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Hepatoprotective Effect of SGLT2 Inhibitor on Nonalcoholic Fatty Liver Disease

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Abstract

A fourth of the adult population is now suffering from nonalcoholic fatty liver disease (NAFLD) worldwide. Nonalcoholic steatohepatitis (NASH), a severe form of NAFLD, can lead to liver-related mortality. NAFLD/NASH is closely associated with type 2 diabetes. Although pioglitazone is now recommended as the 1st line therapy for

NASH with type 2 diabetes, pioglitazone has several safety concerns such as body weight gain, heart failure, fluid retention, and bone fracture in women. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have a variety of functions such as glycemic control, bodyweight reduction, and decreased body pressure. Accumulating evidence has shown that this agent has also cardioprotective and renoprotective effects in patients with or without type 2 diabetes. Recent studies that SGLT2 inhibitor can also reduce in transaminase activities or hepatic fat content in NAFLD. NAFLD patients with type 2 diabetes can be indicated for SGLT2 inhibitor, because they are obese, have insulin resistance, and at high risk of cardiovascular events. The phase 3 study of dapagliflozin for NAFLD (DEAN study) is now ongoing. It remains unknown whether this agent can ameliorate hepatic fibrosis in NASH, leading to improved over-all or liver-related survival. Since the leading cause of NAFLD mortality is cardiovascular events, SGLT2 inhibitors will become the 1st line treatment for NAFLD/NASH.

Keywords

Nonalcoholic Fatty Liver Disease; Sodium-glucose Cotransporter 2; Glucagon like Peptide-1; Hepatic Fibrosis; Hepatocarcinogenesis

Introduction

Nonalcoholic fatty liver disease (NAFLD) includes 10-20% of nonalcoholic steatohepatitis (NASH), which has a high risk of dying from the liver-related disease. Although there is no established pharmacotherapy for NASH, there is great expectation for novel diabetic drugs that have a weight loss effect. In particular, SGLT2 inhibitors are expected to have multifaceted effects such as weight loss, visceral fat reduction, and blood pressure reduction in addition to blood glucose lowering effects, and large-scale clinical trials have demonstrated the protective effects on organs such as heart and kidney (EMPA-REG outcome, CVD-REAL study, CANVAS program, CREDENCE trial [1], DECLARE trial, DAPA-HF study [2]). In recent years, it has been reported that SGLT2 inhibitors improve hepatic steatosis and ALT level, and the hepatoprotective effects of SGLT2 inhibitors have attracted attention.

Diabetes and Liver Disease

According to the cause of death survey of diabetic patients nationwide (2001-1010, n = 45,708), 9.3% died from liver disease (6.0% liver cancer, 3.3% cirrhosis), ranking third after heart disease and pneumonia Met. According to the Ministry of Health, Labor and Welfare's NASH research group, among diabetics, the risk of death from hepatocellular carcinoma was the highest among malignant tumors [3]. When FibroScan was performed on 1,918 diabetic patients in Hong Kong, hepatic steatosis was detected in 73%, and advanced hepatic fibrosis (≥9.6 kPa) was detected in 18%. Similarly, the Rotterdam study in the Netherlands found elevated liver stiffness in one in six people with diabetes. On the other hand, in the study of 1,365 cases of NAFLD diagnosed by liver biopsy of Japan Study Group of NAFLD (JSG-NAFLD), the presence of diabetes was a risk factor for advanced fibrosis of NASH [4]. In the JSG-NAFLD study, a high HOMA-IR index, an indicator of insulin resistance, was an independent risk factor for advanced fibrosis in non-diabetic patients [5]. Thus, it is suggested that diabetes and insulin resistance not only cause NAFLD but also promote liver fibrosis progression.

Current Status of Treatment for Diabetes with NASH / NAFLD

The guidelines in Europe, the United States, and Japan recommended the administration of PPARγ agonist (pioglitazone: PIO) for the treatment of diabetes with NASH, and its usefulness has been established in the long-term data of the United States over three years. However, there are concerns about side effects such as weight gain, edema, fractures, and carcinogenesis. The usefulness of metformin (MTF), the first-line diabetic drug, for NASH / NAFLD is not clear, and currently not recommended from a therapeutic point of view. In addition, the usefulness of DPP4 inhibitors has been studied in a small number of cases, and conflicting results have been accumulated. We hope to see the results of DPP4 inhibitors in future large-scale clinical trials [6]. On the other hand, the efficacy of liraglutide for NASH was demonstrated for glucagon like peptide-1 (GLP-1) receptor agonists (LEAN test), and its efficacy was also demonstrated in a pilot study of JSG-NAFLD

(LEAN-J test). Dulaglutide, a once-weekly injection GLP-1 receptor agonists, is easy to use, has high patient satisfaction, and can be easily used by non-specialists [7]. We reported that the 12-week administration of dulaglutide reduced liver function and body fat, and also reduced liver stiffness by FibroScan. Currently, a global development study (NASH-SEMA study, NCT02970942) for NASH using a novel GLP-1 agonist semaglutide, is ongoing and we hope to see results in the near future.

Efficacy of SGLT2 Inhibitor for Liver Dysfunction Associated with Type 2 diabetes

In order to investigate the effects of SGLT2 inhibitors on liver function in Japanese patients with type 2 diabetes, a sub-analysis of canagliflozin in a Japanese clinical trial was performed [8]. In a sub-analysis of the phase 2 trial, ALT levels were significantly lower in the 12-week canagliflozin-treated group (n = 47) than in placebo (n = 59) in patients with abnormal ALT. In a sub-analysis of the phase 3 trial, canagliflozin at 52 weeks reduced ALT levels in 89% of abnormal ALT cases (n = 195), with an average reduction of 16 IU / L. The decrease in ALT was inversely correlated with the ALT value before treatment, and better effects were obtained in patients with abnormal ALT. Similarly, a sub-analysis of a phase 2 study of canagliflozin from Canada reported that hepatobiliary enzymes improved over placebo and DPP-4 inhibitors and that ALT improvement correlated with HbA1c and body weight improvement. According to the phase 3 clinical trial of luseogliflozin, the group treated with luseogliflozin (n = 79) had significantly improved AST, ALT, and GGT compared to placebo [9]. These results suggested that the hepatoprotective effect of SGLT2 inhibitors in type 2 diabetes patients.

Usefulness of SGLT2 Inhibitor for Diabetes with NASH/NAFLD

Therefore, SGLT2 inhibitors are also expected to be effective for NAFLD / NASH. We performed a retrospective comparative analysis of 24 NAFLD treated with SGLT2 inhibitors for 24 weeks and 21 NAFLD treated with DPP-4 inhibitors for 24 weeks and found that SGLT2 inhibitors had effects on weight loss, ALT level, and body fat reduction. According to the histological examination of the liver by Akuta et al., all cases (n = 9) showed improvement in steatosis, and three cases showed improvement in liver fibrosis [10]. Two randomized controlled trials (RCTs) have recently been reported from Japan. A comparison of 32 cases of diabetes with NAFLD divided into MTF group and luseogliflozin group showed that luseogliflozin at 6 months showed higher body weight, HbA1c, visceral fat area, and hepatic steatosis was significantly improved [11]. In addition, in open RCT of ipragliflozin 50 mg and PIO 15-30 mg, administration of ipragliflozin for 24 weeks improved liver fat and liver function similarly to PIO, but significantly reduced body weight and body fat compared to PIO [12]. As described above, SGLT2 inhibitors may be superior to other diabetes drugs in NAFLD / NASH treatment. A phase 3 clinical trial with dapagliflozin (DEAN trial) is ongoing.

Mechanism of action of SGLT2 Inhibitor and Improvement of Fatty Liver

The mechanism by which SGLT2 inhibitors improve NAFLD / NASH is unclear. First of all, simply lowering body fat by calorie loss and improving insulin resistance may be considered. We reported that luseogliflozin reduced hepatic steatosis for 24 weeks by assessing hepatic steatosis using MRI (LEAD study) (**Fig-1**) [13]. Empagliflozin also significantly reduced hepatic steatosis compared to other hypoglycemic agents from India (E-LIFT test) (**Fig-1**) [14]. According to a report from Dokkyo University, liver fat measured by FibroScan (CAP) decreased significantly from 314 ± 61 to 290 ± 73 dB/m [15]. These results suggested that SGLT2 inhibitors reduce hepatic fat content. The issue is whether it may suppress inflammation and fibrosis, but in animal experiments, decreased liver lipid synthesis, suppression of inflammatory cytokines, activation of PPARα, antioxidant action (increased reduced glutathione), and mechanisms such as suppression of fibrosis and increase of FGF-19 have been reported. There are reports that white adipocytes increase thermogenesis by brown adipogenesis, and that activation of M2 macrophages improves insulin sensitivity [16]. The mechanism by which SGLT2 inhibitors increase glucagon secretion in pancreatic α-cells and induce gluconeogenesis and β-oxidation is

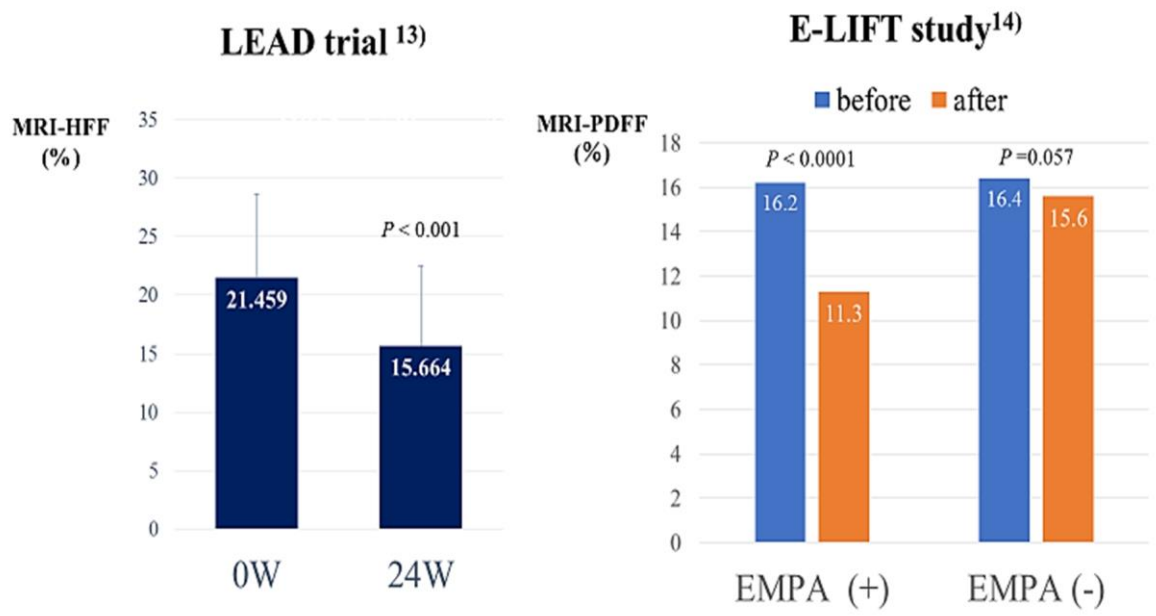

Fig-1: Effect of SGLT2 inhibitors on hepatic fat content evaluated by magnetic resonance imaging: two prospective trials

LEAD trial : Lusepgliflozin 2.5mg/day for 24wk significantly reduced hepatic fat content evaluated by MRI-HFF (hepatic fat fraction) in 39 NAFLD patients with type 2 diabetes

E-LIFT : NAFLD patients (n=22) significantly reduced hepatic fat content by MRI-PDFF (proton density fat fraction) compared to those without receiving SGLT2 inhibitors.

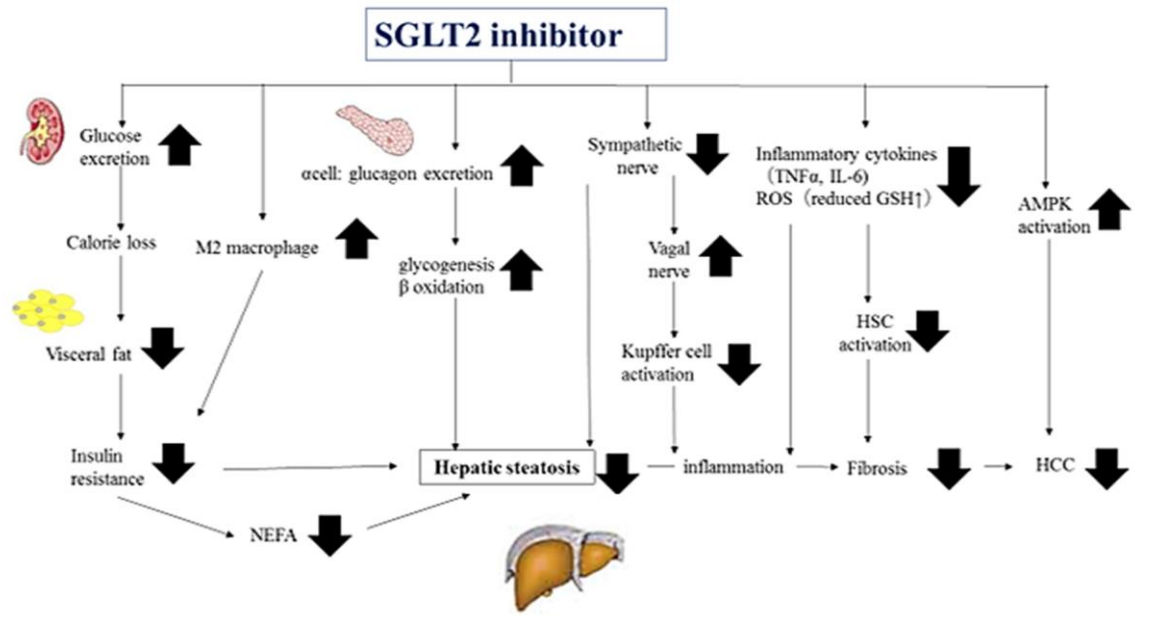

Fig-2: Plausible mechanisms of action of SGLT2 inhibitor in hepatoprotection

also speculated. In addition, SGLT2 inhibitors suppress sympathetic nerve activity and enhance vague nerve, which may exert anti-inflammatory effects by suppressing Kupffer cell activation (**Fig-2**).

Who are the best Indications for SGLT2 Inhibitors? (Table-1)

The factors that determine the therapeutic effect of SGLT2 inhibitors are unclear. Many reports to date

Table-1: Indications of SGLT2 Inhibitors for NAFLD/NASH
· None/mild hepatic fibrosis
· Elevated ALT
· Adherence to life-style modification (no binge eating)
· No treatment with sulphonyl urea or exogenous insulin
· Preserved excretion of exogenous insulin
· Absence of sarcopenia
· With heart failure
· With early stage of CKD (eGFR>30)

indicate that ALT levels before treatment are high and effective. Administration of canagliflozin to NASH with hepatic fibrosis (stage 1-3) has a lower ALT lowering effect in mild hepatic fibrosis (stage 1) than in stage 2/3 [17]. In some cases cannot follow the diet, there is a case where appetite is promoted and rebound, so a case where a certain diet is observed is a good indication. Based on the inhibitory effect of canagliflozin on the progression of nephropathy (CREDENCE study [1]) and dapagliflozin on heart failure (DAPA-HF study [2]), it is a drug that should be used preferentially in patients with the cardiorenal disease. Considering safety, patients with a low blood sugar risk, such as the elderly, patients receiving SU drugs, and patients receiving insulin therapy, should carefully determine their indications. Cases reported for cirrhosis are only case reports [18], but caution is required when administering cirrhosis complicated with sarcopenia due to the possibility of reduced muscle mass. We also limit cases of the poor hepatic reserve to cases of Child A or so because dehydration may lead to deterioration of encephalopathy. On the other hand, since it has a sodium excretion function, it is expected to improve ascites in patients with ascites [19].

Challenges of SGLT2 Inhibitors in NASH Treatment

The greatest concern with SGLT2 inhibitor administration is side effects. In addition to pollakiuria, dehydration and urinary tract infection, there are serious reports of diabetic ketoacidosis and lower limb amputation. In our case, NAFLD/NASH cases are obese, and there are many cases of early diabetes before the introduction of SU agent or insulin, and no serious side effects occur because insulin secretion is relatively maintained. However, genital and urinary tract infections such as genital pruritus and cystitis occur frequently, and they often use antifungal ointments and oral antibiotics. In addition, as a countermeasure against SGLT2 inhibitor ineffective cases and cases with increased appetite, use with MTF, GLP-1 receptor agonist, etc. should be considered. In Europe and the United States, it is reported that it is effective for non-obese patients and non-diabetic patients, but it is necessary to consider the benefits based on medical economic benefits.

SGLT2 Inhibitor and Cancer Suppression Effect

In view of the increasing ratio of malignant tumors as a cause of death in diabetic patients in Japan, it is hoped that future diabetic drugs will have carcinogenesis-suppressing effects in addition to cardio-, renal- and hepatoprotective effects. Among antidiabetic drugs, insulin and SU drugs have a concern of promoting hepatocarcinogenesis, PIO has no certain consensus, and MTF has a hepatocarcinogenesis inhibitory effect from many meta-analyses. On the other hand, the effects of new diabetes drugs, such as DPP4 inhibitor, GLP-1 receptor agonist, an SGLT2 inhibitor, on hepatocarcinogenesis are not clear, but according to a report by Dr. Kawaguchi from Kurume University,

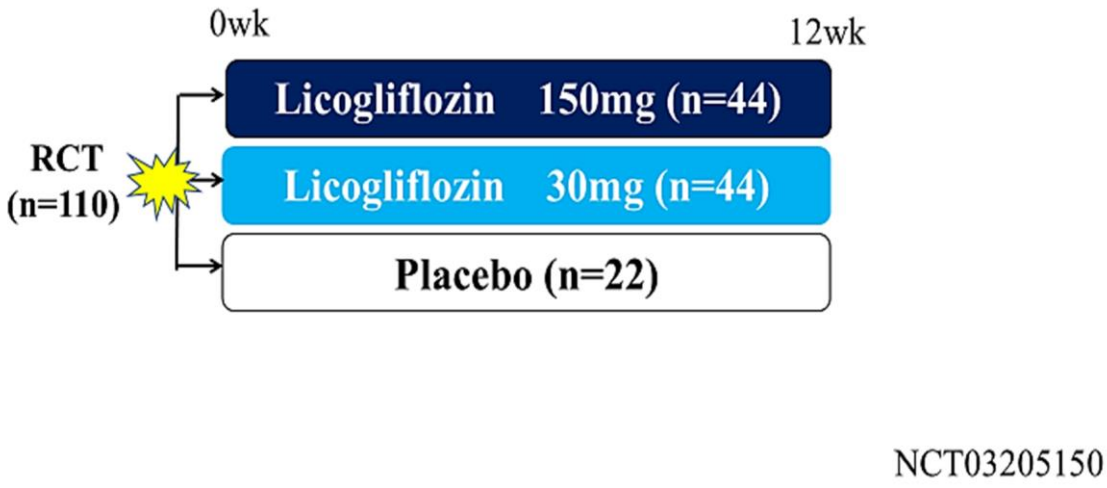

Fig- 3: Protocol of a phase 2 study of licogliflozin (SGLT1/2 dual inhibitor) for NASH

DPP4 inhibitor at least do not increase HCC [20]. Prospective clinical trials and validation by big data analysis will be required in the future. There were concerns that dapagliflozin may increase the frequency of bladder and breast cancer, but the effect of SGLT2 inhibitors on carcinogenesis is unknown at present. On the other hand, in recent years, attention has been paid to the potential of SGLT2 inhibitors to suppress carcinogenesis. Sugar uptake is essential for cancer cell growth, but animal studies show that SGLT2 is expressed in prostate and pancreatic cancer cells and that SGLT2 inhibitors can suppress sugar uptake in cancer cells. Gifu University reported that tofogliflozin suppressed hepatocarcinogenesis in the DEN-induced obesity/diabetes carcinogenesis model [21]. Canagliflozin inhibits complex I of the mitochondrial respiratory chain, increases intracellular AMP and ADP and activates AMP-activated protein kinase (AMPK). Future large-scale clinical trials will test whether SGLT2 inhibitors can suppress hepatocarcinogenesis in humans.

Future Perspective of SGLT Inhibitors

Dual SGLT1/2 inhibitors such as sotagliflozin (LX4211, Lexicon) and licogliflozin (Novartis) are now under development. Sotagliflozin has been established to be effective in T1DM patients uncontrolled with insulin. Although phase 3 and 2 trials are now ongoing for the treatment of patients with type 2 diabetes and heart failure, respectively, NASH studies have never been considered. Licogliflozin is a once-daily, oral compound, SGLT1/2 dual inhibitor. The phase 2a study in 110 obese patients with NASH stage 1-3 was completed（NCT03205150). The primary outcome changes from baseline in ALT at week 12. Enrolled patients were randomly divided into three groups including licogliflozin 30mg/d (n=44), licoglifolzin 150mg/d (n=44), and placebo (n=22) (NCT03205150) (**Fig-3**). In the Liver Meeting 2019®, Harrison and colleagues demonstrated dose-dependent improvement in liver enzymes and PDFF associated with weight loss. However, 76.5% of patients in the higher dose group experienced diarrhea vs ~40% for placebo and low dose group.

Conclusion

SGLT2 inhibitors have a hepatoprotective effect in addition to a cardio-renal protective effect and can be a first-line drug in type 2 diabetes with NASH (**Table-2**). Future tasks include establishing evidence through prospective clinical trials, including elucidation of the mechanism of action, predictors of

Table-2: Antidiabetic Drugs on the view of NASH/NAFLD

Drug	Body Weight	Hepatocarcin Ogenesis	Efficacy for NASH/NAFLD	CVD event reduction	Body fat	Costs	Drawbacks
Sulphonyl Urea Insulin	↑	↑	X ?	Δ?	↑	$/$~$ $ $ $	Hypoglycemia
Metformin	↓	↓	Δ ?	O	↓	$	Lactic Acidosis
Pioglitazone	↑	?	⓪: DM+ X~Δ: DM-	O	↑	$ $	Edema, Heart Failure, Osteopenia
DPP-4 Inhibitor	→	?	x~Δ? No Effect on Steatosis	Δ	→	$ $ $	Increased IBD risk?
GLP-1 Receptor Agonist	↓	?	⓪	⓪	↓	$ $ $ $	Injection only
SGLT2 Inhibitor	↓	?	O	⓪	↓	$ $ $	Urogenital Infections

effects, measures to avoid side effects, and improved prognosis, and establishing medical economic benefit.

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