Effect of dapagliflozin on 24-h glycaemic variables in Japanese patients with type 2 diabetes mellitus receiving basal supported oral therapy: The DBOT study

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Abstract

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

Methods: Changes in daily blood glucose variability including time in ranges during continuous glucose monitoring (CGM) and diabetes-related biochemical variables before and after add-on or no add-on of dapagliflozin were evaluated in the multicentre, randomised, two-arm, open-label, parallel-group comparison study.

Results: Among 36 participants, 18 were included in the no add-on group and the other 18 were included in the dapagliflozin add-on group. Age, men gender, and body mass index were comparable between the groups. There were no changes before and after CGM 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 standard deviation (SD) glucose (57–45, P <0.05), but not minimum glucose, 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-OHDG as well as HbA1c decreased.

Conclusions: This study showed the short-term and long-term efficacies of dapagliflozin in type 2 diabetes patients on BOT. A preferable 24-h glucose profile in “time in ranges” and an improvement in reactive oxygen species warrant us to evaluate these benefits of dapagliflozin in larger clinical studies.

Background

Because type 2 diabetes mellitus is a progressive disease, maintaining the glycaemic targets with oral monotherapy is habitually 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, but a substantial number of patients require bolus insulin before meals to achieve glycaemic 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-supported oral therapy, BOT).[3] The addition of OADs to basal insulin is effective in achieving glycaemic control and insulin requirements.[4, 5] However, negative effects of this combination therapy have been reported. Among 5,663 German diabetes patients 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 and efficacy of BOT still need to be elucidated.[1, 3]

Sodium glucose cotransporter 2 (SGLT2) inhibitors are a relatively new class of OAD that can reduce hyperglycaemia by increasing urinary glucose excretion independent of insulin secretion or action.[1] SGLT2 inhibitors are administered as either monotherapy or dual/triple therapy with other OADs and also in combination with insulin.[7] SGLT2 inhibitors plus insulin therapy is considered one of the promising

strategies for optimal glucose control, but 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.[8] Recently, the Advanced Technologies & Treatments for Diabetes (ATTD) consensus panel identified “time in ranges” as a measure of glycaemic control, which provides more actionable information than HbA1c alone.[9] Currently, no study has assessed the “time in ranges” in combination therapy including SGLT2 inhibitors and insulin.

This multicentre, randomised, open-label, parallel-group comparison study aimed to evaluate the impact of dapagliflozin for 12 weeks on 24-hour glucose variables using “time in ranges” and on diabetes-related biochemical variables, in Japanese type 2 diabetes patients 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 multicentre, randomised, open-label, parallel-group design and was conducted to assess the effect of no add-on or add-on of dapagliflozin for 12 weeks on change in 24-h blood glucose variables and 12-week diabetes-related variables in patients with type 2 diabetes mellitus who received BOT.

Participants

The study protocol is shown in **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 Society (JDS) and who received basal insulin alone or BOT [25], (2) HbA1c levels between 7.0% and 9.9% and (2) eGFR over 45 mL/min/1.73 m^2 were included in the study. Patients (1) with type 1 diabetes or secondary diabetes, (2) with a history of severe hypoglycaemia or a frequent history of asymptomatic hypoglycaemic 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 (7) who had been considered to be inappropriate by the attending physician or the principal investigator were excluded.

Intervention

Dapagliflozin was administered at a dose of 5 mg once daily after breakfast. During the 12-week period, antihyperglycemic agents other than dapagliflozin were unchanged, except when unacceptable hyperglycaemia, hypoglycaemia, or adverse events occurred. The diet/exercise therapy and the combination anti-hyperglycaemic agents remained unchanged from baseline until the end of the study.

Endpoints

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

CGM And Time In Ranges

CGM: Before Day 1, patients treated with basal insulin were randomly assigned to either the add-on group or no add-on group. CGM was performed using iPro2 (Medtronic, Minneapolis, MN, USA) as described. At Days 3–5, the investigators either administered 5 mg of dapagliflozin once daily as add-on or no add-on was provided and performed CGM. The dose of insulin was expected to be comparable at 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 dose of insulin was titrated by attending physicians to optimise glycaemic control. OADs were not changed during the study period. Glucose ranges were evaluated at four time zones: 0–7, 7–12, 12–19, and 19–24.

Time in ranges: The metric includes three key CGM measurements: % 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) [9]. The primary goal for effective and safe glucose control is recommended to increase the TIR while reducing the TBR [9]. We assessed the percentage of TIR, TAR, and TBR at day 2 and at day 5 with or without dapagliflozin add-on.

Routine 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 (ALT), aspartate transaminase (AST), gamma-glutamyl transpeptidase (γ-GTP), total high-density lipoprotein (HDL), low-density lipoprotein (LDL) cholesterol, and triglycerides. All tests were performed using standard laboratory procedures. We calculated eGFR using the Japanese formula for GFR estimation: eGFR ($mL/min/1.73\ m^2$) = 194 x serum creatinine $(mg/dL)^{-1.094}$ x age $(years)^{-0.287}$ [10]. Urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG) was measured by the ELISA method.

Statistical analysis

The average was estimated, and each value was expressed as the mean ± the standard deviation. Categorical parameters were expressed as percentages. The t-test or chi-square test was used to compare the groups. Clinical data before initiating therapy either with dapagliflozin or not within the 12-week

treatment period were compared using the paired t-test. All analyses were performed using GraphPad software (version 7.03, San Diego, CA, 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 the other 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 kg/m^2, FPG was 159.5 mg/dl, and HbA1c was 8.11%. The mean of CGM Day 2 sensor glucose was 192.5 mg/dl, maximum glucose was 296.6 mg/dl, minimum glucose was 96.3 mg/dl, and SD glucose was 55.6 mg/dl. No significant difference was observed in the baseline parameters between the no add-on and dapagliflozin add-on groups. There were not major safety variables such as hypoglycaemic symptoms and dehydration in both groups.

Table 1
Baseline characteristics of participants

Parameters	No add-on	Dapagliflozin add-on	P
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
Systolc blood pressure, mmHg	143.8 (24.8)	145.2 (24.7)	0.86
Diastolic blood pressure, mmHg	76.7 (12.7)	78.1 (13.6)	0.76
Fasting plasma glucose, mg/dl	150.9 (54.1)	168.1 (40.3)	0.32
HbA1c, %	8.08 (1.25)	8.14 (0.92)	0.87
8OHdG, ng/mL	5.17 (2.70)	5.24 (3.16)	0.96
Medications			
Basalin insulin, %	100	100	-
Basalin insulin, unit	11.2 (5.6)	12.2 (10.2)	0.78
Oral anti-diabetic agensts			
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	-
Anti-hypertensive agents			
Calcium channel blockers, %	28	39	0.48
Angiotensin II Receptor Blocker, %	33	39	0.73
Angiotensin converting enzyme inhibitors, %	17	11	0.29

Parameters	No add-on	Dapagliflozin add-on	P
Diuretics, %	0	0	-
β channel 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) or n (%)			

Twenty-four-hour Glucose Variability

Mean values (SD) of 24-h glucose are shown in Fig. 1, and mean values (min–max) of 24-h glucose are shown in **Figure S2.** The mean, maximum, minimum, and SD values of day 2 (D2) and day 5 (D5) were compared (Fig. 2). In the dapagliflozin add-on group, a decrease in blood glucose level was observed at 0–7 h and 12–19 h (Fig. 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 at 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 (**Table S1**). TIR, TAR, and TBR were comparable between Day 2 and Day 5 in the no add-on group (Fig. 3); however, TIR increased and TAR decreased at 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 Fig. 4. HbA1c, BW, and urinary 8OHdG did not change in the control group but decreased in the dapagliflozin add-on group (**Table S2**, Fig. 4). No significant difference was observed between FPG and SBP in both groups (Fig. 4). Insulin was still used during the 12-week period in both groups (**Table S2**).

Discussion

This multicentre, randomised, open-label, parallel-group comparison study evaluated the short-term and long-term efficacies of dapagliflozin in type 2 diabetes patients on BOT. We obtained two main results. First, we observed dissimilar changes in the 24-h glucose variables in the add-on and no add-on groups on BOT. The addition of dapagliflozin had positive results on mean blood glucose, maximum blood glucose, standard deviation, and time in ranges in CGM. Second, the levels of urinary -OHdG, which is 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 preferable 24-h glucose profile and the long-term efficacy on oxidative stress in type 2 diabetes patients on BOT.

Twenty-four-hour Glucose Variables And Dapagliflozin

SGLT2 inhibitors plus insulin therapy showed a reduction in HbA1c, daily insulin dose, and body weight and an improvement in insulin resistance, β-cell function, and cardiovascular benefits.[7] 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.[11] Inagaki et al. reported the efficacy and safety of canagliflozin in combination with insulin therapy in Japanese type 2 diabetes patients.[12] HbA1c and body weight after the 16th week 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 hypoglycaemia was higher in the canagliflozin group.[12] In our study, the incidence of hypoglycaemia 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.[12] and the incidence of hypoglycaemia associated with SGLT add-on observed in our study. The difference in insulin preparations (BOT, basal-bolus insulin therapy, or R/NPH mix insulin[12] vs. BOT in our study) could be one of the reasons. Our study is the first to assess TIR as a measure of glycaemic control beyond A1C 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 positive profiles of SGLT2 inhibitors in TIR in type 1[13] and type 2 diabetes patients.[14] However, no previous study has assessed TIR in the combination therapy with SGLT2 inhibitors and insulin.

In the present study, TIR in the no add-on group remained unchanged, whereas it was significantly increased in the dapagliflozin add-on group (Fig. 4). The increase in TIR was obtained by decreasing TAR without increasing TBR, which can be regarded as an effective and safe result.[9]

Long-term Diabetes-related Variables And Dapagliflozin

In this study, HbA1c and body weight significantly improved at 12 weeks after dapagliflozin administration, although there was no significant difference in FPG or blood pressure levels. Long-term complications were prevented as evidenced by the significant improvements in HbA1c and/or TIR.[9] Beck et al. reported that progression of diabetic retinopathy and microalbuminuria was associated with changes in TIR[15]: 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 type 2 diabetes patients with advanced retinopathy, and the prevalence of DR decreased with increasing TIR.[16]

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.[17] In this study, the dapagliflozin add-on group showed a significant decrease in the urinary 8-OHdG level at 12 weeks. Previous studies have reported that the administration of SGLT2 inhibitors decreased the 8-OHdG levels (canagliflozin[18], ipragliflozin[19], and empagliflozin[20]). As a mechanism of ROS enhancement in diabetes, various metabolic abnormalities mediated by hyperglycaemia, namely, advanced glycation end product production, polyol metabolic abnormality, and enhanced mitochondrial superoxide production, have been reported.[17, 21, 22] A decrease in NO production[23, 24] or an improvement in glycaemic control[25–28] has been reported to improve vascular endothelial function in patients with type 2 diabetes. In fact, improvement in endothelial dysfunction was reported after use of SGLT2 inhibitors.[29, 30] One of the possible mechanisms of dapagliflozin's secondary prevention of coronary artery disease is through suppression of oxidative stress.[31] Although the mechanism by which urinary 8-OHdG was decreased by SGLT2 inhibitors remains unclear, their multiple beneficial effects such as weight loss,[32] reduction in blood pressure levels,[33, 34] improvement in lipid profile,[35] and decrease in uric acid[34, 36] might be related to the decrease in 8-OHdG.

Limitations: The strengths of our study are as follows: this was the first randomised controlled trial to directly compare the effects of no add-on or add-on of an SGLT2 inhibitor on glucose fluctuation in type 2 diabetes patients on BOT; there were no significant biases in the pre-treatment for type 2 diabetes mellitus in both study arms. We could assess the relationship between glucose fluctuations and other metabolic parameters. However, our small sample size may limit our ability to draw a conclusion. Other major limitations of this study were lack of double blinding, short study duration, and lack of dietary uniformity because of the ambulatory care setting. To resolve these potential issues, our findings need to be validated in a larger scale, long-term, dietary-controlled double-blind trial.

Conclusions

In summary, this multicentre, randomised, open-label, parallel-group comparison study was conducted to explore the short-term and long-term efficacies of dapagliflozin in type 2 diabetes patients on BOT. A preferable 24-h glucose profile in “time in ranges” and an improvement in ROS by dapagliflozin warrant us to evaluate these benefits in larger clinical studies.

List Of Abbreviations

SGLT2: sodium glucose transporter 2, OADs: oral antidiabetic drugs, BOT: basal-supported oral therapy (BOT), BMI: body mass index; FPG: fasting plasma glucose, HbA1c: hemoglobin A1c; TIR: time in the target glucose range, TBR: time below the target glucose range, TAR: time above the target glucose range, CGM: continuous glucose monitoring, 8-OHdG: 8-hydroxy-2’-deoxyguanosine, ATTD: Advanced Technologies & Treatments for Diabetes, ROS: reactive oxygen species

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board (Tokushima University Hospital #2457; Fukushima Medical University Hospital #2947) and was conducted in accordance with the ethical standards of the clinical trials (including the Helsinki Declaration and Good Clinical Practice). A written informed consent was obtained from all patients before enrolment.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

Y.T. and KO have received lecture fees from Ono Pharmaceutical Co. S.Y. have received lecture fees from AstraZeneca K.K. Ma.S and Mi.S. have received lecture fees from Ono Pharmaceutical Co., Ltd and AstraZeneca K.K.

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Author contributions

Study design, methodology and conduct, Mi.S.; Investigation, A.K. and Mi.S.: recruiting and data sampling, A.K., N.M., T.O., H.S., Y.O., R.T., K.O., Y.T., M.H., K.N., S.Y.: writing—original draft preparation, A.K. and Mi.S.; writing—review and editing, Mi.S.; validation and review, H.M., Ma.S.: funding acquisition, Mi.S. All authors have read and agreed to the published version of the manuscript.

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Figures

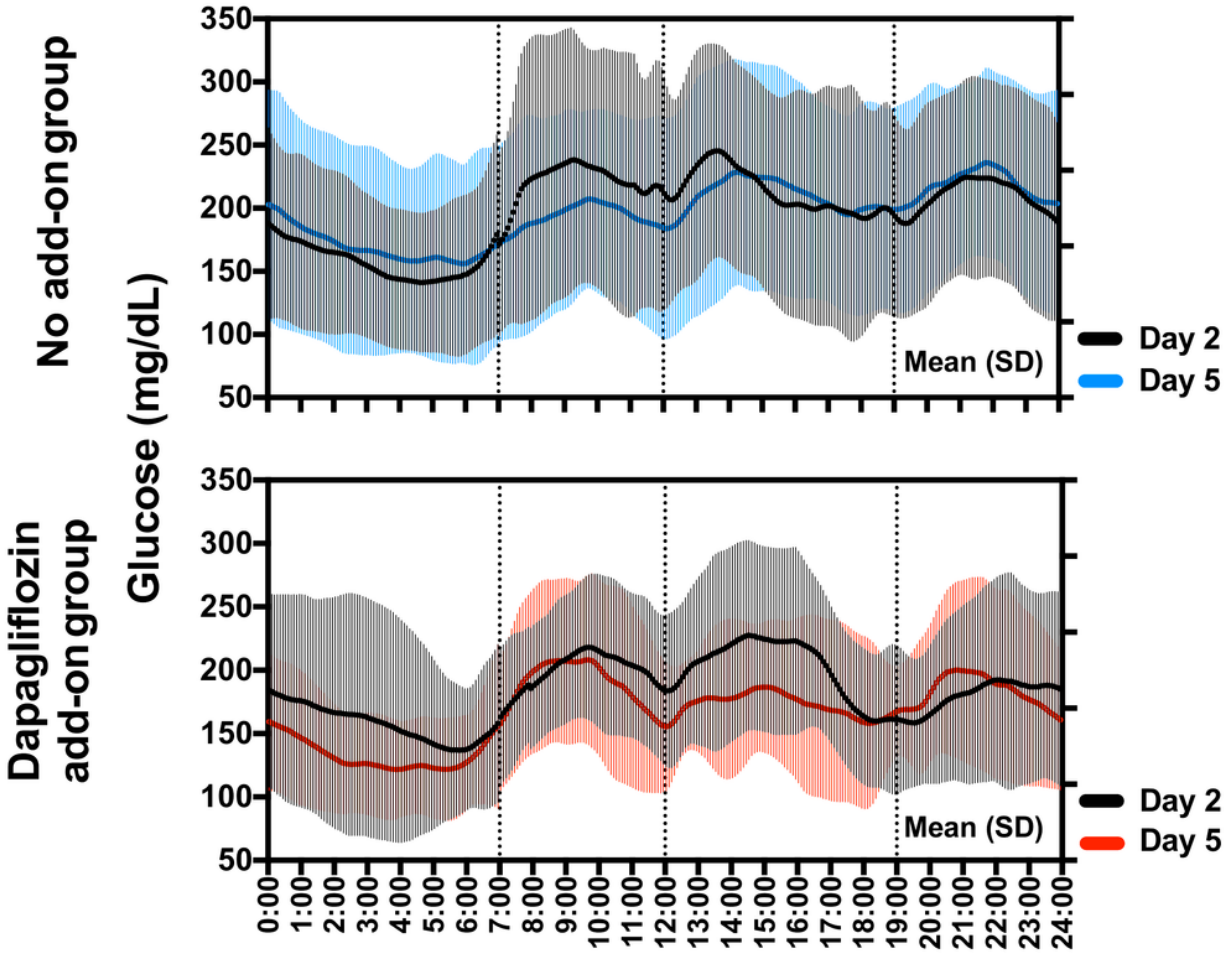

Figure 1

Figure 1

Mean variations in 24-h blood glucose measured using a continuous glucose monitoring system in the no add-on and dapagliflozin add-on groups. Lines represent mean (solid) ± 95% confidence interval (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 time periods into 0000–0700 h (bed time), 0700–1800 h (morning time), 0700–1800 h (day time), and 1800–0000 h (night time). Patients took a standard regimen of breakfast, lunch, and supper.

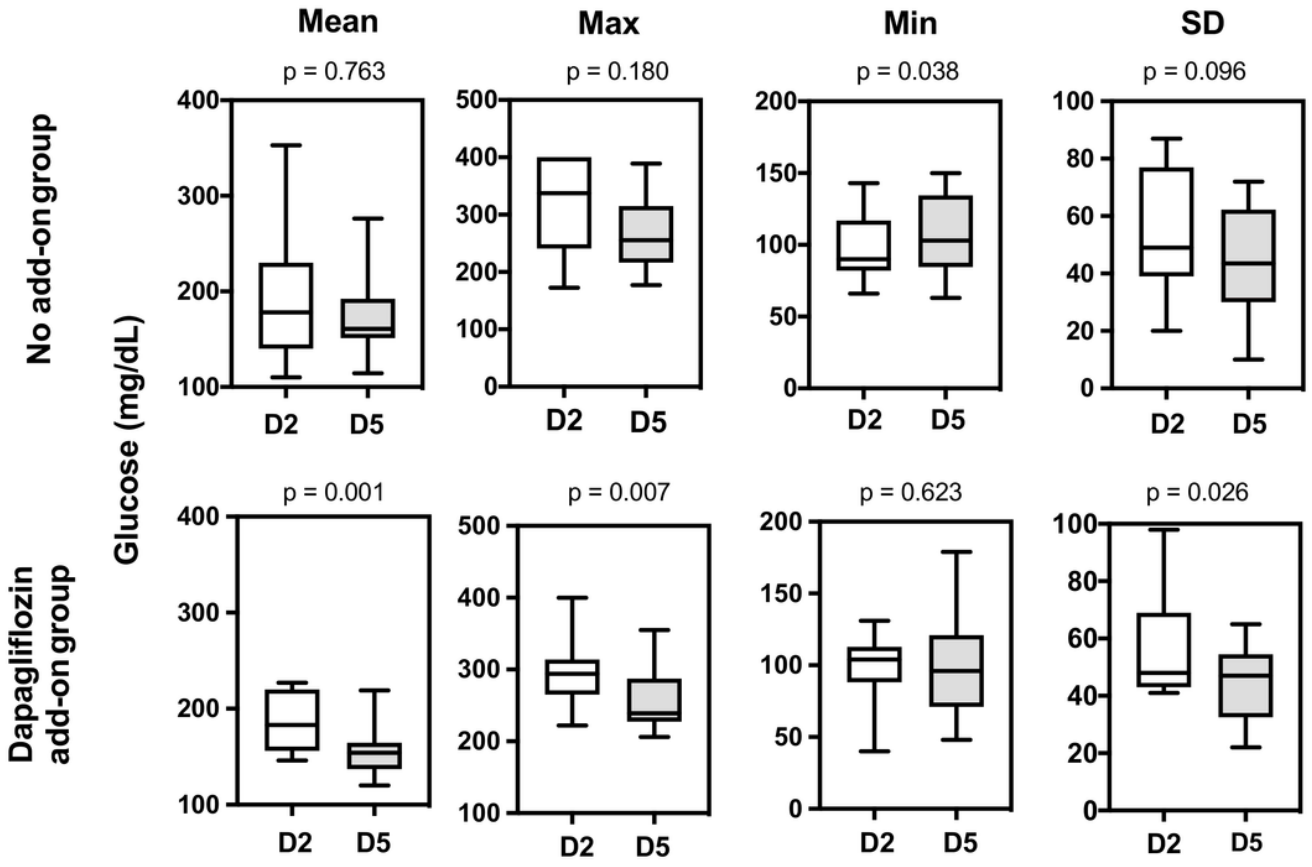

Figure 2

Figure 2

Levels of mean glucose, maximum (max) glucose, minimum (min) glucose, and standard deviation (SD) glucose within 24 h 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 h on Day 2 (D2) and Day 5 (D5). P values obtained by two-tailed paired t test.

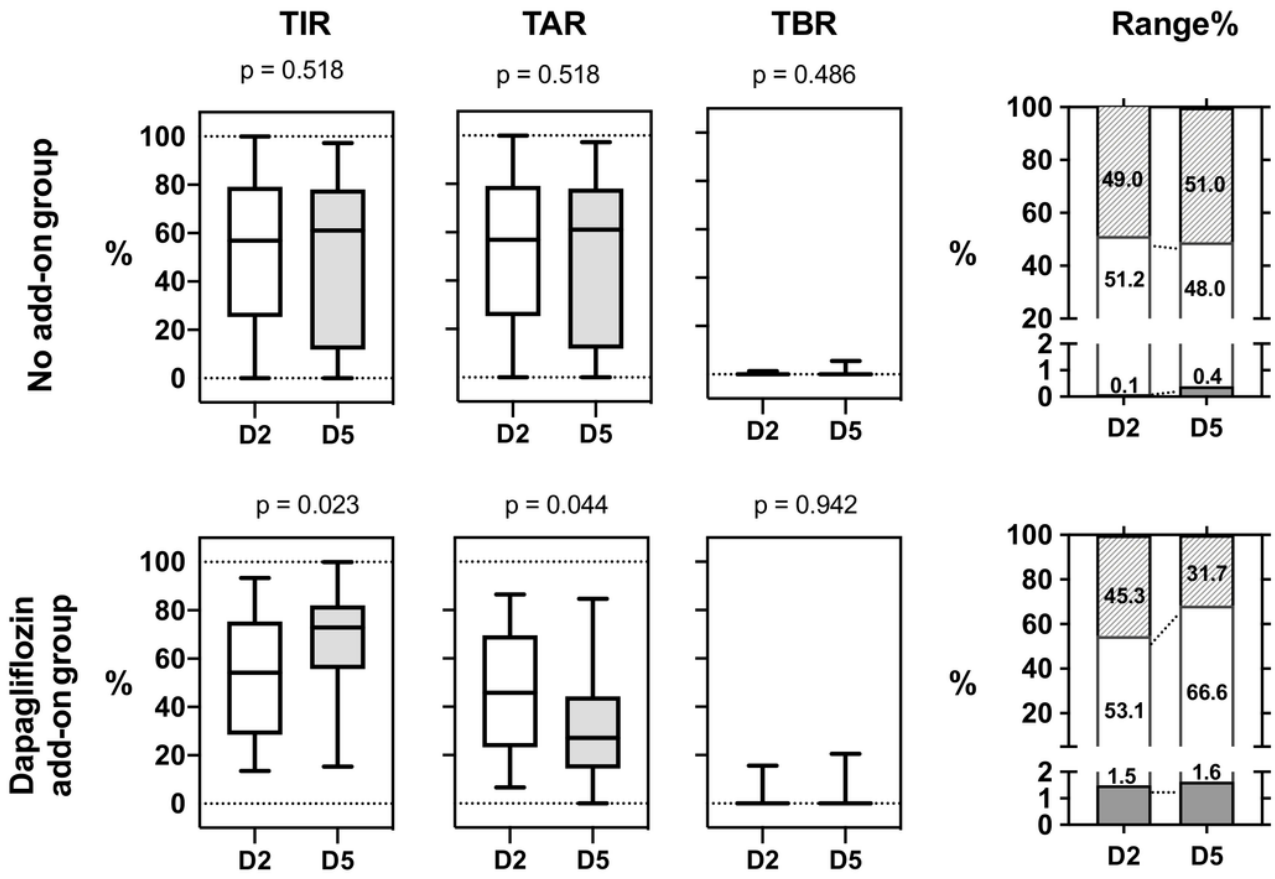

Figure 3

Figure 3

Time in ranges. % 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) are shown. Boxes represent the mean ± SD, and whiskers represent the min to max glucose levels within 24 h on Day 2 (D2) and Day 5 (D5) in the no add-on (n = 18) and dapagliflozin add-on (n = 18) groups. P values obtained by two-tailed paired t test.

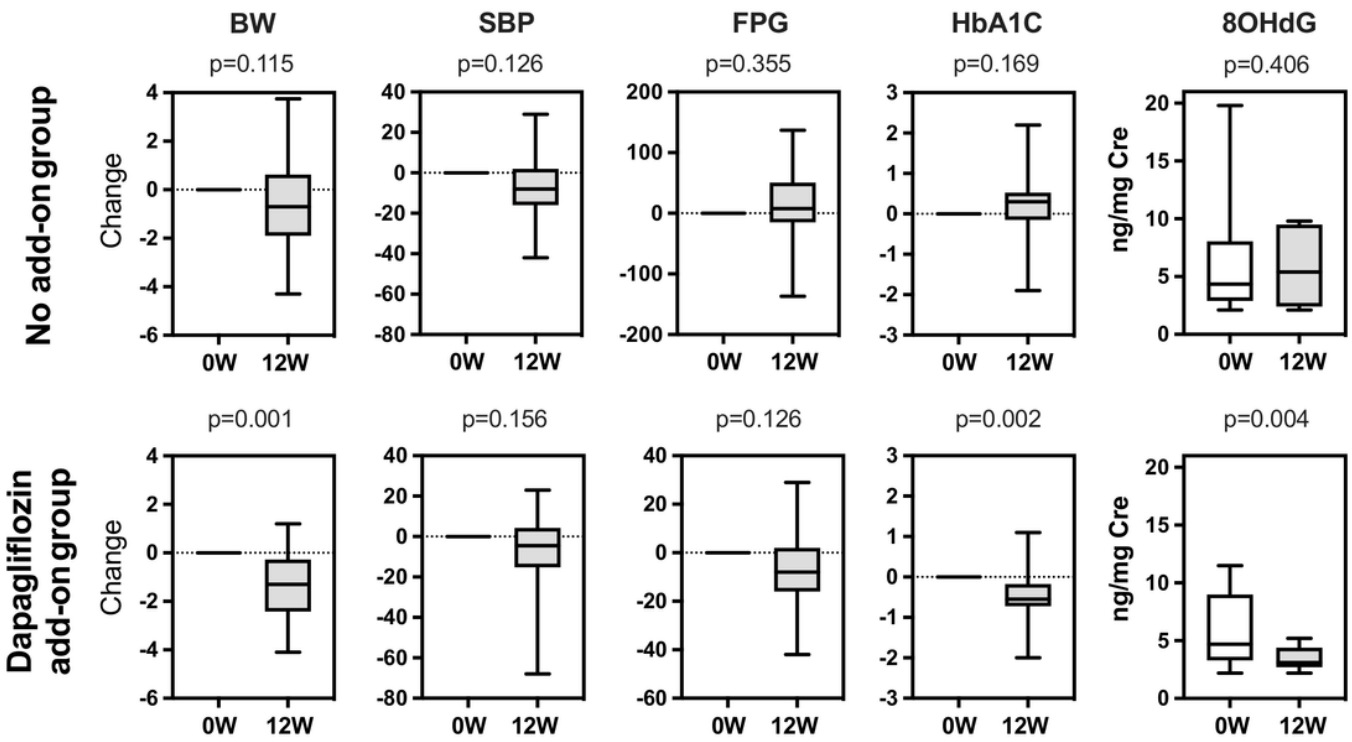

Figure 4

Figure 4

Change 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. Boxes represent the mean ± SD, and whiskers represent the min to max glucose levels. BW: body weight, SBP: systolic blood pressure, FPG: fasting plasma glucose, 8OHdG: 8-hydroxy-2'-deoxyguanosine. P values obtained by two-tailed paired t test.

Supplementary Files

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