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Original research

Clinical comparison of tofogliflozin and empagliflozin based on an analysis of 24-h accumulated urine in Japanese patients with type 2 diabetes mellitus

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ABSTRACT

Aim: In Japan, six sodium-glucose co-transporter 2 inhibitors have been approved for use, and some agents are associated with a significant decrease in cardiovascular events. In this study, the effects of tofogliflozin and empagliflozin were compared.

Methods: Patients with type 2 diabetes mellitus who were administered tofogliflozin (n = 10) and empagliflozin (n = 12) were extracted. The clinical parameters and 24-h accumulated urine samples before and after 48 weeks were analyzed with generalized linear mixed model.

Results: Both groups showed significant differences in the following parameters: body weight ($p < 0.0001$), mean blood pressure ($p = 0.006$), glycated hemoglobinA_{1c} ($p < 0.0001$), alanine aminotransferase ($p < 0.0001$), high-density lipoprotein cholesterol ($p < 0.0001$), homeostatic model assessment 2 (%S) ($p = 0.006$), volume of 24-h accumulated urine ($p < 0.0001$), and 24-h urine glucose excretion ($p < 0.0001$). The hematocrit differed significantly over the study period ($p < 0.0001$); however, empaglifozin had a significantly stronger effect on the hematocrit than tofoglifozin ($p = 0.007$). In contrast, triglyceride, low-density lipoprotein cholesterol, estimated glomerular filtration rate, and 24-h creatinine clearance rates were not significantly different in both groups.

Conclusions: The present results indicate that empagliflozin and tofogliflozin influence certain clinical parameters similarly; however, empagliflozin significantly increased the hematocrit than tofogliflozin. Differences in the effects of tofogliflozin and empagliflozin might influence cardiovascular events.

1. Introduction

Sodium-glucose co-transporter (SGLT) 2 inhibitors enhance glucose elimination via urine. Therefore, they exhibit a glucose-lowering effect and induce weight loss via calorie loss. SGLT2 inhibitors may be effective in patients with type 2 diabetes mellitus (T2DM) with obesity. However, individual differences greatly influence urine volume, glucose excretion, and weight loss. Even if glucose-lowering effects of SGLT2 inhibitors have not been observed, their clinical effects have been reported previously by Cherney et al. (2018). Currently, six SGLT2 inhibitors have been approved clinically in Japan. The characteristics of each SGLT2 inhibitor, such as half-life ($T_{1/2}$), binding ratio for SGLT2, pharmacokinetics (e.g., metabolism and excretion), and selectivity ratio for SGLT1/SGLT2, have been reported previously. In the present study, tofogliflozin and empagliflozin, which are highly selective inhibitors of SGLT2 and SGLT1 (ratio of half-maximal inhibitory concentration against SGLT2/SGLT1 activity: 2900 for tofogliflozin (Suzuki et al., 2012) and 5000 for empagliflozin (Interview form of Jardian, 2017)), respectively, were assessed. Tofogliflozin and empagliflozin have low protein-binding ratios (82.3–82.6% for tofogliflozin (Interview form of Apleway, 2016) and 84.7% for empagliflozin (Interview form of Jardian, 2017)) and high urinary excretion rates of their non-metabolized forms (16.1% for tofogliflozin (Interview form of Apleway, 2016); 21.3% and 22.9% for 10 and 25 mg empagliflozin (Interview form of Jardian, 2017), respectively). These characteristics of tofogliflozin and empagliflozin are believed to contribute to their strong inhibition of SGLT2 *in vivo*. However, the $T_{1/2}$ values of the two drugs are markedly different (5.29 h for tofogliflozin[2] and 9.88 h for empagliflozin (Interview form of Jardian, 2017)).Tofogliflozin may be a strong inhibitor of SGLT2 because of its high selectivity for the co-transporter (Interview form of Apleway, 2016). Empagliflozin inhibits SGLT2 as strongly as tofogliflozin; however, its half-life is longer than that of

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tofogliflozin (Interview form of Apleway, 2016; Interview form of Jardian, 2017). The EMPA-REG OUTCOME trial revealed that cardiovascular diseases were improved in patients administered empagliflozin (Zinman et al., 2015); however, a large-scale clinical trial using tofogliflozin has not yet been performed. In the present study, the clinical effects of tofogliflozin and empagliflozin were compared via analysis of 24-h accumulated urine samples of patients with type 2 diabetes mellitus, and we aimed to clarify differences in the effects of these SGLT2 inhibitors.

2. Methods

2.1. Study design and study patients

This retrospective, observational study was conducted in a clinical setting. The inclusion criteria were as follows: T2DM patients, 1) treated with an SGLT2 inhibitor from March 2014 to March 2017 for more than 48 weeks; 2) 24-h accumulated urine samples obtained regularly during administration of SGLT2 inhibitors; 3) data regarding 24-h accumulated urine sample being useful before and after 48 weeks of administration of SGLT2 inhibitor. Following were the exclusion criteria: 1) severe renal dysfunction, severe liver dysfunction, severe heart failure, or severe infection, 2) irregular use of SGLT2 inhibitor, and 3) individuals who opted to drop out of the study. Based on the aforementioned criteria, 10 patients receiving 20 mg tofogliflozin once daily (Tofo group) and 12 patients receiving 10 mg empagliflozin once daily (Empa group) were included. This retrospective, observational study was approved by the Human Ethics Committee of Kanagawa Medical Association (11 Jun 2018) and the opt-out approach was adopted to obtain informed consent from the patients. This paper follows the standards for reporting observational studies outlined manuscript was created according to the STROBE statement.

2.2. Sample analyses

On analyzing 24-h accumulated urine samples, the mean urine creatinine levels were determined to exclude samples unsuitable for the study. Urine samples were used when the creatinine level was within ± 30% of the mean value. Blood analysis, spot urine analysis, and analysis of 24-h accumulated urine samples were conducted by BML Co. (Tokyo, Japan). Homeostatic model assessment (HOMA) 2 (%S) and HOMA 2 (%B) were performed using HOMA Calculator software developed at the Diabetes Trials Unit of the Oxford Centre for Diabetes, Endocrinology and Metabolism (Oxford, UK).

2.3. Statistical analysis

IBM SPSS Statistics 24.0 software program (IBM Inc., Armonk, NY, USA) was used for statistical analyses. Comparisons between the two groups were analyzed using a Student's *t*-test for normally distributed data and the Mann-Whitney *U* test for non-normally distributed data. The chi-square test was performed to analyze categorical data. Longitudinal data were analyzed using a generalized linear mixed model, in which factors of group and time were set as the fixed effect and time factor was also set as the repeated effect. If time was a significant factor, further analysis was performed using Dunnett's test; furthermore, when group factors were significant, further analysis was performed using the Student's *t*-test. A non-parametric longitudinal data was analyzed using Friedman's test and significant findings were further analyzed using the Wilcoxon signed rank test followed by Bonferroni's correction. The statistical significance was considered at p-values less than 0.05. However, in a case of p values more than 0.05 in which GLMM analysis, 95% confidence intervals were presented for an interval estimation. The parametric data were expressed as mean ± standard deviation and the non-parametric data were expressed as [median; 25th percentile, 75th percentile values].

Table 1
Baseline characteristics of patients.

	Mean ± standard deviation (range)		Statistics
	Tofo group (n = 10)	Empa group (n = 12)	
Age (years)	52.6 ± 8.4 (39–66)	52.6 ± 8.0 (43–61)	n.s.
Sex (men/women)	4/6	9/3	n.s.
Body weight (kg)	80.7 ± 12.3 (66.2–105.2)	84.3 ± 19.0 (62.0–121.4)	n.s.
Body mass index	30.7 ± 4.3 (25.5–39.3)	30.7 ± 7.0 (24.3–43.4)	n.s.
Duration of diabetes mellitus (years)	11.1 ± 5.0	8.0 ± 2.9	n.s.
Complications			
Retinopathy	2	2	n.s.
Nephropathy	5 (ACR 2.7–565.9 μg/g) Cr)	6 (ACR 2.7–609.1 μg/g Cr) 1, proteinuria (1.82 g/day)	n.s.
Urine ACR	(26.7; 5.1, 146.0)	(20.4; 3.0, 120.9)	n.s.
Hypertension	8	12	n.s.
Dyslipidemia	10	12	n.s.
Fatty liver	10	10	n.s.
Glucose-lowering agents			
SGLT2 inhibitor alone	1	2	n.s.
BG	8	6	n.s.
SU	6	6	n.s.
DPP4 inhibitor	3	3	n.s.
αGI	3	5	n.s.
GLP1RA	4	2	n.s.
Pioglitazone	1	1	n.s.
Glinide	1	0	n.s.
Insulin	2	2	n.s.

Abbreviations: ACR, albumin to creatinine ratio; BG, biguanide; Cr, Creatinine; DPP4, dipeptidyl peptidase-4; EMPA, empagliflozin; GLP1RA, glucagon-like peptide-1 receptor agonist; n.s., not significant; SGLT2, sodium-glucose cotransporter 2; SU, sulphonylurea; TOFO, tofogliflozin; αGI, α-glucosidase inhibitor. Within parenthesis means; median value, 25th percentile value, 75th percentile value.

3. Results

3.1. Patient characteristics

Patient demographic information is summarized in Table 1. Middle-aged and obese T2DM patients with chronic T2DM were included, with no significant difference in age, sex ratio, body weight, or duration of T2DM between the Tofo and Empa groups. Half of the patients in both groups had diabetic nephropathy, almost all patients had hypertension, and all patients had dyslipidemia.

3.2. Adverse effects and concomitant medication

Among the adverse events occurring among patients, mild dry mouth (n = 2), mild frequent urination (n = 1), and *Candida* vaginitis (n = 1) were reported in the Tofo group but not in the Empa group. Balanitis (n = 1) and urinary tract infection (n = 1) were reported in the Empa group. These infections were not severe and improved upon treatment with antibiotics after temporary discontinuation of SGLT2 inhibitors.

One of the objectives of the present study was to investigate the clinical applications of SGLT2 inhibitors and to determine whether treatment is administered in accordance with the recommendations of the Japanese Diabetes Association on the safe use of SGLT2 inhibitors. The doses of concomitantly used sulphonylureas (SUs) were reduced (n = 2, Tofo group; n = 3, Empa group) in some patients. In other patients, SU use was discontinued (n = 3, Tofo group; n = 1, Empa group). Severe hypoglycemia did not occur in any patient. Attention was paid to excessive reduction in blood pressure (BP). The doses of

Table 2
Clinical findings over the study period.

Mean ± Standard deviation or [median; 25th percentile, 75th percentile values]						
		Baseline value	Week 12	Week 24	Week 48	GLMM analysis
Body weight (kg)	Tofo group	80.7 ± 12.3	76.7 ± 11.6* (p < 0.0001)	75.7 ± 11.6* (p < 0.0001)	75.3 ± 11.8* (p < 0.0001)	p < 0.0001
	Empa group	84.3 ± 19.0	80.8 ± 18.4* (p < 0.0001)	80.3 ± 19.0* (p < 0.0001)	79.0 ± 17.9* (p < 0.0001)	
Mean BP at office (mmHg)	Tofo group	106.2 ± 11.3	101.2 ± 10.0	96.7 ± 9.3 * (p = 0.021)	100.0 ± 9.1	p = 0.007
	Empa group	113.8 ± 9.8	109.3 ± 9.7	108.4 ± 12.2	106.0 ± 10.4* (p = 0.046)	
HbA_{1c} (%)	Tofo group	7.9 ± 0.9	7.5 ± 1.1	7.7 ± 1.3	7.3 ± 1.0* (p = 0.008)	p < 0.0001
	Empa group	7.8 ± 0.7	7.2 ± 0.8* (p < 0.0001)	7.3 ± 0.8* (p < 0.0001)	7.2 ± 0.8* (p < 0.0001)	
ALT (IU/mL)	Tofo group	50 ± 31	39 ± 21	30 ± 15* (p = 0.017)	31 ± 16* (p = 0.024)	p < 0.0001
	Empa group	54 ± 31	35 ± 21* (p = 0.008)	31 ± 16* (p = 0.001)	33 ± 17* (p = 0.004)	
Triglycerides (mg/dL)	Tofo group	197 ± 102	129 ± 56	135 ± 78	151 ± 93	p < 0.0001
	Empa group	206 ± 122	181 ± 135	154 ± 73	158 ± 94	
HDL-cholesterol (mg/dL)	Tofo group	47 ± 8	49 ± 8	55 ± 10* p < 0.0001)	52 ± 11* (p = 0.015)	p < 0.0001
	Empa group	55 ± 35	57 ± 31	61 ± 32* (p = 0.001)	60 ± 34* (p = 0.005)	
LDL-cholesterol (mg/dL)	Tofo group	93 ± 17	90 ± 220	94 ± 14	95 ± 14	n.s. (p = 0.364)
	Empa group	105 ± 30	110 ± 33	112 ± 33	115 ± 37	
eGFR (mL/min/1.73 m^2)	Tofo group	89.4 ± 22.0	89.0 ± 22.7	82.3 ± 18.0	85.6 ± 22.7	n.s. (p = 0.722)
	Empa group	84.7 ± 24.9	84.1 ± 23.1	86.3 ± 25.4	86.2 ± 29.3	
Hematocrit (%)	Tofo group	44.5 ± 4.6	44.9 ± 3.5	46.6 ± 3.3	46.4 ± 2.2	p < 0.0001
	Empa group	46.5 ± 2.9	49.8 ± 3.7* (p < 0.0001)	50.5 ± 3.6* (p < 0.0001)	50.9 ± 2.8* (p < 0.0001)	
HOMA2 (%S)	Tofo group (n = 8)	63.0 ± 30.2	104.0 ± 38.4* (p = 0.034)	120.4 ± 44.5* (p = 0.003)	96.9 ± 32.2	p = 0.006
	Empa group (n = 10)	105.7 ± 65.4	143.0 ± 47.2	140.6 ± 69.1	118.8 ± 48.4	
HOMA2 (%B)	Tofo group (n = 8)	39.7 ± 13.7	50.5 ± 29.0	43.5 ± 25.9	50.5 ± 29.0	n.s. (p = 0.523)
	Empa group (n = 10)	54.2 ± 27.3	40.3 ± 11.0	38.7 ± 8.7	49.6 ± 22.3	
24-h accumulated urine volume	Tofo group	1790.0 ± 756.3	2350.0 ± 676.5	2420.0 ± 541.1* (p = 0.032)	2705.0 ± 523.0* (p = 0.002)	p < 0.0001
	Empa group	1883.3 ± 726.8	2425.0 ± 520.7* (p = 0.005)	2597.5 ± 562.6* (p < 0.0001)	2468.1 ± 673.1* (p = 0.003)	
24-h urine salt excretion	Tofo group	11.0 ± 3.1	12.1 ± 4.1	12.8 ± 5.8	12.7 ± 4.5	n.s. (p = 0.555)
	Empa group	11.0 ± 4.4	11.6 ± 5.2	11.7 ± 3.2	11.6 ± 3.7	
Creatinine clearance calculated from 24-h urine analysis	Tofo group	135.4 ± 59.6	125.8 ± 39.5	123.2 ± 31.3	145.4 ± 64.0	n.s. (p = 0.423)
	Empa group	143.6 ± 55.7	134.4 ± 50.5	131.7 ± 42.0	143.2 ± 79.3	
						Friedman test
24-h urine glucose excretion	Tofo group	[13.6; 0.0, 38.3]	[149.2; 79.4, 198.7]* (p < 0.0001)	[123.3; 78.5, 178.3]* (p = 0.019)	[146.7; 86.4, 187.5]* (p = 0.003)	p < 0.0001
	Empa group	[6.2; 0.0, 13.1]	[111.1; 89.0, 179.7]* (p = 0.008)	[123.9; 94.7, 198.3]* (p < 0.0001)	[118.7; 85.2, 167.1]* (p = 0.003)	p < 0.0001

Asterisk* shows statistical significant when compared to baseline value.
Within parenthesis values mean statistical significant levels when compared to the baseline value.

some antihypertensive drugs were reduced (n = 6, Tofo group; n = 5, Empa group). However, two patients in the Empa group needed increased doses of antihypertensive medications.

3.3. Clinical findings after tofogliflozin and empagliflozin treatment

Clinical findings over the study period are shown in Table 2 and Fig. 1a. Compared to baseline values, body weight (p < 0.0001), mean blood pressure (MBP) (p = 0.006), glycated hemoglobin (HbA_{1c}) level (p < 0.0001), and alanine aminotransferase (ALT) (p < 0.0001) levels decreased significantly, while HDL-cholesterol levels (p < 0.0001) and HOMA2(%S) (p = 0.006) increased significantly throughout the treatment period irrespective of the differences between two groups. In contrast, the hematocrit increased significantly (p < 0.0001) throughout the study period and differed significantly between the two groups (p = 0.005, 0.017 and 0.001 at week 12, week 24 and week 48 respectively). There were no significant differences in triglyceride levels, LDL-cholesterol, estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2), and HOMA2 (%B) over the in either group.

Multiple linear regression analysis was also performed, and independent predictors of Δhematocrit were identified (r = 0.65, p < 0.016). The use of empagliflozin and male sex were independent factors influencing changes in the hematocrit with regression coefficient values (p value, [95%CI]) of 3.81 (p = 0.006, [1.24–6.37]) and 3.90 (p = 0.011, [1.03–6.78]), respectively.

3.4. Urine analysis

The findings of 24-h accumulated urine analysis are shown in Table 2 and Fig. 1b. The volume of 24-h accumulated urine in both groups increased significantly to > 600 mL/day over the study period (p < 0.0001). Similarly, 24-h urinary glucose excretion increased significantly to approximately 120 g/day in both groups throughout the study period (p= < 0.0001). These results did not differ significantly between the two groups. There were no significant differences in 24-h urinary salt excretion or creatinine clearance in either group during the study period.

4. Discussion

In this study, we compared the effects of tofogliflozin and empagliflozin via analysis of 24-h accumulated urine samples in patients with type 2 diabetes mellitus. The two drugs affected clinical parameters differently, and empagliflozin demonstrated a stronger effect on hematocrit than tofogliflozin.

Analysis of 24-h accumulated urine samples is useful when

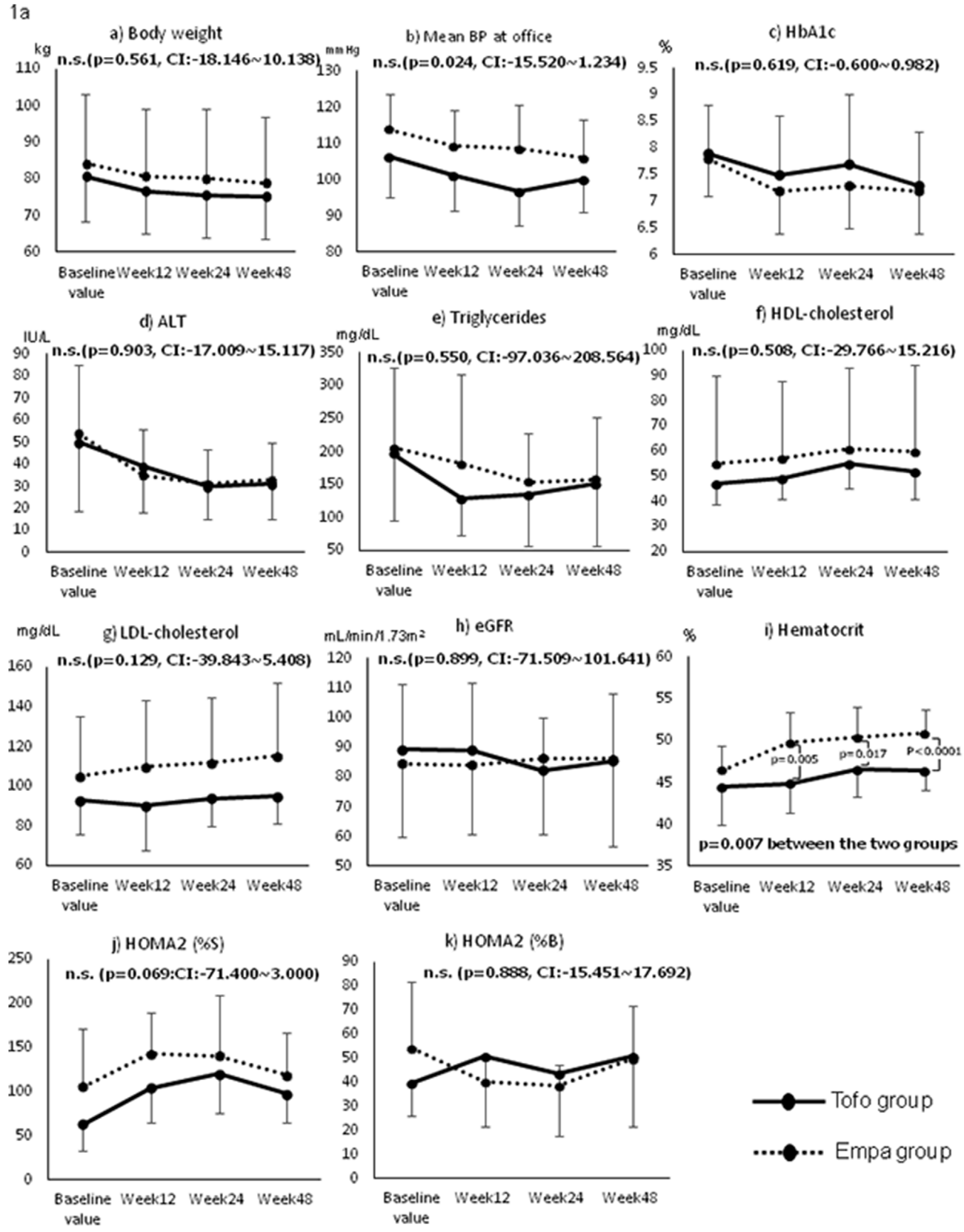
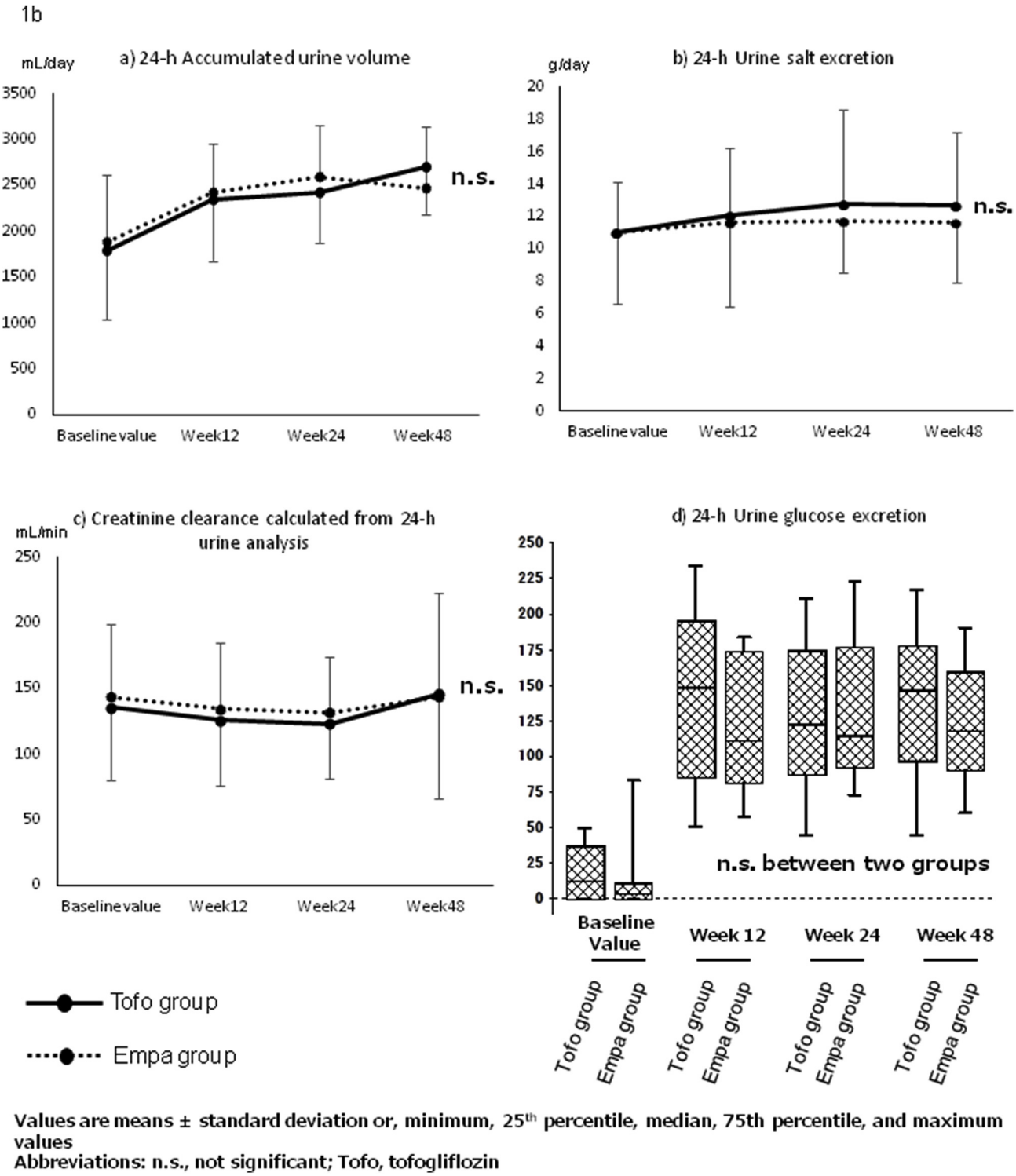


Fig. 1. a. Comparison of clinical findings after SGLT2 inhibitor treatment between two groups. **b.** Comparison of 24-h accumulated urine analysis after SGLT2 inhibitor treatment between two groups.



Values are means ± standard deviation or, minimum, 25th percentile, median, 75th percentile, and maximum values
Abbreviations: n.s., not significant; Tofo, tofogliflozin

Fig. 1. (*continued*)

evaluating the effects of SGLT2 inhibitors, as they enhance urinary excretion of glucose. List et al. (2009) reported that 52–85 g urinary glucose was excreted each day after treatment of patients with 2.5–50 mg dapagliflozin for 12 weeks. Furthermore, 77.9–89.8 g urinary glucose was excreted each day after treatment with 10–100 mg empagliflozin for 8 d (Heise et al., 2013); 80.9 and 93.0 g urinary glucose/day, 10 and 25 mg empagliflozin, respectively, for 4 weeks (Kanada et al., 2013). Daily urinary glucose excretion rates reported with other SGLT2 inhibitors are as follows: 109 and 113 g glucose with 50 and 100 mg ipragliflozin, respectively, after 14 d of treatment (Interview form of Suglat®, 2016); 117 and 129 g glucose, 2.5 and 5 mg luseogliflozin after 7 d of treatment (Interview form of Lusefi®, 2016). The aforementioned studies were short-term observational studies, whereas the present study is a long-term (48 weeks) observational study. In the present study, following treatment with 20 mg tofogliflozin, urinary glucose excretion rapidly increased from 21 g/d to 142 g/d. Furthermore, glucose excretion in urine was 138 g/d after 48 weeks of treatment. Similarly, urinary glucose excretion with 20 mg empagliflozin rapidly increased from 20 g/d to 112 g/d. Glucose excretion in urine was 144 g/d after 48 weeks of treatment.

Because the present study was a retrospective, observational clinical trial, it is difficult to compare the present results with those of randomized controlled studies. However, urinary glucose excretion displayed a sustained significant increase. Additionally, both tofogliflozin and empagliflozin have a strong and continuous inhibitory effect on SGLT2. Any difference in the effects of SGLT2 inhibitors may affect the levels of urinary glucose excretion. This may result in additional pleiotropic and adverse effects. Currently, few studies have reported differences between SGLT2 inhibitors. In Japan, Yoshida (2015) reported that tofogliflozin reduced the frequency of urinary glucose excretion during night-time and improved the quality of life more strongly than ipragliflozin because of its shorter $T_{1/2}$.

In the present study, both tofogliflozin and empagliflozin decreased HbA_{1c} levels. Changes in HbA_{1c} levels after 48 weeks of treatment with tofogliflozin and empagliflozin were −0.63 and −0.59%, respectively, similar to previously results (Interview form of Apleway, 2016). Concomitant use of other hypoglycemic agents was reduced or not required during the study, suggesting that tofogliflozin and empagliflozin have a potent hypoglycemic effect. Weight loss is often associated with the use of SGLT2 inhibitors; however, its extent varies with drug dosage, concomitant use of other hypoglycemic agents, and treatment duration. Previous studies reported weight loss ranging 2.58–3.41 kg after treatment with tofogliflozin (Tanizawa et al., 2014), ipragliflozin (Kashiwagi et al., 2015), dapagliflozin (Kaku et al., 2014), luseogliflozin (Seino et al., 2015), canagliflozin (Inagaki et al., 2015), and empagliflozin (Kadowaki et al., 2015) for 52 weeks. In the present study, weight loss after 48-week treatment was 5.4 kg with tofogliflozin and 5.3 kg with empagliflozin, both being higher than previously reported values, probably because the patients in the present study received guidance on diet and lifestyle modifications from nutritionists on a regular basis. Therefore, attention was paid to body weight during the study. Another reason may be the collection of urine over 24 h. Thus, careful monitoring may have encouraged patients to reduce calorie and salt intake. Although 24-h urine sampling for analysis has certain demerits, the present results confirm the usefulness of such an analysis. Both tofogliflozin and empagliflozin induced similar changes in urinary glucose excretion over 24 h, 24-h accumulated urine volume, HbA1c levels, body weight, BP, and liver function. These changes may have resulted from the inhibition of SGLT2.

In the present study, hematocrit increased upon treatment with empagliflozin; however, it remained unchanged upon treatment with tofogliflozin. Initially, increases in hematocrit by SGLT2 inhibitors were considered a sign of dehydration or volume reduction due to osmotic diuretic effect resulting from urine glucose excretion. Therefore, cerebral infarction, observed to be associated with SGLT2 inhibitor use in Japan, was considered an adverse effect of these drugs. However, hematocrit was not necessarily increased upon tolvaptan administration in patients with exacerbation of heart failure in the EVEREST study (Greene et al., 2013); this was further confirmed by Sano et al. (2016). Thus, hematocrit has been suggested to not be considered when evaluating circulating volume. Heerspink and de Zeeuw reported that an initial increase in erythropoietin levels during treatment with dapagliflozin possibly resulted from an increase in hematocrit (Heerspink and de Zeeuw, 2010). With chronic kidney disease (CKD) progression, erythropoietin-producing cells in the renal tubules transform into fibroblasts, thereby decreasing erythropoietin levels and potentially exacerbating renal anemia, and increasing the production of inflammatory cytokines and extracellular matrix proteins, which cause CKD progression (Souma et al., 2013). Terami reported that dapagliflozin reduces oxidative stress in rats with diabetic nephropathy (Terami et al., 2014). Furthermore, the anti-inflammatory effect of SGLT2 inhibitors enhances the recovery of erythropoietin-producing cells in the renal tubules and increases hematocrit. An association between changes in hematocrit and an increase in cardiovascular events has been reported previously (Gotoh et al., 2015). Results of the EMPA-REG OUTCOME trial revealed significant improvements in cardiovascular events and an increase in the hematocrit (Zinman et al., 2015; Inzucchi et al., 2018) following treatment with empagliflozin. The increase in the hematocrit was believed to be associated with improved cardiovascular events. Hematocrit was increased in comparison with baseline levels by 4.1 ± 4.9% and 4.3 ± 4.7% by 10 and 25 mg empagliflozin, respectively (Kohler et al., 2017). Furthermore, tofogliflozin reportedly increased hematocrit by 1.87 ± 5.23% (Utsunomiya et al., 2017) and 1.55% (Aso, 2016) in the respective studies. It therefore appears that empagliflozin increases the hematocrit to a greater extent than tofogliflozin; however, direct, prospective, comparative studies are required to confirm this. A meta-analysis of 27 randomized controlled trials revealed that an increase in the hematocrit was greater with empagliflozin than with other SGLT2 inhibitors (Baker et al., 2014). Increase in the hematocrit is probably associated with BP because two patients only in the Empa group required increased doses of antihypertensive medication. The inhibition of glucose reabsorption in proximal renal tubules is a common mechanism of SGLT2 inhibitors and the excretion of urinary glucose was not different between tofogliflozin and empagliflozin, which was shown in this previous study. Sha reported the lack of sustained effect on hematocrit has been observed by the administration of canagliflozin (Sha et al., 2014). The characteristics of each SGLT2 inhibitor, such as half-life ($T_{1/2}$), binding ratio for SGLT2, pharmacokinetics (e.g., metabolism and excretion), and selectivity ratio for SGLT1/SGLT2, have been reported previously and, furthermore, slight differences such as the presence or absence of Sulfur-group of Fluorine-group are also observed in the structural formula. However, how these differences affect changes in hematocrit has not been investigated. Whether the differences between each SGLT2 inhibitors occur in the antioxidant effect or the production of inflammatory cytokines and extracellular matrix proteins, as described above, should be clarified in future research.

In the present study, eGFR was increased upon treatment with empagliflozin; however, it decreased upon treatment with tofogliflozin. Although these changes are not significant, they suggest differences in renal effects between tofogliflozin and empagliflozin.

This study is a retrospective, observational study and has some limitations; for instance, this was a small-scale study with differences in certain clinical characteristics, even at baseline and there is a possibility that confounding factors cannot be fully controlled. In these small samples, statistical analysis of the clinical findings with generalized linear mixed model was possible, which were largely altered upon administration of the SGLT2 inhibitor; these alterations included changes in glucose excretion or body weight; however, these might not be adequate for a comparative analysis between the two groups. Future studies are required to examine the differences in the effects of SGLT2 inhibitors in a larger number of patients over a longer period.

5. Conclusion

In this study, we observed that empagliflozin and tofogliflozin affected certain clinical parameters. While many of these parameters remained unchanged, between the two groups, empagliflozin had a significantly stronger effect on hematocrit than tofogliflozin. In addition, 24-h urinary glucose excretion or creatinine clearance did not differ significantly in either group.

Conflicts of interest

There are no conflicts of interest to declare.

Author contributions

Dr Kobayashi carried out research planning and case accumulation, and Dr Hatori carried out statistical analysis. Dr Kobayashi, Dr Toyoda and Dr Hatori cooperated in interpreting the analysis results and preparing this manuscript.

Data statement

Our dataset is able to access from Dryad repository; https://doi.org/10.5061/dryad.2498d8n.

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Appendix A. Supplementary data

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