ORIGINAL RESEARCH

Observational Study on Unhealthy Eating Behavior and the Effect of Sodium-Glucose Cotransporter 2 Inhibitors: The Luseogliflozin Ehime Diabetes Study

Shinya Furukawa (iD) · Teruki Miyake · Hiroaki Miyaoka ·
Bunzo Matsuura · Yoichi Hiasa

ABSTRACT

Introduction: Luseogliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor. Unhealthy eating behavior is associated with diabetes, hypertension, and obesity. However, evidence regarding the effect of medications, including SGLT2 inhibitors, on unhealthy eating behavior is limited. This study investigated the association between unhealthy eating behavior and the laboratory and physical findings of Japanese patients with type 2 diabetes given luseogliflozin once daily for 24 weeks.
Methods: Twenty-nine patients with type 2 diabetes mellitus were enrolled in a 24-week prospective, open-label, single-arm pilot study. The information regarding unhealthy eating behaviors (eating fast, late dinner, nighttime snack, skipping breakfast, and eating until full) was obtained using self-reported questionnaires.
Results: The baseline rate of eating fast, late dinner, nighttime snack, skipping breakfast, and eating until full was 51.7%, 24.1%, 24.1%, 10.3% and 55.2%, respectively. After administration of luseogliflozin, fasting plasma glucose, HbA1c, aspartate aminotransferase (ALT), weight, body mass index, and waist measurement all decreased significantly. High-density lipoprotein cholesterol and hematocrit increased significantly. In the healthy eating behavior group, the improvements of fasting plasma glucose and ALT, but not other variables, were attenuated. HbA1c level was significantly improved in patients with eating fast, while other unhealthy eating behaviors attenuated the effect of luseogliflozin for HbA1c. The effect of leseogliflozin on the relationship between eating behavior and weight reduction was inconsistent after administration luseogliflozin.
Conclusion: Luseogliflozin might be more effective for controlling plasma glucose in patients with type 2 diabetes who have a tendency to eat fast, but it might have less effect on those with other unhealthy eating habits.

Keywords: Eating fast; Eating habits; HbA1c; Sodium-glucose cotransporter 2; Weight

S. Furukawa (✉)
Health Services Center, Ehime University, Bunkyo, Matsuyama, Ehime 790-8577, Japan
e-mail: shinya.furukawa@gmail.com

T. Miyake
Department of Gastroenterology and Metabology, Ehime University Graduate School of Medicine, Shitsukawa, Toon, Ehime, Japan

H. Miyaoka · B. Matsuura
Department of Internal Medicine, Saiseikei Matusyama Hospital, Matsuyama, Ehime, Japan

Y. Hiasa
Department of Lifestyle-Related Medicine and Endocrinology, Ehime University Graduate School of Medicine, Toon, Japan

Key Summary Points

Why carry out this study?

Unhealthy eating behavior is associated with insulin resistance, obesity, central obesity, postprandial hyperglycemia, and the onset of diabetes. However, evidence regarding unhealthy eating behavior and effect of antidiabetic drug was limited.

Unhealthy eating habits might attenuate the effects of SGLT2 inhibitors, including plasma glucose and weight loss.

What was learned from the study?

The effect of luseogliflozin on HbA1c levels in the unhealthy eating behaviors group might be attenuated.

Significant improvement for HbA1c was observed in patients with eating fast, while their other unhealthy behaviors attenuated the effect of luseogliflozin.

The association between unhealthy eating and weight reduction was inconsistent.

Fast-eating habits may increase the efficacy of SGLT2 inhibitors in humans.

Interventions in eating habits (excluding fast-eating habits) may enhance the therapeutic effect of SGLT2 inhibitors.

More research on the relationship between eating habits and diabetes drugs is needed.

INTRODUCTION

Eating behaviors are known to be changeable by appropriate interventions. Eating behaviors are thought to be involved in the onset of cardiovascular diseases, diabetes, and cancer [1]. The association between unhealthy eating behaviors and non-communicable diseases has been previously examined. Eating until full is associated with obesity and central obesity [2, 3]. Skipping breakfast is positively associated with obesity [4], low-density lipoprotein cholesterol [5], and the onset of diabetes [6]. Eating fast is associated with obesity [7–10], blood pressure [7–9], postprandial hyperglycemia [9, 11], and insulin resistance [12].

These findings suggest that unhealthy eating habits may weaken the therapeutic effects of oral anti-hypoglycemic agents in patients with type 2 diabetes mellitus. The relapse of poor blood glucose after sitagliptin use was more common in patients with unhealthy eating habits [13]. Regarding the relationship of unhealthy eating habits and sodium-glucose cotransporter 2 (SGLT2) inhibitors, an inverse correlation between the amount of visceral fat and the number of unhealthy eating habits has been shown in patients with Japanese type 2 diabetes receiving SGLT2 inhibitors [14]. However, although eating habits are considered to be changeable by appropriate interventions, evidence on the relationship between eating behaviors and the effects of anti-hypoglycemic agents is limited. Many previous clinical studies have focused on the hypoglycemic and weight-loss effects of SGLT2 inhibitors. Unhealthy eating habits might attenuate the effects of SGLT2 inhibitors, including plasma glucose and weight loss.

In this study, we explored the relationship between eating habits and the effects of luseogliflozin (an SGLT2 inhibitor) on plasma glucose and weight loss in patients with type 2 diabetes mellitus.

METHODS

Subjects

We screened the patients with type 2 diabetes mellitus aged 20–80 years old. Patients were given a detailed description of the present study and were informed of possible risks and benefits of participation prior to providing their written informed consent and study enrollment. The inclusion criteria were BMI above 23 kg/m² and estimated glomerular filtration rate (eGFR) above 30 mL/min/1.73 m². Exclusion criteria were severe hypoglycemia, pregnancy,

treatment for skin disease within the last 2 months, repeated urinary and genital infections, cancer, type 1 diabetes, ketoacidosis, severe liver injury, otorhinolaryngology, hypothyroidism, neurological disorders, acromegaly, hepatitis, lactating, cerebral infarction with paralysis, history of ischemic heart diseases, stroke within the last 2 months, heart failure, and previous treatment with another SGLT2 inhibitor. We also excluded patients who were considered ineligible for the study by their attending physician. This study protocol was approved by the ethics committee of Ehime University of Medical School (approval no. 1604004, UMIN 000023649) and developed in accordance with the ethical guidelines of the Declaration of Helsinki.

Study Design

This was a 24-week prospective, open-label, single-arm multicenter trial. Luseogliflozin was initially administered orally in doses of 2.5 mg once daily for 24 weeks. The physician in charge could change the luseogliflozin dosage from 2.5 to 5 mg if a patient's plasma glucose control was insufficient.

Study Endpoints

The primary endpoint was improvement of HbA1c and to investigate the association between eating behavior and the change of HbA1c from baseline to 24 weeks. Secondary endpoints in this study were weight loss and to investigate to association between eating behavior and weight change from baseline to 24 weeks.

Definition of Eating Habits

Information regarding eating behaviors were determined from a self-administered questionnaire.

Subjects were considered to have skipped breakfast, engaged in bedtime snacking, eaten a late-night dinner, and eating until full if they answered "Yes" to the questions "Do you skip breakfast at least three times per week?", "Do you eat snacks after dinner at least three times per week?", "Do you eat dinner within 2 h before bedtime at least three times per week?", and "Do you tend to eat too much?", respectively. Fast eating was identified if they answered "fast" to the question "Do you think your meal-eating speed is usually rapid compared with other people's?" (from among three response options [slow, normal, and fast]). Self-reported eating speed showed a high level of agreement with eating speed reported by friends: the percentages of exact and adjoining answers (e.g., "very fast" and "fast" were regarded as agreeing) were 46% and 47%, respectively [15].

Measurements

Height was measured to the nearest millimeter using a stadiometer with the subject standing completely erect. Weight was measured with the subject wearing light clothing. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Statistical Analysis

We divided the two groups based on number of unhealthy eating behaviors: unhealthy eating behavior group (at least two unhealthy eating behaviors, $n = 16$) and healthy eating behavior group (at most one unhealthy eating behavior, $n = 13$). The primary and secondary endpoints were analyzed using Wilcoxon signed-rank test. All analyses were performed with JMP 9.4 (SAS Institute, Cary, NC, USA). The significance level (two tail) for each test was at most 0.05.

RESULTS

Subject Characteristics

Table 1 shows the characteristics of the 29 study patients. The mean age, weight, BMI, and duration of diabetes were 65.2 years, 72.9 kg, 27.2 kg/m², and 14.0 years, respectively. The mean HbA1c and fasting plasma glucose were 7.73% and 158.0 mg/dl, respectively. The

Table 1 Patient characteristics at baseline

Variable	N (%)
Age, years, mean ± SD	65.2 ± 9.4
Male gender, N (%)	17 (58.6)
Diabetes duration, years, mean ± SD	14.0 ± 8.5
Weight, kg, mean ± SD	72.2 ± 15.3
BMI, kg/m², mean ± SD	27.20 ± 4.09
Waist, cm, mean ± SD	97.5 ± 11.8
Fasting plasma glucose, mg/dl, mean ± SD	158.0 ± 38.4
HbA1c, %, mean ± SD	7.73 ± 1.17
Unhealthy eating behavior	
Eating fast (%)	15 (51.7)
Late dinner (%)	7 (24.1)
Nighttime snack (%)	7 (24.1)
Skipping breakfast (%)	3 (10.3)
Eating until full (%)	16 (55.2)
Number of unhealthy eating behaviors	
0, n (%)	6 (20.7)
1, n (%)	7 (24.1)
2 or more, n (%)	16 (55.2)

SD standard deviation, BMI body mass index

frequency of eating fast, late dinner, nighttime snack, skipping breakfast, and eating full was 51.7%, 24.1%, 24.1%, 10.3%, and 55.2%, respectively. About half of the patients had two or more unhealthy eating behaviors in this study.

Changes of Laboratory and Physical Findings After Administration of Luseogliflozin

After administration, fasting plasma glucose, HbA1c, and ALT level decreased significantly, and hematocrit and HDL-cholesterol increased significantly. Weight, BMI, and waist measurement also significantly decreased (Table 2).

Association Between Unhealthy Eating Behaviors and Change of Laboratory and Physical Findings After Administration of Luseogliflozin

The change of fasting plasma glucose and ALT was not significant in the healthy eating behavior group, while fasting plasma glucose and ALT were significantly improved in the unhealthy eating behavior group. The changes of HbA1c, hematocrit, weight, and waist measurement were significantly improved in both groups (Table 3).

Table 2 Laboratory and physical findings before and after administration of luseogliflozin for 24 weeks

	Baseline	24 weeks	p value
Laboratory findings			
Fasting plasma glucose, mg/dl, mean ± SD	158.0 ± 38.4	139.1 ± 22.0	0.006
HbA1c, %, mean ± SD	7.73 ± 1.17	7.36 ± 1.06	0.004
ALT, IU/ml, mean ± SD	28.8 ± 13.6	22.5 ± 10.3	0.006
Uric acid, mg/dl, mean ± SD	5.57 ± 1.44	5.40 ± 2.47	0.66
Creatinine, mg/dl, mean ± SD	0.81 ± 0.22	0.84 ± 0.22	0.15
Hematocrit, mean ± SD	42.2 ± 3.2	44.3 ± 3.0	0.001
BNP, ng/ml, mean ± SD	26.3 ± 35.3	23.6 ± 25.0	0.54
T-chol, mg/dl, mean ± SD	185.9 ± 31.4	181.6 ± 45.8	0.52
TG, mg/dl, mean ± SD	116.6 ± 55.3	101.9 ± 49.1	0.052
LDL-cholesterol, mg/dl, mean ± SD	104.8 ± 23.3	97.7 ± 22.6	0.051
HDL-cholesterol, mg/dl, mean ± SD	55.0 ± 12.7	58.5 ± 14.8	0.027
UACR, mg/gCr, mean ± SD	48.2 ± 67.0	42.6 ± 67.0	0.70
Physical findings			
Weight, kg, mean ± SD	72.2 ± 15.3	69.7 ± 15.1	0.001
BMI, kg/m^2, mean ± SD	27.20 ± 4.09	26.30 ± 4.13	0.001
Waist, cm, mean ± SD	97.5 ± 11.8	94.7 ± 12.9	0.001
Systolic blood pressure, mmHg, mean ± SD	134.4 ± 16.2	132.2 ± 14.7	0.41
Diastolic blood pressure, mmHg, mean ± SD	80.2 ± 10.6	80.7 ± 11.2	0.80
Pulse, beats per minute, mean ± SD	77.5 ± 13.4	75.9 ± 12.1	0.32

SD standard deviation, *ALT* aspartate aminotransferase, *TG* triglyceride, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *BNP* B-type natriuretic peptide, *UACR* urine albumin creatinine ratio, *T-chol* total cholesterol, *BMI* body mass index

Association Between Each Unhealthy Eating Behavior and Change of HbA1c

Table 4 shows the association between unhealthy behavior and change of HbA1c. In patients with fast eating behavior, HbA1c was improved significantly. In contrast, in patients with other unhealthy eating behaviors, the change of HbA1c was not significant.

Association Between Each Unhealthy Eating Behavior and Weight Change

Significant weight reduction was found regardless of fast eating behavior, nighttime snack, and eating until full. On the other hand, weight reduction was observed in the patients without late dinner and breakfast skipping behaviors (Table 5).

Table 3 Influence of unhealthy eating behaviors on laboratory and physical findings before and after administration of luseogliflozin for 24 weeks

	Baseline	24 weeks	*p* value
Fasting plasma glucose, mg/dl, mean ± SD			
0 or 1 (*n* = 13)	142.5 ± 23.6	135.8 ± 20.8	0.30
2 or more (*n* = 16)	170.5 ± 43.9	141.8 ± 23.3	0.011
HbA1c, %, mean ± SD			
0 or 1 (*n* = 13)	7.23 ± 0.66	7.02 ± 0.52	0.029
2 or more (*n* = 16)	8.14 ± 1.34	7.64 ± 1.30	0.040
ALT, IU/ml, mean ± SD			
0 or 1 (*n* = 13)	22.2 ± 10.2	18.5 ± 5.4	0.11
2 or more (*n* = 16)	34.1 ± 13.8	25.8 ± 12.2	0.009
Hematocrit, mean ± SD			
0 or 1 (*n* = 13)	40.00 ± 2.88	43.00 ± 2.42	0.001
2 or more (*n* = 16)	43.62 ± 2.67	45.28 ± 3.03	0.006
Weight, kg, mean ± SD			
0 or 1 (*n* = 13)	70.1 ± 12.3	68.2 ± 12.2	0.001
2 or more (*n* = 16)	74.0 ± 17.6	71.0 ± 17.4	0.001
Waist, cm, mean ± SD			
0 or 1 (*n* = 13)	95.7 ± 7.2	93.1 ± 8.2	0.001
2 or more (*n* = 16)	99.0 ± 14.6	96.0 ± 15.9	0.027

ALT aspartate aminotransferase, *SD* standard deviation

Relationship Between HbA1c Change and Weight Reduction

In the healthy eating group, a significant positive relationship between HbA1c change and weight reduction was found ($r = 0.600$, $p = 0.030$) (Fig. 1). In the unhealthy eating group, on the other hand, HbA1c change was not related to weight reduction ($r = 0.339$, $p = 0.20$). In sensitive analysis, a similar positive relationship between HbA1c improvement and weight reduction was shown in patients with eating full ($r = 0.504$, $p = 0.046$), and without nighttime snack ($r = 0.430$, $p = 0.046$) and late dinner ($r = 0.543$, $p = 0.009$). No relationship between HbA1c improvement and weight reduction was found regardless of eating fast or skipping breakfast.

DISCUSSION

In the present study, we found that administration of luseogliflozin led to changes in laboratory findings including HbA1c, as well as clinical findings. The effect of luseogliflozin on HbA1c levels in the unhealthy eating behaviors group might be attenuated. Significant improvement in HbA1c levels was observed in subjects with fast eating behavior, while in subjects with unhealthy behaviors the effect of luseogliflozin was attenuated. On the other

Table 4 Influence of unhealthy eating behaviors on HbA1c before and after administration of luseogliflozin for 24 weeks

Unhealthy eating behavior	HbA1c, %, mean ± SD		p value
	Baseline	24 weeks	
Eating fast			
No (n = 14)	7.21 ± 0.75	7.13 ± 0.53	0.54
Yes (n = 15)	8.22 ± 1.30	7.58 ± 1.37	0.006
Late dinner			
No (n = 22)	7.56 ± 1.10	7.25 ± 1.03	0.004
Yes (n = 7)	8.29 ± 1.30	7.71 ± 1.12	0.27
Nighttime snack			
No (n = 22)	7.48 ± 0.83	7.04 ± 0.53	0.007
Yes (n = 7)	8.52 ± 17.3	8.39 ± 1.61	0.60
Skipping breakfast			
No (n = 26)	7.70 ± 1.13	7.30 ± 1.02	0.010
Yes (n = 3)	8.03 ± 1.74	7.93 ± 1.47	0.58
Eating until full			
No (n = 13)	8.12 ± 1.46	7.58 ± 1.47	0.024
Yes (n = 16)	7.42 ± 0.78	7.19 ± 0.53	0.17

SD standard deviation

hand, the association between unhealthy eating and weight reduction was inconsistent.

This is the first study to explore the association between eating behaviors and SGLT2 inhibitor effects in patients with type 2 diabetes mellitus. Unhealthy eating behaviors might affect the onset of several chronic diseases. In particular, eating fast is closely associated with obesity [7–10] and postprandial hyperglycemia [9, 11]. In a systematic review and meta-analysis, an association between eating rate and obesity was found [10]. In a Korean cross-sectional study of 8775 adults, the percentage of high glucose and obesity in the fastest eating group (taking less than 5 mins per meal) was significantly higher than that in the slow eating rate group (taking more than 15 mins) [7]. In a US cross-sectional study of 56,865 subjects, a very strong association between eating rate and BMI was found [8]. In a Japanese cross-sectional study of 7275 individuals, eating rate was associated with obesity and waist circumference [9].

In two Japanese and one US longitudinal study, fast eating rate was associated with weight gain [9, 16, 17]. In another study, eating rate was not correlated with fasting plasma glucose level, while an inverse association between eating rate and HbA1c was found [9]. On the other hand, in an interventional study of healthy Japanese women, it was found that a fast eating rate increased fasting plasma glucose and postprandial glucose [11]. Thus, eating fast might cause weight gain and postprandial hyperglycemia. However, the effectiveness of interventions on eating rate for controlling glucose level and weight is still unclear.

In the present study, after administration of leseogliflozin, a significant improvement of HbA1c in patients with fast eating behavior was observed, while other unhealthy eating

Table 5 Influence of unhealthy eating behavior on weight before and after administration of luseogliflozin for 24 weeks

	Weight, kg, mean ± SD		p value
	Baseline	**24 weeks**	
Eating fast			
No (n = 14)	69.3 ± 12.3	67.7 ± 12.1	0.001
Yes (n = 15)	75.0 ± 17.7	71.6 ± 17.7	0.012
Late dinner			
No (n = 22)	72.0 ± 11.5	70.0 ± 12.0	0.001
Yes (n = 7)	72.7 ± 25.1	68.6 ± 23.6	0.12
Nighttime snack			
No (n = 22)	71.0 ± 11.7	68.6 ± 12.2	0.007
Yes (n = 7)	76.0 ± 24.4	73.3 ± 22.8	0.015
Skipping breakfast			
No (n = 26)	70.1 ± 11.7	67.7 ± 11.9	0.002
Yes (n = 3)	89.9 ± 32.4	87.3 ± 30.0	0.22
Eating until full			
No (n = 13)	76.1 ± 17.7	72.1 ± 16.9	0.007
Yes (n = 16)	69.0 ± 12.9	67.7 ± 13.8	0.017

SD standard deviation

behaviors attenuated the effect of luseogliflozin for HbA1c.

The underlying mechanism linking eating fast and change of HbA1c remains unclear. Eating fast has been found to be closely associated with postprandial hyperglycemia [11]. Luseogliflozin has been found to improve mainly postprandial hyperglycemia via urinary glucose excretion [18, 19]. After administration of the SGLT2 inhibitor, glucagon-like peptide 1 to glucose response to eating was enhanced [20–22]. Thus, in patients with fast eating behavior, luseogliflozin might be effective for controlling plasma glucose and weight via urinary glucose excretion, improved hyperglycemia, and enhanced GLP-1 response. However, further research regarding eating behaviors and SGLT2 inhibitors is needed.
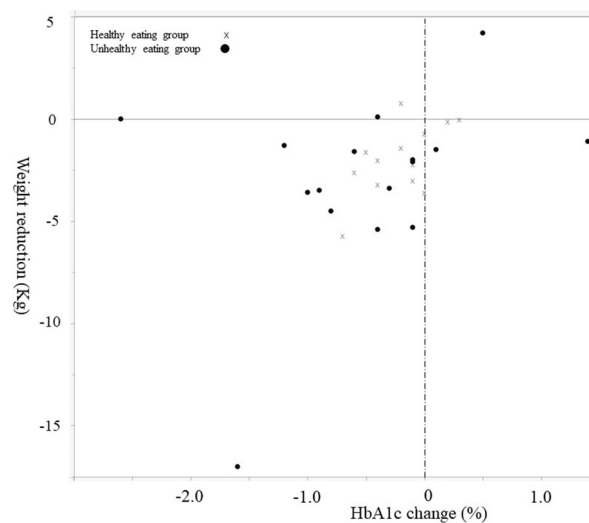
Fig. 1 Relationship between HbA1c change and weight reduction and unhealthy eating behaviors. Significant positive relationship between HbA1c change and weight reduction was found in only the healthy eating group (r = 0.600, p = 0.030). In the unhealthy eating group, on the other hand, no relationship between HbA1c change and weight reduction was found (r = 0.339, p = 0.20). (x, healthy eating group; black circle, unhealthy eating group)

Our study has several limitations. First, this was one-arm, open-label pilot study. Additionally, the sample size was too small to make firm conclusions regarding eating behavior and the effects of SGLT2 inhibitors. Thus, further large-scale studies regarding eating behavior and the effects of SGLT2 inhibitors are warranted. Second, the eating behaviors were elicited using a self-administered questionnaire. However, self-reported fast eating behavior has been validated in other studies [15]. Self-reported eating speed showed a high level of agreement with eating speed reported by friends: the percentages of exact and adjoining answers (e.g., "very fast" and "fast" were regarded as agreeing) were 46% and 47%, respectively [15]. Third, the nutrition data in this cohort were lacking. Finally, in the present study, we assessed the effect of luseogliflozin on eating behaviors and clinical parameters. It is unclear whether other SGLT 2 inhibitors have similar effects.

CONCLUSIONS

In Japanese patients with type 2 diabetes, luseogliflozin might be more effective among patients who exhibit fast eating behavior, while other unhealthy eating behaviors might weaken the effect of luseogliflozin on plasma glucose control.

Compliance with Ethics Guidelines. This study protocol was approved by the ethics committee of Ehime University of Medical School (Toon, Ehime, Japan; E-mail; rinri@m.e-hime-u.ac.jp, Approval no. 1604004), and University Hospital Medical Information Network ID: UMIN 000023649) and developed in accordance with the ethical guidelines of the Declaration of Helsinki. Patients were given a detailed description of the present study and were informed of possible risks and benefits of participation prior to providing their written informed consent and study enrollment.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion. Physical activity and good nutrition: essential elements to prevent chronic diseases and obesity 2003. Nutr Clin Care. 2003;6:135–8.

2. Maruyama K, Sato S, Ohira T, et al. The joint impact on being overweight of self reported behaviours of eating quickly and eating until full: cross sectional study. BMJ. 2008;337:a2002.

3. Ochiai H, Shirasawa T, Nanri H, et al. Eating quickly is associated with waist-to-height ratio among Japanese adolescents: a cross-sectional survey. Arch Public Health. 2016;74:18.

4. Mesas AE, Muñoz-Pareja M, López-García E, Rodríguez-Artalejo F. Selected eating behaviours and excess body weight: a systematic review. Obes Rev. 2012;13:106–35.

5. Bonnett JP, Cardel MI, Cellini J, Hu FB, Guasch-Ferré M. Breakfast skipping, body composition, and cardiometabolic risk: a systematic review and meta-analysis of randomized trial. Obesity (Silver Spring). 2020;28:1098–109.

6. Mekary RA, Giovannucci E, Willett WC, van Dam RM, Hu FB. Eating patterns and type 2 diabetes risk in men: breakfast omission, eating frequency, and snacking. Am J Clin Nutr. 2012;95:1182–9.

7. Lee KS, Kim DH, Jang LS, et al. Eating rate is associated with cardiometabolic risk factors in Korean adults. Nutr Metab Cardiovasc Dis. 2013;23:635–41.

8. Nagahama S, Kurotani K, Pham NM, et al. Self-reported eating rate and metabolic syndrome in Japanese people: cross-sectional study. BMJ Open. 2014;4:e005241.

9. Ohkuma T, Fujii H, Iwase M, et al. Impact of eating rate on obesity and cardiovascular risk factors according to glucose tolerance status: the Fukuoka Diabetes Registry and the Hisayama Study. Diabetologia. 2013;56:70–7.

10. Ohkuma T, Hirakawa Y, Nakamura U, et al. Association between eating rate and obesity: a systematic review and meta-analysis. Int J Obes (Lond). 2015;39:1589–96.

11. Saito Y, Kajiyama S, Nitta A, et al. Eating fast has a significant impact on glycemic excursion in healthy women: randomized controlled cross-over trial. Nutrients. 2012;12:2767.

12. Otsuka R, Tamakoshi K, Yatsuya H, et al. Eating fast leads to insulin resistance: findings in middle-aged Japanese men and women. Prev Med. 2008;46: 154–9.

13. Yamamoto C, Miyoshi H, Ono K, et al. Ipragliflozin effectively reduced visceral fat in Japanese patients with type 2 diabetes under adequate diet therapy. Endocr J. 2016;63:589–96.

14. Tajiri Y, Tsuruta M, Ohki T, et al. Long-term efficacy of sitagliptin for the treatment of type 2 diabetic patients in Japan. Endocr J. 2012;59:197–204.

15. Sasaki S, Katagiri A, Tsuji T, Shimoda T, Amano K. Self-reported rate of eating correlates with body mass index in 18-y-old Japanese women. Int J Obes Relat Metab Disord. 2003;27:1405–10.

16. Gerace TA, George VA. Predictors of weight increases over 7 years in fire fighters and paramedics. Prev Med. 1996;25:593–600.

17. Otsuka R, Tamakoshi K, Yatsuya H, et al. Eating fast leads to obesity: findings based on self-administered questionnaires among middle-aged Japanese men and women. J Epidemiol. 2006;16:117–24.

18. Nisumira 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;17:800–4.

19. Sumikawa Y, Omiya H, Watase H, et al. Substantial effects of luseogliflozin revealed by analyzing responses to postprandial hyperglycemia: post hoc subanalyses of a randomized controlled study. Adv Ther. 2016;33:1215–30.

20. Taskebayashi K, Hara K, Terasawa T, et al. Effect of canagliflozin on circulating active GLP-1 levels in patients with type 2 diabetes: a randomized trial. Endocr J. 2017;64:923–31.

21. 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.

22. Ueno H, Nakazato H, Ebihara E, et al. Effects of ipragliflozin on postprandial glucose metabolism and gut peptides in type 2 diabetes: a pilot study. Diabetes Ther. 2018;9:403–11.