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The effects of 12-month administration of tofogliflozin on electrolytes and dehydration in mainly elderly Japanese patients with type 2 diabetes mellitus

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Abstract

Objective: To assess the effect of 12 months of treatment with tofogliflozin on electrolytes and dehydration in Japanese patients with type 2 diabetes mellitus (T2DM)

Methods: This retrospective study involved mainly elderly patients with T2DM who had received tofogliflozin for 12 months. Data on glycated haemoglobin (HbA1c), serum electrolytes (sodium, potassium, chloride), haematocrit, estimated glomerular filtration rate (eGFR) and blood urea nitrogen (BUN)/creatinine ratio were retrieved and analysed.

Results: Data from 69 patients (77% of whom were ≥65 years) showed that there was a significant reduction in HbA1c over the 12-month treatment period with tofogliflozin. However, the drug had no significant effect on levels of haematocrit, electrolytes, eGFR or BUN/creatinine ratio.

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Conclusion: This retrospective analysis of data from mainly elderly Japanese patients with T2DM showed that 12-month administration of tofogliflozin exhibited glucose-lowering capabilities with accompanying low risk of electrolyte abnormalities and dehydration.

Keywords
Tofogliflozin, SGLT2 inhibitor, electrolytes, sodium, potassium, elderly patients, HbA1c, kidney function

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Introduction

Hyperglycaemia is a major manifestation of type 2 diabetes mellitus (T2DM).[1] Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a class of glucose-lowering drugs that inhibit glucose reabsorption in the renal proximal tubules and excrete glucose into the urine resulting in lowered blood glucose.[2] The SGLT2 inhibitors have been endorsed as a therapeutic option for hyperglycaemia by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).[1] Currently, there are six SGLT2 inhibitors commercially available in Japan for the treatment of T2DM; ipragliflozin, dapagliflozin, tofogliflozin, canagliflozin, empagliflozin and luseogliflozin.[3] Nevertheless, safety is a major concern associated with the use of SGLT2 inhibitors because unexpected serious adverse reactions such as urinary tract infections, dehydration and skin disorders have been recorded shortly after their initiation.[4] These unfavourable events led a committee of Japanese experts to publish '*Recommendations on appropriate usage of SGLT2 inhibitors*' in June 2014.[5] Since the Japanese T2DM patient population has a high proportion of elderly individuals safety in these patients is of paramount importnace.[6] Accordingly, a one-year post-marketing surveillance (PMS) of tofogliflozin was conducted in elderly patients with type 2 diabetes shortly after the drug's launch.[7] The study concluded that the incidence of adverse events in elderly patients >65 years was similar to that observed in other studies that had included patients from the general population.[7]

SGTL2 inhibitors, including tofogliflozin, act on the proximal tubules and exert mild osmotic diuresis.[8] Although SGTL2 inhibitors have been reported to affect serum magnesium, potassium and phosphate levels,[9] little is known regarding their long-term effects on electrolytes in Japanese patients with T2DM, particularly in the elderly. Therefore, the aim of this study was to assess the effect of 12 months of treatment with tofogliflozin on serum electrolytes (i.e., sodium, potassium, chloride) and dehydration in Japanese patients with T2DM, a large proportion of whom were ≥65 years of age.

Patients and methods

This retrospective study included patients aged >17 years of age with a diagnosis of T2DM who attended clinics at the Kanazawa Medical University Himi Municipal Hospital from April 2013 to March 2016. All patients had received a single 20 mg dose of tofogliflozin daily for 12 months. Patients with significant comorbid conditions were excluded. Demographic

and baseline characteristics and data that had been collected throughout the 12-month treatment period were extracted from patients' medical records. Serum glycated haemoglobin (HbA1c) was used as an index of glycaemic control and levels of haematocrit, estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN), creatinine were used as an index of dehydration. Serum electrolyte (i.e., sodium, potassium, chloride) concentrations had also been measured at 0, 3, 6 and 12 months.

The study was conducted in accordance with the guidelines of the Declaration of Helsinki, and was formally approved by the Clinical Research Ethics Committee of Kanazawa Medical University Himi Municipal Hospital (receipt no. 107).

Statistical analyses

The data were analysed using the freely available EZR (Easy R) software.[10] For each variable, differences between baseline (0 month) and each timepoint (i.e., 3, 6, 12 month) were assessed by paired *t*-tests.

Linear regression analysis was used to assess the effects of tofogliflozin where the treatment period (months) was used as the independent variable and the dependent variables were: HbA1c, haematocrit, electrolytes and eGFR. The formula was as follows:

$$Y \text{ (dependent variable)} = \beta 0 \text{ (constant)} + \beta 1 \text{ (slope of regression)} \times X \text{ (treatment period)} + \varepsilon \text{ (random error)}$$

If the slope of the regression line was significantly different from zero, it was concluded that there was a significant relationship between the independent and dependent variables. The null hypothesis was that the slope of the regression curve was equal to zero (i.e., $\beta 1 = 0$). A *P*-value <0.05 was considered to indicate statistical significance.

Results

In total, 69 patients (32 men, 37 women) were included in the study and their demographic data are summarized in Table 1. Ages ranged from 17 to 92 years and the mean ± SD age of the group was 70.4 ± 14.9; 53 (77%) patients were ≥65 years. Mean ± SD baseline HbA1c was 7.4 ± 1.0% and haematocrit was 41.9 ± 6.7%. A large

Table 1. Characteristics of patients involved.

Baseline characteristics	
No. participants	69
Age, years	70.4 ± 14.9
Age	
<65 years, *n*	16
≥65 years, *n*	53
Sex,	
Male	32 (46)
Female	37 (54)
HbA1c, %	7.4 ± 1.0
Haematocrit, %	41.9 ± 6.7
Weight, kg	61.6 ± 12.7
Systolic blood pressure, mmHg	129 ± 17
Diastolic blood pressure, mmHg	74 ± 12
Glucose, mg/dl	171 ± 65
Lactate dehydrogenase, IU/l	185 ± 33
Albumin, g/dl	4.1 ± 0.4
Aspartate aminotransferase, IU/l	22.4 ± 11.9
Alanine aminotransferase, IU/l	22.4 ± 19.6
Triglyceride, mg/dl	164 ± 82
Gamma-glutamyl transpeptidase, IU/l	73.6 ± 25.5
Creatinine, mg/dl	0.8 ± 0.4
Estimated glomerular filtration rate, ml/min/1.73m^2	73.6 ± 25.5
Blood urea nitrogen, mg/dl	16.8 ± 4.8
Diuretics	9 (13)
Anti-diabetic treatment	
Dipeptidyl peptidase-4 inhibitor	55 (80)
Sulfonylurea	14 (20)
Biguanide	19 (28)
Insulin	5 (7)
Thiazolidinedione	5 (7)
Glinide	2 (3)

Data are presented as mean ± SD or *n* (%).
HbA1c, glycated haemoglobin.

Table 2. Differences in baseline values between age groups (<65 years and ≥65 years).

Variable	Age <65 years (*n*=16)	Age (≥65 years) (*n*=53)	Statistical significance
Age, years	49.4 ± 14.8	76.4 ± 7.3	–
HbA1c, %	8.1 ± 1.5	7.4 ± 1.5	*ns*
Na^+, mEq/l	122 ± 48	134 ± 27	*ns*
K^+, mEq/l	3.9± 1.6	4.3 ± 0.7	*ns*
Cl^-, mEq/l	91 ± 36	103 ± 15	*ns*
Haematocrit, %	37.0 ± 14.7	38.6 ± 7.5	*ns*
eGFR, ml/min/1.73m^2	85.3 ± 47.8	68.1 ± 22.7	*P*=0.049
BUN/Creatinine ratio, mg/dl	19.6 ± 11.2	21.0 ± 7.1	*ns*

HbA1c, glycated haemoglobin; Na^+, sodium; K^+, potassium; Cl^-, chloride; eGFR, Estimated glomerular filtration rate; BUN, Blood urea nitrogen; *ns,* not statistically significant.

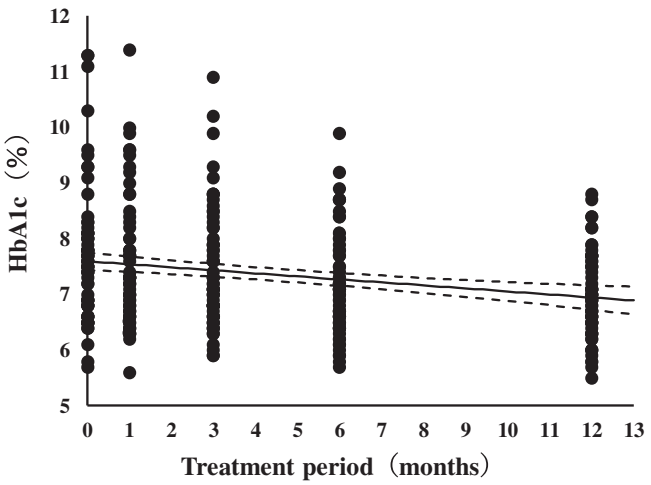

Figure 1. Serum glycated haemoglobin (HbA1c, %) vs time profile in elderly patients with T2DM administered 20 mg tofogliflozin daily for 12 months. The dashed and solid lines show linear regression curve and its 95% confidence intervals.

proportion of patients (80%) were using dipeptidyl peptidase-4 (DPP-4) inhibitors. The next most commonly used anti-diabetic agents were biguanides (28% patients); diuretics were used by 13.0% patients. No symptomatic hypoglycaemic episodes and no serious adverse events were recorded for any of these patients during the 12-month treatment period on tofogliflozin.

Table 2 shows baseline values according to age group (i.e., <65 and ≥65 years). Although values for HbA1c, Na^+, K^+, Cl^-, haematocrit and BUN/creatinine ratio were similar, eGFR values for the older age group tended to be lower than those for the younger age group (*P*=0.049).

Levels of HbA1c following administration of tofogliflozin for the 69 patients are shown in Figure 1. Mean ± SD HbA1c values (%) at 0, 1, 3, 6, and 12 months were 7.6 ± 1.5, 7.4 ± 1.4, 7.2 ± 1.6, 6.8 ± 1.7 and 6.9±1.1, respectively. Values were significantly different between baseline and 6 months (*P*=0.008, paired t-test) and

Table 3. Results of linear regression analyses.

Variable	Coefficient	Estimate	Standard error	Statistical significance
HbA1c, %	β0	7.593	0.079	$P<0.0001$
	β1	–0.054	0.0134	$P<0.0001$
Na^+, mEq/l	β0	138.841	0.644	$P<0.0001$
	β1	0.15427	0.104	*ns*
K^+, mEq/l	β0	4.385	0.033	$P<0.0001$
	β1	–0.002	0.005	*ns*
Cl^-, mEq/l	β0	104.432	0.236	$P<0.0001$
	β1	0.095	0.038	*ns*
Haematocrit, %	β0	41.009	0.521	$P<0.0001$
	β1	0.19	0.084	*ns*
eGFR, ml/min/1.73m^2	β0	73.925	2.019	$P<0.0001$
	β1	–0.062	0.327	*ns*
BUN/creatinine ratio, mg/dl	β0	21.92	0.5059	$P<0.0001$
	β1	0.135	0.082	*ns*

HbA1c, glycated haemoglobin; Na^+, sodium; K^+, potassium; Cl^-, chloride; eGFR, Estimated glomerular filtration rate; BUN, Blood urea nitrogen; *ns,* not statistically significant.
β, constant; β1, slope of regression or regression coefficient.

baseline and 12 months (P=0.0009, paired t-test). Linear regression analysis showed that the decrease in HbA1c was statistically significant (Table 3, P <0.0001).

Serum sodium ion concentrations for all patients are shown in Figure 2. Mean ± SD values (mEq/l) at 0, 1, 3, 6, and 12 months were 131 ± 33, 136 ± 24, 134 ± 29, 130 ± 37 and 134 ± 29, respectively. No differences were found between timepoints (paired t-test) and the overall change in sodium was not significant (linear regression; Table 3).

Potassium ion concentrations for all patients are shown in Figure 3. Mean ± SD values (mEq/l) at 0, 1, 3, 6, and 12 months were 4.2 ± 1.0, 4.3 ± 0.9, 4.2 ± 1.0, 4.0 ± 1.2 and 4.2 ± 1.0, respectively. No differences were found between timepoints (paired t-test) and the overall change in potassium was not significant (linear regression; Table 3).

Chloride ion concentrations for all patients are shown in Figure 4. Mean ± SD values (mEq/l) at 0, 1, 3, 6, and 12 months were 100 ± 22, 101 ± 18, 100 ± 22, 98 ± 28 and 101 ± 22, respectively. No differences were found between timepoints (paired t-test). However, linear regression analysis showed that the overall change in chloride was statistically significant (P=0.0133; Table 3).

Haematocrit values for all patients are shown in Figure 5. Mean ± SD values (%) at 0, 1, 3, 6, and 12 months were 38.2 ± 9.5, 39.7 ± 10.3, 40.3 ± 10.5, 39.8 ± 14.7 and 40.9 ± 10.1, respectively. No differences were found between timepoints (paired t-test) and the overall change in haematocrit values was not significant (linear regression; Table 3).

Values for eGFR for all patients are shown in Figure 6. Mean ± SD values (ml/min/1.73m^2) at 0, 1, 3, 6, and 12 months were 72.1 ± 30.9, 69.1 ± 27.9, 68.8 ± 29.4, 69.1 ± 31.3 and 69.8 ± 30.0, respectively. No differences were found between timepoints (paired t-test) and the overall change in eGFR was not significant (linear regression; Table 3).

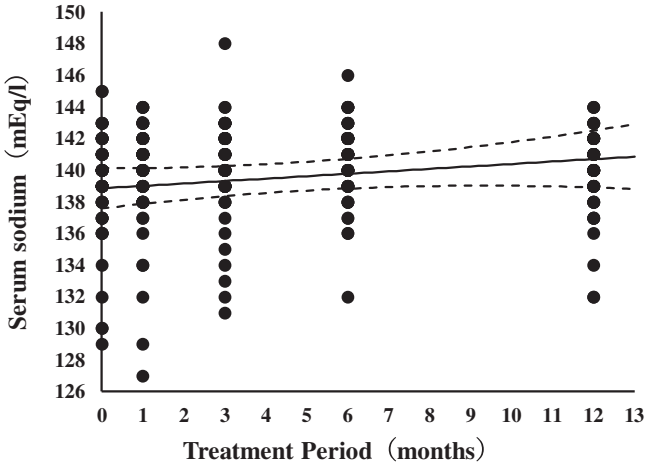

Figure 2. Serum sodium ion concentration vs time profile in elderly patients with T2DM administered 20 mg tofogliflozin daily for 12 months. The dashed and solid lines show linear regression curve and its 95% confidence intervals.

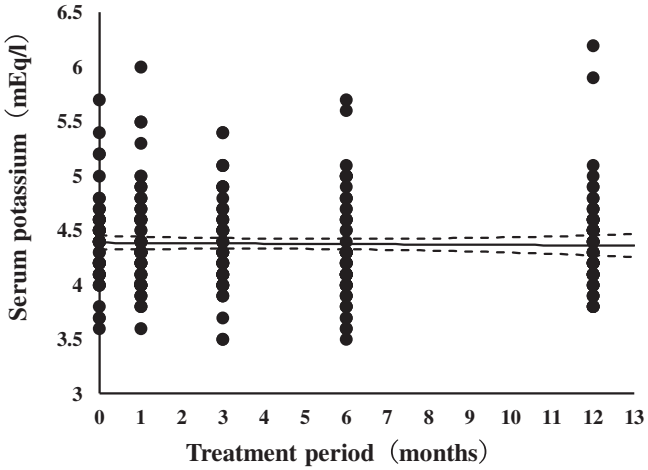

Figure 3. Serum potassium ion concentration vs time profile in elderly patients with T2DM administered 20 mg tofogliflozin daily for 12 months. The dashed and solid lines show linear regression curve and its 95% confidence intervals.

BUN/creatinine ratio values for all patients are shown in Figure 7. Mean $\pm$ SD values (mg/dl) at 0, 1, 3, 6, and 12 months were 21.6 ± 7.1, 21.7 ± 6.6, 22.9 ± 5.9, 23.3 ± 5.7 and 23.2 ± 6.7, respectively. No differences were found between time-points (paired t-test) and the overall change in BUN/creatinine ratio was not significant (linear regression; Table 3).

Discussion

While SGLT2 inhibitors, including tofogliflozin, are known to ameliorate body

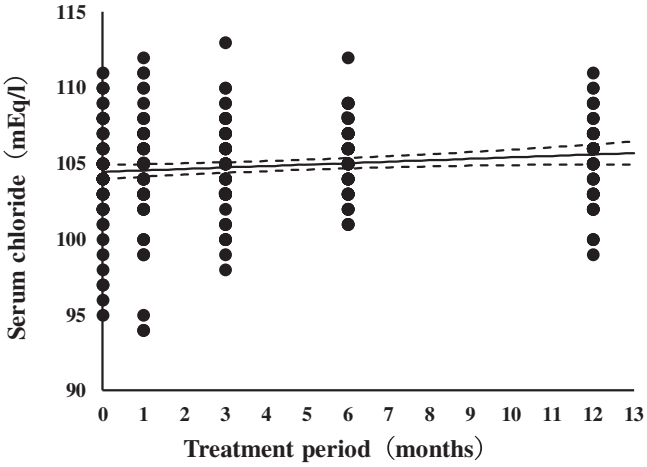

Figure 4. Serum chloride ion concentration vs time profile in elderly patients with T2DM administered 20 mg tofogliflozin daily for 12 months. The dashed and solid lines show linear regression curve and its 95% confidence intervals.

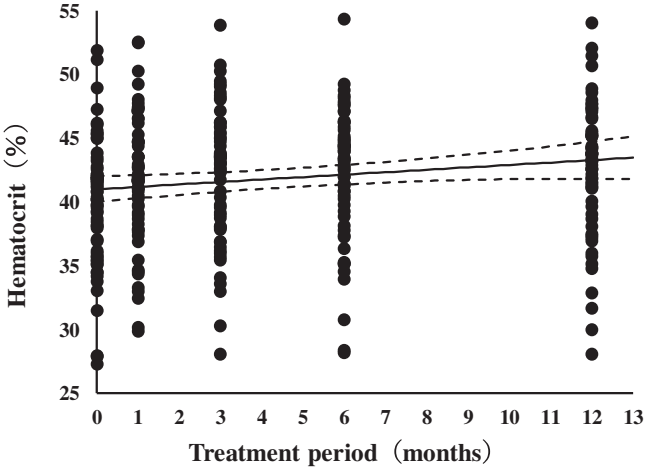

Figure 5. Serum haematocrit vs time profile in elderly patients with T2DM administered 20 mg tofogliflozin daily for 12 months. The dashed and solid lines show linear regression curve and its 95% confidence intervals.

weight, blood pressure, liver function, serum lipids and uric acid, as well as improving glucose metabolism in patients with T2DM.[11] they are associated with side effects including urinary tract infections, hypoglycaemia, dehydration, and skin complications.[4] Indeed, hyperketonaemia, ketonuria and pollakiuria have been reported in Japanese patients with T2DM following treatment with tofogliflozin.[12] To our knowledge, this present study is the first to investigate the long-term effects of tofogliflozin on electrolyte concentrations (i.e., sodium potassium, chloride) in mainly elderly Japanese patients

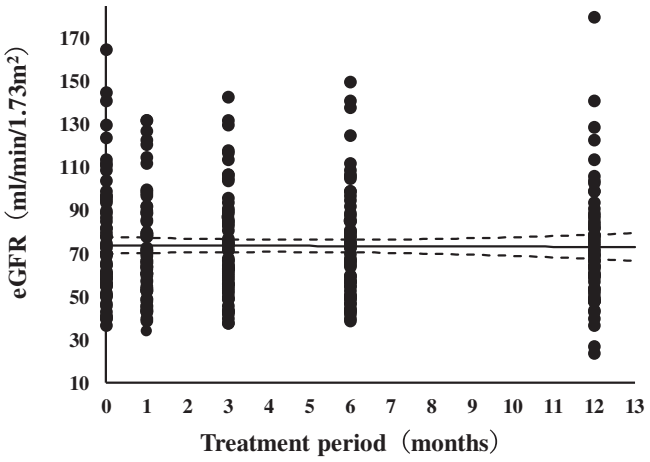

Figure 6. Estimated glomerular filtration rate (eGFR) vs time profile in elderly patients with T2DM administered 20 mg tofogliflozin daily for 12 months. The dashed and solid lines show linear regression curve and its 95% confidence intervals.

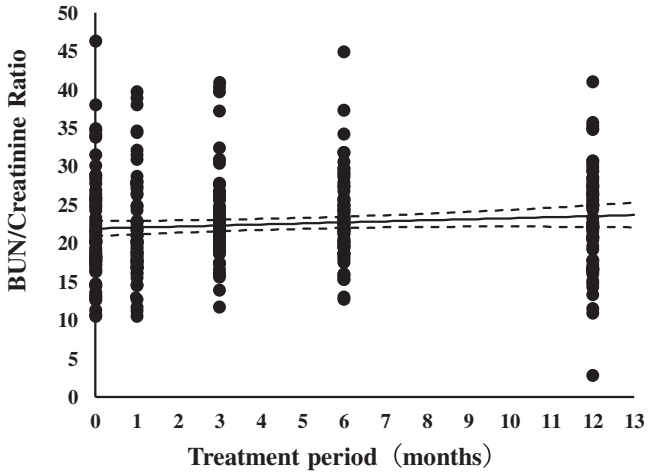

Figure 7. Blood urea nitrogen - creatinine ratio (BUN/Creatinine) vs time profile in elderly patients with T2DM administered 20 mg tofogliflozin daily for 12 months. The dashed and solid lines show linear regression curve and its 95% confidence intervals.

with T2DM. Although serum electrolyte concentrations following tofogliflozin treatment have been assessed previously, by comparison with this present study, the investigation involved 20 younger adults with T2DM and the assessment period was just eight weeks.[13]

This present study showed that while there was a significant reduction in HbA1c over the 12-month treatment period with tofogliflozin, the drug had no effect on haematocrit, electrolytes, eGFR or BUN/creatinine ratio. The favourable effects of tofogliflozin on HbA1c levels observed in

this study are consistent with previous findings which have shown that HbA1c gradually decreases during the first three months of treatment and are then maintained at constant low levels thereafter.[14] However, by comparison with our results, a previous study observed an increase in haematocrit from 40.3% to 42.6% after eight weeks of treatment with tofogliflozin.[13] The authors concluded that the effect may be attributed to haemoconcentration because of osmotic diuresis.[13] Interestingly, although 13% of the subjects in our study used diuretics, which are known to elevate haemoconcentration, haematocrit levels across the whole population remained stable throughout the 12 months of tofogliflozin treatment. In addition, our results were obtained from a population where 77% patients were $\geq$65 years of age and had significantly lower kidney function than younger patient as assessed by eGFR. However, there were no differences between younger and older patients in baseline values for HbA1c, haematocrit, electrolytes and BUN/creatinine ratios. In addition, although the patients in the present study used a variety of other anti-T2DM drugs, no previous drug-drug interaction has been reported for tofogliflozin.[15,16]

Limitations of the present study include the small sample size, the retrospective design and lack of a control group. In addition, confounding factors such as food and fluid intake, concurrent medications and medical history were not considered and may have influenced the study outcome. Furthermore, only serum levels of sodium, potassium and chloride were assessed. Previous research has suggested tofogliflozin has an effect on magnesium and phosphate levels.[9] Therefore, future longitudinal, controlled, prospective investigations involving large numbers of patients and assessing more electrolytes are required to confirm the current results.

In conclusion, this retrospective analysis of data from mainly elderly Japanese patients with T2DM showed that 12-month administration of tofogliflozin exhibited glucose-lowering capabilities with accompanying low risk of electrolyte abnormalities and dehydration.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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