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ORIGINAL ARTICLE

Sodium–glucose cotransporter 2 inhibitors improved time-in-range without increasing hypoglycemia in Japanese patients with type 1 diabetes: A retrospective, single-center, pilot study

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ABSTRACT

Aims/Introduction: Studies have shown that sodium–glucose cotransporter 2 (SGLT2) inhibitors increased time-in-range (TIR; percentage of time glucose level remains between 3.9 and 10.0 mmol/L [70–180 mg/dL]) and decreased glycemic variability in patients with type 1 diabetes. The aim of this study was to investigate the effects of SGLT2 inhibitors on TIR, glycemic variability and glucose control in Japanese patients with type 1 diabetes in a real clinical setting.

Materials and Methods: We designed a single-arm, retrospective cohort study to analyze data from patients starting to use ipragliflozin or dapagliflozin and who used a sensor-based flash glucose monitoring system between February 2019 and August 2019. We measured TIR, time above range >180 mg/dL (percentage of time with glucose level of >180 mg/dL or >10.0 mmol/L), time below range <70 mg/dL (percentage of time with glucose level of <70 mg/dL or <3.9 mmol/L), mean glucose and standard deviation, and coefficient of variation for glycemic variability, and then compared the data before and after SGLT2 inhibitors treatments.

Results: We enrolled 15 patients in the study. The total dosages of basal insulin decreased significantly, but the total doses of bolus insulin did not change significantly. TIR increased significantly by approximately 11.6%; the time below range <70 mg/dL remained unchanged; and the mean glucose and standard deviation decreased significantly, whereas the coefficients of variation did not.

Conclusions: SGLT2 inhibitors improved TIR and the mean glucose level and standard deviation without increasing the time below range <70 mg/dL in patients with type 1 diabetes.

INTRODUCTION

Hypoglycemia is a risk factor for cardiovascular complications and dementia in patients with diabetes[1,2]. By contrast, continuous hyperglycemia leads to microvascular and macrovascular complications[3]. Thus, the triumvirate of strategies for glucose control includes reduction in hyperglycemia and hypoglycemia, and maintenance of a small glycemic variability (that is, a small coefficient of variation [CV] for glucose level)[4]. In addition to that, the recent International Consensus proposed a glucose target based on continuous glucose monitoring data. Increasing the target time-in-range (TIR; percentage of time with glucose level between 3.9 and 10.0 mmol/L [70–180 mg/dL]) is

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important to archive target glucose control[5], but hypoglycemia and hyperglycemia occur frequently in patients with type 1 diabetes[6,7]. In addition, low C-peptide values, reflecting inadequate endogenous insulin secretion, have been associated with increased glycemic variability and hypoglycemia[8], and maintenance of glucose control is difficult in patients with type 1 diabetes (especially for those with low C-peptide values)[9,10]. Studies have reported the effects of sodium–glucose co-transporter 2 (SGLT2) inhibitors for glucose control and glycemic variability in patients with type 1 diabetes with low C-peptide value[11-14]. A randomized trial that showed ipragliflozin improved the glycated hemoglobin (HbA1c), and reduced the total insulin dose and bodyweight in Japanese patients with type 1 diabetes with C-peptide values of <0.1987 nmol/L[13]. Another randomized trial showed dapagliflozin improved the mean glucose, mean amplitude of glucose excursion and TIR without increasing the time below range (TBR) in patients with type 1 diabetes with C-peptide values of <0.23 nmol/L[14]. These results showed that SGLT2 inhibitors might be useful for patients with type 1 diabetes having difficulty maintaining adequate glucose control. However, whether these SGLT2 inhibitors improve glycemic variability and TIR, and contribute to improved glucose control in Japanese patients with type 1 diabetes remains unclear. In addition, the results of other studies did not include data from real-world clinical practice. The aim of the present study was to investigate the efficacy of SGLT2 inhibitors in terms of glucose control (that is, for TIR and glycemic variability) in Japanese patients with type 1 diabetes with low C-peptide values.

METHODS

Study populations

In Japan, two types of SGLT2 inhibitors are approved by the insurances: ipragliflozin and dapagliflozin. We enrolled Japanese outpatients with type 1 diabetes who had started taking ipragliflozin (50 mg/day) or dapagliflozin (5 mg/day) and who monitored their glucose level with sensor-based flash glucose monitoring (FGM) systems (Free Style Libre; Abbott Diabetes Care, Witney, UK) in a real-world clinical practice setting between February 2019 and August 2019. We defined the following inclusion criteria: the patients were aged between 18 and 75 years; they had used insulin for >1 year; their HbA1c was between 52 and 96 mmol/L (7.0–11.0%); and their C-peptide index (CPI = C-peptide / fasting plasma glucose × 100) was <0.2 (insulin-dependent status). We excluded patients lacking glucose data from the sensor-based FGM as a result of system data updates, those missing >30% of their readings, those reading carried out only by clinicians and those with diabetic ketoacidosis. We included patients using continuous subcutaneous insulin infusions. This study had no carbohydrate counting cases. Figure 1 shows the flow chart of patient enrollment. After the application of these criteria, we analyzed data from 15 patients, including one with a continuous subcutaneous insulin infusion. The ethics committee at Jichi Medical University, Saitama Medical Center, approved the study (approval number S19-005), and we carried it out in compliance with the tenets of the Declaration of Helsinki.

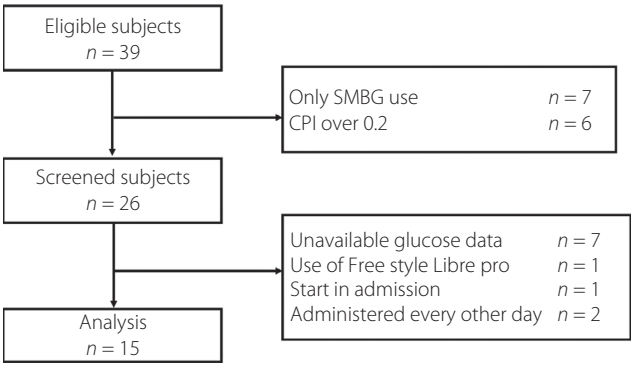

Figure 1 | Flow chart of patient enrollment. CPI, C-peptide index; SMBG, self-monitoring of blood glucose.

Glucose data collection

We analyzed sensor-based FGM system readings. The sensor was attached to the back of the upper arm by patients, and it continuously estimated interstitial glucose levels using a wired enzyme technology. The sensors automatically stored glucose data in the memory of the device every 15 min for eight consecutive hours after scanning by patients, and they could be used for up to two consecutive weeks unless the sensor came off the arm because it was knocked off or any other contact. The data in the sensor could be downloaded to the reader using radio frequency identification. Physicians downloaded the stored data in the reader to a computer during clinic visits[15,16]. The glucose data from the sensor-based FGM system were visible to all patients at all times and during physician visits. We used all the data, including after sensor replacement.

Study design and protocol

This was a single-arm, retrospective cohort study at a single center. Figure 2 shows the study protocol. We analyzed glucose data from sensor-based FGM systems for the 5 days closest to each visit (without including data from the visit day), and estimated the mean glucose value, standard deviation (SD), CV as glycemic variability, TIR, time above range (TAR) >180, TAR >250, TBR <70, TBR <54 mg/dL[5], mean amplitude of glucose excursion[17] and glucose level scanning rates during each 5-day period, considering the daily change and day-by-day variability in the glucose level of type 1 diabetes. In addition, we divided days into three time periods: (i) nocturnal period (00.00–05.59 hours); (ii) day time period (06.00–17.59 hours); and night time period (18.00–23.59 hours).

Clinical background data collection

We obtained baseline demographic data of patients, such as age; sex; body mass index; age at type 1 diabetes diagnosis; duration of type 1 diabetes; total dosages of basal, bolus and

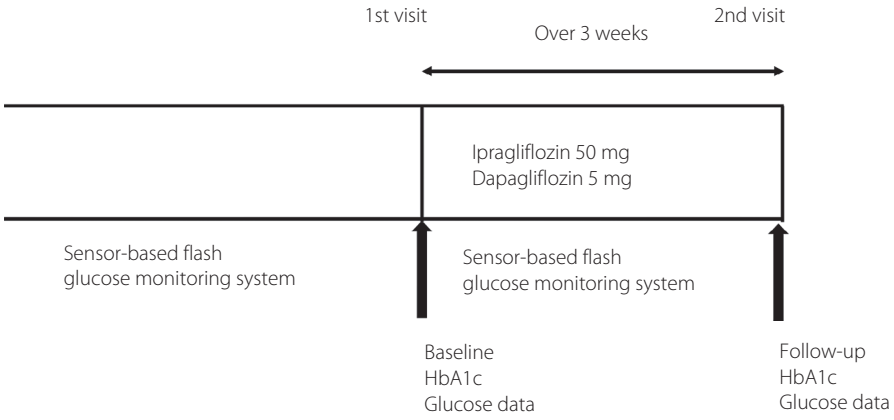

Figure 2 | Study protocol. We enrolled Japanese patients with type 1 diabetes who had initiated treatments with ipragliflozin (50 mg/day) or dapagliflozin (5 mg/day). We analyzed the glucose data of sensor-based flash glucose monitoring system for 5 days closest to the day of the first and second visits (over 3 weeks apart). HbA1c, glycated hemoglobin.

total insulin; and the presence of diabetic complications (neuropathy, retinopathy and nephropathy) through patient interviews or from medical charts. We defined prevalent cardiovascular disease (CVD) as a history of composite events including angina pectoris, myocardial infarction and stroke.

We collected blood and urine samples at the Jichi Medical University, Saitama Medical Center, Saitama, Japan. The blood samples were centrifuged at 3,400 *g* value for 15 min at room temperature, and laboratory values were measured in the local facilities. The estimated glomerular filtration rate (eGFR) was calculated by eGFR (mL/min/1.73 m^2) = 194 × serum creatinine (mg/dL)$^{-1.094}$ × age$^{-0.287}$ × 0.739 (if the participant was a woman)[18].

Statistical analysis

We expressed continuous variable data as the mean ± SD, and categorical variable data as numbers and percentages. We used Pearson's correlation to assess correlations between HbA1c and TIR, CV, and mean glucose values. We applied paired *t*-tests for skewed variables, and Wilcoxon signed-rank test for unskewed variables to compare each parameter before and after using each SGLT2 inhibitor. We excluded missing data from the sensor-based FGM system glucose levels to estimate each parameter. We carried out all statistical analyses using EZR (Jichi Medical University, Saitama Medical Center), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), and a modified version of R commander designed to add statistical functions frequently used in biostatics[19]. We considered all *P*-values <0.05 as statistically significant.

RESULTS

We compared HbA1c and total insulin dose between baseline and 3 months earlier; however, there were no significant changes, as observed in the Table S1. Table 1 shows baseline patients' characteristics. The mean HbA1c was 8.9 ± 1.1%. We found no patients with a history of CVD. A total of 11 patients started using ipragliflozin (50 mg/day), and four patients started using dapagliflozin (5 mg/day). We found an inverse correlation between the baseline HbA1c and the baseline TIR (r = –0.660, P = 0.007), but the association between the HbA1c and the CV was not significant (Figure S1a-c). This correlation was also seen after administration of SGLT2 inhibitors (Figure S1d-f).

Table 2 shows the insulin and glucose variable changes before and after using SGTL2 inhibitors. We found significant overall TIR improvements, nocturnal (00.00–05.59 hours) and

Table 1 | Clinical baseline characteristics of the patients

Clinical parameters	
n	15
Types of SGLT2 inhibitors (ipragliflozin, *n* [%]/dapagliflozin, *n* [%])	11 [73.3]/4 [26.7]
Age (years)	51.8 ± 15.7
Men, *n* (%)	7 (46.7)
BMI (kg/m^2)	24.3 ± 3.4
Hypertension, *n* (%)	2 (13.3)
Hyperlipidemia, *n* (%)	1 (6.7)
Prevalent CVD, *n* (%)	0 (0)
Hemoglobin A_{1c} (%)	8.9 ± 1.1
Diabetes duration (years)	15.2 ± 10.9
Age of diagnosis for type 1 diabetes (years)	36.5 ± 13.9
eGFR (mL/min/1.73 m^2)	92.1 ± 19.3
Neuropathy, *n* (%)	5 (33.3)
Retinopathy, *n* (%)	5 (33.3)
Nephropathy, *n* (%)	0 (0)

Data are presented as *n* (%) for categorical variables and as the mean ± standard deviation for continuous variables. BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; SGLT2, sodium–glucose cotransporter 2.

Table 2 | Insulin and glucose variable changes before and after using sodium–glucose cotransporter 2 inhibitors

Clinical parameters	Before	After	*P*-value
n	15	15	–
Total dose of basal insulin (units)	13.0 (10.0–16.0)	12.8 ± 4.4	0.011
Total dose of bolus insulin (units)	27.1 ± 8.9	26.1 ± 9.3	0.264
Total insulin dose (units)	41.0 ± 10.8	39.0 ± 9.9	0.135
Bodyweight, kg (n = 12)	69.1 ± 14.6	67.9 ± 13.7	0.136
In all time			
Rate of scan (%)	90.2 ± 8.5	87.8 ± 9.1	0.192
Mean glucose (mg/dL)	206.0 ± 45.7	185.4 ± 48.4	0.041
SD of glucose (mg/dL)	79.8 ± 18.5	59.2 (57.5–90.8)	0.048
CV of glucose (%)	39.5 ± 8.7	38.9 ± 7.6	0.777
TAR >250 mg/dL (%)	29.9 ± 19.7	12.2 (5.6–26.7)	0.055
TAR >180 mg/dL (%)	55.2 ± 17.8	43.5 ± 19.1	0.035
TIR (%)	40.1 ± 16.7	51.7 ± 17.2	0.031
TBR <70 mg/dL (%)	1.9 (0.0–19.2)	1.8 (0.2–7.2)	0.529
TBR <54 mg/dL (%)	0.2 (0.0–2.0)	0.4 (0.0–2.6)	0.415
MAGE (mg/dL)	193.4 ± 39.6	164.9 (137.7–203.0)	0.303
Nocturnal period (00.00–05.59 hours)			
Rate of scan (%)	97.5 (86.3–100.0)	93.3 (82.9–99.2)	0.45
Mean glucose (mg/dL)	164.4 (142.7–236.7)	152.4 (130.6–192.2)	0.041
SD of glucose (mg/dL)	66.4 ± 25.7	57.1 ± 22.0	0.086
CV of glucose (%)	36.4 ± 14.7	33.8 ± 10.8	0.339
TAR >250 mg/dL (%)	18.3 (2.7–38.9)	5.5 (0.4–29.6)	0.208
TAR >180 mg/dL (%)	46.2 ± 31.9	21.1 (16.2–52.7)	0.047
TIR (%)	46.3 ± 29.5	59.3 ± 28.9	0.007
TBR <70 mg/dL (%)	0.9 (0.0–19.2)	0.0 (0.0–6.5)	0.359
TBR <54 mg/dL (%)	0.0 (0.0–6.3)	0.0 (0.0–1.7)	0.834
Day time period (06.00–17.59 hours)			
Rate of scan (%)	98.3 (94.0–100.0)	97.1 (89.6–100.0)	0.480
Mean glucose (mg/dL)	216.5 ± 41.3	187.5 ± 51.7	0.008
SD of glucose (mg/dL)	78.3 ± 17.5	62.5 (54.2–83.7)	0.055
CV of glucose (%)	36.7 ± 7.6	37.9 ± 7.9	0.485
TAR >250 mg/dL (%)	33.8 ± 18.6	13.6 (4.8, 20.9)	0.015
TAR >180 mg/dL (%)	62.6 ± 19.1	46.6 ± 21.4	0.015
TIR (%)	33.9 ± 18.1	48.3 ± 18.3	0.022
TBR <70 mg/dL (%)	2.2 (0.0–6.2)	3.3 (0.0–8.4)	0.666
TBR <54 mg/dL (%)	0.0 (0.0–0.4)	0.8 (0.0–2.4)	0.236
Night time period (18.00–23.59 hours)			
Rate of scan (%)	87.5 (72.1–96.3)	77.5 (68.3–93.8)	0.315
Mean glucose (mg/dL)	193.3 ± 45.1	194.6 ± 50.5	0.937
SD of glucose (mg/dL)	73.0 ± 24.9	65.6 ± 19.2	0.299
CV of glucose (%)	38.4 ± 11.7	34.7 ± 9.7	0.316
TAR >250 mg/dL (%)	25.2 ± 21.5	17.7 (9.5, 32.3)	0.410
TAR >180 mg/dL (%)	51.0 ± 20.6	51.7 ± 25.5	0.940
TIR (%)	43.9 ± 17.8	44.7 ± 23.3	0.926
TBR <70 mg/dL (%)	0.0 (0.0–3.7)	0.0 (0.0–3.2)	0.363
TBR <54 mg/dL (%)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.855

Data are presented as the mean ± standard deviation (SD) for unskewed variables, and as medians with interquartile range for skewed variables. We considered $P < 0.05$ as statistically significant. CV, coefficient of variation; MAGE, mean amplitude of glucose excursion; TAR, time above range; TBR, time below range; TIR, time-in-range.

day time (06.00–17.59 hours) periods (Figure 3). The mean glucose level and SD both improved after the administration of SGLT2 inhibitors (Figure 4). The baseline total dosages of basal and bolus insulin were 13.0 units (interquartile range 10.0–16.0 units) and 27.1 ± 8.9 units, respectively. Total dosages of basal insulin decreased significantly, but the total dosages of

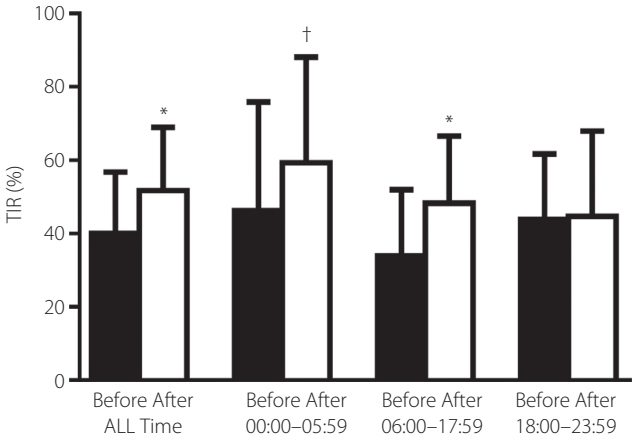

Figure 3 | Time-in-range (TIR) changes before and after using sodium–glucose cotransporter 2 inhibitors. The numbers represent different daily time intervals (00.00–05.59 hours, 06.00–17.59 hours and 18.00–23.59 hours). Analyses were carried out using the paired *t*-test for skewed variables, and Wilcoxon signed-rank test for unskewed variables. $^{*}P < 0.05$, $^{\dagger}P < 0.01$. Data are expressed as the mean ± standard deviation.

bolus insulin and total insulin did not decrease significantly (Table 2). The overall baseline TIR, TAR >180 and TBR <70 mg/dL were 40.1 ± 16.7%, 55.2 ± 17.8% and 1.9% (interquartile range 0.0–19.2%), respectively. Overall TIR increased significantly by approximately 11.6% (Table 2). Although the overall TAR >180 mg/dL were significantly decreased, the TBR <70 mg/dL did not change after SGLT2 inhibitors. Daytime TIR (06.00–17.59 hours) were relatively lower than other TIR, and this was especially true before using SGLT2 inhibitors (Table 2). The overall baseline mean glucose, SD and CV of glucose were 206.0 ± 45.7, 79.8 ± 18.5 mg/dL and 39.5 ± 8.7%, respectively. Although the overall mean glucose and SD decreased significantly, the overall CV of glucose did not decrease. Figure 5 shows glucose data from the sensor-based FGM systems every 15 min before and after using SGLT2 inhibitors. In this study period, none of the patients forgot to take SGLT2 inhibitors or had adverse events associated with using of SGLT2 inhibitors.

DISCUSSION

We investigated the effects of SGLT2 inhibitors on glucose control, especially for TIR and glycemic variability in Japanese patients with type 1 diabetes with low C-peptide in the real-world clinical practice. The present results showed that using SGLT2 inhibitors improves the TIR by reducing TAR >180 mg/dL and without increasing TBR <70 mg/dL. SGLT2 inhibitors also improved the mean glucose and the SD, but not the CV of glucose.

Other studies showed that both dapagliflozin and canagliflozin improved TIR without increasing TBR <70 mg/dL[12,14]. Thus, the present study supports those findings in a real-world clinical situation. In this study, the insulin titration depended on attending physicians and there was no protocol, but the rate of reduction in

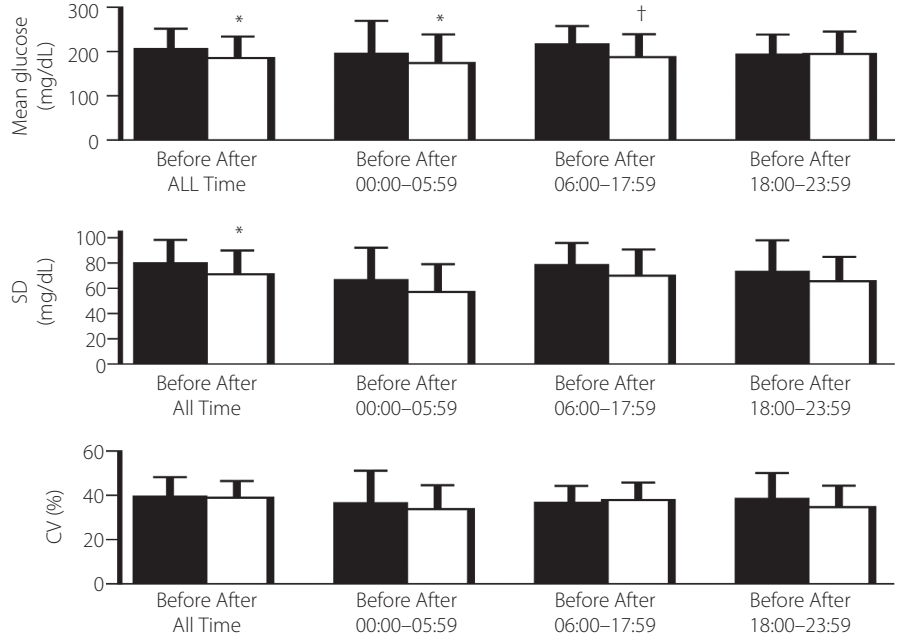

Figure 4 | Mean glucose, standard deviation (SD) and coefficient of variation (CV) changes before and after using sodium–glucose cotransporter 2 inhibitors. The numbers represent different daily time intervals (00.00–05.59 hours, 06.00–17.59 hours and 18.00–23.59 hours). Analyses were carried out using the paired *t*-test for skewed variables, and Wilcoxon signed-rank test for unskewed variables. $^{*}P < 0.05$. Data are expressed as the mean ± SD.

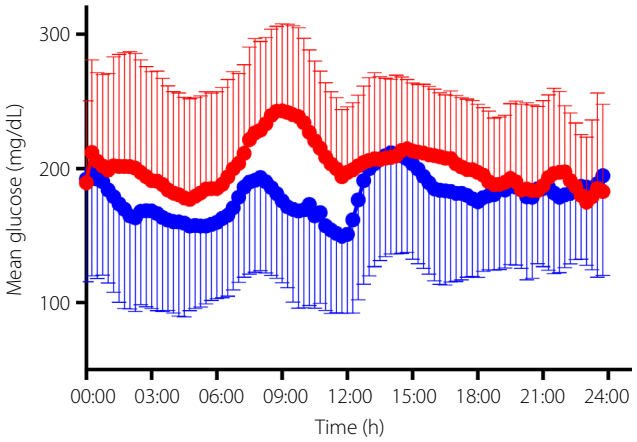

Figure 5 | Mean glucose profiles before and after sodium–glucose cotransporter 2 inhibitors. Red circles indicate mean glucose before sodium–glucose cotransporter 2 inhibitor administration, and blue circles indicate mean glucose after sodium–glucose cotransporter 2 inhibitor administration. Data are expressed as the mean ± standard deviation.

basal and bolus insulin was relatively lower in the present study than in other studies[13,20,21]. However, the TBR <70 and TBR <54 mg/dL remained unchanged after SGLT2 inhibitors administration. This result might be explained by relatively lower baseline total dosages of insulin (41 units in this study vs 50–60 units in previous studies) and higher baseline HbA1c (8.9% in the present study vs 8.5–8.7% in previous studies)[13,20,21]. In the present study, SGLT2 inhibitors did not increase TIR during night-time. One reason for this might be because the rate of scans at night were relatively lower than that at other times before and after SGLT2 inhibitor administration.

SGLT2 inhibitors decrease the reabsorption of glucose and increase the excretion of glucose according to glycemic level[22]. Therefore, when glucose level is low, SGLT2 inhibitors reduce the excretion of glucose and do not cause hypoglycemia[23]. A study using healthy mice showed that SGLT2 was expressed in alpha cells, and SGLT2 inhibitors led to increasing glucagon and hepatic gluconeogenesis in the fasting state[24]. In other studies, although SGLT2 inhibitors reduced the fasting glucose level, they increased endogenous glucose production and glucagon[25,26]. Okajima *et al.*[27] showed that ipraglifrozin reduced TBR <70 mg/dL from 00.00 to 08.00 hours in type 2 diabetes patients with basal–bolus therapy. The present study showed SGLT2 inhibitors did not increase TBR <70 mg/dL from 00.00 to 06.00 hours in type 1 diabetes patients. This difference might be because of prospective and retrospective designs or difference of diabetes type. However, in situations with high glucose level, SGLT2 inhibitors increase the excretion of glucose and cause a reduction in hyperglycemia[23]. The present study showed that SGLT2 inhibitors can help patients with type 1 diabetes control their glycemic levels, because they increase the TIR by reducing the TAR >180 mg/dL without increasing the TBR <70 mg/dL.

Clinically, overall TIR was increased by 11.6%. Other studies showed that 10% reductions in TIR led to a 0.6–0.8% reduction in HbA1c[28,29]. A 2.0% reduction in HbA1c in type 1 diabetes led to a 50–76% reduction in the development and progression of microvascular complications in the Diabetes Control and Complications Trial, which enrolled patients with type 1 diabetes with intensive or conventional therapy[30,31]. This effect was maintained for a long time and reduced the rates of macrovascular complications, such as CVD events by 42%[32]. Another study showed that an ~1% increase in HbA1c led to a 15% risk increase in CVD, but this change was not significant[33]. Therefore, from the viewpoint of improved glucose control, SGLT2 inhibitors might reduce rates of complications by microvascular and macrovascular events, especially in patients with type 1 diabetes with low C-peptide through improvement of their TIR.

In contrast, in the present study, SGLT2 inhibitors improved mean glucose and SD of glucose, but not CV of glucose in patients with type 1 diabetes with low C-peptide in the real-world clinical practice. A study using canagliflozin showed reduced mean glucose and SD of glucose, but not CV of glucose between the placebo and canagliflozin group[12]. The present study was consistent with a previous study, and because both mean glucose and SD of glucose were reduced, the CV of glucose might remain constant. A cross-sectional study showed that every 1-mmol/L (18 mg/dL) increase in the SD of glucose leads to an 8% risk increase for asymptomatic hypoglycemia[34]. In contrast, that study showed that every 1-mmol/L (18 mg/dL) increase in mean glucose led to a 4% risk decrease for asymptomatic hypoglycemia[34]. SGLT2 inhibitors might be useful for the improvement of the mean and SD of glucose, and they did not increase hypoglycemic events in the real-world clinical practice.

The present study had some strengths; first, we estimated TIR using a sensor-based FGM system. If patients estimate that variability and TIR in clinical situations, they would be encouraged to use SGLT2 inhibitors. Second, we estimated TIR and glycemic variability in the real-world clinical setting, and confirmed results from trials.

We are aware of some limitations of the present study. First, this study was a single-arm, retrospective observational study. The attending physicians determined the amount of insulin reduction. Furthermore, this study had no control groups. The results showing that SGLT2 inhibitors improve TIR and SD of glucose might be due to placebo effects. To solve that problem, a large database of the real-world clinical practice and propensity scores would be necessary. Furthermore, we did not sufficiently evaluate the adverse effects. Second, our study period was small and short, therefore, the long-term effects remain unknown. Evaluating long-term effects and safety of SGLT2 inhibitors in patients with type 1 diabetes remains important.

In conclusion, the treatment with SGLT2 inhibitors improved TIR, mean glucose value and SD without increasing TBR (<70 mg/dL) in Japanese patients with type 1 diabetes with low

C-peptide values in real-world practice. SGLT2 inhibitors might help patients with type 1 diabetes to improve their glycemic control.

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DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Goto A, Arah OA, Goto M, *et al*. Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. *BMJ* 2013; 347: f4533.
2. Whitmer RA, Karter AJ, Yaffe K, *et al*. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA* 2009; 301: 1565–1572.
3. Stratton IM, Adler AI, Neil HA, *et al*. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000; 321: 405–412.
4. Monnier L, Colette C, Owens DR. The application of simple metrics in the assessment of glycaemic variability. *Diabetes Metab* 2018; 44: 313–319.
5. Battelino T, Danne T, Bergenstal RM, *et al*. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care* 2019; 42: 1593–1603.
6. Donnelly LA, Morris AD, Frier BM, *et al*. Frequency and predictors of hypoglycaemia in Type 1 and insulin-treated Type 2 diabetes: a population-based study. *Diabet Med* 2005; 22: 749–755.
7. Miller KM, Foster NC, Beck RW, *et al*. Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D exchange clinic registry. *Diabetes Care* 2015; 38: 971–978.
8. Christensen MB, Gaede P, Hommel E, *et al*. Glycaemic variability and hypoglycaemia are associated with C-peptide levels in insulin-treated type 2 diabetes. *Diabetes Metab* 2019; 46: 61–65.
9. The Diabetes Control and Complications Trial Research Group. Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in the diabetes control and complications trial. A randomized, controlled trial. *Ann Intern Med* 1998; 128: 517–523.
10. Lachin JM, McGee P, Palmer JP, *et al*. Impact of C-peptide preservation on metabolic and clinical outcomes in the Diabetes Control and Complications Trial. *Diabetes* 2014; 63: 739–748.
11. Famulla S, Pieber TR, Eilbracht J, *et al*. Glucose exposure and variability with empagliflozin as adjunct to insulin in patients with type 1 diabetes: continuous glucose monitoring data from a 4-week, randomized, placebo-controlled trial (EASE-1). *Diabetes Technol Ther* 2017; 19: 49–60.
12. Rodbard HW, Peters AL, Slee A, *et al*. The effect of canagliflozin, a sodium glucose cotransporter 2 inhibitor, on glycemic end points assessed by continuous glucose monitoring and patient-reported outcomes among people with type 1 diabetes. *Diabetes Care* 2017; 40: 171–180.
13. Kaku K, Isaka H, Sakatani T, *et al*. Efficacy and safety of ipragliflozin add-on therapy to insulin in Japanese patients with type 1 diabetes mellitus: a randomized, double-blind, phase 3 trial. *Diabetes Obes Metab* 2019; 21: 2284–2293.
14. Mathieu C, Dandona P, Phillip M, *et al*. Glucose variables in type 1 diabetes studies with dapagliflozin: pooled analysis of continuous glucose monitoring data from DEPICT-1 and -2. *Diabetes Care* 2019; 42: 1081–1087.
15. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, *et al*. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. *Lancet* 2016; 388: 2254–2263.
16. Haak T, Hanaire H, Ajjan R, *et al*. Flash glucose-sensing technology as a replacement for blood glucose monitoring for the management of insulin-treated type 2 diabetes: a multicenter, open-label randomized controlled trial. *Diabetes Ther* 2017; 8: 55–73.
17. Service FJ, Molnar GD, Rosevear JW, *et al*. Mean amplitude of glycemic excursions, a measure of diabetic instability. *Diabetes* 1970; 19: 644–655.
18. Matsuo S, Imai E, Horio M, *et al*. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; 53: 982–992.
19. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant* 2013; 48: 452–458.
20. Henry RR, Rosenstock J, Edelman S, *et al*. Exploring the potential of the SGLT2 inhibitor dapagliflozin in type 1 diabetes: a randomized, double-blind, placebo-controlled pilot study. *Diabetes Care* 2015; 38: 412–419.
21. Mathieu C, Dandona P, Gillard P, *et al*. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (the DEPICT-2 Study): 24-week results from a randomized controlled trial. *Diabetes Care* 2018; 41: 1938–1946.
22. DeFronzo RA, Hompesch M, Kasichayanula S, *et al*. Characterization of renal glucose reabsorption in response to dapagliflozin in healthy subjects and subjects with type 2 diabetes. *Diabetes Care* 2013; 36: 3169–3176.
23. Vallon V, Thomson SC. Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. *Diabetologia* 2017; 60: 215–225.
24. Bonner C, Kerr-Conte J, Gmyr V, *et al*. Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion. *Nat Med* 2015; 21: 512–517.

25. Merovci A, Solis-Herrera C, Daniele G, *et al*. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. *J Clin Invest* 2014; 124: 509–514.
26. Ferrannini E, Muscelli E, Frascerra S, *et al*. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. *J Clin Invest* 2014; 124: 499–508.
27. Okajima F, Nagamine T, Nakamura Y, *et al*. Preventive effect of ipragliflozin on nocturnal hypoglycemia in patients with type 2 diabetes treated with basal-bolus insulin therapy: an open-label, single-center, parallel, randomized control study. *J Diabetes Investig* 2017; 8: 341–345.
28. Vigersky RA, McMahon C. The relationship of hemoglobin A1C to time-in-range in patients with diabetes. *Diabetes Technol Ther* 2019; 21: 81–85.
29. Beck RW, Bergenstal RM, Cheng P, *et al*. The relationships between time in range, hyperglycemia metrics, and HbA1c. *J Diabetes Sci Technol* 2019; 13: 614–626.
30. American Diabetes Association. Glycemic targets: standards of medical care in diabetes-2019. *Diabetes Care*. 2019; 6: S61–S70.
31. Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, *et al*. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; 329: 977–986.
32. Nathan DM, Cleary PA, Backlund JY, *et al*. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005; 353: 2643–2653.
33. Selvin E, Marinopoulos S, Berkenblit G, *et al*. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004; 141: 421–431.
34. Monnier L, Wojtusciszyn A, Colette C, *et al*. The contribution of glucose variability to asymptomatic hypoglycemia in persons with type 2 diabetes. *Diabetes Technol Ther* 2011; 13: 813–818.

SUPPORTING INFORMATION

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

Figure S1 | (a) Correlation between baseline glycated hemoglobin (HbA1c) and time-in-range (TIR) before sodium–glucose cotransporter 2 (SGLT2) inhibitor administration. (b) The correlation between baseline HbA1c and coefficient of variation (CV) of mean glucose. (c) The correlation between baseline HbA1d and mean glucose. (d) The correlation between baseline HbA1c and time-in-range (TIR) after SGLT2 inhibitor administration. (e) The correlation between baseline HbA1c and CV of mean glucose after SGLT2 inhibitor administration. (f) The correlation between baseline HbA1c and mean glucose after SGLT2 inhibitor administration.

Table S1 | Total dosage of insulin and glycated hemoglobin changes between 3 months before baseline and at baseline.