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CLINICAL TRIAL

Simplification of complex insulin regimens using canagliflozin or liraglutide in patients with well-controlled type 2 diabetes: A 24-week randomized controlled trial

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Canagliflozin, Quality of life, Type 2 diabetes

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ABSTRACT

Aims/Introduction: We investigated the potential use of canagliflozin, in comparison with liraglutide, as an alternative to bolus insulin in patients with well-controlled type 2 diabetes mellitus receiving multiple daily insulin injection therapy.

Materials and Methods: In 40 patients, with glycated hemoglobin (HbA1c) levels <7.5% controlled by multiple daily insulin injection therapy, all bolus insulin was randomly switched to canagliflozin (100 mg/day) or liraglutide (0.3–0.9 mg/day) for 24 weeks. Basal insulin was continued with dose adjustment according to a predefined algorithm. The end-points were the change in the HbA1c level, glycemic variability assessed by continuous glucose monitoring, body mass index, insulin dose, quality of life (QOL) and safety assessments. Factors influencing the changes in QOL were also assessed using a simple regression analysis.

Results: The change in HbA1c from baseline was comparable between the treatments. Both treatments maintained the HbA1c level to the baseline levels with stable glucose variability and no severe hypoglycemia for 24 weeks, decreased total insulin dose, and significantly increased the QOL score. The change in QOL was significantly associated with injection frequency.

Conclusions: For patients with well-controlled type 2 diabetes mellitus, under the support of basal insulin, complex insulin regimens can be simplified by replacing all bolus insulin with once-daily canagliflozin or liraglutide, which improves patients' QOL.

INTRODUCTION

Multiple daily insulin injection therapy (MDI) is indicated for conditions such as perioperative periods, severe infection, acute metabolic disorder and pregnancy, and is effective for resolving glucose toxicity under poor glycemic control. However, insulin titration might cause hypoglycemia and weight gain before optimal glycemic control[1,2]. Intensive MDI significantly increases the frequency of severe hypoglycemia[3], which is associated with an increase in cardiovascular events and mortality[4]. MDI impairs daily activity and lowers patient quality of life (QOL)[5], which might lead to poor adherence to insulin injections and poor glycemic control[6,7]. Therefore, sometimes MDI might become overtreatment or inadequate, and the simplification of insulin therapy has been attempted to address such issues after reaching their target control by MDI. For example, bolus insulin has been replaced with oral medications, such as mitiglinide[8,9] or glucagon-like peptide-1 receptor agonist (GLP-1RA) injections[10,11]. However, there is no established strategy for simplifying the complex insulin regimen after achieving the target glycemic control.

Sodium–glucose cotransporter (SGLT)2 inhibitors and GLP-1RAs are major classes of glucose-lowering drugs that have a lower risk of inducing hypoglycemia and have weight loss benefits[12]. SGLT2 inhibitors are oral agents that increase caloric loss through urinary glucose excretion[13], whereas GLP-1RAs, except oral semaglutide, are injectable agents that increase insulin secretion, decrease glucagon secretion and gastric emptying rate, and increase satiety[14,15]. Canagliflozin, taken once daily, is

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an SGLT2 inhibitor, and liraglutide, injected once daily, is a GLP-1RA. Both canagliflozin and liraglutide have been shown to significantly decrease cardiovascular event risk[16,17].

The American Diabetes Association/European Association for the Study of Diabetes have recommended the active use of SGLT2 inhibitors and GLP-1RAs[18]. Recently, direct head-to-head comparative studies of SGLT2 inhibitors and GLP-1RAs, exploring the effects of treatment intensification on glycemic control and body weight reduction, have been reported[19–21]. However, a few comparative studies have assessed the potential of SGLT2 inhibitors and GLP-1RAs as alternatives to bolus insulin, several times a day for postprandial glucose control, as a strategy for simplifying complex insulin regimens in patients who have received MDI. Specifically, no prospective studies have assessed the replacement of bolus insulin with SGLT2 inhibitors, but it has been reported that the replacement of bolus insulin with GLP-1RA is possible and could improve QOL[10,11]. However, previous meta-analyses have reported that the integration of SGLT2 inhibitors into insulin therapy could significantly improve glycemic control and reduce total dosage of daily insulin in patients with type 1 diabetes and type 2 diabetes mellitus[22,23].

Therefore, we hypothesized that SGLT2 inhibitors, as well as GLP-1RAs, would be effective for simplifying complex insulin regimens in patients with type 2 diabetes mellitus who are well-controlled by MDI. To test this hypothesis, we investigated the safety and effectiveness of complex insulin regimen simplification by replacing all bolus insulin with either canagliflozin or liraglutide in patients with well-controlled type 2 diabetes mellitus who received MDI, as a prospective 24-week randomized controlled trial.

MATERIALS AND METHODS

Study design and population

This was a 24-week, prospective, randomized, open-label, parallel-group, comparative study carried out from October 2015 through February 2018. The key inclusion criteria were patients with type 2 diabetes mellitus who received MDI of ultra-rapid insulin and insulin glargine or degludec for ≥24 weeks before screening, aged ≥20 years, glycated hemoglobin (HbA1c) <7.5%, diabetes duration of 1–25 years and body mass index (BMI) >22 kg/m^2. The key exclusion criteria were the use of GLP-1RAs, dipeptidyl peptidase-4 inhibitors or SGLT2 inhibitors, severe or acute complications, chronic bowel disease, malignancy and heavy alcohol consumption. The complete inclusion and exclusion criteria are listed in Table S1.

The present study was registered at the University Hospital Medical Information Network Clinical Trial Registry (UMIN000019382), a non-profit organization in Japan that satisfies the requirements of the International Committee of Medical Journal Editors. The study was approved by the ethics committee of Toho University Omori Medical Center, and carried out in accordance with the World Medical Association Declaration of Helsinki (2013 revision) and current legal regulations in Japan. All patients provided written informed consent before participating in the study.

Randomization and study intervention

Eligible patients were randomly assigned to the canagliflozin plus basal insulin therapy (Cana) group or liraglutide plus basal insulin therapy (Lira) group, at a 1:1 ratio using a computer-based dynamic allocation system to balance BMI (<25 or ≥25 kg/m^2) and basal insulin dose (<15 or ≥15 units/day) at baseline. Baseline measurements were carried out over a 6-week screening period. After baseline data collection, all bolus insulin administration was discontinued, and either canagliflozin (100 mg/day) or liraglutide (0.3 mg/day) initiated with basal insulin administration was continued (Figure S1). The day when medication was switched was considered the start date of the study and the study was carried out for 24 weeks. Any concomitant prescriptions were fixed. Additionally, patients were instructed to maintain their food intake and physical activity.

Throughout the study, all patients measured self-monitored blood glucose levels using OneTouch VerioVue® meters (Johnson & Johnson, New Brunswick, NJ, USA) before breakfast every day and when experiencing hypoglycemic symptoms. The dose of basal insulin was titrated by patients according to a predefined algorithm[24] based on the pre-breakfast self-monitored blood glucose values (Table S2). In the Cana group, 100 mg/day, the maximum dose permitted in Japan, was administered throughout the study period. In the Lira group, patients were instructed to increase the dose by 0.3 mg/day every 2 weeks until it reached 0.9 mg/day, the maximum permitted dose in Japan when the present study was being carried out, unless any adverse effects threatened daily activity. In the case of intolerable adverse effects, the drug dose in the Lira group was decreased to the previous dose, and the study was continued; however, if the symptoms persisted even at a dose of 0.3 mg/day, patients were excluded from the study.

Clinical and biochemical data were collected at baseline, and 12 and 24 weeks (Figure S1). Blood tests were carried out after overnight fasting. HbA1c, fasting plasma glucose level and estimated glomerular filtration rate were measured at the central laboratory in Toho University Omori Medical Center, Tokyo, Japan.

Study outcomes

The primary end-point was the change in HbA1c at 12 and 24 weeks. The secondary end-points were glucose variability assessed by continuous glucose monitoring (CGM), body weight, BMI, dose of total and basal insulin, QOL, and frequency of hypoglycemia in safety assessment, at the time points shown in Figure S1. The factors influencing the change in QOL were also investigated using a simple regression analysis.

Continuous glucose monitoring

Medtronic iPro®2 (Medtronic, Dublin, Ireland) was used for CGM. All patients underwent CGM for four consecutive days

and carried out at least four calibrations per day. Data of the second through fourth day after wearing the CGM were analyzed. The mean glucose value and standard deviation were calculated using EasyGV© v9.0.R[25]. Three key CGM measurements recommended in the international consensus[26] were also calculated: the percentage of time per day within the target glucose range (70–180 mg/dL), above the target glucose range (>180 mg/dL) and below the target glucose range (<70 mg/dL). The minimum blood glucose level was also extracted from the CGM data. In addition to the 24-h period, CGM data were evaluated during the day (between 06.00 and 24.00 hours) and night (between 00.00 and 06.00 hours) separately.

Diabetes therapy-related quality of life

Quality of life was evaluated using the diabetes therapy-related QOL (DTR-QOL) questionnaire[27]. The DTR-QOL questionnaire consists of four domains: domain 1 'burden on social activities and daily activities,' domain 2 'anxiety and dissatisfaction with treatment,' domain 3 'hypoglycemia,' and domain 4 'satisfaction with treatment.' The total score and each domain score were converted to a scale of 0–100; a higher DTR-QOL score indicates a better QOL under the diabetes treatment[27,28].

Safety

Safety was assessed in 39 patients excluding a patient who withdrew from the study. The patients were monitored for adverse events through regular medical checkups. All adverse events, with or without any association with the study drugs, were diligently reported and documented. Low blood glucose (<70 mg/dL) assessed by self-monitored blood glucose, not by CGM, with or without symptoms and a hypoglycemic episode with typical symptoms was defined as hypoglycemia. Severe hypoglycemia was defined as an event requiring assistance by another person to actively administer carbohydrates or glucagon, or carry out other resuscitation actions[29]. Hyperglycemia was defined as fasting blood glucose ≥180 mg/dL or HbA1c ≥9.0%, despite a sufficient increase in basal insulin according to the algorithm. If patients became severely hypoglycemic or hyperglycemic and the attending physician recommended discontinuation, the study was discontinued, and the patient resumed MDI.

Statistical analysis

The end-points were analyzed using the full analysis set. The full analysis set included patients who were enrolled in the study and completed the 24-week treatment period. Analyses were carried out depending on the data distribution pattern; for continuous data, comparisons of data between groups were carried out using the two-sample *t*-test or Wilcoxon rank-sum test, and comparison of data between baseline and post-treatment within each group was carried out using the one-sample *t*-test or Wilcoxon signed-rank test. Sex, the use of α-glucosidase inhibitors or glinides and the incidence of gastrointestinal symptoms or hyperphagia were compared using Fisher's exact test, whereas other categorical variables were compared using the χ^2-test. The data are expressed as the mean ± standard deviation or median (first and third quartiles). Simple regression analyses were carried out to clarify the factors influencing the change in QOL. A multiple linear regression analysis was carried out with the change in QOL as the dependent variable, and body weight, HbA1c and injection frequency as the independent variables. All statistical tests were two-sided at a 5% significance level and analyzed using SAS® v9.3 (SAS Institute, Cary, NC, USA) by the staff of Soiken Holdings Inc. (Osaka, Japan); they were blinded to the study groups.

RESULTS

Patient characteristics

Of the 67 patients assessed for eligibility, 27 were deemed ineligible (24 patients did not meet the inclusion criteria and three patients denied consent). A total of 40 patients were enrolled and randomized, and 34 patients completed the study and were included in the full analysis set (17 patients in both groups; Figure 1). Three patients in each group discontinued the study. In the Cana group, one patient discontinued due to hyperglycemia, another discontinued due to hyperphagia caused by canagliflozin or quitting smoking and the other patient discontinued due to an unrelated gallstone surgery. In the Lira group, one patient discontinued due to agreement withdrawal, one due to persistent nausea accompanying appetite loss, even at 0.3 mg/day, and one was due to orthostatic hypotension (Figure 1). At week 12, the dose of liraglutide was increased from 0.6 to 0.9 mg/day and maintained 0.9 mg/day until the end of this study for eight patients. However, the remaining eight patients maintained 0.6 mg/day until the end of the study, and 0.3 mg/day was continued throughout the study period for one patient due to gastrointestinal symptoms or based on the assessment of the attending physicians. Finally, the median dose of liraglutide in the Lira group was 0.6 mg/day. The baseline clinical characteristics are summarized in Table 1. The mean age of the patients was 57.1 years, with a mean BMI of 26.9 kg/m^2, a mean HbA1c of 6.7% and a mean total insulin dose of 0.4 U/kg/day. Overall, there were no significant differences in any clinical or biochemical parameters between the groups at baseline (Table 1). Additionally, all indices of glucose variability except for daytime above the target glucose range were not significantly different between the groups (Table S3).

Simplification maintained good glycemic control, reduced total insulin dose and improved QOL in both groups

The primary end-point – change in HbA1c from baseline – was comparable between the groups (Table 2). However, the HbA1c levels were well maintained for 24 weeks in both groups: 6.7 ± 0.7% in the Cana group and 6.2 ± 0.8% in the Lira group. The number of patients with improved HbA1c level from baseline at 24 weeks was 10 (58.8%) in the Cana group

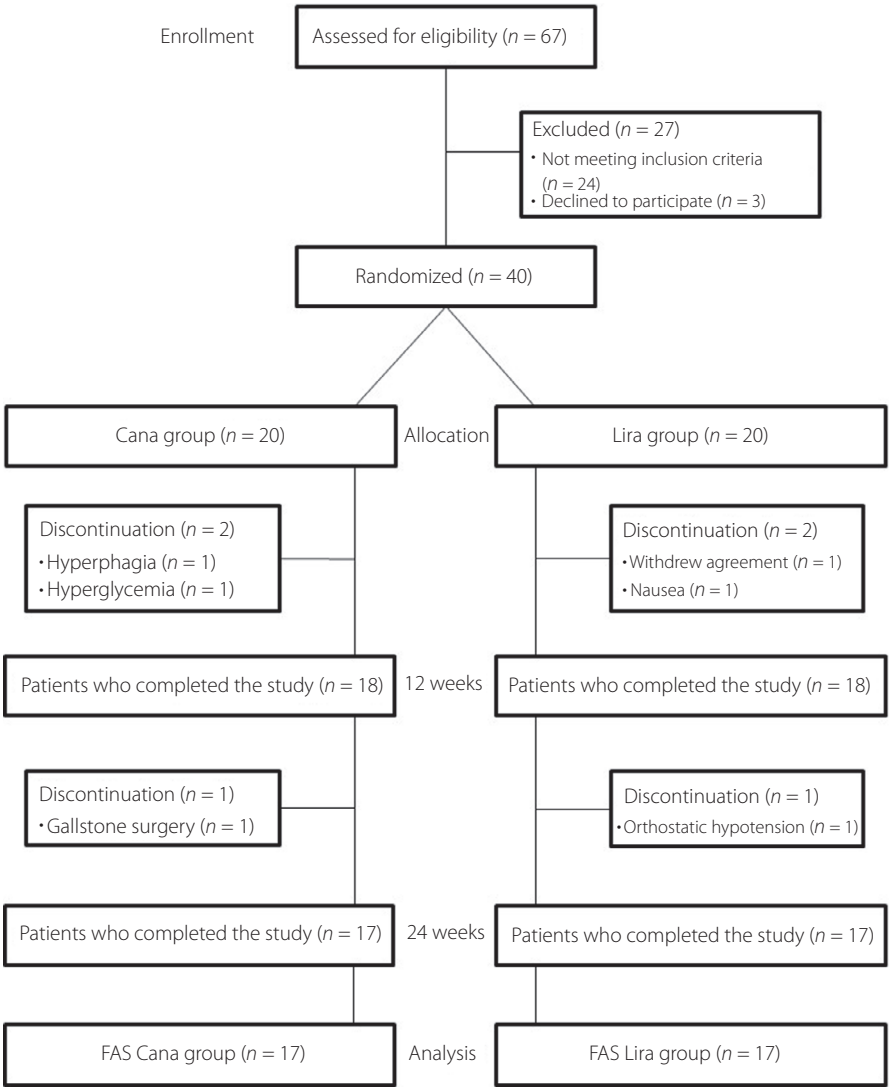

Figure 1 | Flow diagram of patient screening, enrollment, allocation and analysis. Cana, canagliflozin plus basal insulin therapy; FAS, full analysis set; Lira, liraglutide plus basal insulin therapy.

and 11 (64.7%) in the Lira group, and there was no significant difference between the groups ($P = 0.724$). All secondary endpoints, excluding the frequency of injection, were also comparable between the groups. All indices of glucose variability assessed by CGM were not altered from baseline in both groups (Table S3). Both body weight and BMI decreased for 24 weeks in both groups; however, a significant reduction was observed only in the Lira group (Table 2). There were no differences in the changes in the HbA1c level, CGM items or body weight between 0.9 mg/day and other doses in the Lira group (data not shown). The change in insulin dose was comparable between the groups (Table 2). Additionally, the total insulin dose decreased significantly in both groups (34% and 48% from baseline on an average in the Cana and Lira groups, respectively) owing to the withdrawal of bolus insulin. However, the dose of basal insulin significantly increased from baseline in both groups (on an average, 45% and 39% from baseline in the Cana and Lira groups, respectively). The frequency of injection was significantly decreased in the Cana group compared with that in the Lira group (−3.0 vs −2.0 times per day, respectively, Table 2). The scores of DTR-QOL questionnaire were significantly increased from baseline in both groups (Table 2). Although no significant difference was observed in each domain score of DTR-QOL between the groups, the total score of DTR-QOL was higher, from baseline, in the Cana group than in the Lira group, trending toward significance (Table 2). The QOL scores were significantly increased in all domains in the Cana group, whereas only the score of domain #4 was significantly increased in the Lira group (Table 2).

Table 1 | Patient characteristics at baseline

Baseline parameters	Cana group (n = 17)	Lira group (n = 17)	P-value
Age (years)	55.9 ± 13.0	58.2 ± 11.5	0.58
Men, n (%)	13 (76.5)	13 (76.5)	1.00
Body weight (kg)	76.7 ± 7.5	73.7 ± 12.2	0.39
Body mass index (kg/m^2)	27.0 ± 3.3	26.8 ± 3.1	0.86
Duration of diabetes (years)	10.4 ± 6.9	7.8 ± 7.0	0.28
HbA1c (%)	6.8 ± 0.7	6.4 ± 0.6	0.13
Fasting plasma glucose (mg/dL)	138.4 ± 26.3	121.2 ± 22.3	0.07
Estimated GFR (mL/min/1.73 m^2)	74.1 ± 15.7	74.8 ± 23.7	0.92
Total insulin dose (U/day)	34.5 ± 13.9	29.6 ± 12.1	0.28
Total insulin (U/kg/day)	0.4 ± 0.2	0.4 ± 0.2	0.44
Basal insulin dose (U/day)	16.1 ± 7.9	12.1 ± 7.4	0.14
Basal insulin (U/kg/day)	0.2 ± 0.1	0.2 ± 0.1	0.20
Degludec U-100, n (%)	10 (58.8)	6 (35.3)	0.17
Glargine U-100, n (%)	7 (41.2)	11 (64.7)	0.17
Bolus insulin dose (U/day)	18.4 ± 7.8	17.5 ± 6.5	0.70
Bolus insulin (U/kg/day)	0.2 ± 0.1	0.2 ± 0.1	0.93
Frequency of injection (times/day)	4.0 [4.0, 4.0]	4.0 [4.0, 4.0]	1.00
Other antidiabetic drugs			
None, n (%)	10 (58.8)	13 (76.5)	0.27
Biguanides, n (%)	6 (35.3)	4 (23.5)	0.45
α-Glucosidase inhibitors, n (%)	1 (5.9)	0	1.00
Glinides, n (%)	1 (5.9)	0	1.00
DTR-QOL			
Total score	54.6 ± 18.6	59.9 ± 15.1	0.37
Domain 1 score	57.5 ± 22.6	66.0 ± 14.0	0.20
Domain 2 score	50.8 ± 21.3	53.9 ± 19.6	0.65
Domain 3 score	57.2 ± 28.2	64.8 ± 32.0	0.47
Domain 4 score	50.6 ± 16.1	48.5 ± 21.2	0.74

Data are the mean ± standard deviation or median (1st quartile, 3rd quartile). Cana, canagliflozin plus basal insulin therapy; DTR-QOL, diabetes therapy-related quality of life; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; Lira, liraglutide plus basal insulin therapy.

Improvement in QOL associated with a decrease in the frequency of injection

The factors influencing the changes in the total DTR-QOL score were also investigated using the simple regression analysis in 34 patients who completed the study. Only the change in the frequency of injection was significantly and negatively associated with the change in the total DTR-QOL score (Table 3). Additionally, the multiple linear regression analysis showed the change in the injection frequency was the significant contributor to the change in the QOL score (β = –6.96, P = 0.014; Table S4).

Safety outcomes

There were no severe adverse events, such as hospitalization; severe hypoglycemia, as defined in the Materials and Methods (Safety); or ketoacidosis in either group (Table 4). Several non-severe hypoglycemic events were similarly observed in both groups. Hyperglycemia was observed in one patient with HbA1c ≥9.0% in the Cana group and in none in the Lira group. Notably, urinary ketone bodies were not detected in the Cana group. Gastrointestinal symptoms, such as nausea, constipation, diarrhea, dyspepsia and appetite loss, were significantly more prevalent in the Lira group than in the Cana group (n = 6 vs 1, respectively, P = 0.044). Hyperphagia was observed in five patients in the Cana group, and one patient developed hyperglycemia and had to discontinue the study; in contrast, hyperphagia was observed in two patients without hyperglycemia in the Lira group. There was no significant difference in the incidence of hyperphagia between the groups (P = 0.408).

DISCUSSION

To our knowledge, this is the first prospective and randomized controlled study to evaluate the effects of simplifying MDI therapy. We directly compared the simplification methods between canagliflozin and liraglutide as potential alternatives to all bolus insulin; canagliflozin, as well as liraglutide, maintained good glycemic control for 24 weeks. No significant differences were observed in the secondary end-points except for the frequency of injections. Both body weight and BMI decreased for 24 weeks similarly in both groups. Although the daily basal insulin dose increased from baseline, the dose of daily total

Table 2 | Primary and secondary outcomes

	Weeks	Cana group (n = 17)	P-value†	Lira group (n = 17)	P-value†	P-value‡
ΔHbA1c (%)	12	0.1 ± 0.5	0.38	0.0 ± 0.7	0.82	0.78
	24	−0.1 ± 0.6	0.72	−0.2 ± 0.6	0.20	0.51
ΔBody weight (kg)	12	−1.2 ± 2.5	0.05	−1.2 ± 2.1	0.03	0.99
	24	−1.3 ± 3.3	0.12	−1.5 ± 2.9	0.05	0.90
ΔBody mass index (kg/m^2)	12	−0.4 ± 0.8	0.05	−0.5 ± 0.8	0.02	0.91
	24	−0.5 ± 1.1	0.11	−0.6 ± 1.0	0.04	0.80
Δ Total insulin dose (U/day)	12	−13.3 ± 7.7	<0.001	−14.7 ± 7.5	<0.001	0.61
	24	−11.4 ± 6.4	<0.001	−13.3 ± 8.5	<0.001	0.46
ΔBasal insulin dose (U/day)	12	5.1 ± 4.8	<0.001	2.8 ± 4.6	0.02	0.16
	24	7.1 ± 6.5	<0.001	4.2 ± 6.9	0.02	0.22
ΔFrequency of injection (times/day)	24	−3.0 [−3.0, −3.0]	<0.001	−2.0 [−2.0, −2.0]	<0.001	<0.001
DTR-QOL scores						
ΔTotal score	24	12.6 ± 9.0	<0.001	6.1 ± 9.9	0.02	0.05
ΔDomain 1 score	24	11.2 ± 9.8	<0.001	4.4 ± 10.2	0.10	0.06
Δ Domain 2 score	24	13.6 ± 13.3	<0.001	4.6 ± 13.5	0.18	0.06
Δ Domain 3 score	24	12.7 ± 19.2	0.015	9.8 ± 24.6	0.12	0.70
Δ Domain 4 score	24	16.4 ± 12.6	<0.001	10.1 ± 17.9	0.03	0.24

Data are the mean ± standard deviation or median (1st quartile, 3rd quartile). Cana, canagliflozin plus basal insulin therapy; DTR-QOL, diabetes therapy-related quality of life; HbA1c, glycated hemoglobin; Lira, liraglutide plus basal insulin therapy. †Comparison of values at baseline and 12 or 24 weeks within each group. ‡Comparison between the two groups.

Table 3 | Association between change in the diabetes therapy-related quality of life total score and other clinical parameters assessed by simple regression analysis

	n	β	P-value
Age (years)	34	0.04 ± 0.14	0.76
Sex	34	2.64 ± 4.02	0.52
Body weight at baseline (kg)	34	0.02 ± 0.17	0.90
Body mass index at baseline (kg/m^2)	34	0.42 ± 0.54	0.45
Duration of diabetes (years)	34	0.12 ± 0.25	0.63
HbA1c at baseline (%)	34	4.10 ± 2.51	0.11
Total insulin dose at baseline (U/day)	34	0.07 ± 0.13	0.59
Total insulin at baseline (U/kg/day)	34	6.69 ± 10.39	0.52
Basal insulin dose at baseline (U/day)	34	0.15 ± 0.22	0.51
Basal insulin at baseline (U/kg/day)	34	13.46 ± 17.01	0.43
Bolus insulin dose at baseline (U/day)	34	0.07 ± 0.25	0.79
Bolus insulin at baseline (U/kg/day)	34	6.62 ± 19.15	0.73
ΔBody weight at 24 weeks (kg)	34	−0.48 ± 0.56	0.40
ΔBody mass index at 24 weeks (kg/m^2)	34	−1.57 ± 1.62	0.34
ΔHbA1c at 24 weeks (%)	34	−0.27 ± 2.97	0.93
ΔTotal insulin dose at 24 weeks (U/day)	34	−0.19 ± 0.23	0.42
ΔTotal insulin at 24 weeks (U/kg/day)	34	−15.25 ± 17.90	0.40
ΔBasal insulin dose at 24 weeks (U/day)	34	−0.16 ± 0.26	0.54
ΔBasal insulin at 24 weeks (U/kg/day)	34	−12.34 ± 19.83	0.54
ΔFrequency of injection at 24 weeks (times/day)	34	−6.85 ± 2.62	0.013

Data are regression coefficients ± standard error. HbA1c, glycated hemoglobin.

insulin was significantly reduced owing to the discontinuation of bolus insulin in both groups.

Both treatments were well tolerated, as shown by safety profiles, with no episodes of severe hypoglycemia, ketoacidosis or other adverse effects that required hospitalization. Subsequently, the DTR-QOL score was significantly improved from baseline to 24 weeks in both groups. The simple linear regression analysis showed that the change in the QOL was significantly

Table 4 | Summary of adverse events

	Cana group (n = 20)	Lira group (n = 19)
Hospitalization for adverse events	0	0
Hypoglycemia		
Severe (0–24 weeks)	0	0
Non-severe		
0–12 weeks	4	2
12–24 weeks	5	3
Hyperglycemia	1	0
Diabetic ketosis or ketoacidosis	0	0
Others		
Gastrointestinal symptoms	1	6
Hyperphagia	5	2
Fatigue	2	0
Upper respiratory tract infection	2	1
Urinary ketone body	0	1
Urinary tract infection	1	0
Chest discomfort	1	0
Orthostatic hypotension	1	1
Palpitation	1	0
Hypotension	1	0
Syncope	1	0
Back pain	0	1
Memory loss	1	0
Peripheral neuropathy	1	1

Cana, canagliflozin plus basal insulin therapy; Lira, liraglutide plus basal insulin therapy.

associated with injection frequency. Overall, under the support of basal insulin, once-daily canagliflozin intake and liraglutide injection can be an alternative to bolus insulin administered multiple times a day in patients with type 2 diabetes mellitus well-controlled by MDI.

To date, no prospective studies have evaluated the potential application of SGLT2 inhibitors as alternatives to insulin therapy. This might be because the use of SGLT2 inhibitors as alternatives to insulin could induce ketoacidosis in patients with depleted insulin secretion[30]. However, considering the findings of previous meta-analyses[22,23], we hypothesized that as long as basal insulin was continued and adjusted appropriately, all bolus insulin multiple times a day could be replaced safely with an SGLT2 inhibitor administered once daily, which would also improve patient QOL. Here, all bolus insulin was replaced with canagliflozin, supported with adjusted basal insulin continuation.

One patient developed hyperglycemia with HbA1c ≥9.0% and had to resume bolus insulin; however, severe hyperglycemia or ketoacidosis was not observed. The hyperglycemia could not be predicted in advance, because clinical characteristics regarding the duration of diabetes, HbA1c, BMI or insulin dose at baseline did not differ between the patient and others. However, the patient developed hyperphagia after canagliflozin supplementation, which might have caused hyperglycemia, at least partially. As SGLT2 inhibitors might increase appetite and cause hyperphagia[31,32], adherence to diet therapy is indispensable for the success of MDI simplification using SGLT2 inhibitors.

Another patient discontinued due to hyperphagia assessed by the attending physician. The non-significant reduction in body weight and BMI in the Cana group could also be attributed to hyperphagia. Additionally, the non-significant reduction in body weight and BMI could be due to the well-controlled glycemic level, as SGLT2 inhibitors reduce plasma glucose levels by increasing urinary glucose excretion depending on the glycemic level, and subsequently decrease body weight[13]. A previous meta-analysis reported that the supplementation with SGLT2 inhibitors on insulin therapy significantly decreased body weight and reduced the total dose of daily insulin in patients with uncontrolled type 2 diabetes mellitus with HbA1c at approximately 8.5%[23]. Finally, in 85% of the patients, canagliflozin could maintain glycemic control, including glucose fluctuation, similar to that at baseline for 24 weeks and significantly improved the QOL.

Liraglutide similarly maintained good glycemic control. Regarding the simplification of MDI by the replacement of bolus insulin with liraglutide, there is also a risk of hyperglycemia or ketoacidosis in insulin-deficient conditions[33]. To minimize such risks, insulin secretion capacity was assessed with a glucagon stimulation test or fasting serum C-peptide level in previous studies; however, there has been no consensus

regarding such cut-off values[10,11], specifically in patients on MDI.

Japanese patients with type 2 diabetes mellitus who could switch bolus insulin with GLP-1RA had a mean HbA1c of 7.1–7.5% and a mean total insulin doses of 0.32–0.38 U/kg/day at baseline[10,11]. Additionally, white patients who switched from MDI to insulin degludec and liraglutide (IDegLira) had a mean HbA1c level of 6.4% and a mean total insulin dose of 0.47 U/kg/day at baseline[34]. Such clinical characteristics were similar to those observed in the present study.

The results suggest that patients with type 2 diabetes mellitus receiving MDI and already showing good glycemic control with a relatively low dose of insulin can maintain good glycemic control after the replacement of all bolus insulin with GLP-1RAs, as long as basal insulin administration is continued. Notably, here, the residual insulin secretion capacity of each patient was not assessed, but the patients in the Lira group could be treated with a median of 0.6 mg/day liraglutide, which was lower than the permitted maximum dose (0.9 mg/day) in Japan when the present study was performed. A previous study also reported that liraglutide improved glycemic control at doses of 0.3 and 0.6 mg/day[35]. Even if the dose cannot be increased to the maximum dose considering the potential adverse effects, such simplification is worth exploring with the support of basal insulin adjustment.

Although the improvement in the QOL scores was comparable between the groups, in contrast to the significant increase from baseline in all domains of DTR-QOL scores in the Cana group, only the domain #4 score had significantly increased in the Lira group. Therefore, the total DTR-QOL score increased more in the Cana group, from baseline, than in the Lira group, and the difference between the groups was trending significance. This could be partially because canagliflozin does not reduce appetite, whereas liraglutide does, and canagliflozin is cheaper than liraglutide. Furthermore, the frequency of injection was significantly lower in the Cana group than in the Lira group.

In previous studies, an improvement in the QOL has been associated significantly with less frequent injections, reduced insulin doses and decreased body weight[5,36,37]; however, here, only the less frequent injections were significantly associated with improved QOL. Consequently, the lower frequency of injection in the Cana group could have facilitated the improvement in QOL in several more domains than that in the Lira group.

Recently, fixed-ratio combination therapies of basal insulin and GLP-1RAs, such as IDegLira, and insulin glargine and lixisenatide, are increasingly used extensively as once-daily injection therapies[38,39]. Therefore, the administration of IDegLira to the Lira group could result in the frequency of injection being similar to that in the Cana group, which might further improve the DTR-QOL score.

The pathophysiology of diabetes and the effects of drugs vary among different ethnicities, such as East Asian people and white people. Type 2 diabetes mellitus in East Asian people is characterized by lower BMI, fewer insulin requirements, higher insulin sensitivity and lower β-cell function than white people[40,41]. A meta-analysis comparing the efficacy and adverse effects of SGLT2 inhibitors between Asians and non-Asians with type 2 diabetes mellitus showed no significant differences in the reduction of HbA1c or loss of weight[42]. Contrarily, a study comparing the postprandial plasma glucose levels after a single-dose injection of lixisenatide, a GLP-1RA, between Japanese people and white people showed a greater decrease in Japanese people with type 2 diabetes mellitus[43].

Additionally, a recent report showed that a missense mutation (Arg131Gln) in the gene encoding the GLP-1 receptor is common in Japanese people, but rare in European people, which is a potential marker of clinical response to GLP-1RA in Japanese and East Asian people[44]. However, it has been reported that the differences in insulin sensitivity and β-cell function between Japanese people and white people were not significant after BMI adjustment[41]. Furthermore, even in white people, patients with a normal or near-normal HbA1c using low doses of total insulin maintained excellent glycemic control when switching from MDI to IDegLira[34]. Overall, this simplification might be effective in not only Japanese people, but also white people.

The present study had some limitations. First, the number of participants was low. We referred to previous simplification studies on liraglutide; however, there are no reports on simplification studies focusing on SGLT2 inhibitors; consequently, the sample size was exploratively estimated. A significant difference between the groups might be observed in the improvement of DTR-QOL with a larger sample size. Second, the study duration was just 24 weeks; therefore, the potential long-term benefits of simplification on the complications associated with diabetes remain unclear. Finally, the study was carried out at a single center in Japan. The pathophysiology of diabetes could vary among different ethnicities, as aforementioned. Additionally, the standard doses of canagliflozin and liraglutide vary across countries. Therefore, the results need to be validated in large-scale, long-term, multicenter, international trials.

Complex insulin regimens could be simplified by the replacement of all bolus insulin with once-daily canagliflozin or liraglutide, supported by basal insulin supplementation, in patients with well-controlled type 2 diabetes mellitus. Notably, such a simplification could improve patient QOL. In addition to clinical guidelines or statements based on evidence from large cardiovascular outcome trials[18,45], the present study provides evidence for patient-centered therapy focusing on the QOL in type 2 diabetes mellitus patients receiving insulin medication.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Inclusion and exclusion criteria.

Table S2 | Algorithm for basal insulin titration by self-monitoring.

Table S3 | Results of continuous glucose monitoring.

Table S4 | Results of multiple regression analysis.

Table S5 | Study design.