


Effect of dapagliflozin on 24-hour glycemic variables in Japanese patients with type 2 diabetes mellitus receiving basal insulin supported oral therapy (DBOT): a multicenter, randomized, open-label, parallel-group study

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To cite: Kudo A, Machii N, Ono T, *et al.* Effect of dapagliflozin on 24-hour glycemic variables in Japanese patients with type 2 diabetes mellitus receiving basal insulin supported oral therapy (DBOT): a multicenter, randomized, open-label, parallel-group study. *BMJ Open Diab Res Care* 2023;**11**:e003302. doi:10.1136/bmjdr-2022-003302

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/bmjdr-2022-003302>).

Received 30 December 2022
Accepted 4 March 2023



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ABSTRACT

Introduction This study aimed to evaluate the impacts of dapagliflozin on 24-hour glucose variability and diabetes-related biochemical variables in Japanese patients with type 2 diabetes who had received basal insulin supported oral therapy (BOT).

Research design and methods Changes in mean daily blood glucose level before and after 48–72 hours of add-on or no add-on of dapagliflozin (primary end point) and diabetes-related biochemical variables and major safety variables during the 12 weeks (secondary end point) were evaluated in the multicenter, randomized, two-arm, open-label, parallel-group comparison study.

Results Among 36 participants, 18 were included in the no add-on group and 18 were included in the dapagliflozin add-on group. Age, gender, and body mass index were comparable between the groups. There were no changes in continuous glucose monitoring metrics in the no add-on group. In the dapagliflozin add-on group, mean glucose (183–156 mg/dL, $p=0.001$), maximum glucose (300–253, $p<0.01$), and SD glucose (57–45, $p<0.05$) decreased. Time in range increased ($p<0.05$), while time above the range decreased in the dapagliflozin add-on group but not in the no add-on group. After 12-week treatment with dapagliflozin add-on, 8-hydroxy-2'-deoxyguanosine (8OHdG), as well as hemoglobin A1c (HbA1c), decreased.

Conclusions This study showed that the mean daily blood glucose and other daily glucose profiles were amended after 48–72 hours of dapagliflozin add-on in Japanese patients with type 2 diabetes who received BOT. The diabetes-related biochemical variables such as HbA1c and urinary 8OHdG were also obtained during the 12 weeks of dapagliflozin add-on without major adverse events. A preferable 24-hour glucose profile in 'time in ranges' and an improvement in reactive oxygen species by dapagliflozin warrant us to evaluate these benefits in larger clinical studies.

Trial registration number UMIN000019457.

INTRODUCTION

Because type 2 diabetes mellitus is a progressive disease, maintaining the

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Sodium-glucose cotransporter 2 (SGLT2) inhibitors improve glycemic control and insulin requirements and show cardiovascular benefits when used in basal insulin supported oral therapy.
- ⇒ There is a lack of previous randomized controlled intervention trials to evaluate daily glucose profiles in patients with type 2 diabetes treated with SGLT2 inhibitors on basal insulin supported oral therapy.

WHAT THIS STUDY ADDS

- ⇒ This trial found beneficial effects of dapagliflozin on daily blood glucose variables, including mean, maximum, SD, and time in ranges in basal insulin supported oral therapy.
- ⇒ Improvements in glycemic controls and oxidative stress were also found after 12 weeks of dapagliflozin treatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Improvements in 24-hour glucose profile and reactive oxygen species highlight the benefits of dapagliflozin in basal insulin supported oral therapy.
- ⇒ The study participants who had been treated on oral antidiabetic drugs could be applicable to people with type 2 diabetes who are not on basal-bolus insulin regimens.

glycemic targets with habitual use of oral monotherapy is possible for only years, after which oral combination therapy is necessary.¹ Patients with long duration of diabetes often require insulin therapy and benefit from it. Basal insulin alone is the most convenient initial insulin regimen. Still, a substantial number of

patients require bolus insulin before meals to achieve glycemic targets (basal-bolus).¹ However, unwillingness to receive the basal-bolus therapy, due to reasons such as cost and complexity, limits its application.² Alternatively, basal insulin is administered with oral antidiabetic drugs (OADs) (basal insulin supported oral therapy (BOT)).³ The addition of OADs to basal insulin is effective in achieving glycemic control and insulin requirements.^{4,5} However, negative effects of this combination therapy have been reported. Among 5663 German patients with diabetes who received BOT, discontinuation occurred in 35.7%; of them, 46.7% discontinued oral therapy, 32.7% discontinued insulin, and 20.6% started basal-bolus treatment.⁶ Collectively, the algorithm of BOT still needs elucidation.^{1,3}

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a relatively new class of OAD that can reduce hyperglycemia by increasing urinary glucose excretion independent of insulin secretion or action.⁷ SGLT2 inhibitors are administered as either monotherapy or dual/triple therapy with other OADs and also in combination with insulin.^{8,9} SGLT2 inhibitors plus insulin therapy is considered one of the promising strategies for optimal glucose control. Still, the advantages and disadvantages of this therapy remain unclear. The benefits and utility of continuous glucose monitoring (CGM) are widely recognised in individuals with insulin-requiring diabetes.¹⁰ Recently, the Advanced Technologies & Treatments for Diabetes (ATTD) consensus panel identified 'time in ranges' as a measure of glycemic control, which provides more actionable information than hemoglobin A1c (HbA1c) alone.¹¹ Currently, there are few studies on the evaluation of 'time in ranges' in combination therapy involving SGLT2 inhibitors and insulin.¹²

This multicenter, randomized, open-label, parallel-group comparison study aimed to evaluate primarily the impact of dapagliflozin on short-term (48–72 hours) changes in 24-hour glucose variables using 'time in ranges' and secondarily long-term (12 weeks) changes in diabetes-related biochemical variables in Japanese patients with type 2 diabetes who received BOT with or without dapagliflozin.

METHODS

Study design

Study patients were recruited from the DBOT trial registered in the UMIN Clinical Trials Registry (UMIN000019457, date of registration: March 24, 2016, https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000022501). The trial had a multicenter, randomized, open-label, parallel-group design. It was conducted to assess the effect of no add-on or add-on of dapagliflozin on short-term (48–72 hours) change in 24-hour blood glucose variables and on long-term (12 weeks) changes in

diabetes-related variables in patients with type 2 diabetes mellitus who received BOT.

Participants

The study protocol is shown in online supplemental figure S1. We screened patients with type 2 diabetes aged 20–79 years who regularly visited the Fukushima Medical University, Tokushima University Hospital, Tomishiro Central Hospital, Ohama Daiichi Hospital, Shonan Hospital, Iwaki Kyoritsu Hospital, and Taneda Clinic. Patients with (1) type 2 diabetes mellitus diagnosed according to the criteria of the Japan Diabetes Society¹³ and who received basal insulin alone or BOT, (2) HbA1c levels between 7.0% and 9.9% and (3) estimated glomerular filtration rate (eGFR) over 45 mL/min/1.73 m² were included in the study. Patients (1) with type 1 diabetes or secondary diabetes, (2) with a history of severe hypoglycemia or a frequent history of asymptomatic hypoglycemic episodes, (3) with severe renal, liver or cardiovascular disease or malignant neoplasm within 5 years, (4) with a greater risk for dehydration, (5) who are pregnant or lactating, (6) with a history of allergy or hypersensitivity or contraindications to dapagliflozin, and (7) who had been considered to be inappropriate by the attending physician or the principal investigator were excluded.

Intervention

The recruited patients were randomized at a ratio of 1:1 either to a no add-on group or a dapagliflozin add-on group. Randomization was stratified according to gender, age and HbA1c. Dapagliflozin was administered at a dose of 5 mg once daily after breakfast. We instructed the attending physicians to titrate insulin doses while oral medications remained the same during the 12 weeks, except when unacceptable hyperglycemia, hypoglycemia, or adverse events (AEs) occurred. The diet/exercise therapy and the combination of antihyperglycemic agents remained unchanged from baseline until the end of the study.

End points

The primary end point for the DBOT study was the change in mean daily blood glucose level before (at days 1–2) and after (at days 3–5) add-on or no add-on of dapagliflozin. The secondary end points were diabetes-related biochemical and major safety variables during the 12 weeks. Major safety variables included AEs, adverse drug reactions, abnormal or unexpected changes in laboratory test values, vital signs, and 12-lead ECG.

CGM and time in ranges

Continuous glucose monitoring

Before day 1, patients treated with basal insulin were randomly assigned to either the add-on or no add-on groups. As described, CGM was performed using iPro2 (Medtronic, Minneapolis, Minnesota, USA). At days 3–5, the investigators either administered 5 mg

of dapagliflozin once daily as an add-on or no add-on was provided and performed CGM. The insulin dose was expected to be comparable on days 1–2 and days 3–5. After day 6 until 12 weeks, add-on or no-add-on of dapagliflozin was maintained, and the insulin dose was titrated by attending physicians to optimise glycemic control. OADs were not changed during the study period. Glucose ranges were evaluated at four time ranges over a single day: 0–7, 7–12, 12–19, and 19–24 hours.

Time in ranges

The metric includes three key CGM measurements: per cent of readings and time per day within the target glucose range (TIR), time below the target glucose range (TBR), and time above the target glucose range (TAR).¹¹ The primary goal for effective and safe glucose control is recommended to increase the TIR while reducing the TBR.¹¹ We assessed the percentage of TIR, TAR, and TBR at day 2 and on day 5 with or without the dapagliflozin add-on.

Biochemical measurements

Blood samples were collected after an overnight fast. HbA1c was measured using the latex agglutination method. The systolic and diastolic blood pressures were measured in the sitting position after at least 5 min rest, using electronic sphygmomanometers. Body mass index (BMI) was calculated as the weight divided by height in meters squared (kg/m^2). Routine tests included alanine transaminase, aspartate transaminase, gamma-glutamyl transpeptidase, total high-density lipoprotein, low-density lipoprotein cholesterol, and triglycerides. All tests were performed using standard laboratory procedures. We calculated eGFR using the Japanese formula for GFR estimation: $\text{eGFR} (\text{mL}/\text{min}/1.73 \text{ m}^2) = 194 \times \text{serum creatinine} (\text{mg}/\text{dL})^{-1.094} \times \text{age} (\text{years})^{-0.287}$.¹⁴ Urinary 8-hydroxy-2'-deoxyguanosine (8OHdG) was measured by the ELISA method (Highly Sensitive ELISA kit for 8OHdG, Japan Institute for the Control of Aging, Shizuoka, Japan).

Statistical analysis

The normalities of values were estimated by the Shapiro-Wilk test and normal Q-Q plot. Continuous and parametric values were expressed as mean (SD), and non-parametric variables as median (IQR). The two-tailed unpaired Student's t-test and Mann-Whitney U test were used for parametric and non-parametric data, respectively. The categorical variables were shown as percentages and analyzed using the χ^2 test. Intergroup comparisons were performed between the add-on and the dapagliflozin add-on groups at baseline and after 12-week treatment. Intragroup paired comparisons were made before and after the 12-week treatment. The values of $p < 0.05$ were considered statistically significant. All analyses were performed

using GraphPad software (V.9.51, San Diego, California, USA).

RESULTS

General characteristics

Patient's general characteristics are shown in table 1. Among 36 participants, 18 were included in the no add-on group, while 18 were included in the dapagliflozin add-on group. The mean age of the participants was 65.3 years, and 61.1% were men. The mean BMI was $25.4 \text{ kg}/\text{m}^2$, fasting plasma glucose (FPG) was $159.5 \text{ mg}/\text{dL}$, and HbA1c was 8.11%. The mean of CGM day 2 sensor glucose was $192.5 \text{ mg}/\text{dL}$, maximum glucose was $296.6 \text{ mg}/\text{dL}$, minimum glucose was $96.3 \text{ mg}/\text{dL}$, and SD glucose was $55.6 \text{ mg}/\text{dL}$. No significant difference was observed in the baseline parameters between the no add-on and dapagliflozin add-on groups. In both groups, we instructed the attending physicians to titrate insulin doses, while oral medications remained the same before and after. In the no add-on group, insulin levels did not change before and after no add-on treatment, but this was coincidental. Both groups had no serious AEs, such as severe hypoglycemic symptoms and dehydration.

Twenty-four-hour glucose variability

Mean values (SD) of 24-hour glucose are shown in figure 1 and mean values (min–max) of 24-hour glucose are shown in online supplemental figure S2. The mean, maximum, minimum, and SD values of day 2 and day 5 were compared (figure 2). In the dapagliflozin add-on group, blood glucose levels were decreased at 0–7 hours and 12–19 hours (figure 1). No changes were observed in the mean blood glucose level, maximum blood glucose level, and SD in the no add-on group. In the dapagliflozin group, the mean blood glucose level ($p = 0.001$), maximum blood glucose level ($p < 0.01$), and SD ($p < 0.05$) decreased on day 5. An increase in the minimum blood glucose level was observed in the no add-on group, while no change was observed in the dapagliflozin add-on group. The mean blood glucose level was decreased by 14.8% in the dapagliflozin group, compared with 0.9% in the no add-on group (online supplemental table S1). TIR, TAR, and TBR were comparable between day 2 and day 5 in the no add-on group (figure 3); however, TIR increased, and TAR decreased on day 5 in the dapagliflozin add-on group.

Glucose control after the 12-week treatment

Changes in diabetes-related variables at 12 weeks after administration are shown in figure 4. Body weight, HbA1c, and urinary 8OHdG did not change in the control group but decreased in the dapagliflozin add-on group (online supplemental table S2, figure 4). HbA1c and urinary 8OHdG were lower in the dapagliflozin add-on group than in the control group (*, figure 4). No significant difference before and after treatment was observed between FPG and systolic blood pressure in

Table 1 Baseline characteristics of participants

Parameters	No add-on	Dapagliflozin add-on	P value
N	18	18	
Age, years	65.5 (10.9)	64.9 (12.7)	0.88
% Male	50	72	
BMI, kg/m ²	24.5 (3.3)	26.3 (5.3)	0.25
Waist circumference, cm	88.9 (9.1)	92.6 (11.5)	0.29
Systolic blood pressure, mm Hg	144 (25)	145 (25)	0.86
Diastolic blood pressure, mm Hg	77 (13)	78 (14)	0.76
Fasting plasma glucose, mg/dL	151 (54)	168 (40)	0.32
HbA1c, %	8.08 (1.25)	8.14 (0.92)	0.87
8OHdG, ng/mL	4.35 (2.90, 8.05)	4.70 (3.30, 9.00)	0.84
Medications			
Basal insulin, %	100	100	–
Basal insulin, unit	11.2 (5.6)	12.2 (10.2)	0.78
Oral antidiabetic agents			
Biguanides, %	61	50	0.50
Sulfonylureas, %	11	11	1.00
Glinides, %	6	6	1.00
Thiazolidinediones, %	17	28	0.42
α-Glucosidase inhibitors, %	17	17	1.00
GLP1RA, %	0	0	–
DPP4 inhibitors, %	56	50	0.74
SGLT2 inhibitors, %	0	0	–
Antihypertensive agents			
Calcium channel blockers, %	28	39	0.48
Angiotensin II receptor blocker, %	33	39	0.73
ACE inhibitors, %	17	11	0.29
Diuretics, %	0	0	–
β-Blockers, %	11	28	0.21
Lipid-lowering agents			
Statin, %	50	61	0.50
Fibrates, %	0	11	0.15
Ezetimibe, %	17	0	0.07

Values are mean (SD), median (IQR) or n (%).

BMI, body mass index; DPP4, dipeptidyl-peptidase 4; GLP1RA, glucagon-like peptide 1 receptor agonists; HbA1c, hemoglobin A1c; 8OHdG, 8-hydroxy-2'-deoxyguanosine; SGLT2, sodium-glucose cotransporter 2.

both groups (figure 4). Insulin was still used during the 12 weeks in both groups (online supplemental table S2).

DISCUSSION

This study evaluated the changes in mean daily blood glucose levels before and after 48–72 hours of add-on or no dapagliflozin (primary end point), diabetes-related biochemical variables and major safety variables during the 12 weeks (secondary end point) in Japanese patients with type 2 diabetes who received BOT. We obtained two main results. First, we observed

different changes in the 24-hour glucose variables in the add-on and no add-on groups on BOT. The addition of dapagliflozin had positive effects on mean blood glucose and maximum blood glucose, SD, and time in ranges in CGM. Second, the levels of urinary 8OHdG, an oxidative stress marker, and HbA1c decreased after 12 weeks of treatment with dapagliflozin as the add-on therapy. This study showed for the first time that SGLT2 inhibitors show a short time (48–72 hours) improvement in 24-hour glucose profile in patients with type 2 diabetes on BOT. This study also found that the add-on

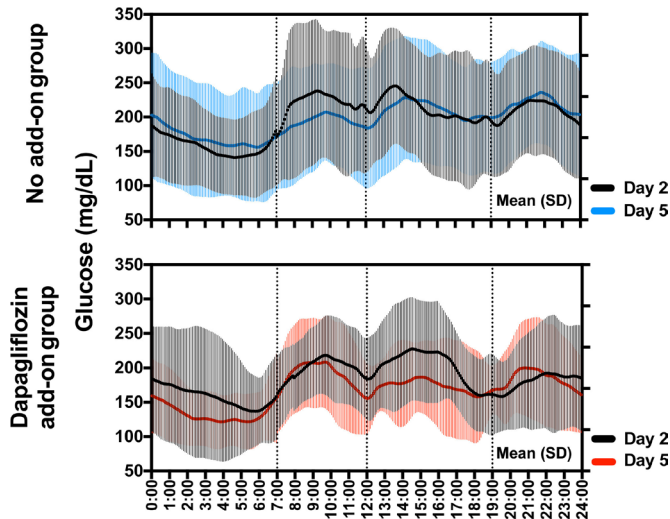


Figure 1 Mean variations in 24-hour blood glucose were measured using a continuous glucose monitoring system in the no add-on and dapagliflozin add-on groups. Lines represent the mean (solid)±95% CI (dotted) of blood glucose levels on day 2 (black) and day 5 (blue and red, respectively) in the no add-on (n=18) and dapagliflozin add-on (n=18) groups. To present the daily variations in glucose levels, we divided the periods into 0–7 hours, 7–12 hours, 12–19 hours, and 19–24 hours. Patients took a standard regimen of breakfast, lunch, and supper.

of dapagliflozin showed long-term efficacy on oxidative stress in such patients.

Twenty-four-hour glucose variables and dapagliflozin

SGLT2 inhibitors plus insulin therapy have been reported to show a reduction in HbA1c, daily insulin dose, and body weight and an improvement in insulin resistance,

beta-cell function, and cardiovascular benefits.⁹ However, the advantages and disadvantages of this therapy when used for optimal glucose control remain unclear. There are reports on the effectiveness of combining SGLT2 inhibitors with various insulin preparations.¹⁵ Inagaki *et al* reported the efficacy and safety of canagliflozin in combination with insulin therapy in Japanese patients with type 2 diabetes.¹⁶ HbA1c and body weight after 16 weeks of canagliflozin treatment were lower than those in the placebo group, which were in line with our findings. No significant side effects were noted, but the incidence of hypoglycemia was higher in the canagliflozin group.¹⁶ In our study, the incidence of hypoglycemia was not increased in the dapagliflozin group compared with that in the no add-on group. We cannot explain the reason for the discrepancy between the results reported by Inagaki *et al*¹⁶ and the incidence of hypoglycemia associated with the SGLT2 add-on observed in our study. The difference in insulin preparations (BOT, basal-bolus insulin therapy, or R/NPH mix insulin¹⁶ vs BOT in our study) could be one of the reasons. Our study is the first to assess TIR as a measure of glycemic control beyond HbA1c in BOT with or without SGLT2 inhibitors. The ATTD consensus panel recommends that the primary goal for effective and safe glucose control is to increase the TIR while reducing the TBR. SGLT2 inhibitors showed favourable profiles of SGLT2 inhibitors in TIR in patients with type 1¹⁷ and type 2 diabetes.¹² Henry *et al* evaluated TIR in people with type 2 diabetes on insulin therapy either with dapagliflozin or placebo, showing that there was no difference in TIR between the dapagliflozin and placebo groups.¹² The discrepancy between their results and ours might be explained by the difference in the

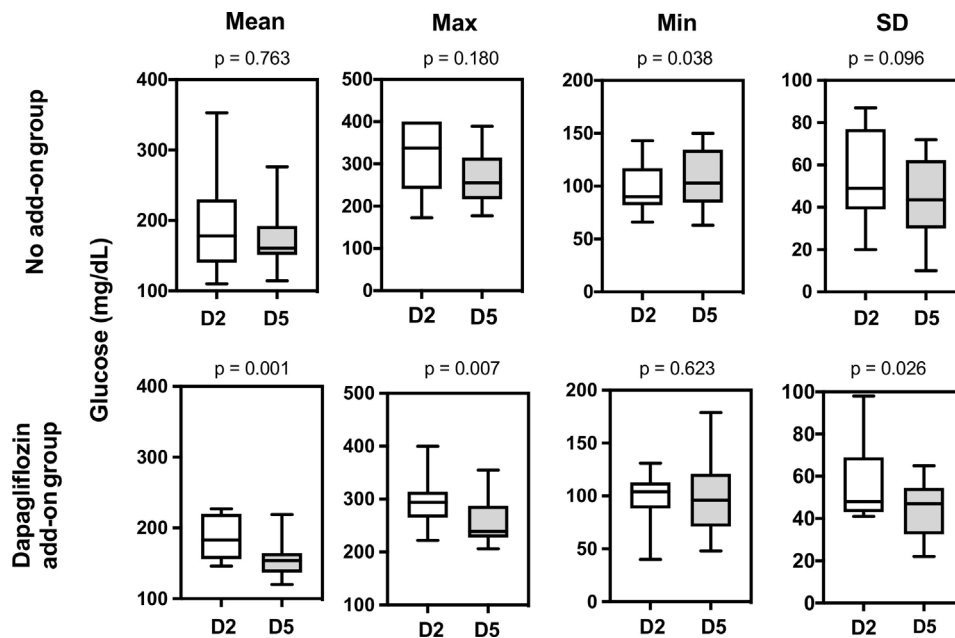


Figure 2 Levels of mean glucose, maximum (max) glucose, minimum (min) glucose, and SD glucose within 24 hours in the no add-on (n=18) and dapagliflozin add-on (n=18) groups. Boxes represent the mean±SD, and whiskers represent min to max glucose levels within 24 hours on day 2 (D2) and day 5 (D5). P values were obtained by a two-tailed paired t-test.

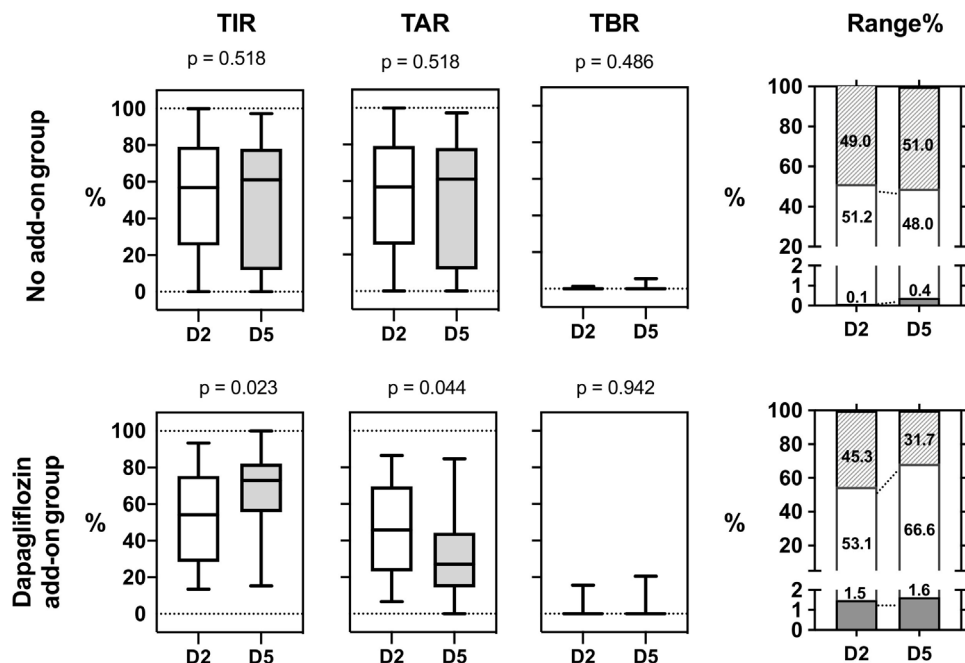


Figure 3 Time in ranges. Per cent of readings and time per day within the target glucose range (TIR), time above the target glucose range (TAR), and time below the target glucose range (TBR) are shown. Boxes represent the mean±SD, and whiskers represent the min to max glucose levels within 24 hours on day 2 (D2) and day 5 (D5) in the no add-on (n=18) and dapagliflozin add-on (n=18) groups. P values were obtained by a two-tailed paired t-test.

protocol. Henry *et al* recruited people with diabetes on insulin therapy with higher doses (≥ 30 U/day vs no dose requirement in ours) and with more than one type of insulin (71.2% used short-acting or intermediate-acting insulin alone or in combination with long-acting insulin

vs long-acting insulin alone in ours).¹² In addition, the timing of measurements of TIR was different: days 21–28 in Henry *et al*¹² vs 48–72 hours in ours after initiation of dapagliflozin. A more uniform population regarding insulin therapy and an earlier period in ours might bring

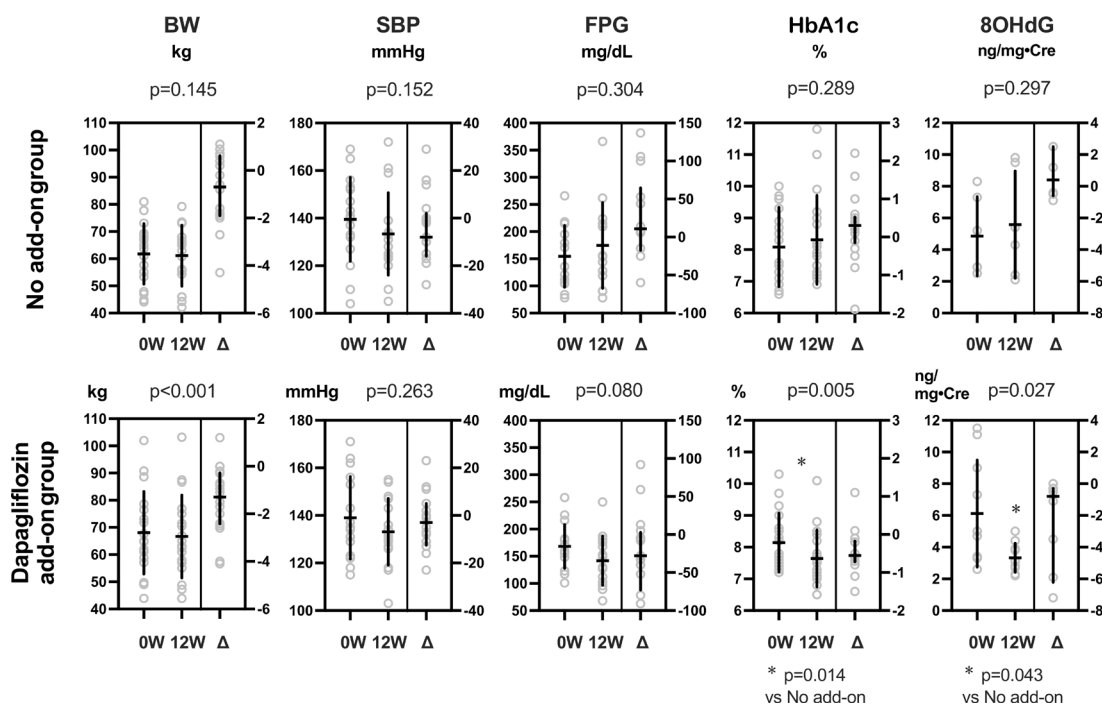


Figure 4 Changes and differences (Δ) of diabetes-related variables from 0 week (0W) and at 12 week (12W) in the no add-on (n=18) and dapagliflozin add-on (n=18) groups. Circles represent individual values; bars indicate mean±SD or median (IQR). BW, body weight; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; SBP, systolic blood pressure; 8OHdG, 8-hydroxy-2'-deoxyguanosine. P values were obtained by two-tailed paired Wilcoxon test between 0W and 12W and unpaired Wilcoxon test between no add-on and dapagliflozin add-on at 12W. *P values between no add-on and dapagliflozin add-on at 12W.

the improved 24-hour glucose profile in the dapagliflozin add-on group. However, this notion should be carefully interpreted in future studies.

In the present study, TIR in the no add-on group remained unchanged, whereas it was significantly increased in the dapagliflozin add-on group (figure 4). The increase in TIR was obtained by decreasing TAR without increasing TBR, which can be regarded as an effective and safe result.¹¹

Reportedly, long-term complications could be amended at least partly by the significant improvements in HbA1c and/or TIR.¹¹ Beck *et al* reported that progression of diabetic retinopathy and microalbuminuria was associated with changes in TIR¹⁸: a 10% decrease in TIR was shown to increase the risk of developing retinopathy by 64%; the risk of developing microalbuminuria increased by 40% for every 10% decrease in TIR. Lu *et al* also showed that TIR was lower in patients with type 2 diabetes with advanced retinopathy, and the prevalence of diabetic retinopathy decreased with increasing TIR.¹⁹ However, evidence about the long-term effects of an improved TIR is still lacking and requires results in future studies.

Long-term diabetes-related variables and dapagliflozin

Long-term diabetes-related variables of SGLT2 inhibitors have been reported in conjunction with insulin therapy. In two meta-analyses evaluating the add-on effects of SGLT2 inhibitors in people treated with either basal insulin alone or basal plus bolus insulin, SGLT2 inhibitors have improved the HbA1c, fasting plasma glucose, and body weight and decreased the dose of insulin without increasing the risk of hypoglycemia.^{8,9} The studies evaluating the effect of SGLT2 inhibitors in people with basal insulin alone, the same as in this study, are limited. Rosenstock *et al*²⁰ reported that 5 or 10 mg of empagliflozin added to basal insulin decreased HbA1c at ~0.6%–0.8% and reduced body weight ~1–2 kg with a similar risk of hypoglycemia to placebo for 12–78 weeks. This result is consistent with our results. In the current study, dapagliflozin added to basal insulin reduced HbA1c by –0.5% and body weight by 1.4 kg after 12 weeks.

The reduction in HbA1c and weight loss with SGLT2 inhibitors observed in previous reports^{8,9,20} and ours can be explained as follows. A sustained decrease in daily glucose concentration through urinary glucose excretion is the primary mechanism of declined HbA1c by SGLT2 inhibitors.⁷ Two indirect mechanisms are also considered for declined HbA1c. Reducing hyperglycemia by SGLT2 inhibitors could correct two core defects present in type 2 diabetes mellitus: pancreatic β -cell dysfunction and insulin resistance.²¹ The body weight reduction by SGLT2 inhibitors may influence decreases in HbA1c.⁷ Based on data from animal studies and clinical trials, the effects of SGLT2 inhibitors on urinary sodium excretion and diuresis appear to be transient.²² The composition of body weight reduction in SGLT2 inhibitors therapy at ~16 weeks is body water 15%–35%, body fat 50%–75%,

subcutaneous fat 25%–45%, and visceral fat ~25%.²³ Combined above, improvement in insulin sensitivity by reducing visceral fat²⁴ can be linked to decreased HbA1c in people treated with SGLT2 inhibitors.²¹

Oxidative stress, defined as an imbalance between the production of reactive oxygen species (ROS) and antioxidant defence systems, has been associated with the development of diabetes and its complications.²⁵ In this study, the dapagliflozin add-on group showed a significant decrease in the urinary 8OHdG level at 12 weeks. Previous studies have reported that the administration of SGLT2 inhibitors decreased the 8OHdG levels (canagliflozin,²⁶ ipragliflozin,²⁷ and empagliflozin²⁸). As a mechanism of ROS enhancement in diabetes, various metabolic abnormalities mediated by hyperglycemia, namely, advanced glycation end-product production, polyol metabolic abnormality, and enhanced mitochondrial superoxide production, have been reported.^{25,29,30} Increased ROS is associated with human vascular endothelial dysfunction.³¹ Endothelial dysfunction is considered one of the main mechanisms of vascular complications due to chronic hyperglycemia.³² Therefore, a sustained decrease in ROS could be linked at least partly to protection against diabetic vascular complications by anti-diabetic drugs.³² In fact, improvement in endothelial dysfunction was reported after the use of SGLT2 inhibitors.^{33,34} One of the possible mechanisms of dapagliflozin's secondary prevention of coronary artery disease is considered through suppression of ROS.³⁵ Although the mechanism by which SGLT2 inhibitors decreased urinary 8OHdG remains unclear, their multiple beneficial effects such as weight loss,³⁶ reductions in blood pressure levels,^{37,38} improvements in lipid profile,³⁹ and decrease in uric acid^{38,40} might be related to the reduction in 8OHdG.

Limitations

The strengths of our study are as follows: this was the first randomized controlled trial to directly compare the effects of no add-on or add-on of an SGLT2 inhibitor on glucose fluctuation in patients with type 2 diabetes on BOT; there were no significant biases in the pretreatment for type 2 diabetes mellitus in both study arms. We could assess the relationship between glucose fluctuations and other metabolic parameters.

However, there are limitations to our study. First, our small sample size may limit our ability to conclude. Second, this study was lack of double blinding, short study duration, and lack of dietary uniformity because of the ambulatory care setting. Our findings must be validated in a larger, long-term, dietary-controlled double-blind trial to resolve these potential issues. Third, we did not measure glucose oscillation markers such as glycated albumin/HbA1c ratio other than those based on continuous glucose monitoring. This study cannot determine the relationship between the effects of dapagliflozin on short-term glycemic variables and long-term biochemical variables. We have only determined the short-term

glycemic variability on days 2 and 5, not the long-term. HbA1c was significantly lower in the dapagliflozin add-on group only, which may suggest that TIR was better than no add-on. Meanwhile, decreasing body weight might include mechanisms other than improving short-term glycemic variability. Henry *et al* evaluated TIR at days 21–28 on various insulin combinations, either with dapagliflozin or placebo, showing no difference in TIR.¹² Taken above, we cannot argue how the short-term effect could affect the long-term variables and further explain the clinical benefits of dapagliflozin observed in the previous large-scale clinical trials. Future large-scale studies to evaluate the long-term effects of dapagliflozin on BOT are needed to clarify this point.

Fourth, fewer CGM data were obtained than recommended, so the CGM data must be interpreted as directional or suggestive.¹¹ We took CGM measures on day 2 (the baseline 48 hours of data) and day 5 (48–72 hours after the dapagliflozin add-on). We wanted to see acute effects in the first 48–72 hours. The reason was that after 1–2 weeks of dapagliflozin use, weight loss and insulin adjustment would be assumed, and the difference between the direct effect of dapagliflozin and the effect of weight loss would not be discernible. However, the method differs from the general CGM guideline,¹¹ limiting our interpretation of CGM measures. Fifth, over 50% of our patients had taken biguanide and DPP-4 inhibitors. Although combinations of SGLT-2 inhibitors and both OADs could differ in glucose-lowering efficacy,⁴¹ we could not compare the efficacy of the combination therapy primarily due to the small sample size.

CONCLUSION

In conclusion, this multicenter, randomized, open-label, parallel-group comparison study demonstrated that mean daily blood glucose and other daily glucose profiles were amended after 48–72 hours of dapagliflozin add-on in Japanese patients with type 2 diabetes who received BOT. The diabetes-related biochemical variables such as HbA1c and urinary 8OHdG were also obtained during the 12 weeks of dapagliflozin add-on without major AEs. A preferable 24-hour glucose profile in ‘time in ranges’ and an improvement in ROS by dapagliflozin warrant us to evaluate these benefits in more extensive clinical studies.

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Acknowledgements The authors sincerely thank Hiroko Ohashi for her excellent assistance. The authors would also like to thank the patients, the staff in our hospital and clinic and the investigators for all their support.

Contributors Study design, methodology, and conduct: MSh; investigation: AK and MSh; recruiting and data sampling: AK, NM, TO, HS, YO, RT, KO, YT, MH, KN, SY; writing—original draft preparation: AK and MSh; writing—review and editing: MSh; validation and review: HM and MSa; funding acquisition: MSh; guarantor: MSh. All authors have read and agreed to the published version of the manuscript.

Funding This study was supported by the Japan Society for the Promotion of Science (JSPS) (grant numbers: 16K01823 to MSh and 17K00924 to AK and MSh) and supported by Ono Pharmaceutical and AstraZeneca.

Competing interests YT and KO have received lecture fees from Ono Pharmaceutical. SY have received lecture fees from AstraZeneca. KK, MSa, and MSh have received lecture fees from Ono Pharmaceutical and AstraZeneca.

Patient consent for publication Not applicable.

Ethics approval This study was approved by Tokushima University Hospital #2457 and Fukushima Medical University Hospital #2947. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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