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Efficacy of Intermittent Empagliflozin Supplementation on Dietary Self-Management and Glycemic Control in Patients With Poorly Controlled Type 2 Diabetes: A 24-Week Randomized Controlled Trial

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ABSTRACT

Aims: This study was designed to explore the effects of intermittent use of empagliflozin, a sodium glucose cotransporter 2 inhibitor, on dietary self-management and glycemic control in patients with inadequately controlled type 2 diabetes.

Materials and Methods: This is a prospective, randomized, open-label, blinded-endpoint, parallel-group, comparative clinical trial of 50 type 2 diabetes patients treated with no more than 3 oral anti-diabetic drugs (HbA1c ≥ 7.0% but <10.0%). The patients were randomized to take 10 mg/day empagliflozin either everyday (the regular group, n=25) or on the day when patients considered they had overeaten (the intermittent group, n=25) for 24 weeks. We limited empagliflozin prescription to half of the required period in the intermittent group. The primary endpoint was a change in HbA1c at the end of 24-week treatment period relative to the baseline. The secondary outcomes included changes in body weight, daily energy intake and diabetes-treatment related quality of life (DTR-QOL). Energy intake was assessed by a diet-specific validated questionnaire rather than actual assessments of food intake.

Results: Intake rate of empagliflozin was 96.7±7.2% and 45.7±7.0% for the regular group and the intermittent group, respectively. Interestingly, ΔHbA1c was identical in the two groups (-0.64±0.19% and -0.65±0.17%, respectively). Body weight decreased (-2.72±0.52 kg and -1.50±0.45 kg, respectively) and DTR-QOL increased significantly from baseline in both groups. However, energy intake decreased significantly only in the intermittent group (-221.0±108.3 kcal/day).

Conclusions: Intermittent empagliflozin supplementation is a useful therapeutic option that empowers dietary self-management and improves glycemic control accompanied with body

weight loss and increase in DTR-QOL in patients with inadequately controlled type 2 diabetes.

ClinicalTrials.gov number: UMIN000019253

Keywords: Intermittent use, Empagliflozin, Self-management

1 INTRODUCTION

Various types of glucose-lowering agents are available for the treatment of diabetes, but lifestyle intervention and self-management of diet and exercise are important for the long-term care of patients with type 2 diabetes.[1-7] Lifestyle intervention has also been proved for its cost-effectiveness.[8,9] Thus, education and support on self-management are critical elements of care for all patients with type 2 diabetes.[10] However, the best tools or strategies appropriate for patient education and approaches to improve adherence to healthy eating patterns remain to be defined and standardized.

The selection of the most appropriate glucose-lowering agents for treatment of individual patients should take into consideration the prevention of hypoglycemia, weight gain, and cardiovascular events, as demonstrated in the recent results of large clinical trials, including ACCORD, ADVANCE, VADT, LEADER, EMPA-REG OUTCOME, SUSTAIN6, and CANVAS.[11-17] Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a group of glucose-lowering agents that reduce renal glucose reabsorption in the proximal convoluted tubules, leading to increased urinary glucose excretion, with resultant fall in plasma glucose concentration.[18] In addition to their glucose lowering effects, SGLT2i are known to reduce body weight, lipid parameters, blood pressure, and cardiovascular events.[15,17,19] Another group of glucose-lowering agents, the glucagon-like peptide-1 receptor agonists, can also reduce body weight and cardiovascular events,[14,16] but these agents act by suppressing appetite whereas SGLT2i do not have this effect. Body weight reduction without suppression of appetite may contribute to the observed enhancement of patients' quality of life (QOL) reported in treatment with SGLT2i.[20] In this regard, chronic glycosuria is reported to elicit an

adaptive increase in energy intake by stimulating appetite.[21] Thus, adherence to diet therapy is indispensable for the therapeutic efficiency of SGLT2i and we should consider empowerment of the patients' self-management of diet when SGLT2i are prescribed.

Intermittent use of any glucose-lowering agents is not common in diabetes pharmacotherapy. However, with regard to SGLT2i, intermittent use can reduce the probability of adverse events, such as urinary tract and genital infections, volume depletion, and ketoacidosis, including euglycemic ketoacidosis,[22] compared to the regular use due to the limited chance of SGLT2i intake. In addition, the cost of medications can be largely saved by intermittent prescription compared to the regular prescription since SGLT2i is relatively expensive medicine compared to other glucose-lowering agents.[23]

Based on the above, we hypothesized that intermittent use of empagliflozin, a SGLT2i, supports dietary self-management. To test this hypothesis, we limited empagliflozin prescription to half of the necessary period and advised patients to take the medication on the day after they had overeaten in the intermittent group. We also encouraged the patients to adhere to diet and exercise therapy at every visit. It was expected that patients would have greater interest in their diet habits and effectiveness of empagliflozin than conventional therapy, leading to make a better effort on dietary self-management on the day when they did not take empagliflozin. Thus, the present prospective randomized controlled clinical trial assessed the efficacy of intermittent empagliflozin supplementation on self-management of diet and glycemic control, in comparison to regular use of empagliflozin, in patients with inadequately controlled type 2 diabetes.

2 MATERIALS AND METHODS

2.1 Study design and procedures

The present study is a prospective, randomized open-label, blinded-endpoint, parallel-group, comparative study, registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN000019253), a non-profit organization in Japan that meets the requirements of the International Committee of Medical Journal Editors (ICMJE). The study was approved by the Medical Ethics Committee of Toho University (approval #M16002) and conducted according to the Declaration of Helsinki and current legal regulations in Japan. All study patients provided written informed consent before participating in the study.

The eligible subjects were randomly assigned in equal numbers into two groups; the intermittent group: 10 mg/day empagliflozin was used on an intermittent basis, and the regular group: 10 mg/day empagliflozin was used regularly. In the intermittent group, patients were advised to take empagliflozin basically on the day after they had overeaten, but they were allowed to make decision whether they should take empagliflozin or not. To secure the intermittent use, empagliflozin prescription was limited to half of the necessary period and thus the maximum chance of empagliflozin intake was limited to half of the regular group. Randomization was performed using a dynamic allocation method using HbA1c values for allocation. Diet therapy (daily total energy intake = 25-30 kcal X standard body weight, where standard body weight = height (m) × height (m) × 22) was administered to all patients before enrollment in this study. After enrollment, all patients were prohibited from changing the dose of concomitant drugs or adding any other medications, including other glucose-lowering agents, anti-hypertension drugs, or lipid-lowering agents. Baseline

measurements of blood variables and questionnaires on diet and QOL were performed during the 4-6 weeks of the screening period. After baseline data collection, the assigned therapies were started. The empagliflozin initiation date was set as the study start date. The assigned treatment was continued for 24 weeks (duration of the study).

Clinical and biochemical data were collected at baseline and after the 4-, 8-, 12-, 18-, 24-week treatment period. Blood tests were carried out after overnight fast. The indicated parameters were measured at the central laboratory of our hospital. Questionnaires on diet and QOL were applied at baseline and after 12- and 24-week treatment.

Diabetes-Treatment-Related Quality of Life (DTR-QOL)

A short version of the Diabetes Therapy-Related QOL (DTR-QOL) questionnaire,[24] DTR-QOL17, was used to evaluate patients' QOL. The DTR-QOL17 includes the four domains structure of the original one with the following items: domain 1, Q2, Q3, Q4, Q6, Q7, Q10 and Q11; domain 2, Q14, Q20, Q21, Q22, Q23 and Q24; domain 3, Q16, Q17 and Q18; domain 4, Q27 (*see* Supplementary Information). The total score and domain scores were calculated and converted to a scale of 0-100, as described in the original DTR-QOL.[24]

Energy intake

Energy intake was assessed by the validated questionnaire: Brief self-administered Diet-History Questionnaire (BDHQ).[25,26]

2.2 Patient population

A total of 50 Japanese patients with type 2 diabetes who regularly visited the Outpatient Clinic of our hospital participated in the study. The inclusion criteria were as follows: *1)* type

2 diabetes patients who have been treated for more than 12 weeks with less than three types of oral glucose-lowering agents, in addition to diet and exercise; *2)* HbA1c (National Glycohemoglobin Standardization Program; NGSP) level of ≥ 7.0% to <10.0%; *3)* males and females aged 20 to 80 years; and *4)* signing written consent form to participate in the study. The following criteria were used to exclude subjects from the study: *1)* patients with type 1 diabetes or secondary diabetes; *2)* patients who, within 12 weeks before signing the consent form, had used SGLT2i, glucagon-like peptide-1 receptor agonists, or insulin; *3)* patients with severe infections, were scheduled for surgery, or suffered serious trauma recently; *4)* patients with serious liver or renal functional failure [serum creatinine ≥ 1.3 mg/dL or estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73 m^2]; *5)* patients dependent on alcohol or illicit drugs; *6)* female patients who were pregnant or breastfeeding, possibly pregnant, or planning to become pregnant within the study period; *7)* patients with dehydration (abnormal test results of hematocrit and blood urea nitrogen values, and complaint of symptoms of dehydration); *8)* patients with urinary tract or genital infections within 12 weeks before consent; *9)* patients with severe ketosis, diabetic coma or precoma; and *10)* patients considered unsuitable subjects by the attending physician.

2.3 Study outcome

The primary study outcome was a change in HbA1c [" HbA1c (=value at baseline - value at week 24)]. The secondary endpoints included changes in the values of the following parameters at the end of the 24-week treatment, relative to the baseline: *1)* body weight; *2)* total energy intake (kcal/day); and *3)* DTR-QOL total score.

2.4 Sample size and statistical analysis

Due to the lack of information on intermittent use of any glucose-lowering agents, we set the sample size to 25 cases per group using previous data on SGLT2i regular use.[27] The primary and secondary endpoints were analyzed on the full analysis set (FAS). FAS includes subjects who were enrolled in the study and completed 24-week treatment, however, research subjects with any significant study protocol violation such as over 7 days longer or shorter treatment period in both groups and poor adherence (intake ratio <70%) only in the regular group were excluded. Comparisons of the baseline data between groups were conducted by two-sample t-test or Wilcoxon rank sum test for continuous data depending on the data distribution pattern, and Chi-square test for categorical data. Changes in various parameters due to the treatment were analyzed using the mixed effects model for repeated measures (MMRM): weeks 4, 8, 12, 18, 24 for HbA1c and body weight; weeks 12 and 24 for DTR-QOL and BDHQ. The MMRM model included treatment group, time, interaction between treatment groups and time, and baseline values, age, gender; an unstructured covariance structure was used to model the covariance within-subject variability. All statistical tests were two-sided with a 5% significance level and conducted using the SAS software version 9.3 (SAS Institute, Cary, NC). All statistical analyses were performed by the staff of Soiken Holdings Inc. (Osaka, Japan) who were blinded to the study groups.

2.5 Adverse events (AEs)

AEs were assessed in patients who received at least 1 dose of empagliflozin.[28] AEs were detected on the basis of patients' voluntary complaints or through physical examination, laboratory tests, or other assessments.[29] Hypoglycemia was defined with plasma glucose d3.9 mmol/l and /or requiring assistance.[28,29] Increase in liver enzymes was defined as at least 3 times higher than the upper limit of normal range.[22]

2.6 Human rights and ethical principles of study subjects

The study protocol complied with the "World Medical Association Declaration of Helsinki" (2013 revision), and "Ethical Guidelines for Medical and Health Research Involving Human Subjects" (December 22, 2014, Ministry of Education, Culture, Sports, Science and Technology/Ministry of Health, Labor and Welfare), and all other relevant laws and regulations.

3 RESULTS

3.1 Clinical characteristics of the two groups

A total of 50 patients were enrolled in this study between October 2015 and October 2016. They were randomized into the intermittent group (n=25) and the regular group (n=25). Of the total, 5 patients withdrew agreement due to changed mind by themselves spontaneously, by advice from families, or by second opinion from another doctor and an AE, which was cerebral infarction and happened before starting intake of empagliflozin after allocation. One patient in the regular group discontinued this study at 12 weeks by choice of the patient. Forty-four patients completed the study, but the FAS population included 22 patients in the intermittent group and 16 patients in the regular group after exclusion of research subjects with significant study protocol violation such as over 7 days longer or shorter treatment period in both groups and poor adherence (intake ratio <70%) in the regular group (Figure 1). The empagliflozin intake ratio for 24 weeks was 97±7% and 46±7% for the regular group and intermittent group, respectively. Table 1 shows the baseline clinical characteristics of the patients. There were no significant differences in all the clinical characteristics between the two groups.

3.2 Identical changes in glycemic control in the two Groups

The primary endpoint of this study was ” HbA1c after 24-week treatment. Table 2 shows the adjusted HbA1c values at week 24 and the ” HbA1c values. HbA1c improved significantly in both groups after 24 weeks treatment (Table 2). Furthermore, interestingly, the fall in HbA1c was identical in the two groups through 24 weeks (Figure 2A).

3.3 Changes in body weight, energy intake, and DTR-QOL

Body weight decreased significantly after the 24-week treatment in both groups (Table 2). The reduction was significantly larger in the regular group compared to the intermittent group at 8 and 12-weeks (Figure 2B). Interestingly, the daily total energy intake decreased significantly only in the intermittent group, and the reduction from baseline was larger at 24-weeks than 12-weeks (Table 2, Figure 2C). The proportions of the three major nutrients did not change during the treatment in both groups (data not shown). DTR-QOL increased significantly in both groups, but the increase was significantly larger in the regular group compared to the intermittent group (Table 2, Figure 2D). The changes of individual domains of DTR-QOL were also assessed and shown in Supplementary Figure S1.

3.4 Adverse events

AEs occurred during the treatment period are shown on Supplementary Table S1. Most frequently reported AE was pollakiuria. Due to the small number of AEs, the statistical difference between the two groups was not assessed in the present study. But, > none of the patients discontinued this study due to AEs in both groups.

4 DISCUSSION

Our prospective randomized clinical trial compared the effects of 24-week intermittent use of empagliflozin with regular use on glycemic control. Although it is not possible from this small study to draw conclusions regarding impact of the regimen on benefits or safety concerns associated with this compound or other agents in the SGLT2 class, quite interestingly, HbA1c decreased significantly in the intermittent group and the reduction was similar to that observed in the regular group. Importantly, the daily total energy intake decreased significantly only in the intermittent group, while body weight decreased and DTR-QOL increased significantly in both groups. Thus, based on these results, we conclude that the intermittent use of empagliflozin might be a useful therapeutic option that empowers dietary self-management and improves glycemic control in patients with inadequately controlled type 2 diabetes.

Type 2 diabetes is one of the major risk factors for progression of atherosclerosis and development of cardiovascular diseases.[30,31] Recently, the EMPA-REG OUTCOME study reported that treatment with empagliflozin reduced cardiovascular mortality and hospitalization for heart failure among patients with Type 2 diabetes.[32] Thus, empagliflozin is currently recommended by the American Diabetes Association[23] for patients with Type 2 diabetes and established atherosclerotic cardiovascular disease. In this study, regular use of empagliflozin significantly lowered HbA1c and body weight and increased DTR-QOL. However, there is concern that weight loss by long-term SGLT2i treatment can be potentially attenuated through adaptive increase in energy intake, as demonstrated in studies of rats[33] and humans.[21] Although no increase in daily total energy intake was observed in our regular

group, Horie *et al*[34] reported recently an increase in sugar intake as a form of compensatory hyperphagia in the absence of increased daily total energy intake or proportions of the three major nutrient groups in patients with type 2 diabetes following 3-month treatment with dapagliflozin, another SGLT2i. Thus, the regular use of SGLT2i may disturb the self-management of diet.

Nutrition therapy has been studied and recommended as an essential treatment for type 2 diabetes.[3-7] To facilitate nutrition therapy and dietary self-management, self-management education and support plays a critical role.[10,35] However, unfortunately, a large percentage of patients with diabetes do not receive any structured diabetes education and/or nutrition therapy.[36,37] In addition, weight regain and inevitable progressive increase in HbA1c are reported even with intensive lifestyle interventions.[1,2,5,6,38] Therefore, better methods for supporting dietary self-management are desirable and clinically needed.[5,7,10,35] In the present study, intermittent use of empagliflozin with encouragement of self-management of diet was associated with significant decrease in daily total energy intake at 24 weeks from baseline (Table 2, Figure 2C). Notably, nutritional therapy by registered dietitian was provided to all patients of both groups before enrollment in this study, and dietary self-management was encouraged by the physicians briefly at each clinical visit during the study period in both groups. Therefore, education and support regarding dietary self-management carried no additional fees or required no extra staff or labor in the present study.

We suggested the intermittent use of empagliflozin as adjunct to diet therapy with detailed information about the effect of empagliflozin. Although the possibility that there was

some psychological pressure not to overeat in the intermittent group can't be excluded, we sought to take a supportive attitude toward feeding behavior. In addition, though the prescription was limited to half of the necessary period, we allowed patients to make decision whether they should take empagliflozin or not, but never forced more strict energy restriction to avoid taking drug. This intermittent empagliflozin supplementation would encourage the patients to continuously self-manage their diet, then these patients could realize their achievements on HbA1c and body weight reduction and feel the self-efficacy (confidence in the ability to execute a behavior[39] and manage their life[40]), and this would further motivate their dietary self-management. Therefore, although diet therapy is usually frustrating and a burden resulting in decreasing motivation for self-management,[41,42] QOL was not decreased but increased compared to the baseline under the condition of decreased dietary intake in the intermittent group. Importantly, none of the subjects of the intermittent group discontinued the study with any complaint or adverse events. Taken together, intermittent empagliflozin supplementation combined with encouragement of dietary self-management by physicians seems an ideal therapeutic option that can empower dietary self-management with patients' satisfaction and meaningful reduction in body weight and HbA1c.

Interestingly, the decrease in daily total energy intake was larger at 24 weeks than at 12 weeks in the intermittent group (Figure 2C). This finding suggests that patients of the intermittent group were self-motivated for reducing body weight and HbA1c and by spontaneously reducing the daily total energy intake during the second half of the study. In support of this conclusion, the DTR-QOL was significantly higher at 12 and 24 weeks compared to baseline in the intermittent group. The increase in DTR-QOL coupled with the

reduced daily total energy intake is an important finding because freedom to eat and drink was found as the most important item for QOL in the PANORAMA multinational study of patients with type 2 diabetes.[43] The increase in DTR-QOL (Figure 2D) were sharper during the first 12 weeks and remained essentially stable thereafter. Notably, the tendency was remarkable in the change of Domain 2 (anxiety and dissatisfaction with treatment) and 4 (satisfaction with treatment) (Supplementary Figure S1B and D). The increase in DTR-QOL seemed to associate with body weight loss consistently with previous reports.[20,44-47] Whereas, increasing self-efficacy has been known to associate with higher QOL, too.[40,48] Thus, the significant increase in DTR-QOL in intermittent group might be affected by both body weight loss and increasing self-efficacy. But at 24 weeks, the Domain 1 (burden on social activities and daily activities) decreased only in intermittent group (Supplementary Figure S1A), resulting in the large difference in total score of DTR-QOL between two groups. These results may suggest that the impact of changing self-efficacy on QOL is smaller than body weight loss. However, DTR-QOL increased significantly in intermittent group at 24 weeks from baseline, which supports the potential of intermittent empagliflozin supplementation for increasing QOL with increasing self-efficacy and promoting self-management.

Owing to success in the dietary self-management, there were no differences in the reduction of HbA1c at 24 weeks between the two groups (Table 2, Figure 2A) while the chance of empagliflozin intake was around half in the intermittent group compared to the regular group. Although empagliflozin intake ratio for 24 weeks was 97±7% and 46±7% for the regular group and intermittent group respectively, this means patients in the intermittent group took around 92% of the total prescribed medication. In this study, patients were given

detailed information about the act and effect of the empagliflozin from investigators, and they were allowed to make decision whether they should take it or not. Therefore, patients might realize the effectiveness of empagliflozin and hope to take empagliflozin as much as possible with great consideration.

Despite the above important findings on the efficacy of intermittent empagliflozin supplementation, our study has several limitations. First, this study is a single center trial and included only a small number of Japanese. Both regular and intermittent regimens led to similar changes in HbA1c, but this study was not sufficiently powered to draw conclusions regarding group differences. In addition, due to the small sample size, the current data do not permit sound conclusions on group differences in body weight and food intake. There were also some patients who dropped out from this study, and these patients might affect the results. Therefore, it is important to assess the efficacy of intermittent empagliflozin supplementation in a large scale and multicenter clinical trial. Second, the weight loss recorded in this study was relatively mild. Because weight loss was still observed at 24 weeks, larger body weight loss may be expected in longer treatment. However, the baseline body weight was about 76 kg and body mass index was about 28 kg/m^2, so it might be difficult for patients to lose large weight in this study. In addition, 3% weight reduction is reported as the minimum requirement to improve health hazards in obese and overweight Japanese people,[49] while more than 5% body weight reduction is required in the US and Europe.[2] This difference might be attributed to racial differences in the average body mass index. Although the weight loss was slow, HbA1c changed rapidly. In this regard, it is reported that glucose levels improve rapidly when energy intake is reduced, even before much weight is lost.[2,50] Third,

intermittent supplementation is not the official use of SGLT2i. It is difficult to define those patients who are most suitable for this therapeutic option. As a hint, we found some patients who regularly used empagliflozin every other day in the intermittent group (n=5) and their HbA1c levels did not decrease continuously throughout the 24-week period, whereas the other patients who used empagliflozin intermittently were successful in achieving good dietary self-management and glycemic control (Supplementary Figure S1). Thus, careful clinical consideration is necessary for the success of intermittent empagliflozin supplementation therapy. Fourth, it is unknown whether intermittent use of empagliflozin will reduce the cardiovascular events similarly to the previous studies.[15,17] Further investigations with larger population and longer term are necessary to demonstrate the efficacy of intermittent use of empagliflozin on cardiovascular events. Finally, we believe the evidences shown in this study may be partly valuable in real world clinical practice, but further studies are necessary for generalization of SGLT2i intermittent therapy in clinical practice.

In conclusion, we demonstrated in the present study that intermittent empagliflozin supplementation is a useful therapeutic option that empowers dietary self-management and improves glycemic control, together with body weight loss and increase in DTR-QOL in patients with inadequately controlled type 2 diabetes.

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Conflict of interest

N. Kumashiro received lecture fees from Novo Nordisk Inc., Sanofi-Aventis Deutschland GmbH, and Takeda Pharmaceutical Company Limited. T Hirose received research funds from AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Inc., Astellas Pharma Inc., Ono Pharmaceutical Co., Ltd., Novo Nordisk Inc., Sanofi-Aventis Deutschland GmbH, Daiichi-Sankyo Co., Ltd., Eli Lilly Japan K.K., Takeda Pharmaceutical Company Limited, Mitsubishi Tanabe Pharma Corporation, Dainippon Sumitomo Pharma Co., Ltd., Kissei Pharmaceutical Co., Ltd., and Johnson & Johnson, and received lecture fees from Sanofi-Aventis Deutschland GmbH, Eli Lilly Japan K.K., Novo Nordisk Inc, Takeda Pharmaceutical Company Limited, Daiichi-Sankyo Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Merck & Co., Inc, Dainippon Sumitomo Pharma Co., Ltd., Novartis Pharma

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Figure legends

Figure 1. Flow diagram of patient selection, enrollment and treatment allocation.
*At 12 weeks of treatment, all patients were allowed to choose continuation or discontinuation of the study, and one patient of the regular group elected to discontinue the treatment and exit the study. #The intake rate of empagliflozin of <70% of the regular group was set as poor adherence.

Figure 2. Serial changes in HbA_{1c} (A), body weight (B), total energy intake (C), and DTR-QOL: total score (D) during the course of the study. N=16 for the regular group and n=22 for the intermittent group. Data are adjusted mean ± SEM. *p<0.05 for differences between the two groups. #p<0.05; ##p<0.01; ###p<0.001, for differences from baseline within each group.

Table 1. Baseline characteristics

Variable	All patients (*n*=38)	Regular group (*n*=16)	Intermittent group (*n*=22)	*P* value
Male / Female (%)	24 (63.2)/14 (36.8)	8 (50.0)/8 (50.0)	16 (72.7)/6 (27.3)	0.15
Age	54.4±13.6	54.0±13.5	54.7±14.0	0.87
Duration of diabetes (year)	9.1±6.0	9.6±6.2	8.7±5.9	0.64
Body weight (kg)	76.5±14.2	75.8±15.6	77.0±13.5	0.81
Body mass index (kg/m^2)	27.9±3.7	27.9±2.8	27.9±4.2	0.99
Abdominal circumference (cm)	96.5±8.9	96.6±7.5	96.3±10.0	0.91
Systolic blood pressure (mmHg)	139.0±20.1	141.9±23.0	136.9±17.9	0.47
Diastolic blood pressure (mmHg)	79.4±12.7	81.6±13.4	77.9±12.3	0.40
HbA1c (NGSP, %)	8.1±0.7	8.0±0.7	8.1±0.7	0.51
HbA1c (mmol/mol)	64.5±8.0	63.5±8.1	65.3±8.0	0.51
Fasting blood glucose (mg/dL)	177.2±35.6	177.1±38.2	177.3±34.5	0.99
AST (U/L)	24.5 [18.0,37.0]	21.5 [17.5,30.0]	26.5 [19.0,40.0]	0.42
ALT (U/L)	30.0 [17.0,49.0]	22.0 [16.5,48.0]	34.0 [20.0,49.0]	0.51
HDL-C (mg/dL)	50.0±12.2	50.7±12.2	49.5±12.5	0.78
LDL-C (mg/dL)	117±37.9	117±40.5	117±36.9	0.95
Triglyceride (mg/dL)	129 [89.0, 263.0]	142 [78.5, 208]	129 [97.0,272]	0.22
eGFR (mL/min/1.73 m^2)	81.3±23.5	79.3±11.8	82.7±29.5	0.66
Urine Alb/Cr (mg/g.Cre)	21.0 [8.7,81.1]	10.6 [7.7,21.0]	44.4 [14.7,86.5]	0.06
Fasting plasma C-peptide (ng/mL)	3.2±1.5	2.8±0.9	3.5±1.7	0.11
DTR-QOL				
Total score	62.1±18.1	56.1±19.8	66.5±15.7	0.09
Domain 1 score	69.2±21.6	64.6±22.9	72.6±20.5	0.27
Domain 2 score	51.7±24.4	43.0±25.9	58.0±21.6	0.07
Domain 3 score	77.6±21.8	69.3±25.9	83.6±16.3	0.06
Domain 4 score	44.7±22.1	41.7±24.1	46.9±20.8	0.49
Total energy intake (kcal/day)	1704±632	1623±714	1764±576	0.52

Continuous variables are shown as mean±SD with *P* value by two-sample t-test, or median [1st quartile, 3rd quartile] with *P* value by Wilcoxon rank sum test. Categorical variables are shown as *n* (%) with *P* value by Chi-square test. Domain 1 score, Burden on social activities and daily activities;

Domain 2 score, Anxiety and dissatisfaction with treatment; Domain 3 score, Hypoglycemia; Domain 4 score, Satisfaction with treatment

Table 2. Primary and secondary outcomes

Variable		Adjusted mean (SE)		Adjusted mean difference (95%CI)	*P* value
		Regular group (*n*=16)	Intermittent group (*n*=22)		
HbA1c (%, NGSP)	24 week	7.41 (0.19)	7.41 (0.17)		0.98
	” 24 week	-0.64 (0.19)	-0.65 (0.17)	-0.01 (-0.53, 0.51)	0.98
	P value for ”	0.002	<0.001		
Body weight (kg)	24 week	73.75 (0.52)	74.97 (0.45)		0.08
	” 24 week	-2.72 (0.52)	-1.50 (0.45)	1.22 (-0.17, 2.61)	0.08
	P value for ”	<0.001	0.002		
Total energy intake (kcal/day)	24 week	1768 (122.2)	1484 (108.3)		0.09
	” 24 week	63.0 (122.2)	-221 (108.3)	-284 (-615.3, 47.4)	0.09
	P value for ”	0.61	0.049		
DTR-QOL Total score	24 week	73.0 (2.3)	66.2 (2.0)		0.035
	” 24 week	10.9 (2.3)	4.1 (2.0)	-6.8 (-13.0, -0.5)	0.035
	P value for ”	<0.001	0.049		

Data are adjusted mean (standard error) and adjusted mean difference (95% confidence interval) based on the mixed effects model for repeated measures with a model including treatment group, duration of treatment, interaction between treatment group and duration of

treatment, and baseline value, age, gender. An unstructured covariance structure was used to model the covariance within-subject variability.

Supplementary Data

Supplementary Table S1. Summary of adverse events

	Regular group (n=22)	Intermittent group (n=23)
One or more AEs	15 (68.2)	11 (47.8)
Hypoglycemia	0 (0.0)	2 (8.7)
Pollakiuria	7 (31.8)	4 (17.4)
Nasopharyngitis	1 (4.5)	0 (0.0)
Upper respiratory tract infection	3 (13.6)	5 (21.7)
Constipation	5 (22.7)	1 (4.3)
Fatigue	3 (13.6)	0 (0.0)
Tendency to become hungry easily	3 (13.6)	0 (0.0)
Dizziness	2 (9.1)	1 (4.3)
Diarrhea	1 (4.5)	1 (4.3)
Decrease in appetite	1 (4.5)	1 (4.3)
Genital pruritus	2 (9.1)	0 (0.0)
Thirst	1 (4.5)	0 (0.0)
AST increased	1 (4.5)	0 (0.0)
ALT increased	2 (9.1)	0 (0.0)
Bone fracture	0 (0.0)	1 (4.3)

Pneumoniae	0 (0.0)	1 (4.3)

Frequencies are presented as number (percentage) of patients for each adverse event.

AST: Alanine aminotransferase; ALT: Aspartate aminotransferase.

Supplementary Figure S1. Change of individual domains of DTR-QOL.

Change from baseline in Domain1: burden on social activities and daily activities (A), Domain2: anxiety and dissatisfaction with treatment (B), Domain3: hypoglycemia (C), and Domain4: satisfaction with treatment (D). Data are adjusted mean ± SEM. #p<0.05; ##p<0.01; ###p<0.001 for differences from baseline within groups.

Supplementary Figure S2. Changes in HbA1c during the course of the study, relative to the baseline. Patients who were assigned to the intermittent group but took empagliflozin every other day (n=5), are shown separately from the rest of the patients of the intermittent group. Data are adjusted mean ± SEM.

Supplementary Information

Items of the DTR-QOL17, a short version of the DTR-QOL questionnaire (Q numbers are those of the original DTR-QOL).

Domain 1 Burden on social activities and daily activities

Q2. My current diabetes treatment limits the scope of my activities.

Q3. It is difficult to find places on time for my current diabetes treatment.

Q4. My current diabetes treatment interferes with group activities and personal friendship.

Q6. With my current diabetes treatment, the restricted meal times are a burden.

Q7. When I eat out, it is difficult to manage my current diabetes treatment.

Q10. The time and effort required to manage my current diabetes treatment are a burden.

Q11. I am constantly concerned about time to manage my current diabetes treatment.

Domain 2 Anxiety and dissatisfaction with treatment

Q14. I am bothered by weight gain with my current diabetes treatment.

Q20. I am worried about high blood glucose.

Q21. I am dissatisfied that my blood glucose is unstable (high and low).

Q22. I am worried that complications might get worse with my current diabetes treatment.

Q23. I get anxious thinking about living while on my current diabetes treatment.

Q24. I find it unbearable to think that even if I continue my current diabetes treatment, my diabetes may not be cured.

Domain 3 Hypoglycemia

Q16. I am scared of possible low blood glucose.

Q17. I am sometimes bothered by low blood glucose.

Q18. Symptoms due to low blood glucose are uncomfortable.

Domain 4 Satisfaction with treatment

Q27. With my current diabetes treatment, I am confident that I can maintain good blood glucose control.

Figure 1

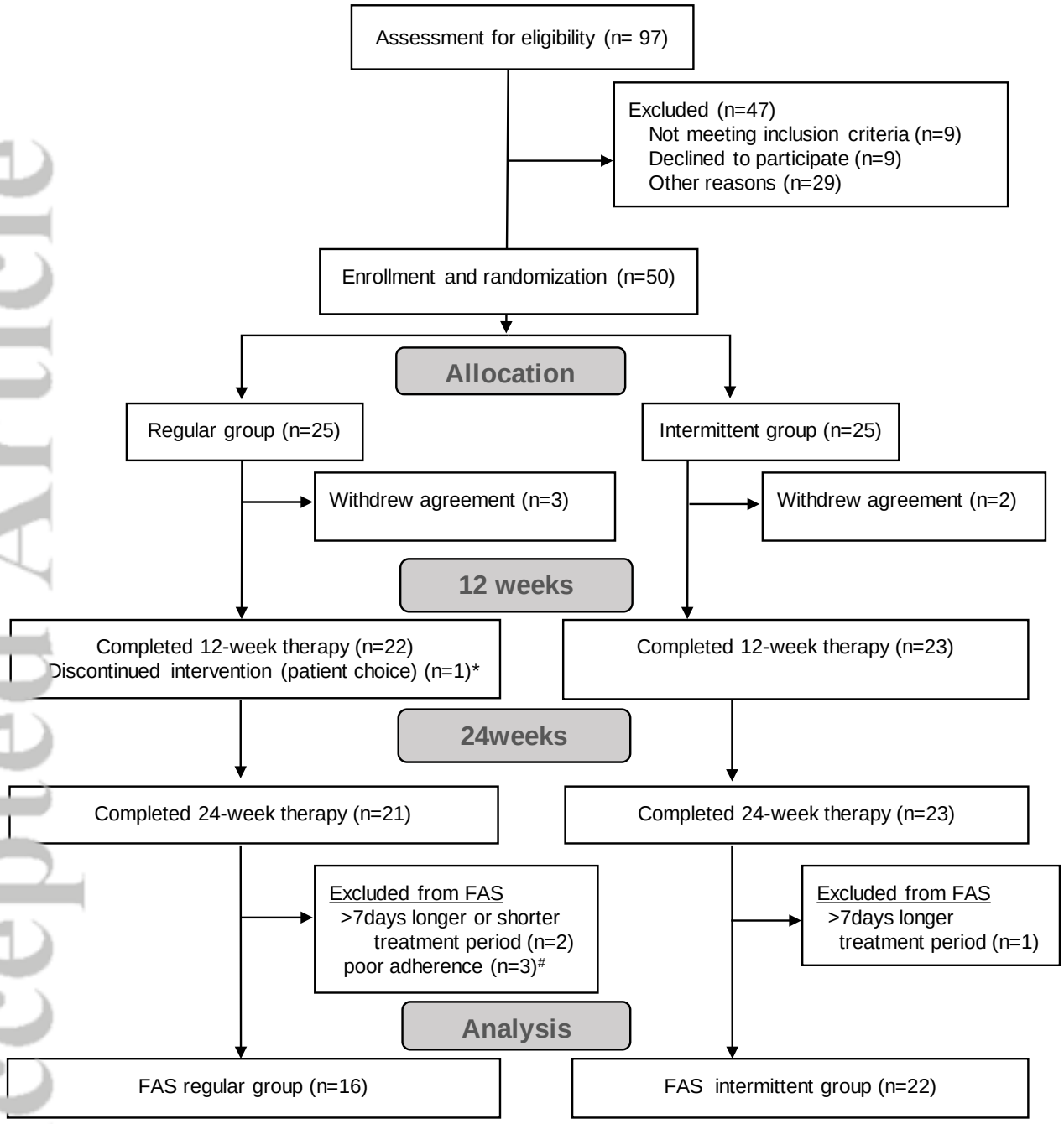

Figure 2