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CLINICAL TRIAL

# Effects of liraglutide and empagliflozin added to insulin therapy in patients with type 2 diabetes: A randomized controlled study

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**Keywords**
Empagliflozin, Insulin therapy, Liraglutide

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## ABSTRACT

**Aims/Introduction:** Liraglutide and empagliflozin suppress cardiovascular events. However, reports on their long-term combined use with insulin therapy or direct comparisons of these drugs are limited.

**Materials and Methods:** This open-label, parallel-group, randomized controlled trial compared the effects of liraglutide and empagliflozin combined with insulin therapy in type 2 diabetes patients. Adult type 2 diabetes outpatients undergoing stable insulin therapy with glycated hemoglobin levels of 7.0–9.5% were enrolled. Participants received 0.9 mg/day liraglutide or 10 mg/day empagliflozin for 24 weeks. The primary end-point was the change in glycated hemoglobin levels from week 0 to 24. Body composition was assessed by dual-energy X-ray absorptiometry.

**Results:** A total of 64 insulin-treated patients were randomized to receive liraglutide or empagliflozin. We analyzed 61 patients (30 liraglutide and 31 empagliflozin) who could be followed up. Liraglutide induced greater changes in glycated hemoglobin and glycated albumin than empagliflozin (glycated hemoglobin −1.24 ± 0.15% vs −0.35 ± 0.11%, $P < 0.0001$; glycated albumin −4.4 ± 0.6% vs −2.4 ± 0.5%, $P < 0.01$). Bodyweight (−1.3 ± 0.4 kg vs −1.5 ± 0.3 kg, $P = 0.69$) or body fat mass/lean tissue mass; urinary albumin excretion (median −5.3 mg/g-creatinine [interquartile range −60.6, 9.9 mg/g-creatinine] vs −12.9 mg/g-creatinine [interquartile range −70.8, −2.0 mg/g-creatinine], $P = 0.23$); and frequency of hypoglycemia did not differ significantly between the groups over a period of 24 weeks. There were no cases of study discontinuation owing to adverse effects.

**Conclusions:** Liraglutide addition to ongoing insulin therapy more effectively reduced glycated hemoglobin and glycated albumin levels than empagliflozin in patients with inadequately controlled type 2 diabetes.

## INTRODUCTION

The early use of glucagon-like peptide-1 (GLP-1) receptor agonists is thought to improve pancreatic β-cell function[1]; furthermore, these agonists are thought to bestow effects, such as cardiovascular protection[2], central nervous system protection and improved insulin resistance[3]. Recently, GLP-1 receptor agonists (GLP-1RA) and insulin treatment have been used together; the long-term combined use with basal insulin has been shown to decrease glycated hemoglobin ($HbA_{1c}$) levels and weight loss, without increasing the frequency of hypoglycemia[4]. Sodium–glucose cotransporter 2 inhibitors (SGLT2i), such as empagliflozin, have also been shown to have a weight-reducing effect and a relatively low risk of hypoglycemia when used as a monotherapy; a 78-week empagliflozin/basal insulin combination study conducted outside of Japan reported a reduction in $HbA_{1c}$ and bodyweight[5].

Recent large-scale clinical trials have shown that GLP-1RA and SGLT2i suppress cardiovascular events, leading to increasing interest in these compounds. Consequently, the American Diabetes Association/European Association for the Study of

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Diabetes statement issued in 2018 recommended the active use of GLP-1RA and SGLT2i, which have established cardiovascular benefits[6]. However, the effects of GLP-1RA and SGLT2i on glucose metabolism after long-term combined use with insulin are not well known. Generally, there are limited opportunities to carry out body composition tests to assess weight loss effects in clinical practice. Furthermore, as there are only a limited number of reports, the effects on multiple organs and various metabolic processes remain unknown. Reports on the long-term combined use of these drugs with insulin and direct comparison tests are limited, especially in Asian individuals.

Thus, we decided to investigate the effects of 24-week liraglutide and empagliflozin treatment on glucose metabolism, body composition and other clinical markers.

## METHODS

### Trial design and intervention

This study was an open-label, randomized controlled trial with a 24-week prospective intervention. The participants included patients who visited Yokohama City University Hospital and Yokohama Chuo Hospital from June 2017 to May 2019. The participants were randomly assigned to the liraglutide group or the empagliflozin group after their consent for this trial was obtained. The patients were assigned 1:1 to liraglutide or empagliflozin, and were randomized by the minimization method carried out using the following allocation adjustment factors: (i) sex (male/female); (ii) diabetes duration (<10 years/≥10 years); (iii) body mass index (<25 kg/m$^2$/≥25 kg/m$^2$); (iv) $HbA_{1c}$ (<8.0%/≥8.0%); and (v) insulin administration method (basal insulin with oral antidiabetic drug/other). Computer-generated randomization systems were used in this trial. Randomization was carried out independently of the investigator and principal investigator. Patients were not informed of the results until the day of study initiation.

After blood and urine tests, and body composition examination at the start of the intervention, liraglutide or 10 mg/day empagliflozin treatment was started, in addition to any prior treatment. Intermediate follow up was carried out at 4 and 12 weeks. If glycemic control was inadequate (fasting blood glucose ≥180 mg/dL or $HbA_{1c}$ ≥8.5%) at 12 weeks after the initiation of the intervention, the dosage was increased to 25 mg/day empagliflozin. In addition, when marked hyperglycemia was sustained (fasting blood glucose ≥200 mg/dL or ≥$HbA_{1c}$ 9.0%), the amount of insulin was increased; basal insulin was increased by 1–2 units to target fasting blood glucose levels of 90–100 mg/dL. Blood and urine tests, and the evaluation of body composition were repeated after the 24-week intervention. $HbA_{1c}$ was measured using the high-performance liquid chromatography method (HLC-723G9; Tosoh, Tokyo, Japan) in both hospitals. Body composition was calculated by dual-energy X-ray absorptiometry (Hologic Discovery A; Marlborough, MA, USA), carried out only at Yokohama City University Hospital, Yokohama, Japan.

Patients subcutaneously injected themselves at approximately the same time each day. The starting liraglutide dose was 0.3 mg/day, 0.6 mg/day after 1 week and 0.9 mg/day after another week. If no side-effects appeared, a final maintenance dose of 0.9 mg/day, the highest available dosage in Japan as of April 2019, was continued for up to 24 weeks. If side-effects occurred during the dose increase, the dose was decreased by 0.3 mg and treatment was continued, if possible. In the empagliflozin group, 10 mg/day was initially administered and continued, at the same dosage, for 24 weeks if the dose increase criteria were not met. In principle, no new nutrition guidance intervention or exercise intervention was administered during the trial.

This study conforms to the provisions of the Declaration of Helsinki, and was approved by the Ethics Committee of Yokohama City University Hospital and Yokohama Chuo Hospital. Funding for this study was self-procurement with no subsidy. The study was registered with the University Hospital Medical Information Network Clinical Trial Registry (registration no. UMIN000027614).

### Criteria for drug reduction and withdrawal

When hypoglycemia occurred in both groups, the treatment was adjusted by reducing the insulin units. Hypoglycemia was defined as <70 mg/dL for blood glucose and the basal insulin was reduced every 2–3 days by 1–2 units, targeting fasting blood glucose levels of 90–100 mg/dL. If it was difficult to avoid hypoglycemia before each meal, even with the adjustment of basal insulin, the bolus insulin was similarly reduced by 1–2 units to achieve a 100 preprandial blood glucose level of 140 mg/dL. If it was still difficult to avoid hypoglycemia, the liraglutide dose was reduced by 0.3 mg.

### Drug increase criteria

When fasting blood glucose was ≥180 mg/dL or $HbA_{1c}$ was ≥8.5% at 12 weeks after the initiation of the intervention, empagliflozin was increased to 25 mg/day. The amount of insulin was basically fixed, except when hypoglycemia occurred. However, when significant hyperglycemia persisted (fasting blood glucose ≥200 mg/dL or $HbA_{1c}$ ≥9.0%) 12 weeks after the initiation of the intervention, the amount of insulin was increased; basal insulin was increased by 1–2 units to target fasting blood glucose levels of 90–100 mg/dL, and the bolus insulin remained unchanged.

### Participants

The inclusion criteria were as follows: (i) outpatients with type 2 diabetes, aged 20–80 years; (ii) patients of either sex; (iii) patients without GLP-1RA, SGLT2i or dipeptidyl peptidase-4 inhibitor (DPP4i) treatment for >8 weeks before intervention (if DPP4i was taken orally, it was washed out for 8 weeks before the start of the study); (iv) patients under insulin therapy glycemic control: 7.0% ≤ $HbA_{1c}$ ≤ 9.5%; (v) fasting plasma C-peptide ≥0.5 ng/mL or casual plasma C- peptide ≥1.0 ng/mL; and (vi) patients that provided voluntary written consent for participation in this study.

The exclusion criteria were as follows: (i) type 1 diabetes or secondary forms of diabetes; (ii) fasting plasma glucose (FPG) <70 mg/dL; (iii) renal dysfunction (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 $m^2$); (iv) steroid medication; (v) hepatic dysfunction (aspartate transaminase and/or alanine aminotransferase >3 times the upper limit of normal); (vi) active malignant neoplasm; (vii) severe infection or injury; (viii) hypersensitivity to liraglutide or empagliflozin; (ix) pregnant or intending to become pregnant during this study; (x) unable to obtain informed consent for this study; and (xi) inadequate use of this therapy.

### End-points and assessments

The primary end-point was difference in $HbA_{1c}$ change from the start of the intervention to after 24 weeks between the two groups. The secondary efficacy end-points were differences in change between the start and 24 weeks of treatment in the following items: (i) the homeostasis model assessment 2-% β (HOMA2-%β) (%) (ii) the homeostasis model assessment 2-IR ( insulin resistance)† ; (iii) fasting plasma C-peptide index (fasting plasma C-peptide [ng/mL] / fasting plasma glucose [mg/dL] × 100); (iv) glycated albumin (GA); (v) FPG (mg/dL); (vi) self-measured postprandial glucose (PPG; mg/dL); (vii) systolic blood pressure (mmHg); (viii) diastolic blood pressure (mmHg); (ix) pulse rate; (x) lipid profile; (xi) serum creatinine (mg/dL), eGFR (mL/min/1.73 $m^2$) and cystatin C (mg/L); (xii) uric acid (mg/dL); (xiii) aspartate transaminase, alanine aminotransferase and gamma-glutamyl transpeptidase (IU/L); (xiv) urine albumin/creatinine ratio (mg/g·Cr); (xv) urine natrium/creatinine ratio; (xvi) insulin dose (units/day); (xvii) bodyweight (BW; kg); (xviii) waist circumference (cm); (xix) fat mass (kg); (xx) body fat percentage (%); (xxi) lean tissue mass (kg); (xxii) hypoglycemic events; (xxiii) medication compliance (%); and (xxiv) other adverse events. †HOMA2-%β, HOMA2-IR: these were calculated from FPG and fasting plasma C-peptide by using the HOMA2 calculator[7] (calculator version 2.2.3, downloaded from: https://www.dtu.ox.ac.uk/homacalculator/download.php).

### Sample size calculation

To show the superiority of liraglutide when liraglutide and empagliflozin decreased $HbA_{1c}$ by 1.30% (Seino 2016)[8] and 0.60 ± 0.10% (Rosenstock 2015)[5], respectively, we calculated that a significant difference should be detected in 95 cases with a standard deviation of 1.2 and a detection power of 80%. Taking the dropout cases into account, a total of 110 cases (55 cases in each group) was set as the target number of registered cases. However, in the interim analysis ($n$ = 49), the effect value of $d$ = 1.19 was used for the difference between the two groups. When we recalculated the sample size, it appeared that there was a significant difference in 52 cases, with 26 cases in each group. Therefore, we finished this study early.

### Statistical analysis

Values are expressed as the mean ± standard deviation for baseline characteristics. The comparative results between the two groups were expressed as the mean ± standard error. Data that were not normally distributed are presented as the median. Analysis of the main evaluation items was carried out using the full analysis set method. The effects of liraglutide and empagliflozin therapy were evaluated by using paired $t$-tests. Evaluation items that did not follow the normal distribution were examined using non-parametric tests. The full analysis set was used for all end-points. Missing data were imputed by the last observation carried forward method. Statistical analyses were computed by using JMP 12.2.0 (SAS Institute Inc., Cary, NC, USA). $P$-values of <0.05 were considered statistically significant.

## RESULTS

### Demographics

Of 66 patients for which consent was obtained, 64 were divided into two groups. Eventually, 61 patients started medication and 59 (96.7%) completed the 24-week trial; two of the 64 patients withdrew consent before the start of medication, and one withdrew from the study owing to a steep deterioration in blood glucose control at the start. Treatment was self-interrupted in two of the 61 patients after 12 weeks, and their data up to 12 weeks were analyzed by last observation carried forward (Figure 1). Baseline parameters were well balanced between the groups (Table 1).

### Efficacy

The change in $HbA_{1c}$ as the primary end-point is shown in Figure 2. There was a significant difference in $\Delta HbA_{1c}$ over a period of 24 weeks: liraglutide −1.24 ± 0.15% versus empagliflozin −0.35 ± 0.11%, $P < 0.0001$. The differences in the change from week 0 to 24 between the two groups are shown in Table 2. Regarding glucose metabolism, a statistically significant difference was observed in two items, $HbA_{1c}$ and GA. There was no difference in FPG and PPG change.

No differences in pancreatic β-cell function were observed between the two groups. Thus, the fasting plasma C-peptide 0 value did not significantly change, and HOMA2-%β showed improvement in both groups after 24 weeks; however, there was no difference between the groups. HOMA-IR also did not significantly change. Insulin dose was maintained for 24 weeks with little change in either group. In the empagliflozin group, two patients met the drug increase criteria and the empagliflozin dose was increased to 25 mg/day. No other differences were observed between the groups regarding changes in serum creatinine, eGFR, liver function and lipids.

Body composition was evaluated by using dual-energy X-ray absorptiometry (Figure 3). Comparisons were made at the start of intervention and 24 weeks later ($n$ = 45). Although the total BW decreased in both groups, there was no difference between the two groups in terms of changes in body fat mass and lean

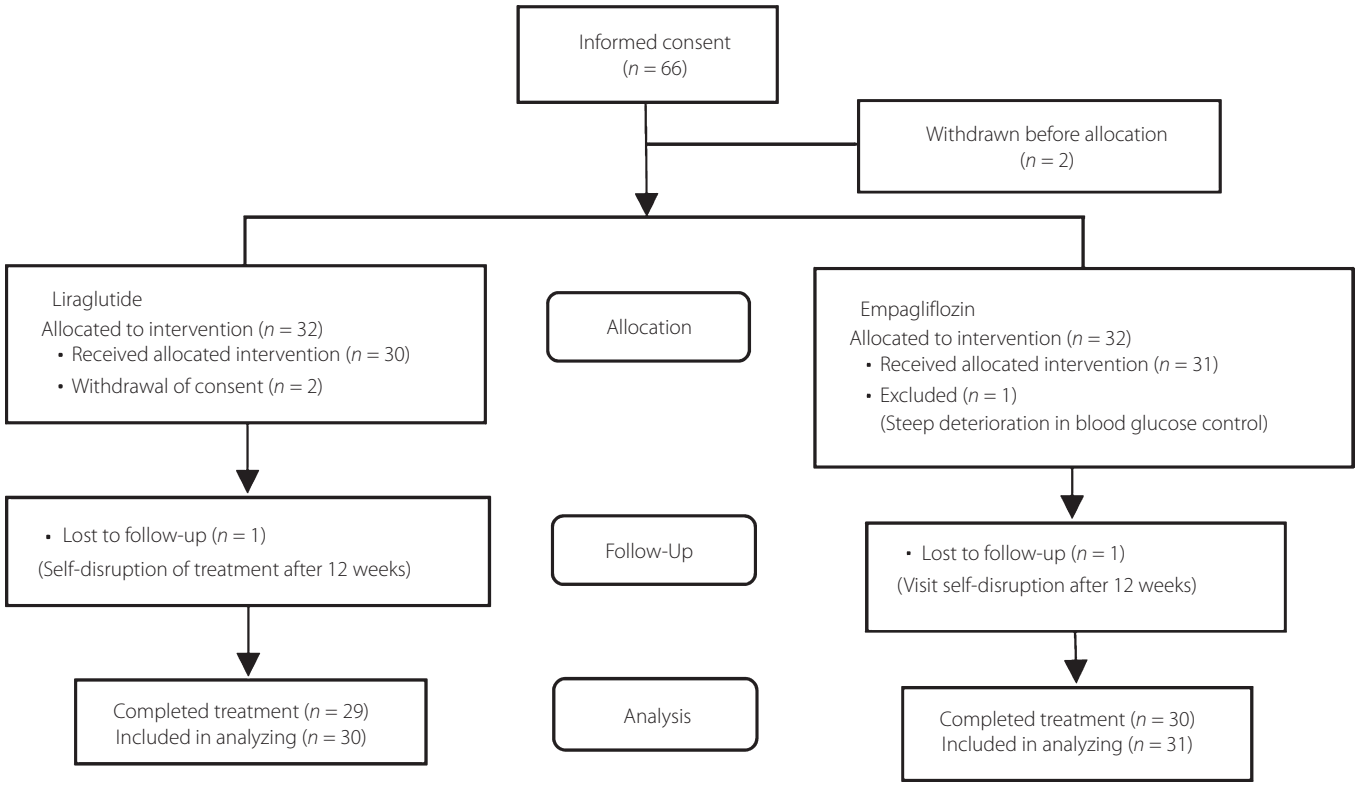


**Figure 1** | Flow diagram for study participants. See text for details of the assignment method and the inclusion/exclusion criteria.

tissue mass; both groups showed nearly the same amount of change.

The urine albumin/creatinine ratio was not normally distributed; the baseline urine albumin/creatinine ratio was: liraglutide, median 52.9 mg/g-creatinine (interquartile range [IQR] 15.7–505.5 mg/g-creatinine) versus empagliflozin, median 66.6 mg/g-creatinine (IQR 20.7–134.2 mg/g-creatinine), $P = 0.71$. There was no difference between the groups in terms of change in urinary albumin excretion (change in urine albumin/creatinine ratio: liraglutide, median −5.3 mg/g-creatinine [IQR −60.6, 9.9 mg/g-creatinine] vs empagliflozin, median −12.9 mg/g-creatinine [IQR −70.8, −2.0], $P = 0.23$). In contrast, urinary natrium excretion remained nearly unchanged pre- and post-administration, and there was no difference between the two groups.

There was no significant difference in blood pressure in the examination room, but neither group had worse values: change in systolic blood pressure: liraglutide, −4.9 ± 2.7 mmHg versus empagliflozin, −1.4 ± 2.7 mmHg, $P = 0.37$; change in diastolic blood pressure: liraglutide, −2.0 ± 1.4 mmHg versus empagliflozin, −2.3 ± 1.9 mmHg, $P = 0.88$. In terms of pulse rate, the mean value was slightly elevated in the liraglutide group; however, there was no difference between the two groups: change in pulse rate: liraglutide, 0.8 ± 1.5 b.p.m. versus empagliflozin, −1.8 ± 1.6 b.p.m., $P = 0.24$ (Table 2).

### Safety

Overall, 37.7% of individuals experienced one adverse effect, and 3.3% of individuals experienced two adverse effects. There were no serious, life-threatening side-effects. There were no cases of test drug discontinuation owing to side-effects.

Hypoglycemia (blood glucose <70 mg/dL) occurred in 21 patients (34.4%), but all cases were non-severe hypoglycemia. There was no difference in hypoglycemia frequency between the two groups ($P = 0.74$). In addition, three cases of abdominal symptoms (severe constipation, diarrhea or anorexia) occurred in the liraglutide group. Two of these patients continued with a reduced dose of liraglutide (0.6 mg/day). In the empagliflozin group, one patient showed vulvar pruritus, but this improved with symptomatic treatment.

## DISCUSSION

The present study showed the following three findings. First, in combination with insulin, liraglutide significantly improved two glucose metabolism markers, $HbA_{1c}$ and GA, compared with empagliflozin. There was no difference in ΔFPG between the two groups. In contrast, although there was a remarkable difference in terms of ΔPPG absolute values, this difference was not statistically significant: ΔPPG: median liraglutide, −32.0 mg/dL (IQR −56.0, −13.0 mg/dL) vs empagliflozin, median −8.0 mg/dL (IQR −57.0, 11.2 mg/dL), $P = 0.05$. Thus, it is possible that

**Table 1** | Clinical characteristics of participants at baseline

| | Liraglutide ($n$ = 30) | Empagliflozin ($n$ = 31) | $P$-value* |
|---|---|---|---|
| Age (years) | 67.2 ± 9.0 | 66.3 ± 9.5 | 0.69 |
| Male, $n$ (%) | 21 (70.0) | 21 (67.7) | 0.85 |
| Bodyweight (kg) | 70.1 ± 14.4 | 69.0 ± 16.0 | 0.77 |
| BMI (kg/m$^2$) | 26.4 ± 4.6 | 25.8 ± 4.1 | 0.60 |
| Body fat percentage (%)† | 28.9 ± 6.5 | 28.5 ± 4.3 | 0.80 |
| Duration of diabetes (years) | 18.8 ± 9.9 | 19.0 ± 10.1 | 0.92 |
| Hypertension, $n$ (%) | 21 (70.0) | 23 (74.2) | 0.72 |
| Hyperlipidemia, $n$ (%) | 19 (63.3) | 24 (74.4) | 0.23 |
| Blood pressure (mmHg) | | | |
| Systolic | 140.4 ± 17.9 | 137.2 ± 16.9 | 0.48 |
| Diastolic | 79.9 ± 10.6 | 78.9 ± 13.8 | 0.75 |
| TG (mg/dL) | 116.3 ± 52.8 | 129.9 ± 76.9 | 0.43 |
| LDL-C (mg/dL) | 108.0 ± 27.7 | 105.2 ± 36.8 | 0.74 |
| HDL-C (mg/dL) | 61.9 ± 21.9 | 59.4 ± 17.2 | 0.62 |
| Serum creatinine (mg/dL) | 0.92 ± 0.28 | 0.90 ± 0.32 | 0.75 |
| eGFR (mL/min/1.73 m$^2$) | 63.3 ± 18.9 | 67.1 ± 22.4 | 0.48 |
| UA (mg/dL) | 5.3 ± 1.3 | 5.7 ± 1.2 | 0.26 |
| FPG (mg/dL) | 167.4 ± 44.3 | 160.7 ± 39.7 | 0.54 |
| PPG (mg/dL)‡ | 197.7 ± 42.8 | 196.1 ± 73.5 | 0.94 |
| $HbA_{1c}$ (%) | 8.04 ± 0.75 | 8.08 ± 0.76 | 0.82 |
| GA (%) | 22.8 ± 4.0 | 21.9 ± 3.7 | 0.38 |
| CPR index | 0.91 ± 0.57 | 1.14 ± 0.94 | 0.25 |
| Antidiabetic drugs | | | |
| Sulfonylurea, $n$ (%) | 1 (3.3) | 0 (0) | 0.31 |
| Glinide, $n$ (%) | 3 (10.0) | 1 (3.2) | 0.29 |
| Thiazolidine, $n$ (%) | 4 (13.3) | 2 (6.5) | 0.38 |
| α-Glucosidase inhibitor, $n$ (%) | 5 (16.7) | 9 (29.0) | 0.26 |
| Metformin, $n$ (%) | 8 (26.7) | 15 (48.4) | 0.08 |
| DPP4 inhibitor, $n$ (%) | 14 (46.7) | 12 (38.7) | 0.54 |
| Insulin administration method | | | |
| Multiple daily injection, $n$ (%) | 24 (80.0) | 24 (77.4) | 0.81 |
| Basal supported oral therapy, $n$ (%) | 6 (20.0) | 7 (22.6) | 0.81 |
| Total insulin dose (units/day) | 26.2 ± 17.3 | 28.3 ± 16.2 | 0.63 |
| Basal insulin dose (units/day) | 13.6 ± 8.2 | 14.6 ± 7.9 | 0.63 |
| Antihypertensive drugs | | | |
| ARB or ACE inhibitor, $n$ (%) | 17 (56.7) | 23 (74.2) | 0.15 |
| Calcium channel blocker, $n$ (%) | 16 (53.3) | 17 (54.8) | 0.91 |
| α-Blocker, $n$ (%) | 3 (10.0) | 2 (6.5) | 0.62 |
| β-Blocker, $n$ (%) | 3 (10.0) | 2 (6.5) | 0.62 |
| Diuretic, $n$ (%) | 5 (16.7) | 4 (12.9) | 0.68 |
| Others, $n$ (%) | 3 (10.0) | 0 (0) | 0.07 |
| Antihyperlipidemic drugs | | | |
| Statin, $n$ (%) | 17 (56.7) | 23 (74.2) | 0.15 |
| Fibrate, $n$ (%) | 0 (0) | 1 (3.2) | 0.33 |
| Small intestine transporter inhibitor, $n$ (%) | 5 (16.7) | 4 (12.9) | 0.68 |
| Others, $n$ (%) | 1 (3.3) | 2 (6.5) | 0.58 |

Data are expressed as the mean ± standard deviation. *$P$-value for the intergroup comparison (liraglutide vs empagliflozin group). †Body fat percentage (%): calculated body composition by dual-energy X-ray absorptiometry, total $n$ = 45 (liraglutide $n$ = 22, empagliflozin $n$ = 23). ‡Postprandial plasma glucose (PPG; mg/dL): total $n$ = 35 (liraglutide $n$ = 15, empagliflozin $n$ = 20). ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CPR index, fasting plasma C-peptide (ng/mL) / fasting plasma glucose (mg/dL) × 100; eGFR, estimated glomerular filtration rate; DPP4, dipeptidyl peptidase 4; FPG, fasting plasma glucose; GA, glycated albumin; $HbA_{1c}$, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; UA, uric acid.

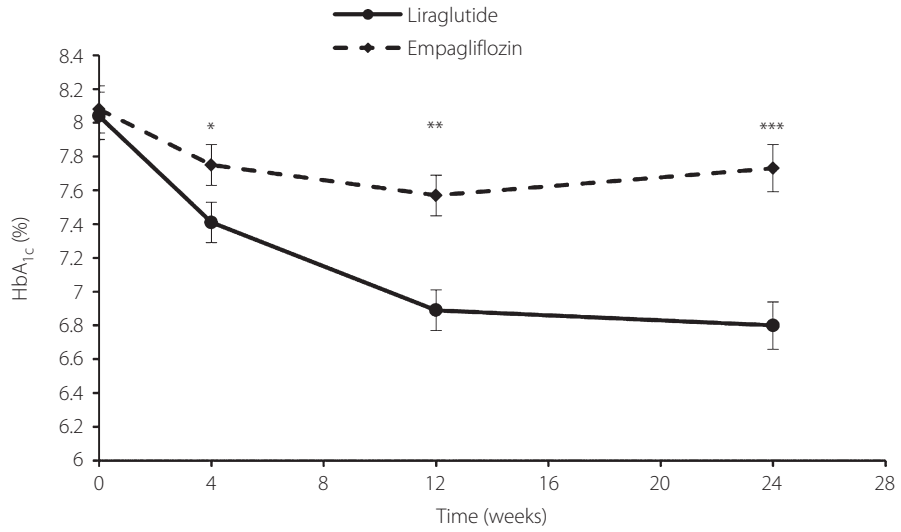


**Figure 2** | Change in glycated hemoglobin ($HbA_{1c}$) levels from the start of the intervention to 24 weeks of the trial. Data are expressed as the mean ± standard error. *$P < 0.01$, **$P < 0.001$, ***$P < 0.0001$: difference in the change between the two groups.

postprandial blood glucose and unevaluated nocturnal blood glucose explain the differences in $HbA_{1c}$ and GA. Although the difference in $HbA_{1c}$ change between the two groups was substantial, the improvement in glycemic control in the liraglutide group was as expected. We hypothesized that owing to plasma C-peptide screening during patient enrollment, the liraglutide treatment was more effective, reflecting pancreatic β-cell function. In addition, although DPP4i are more effective in Asian individuals[9], our results suggested that incretin-related drugs, including liraglutide, are more effective in Japanese and Asian individuals than in Westerners. In contrast, a previous report related to insulin therapy with empagliflozin 10 mg reported that $HbA_{1c}$ decreased −0.6 ± 0.1% during the first 18 weeks, and −0.5 ± 0.1% over the 78-week study[5]. Therefore, although it is necessary to consider differences in patient backgrounds and research methods, the improvement of glycemic control in the empagliflozin group was also as expected.

Second, there was no statistically significant difference between the two groups in terms of BW changes. Weight management improved in both groups, and body fat and lean tissue mass decreased to a similar extent. Previous studies have reported that the administration of luseogliflozin to patients with type 2 diabetes using liraglutide decreased body fat compared with lean mass[10], and that the administration of liraglutide to patients with early type 2 diabetes significantly lowered visceral adipose tissue compared with subcutaneous fat[11]. In addition, previous reports have suggested that GLP-1RA or SGLT2i resulted in a reduction in body fat or visceral adipose tissue[12–14]. However, there are limited reports on body composition using dual-energy X-ray absorptiometry, especially for patients undergoing insulin therapy; thus, more evidence is required regarding the effects of both drugs. In the previous report, treatment with SGLT2i or GLP-1RA without insulin therapy showed a 3.16–6.40-kg reduction in BW over a period of 24 weeks[12,14]. However, in the case of combined use with insulin, a reduction <1.0–2.6 kg in BW was observed in a period of approximately 18–24 weeks[5,13,15]. Thus, despite the differences in patient background in the respective studies, our weight change results when either drug was added are reasonable. This study included a population with an average body mass index of 26, so there were few cases of severe obesity; had many severe obese patients been included, the degree of weight reduction might have been greater. Regarding body composition, not only body fat, but also lean tissue mass decreased in the present study. These results might have been influenced by the fact that the participants were elderly, and 30 of them (49.2%) had no exercise habits before enrolling in this study. In some studies, a decrease in lean body mass has been previously suggested[16], and thus careful evaluations need to be made based on the differences in treatments, patient backgrounds and research contents.

Third, there was no difference in the change in urinary excretion of albumin between the two groups. Previous reports showed that although liraglutide and empagliflozin have different mechanisms of action, both are effective in preventing the progression of nephropathy[17,18]. SGLT2i treatment suppressed albumin excretion, and the expected secondary effects, other than glucose metabolism, were observed. No differences were observed between the groups in terms of secondary end-point clinical markers other than cystatin C (CysC). With regard to renal function, there were no differences in serum creatinine changes (Δserum creatinine: liraglutide, 0.02 ± 0.02 mg/dL vs empagliflozin, 0.05 ± 0.02 mg/dL, $P = 0.33$) and eGFR (ΔeGFR: liraglutide, −1.5 ± 1.1 mL/min/1.73 $m^2$ vs empagliflozin, −3.1 ± 1.4 mL/min/1.73 $m^2$, $P = 0.38$). When CysC was converted to eGFR[19], the change at 24 weeks differed between

**Table 2** | Comparison of clinical parameters

| | Liraglutide ($n$ = 30) | | | Empagliflozin ($n$ = 31) | | | |
|---|---|---|---|---|---|---|---|
| | 0 week | 24 weeks | Change | 0 week | 24 weeks | Change | $P$-value* |
| Bodyweight (kg) | 70.1 ± 2.6 | 68.9 ± 2.6 | −1.3 ± 0.4 | 69.0 ± 2.9 | 67.5 ± 3.0 | −1.5 ± 0.3 | 0.69 |
| Abdominal circumference (cm) | 92.7 ± 2.3 | 90.4 ± 2.2 | −2.3 ± 0.5 | 90.5 ± 2.0 | 88.5 ± 2.2 | −2.1 ± 0.6 | 0.80 |
| BMI (kg/m$^2$) | 26.4 ± 0.8 | 25.9 ± 0.8 | −0.5 ± 0.1 | 25.8 ± 0.7 | 25.2 ± 0.8 | −0.6 ± 0.1 | 0.67 |
| Total weight, DEXA (kg)† | 69.7 ± 2.5 | 68.6 ± 2.4 | −1.1 ± 0.4 | 67.3 ± 2.6 | 65.9 ± 2.7 | −1.3 ± 0.4 | 0.65 |
| Fat mass (kg)† | 20.5 ± 1.4 | 19.9 ± 1.4 | −0.6 ± 0.2 | 19.2 ± 1.0 | 18.5 ± 1.1 | −0.7 ± 0.2 | 0.70 |
| Lean tissue mass (kg)† | 47.2 ± 1.5 | 46.7 ± 1.6 | −0.5 ± 0.3 | 46.1 ± 1.8 | 45.4 ± 1.8 | −0.6 ± 0.4 | 0.80 |
| Body fat percentage (%) † | 28.9 ± 1.4 | 28.6 ± 1.4 | −0.3 ± 0.2 | 28.5 ± 0.9 | 28.1 ± 0.9 | −0.5 ± 0.3 | 0.68 |
| Systolic blood pressure (mmHg) | 140.4 ± 3.3 | 135.5 ± 3.1 | −4.9 ± 2.7 | 137.2 ± 3.0 | 135.7 ± 3.1 | −1.4 ± 2.7 | 0.37 |
| Diastolic blood pressure (mmHg) | 79.9 ± 1.9 | 78.0 ± 2.2 | −2.0 ± 1.4 | 78.9 ± 2.5 | 76.6 ± 2.3 | −2.3 ± 1.9 | 0.88 |
| Pulse rate (b.p.m.) | 75.9 ± 2.2 | 76.7 ± 1.9 | 0.8 ± 1.5 | 78.0 ± 1.8 | 76.1 ± 1.8 | −1.8 ± 1.6 | 0.24 |
| $HbA_{1c}$ (%) | 8.04 ± 0.14 | 6.80 ± 0.14 | −1.24 ± 0.15 | 8.08 ± 0.14 | 7.73 ± 0.14 | −0.35 ± 0.11 | < 0.0001 |
| GA (%) | 22.8 ± 0.7 | 18.3 ± 0.7 | −4.4 ± 0.6 | 21.9 ± 0.7 | 19.5 ± 0.5 | −2.4 ± 0.5 | 0.0088 |
| FPG (mg/dL) | 167.4 ± 8.1 | 135.3 ± 5.9 | −32.1 ± 8.3 | 160.7 ± 7.1 | 140.7 ± 8.0 | −20.0 ± 10.5 | 0.37 |
| PPG, mg/dL (IQR)‡ | 192.0 (168.0, 213.0) | 147.5 (131.0, 182.0) | −32.0 (−56.0, −13.0) | 183.9 (154.0, 228.3) | 166.7 (139.0, 192.3) | −8.0 (−57.0, 11.2) | 0.05 |
| HOMA2-%β (%) | 34.2 ± 3.0 | 53.4 ± 4.9 | 19.3 ± 3.3 | 40.9 ± 4.9 | 51.5 ± 3.9 | 10.6 ± 4.6 | 0.13 |
| HOMA2-IR | 1.4 ± 0.2 | 1.3 ± 0.1 | −0.1 ± 0.2 | 1.6 ± 0.2 | 1.8 ± 0.3 | 0.1 ± 0.2 | 0.42 |
| CPR-index | 0.91 ± 0.10 | 1.20 ± 0.11 | 0.3 ± 0.1 | 1.14 ± 0.17 | 1.23 ± 0.15 | 0.1 ± 0.1 | 0.12 |
| Insulin dose (units/day) | 26.2 ± 3.2 | 25.8 ± 3.1 | −0.4 ± 0.4 | 28.3 ± 2.9 | 27.7 ± 2.9 | −0.5 ± 0.2 | 0.72 |
| Frequency of hypoglycemia (times/case/24 weeks)§ | 1.5 ± 0.7 | | | 1.8 ± 0.6 | | | 0.74 |
| Medication compliance (%)¶ | 99.9 ± 0.1 | | | 99.5 ± 0.3 | | | 0.17 |
| Serum creatinine (mg/dL) | 0.92 ± 0.05 | 0.95 ± 0.06 | 0.02 ± 0.02 | 0.90 ± 0.05 | 0.95 ± 0.06 | 0.05 ± 0.02 | 0.33 |
| eGFR (mL/min/1.73 m$^2$) | 63.3 ± 3.5 | 61.8 ± 3.6 | −1.5 ± 1.1 | 67.1 ± 4.0 | 64.0 ± 4.1 | −3.1 ± 1.4 | 0.38 |
| Cystatin C (mg/L) | 1.14 ± 0.05 | 1.11 ± 0.05 | −0.03 ± 0.02 | 1.11 ± 0.06 | 1.19 ± 0.07 | 0.08 ± 0.02 | 0.0001 |
| Urine albumin/creatinine ratio, mg/g Cr (IQR) | 52.9 (15.7, 505.5) | 33.3 (16.1, 388.7) | −5.3 (−60.6, 9.9) | 66.6 (20.7, 134.2) | 32.1 (12.6, 92.9) | −12.9 (−70.8, −2.0) | 0.23 |
| Urine natrium/creatinine ratio | 1.5 ± 0.1 | 1.3 ± 0.2 | −0.2 ± 0.2 | 1.4 ± 0.2 | 1.3 ± 0.1 | −0.1 ± 0.2 | 0.65 |
| UA (mg/dL) | 5.3 ± 0.2 | 5.4 ± 0.2 | 0.1 ± 0.2 | 5.7 ± 0.2 | 5.5 ± 0.2 | −0.2 ± 0.2 | 0.32 |
| AST (U/L) | 24.7 ± 2.0 | 24.7 ± 1.8 | −0.1 ± 1.4 | 24.5 ± 2.5 | 21.1 ± 0.9 | −3.4 ± 2.5 | 0.25 |
| ALT (U/L) | 22.9 ± 2.3 | 23.3 ± 2.7 | 0.4 ± 2.1 | 24.2 ± 2.3 | 20.9 ± 1.4 | −3.2 ± 2.2 | 0.24 |
| γ-GTP, U/L (IQR) | 28.0 (15.8, 42.5) | 24.5 (1.0, 39.3) | 0 (−4.5, 3.8) | 26.0 (18.0, 60.0) | 26.0 (17.0, 43.0) | −2.0 (−11.0, 1.0) | 0.08 |
| TG (mg/dL) | 116.3 ± 9.6 | 117.6 ± 10.5 | 1.2 ± 7.0 | 129.9 ± 13.8 | 125.8 ± 13.3 | −4.1 ± 9.2 | 0.65 |
| LDL-C (mg/dL) | 108.0 ± 5.1 | 103.1 ± 5.2 | −4.9 ± 4.9 | 105.2 ± 6.6 | 104.1 ± 6.0 | −1.1 ± 2.6 | 0.49 |
| HDL-C (mg/dL) | 61.9 ± 4.0 | 59.3 ± 2.7 | −2.6 ± 2.1 | 59.4 ± 3.1 | 59.4 ± 3.1 | 0.1 ± 1.9 | 0.36 |

Data are expressed as the mean ± standard error and median and interquartile range [IQR]. *$P$-value for the intergroup comparison (liraglutide vs empagliflozin group in the changes from 0 to 24 weeks). †Total weight (dual-energy X-ray absorptiometry [DEXA]; kg), fat mass (kg), lean tissue mass (kg), body fat percentage (%): calculated body composition by DEXA, total $n$ = 45 (liraglutide $n$ = 22, empagliflozin $n$ = 23). ‡Postprandial plasma glucose (PPG; mg/dL): total $n$ = 35 (liraglutide $n$ = 15, empagliflozin $n$ = 20). §Frequency of hypoglycemia (times/case/24 weeks). ¶Medication compliance (%): comparison of frequency in 24 weeks. ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; CPR index, fasting plasma C-peptide (ng/mL) / fasting plasma glucose (mg/dL) × 100; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; GA, glycated albumin; GTP, gamma-glutamyl transpeptidase; $HbA_{1c}$, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA2, homeostasis model assessment 2; IQR, median and interquartile range; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; UA, uric acid.

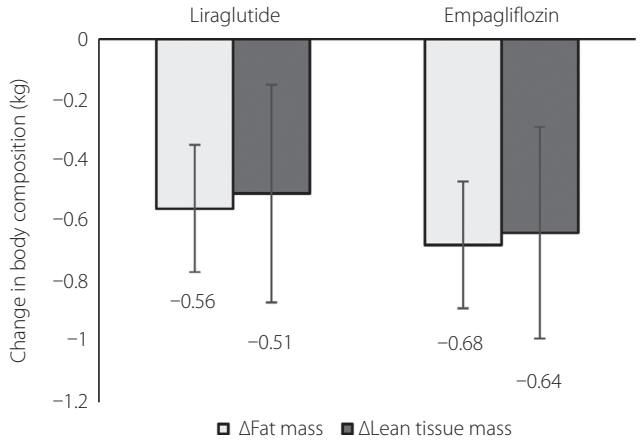


**Figure 3** | Changes in body composition over 24 weeks of the trial. Body composition was assessed by dual-energy X-ray absorptiometry method. Liraglutide $n = 22$, empagliflozin $n = 23$.

the groups (ΔeGFRCysC: liraglutide, 2.1 ± 1.4 mL/min/1.73 $m^2$ vs empagliflozin, −5.1 ± 1.6 mL/min/1.73 $m^2$, $P = 0.0012$). The deterioration of eGFR in the empagliflozin group might be due to a transient decline in renal function at the initial stage of SGLT2 inhibitor administration. Thus, ΔeGFRCysC might be able to detect changes in renal function more sensitively; in any case, it is important to accumulate long-term results. No differences in liver function, lipids and uric acid levels were observed between the two groups.

Only a limited number of comparative studies for GLP-1RA and SGLT2i have been reported, and few studies have examined the long-term results in combination with insulin. Thus, it was important to study the effects of these two drugs in patients with poor glycemic control and a long disease duration (approximately 20 years). As cases of insulin secretion depletion were excluded in the screening for this study, it is possible that liraglutide was more effective in glucose metabolism. There was no difference in body composition between the groups. When using these drugs, it is also necessary to pay attention to sarcopenia, especially in elderly people.

The present study had several limitations. First, cases of severely reduced insulin secretion ability were excluded from this study, and we washed out DPP4i before the start of the study. Discontinuation of DPP4i might have affected glycemic control in some patients, but both $HbA_{1c}$ and insulin dose had no difference in the starting values between the two groups and were not biased. In the future, we need to carefully compare the combination of DPP4i and SGLT2i versus liraglutide.

Second, as this was an open-label study, the possibility of some bias cannot be precluded. Third, regarding the postprandial blood glucose levels with self-monitoring of blood glucose, some participants had difficulty with frequent measurements and the number of participants decreased owing to deficiencies. In this study, postprandial blood glucose was not significantly different (Table 2); however, increasing the number of patients might yield different results. Fourth, the objective assessment of changes in eating behavior in both groups were not achieved. This was a randomized controlled study and we did not provide new nutritional guidance interventions during the study to avoid other biases. Liraglutide has been reported to produce significant improvement in all major scores in an eating behavior questionnaire[20]. However, reports of changes in eating behavior due to both drugs are very limited and further evidence should be accumulated.

The addition of liraglutide to ongoing insulin therapy significantly reduced $HbA_{1c}$ and GA levels than the addition of empagliflozin in patients with inadequately controlled type 2 diabetes. Both groups showed improved glycemic control without severe hypoglycemia. There were no differences between groups in terms of changes in BW and urinary albumin excretion. Future double-blind or cross-over comparative studies, continuous blood glucose monitoring, or eating behavior assessment studies might be required to verify these results.

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## DISCLOSURE

Yasuo Terauchi is on the advisory panel for AstraZeneca, Daiichi Sankyo Company, Limited, Eli Lilly and Company, Merck Sharp & Dohme Corp., Mitsubishi Tanabe Pharma Corporation, Novo Nordisk A/S, and Sanofi; receives research support from Daiichi Sankyo Company, Limited, Eli Lilly and Company, Merck Sharp & Dohme Corp., Novartis Pharmaceuticals Corporation, Novo Nordisk A/S, Ono Pharmaceutical Co., Ltd., Sanofi, Shionogi & Co., Ltd., and Sumitomo Dainippon Pharma Co., Ltd.; and is on the speaker's bureau for Astellas Pharma Inc., AstraZeneca, Bayer Yakuhin, Ltd., Daiichi Sankyo Company, Limited, Eli Lilly and Company, Merck Sharp & Dohme Corp., Mitsubishi Tanabe Pharma Corporation, Novartis Pharmaceuticals Corporation, Novo Nordisk A/S, Ono Pharmaceutical Co., Ltd., Sanofi, Sanwa Kagaku Kenkyusho, Shionogi & Co., Ltd., and Sumitomo Dainippon Pharma Co., Ltd. Hirotatsu Nakaguchi, Yoshinobu Kondo, Mayu Kyohara, Hiromi Konishi and Koji Oiwa declare no conflict of interest.

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