Effects of luseogliflozin on the secretion of islet hormones and incretins in patients with type 2 diabetes

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Abstract. The insufficient activity of insulin and the hyperactivity of glucagon are responsible for glucose intolerance in patients with type 2 diabetes. Whereas sodium-glucose cotransporter-2 (SGLT2) inhibitors improve blood glucose levels in patients with type 2 diabetes, their effects on the secretion profiles of glucagon and incretins remain unclear. Therefore, to investigate the effects of the SGLT2 inhibitor luseogliflozin on metabolic and endocrine profiles, 19 outpatients with type 2 diabetes were administered luseogliflozin for 12 weeks. It is of note that all subjects were treated only with diet and exercise therapy, and we were able to investigate the effects of luseogliflozin separately from the effects of other antidiabetic agents. Body weight, body fat mass, fat-free mass, and muscle mass were significantly reduced after 12 weeks of luseogliflozin administration. Glycosylated hemoglobin significantly decreased from the baseline of 8.2% ± 0.8% to 7.3% ± 0.7% (p < 0.0001). The meal tolerance test demonstrated that luseogliflozin significantly recovered glucose tolerance, accompanied by improved insulin resistance and β-cell function, whereas glucagon secretion was unaffected. Furthermore, GLP-1 secretion was significantly increased after luseogliflozin administration. Thus, luseogliflozin improved metabolic and endocrine profiles accompanied by increased GLP-1 secretion in type 2 diabetic patients without any antidiabetic medication, but did not affect glucagon secretion.

Key words: Type 2 diabetes, Sodium-glucose cotransporter 2 (SGLT2) inhibitor, Glucagon-like peptide-1 (GLP-1), Glucagon

THE INADEQUATE ACTIVITY of insulin and the hyperactivity of glucagon are responsible for impaired glucose tolerance in patients with type 2 diabetes [1]. Sodium-glucose cotransporter-2 (SGLT2) inhibitors increase urinary glucose excretion, leading to improved blood glucose levels and reduced body fat and muscle mass [2]. Their effects on glucagon secretion in patients with type 2 diabetes have also been highlighted. Whereas some studies reported that SGLT2 inhibitors significantly increased fasting or postprandial glucagon secretion [3-8], other studies have shown that SGLT2 inhibitors decreased [9], or had no effects on postprandial glucagon secretion [10]. As most of these studies have used the conventional radioimmunoassay (RIA) method to measure plasma glucagon concentrations, which has been doubted regarding its accuracy in recent years [11-14], researchers have had difficulty in determining the effects of SGLT2 inhibitors on glucagon secretion. Recently, a sandwich enzyme-linked immunosorbent assay (ELISA) kit for measuring glucagon concentration has become available, and the results correlated very well with those of quantitative analysis by liquid chromatography high-resolution mass spectrometry using a stable isotope-labelled peptide as an internal standard [14]. Therefore, in this study, we aimed to obtain precise concentrations of plasma glucagon using this new ELISA kit, as well as to investigate other metabolic and endocrine profiles in diabetic patients treated with luseogliflozin, a selective inhibitor of SGTL2. It is of note that all subjects were treated only with diet and exercise therapy, and hence we were able to investigate the effects of luseogliflozin on metabolic and endocrine profiles separately from the effects of other antidiabetic agents. Moreover, the meal...
tolerance test (MTT) was performed instead of the glucose tolerance test, which enabled the evaluation of the metabolic parameters of diabetic patients on a standardized diet, including fat and protein as well as carbohydrate.

**Materials and Methods**

**Participants**

A total of 19 patients (14 males and 5 females, aged 20–79 years) with type 2 diabetes, controlled only by diet and exercise therapy, with a glycosylated hemoglobin (HbA1c) level of 7.0% to 9.9%, who were being treated at Kitasato University Hospital, Motomiya Diabetes Clinic, or Toshiba Rinkan Hospital, were included in this study. The exclusion criteria were as follows: patients with malignancy or a history of malignancy, liver dysfunction (aspartate aminotransferase [AST] >100 IU/L and/or alanine transaminase [ALT] >100 IU/L), kidney dysfunction (estimated glomerular filtration rate <60 mL/min/1.73 m²) [15], pregnant or possibly pregnant; lactating mothers; patients with endocrine disorders; patients taking any drugs known to affect glucose metabolism; patients being treated for acute diseases; patients with diabetes-associated metabolic ataxia, severe complications of chronic diseases, or geriatric syndrome; patients with a past history of ischemic heart disease, cerebrovascular disease, or recurrent urinary tract infections; and patients being treated for genital infections. The protocol for this study has been approved by a suitably constituted Ethics Committee of the institution (Clinical Research Review Board of the Kitasato Institute, Approval No. CRB3180002.) and it conforms to the provisions of the Declaration of Helsinki. All informed consent was obtained from the subjects. This study has been registered in the UMIN Clinical Trials Registry (UMIN000021977) and the Japan Registry of Clinical Trials (jRCTs031190010).

**Study design**

Luseogliflozin, a highly specific SGLT2 inhibitor with low selectivity for SGLT1, was used in this study. All participants received 2.5 mg of luseogliflozin once daily after breakfast for 12 weeks. The dose was not changed throughout the study period. All participants underwent the MTT before and after the study period, and were not administered any other oral hypoglycemic agents, insulin, or glucagon-like peptide-1 (GLP-1) injection, and no adjustments were made to the medication throughout the study. Furthermore, no diet therapy or exercise interventions were newly started during the study period.

**Measurement of body composition**

Prior to conducting the MTT, body fat mass, body fat percentage, fat-free mass, muscle mass, and total body water of the participants were measured using the body composition analyzer MC-180 (Tanita, Tokyo, Japan) by bioelectrical impedance analysis [16]. The body mass index (BMI) was calculated from the height and weight of the participants as follows: BMI = body weight (kg)/height (m²).

**Meal tolerance test**

All participants underwent MTT both before and 12 weeks after luseogliflozin administration. All participants were asked to fast for 10 hr the night before the test. Owing to the ease of preparation and ingestion, cookies (592 kcal; carbohydrate [78.5 g], protein [8.0 g], and fat [28.5 g]) were used as the test food [17]. All participants were requested to finish eating the cookies within 15 min, and were allowed to only drink water during the MTT. Blood samples were collected before and at 30, 60, 90, 120, and 180 min after the MTT, to measure plasma glucose (PG), insulin, C-peptide immunoreactivity (CPR), glucagon, GLP-1, and gastric inhibitory polypeptide (GIP) levels.

**Biochemical analysis and calculations**

Blood samples for the analysis of glucagon, GLP-1, and GIP concentrations were collected in blood collection tubes containing ethylenediaminetetraacetic acid-2K, dipeptidyl peptidase-4 inhibitor, and aprotinin (Becton, Dickinson and Company). After collection, the blood samples were immediately immersed in ice water and centrifuged. Plasma glucagon and active forms of GLP-1 and GIP levels were measured using a glucagon ELISA kit (Merodia, Uppsala, Sweden), GLP-1 ELISA kit (Merck Millipore, Billerica, Massachusetts, USA), and GIP ELISA kit (Immuno-Biological Laboratories, Gunma, Japan), respectively. PG was measured using the glucose oxidase method (Glucose analyzer GA08III, A&T Corporation, Kanagawa, Japan). Insulin levels were measured by electro-chemiluminescence immunosay (Cobas 8000, Roche Diagnostics, Basel, Switzerland) and RIA. CPR was measured using the chemiluminescent enzyme immunoassay method (Presto II, Fujirebio Inc., Tokyo, Japan). The areas under the curve of PG (PG AUC), insulin (Ins AUC), CPR (CPR AUC), glucagon (glucagon AUC), GLP-1 (GLP-1 AUC), and GIP (GIP AUC) levels during the MTT were calculated by the trapezoidal method [18]. Levels of total protein, albumin, blood urea nitrogen, creatinine, uric acid, serum electrolytes (Na, K, and Cl), serum lipids (triglyceride, high-density lipoprotein [HDL]-cholesterol, and low-density lipoprotein [LDL]-cholesterol), and serum ketone bodies
Evaluation of insulin secretion and sensitivity

The homeostatic model assessment for insulin resistance (HOMA-IR) and Matsuda index were used to evaluate insulin sensitivity, and homeostatic model Assessment of β-cell function (HOMA-β) and disposition index were used to evaluate pancreatic β-cell function. The Matsuda index, which is based on MTT data, has been reported to correlate well with the original index based on the oral glucose tolerance test (OGTT) [19]. The indices above were calculated using the data from PG (G₀, G₃₀, G₆₀, G₉₀, G₁₂₀) and insulin (I₀, I₃₀, I₆₀, I₉₀, I₁₂₀) levels measured at 0, 30, 60, 90 min, and 120 min, respectively, during the MTT, as follows:

\[
\text{HOMA-IR} = \frac{I_0}{G_0} \times \frac{1}{15}
\]

\[
\text{Matsuda index} = 10,000/\sqrt{[G_0 \times I_0 \times (G_0 \times 15 + G_{30} \times 30 + G_{60} \times 30 + G_{90} \times 30 + G_{120} \times 15)]/120 \times (I_0 \times 15 + I_{30} \times 30 + I_{60} \times 30 + I_{90} \times 30 + I_{120} \times 15)/120}
\]

\[
\text{HOMA-β} = \frac{I_0 \times 360}{(G_0 - 63)}
\]

\[
\text{Meal disposition index} = \frac{\text{Matsuda index}}{(I_{30} - I_0)/(G_{30} - G_0)}
\]

Statistical analysis

Statistical analysis was performed using JMP software ver. 10 (SAS Institute Inc., Tokyo, Japan). The Wilcoxon signed rank test was used to evaluate the difference in ordinal data between the two groups. Differences between groups were considered statistically significant when the p-value was less than 0.05.

Results

Clinical characteristics of the participants and changes after luseogliflozin treatment

Baseline clinical characteristics of the study population are summarized in Table 1. The mean age of the participants was 53 ± 14 years, and the mean duration of diabetes was 5 ± 5 years. None of the participants had previously been treated with anti-diabetic drugs.

After the 12-week administration of luseogliflozin, the body weight and BMI of the participants were significantly reduced compared with before treatment (p < 0.0001), accompanied with a significant reduction in body fat mass, fat-free mass, and muscle mass (Table 2). There was no significant difference in the total body water levels after luseogliflozin treatment. No adverse effects were observed in any participants throughout the study period.

There was a significant decrease in fasting PG and HbA1c levels at 12 weeks of luseogliflozin treatment compared with at baseline, i.e., from 168 ± 40 mg/dL and 8.2% ± 0.8% to 133 ± 22 mg/dL and 7.3% ± 0.7%, respectively (p < 0.0001, Table 2). Biochemical analysis demonstrated a significant decrease in serum γ-glutamyl transpeptidase (γGTP) levels (p = 0.010), whereas serum AST and ALT levels tended to be decreased but did not reach statistical significance (Table 2). There was a significant decrease in serum uric acid levels (p = 0.0050), but no significant changes in lipid profiles, such as in the levels of triglycerides, LDL-cholesterol, and HDL-cholesterol. The concentrations of blood ketone bodies were significantly increased after luseogliflozin treatment, which is consistent with many other previous papers showing the effects of SGLT2 inhibitors on the production of ketone bodies [20, 21].

Luseogliflozin treatment improves glucose profiles analyzed by meal tolerance test

To further investigate glucose profiles affected by SGLT2 inhibitors, the MTT was performed before and 12 weeks after luseogliflozin treatment. There was a robust improvement in glucose profiles during the MTT (Fig. 1A, 1B), with no significant changes in serum insulin, CPR, and glucagon levels (Fig. 1C–1H). Measurements of plasma GLP-1 levels resulted in a significant increase in GLP-1 levels 90 and 120 minutes after the meal (Fig. 1I, 1J), whereas plasma levels of GIP were unchanged (Fig. 1K, 1L).

To evaluate insulin sensitivity, HOMA-IR and the Matsuda index were calculated, as the Matsuda index during the MTT has been reported to correlate well with the original index during the OGTT [19]. As shown in Table 2 and Fig. 2, both HOMA-IR and Matsuda index were significantly improved after luseogliflozin

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**Table 1 Clinical characteristics of the study population**

|                      | Mean ± SD |
|----------------------|-----------|
| n                    | 19        |
| Male:Female          | 14:5      |
| Age (years)          | 53 ± 14   |
| Duration of diabetes (years) | 5 ± 5 |
| Height (cm)          | 163.9 ± 8.0 |
| Body weight (kg)     | 77.3 ± 18.0 |
| BMI (kg/m²)          | 28.6 ± 5.9    |
| HbA1c (%)            | 8.2 ± 0.8   |

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(acetoacetic acid and 3-hydroxybutyric acid) were measured using a clinical chemistry analyzer (JCA-BM8040G, JEOL, Tokyo, Japan). Samples for measuring HbA1c were collected in blood collection tubes containing NaF, and HbA1c was measured by an automated glycohemoglobin analyzer (HLC–723, Tosoh, Tokyo, Japan).
|                         | Baseline Mean ± SD | 12 weeks Mean ± SD | p-value |
|-------------------------|--------------------|--------------------|---------|
| Body weight (kg)        | 77.3 ± 18.0        | 74.7 ± 16.7        | <0.0001 |
| BMI (kg/m²)             | 28.6 ± 5.9         | 27.7 ± 5.5         | <0.0001 |
| Body fat mass (kg)      | 22.5 ± 12.9        | 20.9 ± 11.1        | 0.0137  |
| Body fat percentage (%) | 27.1 ± 10.8        | 25.5 ± 10.4        | 0.0032  |
| Fat free mass (kg)      | 55.0 ± 9.5         | 54.1 ± 9.2         | 0.0185  |
| Muscle mass (kg)        | 51.8 ± 8.7         | 50.7 ± 8.7         | 0.0064  |
| Total body water (kg)   | 39.2 ± 5.9         | 38.6 ± 6.0         | 0.1334  |
| HbA1c (%)               | 8.2 ± 0.8          | 7.3 ± 0.7          | <0.0001 |
| Hb (g/dL)               | 14.8 ± 1.4         | 15.3 ± 1.7         | 0.0079  |
| Ht (%)                  | 43.8 ± 3.7         | 45.8 ± 4.4         | <0.0001 |
| Cr (mg/dL)              | 0.70 ± 0.16        | 0.74 ± 0.20        | 0.0872  |
| Na (mEq/L)              | 139 ± 2            | 139 ± 2            | 0.2900  |
| K (mEq/L)               | 4.2 ± 0.3          | 4.2 ± 0.5          | 0.9374  |
| CL (mEq/L)              | 104 ± 2            | 104 ± 3            | 0.5996  |
| Uric acid (mg/dL)       | 5.6 ± 0.9          | 5.1 ± 0.9          | 0.0050  |
| AST (U/L)               | 27 ± 17            | 21 ± 6             | 0.1547  |
| ALT (U/L)               | 36 ± 25            | 25 ± 12            | 0.0549  |
| γGTP (U/L)              | 54 ± 46            | 43 ± 30            | 0.0100  |
| Triglyceride (mg/dL)    | 176 ± 123          | 143 ± 95           | 0.0857  |
| HDL-Cholesterol (mg/dL) | 52 ± 15            | 54 ± 14            | 0.0952  |
| LDL-Cholesterol (mg/dL) | 136 ± 33           | 128 ± 39           | 0.2062  |
| Acetoacetic acid (μmol/L) | 48.5 ± 23.3    | 85.1 ± 64.4        | 0.0020  |
| 3-Hydroxybutyric acid (μmol/L) | 83.3 ± 59.0 | 169.0 ± 203.5     | 0.0062  |
| Fasting PG (mg/dL)      | 168 ± 40           | 133 ± 22           | <0.0001 |
| Fasting Insulin (μU/mL) | 11.0 ± 7.7         | 9.0 ± 5.4          | 0.0799  |
| Fasting CPR (ng/mL)     | 2.0 ± 0.7          | 1.7 ± 0.6          | 0.0092  |
| Fasting Glucagon (pg/mL)| 37.8 ± 12.3        | 36.8 ± 18.3        | 0.4413  |
| Fasting GLP-1 (pmol/L)  | 6.4 ± 10.0         | 7.7 ± 10.4         | 0.0663  |
| Fasting GIP (pmol/L)    | 6.5 ± 5.7          | 7.0 ± 8.2          | 0.6433  |
| PG AUC (mg·min/dL ×10³) | 45.5 ± 8.8         | 36.4 ± 5.5         | <0.0001 |
| Insulin AUC (μU·min/mL ×10³) | 5.6 ± 3.4    | 5.5 ± 3.2          | 0.5678  |
| CPR AUC (ng·min/mL ×10³) | 0.74 ± 0.23     | 0.77 ± 0.21        | 0.1909  |
| Glucagon AUC (pg·min/mL ×10³) | 6.6 ± 2.5    | 6.3 ± 2.7          | 0.6095  |
| GLP-1 AUC (pmol·min/L ×10³) | 1.9 ± 2.1    | 2.2 ± 2.3          | 0.0182  |
| GIP AUC (pmol·min/L ×10³) | 12.6 ± 4.1    | 13.6 ± 4.5         | 0.2837  |
| HOMA-IR                 | 4.4 ± 2.8         | 3.0 ± 1.9          | 0.0031  |
| HOMA-β                  | 43.6 ± 39.7       | 48.8 ± 31.3        | 0.0313  |
| Matsuda index based on MTT data | 3.8 ± 1.9 | 5.2 ± 2.8          | 0.0031  |
| Disposition index based on MTT data | 1.0 ± 0.7 | 1.4 ± 1.0         | 0.0149  |
administration. Moreover, to evaluate β-cell function, HOMA-β and MTT-based disposition index were calculated, which resulted in significant improvement of both indices (Fig. 2C, 2D). These findings suggest that the 12-week administration of luseogliflozin effectively ameliorated glucose tolerance, accompanied by the improvement of both insulin sensitivity and insulin secretion in diabetic patients.

**Discussion**

Whereas SGLT2 inhibitors have been demonstrated to have pleiotropic effects on β-cell function and insulin resistance, as well as on the prevention of cardiovascular outcomes, their effects on glucagon and incretin secretions remain unclear. In this study, the SGLT2 inhibitor luseogliflozin was administered to diabetic patients, who were not taking any antidiabetic drugs, which resulted in no difference in glucagon secretion and a slight but significant increase in GLP-1 secretion after 12 weeks of treatment with luseogliflozin compared with at baseline.

A number of clinical studies have analyzed the effects of SGLT2 inhibitors on glucagon secretion. Some studies reported that the administration of luseogliflozin, dapagliflozin, or empagliflozin for 1 to 12 weeks significantly increased fasting or postprandial glucagon levels [3-8]. In contrast, other studies reported no changes in fasting

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**Fig. 1** Changes in metabolic and endocrine profiles before and after luseogliflozin treatment.

Plasma glucose (A, B), insulin (C, D), CPR (E, F), glucagon (G, H), GLP-1 (I, J), and GIP (K, L) were measured during the meal tolerance test (MTT) before (red line), and after 12 weeks (blue line) of daily treatment with luseogliflozin (2.5 mg). Data are presented as the mean ± SE. * p < 0.05. Abbreviations: PG, plasma glucose; CPR, C-peptide immunoreactivity; GLP-1, glucagon-like peptide-1; GIP, gastric inhibitory polypeptide.

**Fig. 2** Evaluation of insulin sensitivity and β-cell function before and after luseogliflozin treatment.

Insulin sensitivity was evaluated by HOMA-IR (A) and the Matsuda index during the MTT (B), and β-cell function was evaluated by HOMA-β (C) and the disposition index during the MTT (D). Data are presented as the mean ± SE.
or postprandial glucagon levels after treatment with ipragliflozin or dapagliflozin [10]. These studies did not specify the methods used for the measurement of glucagon levels [4, 6, 7, 10] or used the RIA approach [3, 5, 8]. Although RIA assays have been used to measure glucagon levels, there have been issues regarding the sensitivity and specificity of RIA kits for the accurate measurement of plasma glucagon levels [11-14]. The sandwich ELISA kit used in the present study has been demonstrated to have higher accuracy than the RIA, which was validated by liquid chromatography high-resolution mass spectrometry using a stable isotope-labelled peptide as an internal standard [13, 14]. Ueno et al. previously reported that 12 weeks of ipragliflozin administration for type 2 diabetic patients decreased glucagon levels during the MTT using this sandwich ELISA kit [9], which is in contrast to our present study showing that there was no significant effect on glucagon secretion after luseogliflozin treatment. In the previous study, more than half of the subjects were treated with other hypoglycemic agents, such as metformin, dipeptidyl peptidase-4 inhibitors, and sulfonylureas, before starting ipragliflozin administration. As metformin and dipeptidyl peptidase-4 inhibitors can suppress glucagon secretion [22, 23], and this combination therapy may have affected glucagon profiles. In contrast, all participants in our study were managed without any antidiabetic drugs, which may be the most suitable for investigating the direct effects of SGLT2 inhibitors on glucagon secretion. Another possibility is that ipragliflozin is less selective for SGLT2 over SGLT1 than luseogliflozin [24], and hence direct SGLT1 inhibition in β cells by ipragliflozin may have suppressed glucagon secretion in this previous study, which is consistent with a previous study showing that the SGLT2 inhibitor canagliflozin suppressed glucagon secretion by inhibiting SGLT1 in vitro [25].

We measured plasma levels of GLP-1 and found a slight but significant increase in GLP-1 secretions after 12 weeks of luseogliflozin treatment. SGLT1 inhibition has been reported to promote GLP-1 secretion in rodent models, by inhibiting carbohydrate absorption in the upper part of the small intestine, which stimulates GLP-1 release by the residual carbohydrate contents in the lower segment [26]. In the present study, a slight inhibition of SGLT1 by luseogliflozin may have caused a slight increase in GLP-1 release in the lower small intestine. In contrast, a previous study demonstrated that canagliflozin caused substantial increase in plasma GLP-1 levels [27], which is in contrast to our present data. The less potent inhibition of SGLT1 by luseogliflozin compared with canagliflozin [24] may lead to only a slight increase in GLP-1 secretions in our present study, which caused no obvious effects on insulin and glucagon concentrations.

There are several limitations in this study. This was designed as a single arm trial without a control group, the observation period was short, and the sample size was small. Additional studies are hence needed to clearly demonstrate the effects of luseogliflozin on endocrine profiles.

In conclusion, luseogliflozin treatment improved both β-cell function and insulin sensitivity, accompanied by a significant decrease in body fat mass, fat-free mass, and muscle mass. Whereas GLP-1 secretion was significantly increased after SGLT2 inhibitor treatment, glucagon secretion appeared to be unchanged in our study on type 2 diabetic patients not taking any anti-diabetic agents. Further investigations are needed to elucidate the underlying mechanisms by which SGLT2 inhibitors affect the metabolic profiles in various pathways.

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Disclosure

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In this article, we present the following key points:

1. The development and use of SGLT2 inhibitors in the treatment of type 2 diabetes mellitus.
2. The impact of SGLT2 inhibitors on glucose metabolism and endogenous glucose production.
3. The role of SGLT2 inhibitors in improving insulin sensitivity and reducing postprandial hyperglycemia.
4. The effect of SGLT2 inhibitors on body composition and weight loss.
5. The potential for SGLT2 inhibitors to improve other metabolic parameters such as blood pressure and lipids.
6. The importance of considering the individual patient's needs and response to therapy when prescribing SGLT2 inhibitors.

We hope that this article will provide valuable insights and guidance for healthcare professionals in the management of diabetes and related complications.