Research Article

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Ipragliflozin ameliorates liver damage in non-alcoholic fatty liver disease

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Abstract: Background: There are few effective medications for non-alcoholic steatohepatitis (NASH). We investigated the efficacy of ipragliflozin (selective sodium-glucose cotransporter-2 inhibitor [SGLT2I]) for the treatment of patients with type 2 diabetes mellitus (T2DM) complicated by non-alcoholic fatty liver disease (NAFLD).

Methods: We prospectively enrolled patients with T2DM complicated by NAFLD treated at our institutions from January 2015 to December 2016. Patients received oral ipragliflozin (50 mg/day) once daily for 24 weeks. Body composition was evaluated using an InBody720 analyzer. We used transient elastography to measure liver stiffness and the controlled attenuation parameter for the quantification of liver steatosis in patients with NASH.

Results: Forty-three patients with T2DM and NAFLD were enrolled (12 with biopsy-proven NASH and 31 with NAFLD diagnosed by ultrasonography). After 24 weeks, body weight, hemoglobin A1c (HbA1c), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase, body fat mass, and steatosis were significantly decreased compared to baseline measurements in patients with NASH. However, muscle mass was not reduced, and liver stiffness showed a statistically insignificant tendency to decrease. NAFLD patients also showed a significant reduction in body weight, HbA1c, AST, and ALT compared to baseline measurements.

Conclusion: Ipragliflozin may be effective in patients with T2DM complicated by NAFLD.

Keywords: Selective sodium-glucose cotransporter-2 inhibitor; Ipragliflozin; Type 2 diabetes mellitus; Non-alcoholic steatohepatitis; Non-alcoholic fatty liver disease

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1 Introduction

In modern times, obesity and a lack of exercise have increased the incidence of non-alcoholic fatty liver disease (NAFLD) [1, 2]. Untreated NAFLD may cause non-alcoholic steatohepatitis (NASH), cirrhosis, liver failure, and hepatocellular carcinoma and is also a risk factor for type 2 diabetes mellitus (T2DM) and cardiovascular disease [1-5]. Therefore, it is important to identify patients with NAFLD and treat them appropriately.

Several studies evaluated methods for diagnosing NAFLD and demonstrated the usefulness of ultrasonography and magnetic resonance imaging for the measurement of hepatic fibrosis, fat deposition, and splanchnic blood flow including that in the liver [6-11]. These techniques help clinicians to identify patients with NASH, although they are not widely used. There are few treat-

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ments for NAFLD, and the benefits of the available options are limited. Although weight loss is one of most effective treatments for NAFLD, weight reduction is difficult for patients to maintain [12]. On the other hand, previous reports showed vitamin E, pioglitazone, and liraglutide can improve hepatic inflammation and fibrosis in patients with NAFLD [13]. However, in some patients, these agents did not control the pathophysiology of NAFLD, and additional treatment was needed.

Sodium-glucose cotransporter-2 inhibitors (SGLT2Is) suppress sodium-glucose cotransporter-2 in the proximal renal tubules, prevent the reabsorption of glucose filtered at glomeruli, and increase urinary excretion of glucose [14]. Thus, SGLT2Is decrease blood glucose levels and improve glycemic control in patients with T2DM [15]. Additionally, SGLT2Is have been shown to decrease body weight and hepatic transaminase levels in animal models of NAFLD and patients with T2DM [16-27]. Therefore, it is reasonable to conclude that SGLT2Is might improve the pathophysiology of NAFLD. However, evidence demonstrating the efficacy of SGLT2I treatment in NAFLD patients is very limited. Therefore, we investigated the effect of the SGLT2I ipragliflozin in patients with T2DM and NAFLD or NASH.

2 Methods

The Ehime University Hospital Ethics Committee approved the study protocol (Approval ID# 1501013, University Hospital Medical Information Network ID: UMIN000029697). The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki as revised in 1983. Written informed consent was obtained from all study participants.

2.1 Patients

This prospective study analyzed patients diagnosed with T2DM complicated by NAFLD and treated with oral ipragliflozin at Ehime University, Saiseikai Matusyama, Sirituyahatahama, or Matsuyamashimin Hospital from January 2015 to December 2016. The inclusion criteria were a diagnosis of T2DM complicated by NAFLD, age ≥ 20 years, body mass index (BMI) ≥ 22 kg/m2, and hemoglobin A1c (HbA1c) ≥ 6.5 %. Our exclusion criteria were decompensated liver cirrhosis, hepatocellular carcinoma, extrahepatic cancer, serum creatinine level < 2.0 mg/dL, and pregnancy or lactation.

2.2 Diagnosis

Collaborating physicians (from the four hospitals) who specialize in diabetes mellitus were responsible for the diagnosis of T2DM, according to the Japan Diabetes Society criteria. Alcohol consumption consistent with a diagnosis of NAFLD was defined as < 30 g/day for men and < 20 g/day for women [28]. NASH was diagnosed based on the results of a percutaneous liver biopsy performed under ultrasonic or laparoscopic guidance and defined as a combination of steatosis, lobular inflammation, and ballooning degeneration with or without perisinusoidal or pericellular fibrosis [29-31]. Degrees of hepatic fibrosis, inflammation, and steatosis were evaluated by the classification proposed by Brunt et al. [31]. Ultrasound diagnosis of NAFLD required evidence of the four known ultrasonographic criteria for fatty liver including hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring [29].

2.3 Treatment

Patients received oral ipragliflozin (50 mg once a day after breakfast) for 24 weeks. Concomitant use of other SGLT2 inhibitors was not permitted. Additionally, the initiation, discontinuation, or modification of treatments involving diet, exercise, or specified health foods was not allowed during the study period.

2.4 Measurements and evaluation

We recorded a history of prescribed medications, physical examination results, and biochemical measurements for each patient. Venous blood samples were taken in the morning after a 12-hour overnight fast and analyzed for total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), and HbA1c. Moreover, we evaluated body composition and quantified liver steatosis and stiffness in patients with NASH. Body composition, including skeletal muscle mass and body fat mass, was evaluated using an InBody720 analyzer (Biospace Corporation Limited, Seoul, Korea). Liver stiffness and the controlled attenuation parameter (CAP) for the detection and quantification of liver steatosis were measured using transient elastography (TE; FibroScan, Echosens Medical Devices, Paris, France) by a single experienced technician who was blinded to the clinical data of the patient. The measurements were performed using a 3.5 MHz standard probe

on the right hepatic lobe through the intercostal spaces with the patient lying supine. Measurements were considered valid if there were at least ten accurate shots, the success rate was at least 60 %, and the interquartile range was less than 30 % of the median values of the CAP and liver stiffness. The final CAP and liver stiffness values were recorded as the medians of all measurements, and they were expressed in dB/m and kPa, respectively [33].

Patients were diagnosed with dyslipidemia if they had been treated with an antihyperlipidemic agent or their total cholesterol (TC) level was > 220 mg/dl, triglyceride (TG) level was > 150 mg/dl, high-density lipoprotein cholesterol (HDL-c) was < 40 mg/dl, or low-density lipoprotein cholesterol (LDL-c) was > 140 mg/dl [34]. Hypertension was diagnosed if the patient was taking antihypertensive medication or had a resting recumbent blood pressure ≥ 140/90 mmHg on at least two occasions [35].

2.5 Statistical analysis

Data are expressed as numbers (%) or medians (ranges). The paired t-test was used to compare pre- and post-treatment continuous variables after the administration of ipragliflozin. A *p*-value less than 0.05 was considered significant. Statistical analyses were performed using JMP version 12 software (SAS Institute Japan, Tokyo Japan).

3 Results

3.1 Patients

During the study period, 20 patients with biopsy-proven NASH and 40 with NAFLD diagnosed by ultrasonography presented to our diabetes clinics and were included for analysis in our study. Forty-three of the 60 patients (NASH, n = 12; NAFLD, n = 31; age range, 33-69 years) gave informed consent for treatment with SGLT-2 inhibitors in addition to incretin-based drugs. The baseline characteristics of the 12 patients with NASH are shown in Table 1. The mean age in this group was 61.7 years; the average BMI and HbA1c were 29.1 kg/m^2 and 7.6 %, respectively; and the mean concentration of liver enzymes was moderately elevated. The majority of these patients had comorbid hypertension and dyslipidemia. Pioglitazone, insulin, and glucagon-like peptide-1 receptor agonist use was found in 0 %, 0 %, and 8.3 % of these patients, respectively. Histological examination of percutaneous liver biopsies showed the following fibrosis stage distribution in patients with NASH: 1, 2, 3, and 4 in 16.7 %, 25 %, 33.3 % and 25 %, respectively. In the same patients, activity grades 1, 2, and 3 were present in 50 %, 16.7 %, and 33.3 %, respectively.

Table 2 shows the baseline characteristics of the 31 patients with NAFLD. The mean age in this group was 51.1 ± 9.9 years; the average BMI and HbA1c were 30.4 ± 4.8 and 8.4 ± 1.6 %, respectively; and the mean concentration of liver enzymes was mildly raised. Comorbid hypertension and dyslipidemia were identified in 61.2 %, and 77.4 % of the patients with NAFLD, respectively. Pioglitazone, insulin, and glucagon-like peptide-1 receptor agonist use was found in 12.9 %, 29 %, and 3.2 %, of these patients, respectively.

Table 1: Baseline characteristics of 12 patients with non-alcoholic steatohepatitis

Total	**N**	**12**
Sex: male	N (%)	2 (16.7)
Age	years	62 (43-73)
Body mass index	kg/m2	27.7 (23.3-38.5)
Hemoglobin A1c	%	7.65 (6.5-8.6)
Total bilirubin	mg/dL	0.9 (0.5-1.3)
Aspartate aminotransferase	U/L	74 (34-145)
Alanine aminotransferase	U/L	68.5 (29-214)
Gamma-glutamyl transpeptidase	U/L	64 (22-195)
Hypertension	N (%)	11 (91.7)
Dyslipidemia	N (%)	12 (100)
Stage (1: 2: 3: 4)	N	2: 3: 4: 3
Grade (1: 2: 3)	N	6: 2: 4
Antidiabetic agent		
biguanide	N (%)	5 (41.7)
dipeptidyl peptidase-4 inhibitor	N (%)	0 (0)
sulfonylurea	N (%)	3 (25)
alpha-glucosidase inhibitor	N (%)	1 (8.3)
pioglitazone	N (%)	0 (0)
glinide	N (%)	0 (0)
glucagon like peptide-1receptor agonist	N (%)	0 (0)
insulin	N (%)	1 (8.3)

Values are expressed as numbers (%) or medians (range).

3.2 The effect of ipragliflozin on NASH

Compared to baseline measurements, body weight, HbA1c, AST, ALT, and GGT were significantly decreased after 24 weeks of ipragliflozin administration in patients with NASH ($p < 0.05$; Table 3). Although skeletal muscle mass was not reduced significantly, there was a significant reduction in body fat mass ($p = 0.017$; Table 3). Of twelve patients with NASH, six could be evaluated by transient elastography for detection and quantification of liver steatosis and liver stiffness. In these patients, liver steatosis, measured by CAP, was reduced ($p = 0.017$; Table 4). However, although liver stiffness tended to decrease, this tendency was not statistically significant ($p = 0.109$; Table 4).

Table 2: Baseline characteristics of 31 patients with non-alcoholic fatty liver disease:

Total	N	31
Sex: male	N (%)	17 (54.8)
Age	years	51 (33-69)
Body mass index	kg/m2	30 (23.3-41.7)
Hemoglobin A1c	%	8 (6.5-12.7)
Total bilirubin	mg/dL	0.65 (0.38-0.9)
Aspartate aminotransferase	U/L	34.5 (16-80)
Alanine aminotransferase	U/L	55 (15-187)
Gamma-glutamyl transpeptidase	U/L	43.5 (14-577)
Hypertension	N (%)	19 (61.2)
Dyslipidemia	N (%)	24 (77.4)
Antidiabetic agent		
biguanide	N (%)	18 (58.1)
dipeptidyl peptidase-4 inhibitor	N (%)	7 (22.6)
sulfonylurea	N (%)	9 (29)
alpha-glucosidase inhibitor	N (%)	2 (6.5)
pioglitazone	N (%)	4 (12.9)
glinide	N (%)	2 (6.5)
glucagon like peptide-1receptor agonist	N (%)	1 (3.2)
insulin	N (%)	9 (29)

Values are expressed as numbers (%) or medians (range).

3.3 The effect of ipragliflozin on NAFLD

Similarly, the administration of ipragliflozin for 24 weeks significantly decreased body weight, HbA1c, AST, and ALT compared to baseline measurements in the 31 patients with NAFLD ($p < 0.05$; Table 5).

4 Discussion

We examined the effects of ipragliflozin in patients with T2DM complicated by NAFLD diagnosed by ultrasonography or biopsy-proven NASH. We found that administration of ipragliflozin improved the levels of not only HbA1c but also hepatic transaminases and body weight in patients with NAFLD. Moreover, liver steatosis (measured by CAP) and body fat mass were decreased in patients with NASH without a decrease in muscle mass.

Recently, several studies evaluated the efficacy of ipragliflozin in patients with T2DM complicated by a

Table 3: The effect of ipragliflozin in 12 patients with non-alcoholic steatohepatitis

		Baseline	Week 24	p value
Weight	kg	67.8 (55.2-95.5)	66.4 (52.2-94.4)	<0.001
HbA1c	%	7.65 (6.5-8.6)	7.2 (6.1-7.7)	0.003
Aspartate aminotransferase	U/L	74 (34-145)	39.5 (19-156)	0.003
Alanine aminotransferase	U/L	68.5 (29-214)	36.5 (21-228)	0.016
Gamma-glutamyl transpeptidase	U/L	64 (22-195)	31 (21-135)	0.011
				0.011
Skeletal muscle mass	kg	22.75 (17.6-34)	22.25 (17.1-33.5)	0.209
Body fat mass	kg	27.2 (19.2-42)	25.6 (17.4-42.4)	0.017

Values are expressed as medians (range).
The paired t-test was used to analyze continuous variables before and after administration of ipragliflozin. $p < 0.05$ was considered significant.

Table 4: The effect of ipragliflozin on liver stiffness and steatosis in six patients

		Baseline	Week 24	p value
Liver stiffness	(kPa)	10.75 (7.3-20.2)	7.6 (4.8-12.6)	0.109
Steatosis (CAP)	(dB/m)	285.5 (222-338)	258 (163-320)	0.0496

Liver stiffness and the controlled attenuation parameter (CAP) for the detection and quantification of liver steatosis were measured using transient elastography.
Values are expressed as medians (range).
The paired t-test was used to analyze continuous variables before and after administration of ipragliflozin. $p < 0.05$ was considered significant.

Table 5: The effect of ipragliflozin in 31 patients with non-alcoholic fatty liver disease

		Baseline	Week 24	p value
Weight	kg	82 (56-131.8)	80.6 (57.5-125)	<0.001
Hemoglobin A1c	%	8 (6.5-12.7)	6.9 (6.1-9.6)	<0.001
Aspartate aminotransferase	U/L	34.5 (16-80)	24 (14-71)	0.003
Alanine aminotransferase	U/L	55 (15-187)	36.5 (11-97)	0.016
Gamma-glutamyl transpeptidase	U/L	43.5 (14-577)	29 (12-258)	0.141

Values are expressed as medians (range).
The paired t-test was used to analyze continuous variables before and after administration of ipragliflozin. $p < 0.05$ was considered significant.

liver injury [16-19]. Kojima et al. examined 48 patients with T2DM, including 25 diagnosed with hepatic steatosis by ultrasonography, treated with ipragliflozin (50 mg) for 24 weeks and showed that ipragliflozin significantly improved liver injury assessed by serum ALT and HbA1c levels and control of plasma glucose. Further, the change in serum ALT levels did not correlate with a change in body weight [16]. Uchida et al. also reported that administration of ipragliflozin for 24 weeks improved serum AST, ALT, GGT, FPG, and HbA1c levels, irrespective of the change in body weight in patients with T2DM [17]. Takase et al. examined the effect of ipragliflozin for 16 weeks in 21 patients with T2DM and revealed that ipragliflozin decreased body weight, waist circumference, the amount of visceral and subcutaneous fat, HbA1c, insulin, ALT, leptin, and the fatty liver index [18]. Additionally, Ohta et al. administered ipragliflozin to 20 patients with T2DM for 24 weeks and showed that the intrahepatic lipid content by proton magnetic resonance spectroscopy, fat mass index, appendicular skeletal mass index by dual X-ray absorptiometry, and computed tomography measurements of abdominal subcutaneous and visceral fat were decreased. Further, the BMI, FPG, HbA1c, glycoalbumin, LDL-c, AST, ALT, UA, and homeostasis model assessment of insulin resistance [19] were reduced. Although these studies did not include subjects diagnosed with NAFLD, their results were consistent with the effects of ipragliflozin we found in patients with NAFLD or NASH.

Ohki et al. examined the effect of ipragliflozin in 24 patients with T2DM and NAFLD diagnosed by ultrasonography who had not responded to incretin-based therapy [20]. The addition of ipragliflozin for approximately 320 days decreased the BMI, AST, ALT, GGT, HbA1c, and FIB-4 index and increased HDL-c [20]. Additionally, Ito et al. compared the efficacy of ipragliflozin versus pioglitazone in patients with T2DM complicated by NAFLD diagnosed by ultrasonography or computed tomography in an open-label, randomized, active-controlled study [21]. They evaluated the liver-to-spleen attenuation ratio and visceral and subcutaneous fat areas by computed tomography. After 24 weeks the ipragliflozin group showed an increased liver-to-spleen attenuation ratio, HDL-c, and serum adiponectin, while body weight, HbA1c, visceral fat area, subcutaneous fat area, AST, ALT, GGT, serum ferritin, the FIB-4 index, LDL-c, and triglycerides were decreased. Further, while body weight, visceral fat area, and subcutaneous fat area decreased in both groups, the changes found in the ipragliflozin group were significantly greater than those in the pioglitazone group [21].

The effects of other SGLT2Is in patients with NAFLD have also been investigated. Seko et al. conducted a retrospective study to evaluate the efficacy of SGLT2Is in

patients with biopsy-proven NAFLD and T2DM [22]. In this study, an SGLT2I (canagliflozin or ipragliflozin) for 24 weeks in 24 patients was compared with a dipeptidyl peptidase-4 inhibitor (DPP4I; sitagliptin) for 24 weeks in 21 patients. The results showed that SGLT2Is could significantly reduce hepatic transaminase and HbA1c levels as well as body weight in patients with NAFLD and T2DM. While the reductions in ALT and HbA1c were similar between the SGLT2I and DPP4I groups, body weight was significantly reduced in the SGLT2I group compared with the DPP4I group [22]. Tobita et al. assessed the efficacy and safety profile of dapagliflozin in 11 patients with NASH and T2DM [23]. Administration of dapagliflozin for 24 weeks was associated with a significant decrease in BMI, waist circumference, and body fat mass without a change in lean mass or total body water. Serum levels of liver enzyme and type IV collagen 7S were also significantly improved during the study. Insulin, fasting plasma glucose, and HbA1c levels were decreased, whereas the adiponectin level was increased [23]. Additionally, Akuta et al. conducted a prospective study based on serial liver biopsies to investigate the efficacy of canagliflozin for non-alcoholic steatohepatitis complicated by T2DM in five patients [24]. They showed treatment for 24 weeks resulted in improvement in histopathologic features.

Several potential mechanisms could explain the effect of ipragliflozin in NAFLD patients. One study demonstrated that administration of ipragliflozin decreases fatty acid synthesis via suppression of SREBP-1c and upregulated β-oxidation and improves hepatic steatosis in high-fat-diet-induced and leptin-deficient (ob/ob) obese mice irrespective of body weight reduction [16]. Another showed that liver inflammation, hepatocyte apoptosis, and area of fibrosis were improved by increasing β-oxidation and export of very-low-density lipoprotein in NASH model mice administered ipragliflozin [36]. Additionally, SGLT2I administration decreased hepatic proinflammatory cytokines and macrophage infiltration and inhibited inflammation and fibrosis in NASH model mice [37]. Therefore, the same effects might be associated with the actions of ipragliflozin in NAFLD patients.

Our study has several limitations. First, we did not perform a histological examination after ipragliflozin administration in NASH patients. Second, a successful FibroScan could not be performed in NASH patients with thick subcutaneous fat. Third, the study population was relatively small. Finally, our study lacked a placebo group. Therefore, future randomized controlled trials are necessary to evaluate the efficacy of ipragliflozin further in NAFLD patients.

Despite these limitations, our study revealed several important results. Ipragliflozin decreased AST and ALT levels and improved glycemic control in patients with biopsy-proven NASH and NAFLD diagnosed by ultrasonography. Moreover, the number of lipid droplets in the liver and body fat were both decreased in NASH patients without a decrease in muscle mass. In conclusion, our results indicate that ipragliflozin may be an effective new therapy for patients with NAFLD.

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