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Sodium–glucose cotransporter 2 inhibitors reduce day-to-day glucose variability in patients with type 1 diabetes

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Keywords

Glucose variability, Sodium–glucose cotransporter 2 inhibitor, Type 1 diabetes

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ABSTRACT

Aims/Introduction: Sodium–glucose cotransporter 2 inhibitors (SGLT2i) are used worldwide because of their multiple benefits for patients with type 2 diabetes. The purpose of this study was to determine the efficacy and safety of SGLT2i in patients with type 1 diabetes.

Materials and Methods: Patients with type 1 diabetes who had been treated with SGLT2i for >12 weeks were included in this retrospective observation study. We recorded the changes in body mass, insulin dose, blood and urine test data, and adverse events. The changes in day-to-day glucose variability, as the primary end-point, was evaluated using the interquartile range (P25/P75) of the ambulatory glucose data obtained using continuous glucose monitoring.

Results: A total of 51 patients (37 women; mean age 52.7 years) were included. Glycated hemoglobin and body mass significantly decreased by 0.4% and 1.6 kg, respectively. The total required insulin dose decreased by 9.4% (42.7 ± 26.6 – 38.7 ± 24.3 units/day). Continuous glucose monitoring data were obtained from 30 patients. P25/P75 decreased by $17.6 \pm 20.7\%$ during SGLT2i treatment ($P < 0.001$). The percentage of time per day within the target glucose range of 70–180 mg/dL significantly increased (from 42.2 to 55.5%, $P < 0.001$), without an increase in the percentage of time spent in the hypoglycemic range (<70 mg/dL). Urinary ketone bodies were detected in four patients (7.8%), but none developed ketoacidosis.

Conclusions: SGLT2i improved day-to-day glucose variability and time in the target glucose range, without increasing frequency of hypoglycemia, in patients with type 1 diabetes, and reduced glycated hemoglobin, body mass and the required insulin dose.

INTRODUCTION

Sodium–glucose cotransporter 2 inhibitors (SGLT2i) reduce plasma glucose concentrations by inhibiting renal tubular glucose reabsorption, and have been approved for use in patients with type 2 diabetes in many countries since 2012. A large number of patients with type 2 diabetes are currently treated with SGLT2i, in particular those with high risks of

cardiovascular disease or chronic kidney disease, referring substantial clinical evidence to show their beneficial effects on cardiovascular and kidney function^{1,2}.

The daily and day-to-day blood glucose concentrations of patients with type 1 diabetes frequently vary; therefore, it is difficult for many type 1 diabetes patients to achieve their glycemic targets³. The use of SGLT2i has been proposed for type 1 diabetes patients to improve their glycemic control, because of the insulin-independent hypoglycemic effect of these drugs, and beneficial effects have been shown in several phase III clinical trials.

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However, there have been few studies carried out in patients with type 1 diabetes in clinical practice, because this use of SGLT2i has been approved in just a few countries to date. However, a pooled post-hoc analysis carried out on data from Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 Diabetes (DEPICT-1 and -2), phase III clinical studies of dapagliflozin, recently showed that SGLT2i improved daily glucose variability in patients with type 1 diabetes⁴. Nevertheless, although the time per day within the target glucose range of 70–180 mg/dL (TIR) and the mean amplitudes of their glycemic excursions were significantly better in the dapagliflozin group than in the placebo group, the effect of dapagliflozin on day-to-day glucose variability was not analyzed.

We aimed to determine the efficacy and safety of SGLT2i in daily clinical practice, with particular reference to their effects on day-to-day glucose variability, in patients with type 1 diabetes.

METHODS

Study population

Patients were eligible for inclusion in the treatment cohort if they had type 1 diabetes and had been treated with an SGLT2i (dapagliflozin or ipragliflozin) for >3 months. All patients were confirmed with depletion of their insulin secretion by the measurement of plasma C-peptide concentration. Patients who were pregnant or aged <18 years were excluded.

Protocol

This was a multicenter, retrospective, observational study, and was carried out at Hokkaido University Hospital, Kurihara Clinic and Aoki Clinic in Sapporo, Japan. Data were collected between December 2018 and June 2020 at all the clinics. The baseline was defined as the date that SGLT2i treatment was initiated. All data were collected from the patients' medical records. Body mass, body mass index, insulin dose, blood pressure, glycated hemoglobin (HbA1c), casual plasma glucose, estimated glomerular filtration rate and urinary albumin-to-creatinine ratio data were collected for each clinic visit, which were 4 weeks before the initiation of SGLT2i, at baseline, and 4 and 12 weeks after starting SGLT2i treatment.

The primary objective of the study was to assess the clinical effectiveness of SGLT2i for the improvement of day-to-day glucose variability. The changes in variability were analyzed between the start and the completion of 12 weeks of SGLT2i administration. TIR, time below the target glucose range (TBR; <70 mg/dL) and time above the target glucose range (TAR; >180 mg/dL) were measured using continuous glucose monitoring (CGM; FreeStyle Libre; Abbott, Chicago, IL, USA)⁵. Day-to-day glucose variability was evaluated using the interquartile range (P25/P75) of the glucose concentration values in the ambulatory glucose profile, which represents a patient's daily glucose variations during the 2 weeks of CGM⁶. To quantify the P25/P75 range, Image scan (Image; National Institutes of Health, Bethesda, MD, USA) was used to calculate the time-glucose area within the P25/P75 range. The secondary

objectives were to determine the changes in TIR/TBR/TAR, basal–bolus insulin dose, blood pressure, glycemic control and kidney function during the study period, and to assess the safety of SGLT2i in these patients.

To identify the factors influencing the efficacy of SGLT2i with respect to the primary outcome, the relationships between the patients' baseline characteristics and the changes in the measured values were analyzed.

The safety of SGLT2i was analyzed by assessing the frequencies of hypoglycemia, genital infection, dizziness and diabetic ketoacidosis (DKA) during the observation period. Hypoglycemia was defined by the appearance of clear hypoglycemic symptoms and a blood glucose concentration <70 mg/day. The definition of severe hypoglycemia was a hypoglycemic episode that required the assistance of another person to actively administer therapy⁷.

Ethics

The protocol for this research project was approved by a suitably constituted ethics committee of the institutional review board of Hokkaido University Hospital (approval number: 019-0216), and it conforms to the provisions of the Declaration of Helsinki. All informed consent was obtained from the participants using an opt-out consent procedure for this retrospective study. This study was registered with the University Hospital Medical Information Network (UMIN) Center (#R000044887UMIN000039361).

Statistical analysis

The results are expressed as the mean ± standard deviation or median (range). Differences between the two groups were evaluated using Student's *t*-test or Wilcoxon signed-rank test for continuous variables. Categorical variables are expressed as numbers and percentages. *P* < 0.05 was considered to show statistical significance. Correlation coefficients and simple linear regression analyses were used to identify associations between variables. Multivariate linear regression analyses were used to identify factors that were independently associated with the outcomes. All statistical analyses were carried out using JMP Pro software (version 12.0; SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 51 type 1 diabetes patients (14 men and 37 women) were enrolled. Of these, 41 patients were treated using multiple daily injection therapy, and 10 were treated using continuous subcutaneous insulin infusion (CSII). All of the patients being treated with CSII possessed rescue insulin in case of problems with the CSII pump (640G; Medtronic, Dublin, Ireland). A total of 30 patients underwent CGM before and after administration of an SGLT2i.

The baseline clinical and metabolic characteristics of the patients are shown in Table 1. The mean age of the patients was 52.7 ± 12.5 years, their body mass was 64.8 ± 14.0 kg, body mass index 24.9 ± 3.6 kg/m² and estimated glomerular

Table 1 | Characteristics of the participants and changes in these parameters during the 12 weeks of the study

	Baseline	12 weeks	P-value
Age (years)	52.7 ± 12.5		
Sex (male/female)	14/37		
Disease duration (years)	16.3 ± 11.6		
MDI/CSII	41/10		
Bolus insulin (lispro/aspart/glulisine)	23/13/15		
Basal insulin (glargine U100/glargine U300/degludec)†	4/ 4/ 33		
Plasma CPR (ng/mL)	0.0 (0.0–0.2)		
BMI (kg/m ²)	24.9 ± 3.6	24.2 ± 3.4	<0.001
Body mass (kg)	64.8 ± 14.0	63.2 ± 13.0	<0.001
CPG (mg/dL)	195.9 ± 103.7	163.4 ± 81.6	0.55
HbA1c (%)	8.1 ± 1.1	7.7 ± 0.9	<0.001
eGFR (mL/min/1.73 m ²)	77.8 ± 24.3	74.7 ± 23.0	0.95
UACR (mg/gCr)	9.9 (4.6–37.3)	11.0 (5.8–48.5)	0.44
SBP (mmHg)	129.8 ± 13.9	120.1 ± 16.9	<0.05
DBP (mmHg)	76.9 ± 8.6	70.9 ± 11.1	<0.05

n = 51. †Data from 41 patients (multiple daily injection [MDI]). Continuous variables are shown as the mean ± standard deviation or median (25–75% confidence interval). Categorical variables are expressed as the number. P-value of baseline versus 12 weeks (paired-sample t-tests or Wilcoxon signed-rank test). BMI, body mass index; CPG, casual plasma glucose; CPR, C-peptide immunoreactivity; CSII, continuous subcutaneous insulin infusion; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; SBP, systolic blood pressure; UACR, urinary albumin: creatinine ratio.

filtration rate 77.8 ± 24.3 mL/min/1.73 m². Their body mass (decreased from 64.8 ± 14.0 kg to 63.2 ± 13.0 kg, *P* < 0.001), HbA1c (decreased from 8.1 ± 1.1% to 7.7 ± 0.9%, *P* < 0.001) and systolic/diastolic blood pressures (decreased from 129.8 ± 13.9 mmHg to 120.1 ± 16.9 mmHg, *P* < 0.05/76.9 ± 8.6 mmHg to 70.9 ± 11.1 mmHg, *P* < 0.05) significantly decreased during the 12 weeks of SGLT2i administration (Table 1).

There were no significant changes in casual plasma glucose, urinary albumin-to-creatinine ratio, nor estimated glomerular filtration rate during the 12 weeks of SGLT2i administration. However, the total insulin dose (decreased from 42.7 ± 26.6 units to 38.7 ± 24.3 units, *P* < 0.001), bolus insulin dose (decreased from 25.9 ± 15.7 units to 23.8 ± 14.3 units, *P* < 0.05) and basal insulin dose (decreased from 16.8 ± 13.9 units to 14.9 ± 12.3 units, *P* < 0.001) significantly decreased (Table 2). The reduction of basal insulin (−11.3%) was greater compared with that of bolus insulin (−8.1%; *P* < 0.05).

With respect to the primary end-points, assessed using CGM data (Figures 1,S1), the P25/P75 area, which was used to evaluate day-to-day glucose variability, significantly decreased (from 13.9 ± 36.0 × 10⁴ to 11.1 ± 27.8 × 10⁴·min/mg/dL) by 17.6 ± 20.7% (*P* < 0.001; Figure 2a,b; Table 3). TIR significantly increased (from 42.2 ± 21.1 to 55.5 ± 16.3%, *P* < 0.001) and TAR significantly decreased (from 55.9 ± 20.9 to 42.3 ± 16.6%, *P* < 0.001), but TBR did not change during the study period (Figure 2c–e; Table 3). Next, the relationships between P25/P75 or TIR in all the patients, and their age, sex, type of treatment, baseline HbA1c, change in HbA1c, blood pressure, kidney function or insulin dose were evaluated using

bivariate analyses. Although age positively and the urinary albumin-to-creatinine ratio negatively correlated with the change in P25/P75 in the simple linear regression analyses, no significant correlations were found between these variables in the multiple regression analysis (Table S1).

None of the patients experienced any severe hypoglycemic episodes. When hypoglycemia was evaluated using both symptoms and blood glucose concentration, 39 patients (76.5%) were found to have experienced hypoglycemia before initiating SGLT2i treatment, and 27 patients (52.9%) after initiating SGLT2i treatment (*P* < 0.001 for the difference). Urinary ketone bodies were detected in four patients (7.8%), but none experienced ketoacidosis. Furthermore, none of the patients experienced genital infection or dizziness, or discontinued their SGLT2i during the observation period.

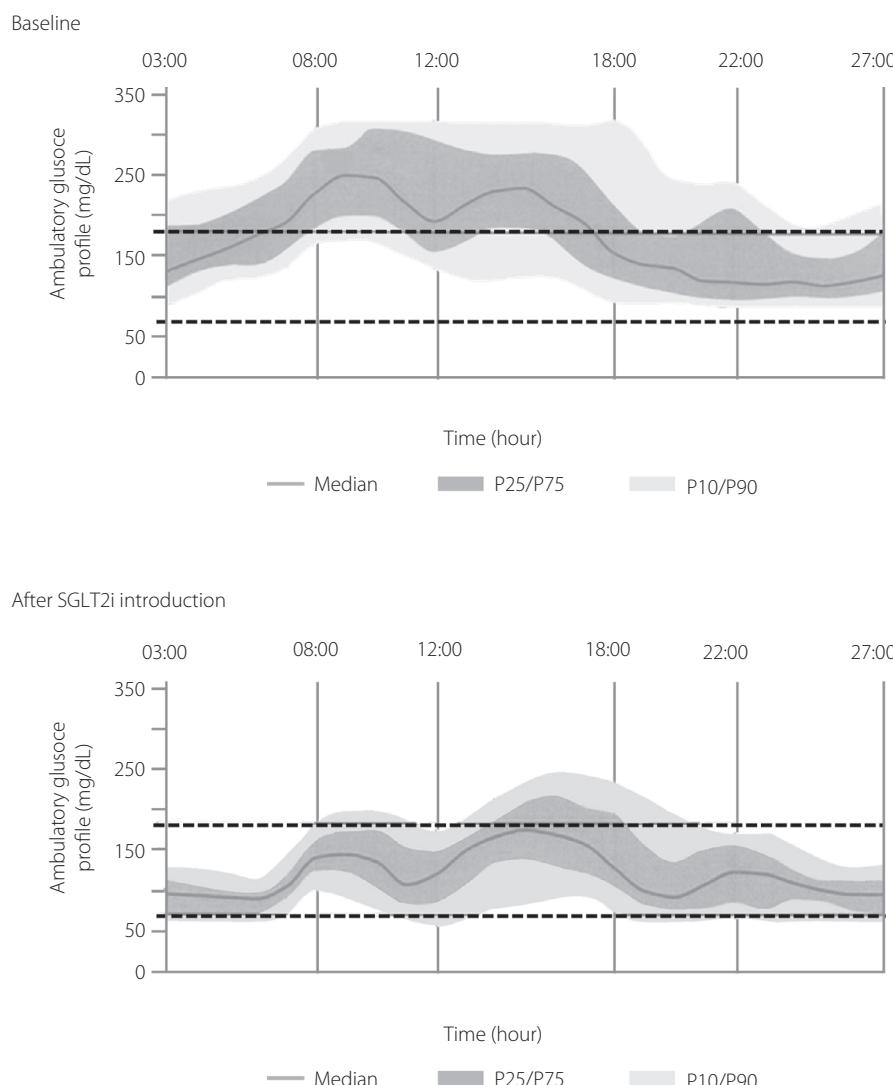
DISCUSSION

In the present study, we showed that SGLT2i have beneficial effects to reduce day-to-day glucose variability in patients with type 1 diabetes. This is the first study to show the benefits of SGLT2i for the glucose variability in a clinical practice setting and as a primary outcome. The effects of SGLT2i to reduce HbA1c, body mass and insulin dose are consistent with those previously reported^{8–10}. A meta-analysis of seven phase II and III studies carried out in patients with type 1 diabetes showed that SGLT2i significantly reduced fasting blood glucose (−12.4 mg/dL) and HbA1c (−0.4%) compared with placebo¹¹. The improvement of HbA1c identified mainly in Western people was similar to that identified in the present Japanese study.

Table 2 | Changes in insulin dose during the 12 weeks of the study

	-4 weeks	0 week	12 weeks
Total insulin dose (units)	42.7 ± 26.6	39.2 ± 26.1** (-8.2%)	38.7 ± 24.3** (-9.4%)
Basal insulin dose (units)	16.8 ± 13.9	15.2 ± 13.3** (-9.5%)	14.9 ± 12.3** (-11.3%)
Bolus insulin dose (units)	25.9 ± 15.7	24.0 ± 15.7** (-7.3%)	23.8 ± 14.3** (-8.1%)

Total $n = 51$. The insulin dose (mean reduction in insulin dose) is shown at each time point. Data are mean ± standard deviation. * $P < 0.05$ between -4 weeks and baseline (0 weeks) or 12 weeks after the introduction of sodium–glucose cotransporter 2 inhibitors. ** $P < 0.001$ between -4 weeks and baseline (0 weeks) or 12 weeks after the introduction of sodium–glucose cotransporter 2 inhibitors.

**Figure 1** | Representative ambulatory glucose profiles at baseline and 12 weeks after the administration of a sodium–glucose cotransporter 2 inhibitor (SGLT2i) commenced. P10, 10th percentile; P25, 25th percentile; P75, 75th percentile; P90, 90th percentile.

Recently, the stabilization of glucose variability has been focused on as one of the goals of glycemic control, because some data showed that the minimization of glucose variability reduced the frequency of cardiovascular events and dementia^{12,13}.

Beneficial effects of SGLT2i on daily glucose variability in patients with type 1 diabetes were first reported after phase II clinical trials of dapagliflozin and sotagliflozin^{8,14}. These were small, short-duration studies carried out using CGM, but they clearly showed

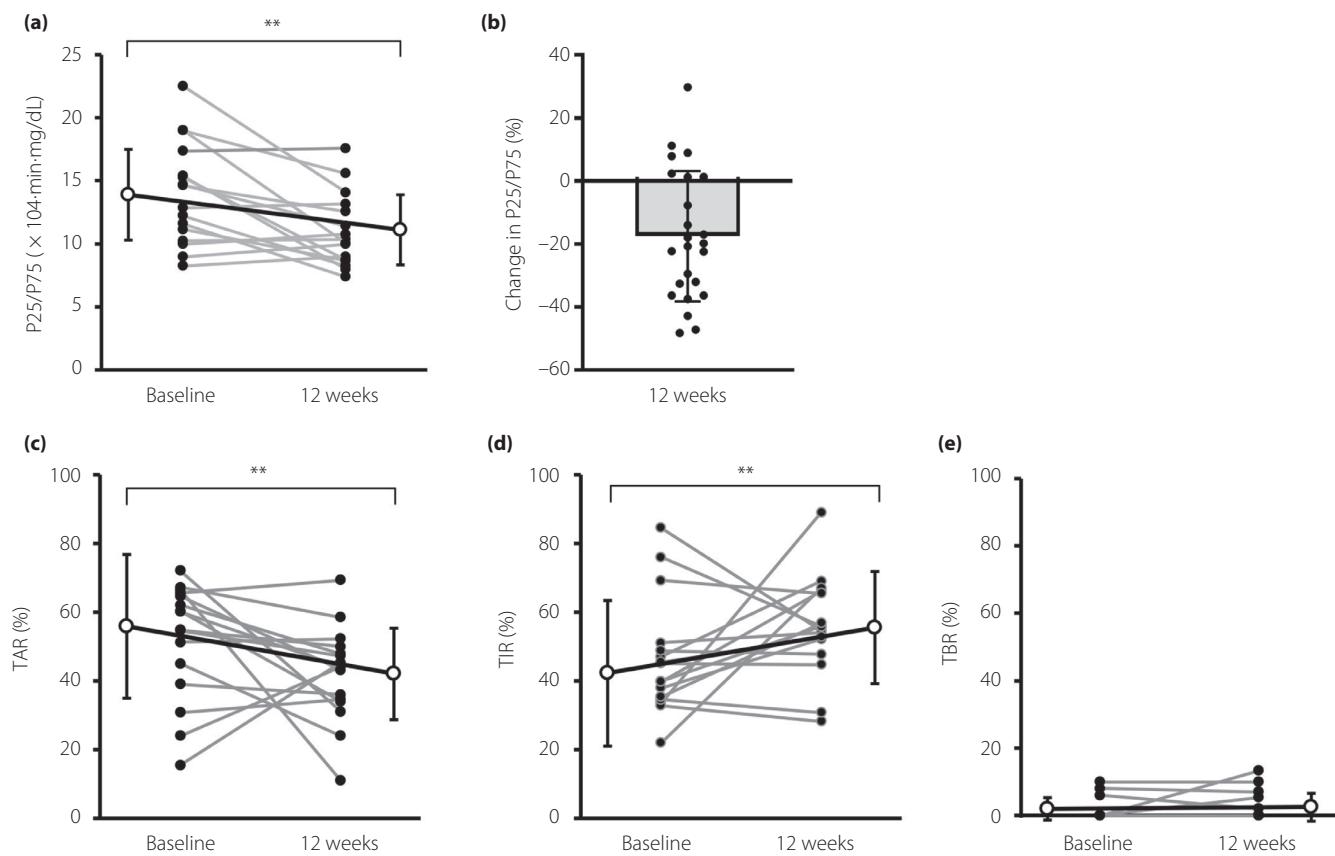


Figure 2 | Comparison of (a,b) day-to-day variability, (c) TAR, (d) TIR and (e) TBR at baseline and 12 weeks after the administration of an sodium-glucose cotransporter 2 (SGLT2) inhibitor commenced. (a) Absolute change in the interquartile range (P25/P75) between baseline and 12 weeks after the administration of an SGLT2 inhibitor commenced. (b) Percentage change in P25/P75 between baseline and 12 weeks after the administration of SGLT2 inhibitors commenced. (c) Time above the normal glucose concentration range (TAR). (d) Time in the normal glucose concentration range (TIR). (e) Time below the normal glucose concentration range (TBR). White circles are the mean \pm standard deviation. ** $P < 0.001$ between baseline and 12 weeks after the introduction of an SGLT2 inhibitor.

Table 3 | Changes in the interquartile range, time above the normal glucose concentration range, time in the normal glucose concentration range and time below the normal glucose concentration range during the 12-week study

	Baseline	12 weeks	P-value
P25/P75 ($\times 10^4 \cdot \text{min/mg/dL}$)	13.9 ± 36.0	11.1 ± 27.8	<0.001
TAR (%)	55.9 ± 20.9	42.3 ± 16.6	<0.001
TIR (%)	42.2 ± 21.1	55.5 ± 16.3	<0.001
TBR (%)	1.97 ± 3.37	2.47 ± 4.12	0.44

Total $n = 30$. Continuous variables are shown as the mean \pm standard deviation. P-value of baseline versus 12 weeks (paired-sample t-tests). P25, 25th percentile; P75, 75th percentile; TAR, time above the normal glucose concentration range; TBR, time below the normal glucose concentration range; TIR, time in the normal glucose concentration range.

that SGLT2i reduced the mean amplitudes of their glycemic excursions or the standard deviation of the daily subcutaneous glucose concentrations of the patients.

A new consensus report regarding CGM was published by the American Diabetes Association in 2019^{5,15}. A beneficial effect of SGLT2i on TIR in Western patients with type 1 diabetes was first identified in the post-hoc analysis of a phase III trial of dapagliflozin (the DEPICT study)⁵. TIR and TAR were significantly improved by administration of this drug, which is consistent with the results of the present study of Asian patients with type 1 diabetes carried out in a clinical practice setting. However, there was no significant difference in TBR between the start and end of the first 12 weeks of SGLT2i administration, although the frequency of symptomatic hypoglycemia was significantly reduced in the present study. These findings might be explained by the small number of incidences of hypoglycemia before SGLT2i administration was initiated. All the insulin pumps used were 640G. There is a possibility that the low glucose suspension function might have affected the hypoglycemia data. Therefore, we excluded the CSII group data and re-evaluated TBR. However, this did not significantly affect TBR (Table S2). Furthermore, TBR might not have

increased, despite a reduction in mean glucose, because of the insulin reduction at baseline, due to close supervision by the physicians. However, the incidence of hypoglycemia could probably be further reduced by adjusting the insulin dose on the basis that glucose variability is reduced by the use of SGLT2i. A reduction in blood glucose without an increase in the risk of hypoglycemia is a potential contributing mechanism for the protective effects of these compounds on the renal and cardiovascular systems¹⁶. Body mass, total insulin dose, TAR and TIR significantly improved in both the multiple daily injection therapy and CSII groups, and there were no differences between these groups. However, there were no significant differences in HbA1c, systolic blood pressure, diastolic blood pressure or P25/P75 in the CSII group (Table S2), which might be explained by the small number of patients who were undergoing CSII. Although a few SGLT2i phase II or III clinical trials have shown improvements in daily glycemic variability in patients with type 1 diabetes, as described above, only one phase II clinical trial assessed day-to-day glucose variability, and found that 7 days' treatment with empagliflozin increased urinary glucose excretion as the primary end-point and reduced the P25/P75 range as a secondary end-point in patients with type 1 diabetes¹⁷. However, the mechanism of this improvement has not been dissected, and the factors influencing this effect have not been investigated to date. We attempted to identify the associated factors in the present study, but did not succeed in finding any significant variables using correlation analysis. Therefore, it would be difficult to predict the potential for further reductions in day-to-day glucose variability.

The results of the present pilot study suggest that SGLT2i might be useful not only for reducing HbA1c while administering less insulin, but also for improving day-to-day glucose variability. Although the mechanism involved in the reduction in glucose variability by SGLT2i were not elucidated in a clinical study, urinary glucose excretion dependent on plasma glucose concentrations and gluconeogenesis in the liver to prevent hypoglycemia are likely to be involved^{18,19}.

SGLT2i administration without a reduction in insulin dose might cause hypoglycemia in patients with type 1 diabetes, as well as in those with type 2 diabetes taking insulin⁸. However, if the insulin administration is not appropriately reduced, the risk of DKA would increase, especially in patients with impaired endogenous insulin secretion. It has been reported that blood ketone body concentrations increase when the insulin dose is reduced by >20% from baseline^{8,20}. The doses of basal and bolus insulin to be administered after SGLT2i treatment were determined by physicians according to the Japanese phase III study data. The reduction guidelines have been recently reported and are recommended by the Japan Diabetes Society²¹. Although the guidelines regarding the rate of reduction of the insulin dose required for patients undergoing SGLT2i treatment were published after the present study commenced, the reduction protocols used were very similar to this recommendation. Specifically, a reduction of 10–20% in the

total insulin dose was made when HbA1c was <7.5%, and no or a small reduction was made when HbA1c was ≥7.5%. In the present study, the mean total insulin dose was reduced by just 9.4%, because some of the participants had HbA1c values of >7.5%. In addition, the reduction was greater with regard to basal insulin than bolus insulin dose, which is consistent with the findings of a randomized controlled trial carried out in Japanese inpatients with type 2 diabetes treated with basal–bolus insulin²². Thus, the addition of an SGLT2i reduced the basal-to-bolus insulin ratio used in the present study.

The limitations of the present study were as follows: small sample size, the lack of a placebo control group and its retrospective design. Therefore, we do not have the actual numerical CGM data and cannot calculate parameters, such as mean of daily difference of blood glucose, to describe day-to-day glucose variability. To resolve these issues, the present findings should be validated in a larger population in a prospective randomized controlled trial. In addition, CGM could not be carried out for every participant who started the administration of an SGLT2i. Furthermore, a previous study showed that CGM values were lower than SMBG values in the lower glucose range, and higher in the higher glucose range²³. Capillary and venous glucose concentrations are similar under steady-state conditions, but might differ under dynamic conditions²⁴. Therefore, CGM data might not be highly accurate and the possibility of such inaccuracies should be considered. Another limitation was the short study duration. However, the improvement in glucose variability could be observed from the start of SGLT2i administration. Furthermore, several previous phase II clinical trials of SGLT2i lasted just a couple of weeks^{8,22}; therefore, 12 weeks might not be too short a period to evaluate the effects of SGLT2i on the study end-points. DKA did not occur during the study period. However, a 12-week period is too short to state the safety regarding the frequency of DKA in this population, and patient education and preparation for possible DKA should be an important consideration when an SGLT2i is added to a patient's treatment regimen.

In conclusion, SGLT2i administration improved both day-to-day glucose variability and time in the target glucose range for patients with type 1 diabetes, in addition to reducing HbA1c, body mass and insulin dose. SGLT2i, alongside adequate insulin adjustment, could reduce the fear of hyper- and hypoglycemia in patients with type 1 diabetes, and would be appropriate for those who have difficulties with glucose variability.

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DISCLOSURE

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | The additional representative ambulatory glucose profiles at baseline and after 12 weeks of administration of an sodium–glucose cotransporter 2 inhibitor.

Table S1 | Relationships between the changes in the interquartile range and other parameters.

Table S2 | Comparison between multiple daily injection and continuous subcutaneous insulin infusion with respect to the characteristics of the participants and the changes during the 12-week study.