Received: 12 October 2016 | Revised: 30 November 2016 | Accepted: 8 December 2016

DOI 10.1111/dom.12848

WILEY

BRIEF REPORT

Sodium-glucose co-transporter-2 inhibitor use and dietary carbohydrate intake in Japanese individuals with type 2 diabetes: A randomized, open-label, 3-arm parallel comparative, exploratory study

Daisuke Yabe MD, PhD[1,2,3,4] | Masahiro Iwasaki PhD[1,3] | Hitoshi Kuwata MD[1,2] | Takuya Haraguchi MD[2] | Yoshiyuki Hamamoto MD, PhD[1,2,3] | Takeshi Kurose MD, PhD[1,2] | Kiminobu Sumita PhD[5] | Hitoshi Yamazato PhD[5] | Shigeto Kanada MD[5] | Yutaka Seino MD, PhD[1,2]

[1]Yutaka Seino Distinguished Centre for Diabetes Research, Kansai Electric Power Medical Research Institute, Kobe, Japan

[2]Centre for Diabetes, Endocrinology and Metabolism, Kansai Electric Power Hospital, Osaka, Japan

[3]Centre for Metabolism and Clinical Nutrition, Kansai Electric Power Hospital, Osaka, Japan

[4]Division of Molecular and Metabolic Medicine, Department of Physiology and Cell Biology, Kobe University Graduate School of Medicine, Kobe, Japan

[5]Medical Corporation Heishinkai OCROM Clinic, Osaka, Japan

Correspondence
Daisuke Yabe and Yutaka Seino, Yutaka Seino Distinguished Centre for Diabetes Research, Kansai Electric Power Medical Research Institute, 1-5-6 Minatojimaminamimachi, Chuo-ku, Kobe 650-0047, Japan.
Email: ydaisuke-kyoto@umin.ac.jp; seino.yutaka@e2.kepco.co.jp

Funding information
This clinical trial was funded by Taisho Toyama Pharmaceutical Co., Ltd. The funder had no involvement in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

This study investigated the safety and efficacy of the sodium-glucose co-transporter-2 (SGLT2) inhibitor luseogliflozin with differing carbohydrate intakes in Japanese individuals with type 2 diabetes (T2D). Participants were randomly assigned to 3 carbohydrate-adjusted meals for 14 days (days 1-14; a high carbohydrate [HC; 55% total energy carbohydrate] and high glycaemic index [HGI] meal; an HC [55% total energy carbohydrate] and low glycaemic index [LGI] meal; or a low carbohydrate [LC; 40% total energy carbohydrate] and HGI meal). All participants received luseogliflozin for the last 7 days (days 8-14), continuous glucose monitoring (CGM) before and after luseogliflozin treatment (days 5-8 and days 12-15) and blood tests on days 1, 8 and 15. Luseogliflozin significantly decreased the area under the curve and mean of CGM values in all 3 groups similarly. Fasting plasma glucose, insulin and glucagon were similar at all time points. Ketone bodies on day 15 were significantly higher in the LC-HGI group compared with the HC-HGI and HC-LGI groups. In conclusion, luseogliflozin has similar efficacy and safety in Japanese people with T2D when meals contain 40% to 55% total energy carbohydrate, but a strict LC diet on this class of drug should be avoided to prevent SGLT2 inhibitor-associated diabetic ketoacidosis.

KEYWORDS

carbohydrate intake, continuous glucose monitoring, glucose variability, glycaemic index, luseogliflozin, SGLT2 inhibitor, type 2 diabetes

1 | INTRODUCTION

Sodium-glucose co-transporter 2 (SGLT2) inhibitors have recently been developed as a novel class of glucose-lowering agents for the management of type 2 diabetes (T2D).[1,2] SGLT2 inhibitors enhance urinary glucose excretion (UGE), thereby ameliorating both pre- and postprandial glucose excursions insulin-independently, and also lead to substantial body weight reduction. Clinical trials have demonstrated the efficacy and safety of SGLT2 inhibitors, as a class, in people with T2D; however, there are concerns regarding severe adverse events associated with the use of SGLT2 inhibitors in real clinical settings.[3] Among these, diabetic ketoacidosis (DKA) near

normoglycaemia or even euglycaemic DKA in individuals receiving SGLT2 inhibitors has drawn considerable attention.[4–6] SGLT2 inhibitors lower plasma glucose and circulating insulin levels through enhancement of UGE; they also enhance glucagon secretion. Reduced insulin and elevated glucagon levels stimulate lipolysis in fat and hepatic ketogenesis, which could trigger onset of euglycaemic DKA under certain conditions, such as insulin-dependent type 1 diabetes (T1D) and T2D characterized primarily by β-cell dysfunction.[4–6] Recently, it was reported that a Japanese patient with T2D on a strict low-carbohydrate diet developed euglycaemic DKA after initiation of the SGLT2 inhibitor ipraglifrozin.[7] It is possible that low carbohydrate intake together with SGLT2 inhibitor usage could have limited circulating insulin levels and thereby induced euglycaemic DKA. The American Diabetes Association sets no general recommendations on the carbohydrate content of meals.[8] The Japanese Diabetes Society recommends that individuals with diabetes should normally take 50% to 60% of total energy from carbohydrates (TEC),[9] but indicates that <50% TEC may be allowed, depending on patient preference and diabetes pathophysiology. However, there has been no examination of safety and efficacy of SGLT2 inhibitors with regard to different meal compositions, especially carbohydrate content and glycaemic index (GI).

In the present study, we compared the efficacy and safety of the SGLT2 inhibitor luseogliflozin in Japanese people with T2D receiving meals of different carbohydrate content (55% vs 40% of TEC) and differing GIs.

2 | METHODS

2.1 | Study protocol

This was a multicentre, randomized, open-label, 3-arm parallel comparative study in Japanese people with T2D (ClinicalTrials.gov, NCT02500186 and UMIN, UMIN000017838). Eligible participants were randomly assigned into 3 groups in a 1:1:1 ratio (Figures S1 and S2). Those participants who were taking 1 oral antidiabetic drug or a glucagon-like peptide-1 (GLP-1) receptor agonist underwent a washout period of at least 4 weeks before randomization. Participants in each group consumed the test meals of 1800 kcal/d with different carbohydrate adjustment (the high carbohydrate [HC]-high GI [HGI] group received 55% TEC and HGI meals; the HC-low GI [LGI] group received 55% TEC and LGI meals; and the low carbohydrate [LC]-HGI group received 40% TEC and HGI meals) for 14 days (days 1-14) as described in Appendix S1. Participants received oral luseogliflozin 2.5 mg before breakfast once daily for the final 7 days (days 8-14). Blood sampling was conducted on days 1, 8 and 15; continuous glucose monitoring (CGM) was performed twice during the trial (days 5-8 and days 12-15), as described in Appendix S1. This trial was conducted in 2 medical institutions in Osaka, Japan after obtaining approval from both ethics committees. Written informed consent was obtained from all participants.

2.2 | Study population

Eligible participants were aged 20 to 64 years, had a treatment history of a single oral hypoglycaemic agent or GLP-1 receptor agonist with glycated haemoglobin (HbA1c) concentration ≤10.0% (≤86 mmol/mol) or no drug treatment with HbA1c concentration 7.0% to 10.0% (53-86 mmol/mol) and body mass index (BMI) ≥20 and <30 kg/m^2. Participants with T1D, renal impairment with estimated glomerular filtration rate <45 mL/min/1.73 m^2, liver disease, cardiac disease, serious gastrointestinal tract disease, history of gastrointestinal surgery, alcohol abuse, malignancy, or pregnancy were excluded. The sample size was determined with reference to a recent clinical trial of luseogliflozin.[10]

2.3 | Study assessments

The primary endpoints were mean, SD, area under the curve (AUC) of glucose levels, and mean amplitude of glycaemic excursions (MAGE) derived from CGM data.[11] Other endpoints included fasting plasma glucose (FPG), insulin, C-peptide, glucagon, ketone bodies and non-esterified fatty acids. These endpoints were assessed in the full analysis set population (ie, participants who received at least 1 dose of luseoglifrozin with at least 1 point of efficacy data available). Adverse events, using system organ class/preferred terms, and adverse drug reactions were summarized for the safety analysis set population (ie, participants who received at least 1 dose of luseoglifrozin with at least 1 point of safety data available).

2.4 | Statistical analysis

All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina). Baseline characteristics were compared using analysis of variance; a significance level of 15% (2-sided) was used to examine the heterogeneity of participant characteristics. Repeated measures were assessed using mixed-design analysis of covariance. The unrestricted least significant difference method was applied to calculate the least squares mean and 95% confidence interval for changes in efficacy variables. Statistical significance was determined at the 5% level.

3 | RESULTS

Twenty-four Japanese people with T2D were recruited and randomly assigned into 3 groups: HC-HGI, HC-LGI and LC-HGI (Figure S1). These groups had similar baseline data (Table 1), the duration of T2D in the LC-HGI group being slightly longer than in the HC-HGI and HC-LGI groups, but the difference was non-significant statistically.

Postprandial CGM values in the HC-HGI group were consistently higher than in the HC-LGI and LC-HGI groups before and after initiation of luseogliflozin treatment (Figure S3). The HC-HGI group had higher peak blood glucose level (BG_{max}), AUC over 48 hours ($AUC_{0\text{-}48h}$), and $AUC_{0\text{-}48h}$ for glucose levels >10.0 mmol/L (high-range $AUC_{0\text{-}48h}$); mean, SD and MAGE values were higher than in the HC-LGI and LC-HGI groups (Table 2), although the differences were not statistically significant. Importantly, luseogliflozin treatment significantly decreased the AUC and the mean of CGM data in all 3 groups. In the LC-HGI group, lower peak blood glucose level (BG_{min}) and area over the curve over 48 hour ($AOC_{0\text{-}48h}$) for glucose levels <3.9 mmol/L (low-range

TABLE 1 Demographic data of participants in full analysis set

	HC-HGI group	HC-LGI group	LC-HGI group	*P*
Number of participants (men, women)	8 (5, 3)	8 (6, 2)	7 (7, 0)	
Age, years	54.3 ± 5.2	55.0 ± 5.0	56.9 ± 7.3	.6838
Duration of type 2 diabetes, years	4.4 ± 3.3	4.5 ± 3.5	7.6 ± 4.3	.1993
BMI, kg/m^2	24.31 ± 2.04	24.50 ± 2.74	26.03 ± 2.66	.3709
Systolic blood pressure, mm Hg	119.9 ± 14.0	123.3 ± 17.8	118.3 ± 9.9	.7939
Diastolic blood pressure, mm Hg	73.0 ± 12.4	76.4 ± 8.1	73.9 ± 5.0	.7506
HbA1c, %	7.56 ± 1.16	7.39 ± 0.85	7.57 ± 0.66	.9069
FPG, mmol/L	7.95 ± 2.33	8.68 ± 2.37	8.63 ± 1.30	.7465
Fasting insulin, pmol/L	55.6 ± 45.1	55.6 ± 22.9	57.6 ± 16.7	.9902
Fasting glucagon, ng/L	185.9 ± 52.7	160.3 ± 30.2	161.6 ± 22.9	.3430
SUIT	27.49 ± 9.45	28.22 ± 15.33	26.53 ± 7.55	.9601
HOMA-IR	3.2 ± 3.2	2.9 ± 1.0	3.2 ± 1.1	.9453
HOMA-β	35.5 ± 20.2	38.8 ± 23.8	34.3 ± 12.3	.8982
Total cholesterol, mmol/L	5.8 ± 1.2	4.9 ± 0.6	5.5 ± 0.8	.2148
HDL cholesterol, mmol/L	1.6 ± 0.5	1.8 ± 0.3	1.2 ± 0.2	.1702
Triglycerides, mmol/L	1.3 ± 1.0	1.8 ± 0.7	1.7 ± 0.7	.4039
Estimated glomerular filtration rate, mL/min/1.73 m^3	86.31 ± 23.07	87.25 ± 13.91	82.05 ± 17.36	.8506

Values are mean ± SD or n (%). Each item was compared among the 3 groups using analysis of variance. A significance of $P < .15$ (2-sided) was taken to indicate heterogeneity among the study groups.

Abbreviations: HOMA-β, homeostatic model assessment of β-cell function; HOMA-IR, homeostatic model assessment of insulin resistance; SUIT, secretory unit of islet in transplantation.

$AOC_{0\text{-}48h}$) post-dose were significantly different from pre-dose, possibly because of a single participant who had extremely low blood glucose levels at night. The participant was not excluded from the analysis set because the low level of glucose was possibly attributable to CGM sensor problems.

The FPG values on days 1, 8 and 15 did not differ among the 3 groups (Figure S4), while FPG values on days 8 and 15 were lower than on day 1 in the HC-LGI and LC-HGI groups and, on day 15, were lower than on day 1 in the HC-HGI group. Insulin and C-peptide levels on days 1, 8 and 15 did not differ among the 3 groups, while insulin and C-peptide levels on day 15 were significantly lower than on day 1 in all 3 groups. Insulin and C-peptide levels on day 15 were reduced, possibly as a result of FPG reduction by combined action of test meals and luseogliflozin because secretory unit of islet in transplantation and homeostatic model assessment of β-cell function (Figure S5) did not change between days 1 and 15. Glucagon on days 1, 8 and 15 did not differ among the 3 groups, while glucagon levels on day 8 and day 15 were lower than on day 1 in all 3 groups, with statistical significance only in the HC-HGI and HC-LGI groups. Unlike previous reports,[12,13] no glucagon elevation was observed in response to luseogliflozin administration.

TABLE 2 Parameters derived from continuous glucose monitoring values

	HC-HGI			HC-LGI			LC-HGI		
	− Luseo	+ Luseo	Difference	− Luseo	+ Luseo	Difference	− Luseo	+ Luseo	Difference
BG_{max}, (mmol/L)	13.17	12.13	−1.05	12.47	11.16	−1.31	11.35	10.29	−1.06
BG_{min}, (mmol/L)	4.56	4.27	−0.29	4.59	4.09	−0.50	4.76	3.79*	−0.97
AUC_{0-48h}, (mmol·h/L)	380.52	340.06	−40.46	345.90	306.74	−39.16	347.08	296.69*	−50.39
High−range AUC_{0-48h}, (mmol·h/L)	20.30	10.57*	−9.73	8.79	2.88*	−5.91	3.89	0.56	−3.33
Low−range AOC_{0-48h}, (mmol·h/L)	0.19	0.53*	0.34	0.10	0.08	−0.02	0.00	1.50*	1.50
Mean (mmol/L)	7.94	7.09	−0.85	7.22	6.40	−0.82	7.24	6.19*	−1.05
SD (mmol/L)	2.20	1.96*	−0.24	1.77	1.70*	−0.08	1.54	1.53	−0.01
MAGE, (mmol/L)	5.28	5.10	−0.18	4.71	4.53	−0.18	4.18	3.87	−0.31
MODD, (mmol/L)	1.28	1.14	−0.14	1.21	1.22	0.01	0.91	1.00	0.09

Minimum mean−square values and the differences of minimum mean−square values of Days 6−7 (− Luseo) and Days 13−14 (+ Luseo) were calculated.
* Indicates $P < 0.05$ versus − Luseo.
Abbreviations: BG_{max}, peak blood glucose level; AUC0−48h, area under the curve over 48 h; high−range AUC_{0-48h}, AUC_{0-48h} for glucose levels ≥ 181 mg/dL; (low−range AOC_{0-48h}, area over the curve over 48 h for glucose levels < 70 mg/dL; HC−HGI, high carbohydrate−high glycemic index; HC−LGI, high carbohydrate−low glycemic index; SD, standard deviation of the mean glucose concentration; LC−HGI, low carbohydrate−high glycemic index; MAGE, mean amplitude of glycemic excursions; MODD, mean of the daily difference.

Ketone bodies on days 1 and 8 did not differ among the 3 groups (day 1: HC-HGI 139.1 ± 193.3 μmol/L; HC-LGI 65.1 ± 41.1 μmol/L and LC-HGI 115.3 ± 158.2 μmol/L; day 8: HC-HGI 183.8 ± 155.4 μmol/L, HC-LGI 196.5 ± 132.8 μmol/L and LC-HGI 262.7 ± 138.1 μmol/L), while ketone bodies on day 15 were significantly higher in the LC-HGI group compared with the HC-HGI and HC-LGI groups (day 15: HC-HGI 502.9 ± 365.2 μmol/L, HC-LGI 360.9 ± 184.7 μmol/L and LC-HGI 752.4 ± 249.2 μmol/L [Figure S4]). Other variables are shown in Figures S4 to S7.

All adverse events were mild in severity (Table S1). Among them, somnolence and urinary frequency were judged as adverse drug reactions; dermatitis was attributable to contact with fixed tape for CGM.

4 | DISCUSSION

In the present study, we found that luseogliflozin ameliorated hyperglycaemia in Japanese people with T2D receiving the 3 different test meals; however, ketone bodies were significantly increased by luseogliflozin in the LC-HGI group.

Luseogliflozin improved $AUC_{0\text{-}48h}$ and mean of CGM data in all 3 groups, indicating that differences in carbohydrate content (55% vs 40% of TEC) and GI (white rice vs brown rice) did not affect the glucose-lowering effects. Luseogliflozin did not affect SD or MAGE values, confirming that SGLT2 inhibitors improve glycaemia without affecting glucose variability.[14]

Luseogliflozin significantly increased ketone bodies in the LC-HGI group compared with the HC-HGI and HC-HGI groups, suggesting that reducing carbohydrate content substantially, together with SGLT2 inhibitor therapy, could trigger euglycaemic DKA. While the euglycaemic DKA cases reported in the USA were mostly in insulin-dependent T1D,[4,5] a number of euglycaemic DKA cases have been reported in Japanese people with T2D receiving SGLT2 inhibitors.[6] This difference might be attributable to the fact that T2D in East-Asian populations, including Japanese populations, is characterized primarily by β-cell dysfunction rather than insulin resistance and subsequent hyperinsulinaemia. Indeed, many euglycaemic DKA cases in Japanese people with T2D receiving SGLT2 inhibitors occurred after withdrawal of sulphonylureas and/or insulin.[6] The present study showed that ketone bodies were significantly increased by luseogliflozin in the LC-HGI group, suggesting that SGLT2 inhibitors might trigger onset of euglycaemic DKA in individuals on a strict LC diet, with or without withdrawal of insulin and/or sulphonylureas.

Limitations of the present study include the lack of UGE measurements because of difficulties in 24-hour urine collection for outpatient participants; however, it is of interest to investigate the effects of carbohydrate intake adjustments on UGE before and after SGLT2 inhibitor treatment. UGE occurs when plasma glucose levels are higher than the renal threshold and SGLT2 inhibitor treatment lowers the threshold.[15] Because glucose profiles of the HC-LGI and LC-HGI groups were similar and lower than in the HC-HGI group before and after luseogliflozin treatment in the present study (Figure S3 and Table 2), the UGEs in the HC-LGI and LC-HGI groups might well be similar and lower than in the HC-HGI group.

It is also uncertain whether 1 week is sufficient to stabilize the effects of dietary interventions in the absence or presence of luseogliflozin; it was previously shown that inter-day variability of daily glucose profiles over 3 consecutive days was minimal (mean of daily difference [MODD] 1.3-1.6 mmol/L) when food consumption was tightly controlled,[16] as it was in the present study (MODD 0.9-1.3 mmol/L); however, the effects during days 8 to 15 might partly be derived from the combined action of luseogliflozin and the dietary interventions.

In addition, the present study compared the effects of SGLT2 inhibitor use and carbohydrate intake adjustments for a short duration with a relatively small sample size; further investigations are necessary to address long-term safety and efficacy of SGLT2 inhibitors in individuals receiving meals of various carbohydrate content.

In conclusion, the present study shows the glucose-lowering effects of luseogliflozin, typical of SGLT2 inhibitors, with limited adverse events in Japanese people with T2D receiving meals consisting of 40% to 55% TEC with either an HGI or a LGI; however, our results suggest that the carbohydrate content of meals can play an important role in SGLT2 inhibitor-associated hepatic ketogenesis and onset of euglycaemic DKA.

ACKNOWLEDGMENTS

The authors are grateful to Yoko Shigefuku of Kansai Electric Power Medical Research Institute and Michiko Yamane of Kansai Electric Power Hospital for secretarial assistance.

Conflict of interest

D. Y. has received consulting and/or speaker fees from MSD KK, Novo Nordisk Pharma Ltd, Takeda Pharmaceutical Co. Ltd and Taisho Toyama Pharmaceutical Co. Ltd, and has also received clinical commissioned/joint research grants from Nippon Boehringer Ingelheim Co., Ltd, Eli Lilly and Company, Taisho Toyama Pharmaceutical Co. Ltd, MSD KK, Ono Pharmaceutical Co. Ltd, Novo Nordisk Pharma Ltd, Arklay Co. Ltd and Takeda Pharmaceutical Co. Ltd. Y. H. has received consulting and/or speaker fees from Novo Nordisk Pharma Ltd. T. K. has received consulting and/or speaker fees from Sanofi KK and has also received clinical commissioned/joint research grants from the Japan vascular disease research foundation. Y. S. has received consulting and/or speaker fees from Eli Lilly Japan KK, Sanofi KK, Novo Nordisk Pharma Inc., Glaxo-Smith-Kline, Taisho Pharmaceutical Co., Ltd, Taisho Toyama Pharmaceutical Co., Ltd, Astellas Pharma Inc., BD, Nippon Boehringer Ingelheim Co., Ltd, Johnson & Johnson and Takeda Pharmaceutical Co. Ltd, and has also received clinical commissioned/joint research grants from Nippon Boehringer Ingelheim Co., Ltd., Eli Lilly and Co., Taisho Toyama Pharmaceutical Co. Ltd, MSD KK, Ono Pharmaceutical Co. Ltd, Novo Nordisk Pharma Ltd and Arklay Co. Ltd. M. I., H. K., T. H., K. S., H. Y. and S. K. have no conflict of interest relevant to this study to report.

Author contributions

D. Y., M. I. and Y. S. contributed to conception and design of the research and analysis and interpretation of data and writing of the manuscript. S. K. contributed to design of the research, collection of data and revision of the manuscript critically for important intellectual content. K. S. and H. Y. contributed to statistical analysis and interpretation of data and writing of the manuscript. H. K., T. H., Y. H. and T. K. contributed to analysis and interpretation of data and revision of the manuscript critically for important intellectual content. All the authors approved the version to be published. D. Y. and Y. S. are the guarantors of this work.

REFERENCES

1. Fujita Y, Inagaki N. Renal sodium glucose cotransporter 2 inhibitors as a novel therapeutic approach to treatment of type 2 diabetes: clinical data and mechanism of action. *J Diabetes Invest*. 2014;5:265-275.
2. Hasan FM, Alsahli M, Gerich JE. SGLT2 inhibitors in the treatment of type 2 diabetes. *Diabetes Res Clin Pract*. 2014;104:297-322.
3. Yabe D, Nishikino R, Kaneko M, Iwasaki M, Seino Y. Short-term impacts of sodium/glucose co-transporter 2 inhibitors in Japanese clinical practice: considerations for their appropriate use to avoid serious adverse events. *Expert Opin Drug Saf*. 2015;14:795-800.
4. Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 inhibitors. *Diabetes Care*. 2015;38:1638-1642.
5. Taylor SI, Blau JE, Rother KI. SGLT2 inhibitors may predispose to ketoacidosis. *J Clin Endocrinol Metab*. 2015;100:2849-2852.
6. Ogawa W, Sakaguchi K. Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: possible mechanism and contributing factors. *J Diabetes Invest*. 2016;7:135-138.
7. Hayami T, Kato Y, Kamiya H, et al. Case of ketoacidosis by a sodium-glucose cotransporter 2 inhibitor in a diabetic patient with a low-carbohydrate diet. *J Diabetes Invest*. 2015;6:587-590.
8. American Diabetes Association. Standards of medical care in diabetes-2016. *Diabetes Care*. 2016;39(suppl 1):S25-S28.
9. Tajima N, Noda M, Origasa H, et al. Evidence-based practice guideline for the treatment for diabetes in Japan 2013. *Diabetol Int*. 2015;6:151-187.
10. Sasaki T, Seino Y, Fukatsu A, Ubukata M, Sakai S, Samukawa Y. Pharmacokinetics, pharmacodynamics, and safety of luseogliflozin in Japanese patients with type 2 diabetes mellitus: a randomized, single-blind, placebo-controlled trial. *Adv Ther*. 2015;32:319-340.
11. McDonnell CM, Donath SM, Vidmar SI, Werther GA, Cameron FJ. A novel approach to continuous glucose analysis utilizing glycemic variation. *Diabetes Technol Ther*. 2005;7:253-263.
12. Ferrannini E, Muscelli E, Frascerra S, et al. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. *J Clin Invest*. 2014;124:499-508.
13. Merovci A, Solis-Herrera C, Daniele G, et al. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. *J Clin Invest*. 2014;124:509-514.
14. Nishimura R, Osonoi T, Kanada S, et al. Effects of luseogliflozin, a sodium-glucose co-transporter 2 inhibitor, on 24-h glucose variability assessed by continuous glucose monitoring in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled, crossover study. *Diabetes Obes Metab*. 2015;17:800-804.
15. DeFronzo RA, Hompesch M, Kasichayanula S, et al. Characterization of renal glucose reabsorption in response to dapagliflozin in healthy subjects and subjects with type 2 diabetes. *Diabetes Care*. 2013;36:3169-3176.
16. Pearce KL, Noakes M, Keogh J, Clifton PM. Effect of carbohydrate distribution on postprandial glucose peaks with the use of continuous glucose monitoring in type 2 diabetes. *Am J Clin Nutr*. 2008;87:638-644.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Yabe D, Iwasaki M, Kuwata H, Haraguchi T, Hamamoto Y, Kurose T, Sumita K, Yamazato H, Kanada S and Seino Y. Sodium-glucose co-transporter-2 inhibitor use and dietary carbohydrate intake in Japanese individuals with type 2 diabetes: A randomized, open-label, 3-arm parallel comparative exploratory study. *Diabetes Obes Metab*. 2017;19:739–743. https://doi.org/10.1111/dom.12848