Glucose-lowering effects of 7-day treatment with SGLT2 inhibitor confirmed by intermittently scanned continuous glucose monitoring in outpatients with type 1 diabetes. A pilot study

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Abstract. The present study used intermittently scanned continuous glucose monitoring (isCGM) in 10 patients with type 1 diabetes mellitus (T1DM) to evaluate the efficacy and safety of 7-day outpatient treatment with the combination of intensive insulin therapy and sodium-glucose transporter 2 inhibitor (SGLT2-I). All participants wore isCGM and were treated with either 50 mg/day ipragliflozin or 5 mg/day dapagliflozin. The primary outcome, percent time with glucose at 70–180 mg/dL (TIR: time in range), improved significantly following the addition of SGLT2-I ($p = 0.005$). TIR increased from 36.0% before addition of SGLT2-I to 70.7% on day 7. Although none of the patients achieved TIR of 70% or higher before the addition of SGLT2-I, 6 patients met that criteria TIR on day 7. The secondary outcome measures, standard deviation (SD) of glucose, average plasma glucose, percent time with glucose at >180 mg/dL (TAR: time above range), maximum plasma glucose, high blood glucose index (HBGI) and average nocturnal plasma glucose (midnight to 05:59 AM) detected by isCGM, also improved significantly by SGLT2-I. There were no significant differences in percent time with glucose at <70 mg/dL (TBR: time below range), minimum plasma glucose and low blood glucose index (LBGI). Our results using isCGM in an actual clinical setting showed that 7-day use of SGLT2-I with intensive insulin therapy improved plasma glucose fluctuations and mean plasma glucose levels without inducing hypoglycemia in patients with T1DM.

Key words: Type 1 diabetes mellitus, Intermittently scanned continuous glucose monitoring, Sodium glucose cotransporter-2 inhibitor

WHILE data from the Japan Diabetes Clinical Data Management Study Group (JDDM) in 2018 showed improvement in glycated hemoglobin (HbA1c) levels over time in Japanese patients with type 1 diabetes mellitus (T1DM) following the development of new insulin preparations, the use of these forms of preparation have been linked to a gradual increase in the body mass index (BMI) in both patients with T1DM and type 2 diabetes mellitus (T2DM) as well as the number of obese patients (JDDM in 2018). Several clinical trials have been conducted to define the indications for use of sodium-glucose transporter 2 inhibitor (SGLT2-I) in T1DM [1-3]. A meta-analysis of 14 such randomized controlled trials

including three phase III clinical trials; the Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 Diabetes (DEPICT-1) trial [1], Empagliflozin as Adjunctive to Insulin Therapy in Type 1 Diabetes (The EASE Trials) [2], and the in Tandem trial of sotagliflozin [3], which is not marketed in Japan, showed that SGLT2-I reduces HbA1c levels by 0.4% compared with placebo, fasting plasma glucose level by 21 mg/dL, systolic blood pressure by 3.4 mmHg, daily insulin dose by 6 units and body weight by 2.7 kg [4]. In Japan, some use of SGLT2-I has been covered by the National Health Insurance for T1DM since December 2018.

In 2019, the international panel of the Advanced Technologies and Treatments for Diabetes (ATTD) Congress issued treatment guidelines for glycemic control targets under continuous glucose monitoring (CGM) [5]. According to these guidelines, the target therapeutic range is a blood glucose level of 70–180 mg/dL for patients, excluding pregnant women. The time in range (TIR) recorded through the CGM is defined as

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the percent time spent at blood glucose level within the above range, while the time below range (TBR) is defined as the percent time spent at blood glucose level in the hypoglycemic range (<70 mg/dL), and the time above range (TAR) represents the percent time spent at blood glucose level in the hyperglycemic range (>180 mg/dL). A TIR of 70% or higher is preferred even in patients with T1DM. The TIR is associated with HbA1c levels and diabetic complications [6], and a recent meta-analysis study of 18 CGM-based studies concluded that TIR levels correlate well with those of HbA1c [7].

Only a few studies have evaluated the effects of SGLT2-I in Japanese patients with T1DM using intermittently scanned continuous glucose monitoring (isCGM), especially those treated at the outpatient clinics. The present study used isCGM to evaluate the early efficacy and safety of the combination of intensive insulin therapy and SGLT2-I in an actual clinical setting in 10 patients with T1DM treated at the outpatient clinic.

Subjects and Methods

Participants

The study participants were 10 patients with T1DM (acute type: 4 patients, slowly progressive type: 5 patients, fulminant type: 1 patient), who visited the outpatient clinic of the Department of Endocrinology, Metabolism and Diabetes, University of Occupational and Environmental Health, Japan. We excluded patients treated with SGLT2-I and those with severe liver dysfunction (aspartate aminotransferase >100 IU/L), estimated glomerular filtration rate (eGFR) of <30 mL/min/ 1.73 m², BMI <18.0 kg/m² and those with history of allergy to SGLT2-I. Although there were no restrictions on the use of oral anti-hyperglycemic agents other than SGLT2-I, changes of drugs and insulin dose were prohibited while wearing the isCGM. The study was approved by the Ethics Committee of the University of Occupational and Environmental Health, Japan (#H27-186).

Study design

This study was a retrospective study. All participants wore isCGM (FreeStyle Librepro[®], Abbott) and the data used for analysis were obtained from day 3 of wearing isCGM to ensure stability of the data. No changes were made to diet or exercise therapy or drugs and insulin dose (except the SGLT2-I). We separated the isCGM data into baseline data (those recorded before treatment from 0:00 on day 3 to 23:59 on day 3 of wearing the isCGM), and those of post-treatment [after treatment with either 50 mg/day ipragliflozin (IPR) ($n = 6$) or 5 mg/day dapagliflozin (DAPA) ($n = 4$) recorded over the

period from 0:00 on day 4 of wearing the isCGM for 7 days). The patients underwent in-hospital education program designed to prevent euglycemic ketoacidosis. The program included advice on drinking sufficient amount of water during the day, avoidance of excess carbohydrate restriction and, information on polydipsia, and detailed side-effects of treatment with SGLT2-I especially when the patients are feeling sick or lack appetite.

Laboratory tests

Blood samples were collected early in the morning after at least 12-h fasting, through a venous line placed in the median vein using an indwelling catheter. Measurement of each parameter was outsourced to SRL Co. (Tokyo, Japan) using standard methods. All samples were stored at -80°C until measurement.

Study outcomes

The primary outcome was percent time at glucose between 70 and 180 mg/dL (TIR) detected by isCGM. The secondary outcomes were standard deviation (SD) of glucose, average plasma glucose, percent time with glucose at <70 mg/dL (TBR), percent time with glucose at >180 mg/dL (TAR), maximum plasma glucose, minimum plasma glucose, high blood glucose index (HBGI), low blood glucose index (LBGI), %coefficient of variation (%CV), SD of glucose during nocturnal period (0:00–05:59) and average plasma glucose during nocturnal period (0:00–05:59) detected by the isCGM. We also defined the glycemic control achieved group as those patients who achieved TIR of $\geq 70\%$ on day 7.

Statistical analysis

Data were expressed as mean $\pm$ SD. Friedman test was used for comparison of the baseline and post-treatment data. The time-course changes in each glucose parameter detected by the isCGM were compared by the Dunnett test (data of Table 2). The spearman correlation was used for analysis of the data listed in Table 3. The Mann-Whitney *U* test was used to compare the achievement and non-achievement groups in Table 4 (achievement group: patients who showed improvement in percent time with glucose at 70–180 mg/dL to $\geq 70\%$ after the combination treatment). The level of statistical significance was set at $p < 0.05$. All statistical analyses were conducted using the Statistical Package for Social association version 21.0 (SPSS Inc., Chicago, IL).

Results

Baseline characteristics

Table 1 shows the baseline characteristics of the patients. The median age of the 10 participants was 59.5

Table 1 Baseline characteristics of patients

Sex (male:female)	10 (4:6)
Age (year)	59.5 (44.8–62.3)
Diabetes duration (years)	5.0 (2.0–8.3)
Body weight (kg)	61.3 (53.0–68.5)
Body mass index (kg/m ²)	22.7 (21.0–27.1)
HbA1c (%)	9.1 (8.8–9.2)
FPG (mg/dL)	101.5 (81.5–188.0)
AST (IU/L)	22.5 (18.0–30.5)
ALT (IU/L)	18.5 (11.0–24.8)
γ -GTP (IU/L)	20.0 (11.0–53.0)
eGFR (mL/min/1.73 m ²)	77.7 (70.2–90.3)
LDL-C (mg/dL)	81.0 (66.5–94.8)
HDL-C (mg/dL)	57.0 (49.0–68.3)
TG (mg/dL)	111.0 (71.0–195.5)
Required insulin dose (u/day)	Total: 34.0 (22.8–57.0) Bolus: 16.0 (12.0–19.5) Basal: 17.0 (9.3–34.0)
Diabetic microangiopathy	neuropathy: 2/10 retinopathy: 1/10 nephropathy: 3/10, micro albumin urea: 11.3 (4.2–46.9)
Endogenous insulin secretion (<i>n</i> = 8)	serum c-peptide immunoreactivity (ng/mL): 0.29 (0.06–0.43) c peptide index: 0.10 (0.03–0.21)
SGLT2-I (<i>n</i>)	Ipragliflozin 50 mg/day: 6, Dapagliflozin 5 mg/day: 4
Other drugs (<i>n</i>)	α -GI: 5, Metformin: 2
Glucose parameters detected by isCGM	
SD of glucose (mg/dL)	69.0 (52.8–76.0)
Average plasma glucose (mg/L)	184.0 (174.2–236.5)
%CV	34.3 (23.3–44.2)
Percent time with glucose at <70 mg/dL (%)	0.5 (0–8.1)
Percent time with glucose at 70–180 mg/dL (%)	39.0 (18.0–59.7)
Percent time with glucose at >180 mg/dL (%)	56.8 (37.8–71.1)
Maximum plasma glucose (mg/dL)	310.5 (288.3–441.8)
Minimum plasma glucose (mg/dL)	73.5 (49.0–130.5)
LBGI	2.5 (0.04–6.7)
HBGI	16.1 (11.5–23.1)

Data are median or number (25–75% values).

HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ -GTP, gamma-glutamyl transpeptidase; eGFR, estimated glomerular filtration rate; SGLT2-I, sodium-glucose cotransporter-2 inhibitor; α -GI, alpha-glucosidase inhibitor; CV, coefficient of variation; LBGI, low blood glucose index; HBGI, high blood glucose index.

years, and 4 were males. The median duration of diabetes was 5.0 years. Participants were mildly obese, with a median BMI of 22.7 kg/m². Renal function was normal, with eGFR of 77.7 mL/min/1.73 m². Laboratory tests showed poor blood glucose control, with median HbA1c

level at 9.1%. The median dose of total insulin was 34.0 u/day (bolus insulin 16.0 u/day and basal insulin 17.0 u/day), while 5 patients used alpha-glucosidase inhibitor, and 2 patients were on metformin. The baseline isCGM data are shown in Table 1.

Changes in glucose parameters detected by isCGM

Fig. 1 shows the mean values of isCGM parameters for all the participants before (Fig. 1A) and after treatment with SGLT2-I for 7 days (Fig. 1B). We also show isCGM data for all the participants at baseline (Supplementary Fig. 1A) and after treatment with SGLT2-I for 7 days (Supplementary Fig. 1B).

As shown in Table 2, SGLT2-I significantly improved TIR from baseline to day 7, the main outcome measure ($p = 0.005$). The improvement was significant from day 5 based on the Dunnett test. SGLT2-I also significantly improved the secondary outcome measures, including SD of glucose, average plasma glucose, TAR, maximum plasma glucose, HBGI and average nocturnal plasma glucose (0:00–05:59) from baseline to day 7 (Table 2). In contrast, SGLT2-I had no effect on %CV, TBR, minimum plasma glucose, LBG1 and SD of nocturnal glucose (0:00–05:59) from baseline to day 7 (Table 2).

Univariate analysis of factors affecting the change in the TIR on day 7 showed a significant negative relationship with the TIR at baseline (Table 3). Comparison of patients with and without TIR of 70% or higher on day 7 showed significant differences in eGFR, baseline mean plasma glucose, baseline maximum plasma glucose, and baseline HBGI between the two groups (Table 4).

Safety

No serious side effects were observed during the study period. After the addition of SGLT2-I, many patients developed hypoglycemia, as recorded by the isCGM, but there were no significant changes in TBR and minimum plasma glucose (Table 2). Furthermore, none of the patients developed severe hypoglycemia associated with disturbance of consciousness or requiring medical intervention. Also, none of the patients developed ketosis or ketoacidosis after the addition of SGLT2-I.

Fig. 1 (A) isCGM data before the addition of SGLT2-I, (B) isCGM data at day 7 after the addition of SGLT2-I. The center solid line is the median, the next outer solid lines are the interquartiles (25th and 75th percentiles), and the dotted lines depict the 10th and 90th percentiles. isCGM, flash glucose monitoring; SGLT2-I, sodium–glucose cotransporter 2 inhibitor.

Table 2 Changes in glucose parameters detected by isCGM

	pre-treatment	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	<i>p</i>
SD of glucose (mg/dL)	69.0 (52.8–76.0)	57.9 (38.6–75.9)	44.2 (33.5–66.9)	46.3 (43.6–57.0)	44.3 (35.5–62.3)	40.9 (33.7–44.4)**	45.4 (28.9–58.7)*	39.9 (34.7–49.1)*	0.005
Average plasma glucose (mg/dL)	184.0 (174.2–236.5)	172.7 (134.6–197.4)*	147.0 (114.6–180.6)**	139.5 (108.6–151.0)***	122.9 (105.2–151.0)***	113.2 (96.9–130.9)***	118.0 (101.5–145.7)***	118.5 (106.1–141.5)***	<0.001
%CV	34.3 (23.3–44.2)	37.7 (27.4–41.3)	30.6 (27.4–43.1)	35.5 (32.5–44.8)	37.3 (29.8–42.3)	35.7 (29.3–40.1)	35.8 (27.0–42.7)	32.9 (28.8–40.4)	0.805
Percent time with glucose at <70 mg/dL (%)	0.5 (0–8.1)	5.2 (0–9.9)	7.3 (0–22.1)	8.3 (0–22.9)	7.3 (0–26.6)	16.2 (1.8–24.0)	12.5 (1.6–21.9)	10.4 (1.6–20.1)	0.318
Percent time with glucose at 70–180 mg/dL (%)	39.0 (18.0–59.7)	45.9 (36.2–73.9)	67.2 (54.1–81.2)**	67.2 (58.3–74.2)**	71.9 (53.9–85.2)**	78.6 (62.0–85.9)***	71.9 (61.4–83.3)***	76.1 (56.7–83.3)***	0.001
Percent time with glucose at >180 mg/dL (%)	56.8 (37.8–71.1)	40.7 (13.8–60.7)	30.7 (13.5–45.9)	24.5 (13.8–38.0)*	18.2 (1.6–46.1)*	7.3 (0.8–20.8)***	17.2 (0–33.6)**	13.0 (3.9–45.3)**	<0.001
Maximum plasma glucose (mg/dL)	310.5 (288.3–441.8)	294.5 (199.8–335.5)	246.5 (190.8–338.0)*	233.5 (216.3–280.0)**	228.0 (183.5–269.3)**	202.0 (180.0–227.8)***	225.5 (174.8–261.5)**	205.5 (182.8–247.0)***	<0.001
Minimum plasma glucose (mg/dL)	73.5 (49.0–130.5)	59.0 (55.0–81.0)	56.0 (45.3–88.8)	46.5 (40.0–84.3)	53.0 (42.3–89.8)	51.5 (41.5–67.5)*	56.5 (45.8–68.0)*	58.5 (45.3–70.3)	0.212
LBGI	2.5 (0.04–6.7)	3.9 (1.7–5.1)	3.8 (0.7–8.3)	5.1 (1.1–8.9)	4.6 (0.6–9.5)	5.2 (2.2–9.4)	4.4 (2.2–6.9)	4.3 (1.8–9.1)	0.624
HBGI	16.1 (11.5–23.1)	13.5 (3.9–16.7)	6.7 (2.6–14.3)**	6.5 (5.0–8.5)**	4.6 (2.9–9.1)***	3.3 (2.8–5.5)***	4.4 (2.0–9.2)***	4.7 (2.7–6.5)***	<0.001
SD of glucose during nocturnal period (00:00–05:59) (mg/dL)	25.9 (13.5–44.1)	16.5 (8.5–38.1)	22.8 (12.4–32.1)	23.4 (14.1–29.4)	22.6 (15.0–27.2)	26.0 (17.9–32.5)	17.9 (11.9–25.0)	19.5 (14.8–21.4)	0.603
Average plasma glucose during nocturnal period (00:00–05:59) (mg/dL)	258.2 (186.3–292.7)	228.6 (117.3–241.8)*	142.2 (108.3–155.7)***	107.1 (76.5–155.6)***	119.9 (100.5–148.1)***	110.6 (98.1–150.5)***	116.7 (97.8–161.2)***	101.4 (74.1–163.8)***	<0.001

Data are median (25–75% values).

p values represent the difference in changes from baseline to day 7, by analysis of Friedman.*p* values indicate the difference between pre-treatment and each day by Dunnett test. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. pre-treatment.

SD, standard deviation; CV, coefficient of variation; LBGI, low blood glucose index; HBGI, high blood glucose index.

Discussion

The results of the present study using isCGM in an actual clinical setting for the treatment of patients with T1DM demonstrated that the combination of SGLT2-I and intensive insulin therapy improved plasma glucose fluctuations and mean plasma glucose levels and at the

same time did not worsen hypoglycemic indices.

In the present study, the TIR, the primary endpoint, increased from 39.0% before the use of SGLT2-I to 76.1% on treatment day 7. Although none of the patients achieved a TIR of 70% or higher before the addition of SGLT2-I, six patients met that TIR criterion on treatment day 7. The SD of glucose, average plasma glucose, TAR, maximum plasma glucose and average nocturnal plasma glucose (*i.e.*, the secondary endpoints) also improved significantly following the addition of SGLT2-I (Table 2). In contrast, no significant changes were observed in various hypoglycemic indices used in this study, such as the TBR and minimum plasma glucose (similar results for the nocturnal-related parameters). The magnitude of the change in TIR on day 7 correlated significantly with the baseline TIR (Table 3). These results indicate that short-term treatment with SGLT2-I resulted in a larger improvement in TIR in patients with poor glycemic control with lower baseline TIR. Analysis of data of patients with and without TIR of $\geq 70\%$ on day 7 also showed significant differences in eGFR, average baseline plasma glucose, baseline maximum plasma glucose, and baseline HBGI between the two groups (Table 4). Based on these results, we conclude that patients with better glycemic control at baseline are more likely to achieve a TIR of

Table 3 Univariate linear regression analysis for predicting change of percent time with glucose at 70–180 mg/dL on day 7

Variable	Univariate Analysis	
	<i>r</i>	<i>p</i> value
Age	0.122	0.738
Diabetes duration	0.621	0.055
Body mass index	0.238	0.509
HbA1c	−0.309	0.385
eGFR	0.017	0.963
Total required insulin dose	0.197	0.585
Percent time with glucose at 70–180 mg/dL at baseline	−0.706	0.023

Data are *p*-value by Spearman rank correlation.

HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate

Table 4 Differences between achieved group and non-achieved group (Percent time with glucose at 70–180 mg/dL $\geq 70\%$)

	achieved group (<i>n</i> = 6)	Non-achieved group (<i>n</i> = 4)	<i>p</i> value
Age (year)	55.0 (40.5–61.5)	62.0 (46.3–62.8)	0.392
Diabetes duration (year)	5.0 (1.8–10.8)	5.5 (2.3–8.0)	0.914
Body mass index (kg/m ²)	22.6 (20.6–25.6)	24.7 (21.3–27.6)	0.670
HbA1c (%)	9.1 (9.0–9.7)	8.9 (8.7–9.0)	0.065
eGFR (mL/min/1.73 m ²)	86.5 (78.2–91.2)	69.2 (65.1–74.7)	0.019
Required insulin dose (u/day)	32.0 (19.5–58.5)	42.5 (26.3–57.3)	0.521
SD of glucose at baseline (mg/dL)	61.4 (47.7–76.0)	69.5 (65.8–84.5)	0.286
Average plasma glucose at baseline (mg/dL)	175.8 (166.7–190.6)	267.6 (186.7–351.6)	0.033
%CV at baseline	35.8 (25.0–44.2)	26.7 (19.5–45.6)	0.476
Percent time with glucose at <70 mg/dL at baseline (%)	2.1 (0–9.1)	0 (0–10.1)	0.363
Percent time with glucose at 70–180 mg/dL at baseline (%)	50.5 (34.9–60.7)	17.7 (0–38.5)	0.054
Percent time with glucose at >180 mg/dL at baseline (%)	47.4 (37.2–59.1)	80.2 (41.7–100.0)	0.199
Maximum plasma glucose at baseline (mg/dL)	291.5 (278.0–317.0)	451.5 (343.5–488.3)	0.019
Minimum plasma glucose at baseline (mg/dL)	60.5 (49.0–93.5)	140.0 (49.8–201.8)	0.392
LBGI at baseline	3.8 (0.5–6.7)	0.7 (0–9.6)	0.476
HBGI at baseline	12.7 (8.8–15.8)	29.0 (16.9–45.9)	0.019

Data are median (25–75% values).

p values for comparison of the achieved and non-achieved groups, by Mann-Whitney *U* test.

HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; SD, standard deviation; CV, coefficient of variation; LBGI, low blood glucose index; HBGI, high blood glucose index.

$\geq 70\%$ on day 7 of treatment with SGLT2-I. The results of the present study are important because they demonstrated in real clinical setting that the addition of SGLT2-I improved the TIR without increasing the incidence of hypoglycemia in patients with T1DM. Although studies using isCGM to assess the effects of SGLT-I on T1DM have been sporadically reported in western countries, the present pilot study is the first to be conducted in an actual clinical setting in Japan.

With regard to the efficacy of SGLT-I in T1DM, Kaku *et al.* [8] reported that the concomitant use of ipragliflozin with insulin significantly improved HbA1c levels (-0.47% , *versus* placebo: -0.36%), reduced body weight (-2.92 kg, *versus* placebo: -2.87 kg), and reduced total daily insulin dose (-6.64 u/day, *versus* placebo: -7.35 u/day). These findings confirmed the similar and earlier results of Mathieu *et al.* [9]. In a study using CGM to evaluate the efficacy of SGLT2-I in patients with T1DM, Rodbard *et al.* [10] reported that the concomitant use of canagliflozin (100 mg or 300 mg) through monitoring by Dexcom G4 Platinum increased the TIR (100 mg: $+11.6\%$, 300 mg: $+10.1\%$) and decreased the TAR (100 mg: -12.7% , 300 mg: -7.6%) without increasing the TBR in patients with T1DM. Similar findings were reported more recently by others [11, 12]. While the present study also yielded similar results, improvement in nocturnal plasma glucose levels has not been reported previously. This finding suggested that SGLT2-I might be especially suited for patients in whom larger insulin doses should be avoided in order to reduce the risk of hypoglycemia. While the present study did not measure glucagon levels, SGLT2-I reportedly promotes glucagon production [13, 14], which might be one of the mechanisms by which it prevents hypoglycemia. In addition, in our previous study [15], which used CGM to assess the effects of SGLT2-I on T2DM, the incidence of hypoglycemia did not increase after 1 week of treatment, and the lowest plasma glucose level at 1 week correlated well with urinary glucose excretion. The results of that study demonstrated substantial inhibition of urinary glucose excretion in patients with the lowest plasma glucose levels.

With regard to the adverse effects of treatment, our results showed no incidence of severe hypoglycemia, the most concerning hypoglycemia-associated event. In the above-mentioned meta-analysis of 14 randomized controlled trials, the incidence of adverse events was comparable between SGLT2-I and placebo, and no significant increase in the incidence of severe hypoglycemia was observed [4]. As described above, the DEPICT-1/DEPICT-2 trial showed that dapagliflozin did not signifi-

cantly increase the TBR compared with placebo [11].

Clinical trials conducted in Japan and other countries have reported that the use of SGLT2-I for T1DM is associated with the risk of diabetic ketoacidosis (DKA) [8, 9, 16, 17]. SGLT2-I increases glucagon production through urinary glucose excretion and its direct action on pancreatic α cells [18]. In turn, glucagon enhances lipolysis and ketogenesis [19]. Decreased sodium reabsorption in the kidney may inhibit ketone body excretion [20]. DKA appears to occur through these mechanisms. In a meta-analysis study, Goldenberg *et al.* [21] reported that the addition of SGLT2-I to the treatment of T1DM increased the risk of DKA by 3.47-fold. In another meta-analysis study, Masri *et al.* [22] also reported that the concomitant use of SGLT2-I for T1DM increased the risk of DKA but did not increase significantly the incidence of other adverse events; hypoglycemia or infection. None of the patients in the present study experienced severe hypoglycemia or ketosis.

The limitations of the present study are: (1) the relatively small sample size of 10 patients, (2) the retrospective study design, (3) the lack of a control group, and (4) the lack of consistency in meal amounts and times due to the conduct of the study in an outpatient setting. We plan in the future to conduct a prospective study with a larger sample size in an inpatient setting.

In conclusion, we have demonstrated in the present study using the isCGM in an actual clinical setting that the addition of SGLT2-I to intensive insulin therapy did not increase the incidence of hypoglycemia and rather improved plasma glucose fluctuations and mean plasma glucose levels in patients with T1DM. Our results suggest that the use of SGLT2-Is in the indicated T1DM patients under careful attention to potential risks, can significantly improve the TIR. Such therapeutic protocol can easily achieve TIR of $\geq 70\%$, which is the recommended target for diabetes therapy recently adopted by consensus.

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Disclosure

Y.O. had received consultancy fees from Astellas, MSD and Ono Pharm Corporation. Y.T. has received speaking fees and/or honoraria from Astellas. All other authors declare no conflict of interest.

Supplementary Fig. 1 24-hr blood glucose levels of the 10 study patients, as measured by the isCGM, at (A) baseline and (B) after 7 days of treatment with insulin combined with SGLT2-I.

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