Increased sugar intake as a form of compensatory hyperphagia in patients with type 2 diabetes under dapagliflozin treatment

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Short running title: Sugar-specific hyperphagia induced by SGLT2 inhibitors

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Key words: SGLT2; dapagliflozin; hyperphagia; BDHQ; diet history; sugar

Abbreviations: Sodium-glucose cotransporter 2, SGLT2; SGLT2 inhibitor, SGLT2i; brief-type self-administered diet history questionnaire, BDHQ; self-administered diet history questionnaire, DHQ; glucagon-like peptide-1, GLP-1; estimated glomerular filtration rate, eGFR; body mass index, BMI; blood urea nitrogen, BUN; aspartate aminotransferase, AST; alanine aminotransferase, ALT; γ-glutamyl transpeptidase, γ-GTP; high-density lipoprotein, HDL; low-density lipoprotein, LDL; standard deviation, SD; 0 month, 0M; 3 months, 3M; protein, P; fat, F; carbohydrate, C.

ABSTRACT

Aims: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) cause substantially less weight loss than would be expected based on their caloric deficits, probably due to enhanced appetite regulation known as “compensatory hyperphagia,” which occurs to offset the negative energy balance caused by increased glycosuria. We examined whether any specific nutrients contributed to the compensatory hyperphagia in diabetic patients taking SGLT2i.

Methods: Sixteen patients with type 2 diabetes were newly administered dapagliflozin 5 mg daily as the experimental SGLT2i group. Sixteen age-, sex- and BMI-matched type 2 diabetes patients not receiving dapagliflozin served as controls. A brief-type self-administered diet history questionnaire (BDHQ) was undertaken just before and 3 months after study initiation to evaluate changes of energy and nutrient intakes in each group.

Results: At 3 months, daily intakes of total calories and the proportions of the three major nutrients were not significantly increased in either group. However, daily sucrose intake was significantly increased after treatment versus the baseline value in the SGLT2i group ($p=0.003$), but not in controls. The calculated intakes of all other nutrients were not significantly changed in either group.

Conclusions: Dapagliflozin treatment specifically increased sucrose intake, which might be an ideal target for nutritional approaches to attenuate compensatory hyperphagia.

1. INTRODUCTION

Sodium-glucose cotransporter 2 (SGLT2) is expressed in the brush-borders of cells in the early proximal convoluted tubules of kidney, and is the most important mediator of glucose reabsorption from the glomerular filtrate. Patients with type 2 diabetes are known to express higher levels of SGLT2 than healthy individuals, enhancing their renal glucose uptake [1]. SGLT2 inhibitors are useful anti-diabetic agents that lower the threshold of renal glucose reabsorption and promote urinary glucose excretion, thereby reducing plasma glucose levels and reducing body weight [2].

However, patients with type 2 diabetes under SGLT2 inhibitor (SGLT2i) treatment have been shown to lose less weight than predicted by the caloric deficits related to urinary glucose excretion [3, 4]. This might be explained by the increased dietary caloric intake seen in animal models of diabetes [5]. Such increased caloric intake is known as "compensatory hyperphagia" and is assumed to be an adaptive response to calorie loss in glycosuria [5]. Dapagliflozin has been shown to dose-dependently increase food and water intake in rats and the dapagliflozin-treated rats lost more weight when hyperphagia was prohibited [5]. In diabetic patients, SGLT2i treatment was shown to induce compensatory hyperphagia based on energy balance dynamics calculated by a mathematical model [3, 4]. However, there has been no report identifying this compensatory increase of energy intake in a clinical setting. Moreover, if compensatory hyperphagia does in fact occur in diabetic patients under SGLT2i treatment, it would be useful to determine whether any specific nutrient contributes unequally to this phenomenon.

The brief-type self-administered diet history questionnaire (BDHQ), a dietary questionnaire developed for assessing dietary habits and nutrition intake in Japanese adults, has been validated and shown to be useful in evaluating the specific nutrient intake based on dietary records [6, 7]. Here, we examined calorie intake including specific nutrient intake data using the BDHQ in patients with type 2 diabetes under SGLT2i treatment.

2. METHODS

2.1. Patients

Eligible diabetic patients were Japanese adult patients age 18 to 75 years with HbA1c ≤ 10.0% under treatment with anti-diabetic agents including injections of insulin and/or glucagon-like peptide-1 (GLP-1) receptor agonists. The participants must be under stable control of diabetes for more than 3 months prior to the inclusion without changing of anti-diabetic agents. None of the participants had previously been treated with SGLT2i. Patients with type 1 diabetes, renal disorder with estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73m^2, liver disease, cardiac disease, chronic pancreatitis, history of gastrointestinal surgery, alcoholic abuse, steroid treatment, or pregnancy were excluded.

2.2. Study design

This was a single-center, open-label, prospective cohort study in Japanese patients with type 2 diabetes at Nagasaki University Hospital from December 2015 to February 2017 (UMIN-CTR, UMIN000020157).

Sixteen type 2 diabetic patients who required additional treatment to improve glycemic control in the clinical setting comprised the SGLT2i group. Sixteen age-, sex-, and body mass index (BMI)-matched type 2 diabetic patients whose treatment remained unchanged served as the control group. Baseline characteristics of both groups are shown in Table 1.

The participants in the SGLT2i group orally received dapagliflozin 5 mg once daily after breakfast. Assessments of clinical features and diet histories were studied in the SGLT2i group and in the control subjects before and 3 months after inclusion in the study (Fig. 1). The seasons of the first assessment in the control group were matched with those

in SGLT2i group to remove the potential influence of season on dietary behavior. In both groups, changes in the anti-diabetic medications during the study period were permitted only when patients developed hypoglycemia. We discontinued dapagliflozin and excluded the participant from the study if we observed the potential adverse events of dapagliflozin such as severe hypoglycemia (<40 mg/dL), severe dehydration, genital or/and urinary infection that needed a medical treatment, stroke, and myocardial infarction. The study was approved by the ethical committee of Nagasaki University Hospital. Informed consent was obtained from all participants.

2.3. Diet-history questionnaire

The participants undertook the BDHQ [6] to provide data for nutrition intake estimates. The BDHQ was developed recently by shortening the self-administered diet history questionnaire (DHQ) that had been designed to assess dietary habits in Japanese adults [8]. The DHQ has been validated using dietary records [8], 24-h urine [9], serum [10], and doubly labeled water methods [11], and has been widely used in epidemiological studies [12-16]. It should be noted that it takes 45-60 minutes to complete the DHQ. The BDHQ, on the other hand, requires only 15 minutes to complete, and is a fixed-portion questionnaire that asks for the consumption frequencies of selected 58 foods, beverages, and seasonings during the preceding month. The food and beverage items listed on the BDHQ were selected to represent foods commonly consumed in Japan, mainly from a food list used in the National Health and Nutrition Survey of Japan [6]. Mean daily intakes of total energy and 99 different nutrients can be estimated by the BDHQ. The food-group intakes and nutrient intakes estimated by the BDHQ have been correlated with an assessment based on 16-day dietary records [6], and the nutrient intakes calculated from the BDHQ have equivalent validity to those from the DHQ regardless of the season or region of Japan [7].

2.4. Study assessments

The primary endpoints were any changes in daily intake of total energy or the amount or energy ratio of any nutrient between baseline and 3 months after starting the study in each group. Other endpoints were any changes of clinical features including body weight, BMI, systolic or diastolic blood pressure, or levels of hematocrit, HbA1c, blood urea nitrogen (BUN), creatinine, eGFR, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP), triglyceride, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, albuminuria, or glycosuria.

2.5. Statistical analysis

The results are given as means ± standard deviations (SDs), unless otherwise indicated. The Wilcoxon signed-rank test was used to test differences of intakes of nutrients or laboratory data between baseline and post-treatment in each group. Statistical analysis was carried out using the statistical software JMP pro version 11.2 (SAS Institute, Cary, NC, USA). P-values less than 0.05 were considered significant.

3. RESULTS

Table 1 represents the baseline characteristics of the subjects with type 2 diabetes who participated in the study. None of the parameters except for the HbA1c levels were significantly different between the SGLT2i group and control group. The dose of insulin or sulfonylurea was decreased when starting dapagliflozin to avoid hypoglycemia in 4 of 10 patients treated with insulin and 3 of 6 patients treated with sulfonylurea in the SGLT2i group. All participants in the two groups completed the study without any adverse events

including hypoglycemia.

Changes of body weight, BMI, blood pressure, and laboratory data between baseline (0M) and 3 months after starting dapagliflozin (3M) in both groups are shown in Table 2. In the SGLT2i group, the body weight, BMI, and levels of serum γ-GTP were significantly decreased, and the hematocrit levels and urinary glucose excretion at 3M were significantly increased compared to those at 0M. Meanwhile, there was no significant change in those parameters between 0M and 3M in the control group.

The baseline daily intakes of total energy, protein (P), fat (F), carbohydrate (C), and the energy ratio of the three major nutrients (P: F: C) were not significantly different between the SGLT2i group and control group (Fig. 2A-2E). The baseline daily intakes of the other 96 nutrients, including the intakes of 10 minerals, 20 vitamins, and 38 saturated acids, calculated from the first BDHQ were not significantly different between the SGLT2i and control groups (Suppl. Table 1). The daily intakes of total energy and each of the three major nutrients at 3M tended to be increased compared to those at 0M in the SGLT2i group, but the differences were not statistically significant. When the daily intake of sucrose was calculated from the total intake of sucrose contained in drinks, ready-made sweets and cooked foods [6], sucrose intake was increased approximately 1.6 times after dapagliflozin treatment than that at baseline in the SGLT2i group (10.6 ± 6.9 vs. 7.4 ± 4.8 g/day, p=0.003) (Fig. 2G). The intakes of the other 95 nutrients including salt were not changed significantly from baseline in the SGLT2i group (Fig. 2F, Suppl. Table 1). In the control group, none of the nutrient intakes changed significantly between the first (0M) and second (3M) BDHQ assessment (Suppl. Table 1).

Since GLP-1 receptor agonists (GLP-1RA) have negative effects on appetite and gastric emptying, we studied the changes in daily intakes of nutrients excluding 11 patients on GLP-1RA. The daily intake of sucrose at 3M was also significantly increased from the baseline in the SGLT2i group (n=9), but not in the control group (n=12) (Suppl. Table 2).

We also examined the difference in sucrose intake before and after adding dapagliflozin between the patients who were under treatment GLP-1RA and those who were not. Sucrose intake was elevated significantly after dapagliflozin treatment in patients without GLP-1RA treatment (n=9), but not in those who were on GLP-1RA (n=7) (Fig. 3).

4. DISCUSSION

A previous study showed that SGLT2 inhibitors caused continuous elevated excretion of glucose in urine in diabetic patients over long-term (>90 weeks) treatment [3]. However, weight loss seen in patients under SGLT2 inhibitors was remarkably less than might be expected from the energy loss typically caused by glycosuria [3, 17]. Several studies using rodent models confirmed that the discrepancy between expected and observed weight loss is attributable to an increase in energy intake [5, 18, 19]. The increase in dietary calorie intake (compensatory hyperphagia) has been considered to be an adaptive response to the calorie loss associated with glycosuria [3].

In the present study, we showed that dapagliflozin reduced body weight and improved liver dysfunction in patients with diabetes (Table 2), which agreed with the findings of a previous study [20-22]. We also observed that the hematocrit levels increased significantly after dapagliflozin treatment (Table 2), as previously reported [23, 24]. The increase in the hematocrit is generally interpreted as a sign of hemoconcentration due to the diuretic effect of SGLT2 inhibitors but was recently suggested to be a result of enhanced erythropoiesis [25].

A previous study in patients with type 1 diabetes treated with empagliflozin for 8 weeks demonstrated increased consumption of carbohydrates, averaging up to 50 g/day, possibly due to compensatory hyperphagia [26]. In this study we prospectively examined

whether compensatory hyperphagia occurred and whether any specific nutrients were preferred in the compensatory hyperphagia in type 2 diabetes patients after administration of dapagliflozin. Our study showed that sucrose was consumed 1.6 times more than at baseline after dapagliflozin treatment when estimated using the BDHQ (Fig. 2G). We did not see significantly increased intake of carbohydrates or any other nutrient studied. Thus, we suggest that sugar craving may be a phenomenon which, at least partially, explains the compensatory hyperphagia in response to increased glycosuria. Meanwhile, no salt craving was observed in patients treated with dapagliflozin (Fig. 2F) even though SGLT2 inhibitors also increase sodium excretion.

It has been shown that the compensatory hyperphagia seen in diabetic mice following dapagliflozin treatment was attenuated when exenatide administration was added [19]. This is consistent with our data since the daily intake especially in sucrose was not increased in the patients under GLP-1RA treatment after adding dapagliflozin, but increased in the patients without GLP-1RA treatment. Similarly, the discrepancy between expected and observed weight loss after dapagliflozin treatment was significantly less in type 2 diabetes patients on chronic metformin therapy than in drug-naïve patients [3]. These phenomena might be explained by the anorectic effects of GLP-1 receptor agonists and metformin. The co-administration of a GLP-1 receptor agonist or metformin might attenuate the central hyperphagic drive that occurs with SGLT2 inhibitor therapy [27].

Regarding the mechanism for compensatory hyperphagia, including the sugar craving associated with SGLT2 inhibitors, there are several possibilities. SGLT2 inhibitors have been shown to markedly increase hepatic glucose production, leading to a reduction in plasma insulin and to a marked increase in plasma glucagon concentration [28]. It has also been shown that the rapid increase in glucose production occurs before the plasma concentration of glucagon can increase sufficiently. DeFronzo et al. postulated that the rapid increase in hepatic glucose production following administration of SGLT2 inhibitors

could be explained either by direct neural connections from the kidney to the liver or an indirect connection via the central nervous system [29]. It has been shown that small amounts of SGLT2 transporters are present in the brain [30]; however, their function remains unknown. It is also unknown whether SGLT2 inhibitors pass the blood-brain barrier and exert their effects in the central nervous system. It is intriguing to consider whether SGLT2 in the brain regulates the desire for sugar. Further study is needed to clarify the mechanisms whereby the increased glycosuria signals the central nervous system to alter appetite regulation, especially that for sugar.

The present study has certain limitations. First, the number of participants was small and the study was not a double-blind randomized controlled trial. The difference in HbA1c levels and anti-diabetic agents at baseline between groups might have contributed to appetite of the participants. Second, the assessment of sucrose intake calculated by the BDHQ may not be fully valid because the detail algorithms used to calculate the intakes of food, beverage and seasonings from the BDHQ have not been published. Third, we did not observe a significant increase in the total calorie intake after dapagliflozin treatment. However, we still believe that the increased sugar consumption associated with dapagliflozin treatment is a part of compensatory “hyperphagia”.

In summary, we demonstrated the dapagliflozin treatment specifically increased sucrose intake in patients with type 2 diabetes. This response might be a form of compensatory hyperphagia to offset the negative energy balance induced by the increase of urinary glucose excretion. Clinicians should take this into consideration when administrating SGLT2 inhibitors. Our study suggests clinicians as well as patients starting SGLT2 inhibitors should be aware of the potential for compensatory hyperphagia including sugar craving and implement strategies to maximize the anti-diabetic effects of SGLT2 inhibitors.

DISCLOSURE

The authors declare no conflict of interest.

ACKNOWLRDGEMENTS

We thank Mr. Shuntaro Sato, an assistant professor at Clinical research center of Nagasaki University Hospital, for his helpful suggestions in the statistical analyses.

FIGURE LEGENDS

Fig. 1. The study design. Japanese individuals with type 2 diabetes treated with anti-diabetic agents were recruited. Sixteen patients who required additional treatment to improve glycemic control in the clinical setting were newly administered an SGLT2 inhibitor and comprised the SGLT2i group. Age-, sex-, and body mass index (BMI)-matched patients whose diabetic treatment did not change comprised the control group.

IC, informed consent; BDHQ, brief-type self-administered diet history questionnaire. 0M, 0 month; 3M, 3 months.

Fig. 2. The changes of daily intakes of total energy and nutrients between 0 and 3 months in the study. Box-and-whisker plots are shown. The symbol × indicates mean values. 0M, 0 month; 3M, 3 months; SGLT2i, SGLT2i group (n=16); CTRL, control group (n=16); P, protein; F, fat; C, carbohydrate. *, $p<0.01$ between 0M and 3M in the SGLT2i group.

Fig. 3. The differences in daily nutrients intakes, HbA1c levels and body weight before (0M) and after adding dapagliflozin (3M) in the patients who had been treated with GLP-1RA or in those without. Box-and-whisker plots are shown. The symbol × indicates mean values. 0M, 0 month; 3M, 3 months; GLP-1RA(-), the patients of SGLT2i group who had not been treated with GLP-1RA (n=9); GLP-1RA(+), the patients of SGLT2i group who had been under GLP-1RA treatment (n=7). *, $p<0.05$ between 0M and 3M.

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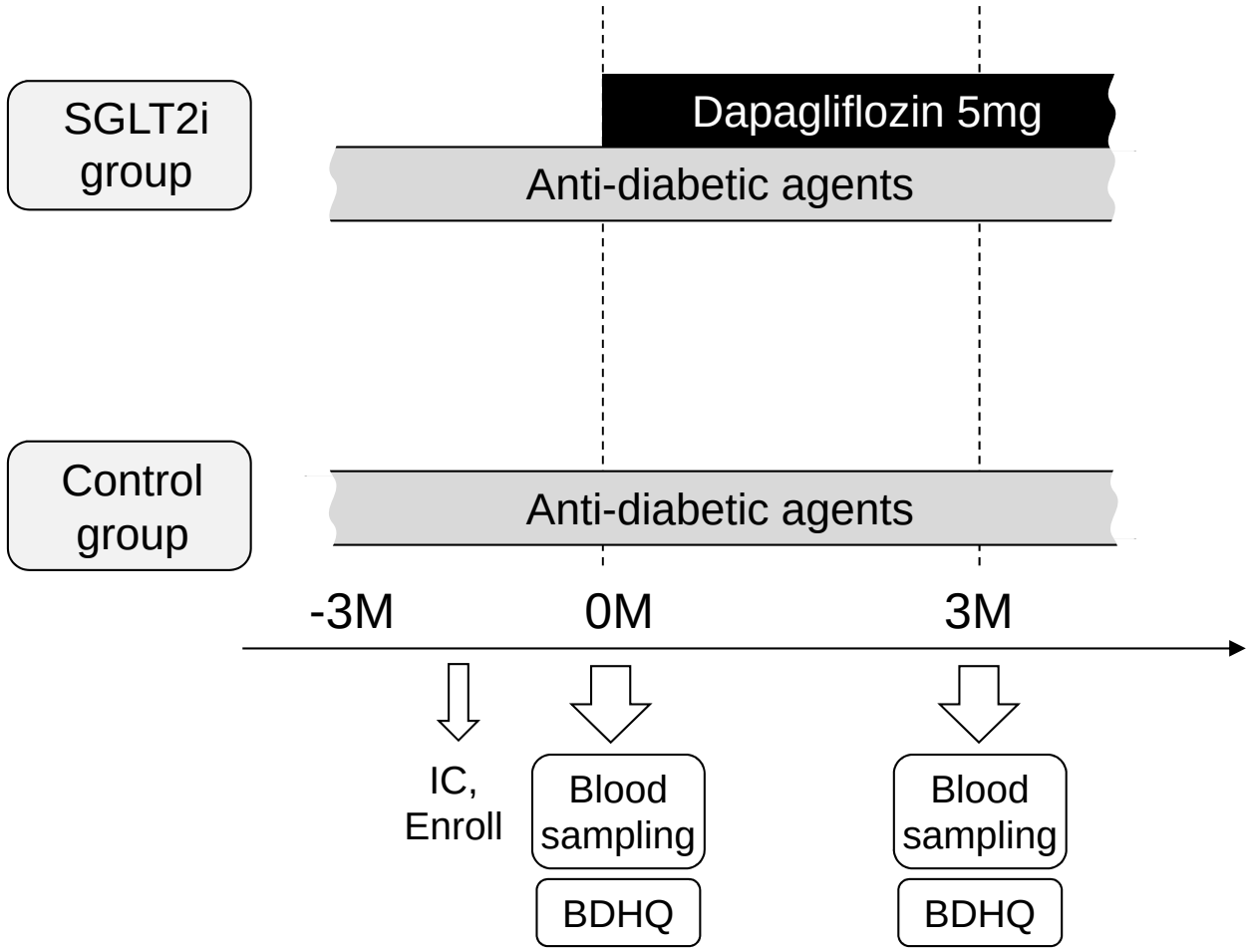
Fig. 1


SGLT2i group
Dapagliflozin 5mg
Anti-diabetic agents
Control group
Anti-diabetic agents
-3M
0M
3M
IC, Enroll
Blood sampling
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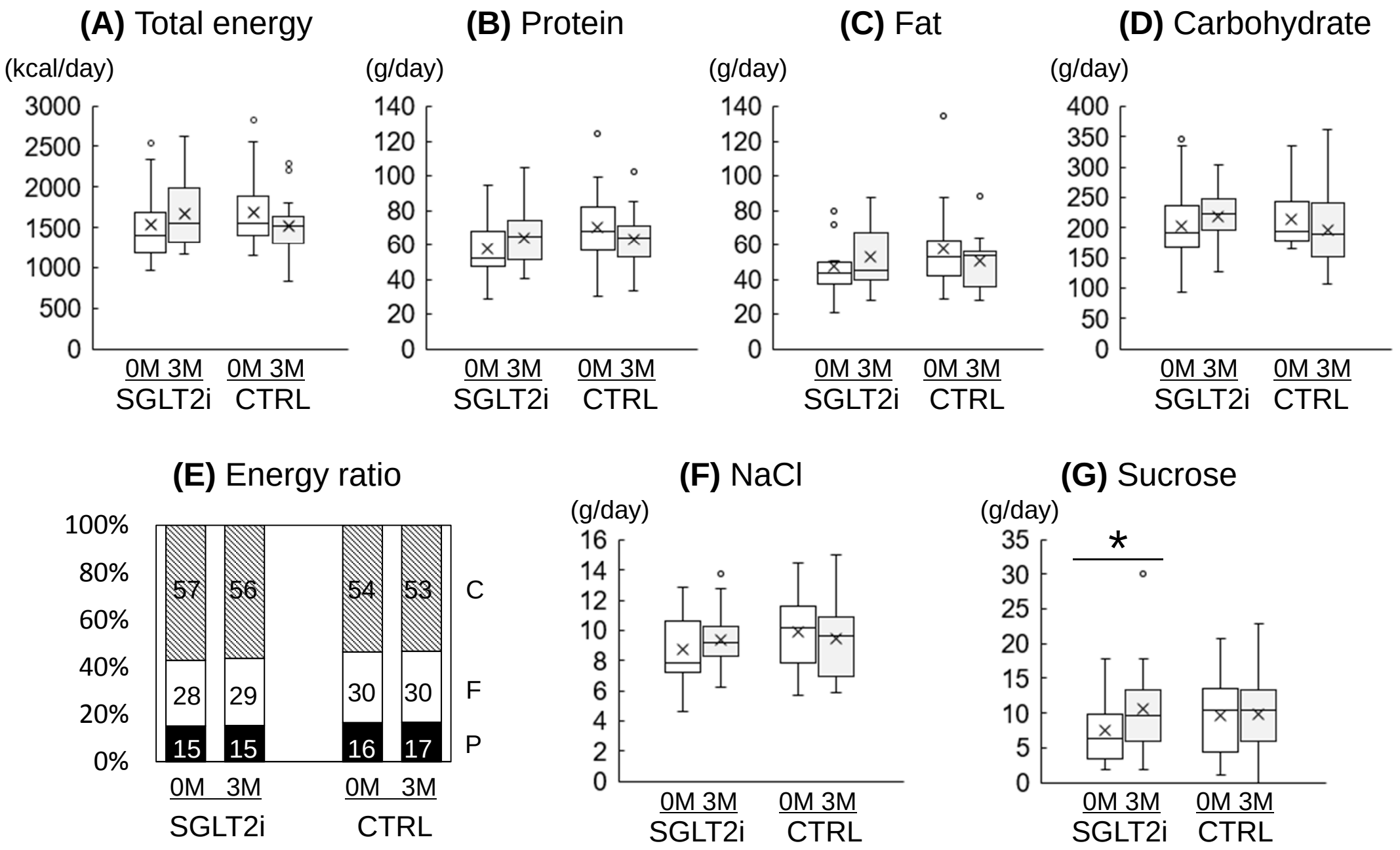
Blood sampling
BDHQ

Fig. 2


(A) Total energy
(kcal/day)
3000
2500
2000
1500
1000
500
0
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SGLT2i CTRL
(B) Protein
(g/day)
140
120
100
80
60
40
20
0
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SGLT2i CTRL
(C) Fat
(g/day)
140
120
100
80
60
40
20
0
0M 3M 0M 3M
SGLT2i CTRL
(D) Carbohydrate
(g/day)
400
350
300
250
200
150
100
50
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0M 3M 0M 3M
SGLT2i CTRL
(E) Energy ratio
100%
80%
60%
40%
20%
0%
57 56 54 53
28 29 30 30
15 15 16 17
C
F
P
0M 3M 0M 3M
SGLT2i CTRL
(F) NaCl
(g/day)
16
14
12
10
8
6
4
2
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0M 3M 0M 3M
SGLT2i CTRL
(G) Sucrose
(g/day)
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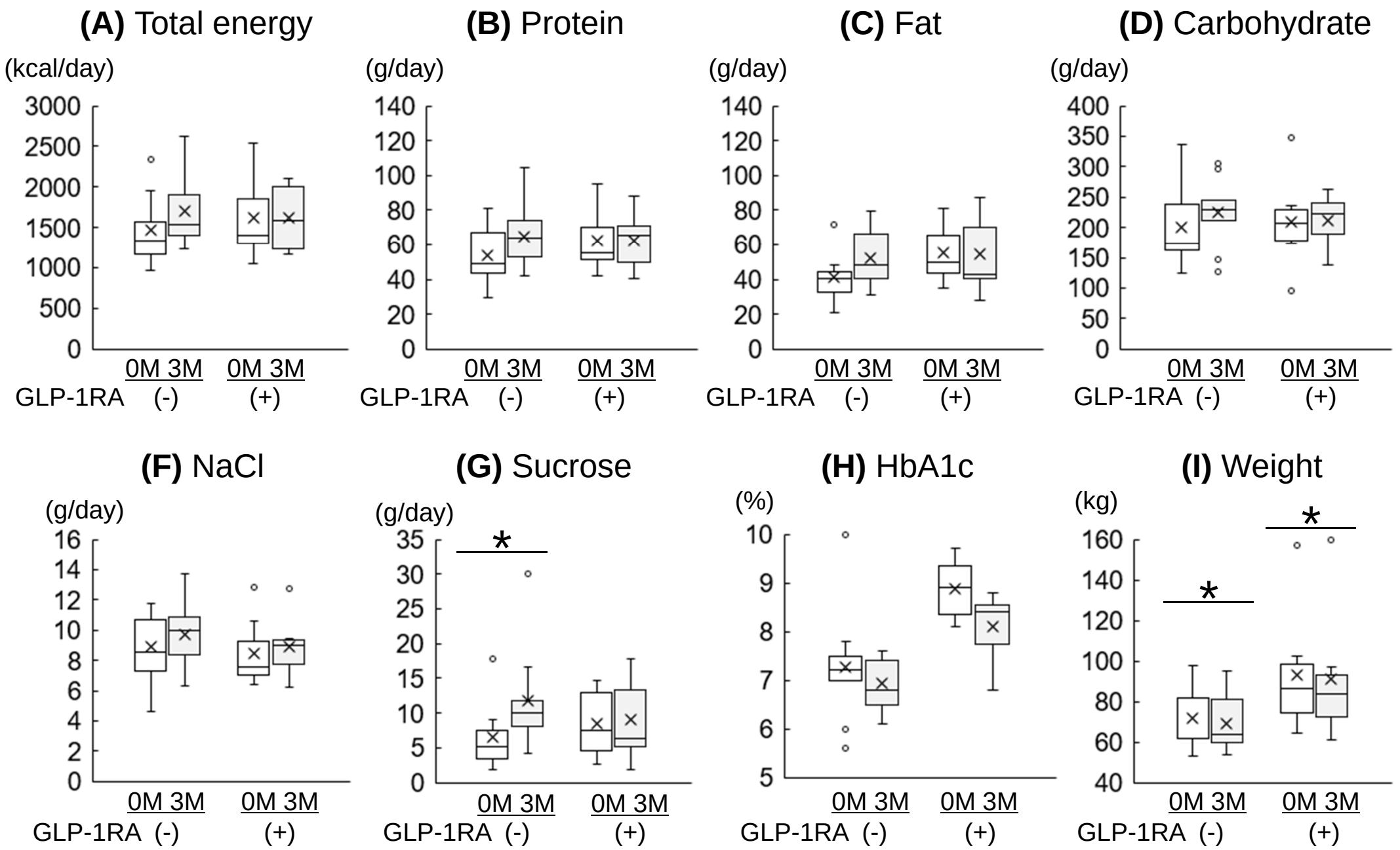
SGLT2i CTRL

Fig. 3


(A) Total energy
(kcal/day)
3000
2500
2000
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GLP-1RA (-) (+)
(B) Protein
(g/day)
140
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GLP-1RA (-) (+)
(C) Fat
(g/day)
140
120
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GLP-1RA (-) (+)
(D) Carbohydrate
(g/day)
400
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GLP-1RA (-) (+)
(F) NaCl
(g/day)
16
14
12
10
8
6
4
2
0
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GLP-1RA (-) (+)
(G) Sucrose
(g/day)
35
30
25
20
15
10
5
0
*
0M 3M 0M 3M
GLP-1RA (-) (+)
(H) HbA1c
(%)
10
9
8
7
6
5
0M 3M 0M 3M
GLP-1RA (-) (+)
(I) Weight
(kg)
160
140
120
100
80
60
40
*
*
0M 3M 0M 3M
GLP-1RA (-) (+)

Table 1. Baseline features of participants

	SGLT2i group (n=16)	**Control group** (n=16)	P-value
Age (years)	51.2 ± 13.9	52.3 ± 12.9	0.81
Sex (Male:Female)	6:10	6:10	----
Height (cm)	161.0 ± 10.6	159.6 ± 8.6	0.67
Body weight (kg)	81.3 ± 25.5	74.5 ± 15.6	0.37
BMI (kg/m^2)	31.0 ± 7.2	29.2 ± 4.8	0.40
HbA1c (%)	7.97 ± 1.29	6.50 ± 0.69	<0.001
eGFR ($mL/min/1.73m^2$)	83.1 ± 27.1	79.8 ± 22.9	0.72
Albuminuria (mg/gCr)	246.2 ± 528.0	47.6 ± 95.1	0.15
Pharmacological treatment (n)			
Insulin	10	4	.
GLP-1 receptor agonist	7	4	
Metformin	15	12	
Sulfonylurea	6	0	
Glinide	0	0	.
DPP4 inhibitor	7	6	
Pioglitazone	1	1	
α-GI	0	1	
Season undertaking first BDHQ (n)			
Spring/Summer/Autumn/Winter	2/3/7/4	2/3/7/4	

SGLT2i, SGLT2 inhibitor; BMI, body mass index; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; DPP4, dipeptidyl peptidase-4; α-GI, α-glucosidase inhibitor; BDHQ, brief-type self-administered diet history questionnaire.

Table 2. The changes in weight, BMI, blood pressure, and laboratory data between 0 and 3 months.

	SGLT2i group (n=16)			Control group (n=16)		
	0M	3M	p-value	0M	3M	p-value
Body weight (kg)	81.3 ± 25.5	78.7 ± 25.7	0.007	74.5 ± 15.6	74.3 ± 16.1	0.55
BMI (kg/m^2)	31.0 ± 7.2	30.2 ± 7.1	0.011	29.2 ± 4.8	29.1 ± 4.9	0.41
Systolic BP (mmHg)	134 ± 10	131 ± 15	0.27	132 ± 18	135 ± 20	0.23
Diastolic BP (mmHg)	76 ± 9	74 ± 11	0.15	77 ± 11	77 ± 16	0.85
Hematocrit (%)	41.3 ± 3.1	43.3 ± 3.3	<0.001	39.9 ± 4.4	41.1 ± 4.1	0.069
HbA1c (%)	8.0 ± 1.3	7.4 ± 0.9	0.090	6.5 ± 0.7	6.9 ± 1.0	0.061
BUN (mg/dL)	13.1 ± 3.1	13.9 ± 3.1	0.40	15.0 ± 6.8	15.4 ± 4.3	0.70
Creatinine (mg/dL)	0.70 ± 0.20	0.71 ± 0.20	0.50	0.72 ± 0.22	0.74 ± 0.21	0.68
eGFR (mL/min/1.73m^2)	83 ± 27	81 ± 21	0.48	80 ± 23	79 ± 25	0.74
AST (IU/L)	30 ± 18	25 ± 14	0.19	21 ± 10	24 ± 9	0.20
ALT (IU/L)	41 ± 35	28 ± 15	0.067	30 ± 24	38 ± 32	0.054
γ-GTP (IU/L)	46 ± 36	32 ± 18	0.015	30 ± 25	29 ± 20	0.49
HDL-C (mg/dL)	49 ± 10	51 ± 13	0.20	54 ± 14	53 ± 11	0.67
LDL-C (mg/dL)	108 ± 27	104 ± 28	0.45	103 ± 37	104 ± 42	0.68
Triglyceride (mg/dL)	174 ± 112	168 ± 176	0.77	149 ± 81	137 ± 50	0.52
Albuminuria (mg/gCr)	246 ± 528	179 ± 237	0.42	48 ± 95	N.D.	----
Glycosuria (g/gCr)	2 ± 4	60 ± 27	<0.001	N.D.	N.D.	----

SGLT2i, SGLT2 inhibitor; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; N.D., not determined.

Supplementary Table 1. The changes of daily intakes of nutrients estimated using a BDHQ between 0 and 3 months in all the participants (n=32).

	SGLT2i group (n=16)			Control group (n=16)		
	0M	3M	P	0M	3M	P
Total energy (kcal)	1531 ± 471	1669 ± 432	NS	1692 ± 450	1522 ± 372	NS
Carbohydrate (g)	204 ± 68	219 ± 52	NS	215 ± 49	196 ± 64	NS
Total protein (g)	57 ± 18	64 ± 18	NS	71 ± 24	64 ± 18	NS
Animal protein (g)	35 ± 12	39 ± 14	NS	45 ± 21	39 ± 16	NS
Vegetable protein (g)	23 ± 7	24 ± 7	NS	25 ± 4	24 ± 6	NS
Total fat (g)	47 ± 17	53 ± 19	NS	58 ± 26	50 ± 16	NS
Animal fat (g)	21 ± 9	24 ± 8	NS	28 ± 15	24 ± 11	NS
Vegetable fat (g)	26 ± 10	29 ± 13	NS	30 ± 12	26 ± 8	NS
Water (g)	1558 ± 409	1628 ± 375	NS	1689 ± 398	1689 ± 470	NS
Ash (g)	14.6 ± 3.7	16.0 ± 3.5	NS	17.5 ± 4.5	16.6 ± 4.3	NS
Sodium (g)	3.5 ± 0.9	3.7 ± 0.8	NS	3.9 ± 1.0	3.7 ± 1.1	NS
Potassium (g)	2.0 ± 0.6	2.2 ± 0.6	NS	2.5 ± 0.7	2.3 ± 0.6	NS
Calcium (mg)	372 ± 128	417 ± 143	NS	544 ± 180	503 ± 172	NS
Magnesium (mg)	193 ± 58	214 ± 56	NS	236 ± 62	222 ± 60	NS
Phosphorus (mg)	822 ± 254	924 ± 253	NS	1050 ± 335	960 ± 291	NS
Iron (mg)	6.2 ± 1.9	7.0 ± 1.9	NS	7.4 ± 1.8	7.0 ± 1.8	NS
Zinc (mg)	6.7 ± 2.0	7.7 ± 2.0	NS	8.1 ± 2.9	7.3 ± 2.0	NS
Copper (mg)	0.9 ± 0.3	1.0 ± 0.3	NS	1.1 ± 0.2	1.0 ± 0.3	NS
Manganese (mg)	3.2 ± 1.1	3.3 ± 1.1	NS	3.2 ± 0.9	3.2 ± 1.1	NS
Retinol (μg)	233 ± 128	316 ± 190	NS	434 ± 304	310 ± 178	NS
β-carotene (mg)	2.9 ± 1.6	3.3 ± 1.5	NS	3.0 ± 1.4	2.9 ± 1.5	NS
Vitamin A (μg)	478 ± 181	593 ± 232	NS	686 ± 298	556 ± 241	NS
Vitamin D (μg)	12.4 ± 5.0	11.9 ± 6.9	NS	14.2 ± 6.7	13.2 ± 6.8	NS
α-tocopherol (mg)	6.2 ± 2.0	7.1 ± 2.2	NS	7.7 ± 2.2	6.9 ± 2.2	NS
Vitamin K (μg)	219 ± 92	237 ± 100	NS	242 ± 126	239 ± 103	NS
Vitamin B1 (mg)	0.6 ± 0.2	0.7 ± 0.2	NS	0.8 ± 0.3	0.7 ± 0.2	NS
Vitamin B2 (mg)	1.0 ± 0.3	1.1 ± 0.3	NS	1.3 ± 0.4	1.2 ± 0.3	NS
Niacin (mg)	15.1 ± 4.0	16.5 ± 5.0	NS	18.1 ± 7.0	16.3 ± 4.6	NS
Vitamin B6 (mg)	1.1 ± 0.3	1.2 ± 0.3	NS	1.3 ± 0.4	1.2 ± 0.3	NS
Vitamin B12 (μg)	8.9 ± 3.6	8.5 ± 4.3	NS	10.3 ± 4.0	9.0 ± 4.1	NS
Folate (μg)	268 ± 73	309 ± 95	NS	327 ± 83	322 ± 98	NS
Pantothenic acid (mg)	5.2 ± 1.6	5.8 ± 1.2	NS	6.5 ± 2.2	5.8 ± 1.5	NS
Vitamin C (mg)	102 ± 40	114 ± 43	NS	126 ± 58	126 ± 53	NS
α-carotene (μg)	386 ± 331	428 ± 318	NS	339 ± 166	301 ± 219	NS
β-carotene (mg)	2.5 ± 1.3	2.9 ± 1.4	NS	2.6 ± 1.2	2.6 ± 1.4	NS
Cryptoxanthin (μg)	386 ± 461	327 ± 276	NS	419 ± 475	355 ± 380	NS

β-tocopherol (μg)	334 ± 109	365 ± 128	NS	374 ± 163	329 ± 111	NS
γ-tocopherol (mg)	12.0 ± 4.3	14.0 ± 6.0	NS	14.2 ± 6.5	12.1 ± 4.7	NS
δ-tocopherol (mg)	2.8 ± 1.0	3.1 ± 1.2	NS	3.2 ± 1.3	2.7 ± 1.0	NS
Saturated fat (g)	12.0 ± 4.8	13.2 ± 4.5	NS	15.4 ± 8.3	13.3 ± 4.7	NS
Monounsaturated fat (g)	17.5 ± 6.6	20.0 ± 7.6	NS	21.2 ± 10.1	18.4 ± 5.7	NS
Polyunsaturated fat (g)	11.9 ± 4.0	13.4 ± 5.2	NS	14.0 ± 5.6	12.2 ± 4.3	NS
Cholesterol (mg)	294 ± 148	354 ± 125	NS	363 ± 134	358 ± 143	NS
Total dietary fiber (g)	9.3 ± 2.4	10.7 ± 3.0	NS	10.6 ± 2.6	10.4 ± 3.3	NS
Soluble dietary fiber (g)	2.3 ± 0.7	2.7 ± 0.8	NS	2.7 ± 0.7	2.6 ± 0.8	NS
Insoluble dietary fiber (g)	6.7 ± 1.6	7.6 ± 2.1	NS	7.7 ± 1.9	7.5 ± 2.4	NS
Salt (g)	8.7 ± 2.3	9.3 ± 2.1	NS	10.0 ± 2.6	9.4 ± 2.7	NS
Sucrose (g)	7.4 ± 4.8	10.6 ± 6.9	0.003	9.7 ± 6.2	9.8 ± 5.9	NS
Alcohol (g)	5.1 ± 10.7	5.2 ± 12.1	NS	1.3 ± 4.7	2.0 ± 6.0	NS
Daidzein (mg)	9.0 ± 6.1	9.2 ± 5.5	NS	9.7 ± 5.9	8.8 ± 4.8	NS
Genistein (mg)	15.3 ± 10.3	15.8 ± 9.4	NS	16.5 ± 10.0	15.1 ± 8.2	NS
n-3 polyunsaturated fat (g)	2.5 ± 0.9	2.6 ± 1.1	NS	2.8 ± 0.9	2.5 ± 0.9	NS
n-6 polyunsaturated fat (g)	9.3 ± 3.3	10.7 ± 4.1	NS	11.1 ± 4.9	9.6 ± 3.5	NS
Butyric acid (mg)	116 ± 75	124 ± 98	NS	203 ± 150	165 ± 104	NS
Caproic acid (mg)	72 ± 46	76 ± 63	NS	131 ± 102	104 ± 70	NS
Caprylic acid (mg)	93 ± 68	78 ± 56	NS	133 ± 125	95 ± 77	NS
Capric acid (mg)	136 ± 86	129 ± 92	NS	215 ± 178	165 ± 112	NS
Decenoic acid (mg)	9.8 ± 6.1	10.2 ± 8.0	NS	17.6 ± 13.6	13.8 ± 9.3	NS
Lauric acid (mg)	402 ± 314	320 ± 214	NS	426 ± 520	362 ± 319	NS
Myristic acid (mg)	897 ± 415	887 ± 431	NS	1221 ± 740	1014 ± 504	NS
Myristoleic acid (mg)	66 ± 30	77 ± 31	NS	100 ± 72	81 ± 37	NS
Pentadecanoic acid (mg)	81 ± 35	85 ± 41	NS	113 ± 61	98 ± 45	NS
Pentadecenoic acid (mg)	0.0 ± 0.0	0.0 ± 0.0	NS	0.0 ± 0.0	0.0 ± 0.0	NS
Palmitic acid (g)	7.1 ± 2.7	8.0 ± 2.6	NS	9.0 ± 4.5	7.9 ± 2.65	NS
Palmitoleic acid (mg)	739 ± 265	824 ± 291	NS	888 ± 427	792 ± 287	NS
Hexadecatrienoic acid (mg)	9.2 ± 4.7	9.4 ± 4.8	NS	9.6 ± 5.5	11.0 ± 5.6	NS
Margaric acid (mg)	114 ± 44	125 ± 48	NS	144 ± 70	126 ± 48	NS
Heptadecenoic acid (mg)	84 ± 31	92 ± 35	NS	103 ± 54	89 ± 35	NS
Stearic acid (g)	2.6 ± 1.0	3.0 ± 1.0	NS	3.3 ± 1.8	2.9 ± 9.7	NS
Oleic acid (g)	15.7 ± 6.0	18.2 ± 7.0	NS	19.2 ± 9.5	16.6 ± 5.1	NS
Linoleic acid (g)	9.0 ± 3.2	10.4 ± 4.0	NS	10.8 ± 4.8	9.3 ± 3.4	NS
α-linolenic acid (mg)	1.5 ± 0.6	1.7 ± 0.8	NS	1.8 ± 0.8	1.5 ± 0.6	NS
γ-linolenic acid (mg)	6.8 ± 4.3	5.2 ± 2.8	NS	7.2 ± 4.7	6.0 ± 3.7	NS
Parinaric acid (mg)	80 ± 44	68 ± 40	NS	74 ± 34	76 ± 43	NS
Arachidic acid (mg)	142 ± 52	158 ± 66	NS	170 ± 76	145 ± 45	NS
Eicosenoic acid (mg)	483 ± 215	470 ± 219	NS	498 ± 160	477 ± 218	NS

Eicosadienoic acid (mg)	42 ± 17	48 ± 19	NS	50 ± 27	46 ± 18	NS
Eicosatrienoic acid (mg)	27 ± 10	30 ± 10	NS	33 ± 17	29 ± 11	NS
Eicosatetraenoic acid (mg)	31 ± 16	26 ± 15	NS	30 ± 13	29 ± 17	NS
Arachidonic acid (mg)	146 ± 62	165 ± 53	NS	169 ± 63	162 ± 63	NS
Eicosapentaenoic acid (mg)	301 ± 147	264 ± 158	NS	307 ± 138	298 ± 156	NS
Behenic acid (mg)	75 ± 147	84 ± 37	NS	88 ± 38	75 ± 26	NS
Docosenoic acid (mg)	335 ± 217	276 ± 177	NS	296 ± 155	311 ± 217	NS
Docosadienoic acid (mg)	0.0 ± 0.0	0.0 ± 0.0	NS	0.0 ± 0.0	0.0 ± 0.0	NS
Docosapentaenoic acid (n-3) (mg)	90 ± 42	81 ± 43	NS	91 ± 35	88 ± 45	NS
Docosapentaenoic acid (n-6) (mg)	7.7 ± 4.4	7.1 ± 3.9	NS	7.6 ± 3.7	8.1 ± 4.4	NS
Docosahexaenoic acid (mg)	500 ± 234	457 ± 244	NS	518 ± 214	506 ± 250	NS
Lignoceric acid (mg)	33 ± 13	37 ± 17	NS	38 ± 18	32 ± 10	NS
Tetracosenoic acid (mg)	52 ± 23	46 ± 24	NS	50 ± 16	47 ± 21	NS
Enanthic acid (mg)	0.5 ± 0.5	0.7 ± 0.7	NS	1.1 ± 0.9	0.9 ± 0.7	NS
Tridecanoic acid (mg)	1.3 ± 1.5	1.9 ± 2.1	NS	3.3 ± 2.6	2.7 ± 2.2	NS
Pentadecanoic acid (mg)	16.3 ± 10.6	17.5 ± 14.2	NS	29.6 ± 22.1	23.9 ± 15.5	NS
Palmitic acid (mg)	8.2 ± 5.3	8.7 ± 7.1	NS	14.7 ± 11.1	11.8 ± 7.8	NS
Margaric acid (mg)	17.0 ± 10.8	17.7 ± 13.9	NS	29.6 ± 22.3	23.8 ± 15.2	NS
Hexadecadienoic acid (mg)	9.7 ± 5.7	9.3 ± 5.8	NS	10.2 ± 5.4	11.4 ± 6.8	NS
Hexadecatetraenoic acid (mg)	8.3 ± 5.3	7.5 ± 4.7	NS	8.6 ± 5.2	9.3 ± 6.2	NS
Henicosapentaenoic acid (mg)	8.1 ± 5.2	7.2 ± 4.5	NS	8.0 ± 4.9	8.7 ± 5.9	NS
Docosatetraenoic acid (mg)	5.4 ± 3.1	5.8 ± 2.2	NS	5.4 ± 2.1	6.1 ± 3.1	NS

SGLT2i, SGLT2 inhibitor; 0M, 0 month (baseline); 3M, 3 months after starting dapagliflozin; P, p-value between 0M and 3M; NS, not significant.

Supplementary Table 2. The changes of parameters and daily intakes of nutrients between 0 and 3 months in the patients who had not been treated with GLP-1RA (n=21).

	SGLT2i group (n=9)			Control group (n=12)		
	0M	3M	P	0M	3M	P
Age (years)	55.8 ± 11.0	----	----	51.1 ± 12.1	----	----
Sex (Male:Female)	4:5	----	----	4:8	----	----
Height (cm)	160.0 ± 11.6	----	----	159.3 ± 9.5	----	----
Body weight (kg)	71.9 ± 16.4	69.4 ± 14.3	0.043	76.2 ± 17.7	76.3 ± 18.2	NS
BMI (kg/m^2)	27.9 ± 4.5	27.1 ± 4.1	NS	29.9 ± 5.3	29.9 ± 5.4	NS
Systolic BP (mmHg)	135 ± 10	126 ± 13	0.023	135 ± 20	138 ± 21	NS
Diastolic BP (mmHg)	79 ± 11	74 ± 10	NS	80 ± 11	80 ± 16	NS
Hematocrit (%)	41.4 ± 3.6	43.8 ± 3.5	0.008	40.7 ± 4.6	42.2 ± 3.9	NS
HbA1c (%)	7.3 ± 1.2	6.9 ± 0.5	NS	6.5 ± 0.7	7.1 ± 1.1	NS
BUN (mg/dL)	14.1 ± 3.4	14.3 ± 3.2	NS	13.7 ± 3.9	14.1 ± 3.3	NS
Creatinine (mg/dL)	0.78 ± 0.19	0.79 ± 0.20	NS	0.67 ± 0.15	0.67 ± 0.16	NS
eGFR ($mL/min/1.73m^2$)	71 ± 11	70 ± 11	NS	84 ± 21	85 ± 25	NS
AST (IU/L)	23 ± 5	23 ± 9	NS	20 ± 9	24 ± 9	NS
ALT (IU/L)	28 ± 12	24 ± 10	NS	29 ± 24	39 ± 36	NS
γ-GTP (IU/L)	33 ± 11	27 ± 11	NS	26 ± 15	26 ± 14	NS
HDL-C (mg/dL)	51 ± 9	55 ± 12	0.047	54 ± 9	53 ± 10	NS
LDL-C (mg/dL)	112 ± 28	105 ± 30	NS	101 ± 31	98 ± 32	NS
Triglyceride (mg/dL)	131 ± 48	119 ± 50	NS	150 ± 90	142 ± 50	NS
Albuminuria (mg/gCr)	75 ± 89	42 ± 41	NS	19 ± 21	24 ± 28	NS
Glycosuria (g/gCr)	1 ± 2	61 ± 30	<0.001	N.D.	N.D.	----
Total energy (kcal/day)	1462 ± 437	1710 ± 468	NS	1715 ± 515	1534 ± 293	NS
Carbohydrate (g/day)	200 ± 64	224 ± 59	NS	215 ± 54	194 ± 59	NS
Protein (g/day)	54 ± 16	65 ± 20	NS	72 ± 27	64 ± 19	NS
Fat (g/day)	41 ± 14	52 ± 17	NS	59 ± 29	52 ± 17	NS
Salt (g/day)	8.9 ± 2.4	9.7 ± 2.1	NS	10.0 ± 2.9	9.4 ± 2.8	NS
Sucrose (g/day)	6.5 ± 4.7	11.9 ± 7.7	0.004	10.2 ± 6.5	9.7 ± 6.1	NS

SGLT2i, SGLT2 inhibitor; GLP-1RA, GLP-1 receptor agonist; 0M, 0 month (baseline); 3M, 3 months after starting dapagliflozin; P, p-value between 0M and 3M; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol, N.D., not determined; NS, not significant.