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ORIGINAL RESEARCH ARTICLE

Clinical Factors Associated with Initial Decrease in Body-Fat Percentage Induced by Add-on Sodium-Glucose Co-transporter 2 Inhibitors in Patient with Type 2 Diabetes Mellitus

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Abstract

Background and objective Obesity is globally recognized as an important clinical problem and sodium-glucose co-transporter 2 (SGLT2) inhibitors are considered a suitable therapy for obese patients with type 2 diabetes mellitus (T2DM). We examined the clinical factors associated with initial decrease in body-fat percentage (Fat %) induced by SGLT2 inhibitors in patients with T2DM.

Methods We retrospectively enrolled patients newly treated with SGLT2 inhibitors in addition to ongoing medications at Jinnouchi Hospital between April 2014 and December 2015. We examined the SGLT2 inhibitor-induced change in body composition by using a bioelectrical impedance analyzer (InBody770®) before SGLT2 inhibitor administration and after 4 weeks' treatment.

Results A total of 175 patients with T2DM were enrolled and we analyzed 148 patients. Add-on SGLT2 inhibitor treatment significantly reduced body weight (-1.04 ± 1.18 kg, $p < 0.01$), total fat quantity (-0.62 ± 1.19 kg, $p < 0.01$), and Fat % ($-0.4 \pm 1.4\%$, $p < 0.01$). Pretreatment levels of glycated hemoglobin (HbA1c) [odds ratio (OR), 1.61; 95% confidence interval (CI), 1.15–2.25, $p < 0.01$] and smoking (OR, 2.65; 95% CI, 1.14–6.15, $p = 0.02$) were significantly associated factors for greater fat-reduction defined as more than 0.4% (median) decrease in Fat % in multivariate logistic regression analysis. In receiver operator characteristic analysis, the cut-off value of pretreatment levels of HbA1c for a greater Fat % decrease was 7.7% (sensitivity 53% and specificity 69%, $p < 0.01$).

Conclusion Additional treatment with SGLT2 inhibitors effectively decreased Fat % in T2DM patients with high HbA1c levels before SGLT2 inhibitor administration. Our results suggest a greater initial response in Fat % reduction to SGLT2 inhibitor therapy in diabetic patients with pretreatment HbA1c levels $\geq 7.7\%$.

Noboru Kurinami and Seigo Sugiyama contributed equally to this study.

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Key Points

Add-on SGLT2 inhibitor treatment significantly reduced body weight, total fat quantity, and body-fat percentage.

Pretreatment HbA1c levels and smoking were significantly associated with greater body fat reduction with SGLT2 inhibitors.

Reduction in body-fat percentage was significantly greater in the higher HbA1c group (pretreatment HbA1c levels $\geq 7.7\%$) than the lower HbA1c group (pretreatment HbA1c levels $< 7.7\%$), but the reduction in body weight was not significantly different between the two groups.

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1 Introduction

It has been well established that obesity is closely involved in the pathogenesis of type 2 diabetes mellitus (T2DM). At present, the incidence of obesity is continually increasing and is globally recognized as an important clinical problem [1]. In patients with T2DM, diabetes treatment accompanied by body fat and weight reduction may become a valuable strategy. This would provide an additional beneficial effect on the fundamental pathophysiology of T2DM.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors inhibit the reabsorption of glucose in the kidney. It is expected that there will be an insulin-independent improvement of hyperglycemia through the promotion of urinary glucose excretion and enhancement of lipolysis with a reduction in glucose incorporation into the somatic cells. A previous report demonstrated that dapagliflozin has an antidiabetic action equivalent to glipizide [2]. In addition, a meta-analysis reported that weight decreases by 1 kg and body fat decreases by 2.73% with SGLT2 inhibitors compared to placebo [3]. Furthermore, weight reduction by dapagliflozin is reported to be mainly due to fat reduction [4]. SGLT2 inhibitors do not have a labelled indication for weight loss, but SGLT2 inhibitors have exhibited weight reduction during treatment of T2DM. Therefore, SGLT2 inhibitors are considered a suitable therapy for obese patients with T2DM. However, the clinical factors associated with effective weight and fat reduction are unknown.

The weight-reducing effect of SGLT2 inhibitors is achieved within 6 months from first administration [5]. It has been reported that ipragliflozin treatment decreased body weight by 1.4 ± 0.5 kg in 7 days [6]. To achieve the initial effectiveness of the SGLT2 inhibitor antidiabetic treatment for T2DM patients, we need to know the baseline clinical factors associated with SGLT2 inhibitor-induced body fat reduction.

In this study, based on results obtained from treatment with add-on SGLT2 inhibitors for glucose reduction of T2DM, we examined the clinical factors associated with initial decrease in Fat % induced by add-on SGLT2 inhibitors in patients with T2DM.

2 Methods

2.1 Subjects and Protocol

Patients with T2DM who visited the Diabetes Care Center of Jinnouchi Hospital between April 2014 and December 2015 and were treated with SGLT2 inhibitors in addition to their ongoing medications were retrospectively registered. We measured body composition using a body composition analyzer (InBody770; Biospace, Seoul, Korea) both before administration of SGLT2 inhibitors and 4 weeks after treatment and calculated the change in composition. Written informed consent was obtained from all patients. The study was conducted in accordance with the Declaration of Helsinki and the Human Ethics Review Committee of Jinnouchi Hospital approved the study protocol.

2.2 Measurement of Body Fat and Muscle Composition

Elementary body composition was measured using a direct, segmental, multi-frequency bioelectrical impedance analyzer (InBody770; Biospace, Seoul, Korea). This analyzer processes 30 impedance measurements using six different frequencies (1, 5, 50, 250, 500, and 1000 kHz) at each of the five body segments (right and left arms, right and left legs, and trunk) and 15 reactance measurements using tetrapolar 8-point tactile electrodes at three different frequencies (5, 50, and 250 kHz) at each of the same five body segments [7, 8]. Body composition analyses were conducted with the subjects clothed as specified by the hospital and performed once before starting SGLT2 inhibitors and again after 4 weeks of treatment.

2.3 Blood Sampling and Measurement of Clinical Parameters

Measurement of glycated hemoglobin (HbA1c) and plasma glucose is routinely performed every month in patients with diabetes mellitus (DM). Moreover, biochemical examinations of blood serum chemistry are usually performed before and after newly started medications including SGLT2 inhibitors to determine drug-induced side effects. Blood samples for HbA1c, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and estimated glomerular filtration ratio (eGFR) were collected from the antecubital vein before SGLT2 inhibitor therapy and analyzed in the Jinnouchi Hospital laboratory. In our clinic body composition in all patients starting SGLT2 inhibitors is routinely measured at initiation and after 4 weeks of SGLT2 inhibitor therapy.

2.4 Statistical Analysis

The Shapiro–Wilk test was used to assess the normal distribution of continuous data. Data were expressed as mean ± standard deviation (SD), and data with skewed distributions were expressed as the median value with interquartile range. Categorical data were presented as frequencies and percentages. Differences between paired samples were analyzed by the *t* test or Wilcoxon signed-

rank test; the differences between two groups were analyzed by the *t* test, Mann–Whitney *U* test, or Fisher's exact test as appropriate. Add-on SGLT2 inhibitor treatment significantly reduced body weight, total fat quantity, and Fat %. However, body weight change and body fat quantity change did not show a strong correlation. Therefore, we used Fat % as the effective parameter in this study. Calculation of the Pearson product-moment correlation coefficient was used to examine the relationships between the weight change with SGLT2 inhibitors and the amount of Fat % change. Multivariate regression analysis was conducted using the significant outcomes by the Pearson product-moment correlation analysis, age, sex, and body mass index (BMI). Median Fat % reduction after add-on SGLT2 inhibitor treatment was $- 0.4\%$. Thus we defined a greater response in fat reduction following SGLT2 inhibitors as more than 0.4% reduction in Fat %, which we analyzed using simple logistic regression analysis with the greater fat reduction as the dependent variable and the various parameters as independent variables. To investigate the clinically associated factors with the greater body fat reduction following SGLT2 inhibitor medication, multivariate logistic regression analysis was conducted among the significant factors of simple logistic regression analysis. The Hosmer–Lemeshow test was conducted to investigate the goodness of fit of the logistic regression model. Receiver-operating characteristic (ROC) curve analysis was conducted to calculate a cut-off value of pretreatment levels of HbA1c for greater body fat reduction. A p-value < 0.05 denoted statistical significance. Statistical analyses were performed using SPSS version 23 (SPSS Inc., Tokyo, Japan).

3 Results

3.1 Subjects

A total of 175 patients with T2DM were enrolled and all patients had body composition measured at the start of the SGLT2 inhibitor add-on therapy, but we were unable to measure body composition in 27 patients at the end of 4 weeks. Thus, 27 patients were excluded. Table 1 shows the baseline characteristics of the participants. SGLT2 inhibitors were newly added to the ongoing medications as follows: dapagliflozin ($n = 46$, 30.9%), tofogliflozin ($n = 45$, 30.4%), luseogliflozin ($n = 35$, 23.6%), ipragliflozin ($n = 20$, 13.5%), and empagliflozin (n = 2, 1.4%). Combined antidiabetic medications were insulin ($n = 44$, 29.7%), glucagon-like peptide-1 (GLP-1) receptor analog ($n = 13$, 8.8%), sulfonylurea ($n = 63$, 42.6%), dipeptidyl peptidase 4 inhibitor ($n = 48$, 32.4%), metformin ($n = 71$, 48.0%), thiazolidine ($n = 15$, 10.1%), glinide ($n = 12$,

Table 1 Clinical characteristics of the study participants

| Characteristic	Value
Males	107 (72.3)
Age (year)	58 (50–63)
Height (cm)	165.9 ± 8.2
Weight (kg)	76.4 (66.0–85.5)
BMI (kg/m^2)	27.5 (25.1–30.2)
Waist circumference (cm)	95.5 (88.2–103.2)
Muscle quantity (kg)	48.9 ± 8.7
Body-fat quantity (kg)	25.0 (18.1–30.3)
Body-fat percentage (%)	32.3 ± 8.0
Hypertension	85 (57.4)
Dyslipidemia	127 (85.8)
Current smoking	39 (26.4)
Hemoglobin A1c (%)	7.5 (7.0-8.2)
Total cholesterol (mg/dl)	178.5 ± 36.4
HDL-cholesterol (mg/dl)	47.5 (40.0–56.0)
LDL-cholesterol (mg/dl)	96.0 (76.0-120.3)
Triglycerides (mg/dl)	121.0 (86.5–194.5)
eGFR (ml/min/1.73 m^2)	71.2 (62.2–83.2)

Data are mean $\pm$ standard deviation (SD), median (25–75th percentile range), or number (%)

BMI body mass index, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *eGFR* estimated glomerular filtration rate

8.1%), and alpha glucosidase inhibitor ($n = 24$, 16.2%). Among the included patients, 85 (57.4%) had hypertension and 127 (85.4%) had dyslipidemia. They were treated with calcium antagonists ($n = 63$, 42.6%), angiotensin II receptor blockers ($n = 75$, 50.7%), angiotensin-converting enzyme inhibitors ($n = 2$, 1.4%), beta blockers ($n = 25$, 26.4%), statins ($n = 76$, 51.4%), and ezetimibe ($n = 18$, 12.2%).

3.2 Change in Body Composition after Add-on SGLT2 Inhibitor Treatment

Add-on SGLT2 inhibitor treatment for 4 weeks significantly reduced body weight ($- 1.04 \pm 1.18$ kg, $p < 0.01$), total fat quantity ($- 0.62 \pm 1.19$ kg, $p < 0.01$), and Fat % ($- 0.4 \pm 1.4\%$, $p < 0.01$). Figure 1 shows the scatter plot diagram of the changes in total body weight and body fat. The body fat changes were significantly correlated with the changes in total body weight, but the correlation was not strong ($r = 0.44$, $p < 0.001$). In Pearson's correlation analysis, reduction in body fat quantity was not statistically significantly correlated with baseline body weight ($r = 0.07$, $p = 0.38$) and baseline BMI ($r = 0.05$, $p = 0.57$).
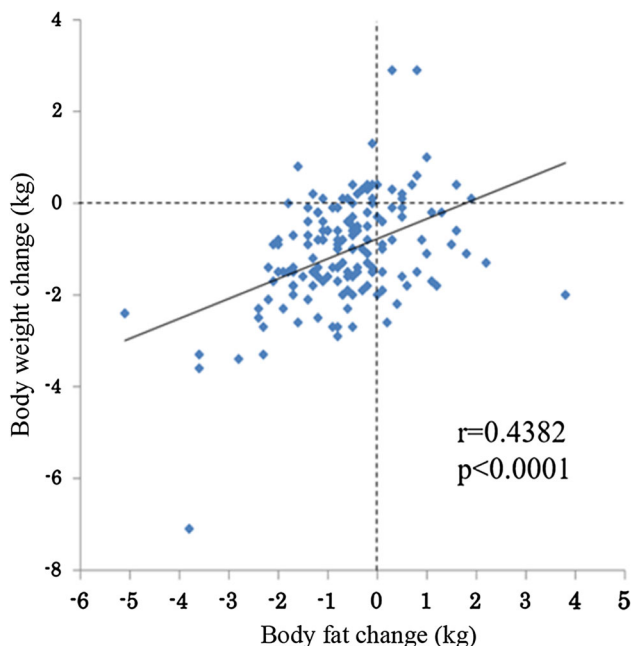
Fig. 1 Relationship between the amount of body weight change and body fat change following add-on SGLT2 inhibitor treatment ($r = 0.44$; $p < 0.0001$). *SGLT2* sodium-glucose co-transporter 2

3.3 Pearson Product-Moment Correlation Analysis for Changes in Fat % after Add-on SGLT2 Inhibitor Treatment

Table 2 shows the results of the simple linear regression analysis conducted for changes in Fat % with various parameters. Pretreatment levels of HbA1c ($r = -0.20$, $p = 0.015$) and estimated eGFR ($r = -0.23$, $p = 0.005$)

Table 2 Results of Pearson product-moment correlation analysis conducted for changes in body-fat percentage

Variable	r	R^2	p value
Age (year)	0.0948	0.0090	0.2517
Height (cm)	− 0.0650	0.0042	0.4322
Weight (kg)	0.0230	0.0005	0.7846
BMI (kg/m^2)	0.0632	0.0040	0.7846
Waist circumference (cm)	0.0270	0.0007	0.7444
Muscle quantity (kg)	− 0.0008	0.0000	0.9920
Body-fat quantity (kg)	0.0367	0.0013	0.6576
Body-fat percentage (%)	0.0398	0.0016	0.6314
Hemoglobin A1c (%)	− 0.1988	0.0395	0.0154
Total cholesterol (mg/dl)	− 0.0369	0.0014	0.6558
HDL-cholesterol (mg/dl)	− 0.0069	0.0069	0.9336
LDL-cholesterol (mg/dl)	− 0.0192	0.0004	0.8171
Triglycerides (mg/dl)	− 0.0849	0.0072	0.3048
eGFR (ml/min/1.73 m^2)	− 0.2310	0.0533	0.0047

BMI body mass index, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *eGFR* estimated glomerular filtration rate

showed a significantly negative relationship with changes in Fat %.

3.4 Simple and Multivariable Regression Analysis for Changes in Fat % after Add-on SGLT2 Inhibitor Treatment

Table 3 shows the results of multivariable regression analysis for changes in Fat % after add-on SGLT2 inhibitor treatment. Pretreatment levels of HbA1c and eGFR were significant and independent factors (pretreatment levels of HbA1c: $\beta = -0.1783$, $p = 0.0319$; eGFR: $\beta = -0.2182$, $p = 0.0072$).

3.5 Logistic Regression Analysis for Fat % change after Add-on SGLT2 Inhibitor Treatment

We defined the greater body fat reduction group as having a reduction of > 0.4% in Fat % (median) after add-on SGLT2 inhibitor treatment. Table 4 shows the results of the simple logistic regression analysis for greater body fat reduction. Pretreatment HbA1c levels as the continuous variable [odds ratio (OR) 1.54; 95% confidence interval (CI) 1.13–2.11, $p < 0.01$] and smoking (OR 2.54; 95% CI 1.18–5.47, $p = 0.02$) were significant factors for greater body fat reduction with SGLT2 inhibitors. The multivariate logistic regression analysis demonstrated that the pretreatment HbA1c levels (OR 1.61; 95% CI 1.16–2.25; $p < 0.01$) and smoking (OR 2.65; 95% CI, 1.14–6.15; $p = 0.02$) were significantly associated factors for greater body fat reduction with SGLT2 inhibitors.

3.6 Receiver Operating Characteristic Curve Analysis of Pretreatment Levels of HbA1c

We conducted an ROC analysis to calculate a cut-off value of pretreatment HbA1c levels for the percentage decrease in greater body fat. The cut-off value of the pretreatment levels of HbA1c for the greater Fat % change after SGLT2 inhibitors therapy was 7.7% (sensitivity 53% and specificity 69%, $p < 0.01$).

3.7 Subgroup Analyses Regarding Pretreatment HbA1c Levels, GLP-1 Analog Treatment, Smoking Status, and Body Mass Index at Baseline for Appreciable Body Fat Reduction by SGLT2 Inhibitors

We compared the percentage changes in body fat after add-on SGLT2 inhibitor treatment between the higher HbA1c group (pretreatment levels of HbA1c $\geq$ 7.7%) and the lower HbA1c group (pretreatment levels of HbA1c < 7.7%). Figure 2 shows that the reduction in

Table 3 Results of multivariate regression analysis for body-fat percentage change after sodium-glucose co-transporter 2 inhibitor treatment

	Unstandardized coefficients		Standardized coefficients	95% CI for B		p value
	B	SEM	β	Lower bound	Upper bound	
Constant	0.0142	0.0156		− 0.0167	0.0451	0.2373
Sex (male)	0.0005	0.0025	0.0155	− 0.0044	0.0054	0.8473
Age (year)	0.0001	0.0001	0.0622	− 0.0001	0.0003	0.4690
BMI (kg/m^2)	0.0002	0.0003	0.0808	− 0.0003	0.0008	0.3352
Hemoglobin A1c (%)	− 0.0021	0.0010	− 0.1783	− 0.0040	− 0.0002	0.0319
eGFR (ml/min/1.73 m^2)	− 0.0002	0.0001	− 0.2182	− 0.0003	− 0.0001	0.0072

$R^2 = 0.0971$. F test for liner relationship was 3.0529 with $p = 0.012$. Variance inflation factors (VIF is an index used to detect the multi-collinearity between exploratory variables): sex 1.0101; age 1.1557; BMI 1.0973; Hemoglobin A1c 1.0649; eGFR 1.0062

BMI body mass index, *eGFR* estimated glomerular rate

Table 4 Results of logistic regression analysis for body-fat percentage change after sodium-glucose co-transporter 2 inhibitor treatment (> 0.4%)

	Simple regression				Multivariate regression			
	OR	95% CI		p value	OR	95% CI		p value
Sex (male)	1.4031	0.6801	2.8944	0.3593	1.2038	0.5477	2.6459	0.6444
Age (year)	0.9954	0.9643	1.0275	0.7771	1.0194	0.9823	1.0579	0.3098
Height (cm)	1.0202	0.9807	1.0614	0.3206				
Weight (kg)	1.0050	0.9839	1.0266	0.6468				
BMI (kg/m^2)	1.0053	0.9359	1.0799	0.8840	1.0197	0.9384	1.1081	0.6449
Waist circumference (cm)	1.0224	0.9950	1.0505	0.1104				
Muscle quantity (kg)	1.0086	0.9719	1.0466	0.6510				
Body-fat quantity (kg)	1.0051	0.9720	1.0394	0.7649				
Body-fat percentage (%)	1.0922	0.0193	61.8618	0.9658				
Hypertension, n (%)	0.7582	0.3945	1.4572	0.4062				
Dyslipidemia, n (%)	0.8949	0.3551	2.2553	0.8138				
Current smoking, n (%)	2.5417	1.1819	5.4657	0.0169[*]	2.6466	1.1396	6.1469	0.0236[*]
Hemoglobin A1c (%)	1.5419	1.1288	2.1061	0.0065[**]	1.6090	1.1517	2.2480	0.0053[**]
Total cholesterol (mg/dl)	1.0015	0.9926	1.0105	0.7391				
HDL-cholesterol (mg/dl)	0.9917	0.9641	1.0202	0.5656				
LDL-cholesterol (mg/dl)	1.0020	0.9912	1.0129	0.7222				
Triglycerides (mg/dl)	1.0009	0.9983	1.0035	0.5143				
eGFR (ml/min/1.73 m^2)	1.0092	0.9888	1.0300	0.3779				

Hosmer–Lemeshow goodness-of-fit χ^2 was 12.84 with a p value of 0.12

BMI body mass index, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *GFR* estimated glomerular filtration rate

[*]$P < 0.05$; [**]$P < 0.01$

Fat % was significantly greater in the higher HbA1c group than the lower HbA1c group (higher HbA1c group − 0.7 ± 1.3% vs. lower HbA1c group − 0.1 ± 1.4%, $p = 0.01$). However, the reduction in body weight was not significantly different among the two groups, as shown in Fig. 3. In other body composition results, the reduction in water (higher HbA1c group − 0.02 ± 0.86 kg vs. lower HbA1c group − 0.56 ± 0.94 kg, $p < 0.01$) and skeletal muscle (higher HbA1c group −0.01 ± 1.09 kg vs. lower HbA1c group −0.68 ± 1.19 kg, $p = 0.04$) was significantly greater in the lower HbA1c group than the higher HbA1c group. However, the reduction in fat (higher HbA1c group − 0.85 ± 1.16 kg vs. lower HbA1c group − 0.46 ± 1.19 kg, $p = 0.04$) was significantly greater in the higher HbA1c group than the lower HbA1c group.

In this study, 13 patients were treated with combined GLP-1 receptor agonists, and these agents did not influence body composition change by SGLT-2 inhibitors (Fat %: GLP-1 receptor agonists; − 0.4 ± 1.4, no GLP-1 receptor agonists; − 0.7 ± 1.2, $p = 0.41$).

Change in body fat percentage (%)
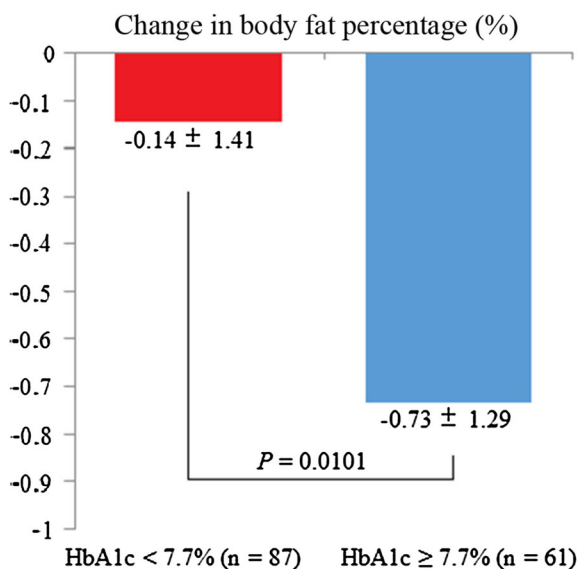
Fig. 2 Changes in Fat % by add-on SGLT2 inhibitor treatment in patients with pretreatment HbA1c levels < 7.7% and those with pretreatment HbA1c levels ≥ 7.7%. Data are mean ± standard deviation. *Fat %* body fat percentage, *SGLT2* sodium-glucose cotransporter 2, *HbA1c* glycated hemoglobin

Body weight change (kg)
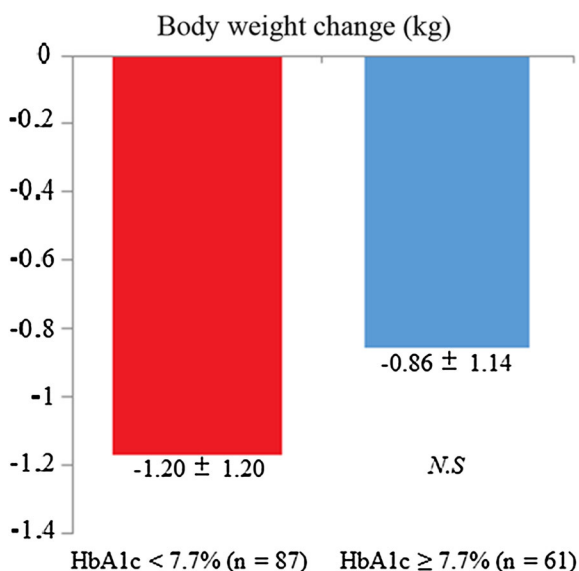
Fig. 3 Changes in body weight as a result of add-on SGLT2 inhibitor treatment in patients with pretreatment HbA1c levels < 7.7% and those with pretreatment HbA1c levels ≥ 7.7%. Data are mean ± standard deviation. *SGLT2* sodium-glucose cotransporter 2, *HbA1c* glycated hemoglobin

We also compared the changes in the Fat % after add-on SGLT2 inhibitor treatment between smokers and non-smokers, and found that the Fat % was significantly reduced in the smoker group (smoker group − 0.8 ± 1.3% vs. non-smoker group − 0.3 ± 1.4%, $p < 0.05$).

A comparison of the changes in Fat % following add-on SGLT2 inhibitor treatment between obese (BMI ≥ 25 kg/

m^2) and non-obese (BMI < 25 kg/m^2) groups showed no significant difference between the two groups (obese group − 0.4 ± 1.5% vs. non-obese group − 0.5 ± 1.0%, $p = 0.69$).

The median levels of Fat % at pretreatment with SGLT2 inhibitors in men and women were 29.7 and 39.34%, respectively. When we compared the changes in Fat % following add-on SGLT2 inhibitor treatment between the excess fat group (over the median) and non-excess fat group (less than the median), there was no significant difference between the two (non-excess fat group − 0.5 ± 1.3% vs. excess fat group − 0.3 ± 1.5%, $p = 0.34$).

In obese patients with good diabetic control (BMI ≥ 25 kg/m^2 and pre-treatment levels of HbA1c < 7.0%), SGLT2 inhibitor therapy significantly decreased the levels of HbA1c (from 6.40 ± 0.15% to 6.29 ± 0.22%, $p = 0.03$). We found no significant changes in the quantity of body fat (from 27.88 to 27.49 kg, p = 0.14) and Fat % (from 35.38 to 35.29%, $p = 0.77$).

The multivariate logistic regression analysis with a nominal variable of the pretreatment HbA1c levels (higher HbA1c ≥ 7.7% and lower HbA1c < 7.7%) also demonstrated that smoking and higher pretreatment levels of HbA1c (≥ 7.7%) were independently and significantly correlated with the greater body fat reduction, as shown in Table 5.

In the non-smoker group, pretreatment levels of HbA1c were also independently and significantly correlated with greater body fat reduction as shown in Table 6 (OR 1.56; 95% CI 1.05–2.37; $p = 0.03$).

4 Discussion

In the present study pretreatment levels of HbA1c and smoking status were significantly associated with SGLT2 inhibitor-induced greater reduction in Fat % in the initial 4 weeks of SGLT2 inhibitor therapy. The effective plasma glucose-lowering and weight-decreasing actions of SGLT2 inhibitors have previously been reported [9], and our results also demonstrated the significant body fat-reducing effects (− 0.62 kg) of SGLT2 inhibitors even over a short treatment period (4 weeks). SGLT2 inhibitor users have been suggested to increase ketoacidosis risk [10, 11], but no patients became ketoacidosic during the present study.

It is reported that SGLT2 inhibitor therapy mainly reduces fat weight [9]. We found a significant correlation between the initial changes in total body weight and Fat % through the 4-week add-on SGLT2 inhibitor treatment, but the relationship was not strong, indicating that the SGLT2 inhibitor-induced weight reduction was not necessarily associated with a reduction in body fat quantity. Body fat reduction is the favorable clinical goal for management of

Table 5 Multivariate logistic regression analysis for body fat percentage reduction, when we divided the patients into two groups by setting a cut-off value of 7.7% of glycated hemoglobin (HbA1c)

	OR	95% CI		p value
		Lower bound	Upper bound	
Sex	1.2384	0.5664	2.7076	0.5922
Sex (male)	1.0156	0.9796	1.0529	0.4002
Age (year)	1.0180	0.9396	1.1031	0.6621
HbA1c ($\geq$ 7.7%, yes)	2.7300	1.3457	5.5384	0.0054*
Current smoker (yes)	2.4825	1.0831	5.6899	0.0317*

BMI body mass index, *OR* odds ratio, *CI* confidence interval

Hosmer–Lemeshow goodness-of-fit χ^2 was 3.21 with *p* value of 0.92

$^{*}P < 0.05$; $^{**}P < 0.01$

Table 6 Multivariate logistic regression analysis for body-fat percentage reduction at subanalysis of only nonsmokers

	OR	95% CI		p value
		Lower bound	Upper bound	
Sex (male)	1.2144	0.5279	2.7939	0.6477
Age (year)	1.0272	0.9859	1.0702	0.2005
BMI	1.0043	0.9122	1.1056	0.9307
Hemoglobin A1c (per 1.0%)	1.5778	1.0514	2.3678	0.0277*

BMI body mass index, *OR* odds ratio, *CI* confidence interval

Hosmer–Lemeshow goodness-of-fit χ^2 was 6.2 with *p* value of 0.625

$^{*}P < 0.05$; $^{**}P < 0.01$

patients with T2DM. In the present study, we evaluated SGLT2 inhibitor-induced changes in Fat % for a good and practical indicator of body fat reduction considering the body composition balance. Because the cut-off value of Fat % for a greater response in fat reduction was not defined in the previous studies and we could not assess whether some Fat % reduction was linked to substantial improvement of metabolic abnormalities, we applied the median value of Fat % reduction after add-on SGLT2 inhibitor treatment in the present study; − 0.4% as the cut-off value. We defined a greater response in fat reduction following SGLT2 inhibitors as more than 0.4% reduction in Fat %.

This study clearly showed that the SGLT2 inhibitor-induced change in Fat % was significantly correlated with the pretreatment levels of HbA1c, and the additional administration of SGLT2 inhibitors to the uncontrolled hyperglycemic state effectively decreased Fat %. In patients with T2DM, SGLT2 inhibitors evoke glycosuria, lowering blood glucose levels, and subsequently liver glyconeogenesis and glucagon secretion occur to prevent hypoglycemia [12, 13]. Because the glucagon receptor is expressed in adipose tissue, the secreted glucagon enhances lipolysis and increases fatty acid release in adipose tissue. The excess energy is stored in white adipose tissue as triglyceride. Fatty acid and glycerol are emitted to maintain the energy balance of whole-body metabolism in a fasting state. It is known that the attenuated action of insulin strongly influences enhanced lipolysis, while the excess levels of glucagon have a weak effect on it. Because the glucose-lowering action of insulin is effective on the overall metabolic balance in a comparatively good glycemic state, the SGLT2 inhibitor-induced, counter-regulated increase in glucagon levels will lower its effects on the lipolysis of fat tissue. Based on these metabolic mechanisms, we considered that the uncontrolled diabetic condition with higher pretreatment levels of HbA1c effectively influences a considerable reduction in Fat % by SGLT2 inhibitors.

In this study, we unexpectedly found that smoking is significantly correlated with changes in the Fat % resulting from add-on SGLT2 inhibitor treatment. The detailed mechanism of smoking on SGLT2 inhibitor-induced fat reduction is presently unknown and this observation might be a chance one. However, in previous clinical observations, smoking decreased body weight while smoking cessation induced body weight gain [14], suggesting that smoking has some kind of influence on body composition, particularly with regard to body fat. It is possible that smoking exhibits enhanced lipolysis and fat-burning action on adipose tissue during hypoglycemia with SGLT2 inhibitors. Because smoking is an important risk factor for cardiovascular disease, instructions to stop smoking are essential for lifestyle management. Smoking might have a favorable effect on body fat reduction with add-on SGLT2 inhibitor treatment, but continuation of smoking is never clinically recommended. Further investigations are

necessary to clarify the mechanisms of the effect of smoking with SGLT2 inhibitors on body fat reduction.

Metabolic syndrome increases the risk of cardiovascular diseases, and its main pathophysiology is insulin resistance. Our previous study showed that a muscle/fat ratio provided a good surrogate indicator of insulin resistance as assessed by the hyperinsulinemic-euglycemic clamp [13]. Thus, fat reduction is potentially a significant strategy for increasing insulin sensitivity in T2DM. Add-on SGLT2 inhibitor treatment itself improves insulin resistance [15] and reduces body-fat weight. The SGLT2 inhibitor-induced change in body composition with fat reduction is synergistically effective for the treatment of patients with metabolic syndrome and obesity. The body fat-reducing effect of SGLT2 inhibitors is stronger in visceral fats than in subcutaneous fat [16]. Therefore, introducing SGLT2 inhibitors will have additional benefits for the treatment of T2DM patients with obesity and insulin resistance.

In the ROC analysis, the cut-off value of pretreatment levels of HbA1c for a greater decrease in Fat % of add-on SGLT2 inhibitor treatment was 7.7%. The baseline BMI and the Fat % did not significantly correlate with the Fat % reduction. We demonstrated that the body fat-reducing action of SGLT2 inhibitors was not significantly effective in patients with better glucose control of < 7.7% HbA1c. In the normal animal model, SGLT2 inhibitors did not show significant weight reduction in non-diabetic mice fed a high-fat diet [17]. It seems that the administration of SGLT2 inhibitors offers additional benefits to patients with T2DM and a high HbA1c ($\geq$ 7.7%) and is more effective for significantly reducing body-fat weight in patients with high HbA1c than in those with low HbA1c.

Our study had some limitations. The study was retrospective and did not include a control group. We did not measure fasting blood glucose levels in all participants. We did not compare body fat change with the dual-energy X-ray absorptiometry (DEXA) and other methods. However, we did compare body composition using bioelectrical impedance analysis with InBody770, which is a highly reproducible and reliable method for analyzing body composition in daily clinical practice [7, 8, 18]. As this was a retrospective study, we were not able to investigate various factors such as combined therapy, diet, and exercise, which might affect the results, or different drugs and their doses. Future prospective studies focusing on these points are needed to confirm our results. It has been reported that change in body weight composition with SGLT2 inhibitors differs when administered in combination with GLP-1 receptor agonists [19]. We did not find a significant effect of GLP-1 receptor agonists on changes in Fat % in the present study. Further studies with larger populations should be undertaken to determine whether combined hypoglycemic medications can affect the results.

5 Conclusion

Additional treatment with SGLT2 inhibitors effectively decreased Fat % in patients with T2DM and higher HbA1c levels before SGLT2 inhibitor administration. Our results suggest a greater initial response in the reduction of Fat % in response to SGLT2 inhibitor therapy in patients with diabetes with pretreatment levels of HbA1c more than 7.7%. In patients with T2DM with obesity and poor blood glucose status, SGLT2 inhibitor therapy is clinically expected to improve blood glucose control and reduce Fat %. Thus, the introduction of SGLT2 inhibitors is a practical, effective, and promising strategy to promote aggressive treatment for uncontrolled T2DM at an early stage of DM-therapy.

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