

Differential Effects of SGLT-2 Inhibitors on Liver Function and Nocturia in Patients with Type 2 Diabetes: A Randomized Controlled Trial

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Purpose: This study investigated whether sodium-glucose cotransporter-2 inhibitors (SGLT-2is) improve liver function as a class effect and evaluated their effect on nocturia in patients with type 2 diabetes and metabolic dysfunction-associated steatotic liver disease (MASLD).

Methods: A total of 135 patients with type 2 diabetes and MASLD were randomly assigned to receive tofogliflozin (20 mg/day), dapagliflozin (5 mg/day), or empagliflozin (10 mg/day). Primary outcomes included changes in liver function and fibrosis markers—various transferases, fibrosis-4 index, mac-2 binding protein glycan isomer, and shear wave speed—along with nocturia frequency. Secondary outcomes were glycemic control, body weight, and lipid profiles. Patients were followed for seven months.

Results: The participants had a mean age of 61 years; 43% were female, HbA1c level was 8.7%, and the frequency of nocturia was 0.6 times. All three SGLT-2is significantly improved liver function markers, with no differences between groups. However, nocturia frequency significantly increased with empagliflozin (1.7 times) and dapagliflozin (1.9 times; both $p < 0.001$) but not with tofogliflozin (0.8 times; $p = 0.503$). Tofogliflozin resulted in a significantly smaller nocturia increase than the other two drugs ($p < 0.001$). However, this significant difference persisted up to 1 month; from 3 months onward, urinary frequency improved in all groups, and the difference was not observed. Glycemic control, body weight, and lipid profiles improved similarly across all groups.

Conclusion: SGLT-2is improve liver function as a class effect, but their impact on nocturia frequency differs. Tofogliflozin, likely due to its shorter half-life, has the most favorable nocturia profile and may be preferable for patients at risk. The UMIN Clinical Trial Registry number for this study is UMIN000054278; Clinical Trials Registry date 28/04/2024.

Keywords: type 2 diabetes, sodium-glucose cotransporter-2 inhibitors, nocturia, metabolic dysfunction-associated steatotic liver disease

Introduction

Sodium-glucose cotransporter-2 inhibitors (SGLT-2is) were initially introduced as treatments for type 2 diabetes but have since shown utility in various areas, such as preventing and improving renal and heart failure.^{1–4} Consequently, the use of SGLT-2is has expanded across multiple fields. Recently, studies have highlighted their efficacy in addressing fatty liver disease.^{5–7} Approximately 65% of patients with type 2 diabetes are estimated to have metabolic dysfunction-associated steatotic liver disease (MASLD).^{8,9} Moreover, the prevalence of metabolic dysfunction-associated steatohepatitis (MASH) in these patients can be as high as 66.44%,⁸ indicating that a considerable portion of MASLD in these patients corresponds to MASH. If left untreated, MASH can lead to progressive fibrosis, increasing the risk of severe liver failure

and cardiovascular events.^{10–12} Therefore, improving liver function is as critical a therapeutic goal as glycemic control in patients with diabetes.

However, SGLT-2is are associated with several side effects, and frequent urination is one of the most common, affecting approximately 5% of patients who are prescribed these drugs.¹³

In particular, nocturia in older adults can lead to sleep disturbances because of nighttime awakenings, reduced quality of life,^{14,15} and even increased risks of depression and dementia,¹⁶ as well as falls and fractures.^{17,18} Therefore, addressing this issue is a critical challenge.

In this study, we investigated whether the fatty liver improvement effects of SGLT-2i differ by individual drugs or represent a class effect (a common effect across all drugs in this group), using three different SGLT-2is for evaluation. In addition, we focused on the fact that tofogliflozin has the shortest half-life in the blood and the shortest duration of action among SGLT-2is,¹⁹ and investigated whether its effect on nocturia differs from that of other SGLT-2is.

Materials and Methods

Study Design and Participants

The participants in this study were adults aged 30 years or older who were diagnosed with type 2 diabetes and fatty liver and were classified as having MASLD. Type 2 diabetes is diagnosed when at least two of the following criteria are fulfilled: a fasting plasma glucose level of 126 mg/dL (7.0 mmol/L) or higher, a 2-hour plasma glucose level of 200 mg/dL (11.1 mmol/L) or higher during a 75-g oral glucose tolerance test, a random plasma glucose of 200 mg/dL (11.1 mmol/L) or higher, and a hemoglobin A1c level of 6.5% (48 mmol/mol) or higher.²⁰ Alternatively, patients who have already been diagnosed with type 2 diabetes based on the above tests. In addition, lipid droplets in more than 5% of hepatocytes, using ultrasonography, are defined as steatosis, referred to as fatty liver.²¹ Currently, hepatic steatosis involving more than 5% of the liver parenchyma can be diagnosed using B-mode ultrasonography.^{22,23}

SGLT-2is were initiated or added to the treatment regimen for patients with HbA1c levels $\geq 7.5\%$ (58 mmol/mol). MASLD was diagnosed according to the presence of fatty liver and at least one of the following five criteria:²⁴ 1. a BMI of ≥ 23.0 kg/m² or a waist circumference ≥ 94 cm for men and ≥ 80 cm for women; 2. prediabetes or diabetes treated with anti-diabetic medication; 3. blood pressure $\geq 130/85$ mmHg or treatment with antihypertensive medication; 4. triglyceride (TG) levels ≥ 150 mg/dL or treatment with lipid-lowering medication; and 5. high-density lipoprotein cholesterol (HDL-C) levels ≤ 40 mg/dL for men or ≤ 50 mg/dL for women, or treatment for low HDL-C levels.

The exclusion criteria included patients already receiving SGLT-2is, those using insulin, and individuals with severe liver cirrhosis, severe renal dysfunction, pregnancy, or severe mental illness. In addition, patients with conditions known to cause nocturia, such as prostatic disorders or uterine prolapse, were excluded from the study.

Randomization

Eligible participants were randomized using a permuted block method stratified by age (≥ 65 years or < 65 years), sex (male or female), HbA1c levels ($\geq 9.0\%$ or $< 9.0\%$ [≥ 75 mmol/mol or < 75 mmol/mol]), body weight (BMI ≥ 25.0 or < 25.0 kg/m²), and duration of diabetes (≥ 10 years or < 10 years). The participants were assigned to one of the following three groups in a 1:1:1 ratio: tofogliflozin group (Tofo group), empagliflozin group (Empa group), or dapagliflozin group (Dapa group). This trial is a prospective, randomized, open-label, blinded endpoint (PROBE) study conducted at a single center. The evaluation of liver fibrosis markers and nocturia frequency was independently performed by physicians and research staff from the adjudication committee, both of whom were blinded to treatment allocation.

Study Treatment

In the Tofo group, the participants received tofogliflozin at a dose of 20 mg. In the Empa group, the participants received empagliflozin at a dose of 10 mg. In the Dapa group, the participants received dapagliflozin at a dose of 5 mg. All these SGLT-2is were administered orally after breakfast.

During the study period, discontinuation of these SGLT-2is or the addition of other medications was not permitted unless adverse events occurred. The participants were followed up at outpatient visits initially after 1 month and

subsequently every 2 months for a total of 6 months, resulting in a 7-month observation period. At each visit, measurements of height, weight, BMI, waist circumference, blood pressure, blood tests, body composition, and ultrasound elastography were conducted.

Outcomes

The primary endpoints were changes in the frequency of nocturia and liver function markers, namely aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (γ -GPT), fibrosis-4 (FIB-4) index, and mac-2 binding protein glycan isomer (M2BPGi). In addition, liver fibrosis was evaluated using ultrasound elastography (Aplio i700, Canon Medical Systems, Tokyo). Shear wave speed measurements were interpreted as follows: values between 1.00 and 1.66 m/sec were classified as fibrosis grade (F) 0–1 (normal to mild fibrosis), with higher values indicating progression of fibrosis, ie, increased F score.^{25–27}

Nocturia was defined as waking to urinate at least once during the night,²⁸ with “nighttime” defined as the time between 11:00 pm and 5:00 am in this study.

Secondary endpoints included changes in HbA1c levels, fasting blood glucose, body weight, waist circumference, the lipid profile, and blood pressure. This study was conducted with the approval of the Institutional Review Board (IRB) of Shinkomonji Hospital. Written informed consent was obtained from all of the participants before enrollment. In addition, we confirmed that all research was performed following relevant guidelines/regulations.

This study has been performed in compliance with the Declaration of Helsinki. The trial protocol was registered with the UMIN Clinical Trial Registry (<https://www.umin.ac.jp/ctr/>) under the number UMIN000054278, with an initial registration date of 28/04/2024. The trial protocol is available in the [Supplementary Material](#) accompanying this manuscript.

Statistical Analyses

The sample size was calculated on the basis of the assumption that nighttime was defined as from 11:00 pm to 5:00 am, with the frequency of nighttime urination (nocturia) estimated to be 0.8 times in the Tofo group and 2.1 times in the Empa and Dapa groups. Nocturia frequency was calculated using a method based on the results of a pilot study (data not shown). Assuming a standard deviation of 2, an α error of 0.05, a statistical power of 0.8, and a 10% dropout rate over the 7-month follow-up, a 1:1:1 allocation required 43 participants in each group, resulting in a total sample size of 129 participants. Regarding the baseline characteristics, continuous variables are expressed as the mean $\pm$ standard deviation for descriptive analysis, and categorical variables are expressed as frequencies (%). To examine whether there were any variations in the samples between the groups at baseline, a test of homogeneity of variance (F-test) was conducted. Comparisons of continuous variables between the three groups at baseline and at each time point (1, 3, 5, and 7 months) were performed using an analysis of variance (ANOVA) with Dunnett’s test, and the Tofo group was set as the control. Temporal changes in continuous variables within each group were assessed using an ANOVA with Dunnett’s test, setting the baseline values as the control. In all cases, comparisons of categorical variables were performed using an $m \times n$ chi-square test. In this study, a p -value < 0.05 was not considered significant. Instead, p -values adjusted using the Bonferroni correction (ie, 0.05 divided by the total number of pairwise comparisons) were considered significant under the concept of multiple comparisons. Statistical analyses were performed using SPSS ver. 17.0 (SPSS Inc., Chicago, IL, USA) and R software (version 4.1.1).

Results

Baseline Characteristics

The participants were recruited between April and the end of September 2024. A total of 135 participants were randomly assigned to the three groups ([Figure 1](#)). The participants had a mean age of 61 years and 43% were female. The mean BMI was 24.5 kg/m², the mean HbA1c level was 8.7%, the mean FIB-4 index was 1.84, the mean shear wave speed was 1.51 m/sec, and the mean number of nocturia episodes was 0.6 times. No significant differences in these variables were observed between the groups ([Table 1](#)).

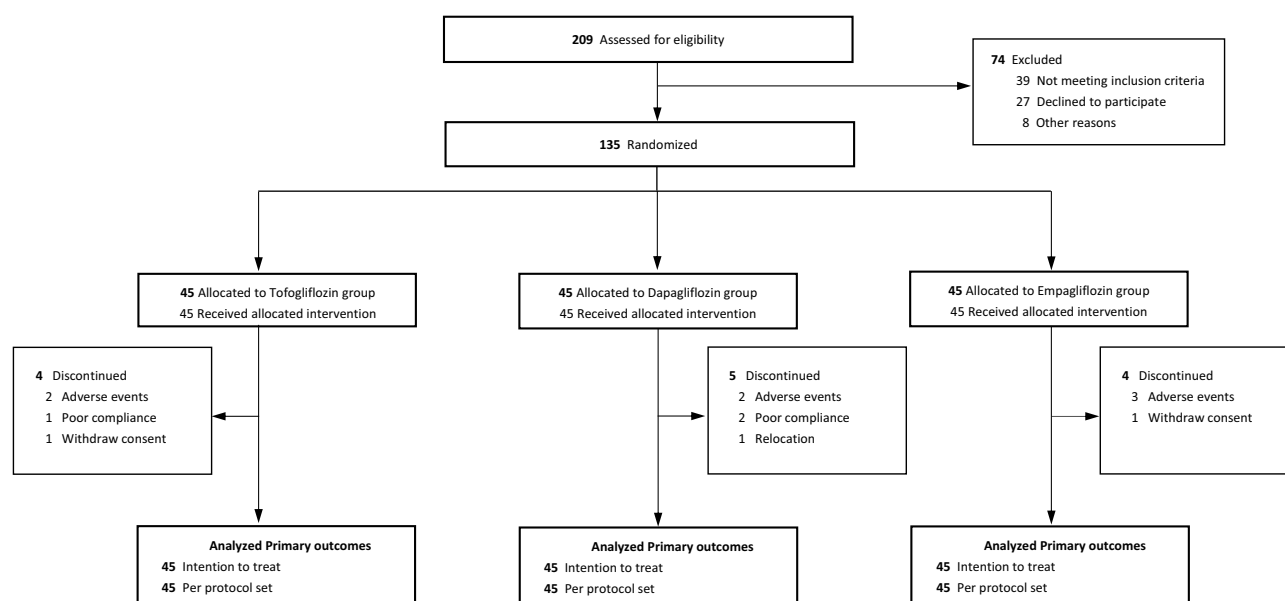


Figure 1 Screening, randomization, and follow-up. A total of 135 participants were randomly assigned to three groups of 45, each receiving a prescribed drug: the Tofo group received 20 mg of tofogliflozin, the Dapa group received 5–10 mg of dapagliflozin, and the Empa group received 10–25 mg of empagliflozin. All participants were followed for seven months. During the study, there were dropouts: 4 in the Tofo group, 5 in the Dapa group, and 4 in the Empa group. However, all participants were included in the analysis according to the intention-to-treat and per-protocol set criteria.

Primary Outcome of MASLD

All groups showed significant reductions in AST, ALT, and γ -GTP levels and the FIB-4 index compared with baseline (all p -values <0.05). In addition, a gradual reduction in shear wave speed-based fibrosis grade was observed compared with baseline across all groups (all p -values <0.05). However, no significant differences in these variables were found between the three groups. Furthermore, no significant changes in M2BPGi levels were observed in any group compared with baseline (Figure 2).

Table 1 Baseline Characteristics

	Tofogliflozin (n=45)	Dapagliflozin (n=45)	Empagliflozin (n=45)	<i>p</i> value
Age – years	61.3 ± 4.1	60.9 ± 4.0	62.8 ± 4.3	0.714
Female sex (%)	19 (42.2)	22 (48.9)	17 (37.8)	0.563
Body mass index – kg/m ²	24.6 ± 4.8	24.9 ± 4.9	24.1 ± 4.5	0.832
Waist circumference male/female – cm	92.3 ± 15.3 / 82.4 ± 13.7	93.5 ± 15.6 / 81.1 ± 13.3	92.9 ± 15.1 / 83.5 ± 13.9	0.854 / 0.761
Blood pressure – mmHg	135 ± 22.4 / 86 ± 12.5	139 ± 24.7 / 88 ± 14.0	137 ± 23.4 / 82 ± 12.6	0.487 / 0.396
Fasting plasma glucose – mg/dl	156 ± 17.3	159 ± 19.1	152 ± 15.8	0.773
HbA1c – % (mmol/mol)	8.7 ± 1.7 (71 ± 13.9)	8.9 ± 1.8 (73 ± 14.8)	8.5 ± 1.6 (69 ± 13.0)	0.584
Triglycerides – mg/dl	157.2 ± 24.8	161.3 ± 25.3	159.4 ± 22.7	0.603
HDL-cholesterol male/female – mg/dl	44.5 ± 9.3 / 50.3 ± 10.1	41.1 ± 8.6 / 51.6 ± 11.4	42.9 ± 9.5 / 53.7 ± 10.7	0.527 / 0.691
LDL-cholesterol – mg/dl	134.5 ± 22.6	131.9 ± 21.4	137.8 ± 22.9	0.418
AST – IU	40.6 ± 10.2	41.7 ± 10.5	43.9 ± 11.0	0.525

(Continued)

Table 1 (Continued).

	Tofogliflozin (n=45)	Dapagliflozin (n=45)	Empagliflozin (n=45)	p value
ALT – IU	44.3 ± 11.9	43.9 ± 10.7	45.5 ± 12.2	0.624
γ-GTP – IU	77.2 ± 15.3	82.1 ± 16.4	79.6 ± 15.8	0.327
Platelet – ×10 ⁴ /μL	19.3 ± 7.6	20.2 ± 8.4	17.6 ± 7.1	0.515
FIB-4 index	1.86 ± 0.31	1.79 ± 0.29	1.88 ± 0.34	0.839
M2BPGi	0.95 ± 0.15	0.92 ± 0.12	0.97 ± 0.17	0.877
Shear wave speed – m/sec	1.54 ± 0.19	1.49 ± 0.20	1.52 ± 0.21	0.652
Already-prescribed drugs				
Sulfonylurea (%)	8 (17.8)	6 (13.3)	5 (11.1)	0.826
Biguanide (%)	23 (51.1)	25 (55.6)	22 (48.9)	0.812
DPP-4i (%)	27 (60.0)	23 (51.1)	25 (55.6)	0.698
Glinide (%)	7 (15.6)	5 (11.1)	8 (17.7)	0.824
α-glucosidase inhibitor (%)	5 (11.1)	6 (13.3)	7 (15.6)	0.930
GLP-1RA (%)	7 (15.6)	8 (17.8)	6 (13.3)	0.938
Frequency of nocturia – times	0.6 ± 0.3	0.4 ± 0.3	0.5 ± 0.3	0.607

Notes: Data are presented as the percentage for binary variables and mean ± SD for continuous variables.

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, gamma-glutamyl transpeptidase; FIB-4, fibrosis-4; M2BPGi, mac-2 binding protein glycan isomer; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist.

Primary Outcome of the Frequency of Nocturia

In the Empa and Dapa groups, the frequency of nocturia significantly increased to 1.7 and 1.9 times, respectively, 1 month after starting medication compared with baseline. In contrast, the Tofo group showed an increase in the frequency of nocturia by only 0.8 times, which was not statistically significant. Consequently, the Tofo group showed a significantly lower frequency of nocturia than the other two groups ($p < 0.001$). This difference persisted until 3 months after the initiation of treatment; however, the frequencies were 1.3, 1.2, and 0.7 times, respectively, with a p-value of 0.010, which did not meet the significance threshold after Bonferroni correction ($p < 0.00227$). In addition, the difference diminished after the fifth month. Over time, the frequency of nocturia decreased in all three groups, with no significant changes from baseline or differences between the groups (Figure 2).

Secondary Outcomes

All three groups showed a significant reduction in weight and waist circumference compared with baseline, with no significant differences between the groups. No significant changes in systolic or diastolic blood pressure were observed in any group compared with baseline. Fasting plasma glucose and HbA1c levels were significantly decreased in all three groups compared with baseline. While the Dapa and Empa groups showed a slight trend of a greater reduction in these variables than the Tofo group, no significant differences were observed between the groups. A significant reduction in TG levels was observed in all three groups, with no significant intergroup differences. In females, no significant changes in HDL-C levels were observed in any group. In contrast, in males, all three groups showed a significant increase in HDL-C levels at 1 month compared with baseline, with no differences between the groups (Figure 3). Low-density lipoprotein-cholesterol levels remained unchanged in all groups compared with baseline, with no difference between the sexes (data not shown).

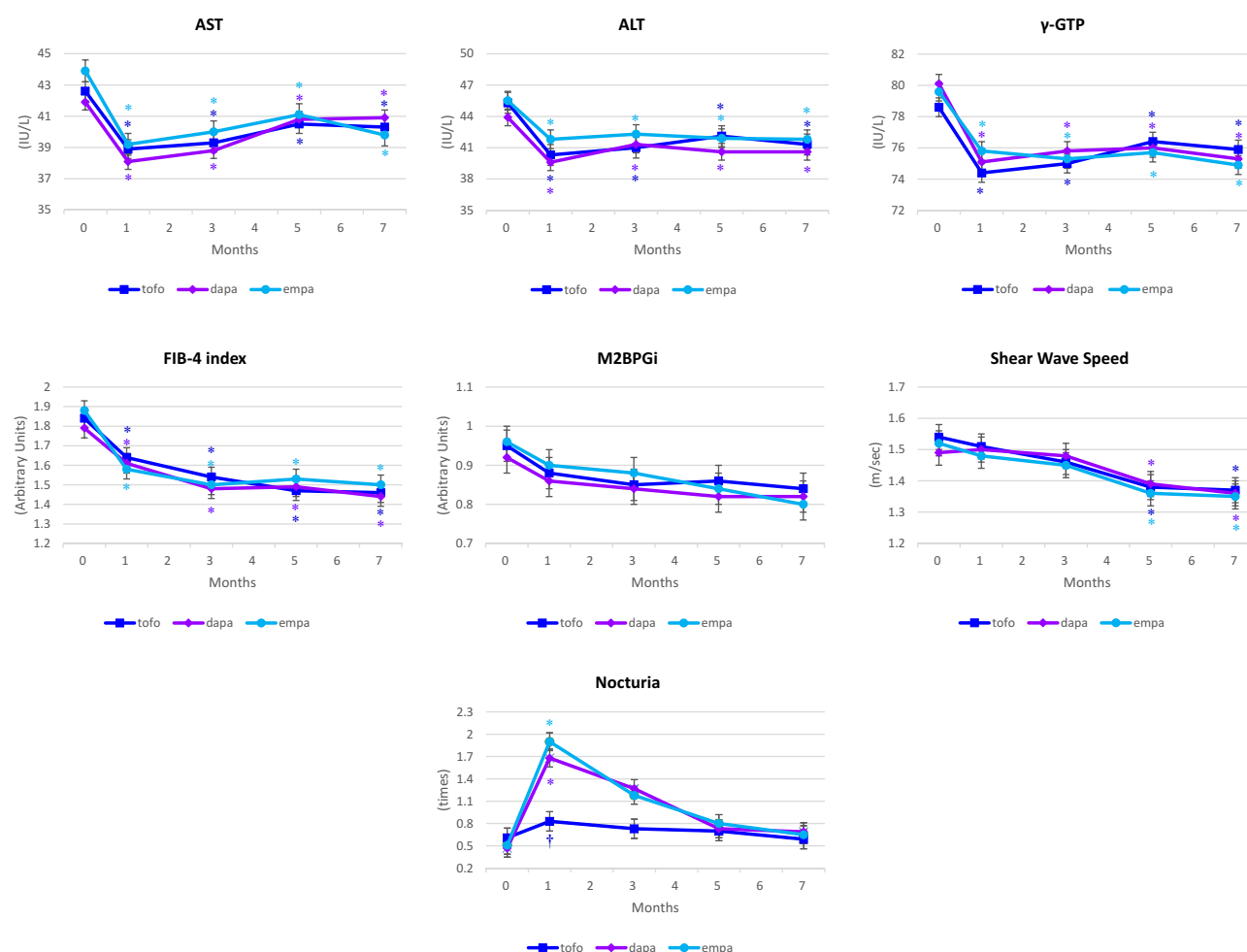


Figure 2 Changes in liver function and nocturia frequency with SGLT-2i treatment. Blue square, tofogliflozin group; purple diamond, dapagliflozin group; sky-blue circle, empagliflozin group. T-bars showed the standard deviations. * To assess time effects using analysis of variance followed by Dunnett's test, baseline measurements (0 months) were compared with those at 1, 3, 5, and 7 months, in each of the three groups. † Comparisons between the Tofo group and the Dapa and Empa groups were conducted at each time point (0, 1, 3, 5, 7 months). The Bonferroni correction defined statistical significance as $p < 0.05 / ([4 \times 3] + [2 \times 5]) = 0.00227$. Therefore, * and † denote $p < 0.00227$. **Abbreviations:** AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GPT, gamma-glutamyl transpeptidase; FIB-4, fibrosis-4; M2BPGi, mac-2 binding protein glycan isomer.

Sub-Analysis

A sub-analysis was conducted by stratifying the participants according to diabetes duration, age, baseline HbA1c levels, and sex. Based on the baseline distributions, participants were categorized into tertiles: 33–59, 60–71, and 72–89 years for age, and 7.5–8.9%, 9.0–10.3%, and 10.4–12.4% for HbA1c levels.

This analysis revealed that older age and higher baseline HbA1c levels were associated with greater effectiveness of tofogliflozin in reducing the frequency of nocturia (Table 2). No significant differences in these variables according to sex were observed. In addition, the frequency of daytime (5:00 a.m. to 11:00 p.m.) urinations increased to 7.9 times in the Tofo group, 7.1 times in the Dapa group, and 6.9 times in the Empa group after one month, with a significant difference among the three groups ($p = 0.0014$). Subsequently, urinary frequency gradually declined, and no significant differences were observed among the groups after three months (Figure 4).

Adverse Events

Genital mycotic infections and urinary tract infections were observed in all three groups (Table 3). No significant differences in the incidence rates of these events were observed between the three groups.

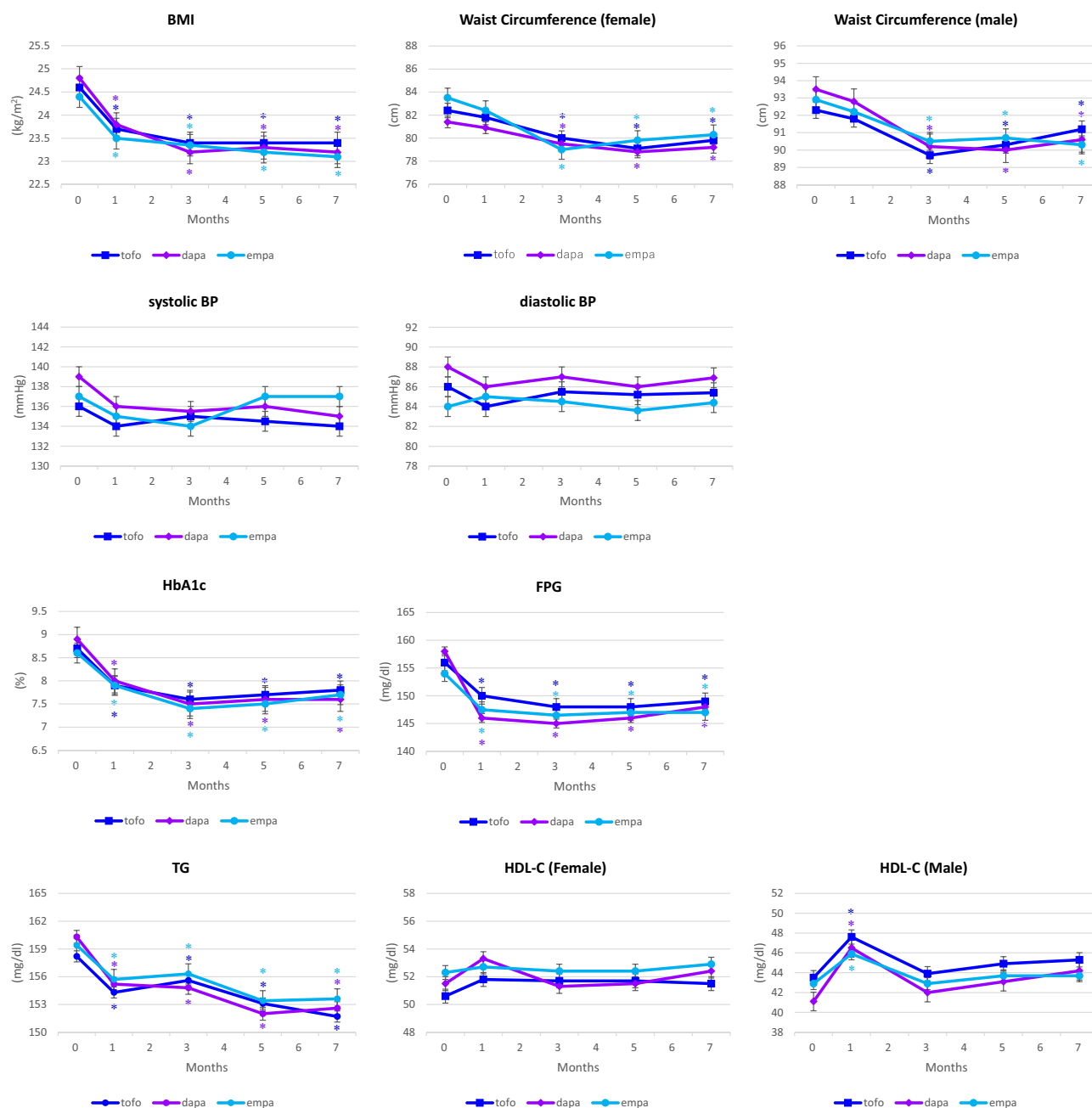


Figure 3 Changes in body weight, blood pressure, blood glucose, and lipid levels with SGLT-2i treatment. Blue square, tofogliflozin group; purple diamond, dapagliflozin group; sky-blue circle, empagliflozin group. T-bars showed standard deviations. *To assess time effects using analysis of variance followed by Dunnett's test, baseline measurements (0 month) were compared with those at 1, 3, 5, and 7 months in each of the three groups. Comparisons between the Tofo group and the Dapa and Empa groups were conducted at each time point (0, 1, 3, 5, 7 months). The Bonferroni correction defined statistical significance as $p < 0.05 / ([4 \times 3] + [2 \times 5]) = 0.00227$. *denotes $p < 0.00227$.

Abbreviations: BMI, body mass index; BP, blood pressure; HbA1c, glycated hemoglobin; FPG, fasting blood glucose; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL, low-density lipoprotein-cholesterol.

Discussion

In this study, tofogliflozin, dapagliflozin, and empagliflozin showed reduced and improved liver function and fibrosis markers associated with MASLD. However, no significant differences in these markers were detected between the three groups. Notably, tofogliflozin significantly reduced the frequency of nocturia 1 month after initiating treatment compared with the other two drugs. However, the difference disappeared after three months. There was no significant difference in weight loss, an improvement in blood glucose levels, or a change in lipid profile between the groups.

Table 2 Frequency of Nocturia

			Tofogliflozin (n=45)	Dapagliflozin (n=45)	Empagliflozin (N=45)	p value
Age – yr.	72 – 89	(n=46)	1.13 (n=15)	1.94 (n=15) [†]	2.01 (n=16) [†]	0.017*
	60 – 71	(n=46)	0.86 (n=14)	1.63 (n=16)	1.47 (n=16)	0.032
	33 – 59	(n=43)	0.60 (n=16)	0.87 (n=14)	0.73 (n=13)	0.508
HbA1c – % (mmol/mol)	10.4–12.4 (90–111)	(n=45)	1.07 (n=14)	2.00 (n=16) [†]	1.93 (n=15) [†]	0.021*
	9.0–10.3 (75–89)	(n=46)	0.94 (n=16)	1.93 (n=14) [†]	1.81 (n=16) [†]	0.001*
	7.5–8.9 (58–73)	(n=44)	0.67 (n=15)	0.93 (n=15)	0.86 (n=14)	0.884
Sex	Female	(n=58)	0.78 (n=19)	1.65 (n=17) [†]	1.71 (n=22) [†]	0.0005*
	Male	(n=77)	0.89 (n=26)	1.91 (n=28) [†]	1.86 (n=23) [†]	<0.0001*
Diabetes Duration – yr.	≥ 10	(n=69)	0.84 (n=22)	1.83 (n=24) [†]	2.02 (n=23) [†]	<0.0001*
	< 10	(n=66)	0.81 (n=23)	1.32 (n=21) [†]	1.58 (n=22) [†]	0.004*

Notes: *The p-values represent the outcomes of the three-group comparison conducted using analysis of variance (ANOVA). [†]If the ANOVA results were significant, a Dunnett's post-hoc analysis was performed to compare the Tofo group with the Dapa group and the Empa group. The Bonferroni correction defined statistical significance as $p < 0.05/2 = 0.025$. Therefore, * and [†] denote $p < 0.025$.

Effect of SGLT-2is on MASLD

Recently, there has been an increase in reports showing the efficacy of SGLT-2is in improving MASLD.^{5–7} However, whether this effect represents a class effect of SGLT-2is remains unclear. Our findings suggest that SGLT-2is have a class effect in improving fatty liver or, at least, that the three drugs used in this study have beneficial effects on MASLD.

A total of 68.8% of patients with type 2 diabetes have been reported to have coexisting MASLD,⁸ which is associated with an increased risk of liver fibrosis.²⁹ However, randomized controlled trials on SGLT-2is have shown a reduction in hepatic fat content as measured by magnetic resonance imaging.^{30,31}

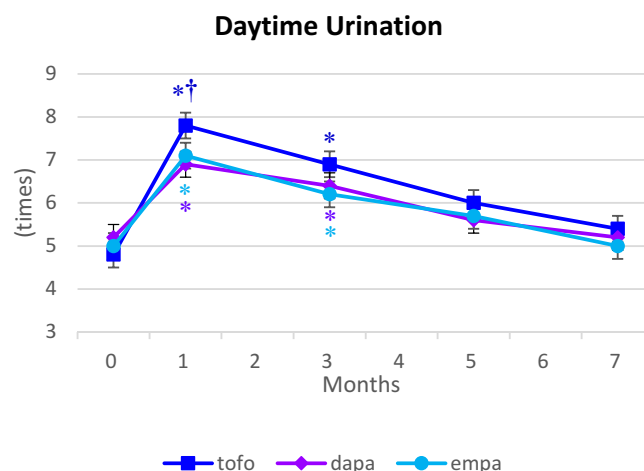


Figure 4 Frequency of daytime urination. The daytime urinary frequency increased after one month to an average of 7.9 times in the Tofo group, 6.9 times in the Dapa group, and 7.1 times in the Empa group, with a statistically significant difference among the three groups ($p = 0.0014$). Subsequently, urinary frequency gradually declined, and no significant differences were observed among the groups after three months. * To assess time effects using analysis of variance followed by Dunnett's test, baseline measurements (0 month) were compared with those at 1, 3, 5, and 7 months in each of the three groups. [†] Comparisons between the Tofo group and the Dapa and Empa groups were conducted at each time point (0, 1, 3, 5, and 7 months). The Bonferroni correction defined statistical significance as $p < 0.05/([4 \times 3] + [2 \times 5]) = 0.00227$. Therefore, * and [†] denote $p < 0.00227$.

Table 3 Frequency of Adverse Events

	Tofogliflozin (n=45) No. of events (%)	Dapagliflozin (n=45) No. of events (%)	Empagliflozin (n=45) No. of events (%)	p value*
Adverse events	12 (26.7)	14 (31.1)	13 (28.9)	0.897
Increased urination (day and night)	4 (8.9)	5 (11.1)	6 (13.3)	0.919
Acute kidney injury	0 (0.0)	1 (2.2)	0 (0.0)	0.882
Genital mycotic infections	3 (6.7)	3 (6.7)	2 (4.4)	0.983
Urinary tract infections	3 (6.7)	2 (4.4)	3 (6.7)	0.983
Pyelonephritis	1 (2.2)	0 (0.0)	1 (2.2)	0.938
Hypotension	1 (2.2)	0 (0.0)	0 (0.0)	0.882
Ketosis or ketoacidosis	0 (0.0)	2 (4.4)	1 (2.2)	0.681
Thirst	0 (0.0)	1 (2.2)	0 (0.0)	0.882

Notes: *The p-value represents the outcome of the three-group comparison conducted using analysis of variance.

SGLT-2is lower blood glucose levels by inhibiting SGLT-2, a protein predominantly expressed in the renal tubules, thereby reducing glucose reabsorption in the kidneys. This mechanism is associated with an improvement in insulin resistance, a reduction in free fatty acids, decreased hepatic fat deposition, and amelioration of intrahepatic inflammation and fibrosis.³² In our study as well, significant improvement in liver fibrosis was observed at five months after the initiation of treatment. Furthermore, SGLT-2is have been shown to enhance insulin sensitivity by increasing adiponectin levels³³ and to promote glucagon-like peptide 1 secretion,^{34,35} both of which may contribute to the improvement of MASLD. Notably, SGLT-2 expression is not limited to the kidneys; it has also been detected in hepatocytes and bile duct epithelial cells.³⁶ This finding suggests that SGLT-2is exert direct effects on the liver or affect hepatic function indirectly through bile acids and the gut microbiota, resulting in reduced hepatic fat deposition and inflammation. The use of SGLT-2is in the treatment of type 2 diabetes has shown potential therapeutic benefits in MASLD, possibly through mechanisms that may indirectly influence the progression of liver disease.^{37,38} In addition, as discussed later, although tofogliflozin has a shorter half-life compared to the other two agents, no significant differences in liver function improvement, including antifibrotic effects, were observed among the three groups. These findings suggest that, similar to its glucose-lowering effects, the improvement in liver function may be independent of the drug's half-life duration.

Effect of SGLT-2is on Nocturia Frequency

Nocturia is defined as the need to urinate during the night, interrupting sleep at least once.²⁸ Nocturia is associated with sleep disturbances,¹⁵ an increased risk of falls and fractures,^{17,18,39} and an elevated risk of depression and dementia.¹⁶ These effects can greatly reduce quality of life, especially in older adults,^{40–42} highlighting the importance of preventing and treating nocturia.

Frequent urination is a common side effect of SGLT-2is, leading to increased urination during the day and at night, which may contribute to nocturia. A randomized controlled trial reported that approximately 5% of individuals experience this side effect.¹³ However, other studies have shown that empagliflozin increases daily urine volume by 500 mL,⁴³ and nearly all individuals taking SGLT-2is exhibit some increase in urinary frequency.⁴⁴ The change in frequency of urination can vary according to the type of SGLT-2i used and the patients' underlying conditions. However, SGLT-2is contribute to the development of frequent urination. This effect is particularly prominent in patients with poor glycemic control at the time of prescription, because osmotic diuresis and nephropathy are thought to further increase the frequency of urination.¹³ On the contrary, several studies have noted that while polyuria is a frequent early complaint, it often subsides within weeks of treatment initiation.^{1,45,46} This timeline coincides with the period in which blood glucose begins to normalize, suggesting a strong correlation between the resolution of polyuria and improved glycemic control. The EMPA-REG and CANVAS

studies involving SGLT-2is demonstrated the greatest improvement in glycemic control at 12 to 13 weeks (approximately 3 months) following drug initiation,^{1,46} aligning with the 3-month time point observed in the present study. Frequent urination caused by SGLT-2is is largely due to osmotic diuresis driven by glucosuria. As blood glucose control improves, the filtered load of glucose decreases, leading to reduced glucosuria and, consequently, decreased urinary frequency.⁴⁷

The blood half-life of tofogliflozin is 5–6 hours,¹⁹ which is shorter than that of empagliflozin (9.88–13.1 hours)⁴⁸ and dapagliflozin (12.9 hours).⁴⁹ Therefore, when tofogliflozin is taken in the morning, its effects are likely to diminish by nighttime. In this study, the frequency of nocturia in the Tofo group did not significantly increase (0.8 times), and this small increase was notably less than that in the other two groups (1.7 and 1.9 times, respectively).

This trend was particularly evident in patients with higher baseline HbA1c levels or older age. Therefore, when initiating SGLT-2i therapy, tofogliflozin may be a more appropriate option for patients with baseline HbA1c levels $\geq 9.0\%$ or those aged ≥ 72 years, given its potential benefit in reducing nocturia frequency. Conversely, the nocturia-reducing effect of tofogliflozin may be limited in patients with baseline HbA1c levels $\leq 8.9\%$ or age ≤ 59 years.

In addition, we did not find any significant differences in the daytime urination frequency or a reduction in HbA1c levels among the three groups.

Adverse Events of SGLT-2is

Regarding adverse events, urinary tract infections and genital infections were observed in all SGLT-2i groups. However, the incidence of these events is comparable to previously reported rates,¹³ with no significant differences between the groups.

Study Limitation

This study has several limitations, such as its single-center design, the fact that only Japanese participants were included, and the 7-month study duration. Liver function may continue to change beyond 7 months. While a significant difference in the frequency of nocturia was observed at 1 and 3 months, this difference diminished over time, suggesting that additional long-term studies may not be required.

Conclusion

All three SGLT-2is led to a reduction in MASLD-related parameters, but no significant differences in these parameters were observed between the groups. These findings suggest that the improvement in fatty liver associated with SGLT-2is may be a class effect. SGLT-2 is now widely recognized not only for their glucose-lowering effects in patients with diabetes but also for their cardioprotective and renoprotective effects. The findings of this study may contribute to the growing body of evidence supporting the potential hepatoprotective effects of SGLT-2 is. Tofogliflozin significantly reduced the frequency of nocturia compared with the other two SGLT-2is. This finding suggests that the shorter half-life in the blood of tofogliflozin may be particularly beneficial for patients with baseline HbA1c levels $\geq 9.0\%$ or age ≥ 72 years.

Data Sharing Statement

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was conducted with the approval of the Institutional Review Board (IRB) of Shinkomonji Hospital. Written informed consent was obtained from all of the participants before enrollment. In addition, we confirmed that all research was performed following relevant guidelines/regulations.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All the authors declare no competing interests in this work.

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