Obesity reviews: an official journal of the International Association for the Study of Obesity*, 2018, 19(12): 1630-1641.

- [16] Nishimiya N, Tajima K, Imajo K, Kameda A, Yoshida E, Togashi Y, Aoki K, Inoue T, Nakajima A, Utsunomiya D, Terauchi Y. Effects of Canagliflozin on Hepatic Steatosis, Visceral Fat and Skeletal Muscle among Patients with Type 2 Diabetes and Non-alcoholic Fatty Liver Disease [J]. *Internal medicine (Tokyo, Japan)*, 2021, 60(21): 3391-3399.
- [17] Ogawa Y, Nakahara T, Ando Y, Yamaoka K, Fujii Y, Uchikawa S, Fujino H, Ono A, Murakami E, Kawaoka T, Miki D, Yamauchi M, Tsuge M, Imamura M, Oka S. Sodium-glucose cotransporter-2 inhibitors improve FibroScan-aspartate aminotransferase scores in patients with nonalcoholic fatty liver disease complicated by type 2 diabetes [J]. *European journal of gastroenterology & hepatology*, 2023, 35(9): 989-996.
- [18] Ferrannini E, Muscelli E, Frascerra S, Baldi S, Mari A, Heise T, Broedl U C, Woerle H J. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients [J]. *The Journal of clinical investigation*, 2014, 124(2): 499-508.
- [19] Leiter L A, Forst T, Polidori D, Balis D A, Xie J, Sha S. Effect of canagliflozin on liver function tests in patients with type 2 diabetes [J]. *Diabetes & metabolism*, 2016, 42(1): 25-32.
- [20] Tyagi K, Madan S, Prakash Bhatt S, Ansari I A, Dutta K, Misra A. Sodium-glucose cotransporter-2 inhibitors in patients with type 2 diabetes mellitus and moderate to severe hepatic fibrosis: A retrospective study [J]. *Clinical nutrition ESPEN*, 2023, 57: 305-310.
- [21] Li Xiaojing, SUN Yuanlong, ZHANG Binbin, Mei Zubing, FENG Qin, HU Yiyang. Efficacy and safety of sodium-glucose cotransporter 2 inhibitors in the treatment of type 2 diabetes mellitus complicated with non-alcoholic fatty liver disease [J]. *Journal of Hepatobiliary Diseases*, 2020, 36(10): 2241-2247.
- [22] Bañares J, Manzano-Núñez R, Prió A, Rivera-Esteban J, Camps-Relats L, Villarejo A, Ruiz-Ortega L, Pons M, Ciudin A, Salcedo M T, Vargas V, Genescà J, Pericàs J M. Risk of infections in patients with NAFLD and Type 2 Diabetes under treatment with SGLT2 inhibitors and relationship with liver outcomes: A retrospective case-control study [J]. *Frontiers in endocrinology*, 2022, 13: 945626.
- [23] Chen Dongmei, Wei Dong. Glucose-sodium cotransporter-2 inhibitors in the treatment of type 2 diabetes mellitus with nonalcoholic fatty liver disease: a meta-analysis *Journal of Integrated Traditional Chinese and Western Medicine Hepatology*, 2021, 31(12): 1100-1104.
- [24] Seko Y, Sumida Y, Sasaki K, Itoh Y, Iijima H, Hashimoto T, Ishii S, Inagaki N. Effects of canagliflozin, an SGLT2 inhibitor, on hepatic function in Japanese patients with type 2 diabetes mellitus: pooled and subgroup analyses of clinical trials [J]. *Journal of gastroenterology*, 2018, 53(1): 140-151.
- [25] Gautam A, Agrawal P K, Doneria J, Nigam A. Effects of Canagliflozin on Abnormal Liver Function Tests in Patients of Type 2 Diabetes with Non-Alcoholic Fatty Liver Disease [J]. *The Journal of the Association of Physicians of India*, 2018, 66(8): 62-66.
- [26] Inoue M, Hayashi A, Taguchi T, Arai R, Sasaki S, Takano K, Inoue Y, Shichiri M. Effects of canagliflozin on body composition and hepatic fat content in type 2 diabetes patients with non-alcoholic fatty liver disease [J]. *Journal of diabetes investigation*, 2019, 10(4): 1004-1011.
- [27] Xiong W, Xiao M Y, Zhang M, Chang F. Efficacy and safety of canagliflozin in patients with type 2 diabetes: A meta-analysis of randomized controlled trials [J]. *Medicine*, 2016, 95(48): e5473.
- [28] Latva-Rasku A, Honka M J, Kullberg J, Mononen N, Lehtimäki T, Saltevo J, Kirjavainen A K, Saunavaara V, Iozzo P, Johansson L, Oscarsson J, Hannukainen J C, Nuutila P. The SGLT2 Inhibitor Dapagliflozin Reduces Liver Fat but Does Not Affect Tissue Insulin Sensitivity: A Randomized, Double-Blind, Placebo-Controlled Study With 8-Week Treatment in Type 2 Diabetes Patients [J]. *Diabetes care*, 2019, 42(5): 931-937.
- [29] Phruksotsai S, Pinyopornpanish K, Euathrongchit J, Leerapun A, Phrommintikul A, Buranapin S, Chattipakorn N, Thongsawat S. The effects of dapagliflozin on hepatic and visceral fat in type 2 diabetes patients with non-alcoholic fatty liver disease [J]. *Journal of gastroenterology and hepatology*, 2021, 36(10): 2952-2959.
- [30] Hayashi T, Fukui T, Nakanishi N, Yamamoto S, Tomoyasu M, Osamura A, Ohara M, Yamamoto T, Ito Y, Hirano T. Correction to: Dapagliflozin decreases small dense low-density lipoprotein-cholesterol and increases high-density lipoprotein 2-cholesterol in patients with type 2 diabetes: comparison with sitagliptin [J]. *Cardiovascular diabetology*, 2017, 16(1): 149.
- [31] Euh W, Lim S, Kim J W. Sodium-Glucose Cotransporter-2 Inhibitors Ameliorate Liver Enzyme Abnormalities in Korean Patients With Type 2 Diabetes Mellitus and Nonalcoholic Fatty Liver Disease [J]. *Frontiers in endocrinology*, 2021, 12: 613389.
- [32] Horibe K, Morino K, Miyazawa I, Tanaka-Mizuno S, Kondo K, Sato D, Ohashi N, Ida S, Yanagimachi T, Yoshimura M, Itoh R, Murata K, Miura K, Arima H, Fujita Y, Ugi S, Maegawa H. Metabolic changes induced by dapagliflozin, an SGLT2 inhibitor, in Japanese patients with type 2 diabetes treated by oral anti-diabetic agents: A randomized, clinical trial [J]. *Diabetes research and clinical practice*, 2022, 186: 109781.
- [33] Pan Juan, Wang Qi, Zhang Yan. Efficacy and safety of dagaglizin combined with metformin in the treatment of type 2 diabetes mellitus with non-alcoholic fatty liver disease [J]. *Guizhou medicine*, 2023, 47(03): 406-407.

- [34] Nie Yan, Ding Hongcheng, Li Yanli, LIAO Chunfen, Julie. Clinical efficacy of daglipzin and metformin in the treatment of type 2 diabetes mellitus with nonalcoholic fatty liver disease [J]. *Jiangsu Medicine*, 2021, 47(03): 286-289. (in Chinese)
- [35] Kuchay M S, Krishan S, Mishra S K, Farooqui K J, Singh M K, Wasir J S, Bansal B, Kaur P, Jevalikar G, Gill H K, Choudhary N S, Mithal A. Effect of Empagliflozin on Liver Fat in Patients With Type 2 Diabetes and Nonalcoholic Fatty Liver Disease: A Randomized Controlled Trial (E-LIFT Trial) [J]. *Diabetes care*, 2018, 41(8): 1801-1808.
- [36] Hüttl M, Markova I, Miklankova D, Zapletalova I, Poruba M, Haluzik M, Vaněčkova I, Malinska H. In a Prediabetic Model, Empagliflozin Improves Hepatic Lipid Metabolism Independently of Obesity and before Onset of Hyperglycemia [J]. *International journal of molecular sciences*, 2021, 22(21).
- [37] Kahl S, Gancheva S, Straßburger K, Herder C, Machann J, Katsuyama H, Kabisch S, Henkel E, Kopf S, Lagerpusch M, Kantartzis K, Kupriyanova Y, Markgraf D, Van Gemert T, Knebel B, Wolkersdorfer M F, Kuss O, Hwang J H, Bornstein S R, Kasperk C, Stefan N, Pfeiffer A, Birkenfeld A L, Roden M. Empagliflozin Effectively Lowers Liver Fat Content in Well-Controlled Type 2 Diabetes: A Randomized, Double-Blind, Phase 4, Placebo-Controlled Trial [J]. *Diabetes care*, 2020, 43(2): 298-305.
- [38] Pokharel A, Kc S, Thapa P, Karki N, Shrestha R, Jaishi B, Paudel M S. The Effect of Empagliflozin on Liver Fat in Type 2 Diabetes Mellitus Patients With Non-Alcoholic Fatty Liver Disease [J]. *Cureus*, 2021, 13(7): e16687.
- [39] Chehrehgosha H, Sohrabi M R, Ismail-Beigi F, Malek M, Reza Babaei M, Zamani F, Ajdarkosh H, Khoonsari M, Fallah A E, Khamseh M E. Empagliflozin Improves Liver Steatosis and Fibrosis in Patients with Non-Alcoholic Fatty Liver Disease and Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial [J]. *Diabetes therapy: research, treatment and education of diabetes and related disorders*, 2021, 12(3): 843-861.
- [40] Tabuchi H, Maegawa H, Tobe K, Nakamura I, Uno S. Effect of ipragliflozin on liver function in Japanese type 2 diabetes mellitus patients: a subgroup analysis of the STELLA-LONG TERM study (3-month interim results) [J]. *Endocrine journal*, 2019, 66(1): 31-41.
- [41] Nakamura I, Maegawa H, Tobe K, Uno S. Correction to: Safety and Effectiveness of Ipragliflozin for Type 2 Diabetes in Japan: 12-Month Interim Results of the STELLA-LONG TERM Post-Marketing Surveillance Study [J]. *Advances in therapy*, 2021, 38(8): 4599-4601.
- [42] Takahashi H, Kessoku T, Kawanaka M, Nonaka M, Hyogo H, Fujii H, Nakajima T, Imajo K, Tanaka K, Kubotsu Y, Isoda H, Oeda S, Kurai O, Yoneda M, Ono M, Kitajima Y, Tajiri R, Takamori A, Kawaguchi A, Aishima S, Kage M, Nakajima A, Eguchi Y, Anzai K. Ipragliflozin Improves the Hepatic Outcomes of Patients With Diabetes with NAFLD [J]. *Hepatology communications*, 2022, 6(1): 120-132.
- [43] Tobe K, Maegawa H, Nakamura I, Uno S. Effect of ipragliflozin on liver function in Japanese type 2 diabetes mellitus patients: subgroup analysis of a 3-year post-marketing surveillance study (STELLA-LONG TERM) [J]. *Endocrine journal*, 2021, 68(8): 905-918.
- [44] Alkabbani W, Gamble J M. Profile of Ipragliflozin, an Oral SGLT-2 Inhibitor for the Treatment of Type 2 Diabetes: The Evidence to Date [J]. *Drug design, development and therapy*, 2021, 15: 3057-3069.
- [45] Shen Yang, Lin Jinjun, Zhao Yu Effect of dapagliflozin on liver function in patients with type 2 diabetes mellitus and fatty liver [J]. *China Practical Medicine*, 2020, 15(25): 130-132
- [46] Gallo S, Calle R A, Terra S G, Pong A, Tarasenko L, Raji A. Effects of Ertugliflozin on Liver Enzymes in Patients with Type 2 Diabetes: A Post-Hoc Pooled Analysis of Phase 3 Trials [J]. *Diabetes therapy: research, treatment and education of diabetes and related disorders*, 2020, 11(8): 1849-1860.
- [47] [Kasahara-Ito N, Fukase H, Ogama Y, Saito T, Ohba Y, Shimada S, Takano Y, Ichihara T, Terao K, Nakamichi N, Kumagai Y, Ikeda S. Pharmacokinetics and Pharmacodynamics of Tofogliflozin (a Selective SGLT2 Inhibitor) in Healthy Male Subjects [J]. *Drug research*, 2017, 67(6): 349-357.
- [48] Sahasrabudhe V, Terra S G, Hickman A, Saur D, Raje S, Shi H, Matschke K, Zhou S, Cutler D L. Pharmacokinetics of Single-dose Ertugliflozin in Patients With Hepatic Impairment [J]. *Clinical therapeutics*, 2018, 40(10): 1701-1710.
- [49] Yamada H, Ohira H, Ikegami F, Nakamura K, Takahashi A, Abe K, Inano A, Shimada S, Miyata K, Saito T, Ohba Y, Terao K, Ohnishi A. Effects of Child-Pugh B Cirrhosis on Pharmacokinetics of Tofogliflozin, a New Sodium-Glucose Co-Transporter (SGLT2) Inhibitor [J]. *Drug research*, 2020, 70(9): 401-409.
- [50] Seino H. Correction to: Efficacy and Safety of Luseogliflozin in Patients with Type 2 Diabetes Complicated by Hepatic Dysfunction: A Single-Site, Single-Arm, Open-Label, Exploratory Trial [J]. *Diabetes therapy: research, treatment and education of diabetes and related disorders*, 2021, 12(10): 2807-2811.
- [51] Shao S C, Kuo L T, Chien R N, Hung M J, Lai E C. SGLT2 inhibitors in patients with type 2 diabetes with non-alcoholic fatty liver diseases: an umbrella review of systematic reviews [J]. *BMJ open diabetes research & care*, 2020, 8(2).