ORIGINAL RESEARCH

Efficacy and Safety of Luseogliflozin in Patients with Type 2 Diabetes Complicated by Hepatic Dysfunction: A Single-Site, Single-Arm, Open-Label, Exploratory Trial

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ABSTRACT

Introduction: Improvements in glycemic control and hepatic function are clinically important goals in the treatment of patients with type 2 diabetes mellitus (T2DM) complicated by hepatic dysfunction. The favorable effects of the sodium–glucose co-transporter inhibitor luseogliflozin on hepatic dysfunction were anticipated for humans. Nevertheless, few clinical studies have confirmed its real-world efficacy on hepatic dysfunction. This trial assessed the efficacy and safety of luseogliflozin in patients with T2DM complicated by hepatic dysfunction.

Methods: This prospective, single-site, single-arm, open-label, exploratory trial included 55 subjects with T2DM complicated by hepatic dysfunction. Subjects were administered luseogliflozin and observed for 52 weeks. The primary endpoints were the change in aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (γ-GTP), and hemoglobin A1c (HbA1c) from baseline to week 52. The secondary endpoints included body weight, body mass index (BMI), waist circumference, blood pressure, fasting plasma glucose (FPG), homeostatic model assessment beta (HOMA-β), homeostatic model assessment of insulin resistance (HOMA-IR), ferritin, Mac-2 binding protein (M2-BP), fatty liver index (FLI), fibrosis-4 (FIB-4) index, type IV collagen 7S domain, nonalcoholic fatty liver disease (NAFLD) fibrosis score, high-sensitivity C-reactive protein (hs-CRP), and interleukin-6 (IL-6).

Results: AST, ALT, γ-GTP, and HbA1c significantly decreased from baseline to week 52. Body weight, BMI, waist circumference, and FPG also significantly decreased. HOMA-IR significantly decreased but HOMA-β was unchanged. FLI, ferritin, M2-BP, and NAFLD fibrosis scores significantly decreased whereas the FIB-4 index and type IV collagen 7S domain did not significantly change. The hs-CRP and IL-6 levels did not significantly change.

Conclusion: Luseogliflozin administration in patients with T2DM complicated by hepatic dysfunction was well tolerated, did not worsen the hepatic condition, and might even be beneficial to improve hepatic function, reduce liver fat, and attenuate liver injury and fibrosis.

Trial Registration: This study was registered under the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR) (No. UMIN000025808) and the Japan Registry of Clinical Trials (jRCT) (No. jRCTs021180017).

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Key Summary Points

Why carry out this study?

Favorable effects of the sodium–glucose co-transporter inhibitor luseogliflozin on hepatic dysfunction are expected in humans.

Few clinical studies have confirmed the real-world efficacy of luseogliflozin in patients with type 2 diabetes mellitus complicated by hepatic dysfunction.

This trial assessed the efficacy and safety of luseogliflozin in patients with type 2 diabetes mellitus complicated by hepatic dysfunction.

What was learned from the study?

Luseogliflozin administration in patients with T2DM and hepatic dysfunction was well tolerated, did not worsen the hepatic condition, and might even be beneficial to improve hepatic function, reduce liver fat, and attenuate liver injury and fibrosis.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13643351.

INTRODUCTION

Previous studies have associated type 2 diabetes mellitus (T2DM) with hepatic dysfunction. The association between T2DM and hepatic dysfunction is classified as follows [1, 2]: (1) hepatic dysfunction caused by T2DM (nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), diabetic hepatopathy, or glycogenic hepatopathy exacerbated by T2DM); (2) T2DM caused by hepatic dysfunction (hepatic diabetes); and (3) hepatic dysfunction simultaneous with T2DM (chronic autoimmune hepatitis and autoimmune hepatic dysfunction). The prevalence of NAFLD in patients with T2DM was as high as 50–70% [3, 4]. Hepatic dysfunction was a major cause of death in patients with T2DM [5–7]. Therefore, improvements in glycemic control and hepatic function are clinically important goals in the treatment of patients with T2DM complicated by hepatic dysfunction.

Novel oral hypoglycemic agents known as sodium–glucose co-transporter 2 (SGLT2) inhibitors have been recently launched. They are widely used in T2DM treatment. SGLT2 inhibitors block renal glucose reabsorption, promote urinary glucose excretion, and lower plasma glucose levels in an insulin-independent manner. Hence, there is a reduced risk of induction of hypoglycemia associated with them. The safety of SGLT2 inhibitors in combination with other hypoglycemic agents has been confirmed [8]. Moreover, SGLT2 inhibitors confer cardiovascular protection [9, 10], reduce body weight [11], lower mean 24-h glucose levels [12], decrease blood pressure [13], and improve blood lipid factors [14].

Luseogliflozin is a type of SGLT2 inhibitor. It improved NASH in an animal T2DM model [15]. The favorable effects of luseogliflozin on hepatic dysfunction could be expected also in humans. Nevertheless, few clinical studies have confirmed its real-world efficacy on hepatic dysfunction [8, 14, 16]. Therefore, the aim of this study was to evaluate luseogliflozin efficacy and safety in patients with T2DM complicated by hepatic dysfunction.

METHODS

Study Design

A single-center, single-arm, open-label, prospective interventional, exploratory trial was conducted from November 2016 to September

2020. It was registered at the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR/registration No. UMIN000025808) and the Japan Registry of Clinical Trials (jRCT/registration No. jRCTs021180017). The study protocol was approved by the Institutional Review Board of Seino Internal Medical Clinic in November 2016 according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Ministry of Health, Labour and Welfare in Japan. As the Clinical Trials Act was dispensed, the study protocol was reinspected and approved by the Fukushima Medical University Certified Review Board and certification was procured from the Minister of Health, Labour and Welfare in Japan in March 2019. The study was conducted in accordance with the Declaration of Helsinki, the Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Ministry of Health, Labour and Welfare in Japan, the Clinical Trials Act, and other current legal regulations in Japan. Written informed consent was obtained from all participants after the study was fully explained to them. To minimize bias, data management and statistical analyses were conducted by third-party entities (DOT World Co. Ltd., Tokyo, Japan; Soiken Inc., Tokyo, Japan).

Patient Population

Patients with T2DM and hepatic dysfunction were included in the present trial. Patient inclusion criteria were (1) men and women aged at least 20 years and no greater than 80 years at the time of trial participation consent; (2) poor glycemic control despite diet and exercise therapy or treatment with hypoglycemic agents for at least 12 weeks; (3) HbA1c $\geq$ 6.5% and $\leq$ 9.5%; (4) BMI $\geq$ 20 kg/m^2; (5) provision of written informed consent; and (6) ALT $\geq$ 31 IU/ L. Patient exclusion criteria were (1) type 1 diabetes mellitus; (2) history of severe ketosis, diabetic coma, or precoma; (3) severe pre- or post-surgical infection or serious trauma; (4) estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2; (5) history of

stroke, myocardial infarction, or other serious cardiovascular complications requiring hospitalization for no more than 6 months prior to giving trial participation consent; (6) existing use of SGLT2 inhibitor; (7) pregnancy, breastfeeding, possible pregnancy, or intention to become pregnant; (8) history of hypersensitivity to luseogliflozin or any of its components; and (9) any conditions deemed inappropriate by the physicians for trial participation.

Study Intervention

As this study was a single-arm trial, randomization was not conducted. The subjects furnished informed consent and then began to consume 2.5 mg luseogliflozin orally once daily either before or after breakfast. The study intervention was conducted for 52 weeks and the subjects were observed at baseline (week 0) and at weeks 12, 24, and 52. All enrolled subjects were prohibited from using any SGLT2 inhibitor other than luseogliflozin during the trial. Moreover, enrolled subjects were not permitted to change the type, usage, or dose of any other therapeutic agents such as antiplatelet, antihypertensive, or antidyslipidemia drugs. They were not allowed to alter the type or degree of diet and exercise therapy during the study, provided that these treatments were safely regulated. Nevertheless, if the study subjects met the following criteria for discontinuation during the study period, the study intervention was discontinued; occurrence of adverse events that make the continuation of the study intervention difficult, occurrence of severe hypoglycemia, visit discontinuation or change of place of residence of the subject, consent withdrawal, use of prohibited concomitant agents, or other conditions that the attending physician considers to be inappropriate to continue the study intervention.

The medical examination by interview, blood collection, urine collection, and measurements of body weight, body mass index (BMI), waist circumference, blood pressure, and pulse were conducted at each observation point according to the observation schedule prespecified in the study protocol. Regarding the

subjects' background, drinking habit and smoking habit of the study subjects were investigated by the medical examination by interview, asking drink or smoke frequency as follows: none, once/weekly, 2–3 times/weekly, and 4 times or more/weekly.

Study Outcomes

The primary endpoints were the change in aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (γ-GTP), and hemoglobin A1c (HbA1c) level from baseline to week 52. The secondary endpoints were (1) changes in AST, ALT, γ-GTP, and HbA1c levels from baseline to weeks 12 and 24; (2) changes in fasting plasma glucose (FPG) level, homeostatic model assessment beta (HOMA-β), homeostatic model assessment of insulin resistance (HOMA-IR), body weight, BMI, waist circumference, blood pressure, NAFLD fibrosis score, fibrosis-4 (FIB-4) index, and fatty liver index (FLI) from baseline to weeks 12, 24, and 52; (3) changes in type IV collagen 7S domain, ferritin, Mac-2 binding protein (M2-BP), and high-sensitivity C-reactive protein (hs-CRP)) level from baseline to weeks 24 and 52; and (4) change in interleukin-6 (IL-6) level from baseline to week 52.

Sample Size Calculation and Statistical Analysis

Since this study was planned as an exploratory study, the target number of enrolled subjects was defined to be 50, based on the possible number of subjects who could give their consent following daily medical examinations at the Seino Internal Medical Clinic.

The primary and secondary endpoints were evaluated on the full analysis set (FAS) which includes all subjects assigned to a study intervention. However, subjects who did not receive the study agent were excluded from the FAS. Subjects for whom no data related to the efficacy endpoints could be obtained after study agent initiation were also excluded from the FAS. The per-protocol set (PPS) excluded subjects from the FAS if they presented with

substantial protocol violations such as eligible criteria nonconformance, use of prohibited drugs, and poor adherence to the study agent. The safety analysis included all treated patients. All two-sided tests were performed and $P < 0.05$ was considered as statistically significant. Summary statistics (number of subjects, mean, standard deviation, minima, median, and maxima) and changes from baseline were calculated for continuous data. A one-sample t test was conducted to identify the change from baseline for intragroup before-and-after comparison. Frequencies and proportions were calculated for the categorical data. Multiple logistic regression analysis was performed to test the relationship between the change in HbA1c and other factors from baseline to week 52. First, by using univariate regression analysis, variables which had a P value less than 0.05 were detected. By using these factors as explanatory variables, multiple regression analysis was performed. SAS version 9.4 (SAS, Cary, NC, USA) was used to perform all statistical analyses.

RESULTS

Baseline Characteristics of Study Participants

Between April 2017 and September 2018, 55 subjects were enrolled in this study and received the intervention (luseogliflozin administration). One subject discontinued the visit to the institution during the study. Five subjects discontinued luseogliflozin use because of adverse events during the study. Hence, 55 subjects were included in both the safety analysis set and the FAS (Fig. 1) and 49 subjects completed the study intervention. The baseline characteristics of the subjects are summarized in Table 1.

Primary Endpoints

The primary endpoints of this study were the change in AST, ALT, γ-GTP, and HbA1c levels from baseline to week 52. The AST, ALT, γ-GTP, and HbA1c significantly decreased from
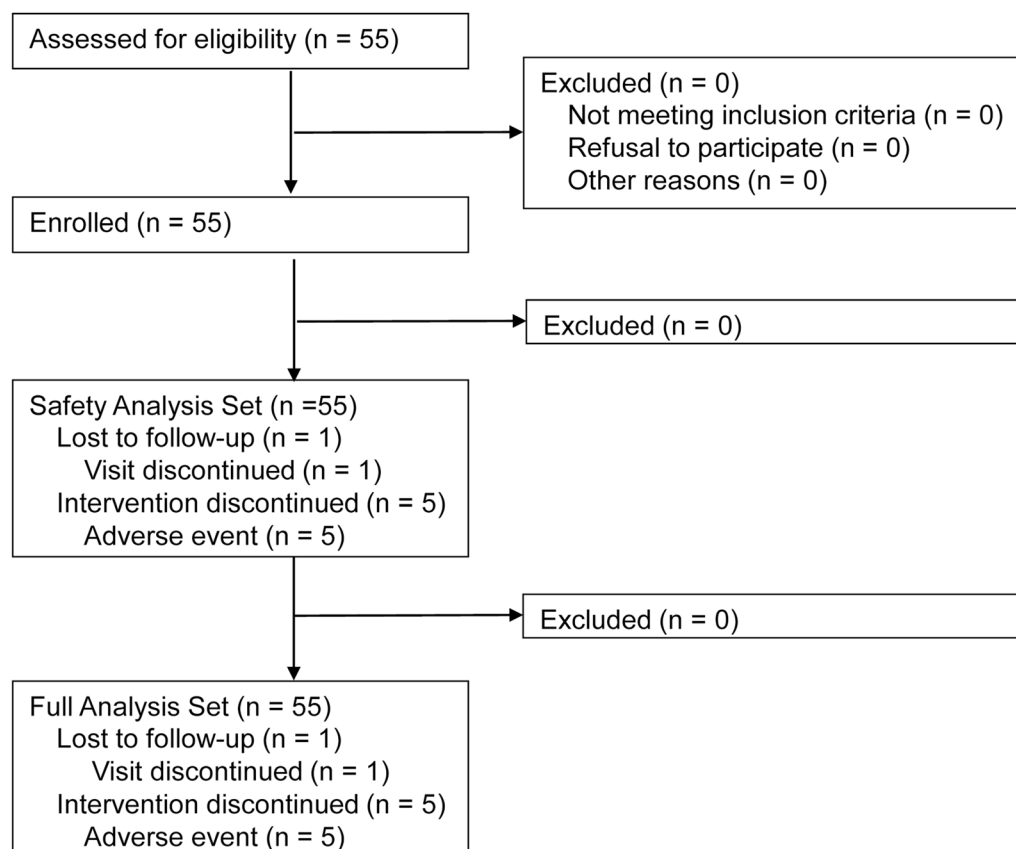
Fig. 1 Flowchart depicting study participant enrollment, allocation, and analysis. All 55 eligible subjects enrolled in this study were included and analyzed in the safety analysis set and full analysis set

baseline to week 52 (Fig. 2). The changes in AST, ALT, γ-GTP, and HbA1c from baseline to week 52 were $- 12.2 \pm 13.0$ IU/L $(P < 0.0001)$, $- 25.2 \pm 23.9$ IU/L $(P < 0.0001)$, $- 21.4 \pm 22.1$ IU/L $(P < 0.0001)$, and $- 0.6\% \pm 0.5\%$ $(P < 0.0001)$, respectively. The AST, ALT, γ-GTP, and HbA1c levels also significantly decreased from baseline to weeks 12 and 24 (Fig. 2). The changes in AST level from baseline were $- 8.9 \pm 11.1$ IU/L $(P < 0.0001)$ and $- 10.5 \pm 13.9$ IU/L $(P < 0.0001)$ at weeks 12 and 24, respectively. The changes in ALT level from baseline were $- 17.5 \pm 19.4$ IU/L $(P < 0.0001)$ and $- 21.0 \pm 26.0$ IU/L $(P < 0.0001)$ at weeks 12 and 24, respectively. The changes in γ-GTP level from baseline were $- 12.5 \pm 19.1$ IU/L $(P < 0.0001)$ and $- 12.8 \pm 26.7$ IU/L $(P = 0.0012)$ at weeks 12 and 24, respectively. The changes in HbA1c level from baseline were $- 0.5\% \pm 0.4\%$ $(P < 0.0001)$ and $- 0.5\% \pm$ 0.5% $(P < 0.0001)$ at weeks 12 and 24, respectively.

Hepatic Function Biomarkers

FLI is a surrogate liver fat marker. FLI significantly decreased from baseline to weeks 12, 24 and 52 (Fig. 3).

M2-BP is a surrogate hepatic fibrosis marker. M2-BP level decreased from baseline to weeks 24 and 52 (Fig. 3). The changes in M2-BP level from baseline were $- 0.06 \pm 0.18$ $(P = 0.0187)$ and $- 0.08 \pm 0.18$ $(P = 0.0027)$ at weeks 24 and 52, respectively.

NAFLD fibrosis score, FIB-4 index, and type IV collagen 7S domain are also hepatic fibrosis markers. The NAFLD fibrosis score significantly decreased from baseline to weeks 12 and 24 (Table 2). However, there was no significant change in NAFLD fibrosis score by

Table 1 Baseline characteristics of subjects

Characteristics	Mean ± standard deviation or n (%)
Age (years)	52.7 ± 11.4
Gender (male/female)	38 (69.1)/17 (30.9)
Height (cm)	165.6 ± 8.3
Body weight (kg)	80.4 ± 14.9
BMI (kg/m^2)	29.2 ± 4.0
Waist circumference (cm)	98.5 ± 9.9
Duration of diabetes mellitus	8.8 ± 6.4
Drinking habit	36 (65.5)
Smoking habit	24 (43.6)
Cerebrovascular complications	3 (5.5)
Diabetic complications	20 (36.4)
Diabetic nephropathy	14 (25.5)
Diabetic neuropathy	4 (7.3)
Diabetic retinopathy	5 (9.1)
Hypertension	30 (54.5)
Dyslipidemia	29 (52.7)
Antidiabetic agents	
Sulfonylurea	11 (20.0)
Biguanide	49 (89.1)
α-Glucosidase inhibitor	6 (10.9)
Glinide	1 (1.8)
Thiazolidinedione	1 (1.8)
DPP4 inhibitor	30 (54.5)
SGLT2 inhibitor	0 (0)
GLP-1 receptor agonist	1 (1.8)
Insulin	1 (1.8)
Combination agent	13 (23.6)
Antihypertensive agent	26 (47.3)
Antithrombotic agent	2 (3.6)

Table 1 continued

Characteristics	Mean ± standard deviation or n (%)
Lipid-lowering agent	22 (40.0)
Antihyperuricemic agent	4 (7.3)
Other concomitant agents	36 (65.5)

Data are presented as mean ± standard deviation or n (%) among 55 subjects in the full analysis set

BMI body mass index, *DPP4* dipeptidyl peptidase-4, *SGLT2* sodium–glucose co-transporter protein 2, *GLP-1* glucagon-like peptide 1

week 52. The FIB-4 index and the type IV collagen 7S domain did not significantly change from baseline.

Ferritin is a hepatic impairment biomarker. Its levels significantly decreased from baseline to weeks 24 and 52 (Table 2).

Inflammation Biomarkers

The hs-CRP and IL-6 levels did not significantly change from baseline either to week 24 and 52 (Table 2).

Vital Signs

Body weight, BMI, and waist circumstance significantly decreased from baseline to weeks 12, 24, and 52 (Table 2). In contrast, the systolic blood pressure significantly decreased only from baseline to week 12 and significant decreases disappeared after week 24. No significant changes were observed for diastolic blood pressure or pulse.

Glucose Metabolism

The fasting plasma glucose levels significantly decreased from baseline to weeks 12, 24, and 52 (Table 2). Plasma insulin and HOMA-IR
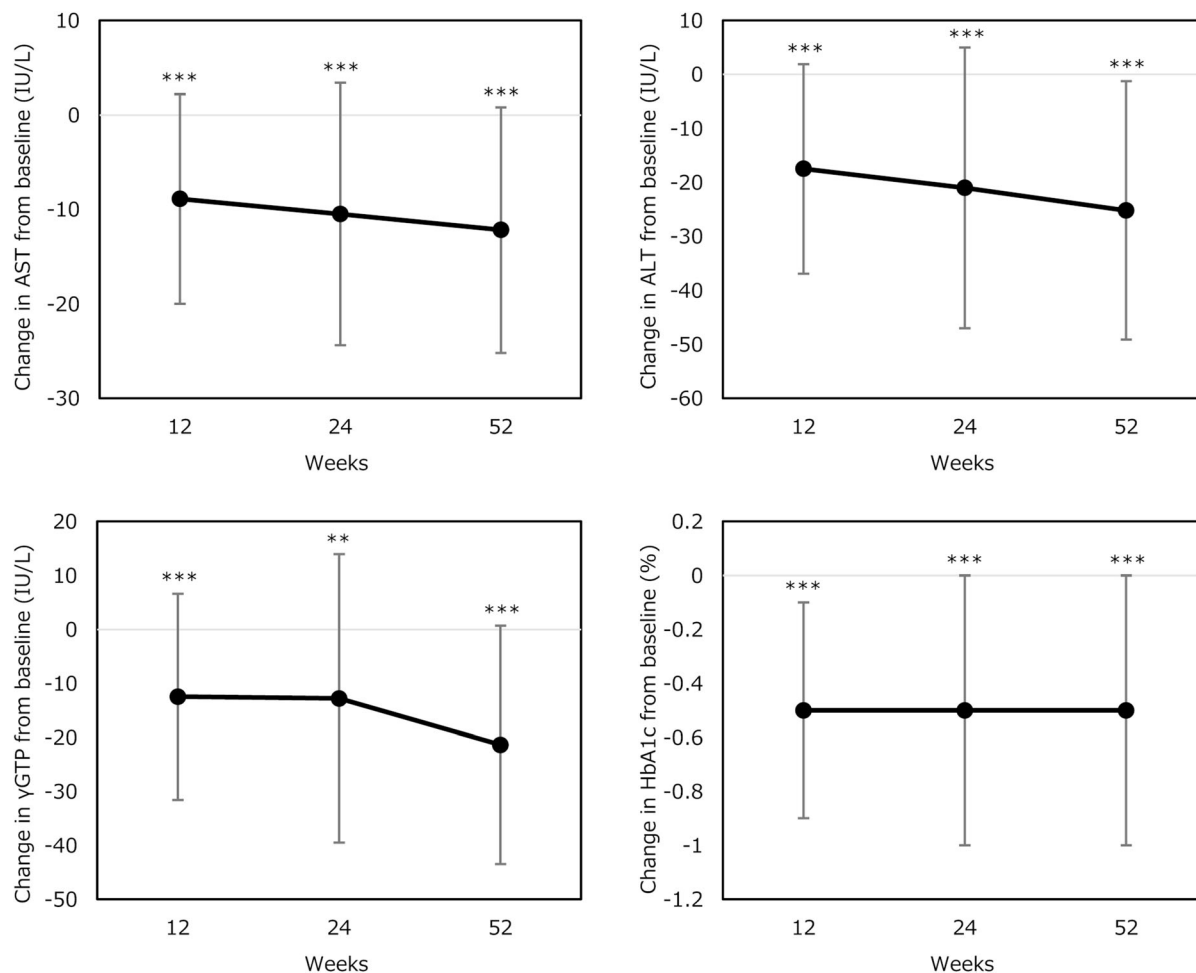
Fig. 2 Change from baseline in the primary endpoints (AST, ALT, γ-GTP, and HbA1c). Data are represented as mean ± standard deviation. *$P < 0.05$; **$P < 0.01$; and ***$P < 0.001$, respectively. AST aspartate aminotransferase, ALT alanine aminotransferase, γ-GTP gamma-glutamyl transpeptidase, HbA1c hemoglobin A1c

significantly decreased from baseline to weeks 12, 24, and 52. HOMA-β did not significantly change from baseline.

Correlation Between Change in HbA1c and Other Factors

By univariate regression analysis, the changes in AST, M2-BP, white blood cell (WBC), and type IV collagen 7S domain from baseline to week 52 were significantly correlated with the change in HbA1c from baseline to week 52. Using these factors as explanatory variables, multiple regression analysis was performed.

Change in AST and type IV collagen 7S domain from baseline to week 52 were significantly correlated with the change in HbA1c from baseline to week 52 (Table 3).

Safety Outcomes

Twenty-four adverse events were reported in 18 out of 55 subjects (32.7%) (Table 4). The most common adverse events were genital infection and dry skin (six subjects each; 10.9%). Four serious adverse events (facial paresis, venous thrombosis, Baker's cyst, and gastric cancer) were reported during the study. Nevertheless,
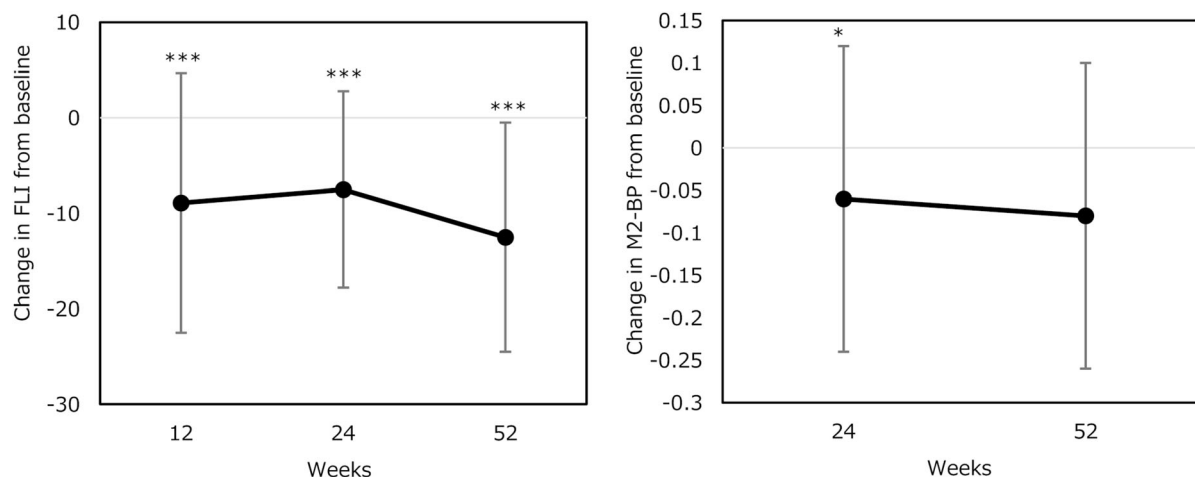
Fig. 3 Change from baseline in hepatic function biomarkers (FLI and M2-BP). Data are represented as mean ± standard deviation. *$P < 0.05$; **$P < 0.01$; and ***$P < 0.001$, respectively. FLI fatty liver index, M2-BP Mac-2 binding protein

none of them was considered to be related to luseogliflozin administration. No hypoglycemia or severe hypoglycemia was reported during the study.

DISCUSSION

The purpose of this study was to assess the efficacy and safety of the SGLT2 inhibitor luseogliflozin in patients with T2DM complicated by hepatic dysfunction. We observed improvement in glycemic control and the hepatic function biomarkers AST, ALT, and γ-GTP. Moreover, FLI (a surrogate liver fat marker), ferritin (a hepatic impairment biomarker), M2-BP, and the NAFLD fibrosis score (hepatic fibrosis biomarkers) were significantly improved in response to luseogliflozin administration.

Several previous studies in patients with T2DM showed that luseogliflozin administration decreased hepatic function biomarkers [8, 14, 16]. A recent single-arm LEAD trial in patients with T2DM and NAFLD demonstrated a significant decrease in hepatic function biomarkers [17]. The results of the present study were consistent with those of previous reports. The present study provided supportive evidence that luseogliflozin improved hepatic function in patients with T2DM complicated by hepatic dysfunction.

Additionally, this study revealed improvement in the hepatic fibrosis biomarkers M2-BP, NAFLD fibrosis score, and ferritin following luseogliflozin administration in patients with T2DM complicated by hepatic dysfunction. However, FIB-4 index score and type IV collagen 7S did not change significantly after luseogliflozin administration. The LEAD trial showed decrease in the AST, ALT, γ-GTP, and ferritin levels in patients with T2DM with NAFLD; however, the hepatic fibrosis markers FIB-4 index, NAFLD fibrosis score, type IV collagen 7S, and M2-BP were unchanged [17]. Hence, luseogliflozin may only be able to ameliorate hepatic dysfunction but not established NAFLD.

The beneficial effects of SGLT2 inhibitors on body weight and composition have been reported [18–21]. The present study demonstrated significant reduction in body weight, BMI, and waist circumstance after luseogliflozin administration. The surrogate liver fat marker FLI significantly decreased in the present study. This finding was consistent with that reported by previous studies which demonstrated decrease in liver fat following SGLT2 inhibitor treatment [22–24] and might explain the hepatic function improvement observed here.

This trial also disclosed that plasma insulin levels and HOMA-IR were significantly decreased by luseogliflozin administration. This finding was consistent with earlier reports of

Table 2 Clinical outcomes

Endpoint	Week	Measurement		Change		
		n	Mean ± SD	*n*	Mean ± SD	*P* value
NAFLD fibrosis score	0	55	4.1 ± 0.6			
	12	54	4.0 ± 0.8	54	− 0.2 ± 0.5	0.0225
	24	52	3.9 ± 0.6	52	− 0.5 ± 0.4	0.0005
	52	50	4.0 ± 0.7	50	− 0.1 ± 0.6	0.1178
FIB-4 index	0	55	3.1 ± 1.8			
	12	54	3.1 ± 1.5	54	− 0.1 ± 0.9	0.6897
	24	51	3.0 ± 1.4	51	− 0.1 ± 0.8	0.3621
	52	47	3.2 ± 1.6	47	0.2 ± 0.9	0.0774
Type IV collagen 7S domain (ng/mL)	0	55	4.6 ± 1.2			
	24	52	4.6 ± 0.8	52	0.0 ± 1.0	0.8387
	52	49	4.6 ± 0.7	49	0.1 ± 1.0	0.4492
Ferritin (ng/mL)	0	55	191.4 ± 144.9			
	24	52	123.9 ± 113.2	52	− 64.6 ± 73.1	< 0.0001
	52	49	113.6 ± 97.9	49	− 76.9 ± 74.2	< 0.0001
hs-CRP (mg/dL)	0	55	0.11 ± 0.13			
	24	52	0.09 ± 0.10	52	− 0.02 ± 0.10	0.1222
	52	49	0.08 ± 0.11	49	− 0.03 ± 0.13	0.0968
IL-6 (pg/mL)	0	55	2.1 ± 2.7			
	52	49	1.6 ± 1.2	49	− 0.3 ± 1.1	0.0847
Body weight (kg)	0	55	80.4 ± 14.9			
	12	53	77.5 ± 14.0	53	− 1.9 ± 1.3	< 0.0001
	24	52	78.0 ± 14.0	52	− 2.6 ± 1.8	< 0.0001
	52	50	77.6 ± 14.2	50	− 3.1 ± 2.5	< 0.0001
BMI (kg/m^2)	0	55	29.2 ± 4.0			
	12	53	28.3 ± 4.0	53	− 0.7 ± 0.5	< 0.0001
	24	52	28.3 ± 3.8	52	− 0.9 ± 0.7	< 0.0001
	52	50	28.0 ± 3.8	50	− 1.1 ± 0.9	< 0.0001
Waist circumstance (cm)	0	55	98.5 ± 9.9			
	12	53	97.0 ± 10.2	53	− 1.6 ± 3.0	0.0003
	24	52	97.2 ± 9.9	52	− 1.6 ± 3.2	0.0006
	52	47	96.7 ± 10.3	47	− 2.4 ± 3.2	< 0.0001
Systolic blood pressure (mm Hg)	0	55	131.9 ± 11.9			

Table 2 continued

Endpoint	Week	Measurement		Change		
		n	Mean ± SD	*n*	Mean ± SD	*P* value
	12	53	127.4 ± 11.6	53	− 4.4 ± 13.0	0.0172
	24	52	130.5 ± 11.2	52	− 1.0 ± 13.2	0.6019
	52	50	129.8 ± 12.5	50	− 1.9 ± 14.6	0.3565
Diastolic blood pressure (mm Hg)	0	55	81.3 ± 9.5			
	12	53	79.2 ± 8.8	53	− 2.1 ± 9.4	0.1178
	24	52	78.7 ± 8.7	52	− 2.4 ± 9.4	0.0731
	52	50	79.8 ± 8.5	50	− 1.4 ± 10.2	0.3223
Pulse	0	53	75.0 ± 10.7			
	12	52	74.3 ± 11.8	50	− 0.3 ± 9.7	0.8163
	24	52	73.7 ± 11.6	50	− 1.3 ± 8.6	0.2809
	52	48	73.8 ± 12.0	46	− 0.8 ± 8.1	0.4930
Fasting plasma glucose (mg/dL)	0	55	148.8 ± 20.7			
	12	54	131.3 ± 17.7	54	− 17.9 ± 15.5	< 0.0001
	24	52	133.2 ± 23.5	52	− 16.8 ± 20.2	< 0.0001
	52	50	130.4 ± 19.8	50	− 18.8 ± 19.5	< 0.0001
Plasma insulin (μU/mL)	0	55	12.8 ± 7.0			
	12	53	10.9 ± 5.7	53	− 2.0 ± 4.6	0.0026
	24	52	11.0 ± 5.8	52	− 2.0 ± 5.0	0.0065
	52	49	11.1 ± 6.9	49	− 1.7 ± 5.4	0.0323
HOMA-β (%)	0	55	55.6 ± 30.1			
	12	53	59.3 ± 28.3	53	3.8 ± 25.3	0.2802
	24	52	61.0 ± 32.1	52	5.7 ± 29.4	0.1710
	52	49	61.5 ± 35.3	49	6.8 ± 26.0	0.0714
HOMA-IR	0	55	4.8 ± 2.7			
	12	53	3.6 ± 2.1	53	− 1.2 ± 1.7	< 0.0001
	24	52	3.7 ± 2.2	52	− 1.2 ± 1.8	< 0.0001
	52	49	3.6 ± 2.4	49	− 1.1 ± 2.2	0.0007

Data are presented as *n* and mean ± standard deviation

NAFLD fibrosis score nonalcoholic fatty liver disease fibrosis score, *FIB-4* fibrosis-4, *hs-CRP* high-sensitivity C-reactive protein, *IL-6* interleukin-6, *BMI* body mass index, *HOMA-β* homeostatic model assessment beta, *HOMA-IR* homeostatic model assessment of insulin resistance

Table 3 Correlation between change in HbA1c and other factors from baseline to week 52

Factor	Partial regression coefficient (95% confidence interval)	P value
AST	0.0110 (0.0014 to 0.0205)	0.0254
M2-BP	0.5722 (− 0.1118 to 1.2563)	0.0987
WBC	− 0.0098 (− 0.0200 to 0.0004)	0.0599
Type IV collagen 7S domain	0.1304 (0.0115 to 0.2493)	0.0324

Data are presented as partial regression coefficient (95% confidence interval)

AST aspartate aminotransferase, *M2-BP* Mac-2 binding protein, *WBC* white blood cell

Table 4 Adverse events

Adverse event	Frequency
Death	0 (0)
Any adverse events	18 (32.7)
Serious adverse event	4 (7.3)
Genital infection	6 (10.9)
Dry skin	6 (10.9)
Balanitis	1 (1.8)
Dehydration	1 (1.8)
Skin rash	1 (1.8)
Constipation	1 (1.8)
Genital itching	1 (1.8)
Facial paresis	1 (1.8)
Arthritis	1 (1.8)
Disc herniation (low back pain)	1 (1.8)
Venous thrombosis	1 (1.8)
Pulled muscle	1 (1.8)
Baker's cyst	1 (1.8)
Gastric cancer	1 (1.8)

Data are presented as *n* (%)

reductions in HOMA-IR (insulin resistance improvement) by SGLT2 inhibitors [25, 26]. In contrast, HOMA-β did not significantly improve in the present study. SGLT2 inhibitors apparently improved pancreatic β-cell function in animal models [27]. However, no study has evaluated the effects of SGLT2 inhibitors on pancreatic β-cell function in humans. A Korean clinical study showed that a group responding well to SGLT2 inhibitors presented with relatively higher HOMA than the group responding poorly to SGLT2 inhibitors. Nevertheless, the HOMA-β level was not associated with SGLT2 inhibitor responsiveness [28]. The results of this study suggested that SGLT2 inhibitors improved insulin resistance but not insulin secretion in the pancreatic β-cells of patients with T2DM.

Here, luseogliflozin administration did not improve inflammation because it did not lower the hs-CRP or IL-6 levels. It has been previously reported that SGLT2 inhibitors suppress inflammation in animal models [29, 30]. However, only a few human trials reported an association between SGLT2 inhibitors and inflammation [31, 32]. Further studies are needed to assess the efficacy of SGLT2 inhibitors in attenuation of inflammation.

By univariate regression analysis, the changes in AST, M2-BP, WBC, and type IV collagen 7S domain from baseline to week 52 were significantly correlated with the change in HbA1c from baseline to week 52. By multiple regression analysis using these factors as explanatory variables, changes in AST and type IV collagen 7S domain were again significant and independent determinants of change in HbA1c. It was reported that change in HbA1c was significantly associated with improvement of hepatic fibrosis [33]. Another study demonstrated that the fibrosis score were significantly improved in ALT responders [34]. Since the hepatic function biomarkers including AST, ALT, and γ-GTP, the glycemic control, and hepatic fibrosis

biomarkers were improved by administration of luseogliflozin to patients with T2DM and hepatic dysfunction in this study, the results in this study were consistent with the previous reports. Inhibition of SGLT2 protein by administration of SGLT2 inhibitor causes improvement of insulin resistance and calorie loss by urinary glucose excretion, resulting enhancement of beta-oxidation, release of very low density lipoprotein (VLDL) from liver, and decrease in hepatic fat, hepatic lipotoxicity, hepatic inflammation, and hepatic fibrosis [35]. These might be the mechanism by which hepatic fibrosis was attenuated by administration of luseogliflozin in patients with T2DM and hepatic dysfunction.

No serious adverse events associated with luseogliflozin were detected in the present study. Genital infection and dry skin were the most commonly observed adverse reactions here but they are well-known side effects of SGLT2 inhibitors. There were no remarkable occurrences of any unknown side effects. No hypoglycemia was recorded during this trial. It was reported earlier that SGLT2 inhibitors lowered plasma glucose in an insulin-independent manner and posed a low risk of inducing hypoglycemia [36]. Moreover, recent large-scale clinical trials demonstrated that SGLT2 inhibitors prevented mortality, macrovascular complications, and renal impairment progression associated with T2DM [9, 10]. Overall, SGLT2 inhibitors are well tolerated in patients with T2DM and hepatic dysfunction.

The study protocol described the enrollment of 50 subjects. Nevertheless, it was feasible for the Seino Internal Medical Clinic to support the enrollment of 55 subjects. The over-registration was reported to the Fukushima Medical University Certified Review Board and approved by them. The last five subjects were excluded and the results of the present study were re-analyzed with only 50 participants. Once again, all primary endpoints (ALT, AST, γ-GTP, and HbA1c) showed significant improvements. Therefore, over-registration by five patients did not influence the outcome of this trial and all 55 subjects were included in the FAS and analyzed.

This study had several limitations. First, there were relatively few enrolled subjects in this trial and it was conducted in only one clinical institution (Seino Internal Medical Clinic) in Japan. Second, it was a single-arm trial. Further larger confirmatory trials are required to confirm the effect of luseogliflozin in patients with T2DM complicated by hepatic dysfunction. Third, the eligibility criterion hepatic dysfunction was defined only by the ALT level (≥ 31 IU/L) at enrollment in this study to simplify the study design and to enroll the study subjects with similar disease condition. Further trials are required to confirm the effect of luseogliflozin in patients with T2DM complicated by hepatic dysfunction of other disease conditions. These constraints may limit the generalizability of this study and large-scale, multicenter randomized controlled trials are required to validate its findings.

CONCLUSIONS

Luseogliflozin administration in patients with T2DM complicated by hepatic dysfunction was tolerated, did not worsen the hepatic condition, and might even be beneficial to improve hepatic function, reduce liver fat, and attenuate liver injury and fibrosis. Further larger confirmatory trials are required to confirm the effect of luseogliflozin in patients with T2DM complicated by hepatic dysfunction.

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