Original Article

Insulin dose reduction in dapagliflozin combination therapy for type 1 diabetes mellitus: the RISING-STAR study

Masahide Hamaguchi,[1,*] Yuta Yoshimura,[1] Hanako Nakajima,[1] Toru Tanaka,[2] Goji Hasegawa,[3] Michiyo Ishii,[4] Hiroshi Okada,[5] Kazuteru Mitsuhashi,[6] Noriyuki Kitagawa,[7] Takuro Okamura,[1] Yoshitaka Hashimoto,[1] Saori Majima,[1] Takafumi Senmaru,[1] Emi Ushigome,[1] Naoko Nakanishi,[1] Mai Asano,[1] Masahiro Yamazaki,[1] Michiaki Fukui,[1] and the RISING-STAR study group

[1]Department of Endocrinology and Metabolism, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan
[2]Department of Diabetes and Endocrinology, Japanese Red Cross Kyoto Daiichi Hospital, 15-749 Honmachi, Higashiyama-ku, Kyoto 605-0981, Japan
[3]Division of Metabolism, Nephrology and Rheumatology, Japanese Red Cross Kyoto Daini Hospital, 355-5 Haruobicho, Kamigyo-ku, Kyoto 602-8026, Japan
[4]Department of Internal Medicine, Otsu City Hospital, 2-9-9 Motomiya, Otsu, Shiga 520-0804, Japan
[5]Department of Diabetes and Endocrinology, Matsushita Memorial Hospital, 5-55 Sotojimacho, Moriguchi, Osaka 570-8540, Japan
[6]Department of Diabetes Internal Medicine, Fukuchiyama City Hospital, 231 Atsunakamachi, Fukuchiyama, Kyoto 620-8505, Japan
[7]Department of Diabetology, Kameoka Municipal Hospital, 1-1 Noda, Shinochoshino, Kameoka, Kyoto 621-8585, Japan

(Received 13 January, 2022; Accepted 29 January, 2022; Released online in J-STAGE as advance publication 17 May, 2022)

To clarify the frequency of hypoglycemia in patients with type 1 diabetes mellitus receiving dapagliflozin combination therapy to reduce their basal insulin dose. Sixty subjects were assigned to two groups according to their basal insulin-to-total daily dose (TDD) ratio: group A (basal insulin/TDD <40%) and group B (≥40%). Reduction of the basal insulin dose was instituted in group B, but not in group A. The number of hypoglycemic events per day and ketosis frequency were the primary and secondary endpoints, respectively. The hypoglycemia frequency before and after the intervention was 0.23 and 0.26 times/day in group A and 0.19 and 0.23 times/day in group B, respectively, with no significant difference between the groups. The total insulin dose reduction was approximately 10% in both groups. Ketosis frequency increased significantly after the intervention (from 0.013 to 0.086 times/day in group A and 0.013 to 0.059 times/day in group B). Time-in-range, mean amplitude of glycemic excursion, and glycated hemoglobin A1c improved in both groups. No significant difference in hypoglycemia frequency was observed between patients with and without reduction of the basal insulin dose. The combination therapy improved glycemic control and patient satisfaction regarding hyperglycemia. Nevertheless, adequate attention to ketosis is crucial.

***Key Words*: diabetes mellitus, type 1, glycemic control, hypoglycemia, insulin**

In type 1 diabetes, β-cell function is impaired, making insulin treatment vital. Evidence for the efficacy and safety of multiple daily insulin injections (MDIs) and continuous subcutaneous insulin infusion (CSII) as treatments for type 1 diabetes has accumulated over the past 30 years.(1) According to the literature, the total basal insulin dose is approximately 50% of the total daily insulin dose (TDD).(2) Recently, Kuroda *et al.*(3) demonstrated that the basal insulin requirement is approximately 30% of TDD in C-peptide-negative type 1 diabetes patients whose diets were prepared by a dietitian. The maximal basal insulin requirement in all subjects was 43.8% of TDD.(3) According to King *et al.*,(4) to prevent excessive treatment, the basal insulin requirement should be computed based on the following: total daily basal insulin = 0.4 × TDD.

Injectable and oral glucose-lowering drugs have been studied for their efficacy as adjuncts to insulin-based treatment of type 1 diabetes.(2) Insulin therapy may result in increased body weight and excessive carbohydrate intake in patients with type 1 diabetes, which leads to an increased risk of macrovascular complications. In individuals with type 1 diabetes, the body mass index is increased, which increases the risk of cardiovascular disorders.(5) While low-carbohydrate diets may reduce the total insulin dose and number of self-injections, they can result in nutritional imbalances.(6) Recently, dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, combined with insulin therapy, was approved to treat type 1 diabetes.(7) Several clinical trials were conducted on SGLT2 inhibitors as adjunctive therapy for type 1 diabetes, and results showed decreased glycated hemoglobin A1c (HbA1c), insulin dose, and body weight.(8–13) Thus, SGLT2 inhibitors can prevent cardiovascular complications in patients with type 1 diabetes, as previously reported in patients with type 2 diabetes.(10,14)

However, SGLT2 inhibitors are associated with a greater number of adverse events, including hypoglycemia and ketoacidosis. Numerous patients with type 1 diabetes struggle to achieve glycemic control and experience significant fluctuations in blood glucose levels despite insulin treatment.(7,15) Hypoglycemia is an important determinant of glycemic control in the treatment of type 1 diabetes.(16) Thus, to prevent hypoglycemia and to achieve glycemic control, reduction of the basal insulin dose has been considered in patients with type 1 diabetes. However, while the addition of an SGLT2 inhibitor to insulin may reduce the risk of hypoglycemia, the use of an SGLT2 inhibitor has been reported to increase the frequency of diabetic ketoacidosis (DKA).(12) Hence, when an SGLT2 inhibitor and insulin are combined, reducing the insulin dose to prevent hypoglycemia may increase the risk of ketoacidosis. On the other hand, maintaining the same insulin dose to prevent ketoacidosis may increase the hypoglycemia risk. Therefore, an algorithm for the concomitant use of an SGLT2 inhibitor and insulin in patients with type 1 diabetes is warranted.

*To whom correspondence should be addressed.
E-mail: mhama@koto.kpu-m.ac.jp

doi: 10.3164/jcbn.22-7

This study aimed to explore whether an SGLT2 inhibitor (dapagliflozin) used with a reduction in basal insulin dose can reduce the frequency of hypoglycemia in patients with type 1 diabetes. We hypothesized that dapagliflozin treatment without basal insulin dose reduction results in a higher frequency of hypoglycemia.

Materials and Methods

Study design. This was a multicenter, open-label, non-randomized, exploratory, prospective, interventional study,[1] and randomized assignment was not conducted. The detailed study protocol of the RISING-STAR study is shown in Supplemental Doc. 1* as well as online.[17]

The RISING-STAR study was designed as an exploratory study. No prior studies have reported how the frequency of hypoglycemia increases after administration of an SGLT2 inhibitor without reducing the basal insulin dose. At first, we hypothesized in patients with type 1 diabetes treated with dapagliflozin combined with insulin, the hypoglycemia frequency increases by 60% without reducing the basal insulin dose. In a previous meta-analysis,[18,19] the hypoglycemia frequency did not increase when insulin was reduced in patients with type 1 diabetes treated with both insulin and dapagliflozin. We assumed that the increase in the hypoglycemia frequency could be suppressed by reducing the basal insulin dose by 10%. The frequency of hypoglycemia has been reported to be 7 ± 6 times/month in patients using glargine and basal insulin for type 1 diabetes.[20]

Next, the subjects were stratified into two groups according to whether basal insulin was higher than the ideal insulin dose or not. The ideal basal insulin dose may be determined based on the basal/total daily dose (TDD) ratio. Kuroda *et al.*,[3] reported that the basal insulin dose for type 1 diabetes is 30–40% of the TDD; thus, a basal/TDD of 0.4 was set as the ideal basal insulin dose for type 1 diabetes in Japan.[21] We characterized a basal/TDD ratio ≥40% as excessive.[19–21] The subjects were stratified into two groups according to the basal/TDD ratio: group A (<0.4) and group B (≥0.4).

We hypothesized that the hypoglycemia frequency would increase by 60% in group A subjects, who were instructed not to reduce their basal insulin dose when they initiated the combination therapy with insulin and dapagliflozin. Similarly, we hypothesized that the hypoglycemia frequency would not increase in group B subjects, who were instructed to reduce their basal insulin dose by 10%, when they also initiated the combination therapy.

Ethics approval and consent to participate. The RISING-STAR study is registered with the Japan Registry of Clinical Trials (jRCTs051190114) and was approved by the ethics committees of the Kyoto Prefectural University of Medicine at December 12, 2019 (CRB5180001). The RISING-STAR study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects.

Intervention description. Figure 1 presents the study design. A period of 4 weeks was established before the intervention (i.e., administration of 5 mg dapagliflozin). During this period, the study subjects were asked to record fasting plasma β-hydroxybutyric acid levels, intermittently scanned continuous glucose monitoring (isCGM) (Freestyle Libre: Flash Glucose Monitoring System; Abbott Japan LLC, Tokyo, Japan), and self-monitored blood glucose (SMBG). The initiation of dapagliflozin administration was set as day zero of the intervention period. After the pre-intervention period, the subjects were stratified into two groups, as described in "Study design" above.

In group A (basal/TDD ratio <0.4), the basal insulin dose was not reduced; however, the subjects were instructed to reduce the bolus insulin dose by 10%. The 10% bolus insulin dose reduction was based on a 10% insulin-to-carbo ratio, which was rounded to the nearest whole number for MDI or rounded down to two decimal places for CSII. The subjects were instructed to follow this procedure for 3 days from the start of the intervention. After the third day, the subjects could titrate both the basal and bolus doses according to the algorithm for basal and bolus insulin titration after dapagliflozin administration.[17]

In group B (basal/TDD ≥0.4), the subjects were instructed to reduce the total insulin dose by 10% by reducing the basal insulin dose alone. The basal insulin dose was rounded down to one decimal place for MDI and two decimal places for CSII. The subjects were instructed to follow the procedure for 3 days from the start of the intervention. After the third day, the subjects

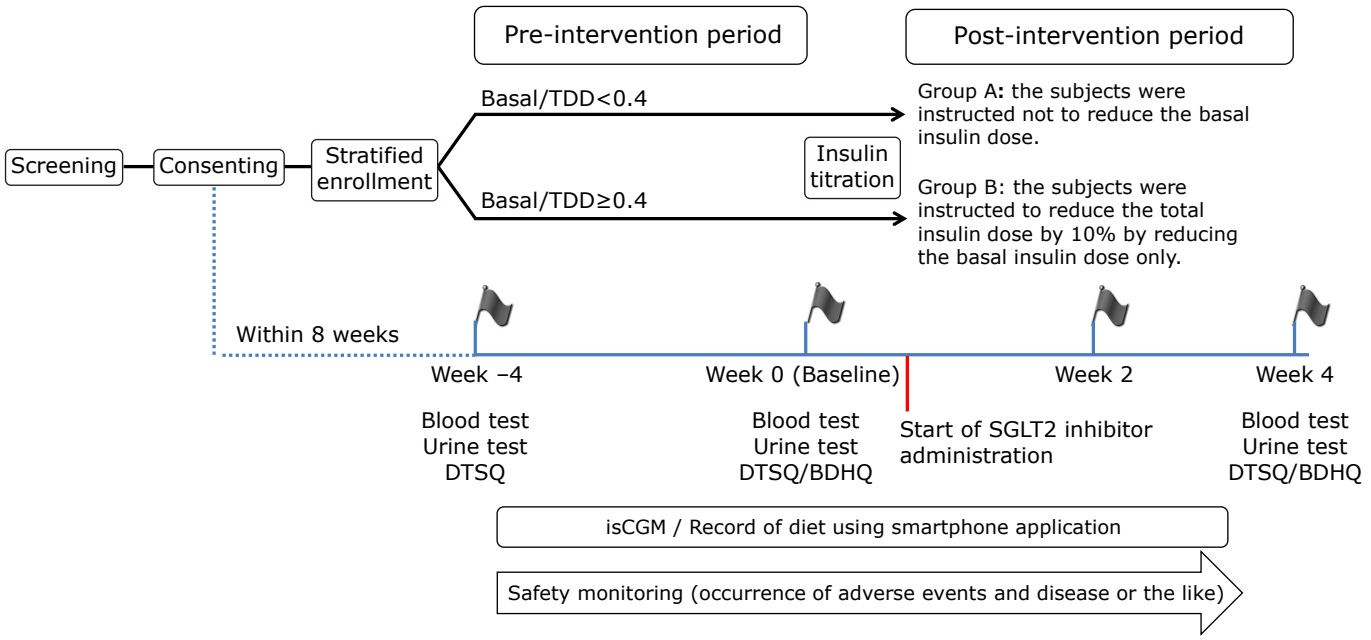

Fig. 1. The design of the study.

*See online. https://doi.org/10.3164/jcbn.22-7

could titrate both the basal and bolus dose according to the same algorithm used in group A.

Moreover, the subjects were instructed to visit the research institutions four times: The subjects visited the research institutions 4 and 0 weeks before the start of intervention and 2 and 4 weeks after start of intervention. They were provided with a digital camera and instructed to take a picture of each meal they ate throughout the intervention period.

Outcomes. The primary endpoint was the frequency of hypoglycemia recorded per day based on SMBG during the intervention period.

Statistical analyses. SAS ver. 9.4 (SAS Institute, Cary, NC) was used. The significance level was set at 0.05 (two-sided), and the confidence coefficient was 0.95 (two-sided); no adjustment for test multiplicity was made. As summary statistics, we calculated the number of cases, mean, SD, and frequency and percentage (%) for categorical variables. When the data deviated significantly from the normal distribution, variable transformations were attempted, as appropriate.

Additional information for study methodology. Additional information regarding participants, sample size and study setting, secondary endpoints, measurements, statistical analyses and analysis population, data handling, baseline characteristics of the study subjects, primary endpoint analysis, secondary endpoint analysis, and safety endpoint analysis are described in Supplemental Doc. 1*.

Results

Study group. Of 60 patients recruited from 2 March 2020 to 29 July 2020, only 29 and 28 patients in groups A and B, respectively, consented to continue after the initial 4-week pre-intervention phase. Subjects were followed until 2 December 2020. The flow of the study subjects is shown in Supplemental Fig. 1*. Patients who withdrew their consent agreed to include the data up to the time of consent withdrawal in the full analysis set. Moreover, the three patients who discontinued their participation met the following exclusion criteria: anemia (hemoglobin ≤13 g/dl in male individuals and ≤12 g/dl in female individuals), hypoalbuminemia (serum albumin ≤3.5 g/dl), and nephrotic syndrome (urinary protein ≥3.5 g/day and serum albumin ≥3.5 g/day) due to a primary disease other than diabetic nephropathy (Supplemental Table 1*).

In this study, there was no randomization, and patients were stratified into two groups based on the basal/TDD ratio (≥0.4 and <0.4). Furthermore, the two groups of patients differed in the percentage of basal insulin dose reduction: group A, 0% basal insulin reduction, and group B, 10% basal insulin reduction. Results showed no significant difference in age and other baseline characteristics between the two groups (Table 1).

Primary endpoint. The frequency of hypoglycemia before and after the intervention was respectively 0.23 and 0.26 times/day in group A ($p = 0.001$) and 0.19 and 0.23 times/day in group B ($p = 0.009$); no significant difference between the two groups was found ($p = 0.69$) (Table 2). After adjusting for the number of hypoglycemic events per day during the pre-intervention period (−4–0 weeks), HbA1c at −4 weeks, and age, the frequency of hypoglycemia after the intervention was 0.250 times/day in group A and 0.255 times/day in group B; no significant difference was noted between the two groups ($p = 0.91$).

Secondary endpoints. The frequency of ketosis (β-hydroxybutyric acid ≥600 μM) increased significantly after the intervention from 0.013 to 0.086 times/day in group A ($p = 0.013$) and from 0.013 to 0.059 times/day in group B ($p = 0.011$). No significant difference in change was seen between the two groups was noted ($p = 0.40$) (Table 3). Similarly, β-hydroxybutyric acid significantly increased in group A (from 59.4 to 131.1 μM; $p = 0.02$) and in group B (from 52.6 to 148.8 μM; $p = 0.02$) after the intervention; however, no significant difference in change was seen was found between the two groups ($p = 0.35$) (Table 3).

Hypoglycemic time, hyperglycemic time, and nocturnal hypoglycemic time based on isCGM. Based on isCGM, time-in-range (70–180 mg/dl) improved from 63.6% to 69.7% in group A and from 59.0% to 69.1% in group B; no significant difference in change was noted between the two groups. The mean amplitude of glycemic excursions (MAGE) improved from 121.7 to 105.0 mg/dl in group A and from 123.4 to 108.0 mg/dl in group B; there was no significant difference in change between the groups. HbA1c decreased by an average of 0.9 mmol/mol in both groups during the 4-week intervention.

In terms of time-below-range and nocturnal hypoglycemia, no significant difference between the two groups was observed; however, they were significantly increased in both groups (Table 3).

Blood and urine examinations. Results of blood and urine examinations are shown in Table 4. In both groups, the red blood cell and hematocrit levels increased significantly; however, no significant difference between the groups was found. The changes in aspartate aminotransferase and alanine aminotransferase levels in group B were significantly lower than those in group A.

Insulin dose. At the hospital, at week 0, the basal insulin dose was reduced in group B. The daily basal insulin dose was reduced from 18.9 to 15.9 units ($p<0.001$), whereas the daily bolus insulin dose was not significantly changed (from 22.6 to 22.7 units; $p = 0.95$) (Supplemental Table 2*). Consequently, the TDD was reduced from 41.5 to 38.5 units ($p<0.001$) and the basal/TDD ratio from 45.6 to 41.4 units ($p = 0.001$).

The subjects in group A were instructed not to reduce their basal insulin dose. In group A, the daily basal insulin dose was not significantly changed (from 10.5 to 10.4 units; $p = 0.39$), whereas the daily bolus insulin dose was reduced from 25.3 to 22.2 units ($p<0.001$). Consequently, the TDD was reduced from 35.7 to 32.6 units ($p<0.001$), whereas the basal/TDD ratio increased from 29.6 to 32.7 units ($p = 0.001$).

According to the study algorithms, the subjects performed self-regulation of the insulin dose during the post-intervention period. After the fourth post-intervention day, the daily basal insulin dose was reduced in group A (from 10.4 to 9.8 units; $p = 0.003$); in group B, the reduction in daily basal insulin dose (from 15.9 to 16.3 units; $p = 0.37$) was within the dose prescribed by their physicians. No significant change in the daily bolus insulin dose after the fourth post-intervention day was noted in either group: from 22.2 to 22.7 units in group A ($p = 0.25$) and from 22.7 to 23.6 units in group B ($p = 0.17$).

Thus, the daily basal insulin dose was reduced in both groups (from 10.5 to 9.8 units in group A and from 18.9 to 16.3 units in group B) (Supplemental Table 2*). However, a statistically significant reduction was achieved in group B, which was instructed to reduce the basal insulin dose. The total insulin dose was reduced from 35.7 to 32.6 units in group A and from 41.5 to 39.8 units in group B. The total insulin dose reduction was the same in both groups. For the combined use of dapagliflozin and insulin, the total insulin dose reduction was approximately 10%.

Diabetes Treatment Satisfaction Questionnaire (DTSQ) results. Question 2 of the DTSQ asks the subjects how often they have recently felt that their blood glucose level was undesirably high. A significant improvement was found in both groups after the intervention: from 3.6 ± 1.2 to 2.5 ± 1.4 ($p = 0.008$) in group A and from 3.7 ± 1.3 to 2.8 ± 1.2 ($p = 0.017$) in group B. However, no significant difference was noted between the groups (Supplemental Table 3*). Moreover, no difference in the Quality of Life (QOL) questions related to hypoglycemia was found between the pre- and post-intervention assessments.

Safety evaluation items. There were no events of severe

*See online. https://doi.org/10.3164/jcbn.22-7

doi: 10.3164/jcbn.22-7

Table 1. Baseline characteristics of the study subjects

		Group A	Group B	*p* value
Number		29	28	
Sex	Male	12 (41.4)	9 (32.1)	0.59
	Female	17 (58.6)	19 (67.9)	
Age, years		58.3 ± 11.8	51.3 ± 14.9	0.05
Height, cm		161.4 ± 7.8	164.0 ± 9.3	0.26
Body weight, kg		61.7 ± 9.0	64.3 ± 12.3	0.37
BMI, kg/m^2		23.7 ± 2.8	23.8 ± 3.1	0.88
HbA1c, %		7.7 ± 0.9	8.1 ± 0.9	0.15
Smoking	No	18 (62.1)	15 (53.6)	
	Current smoker	4 (13.8)	5 (17.9)	0.81
	Ex-smoker	7 (24.1)	8 (28.6)	
Habitual alcohol consumption		16 (55.2)	17 (60.7)	0.79
Allergy		10 (34.5)	5 (17.9)	0.23
Diabetic nephropathy	Stage 1	24 (82.8)	20 (71.4)	
	Stage 2	4 (13.8)	6 (21.4)	0.54
	Stage 3	1 (3.4)	2 (7.1)	
	Stage 4, 5	0 (0.0)	0 (0.0)	
Diabetic retinopathy	None	25 (86.2)	20 (76.9)	
	Simple retinopathy	2 (6.9)	3 (11.5)	0.53
	Preproliferative retinopathy	1 (3.4)	0 (0.0)	
	Proliferative retinopathy	1 (3.4)	3 (11.5)	
Diabetic neuropathy		7 (25.9)	4 (14.8)	0.5
Coronary artery disease		0 (0.0)	1 (3.6)	0.49
Hypertension		11 (37.9)	6 (21.4)	0.25
Dyslipidemia		12 (41.4)	9 (32.1)	0.59
Ultra-rapid-acting insulin		28 (96.6)	27 (96.4)	1
Rapid-acting insulin		2 (6.9)	1 (3.6)	1
Alpha-glucosidase inhibitors		2 (6.9)	1 (3.6)	1
Anti-hypertension drugs		11 (37.9)	6 (21.4)	0.25
Ca antagonist		6 (20.7)	3 (10.7)	0.47
ACE inhibitors		1 (3.4)	1 (3.6)	1
ARB		8 (27.6)	4 (14.3)	0.33
Diuretic		0 (0.0)	2 (7.1)	0.24
Beta-blocker		1 (3.4)	0 (0.0)	1
Alpha-blocker		0 (0.0)	1 (3.6)	0.49
Drugs for dyslipidemia		12 (41.4)	8 (28.6)	0.41
Statins		11 (37.9)	6 (21.4)	0.25
Fibrate		1 (3.4)	1 (3.6)	1
Small intestinal cholesterol transporter inhibitors		1 (3.4)	1 (3.6)	1
Nicotinic acid derivatives		1 (3.4)	2 (7.1)	0.61
Polyunsaturated fatty acids		1 (3.4)	0 (0.0)	1

Categorical variables were expressed as number (%) and were compared by Fisher's exact test. Continuous variables were expressed as mean (SD) and were compared by *t* test.

Table 2. The primary endpoint, hypoglycemia, recorded for Groups A and B before and after administration of dapagliflozin with basal insulin (mean and SD)

		Pre-intervention	Post-intervention	*p* value[†]	Adjusted hypoglycemia frequency, times/day
Hypoglycemia frequency, times/day	A	0.232 ± 0.304	0.269 ± 0.319	0.001	0.250 (0.032)
	B	0.197 ± 0.296	0.233 ± 0.339	0.009	0.255 (0.033)
	p value[‡]	0.68	0.69		0.91
Adjusted mean difference					0.005 (–0.089, 0.100)

Hypoglycemia frequency were expressed as mean ± SD and adjusted hypoglycemia frequency expressed as mean (SE). [†]One-sample *t* test was applied. [‡]Two-sample *t* test was applied. Hypoglycemia frequency during the pre-intervention period (–4 to 0 weeks), HbA1c at –4 weeks, and age were used as covariates.

Table 3. The secondary endpoints recorded for Groups A and B before and after administration of dapagliflozin with basal insulin (mean and SD)

		Pre-intervention	Post-intervention	Change by intervention	*p* value†
Frequency of ketosis, times/day	A	0.013 ± 0.019	0.086 ± 0.161	0.073 ± 0.148	0.013
	B	0.013 ± 0.034	0.059 ± 0.097	0.046 ± 0.085	0.011
	p value‡	0.91	0.46	0.4	
MAGE, mg/dl	A	121.7 ± 27.7	105.0 ± 22.3	−15.3 ± 18.3	<0.001
	B	123.4 ± 23.9	108.0 ± 23.4	−13.7 ± 19.8	0.003
	p value‡	0.81	0.65	0.77	
Time-in-range, %	A	63.6 ± 12.2	69.7 ± 11.7	6.2 ± 11.1	0.007
	B	59.0 ± 16.5	69.1 ± 13.4	9.4 ± 9.1	<0.001
	p value‡	0.25	0.87	0.28	
Time-below-range, %	A	9.9 ± 9.7	12.7 ± 12.6	3.1 ± 4.4	0.001
	B	7.9 ± 6.8	11.4 ± 11.7	3.7 ± 6.2	0.009
	p value‡	0.39	0.71	0.66	
Time-above-range, %	A	26.5 ± 15.4	17.6 ± 12.3	−9.3 ± 11.1	<0.001
	B	33.1 ± 16.9	19.4 ± 13.3	−13.1 ± 9.4	<0.001
	p value‡	0.14	0.61	0.2	
Nocturnal hypoglycemia, %	A	15.8 ± 18.4	20.9 ± 20.5	6.4 ± 8.4	<0.001
	B	11.7 ± 11.6	17.5 ± 14.3	5.8 ± 10.5	0.015
	p value†	0.33	0.51	0.81	

Continuous variables were expressed as mean ± SD. †One-sample *t* test was applied. ‡Two-sample *t* test was applied. MAGE mean amplitude of glycemic excursion.

hypoglycemia (Supplemental Table 4*). DKA was observed in one patient who used continuous subcutaneous insulin infusion treatment after the study observational periods, although the patient recovered with appropriate treatment.

Discussion

The primary endpoint was to determine if there was a change in frequency of hypoglycemia in one of two treatment groups: those who had a 10% basal insulin reduction (whose initial basal insulin dose was >40% of the total daily insulin dose) vs those who had no basal insulin dose reduction (those whose initial basal insulin dose was <40% of the TDD). The latter group had an approximately 10% bolus insulin reduction; thus, the TDD was essentially lowered by 10% in both treatment groups. In this study, hypoglycemia frequency increased in both groups compared with that before the combination therapy. However, no significant difference between the groups was found during the intervention period. The frequency of hypoglycemia worsened in both groups. To avoid this, it is necessary to instruct patients to reduce the amount of insulin during dapagliflozin administration.

However, in line with previous studies,[8–10,12,22,23] the frequency of ketosis (β-hydroxybutyric acid ≥600 μM) significantly increased in both groups. Based on previous studies, reduced basal insulin >20% is a risk for DKA.[8–10,12,22,23] In the current study, DKA occurred in a case with a 10% reduction of basal insulin, although it was after the observational period. Thus, physicians should pay attention to the development of ketosis when they instruct patients with type 1 diabetes to reduce basal insulin dose and use the SGLT2 inhibitor concomitantly.[8–10,12,22,23]

HbA1c did not differ between the two groups, although both groups showed significant improvements in HbA1c. Evaluation of isCGM showed that the MAGE significantly improved in both groups and that time-in-range (70–180 mg/dl) significantly increased; hypoglycemic time and nocturnal hypoglycemic time were also prolonged in both groups. We believe that the improvement in time-in-range in individuals with type 1 diabetes mellitus was due to SGLT2 inhibitor treatment, which has been reported to improve glycemic control.[7] Our findings revealed that concomitant use of dapagliflozin reduces glycemic variability and prolongs time-in-range, which in turn leads to better glycemic control. Additionally, our findings also demonstrated a significant improvement in patients' hyperglycemia-related QOL scores, specifically question 2, thereby indicating an improved glycemic control.

This study has some limitations. This was a pilot study exploring the effect of the addition of dapagliflozin to insulin in patients with type 1 diabetes, and randomization was not performed for safety reasons. Basal insulin dose reduction was indicated in group B, wherein the basal insulin dose was assumed to be higher than the ideal,[21] and no reduction in basal insulin dose was indicated in group A, wherein the basal insulin dose was assumed to be lower than the ideal. The absence of a control group with no reduction of TDD makes it impossible to tell if the similar hypoglycemia rates were due to the 10% reduction of the TDD in either basal or bolus insulin, or if the addition of dapagliflozin with no insulin reduction might have had the same results. A future randomized controlled trial (RCT) is needed to evaluate the decreasing events of hypoglycemia with the addition of dapagliflozin in type 1 diabetes patients by reducing basal insulin dose. In the future RCT, all patients should be divided into two groups with a 10% decrease of basal insulin and no dose change as a control group. In addition, the level of liver enzymes decreased in group B.

In conclusion, among individuals with type 1 diabetes receiving dapagliflozin combination therapy, it is necessary to instruct patients to reduce the amount of insulin, because the frequency of hypoglycemia worsened during dapagliflozin administration. Physicians should consider ketosis when they instruct patients to reduce basal insulin dose and to use SGLT2 inhibitor concomitantly. Regarding glycemic control with dapagliflozin combination therapy, both groups showed a significant decrease in the MAGE, hyperglycemic time, and HbA1c and a significant increase in time-in-range. The concomitant use of dapagliflozin was particularly useful in correcting glycemic variability and hyperglycemia, resulting in improved hyperglycemia-related QOL in the study subjects. Patients with type 1 DM who use <40% of the TDD as basal insulin are likely to be basally underinsulinized and have fasting hyperglycemia; these patients may benefit most from the addition of an SGLT2 inhibitor to improve glycemic control.

*See online. https://doi.org/10.3164/jcbn.22-7

doi: 10.3164/jcbn.22-7

Table 4. Changes in blood and urine examination results following administration of dapagliflozin (mean and SD)

		Pre-intervention	Post-intervention	Change by intervention	*p* value†
Total ketone, μM‡	A	94.2 ± 77.2	189.2 ± 262.9	95.0 ± 270.6	0.029
	B	85.0 ± 57.8	221.3 ± 193.9	136.3 ± 161.3	<0.001
	p value§	0.66	0.4	0.25	
β-hydroxybutyric acid, μM‡	A	59.4 ± 58.3	131.1 ± 205.2	71.7 ± 208.5	0.02
	B	52.6 ± 42.4	148.8 ± 141.9	96.2 ± 119.5	<0.001
	p value§	0.72	0.5	0.35	
Acetoacetic acid, μM	A	34.8 ± 21.4	58.1 ± 59.7	23.3 ± 63.4	0.06
	B	32.5 ± 17.6	72.5 ± 54.7	40.0 ± 45.3	<0.001
	p value§	0.66	0.35	0.26	
HbA1c, mmol/mol	A	60.9 ± 9.3	57.3 ± 8.3	−3.7 ± 3.7	<0.001
	B	64.6 ± 9.5	60.9 ± 8.0	−3.7 ± 3.2	<0.001
	p value§	0.15	0.1	0.98	
Blood glucose, mg/dl	A	175.1 ± 64.4	153.1 ± 50.2	−22.0 ± 85.5	0.18
	B	192.7 ± 87.0	175.8 ± 58.2	−16.9 ± 72.5	0.24
	p value§	0.39	0.12	0.81	
CPR, ng/ml‡	A	0.42 ± 1.34	0.34 ± 0.74	−0.08 ± 0.77	0.78
	B	0.09 ± 0.17	0.13 ± 0.27	0.04 ± 0.12	0.1
	p value§	0.17	0.25		
CPR index‡	A	0.15 ± 0.24	0.44 ± 1.06	−0.01 ± 0.05	0.15
	B	0.09 ± 0.14	0.15 ± 0.26	0.06 ± 0.12	0.26
	p value§	0.88	0.59	0.93	
Erythrocytes, $\times 10^4$/μl	A	456.4 ± 41.5	468.8 ± 38.0	14.0 ± 16.4	<0.001
	B	459.6 ± 41.0	466.4 ± 43.3	10.9 ± 17.7	0.004
	p value§	0.78	0.82	0.51	
Hematocrit, %	A	41.4 ± 3.1	42.9 ± 2.8	1.6 ± 1.6	<0.001
	B	41.3 ± 3.0	42.1 ± 3.7	1.1 ± 1.6	0.003
	p value§	0.92	0.33	0.22	
AST, IU/L‡	A	22.9 ± 10.5	25.1 ± 10.5	2.2 ± 4.7	0.02
	B	22.9 ± 10.4	22.0 ± 11.0	−0.8 ± 7.7	0.32
	p value§	0.95	0.15	0.018	
ALT, IU/L‡	A	19.7 ± 16.3	21.6 ± 16.9	1.9 ± 3.8	0.011
	B	20.7 ± 10.8	18.4 ± 8.2	−2.3 ± 4.7	0.01
	p value§	0.4	0.48	<0.001	
γGTP, IU/L‡	A	20.9 ± 11.5	19.4 ± 9.9	−1.6 ± 3.7	0.021
	B	23.9 ± 17.2	21.0 ± 12.9	−3.8 ± 6.7	<0.001
	p value§	0.66	0.88	0.06	
UA, mg/dl	A	4.5 ± 1.0	4.0 ± 1.2	0.5 ± 0.7	0.002
	B	4.8 ± 1.3	4.2 ± 1.4	−0.6 ± 0.7	<0.001
	p value§	0.36	0.52	0.64	
Serum albumin, g/dl	A	4.18 ± 0.26	4.31 ± 0.28	0.13 ± 0.19	0.001
	B	4.12 ± 0.26	4.15 ± 0.23	0.04 ± 0.23	0.34
	p value§	0.42	0.022	0.13	

Continuous variables were expressed as mean ± SD. †One-sample *t* test was applied. ‡Continuous variables are transformed into log scale. §Two-sample *t* test was applied. CPR, connecting peptide immunoreacivity; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γGTP, gamma-glutamyltransferase; UA, urinalysis.

Author Contributions

MH, design, conduct/data collection, analysis, writing manuscript; YY, conduct/data collection; HN, conduct/data collection; TT, conduct/data collection; GH, design, conduct/data collection; MI, conduct/data collection; HO, conduct/data collection; KM, conduct/data collection; NK, conduct/data collection; TO, conduct/data collection; YH, conduct/data collection; SM, conduct/data collection; TS, conduct/data collection; EU, conduct/data collection; NN, conduct/data collection; MA, conduct/data collection; MY, design, conduct/data collection; MF, design, conduct/data collection.

Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing. The authors also thank all the clinical staff for their assistance with the execution of the clinical trial and Soiken Inc. for their technical assistance in the launch and execution of the trial.

Funding

The RISING-STAR study, including the article processing charge, is funded by AstraZeneca K.K. and Ono Pharmaceutical Co., Ltd. No drugs were donated or funded by the sponsor. The funding bodies had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of Interest

MH received grants from AstraZeneca K.K., Ono Pharma Co. Ltd., Oishi Kenko inc., Yamada Bee Farm and received personal fees from AstraZeneca K.K., Ono Pharma Co. Ltd., Eli Lilly, Japan, Sumitomo Dainippon Pharma Co., Ltd., Daiichi Sankyo Co. Ltd., Mitsubishi Tanabe Pharma Corp., Sanofi K.K., Kowa Pharma Co. Ltd., outside the submitted work.

MA received personal fees from Novo Nordisk Pharma Ltd., Abbott Japan Co. Ltd., AstraZeneca plc, Kowa Pharma Co. Ltd., Ono Pharma Co. Ltd., Sumitomo Dainippon Pharma Co. Ltd., and Takeda Pharma Co. Ltd. outside the submitted work.

MY received personal fees from MSD K.K., Sumitomo Dainippon Pharma Co. Ltd., Kowa Pharma Co. Ltd., AstraZeneca plc, Takeda Pharma Co. Ltd, Kyowa Kirin Co. Ltd., Daiichi Sankyo Co. Ltd., Kowa Pharma Co. Ltd., and Ono Pharma Co., Ltd. outside the submitted work.

YH received grants from Asahi Kasei Pharma and personal fees from Daiichi Sankyo Co. Ltd., Mitsubishi Tanabe Pharma Corp., Sanofi K.K., and Novo Nordisk Pharma Ltd. outside the submitted work.

MF received grants from Ono Pharma Co. Ltd., Oishi Kenko inc., Yamada Bee Farm, Nippon Boehringer Ingelheim Co. Ltd., Kissei Pharma Co. Ltd., Mitsubishi Tanabe Pharma Corp., Daiichi Sankyo Co. Ltd., Sanofi K.K., Takeda Pharma Co. Ltd., Astellas Pharma Inc., MSD K.K., Kyowa Kirin Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Kowa Pharma Co. Ltd., Novo Nordisk Pharma Ltd., Sanwa Kagagu Kenkyusho Co., Ltd., Eli Lilly, Japan, K.K., Taisho Pharma Co., Ltd., Terumo Corp., Tejin Pharma Ltd., Nippon Chemiphar Co., Ltd., Abbott Japan Co. Ltd., and Johnson & Johnson K.K. Medical Co. and received personal fees from Nippon Boehringer Ingelheim Co., Ltd., Kissei Pharma Co., Ltd., Mitsubishi Tanabe Pharma Corp., Daiichi Sankyo Co. Ltd., Sanofi K.K., Takeda Pharma Co. Ltd., Astellas Pharma Inc., MSD K.K., Kyowa Kirin Co. Ltd., Sumitomo Dainippon Pharma Co. Ltd., Kowa Pharma Co. Ltd., Novo Nordisk Pharma Ltd., Ono Pharma Co. Ltd., Sanwa Kagaku Kenkyusho Co. Ltd., Eli Lilly Japan K.K., Taisho Pharma Co., Ltd., Bayer Yakuhin, Ltd., AstraZeneca K.K., Mochida Pharma Co. Ltd., Abbott Japan Co. Ltd., Teijin Pharma Ltd., Arkray Inc., Medtronic Japan Co. Ltd., and Nipro Corp. outside the submitted work.

The other authors declare that they have no competing interests.

References

1 American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes-2019*. *Diabetes Care* 2019; **42(Suppl 1)**: S90–S102.
2 Davidson PC, Hebblewhite HR, Steed RD, Bode BW. Analysis of guidelines for basal-bolus insulin dosing: basal insulin, correction factor, and carbohydrate-to-insulin ratio. *Endocr Pract* 2008; **14**: 1095–1101.
3 Kuroda A, Kaneto H, Yasuda T, *et al*. Basal insulin requirement is ∼30% of the total daily insulin dose in type 1 diabetic patients who use the insulin pump. *Diabetes Care* 2011; **34**: 1089–1090.
4 King AB. How much do I give? Reevaluation of insulin dosing estimation formulas using continuous glucose monitoring. *Endocr Pract* 2010; **16**: 428–432.
5 Edqvist J, Rawshani A, Adiels M, *et al*. BMI, mortality, and cardiovascular outcomes in type 1 diabetes: findings against an obesity paradox. *Diabetes Care* 2019; **42**: 1297–1304.
6 Tascini G., Berioli MG, Cerquiglini L, *et al*. Carbohydrate counting in children and adolescents with type 1 diabetes. *Nutrients* 2018; **10**: 109.
7 Boeder S, Edelman SV. Sodium-glucose co-transporter inhibitors as adjunctive treatment to insulin in type 1 diabetes: a review of randomized controlled trials. *Diabetes Obes Metab* 2019; **21(Suppl 2)**: 62–77.
8 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.
9 Henry RR, Thakkar P, Tong C, Polidori D, Alba M. Efficacy and safety of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to insulin in patients with type 1 diabetes. *Diabetes Care* 2015; **38**: 2258–2265.
10 Dandona P.Mathieu C, Phillip M, *et al*. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol* 2017; **5**: 864–876.
11 Pieber TR, Famulla S, Eilbracht J, *et al*. Empagliflozin as adjunct to insulin in patients with type 1 diabetes: a 4-week, randomized, placebo-controlled trial (EASE-1). *Diabetes Obes Metab* 2015; **17**: 928–935.
12 Rosenstock J, Marquard J, Laffel LM, *et al*. Empagliflozin as adjunctive to insulin therapyin type 1 diabetes: the EASE trials. *Diabetes Care* 2018; **41**: 2560–2569.
13 Buse JB, Garg SK, Rosenstock J, *et al*. Sotagliflozin in combination with optimized insulin therapy in adults with type 1 diabetes: the North American in Tandem1 study. *Diabetes Care* 2018; **41**: 1970–1980.
14 Wanner C, Heerspink HJL, Zinman B, *et al*. Empagliflozin and kidney function decline in patients with type 2 diabetes: a slope analysis from the EMPA-REG OUTCOME trial. *J Am Soc Nephrol* 2018; **29**: 2755–2769.
15 Kovatchev B, Cobelli C. Glucose variability: timing, risk analysis, and relationship to hypoglycemia in diabetes. *Diabetes Care* 2016; **39**: 502–510.
16 Lehecka KE, Renukuntla VS, Heptulla RA. Insight into hypoglycemia in pediatric type 1 diabetes mellitus. *Int J Pediatr Endocrinol* 2012; **2012**: 19.
17 Hamaguchi M, Hashimoto Y, Tanaka T, *et al*. Multicenter, open-label, 2-arm, pilot trial for safe reduction of basal insulin dose combined with SGLT2 inhibitor in type 1 diabetes mellitus: study protocol for a RISING-STAR trial. *Clin Med Insights Endocrinol Diabetes* 2021; **14**: 11795514211040539.
18 Chen J, Fan F, Wang JY, *et al*. The efficacy and safety of SGLT2 inhibitors for adjunctive treatment of type 1 diabetes: a systematic review and meta-analysis. *Sci Rep* 2017; **7**: 44128.
19 Musso G, Gambino R, Cassader M, Paschetta E. Efficacy and safety of dual SGLT 1/2 inhibitor sotagliflozin in type 1 diabetes: meta-analysis of randomised controlled trials. *BMJ* 2019; **365**: l1328.
20 Urakami T, Kuwabara R, Habu M, Okuno M, Suzuki J, Takahashi S. Efficacy and safety of switching to insulin glulisine from other rapid-acting insulin analogs in children with type 1 diabetes. *J Diabetes Investig* 2015; **6**: 87–90.
21 King AB, Kuroda A, Matsuhisa M, Hobbs T. A review of insulin-dosing formulas for continuous subcutaneous insulin infusion (CSII) for adults with type 1 diabetes. *Curr Diab Rep* 2016; **16**: 83.
22 Henry RR, Dandona P, Pettus J, Mudaliar S, Xu J, Hansen L. Dapagliflozin in patients with type 1 diabetes: a post hoc analysis of the effect of insulin dose adjustments on 24-hour continuously monitored mean glucose and fasting β-hydroxybutyrate levels in a phase IIa pilot study. *Diabetes Obes Metab* 2017; **19**: 814–821.
23 Garg SK, Peters AL, Buse JB, Danne T. Strategy for mitigating DKA risk in patients with type 1 diabetes on adjunctive treatment with SGLT inhibitors: a STICH protocol. *Diabetes Technol Therap* 2018; **20**: 571–575.

doi: 10.3164/jcbn.22-7