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Sodium–glucose cotransporter 2 inhibitor-induced changes in body composition and simultaneous changes in metabolic profile: 52-week prospective LIGHT (Luseogliflozin: the Components of Weight Loss in Japanese Patients with Type 2 Diabetes Mellitus) Study

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ABSTRACT

Aims/Introduction: It is unclear how changes in body composition induced by sodium–glucose cotransporter 2 (SGLT2) inhibitor treatment correlate with metabolic profile changes. We aimed to clarify how metabolic profile changes correlate with body component changes, and if SGLT2 inhibitor treatment causes sarcopenia and bone mineral content (BMC) loss.

Materials and Methods: Moderately obese Japanese type 2 diabetes patients, treated with luseogliflozin for a year, were observed prospectively and evaluated for body composition changes. We analyzed the changes in the individual body components during treatment, and their correlation with other clinical variables.

Results: The efficacy analysis set comprised 37 of 43 enrolled patients. The total fat mass significantly decreased early in the treatment at and after week 4, with a mean decrease of −1.97 kg (95% confidence interval −2.66 to −1.28) at week 24. The visceral fat area at week 24 showed an average downward trend, although this was not significant. The changes in visceral fat area in individual patients showed a significant negative correlation with the extent of the baseline visceral fat area ($r = -0.399$, $P = 0.023$). The skeletal muscle mass index showed a significant but small change at and after week 36. The BMC profile showed a transient significant decrease only at week 12. No significant change in BMC was noted at other time-points.

Conclusions: Luseogliflozin treatment brought about favorable changes in body composition and metabolism of moderately obese Japanese type 2 diabetes patients, accompanied by body fat reduction, and minimal muscle and BMC reduction.

INTRODUCTION

Obesity is an independent factor associated with development of insulin resistance, and it leads to increases in mortality[1]. Obesity also causes difficulties in treating type 2 diabetes; in particular, visceral fat accumulation is suspected to be correlated with the deterioration of metabolism, as well as the development and progression of cardiovascular diseases[2]. In recent times, body composition elements other than fat, or lean mass, in addition to body fat accumulation, have come under question in the management of diabetes from not only the perspective of the correction of hyperglycemia, but also the

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maintenance of quality of life. Sarcopenia[3,4], which manifests primarily as decreased skeletal muscle mass, combines with decreased bone mineral content (BMC) and deteriorated bone quality to cause physical frailty, and, thus, increases the risk of developing complications that lower the quality of life and mortality. In the past, there has been concern surrounding type 2 diabetes therapy causing the aforementioned changes in the body components[5,6]. Therefore, in the clinical care of type 2 diabetes patients, it is important to reduce body fat, as well as maintain the skeletal muscle mass, BMC and bone quality at appropriate levels.

Sodium–glucose cotransporter 2 inhibitors (SGLT2-i) have a class effect in the suppression of cardiovascular events[7,8], and aid in the reduction of body fat[9,10]. However, there are unanswered questions pertaining to the body components, such as whether or not glycemic improvement and body fat reduction can be achieved, and if sarcopenia is avoidable in Japanese type 2 diabetes patients, who often have a relatively small amount of body fat.

The Luseogliflozin: the Components of Weight Loss in Japanese Patients with Type 2 Diabetes Mellitus (LIGHT) Study reported herein was carried out in Japanese type 2 diabetes patients treated with a SGLT2-i – luseogliflozin – for up to 52 weeks, in a prospective setting, to evaluate the changes in the body components in correlation with the changes in metabolism.

METHODS

Study participants

The study enrolled Japanese outpatients with type 2 diabetes, who visited the medical institutions participating in this study (Table S1). The participants had a glycated hemoglobin (HbA1c) level ranging from 7.0 to 10.5%, and body mass index (BMI) ranging from 20.0 to 35.0 kg/m^2, and were aged between 20 and 65 years (Table S2).

Study drug administration

The patients received 2.5 mg of luseogliflozin once daily, in the morning, with an optional uptitration to 5 mg, once daily, at week 12 and thereafter, in the case of insufficient efficacy. In principle, once the dose was downtitrated (2.5 mg), uptitration was not allowed (Table S3). Medication compliance was checked by an attending physician through an interview at each visit. Each patient was instructed to continue diet therapy for 52 weeks by the physician at enrollment.

Evaluation variables and evaluation period

The study's evaluation variables and time-points are summarized in Table S4. The body components were measured using whole-body dual-energy X-ray absorptiometry (DXA; Hologic/Discovery, Hologic/Delphi; Hologic Inc., Marlborough, MA, USA; or GE/Lunar Prodigy enCORE 2006; GE Healthcare, Madison, WI, USA) The visceral fat area and subcutaneous fat area were determined through computed tomography cross-sectional images of the abdomen at the umbilicus level. Evaluation of the abdominal computed tomography images was carried out at a designated institution by a single predefined radiologist. Subcutaneous fat area and visceral fat area were analyzed using Slim Vision (CYBERNET SYSTEMS CO., LTD., Tokyo, Japan).

As an indicator for skeletal muscles, the skeletal muscle mass index (SMI) was calculated by the equation[3]: (appendicular lean mass)/(height)^2, based on the data obtained through DXA. The laboratory tests were carried out by LSI Medience Corporation (Tokyo, Japan). The level of C-peptide (C-peptide immunoreactivity) was measured using chemiluminescent immunoassays (ARCHITECT C-peptide; Abbott Laboratories, Abbott Park, IL, USA), adiponectin levels were determined by a latex agglutination assay (LSI Medience) and insulin levels (immunoreactive insulin) were determined by an electrochemiluminescence immunoassay (Roche Diagnostics, Tokyo, Japan).

Statistical analysis

For the analysis of the changes in the individual data, the last observation carried forward imputation method was applied. Statistical analyses were carried out using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA), changes from the baseline were compared using the Wilcoxon signed-rank test and the correlation among the changes was evaluated using Spearman's rank-order correlation coefficient, with a two-sided significance level of 5% ($P < 0.05$). Primary end-point data and some other data are presented as the mean and 95% confidence interval; all other data are presented as mean ± standard deviations.

Ethical considerations

The present study was carried out in compliance with the Declaration of Helsinki, and the ethical guideline for clinical research by the Ministry of Health, Labor and Welfare, in Japan. The study protocol was reviewed and approved by the institutional review boards of The Jikei University School of Medicine (approval number: 26-278) and Independent Ethics Committee (Kitamachi Clinic, approved on 19 August 2014). Informed consent was obtained from all the patients before their participation in this study. The study was registered beforehand at the University Hospital Medical Information Network Clinical Trials Registry (UMIN000015112).

RESULTS

Patient characteristics

The study enrolled 43 type 2 diabetes patients who were treated as outpatients, between October 2014 and June 2015, after obtaining consent to participate in the study (Figure S1). The safety analysis set comprised 39 patients who were initially registered for luseogliflozin treatment, and the efficacy analysis set included 37 patients, after the exclusion of two ineligible patients (1 did not meet the HbA1c criterion, and the other did not meet the BMI criterion). The demographic

backgrounds of the patients in the efficacy analysis set are summarized in Table 1.

Changes in glucose metabolism

The changes in the metabolic parameters are presented in Table 2 and Table S5. From week 4 through week 52, a significant decrease was observed both in the fasting plasma glucose and HbA1c levels, relative to those at the baseline. A biphasic pattern, with a rapid decrease in both the parameters, was noticed until week 8, followed by a stable phase, without a significant difference in the fasting plasma glucose and HbA1c levels between week 24 and week 52.

Table 1 | Demographics (efficacy analysis set)

Age (years)	53.5 ± 8.04
Body height (cm)	167 ± 8.54
Duration of disease (years)	5.70 ± 4.74
Sex	
Male (*n*)	27
Female (*n*)	10
Medications	
Absent (*n*)	9
Present (*n*)	28
No. patients by concomitant medication	
Only sulfonylurea	1
Only biguanide	6
Only dipeptidyl peptidase-4 inhibitor	8
Sulfonylurea + biguanide	3
Biguanide + dipeptidyl peptidase-4 inhibitor	7
Sulfonylurea + biguanide + dipeptidyl peptidase-4 inhibitor	2
Biguanide + other[†]	1
Diabetic complications	
Absent (*n*)	27
Present (*n*)	10
No. patients by diabetic complication	
Diabetic nephropathy[‡]	5
Diabetic neuropathy	1
Diabetic retinopathy[§]	6
Coexisting diseases	
Absent (*n*)	15
Present (*n*)	22
No. patients by coexisting disease (some counted multiple times)	
Hypertension	16
Ischemic heart disease	1
Dyslipidemia	17
Hepatic steatosis	4

Data are shown as mean ± standard deviation. [†]Biguanide + sodium–glucose cotransporter 2 inhibitor + mitiglinide and voglibose. [‡]Phase of diabetic nephropathy: four patients in phases 1 or 2, one patient in phase 3, no patients in phases 4 or 5. [§]Phase of diabetic retinopathy: three patients with simple retinopathy, one patient with pre-proliferative retinopathy, no patient with proliferative retinopathy and two patients in an unknown phase.

Changes in body composition over time

The changes in each body component, over time, are shown in Figure 1, Figure 2 and Table 3. A significant decrease was observed in the total fat mass as early as at week 4, and this decrease continued until week 24, followed by a stable phase until week 52.

In contrast, it should be noted that there was no significant decrease in the SMI at week 24 of treatment. Furthermore, the BMC data were different from the total fat mass data. As shown in Table 3 and Table S6, no significant deviation from the basal BMC value was observed at all the evaluation points up to week 52, except at week 12 (−21.4 g, 95% confidence interval −39.0 to 03.86, $P = 0.014$).

Although the total fat mass decreased, the visceral fat area showed different changes. As shown in Table 3, the visceral fat area did not show a significant change during the treatment course.

Changes in the clinical parameters over time

The changes in the clinical parameters over time are summarized in Table 2 and Table S5. The levels of the serum ketones, including β-hydroxybutyrate and acetoacetate, significantly increased at week 4 and subsequently, the levels were maintained until week 52. The level of β-hydroxybutyrate peaked at week 52 (137 ± 338, $P < 0.001$), but did not reach a dangerously high level at any point.

Factors that changed in association with the changes in the total fat mass and visceral fat area

The changes in the HbA1c levels did not significantly correlate with the changes in the bodyweight (BW), BMI or body components. The correlations of the changes in the total fat mass and subcutaneous fat area with the clinical parameters are summarized in Table 4a and Table 4b, respectively. The change in the total fat mass showed a strong positive correlation with the change in the subcutaneous fat area at week 24 ($r = 0.491$, $P = 0.004$), as well as at week 52 ($r = 0.540$, $P < 0.001$). The change in the total fat mass also showed a significant positive correlation with the changes in the levels of serum ketones and free fatty acids at week 24. The visceral fat area was positively correlated with the changes in the BW and BMI, but not significantly correlated with the changes in the parameters characteristic of metabolic syndrome; that is, abdominal circumference, and levels of fasting plasma glucose, triglyceride and high-density lipoprotein cholesterol. Furthermore, no correlation was detected for the changes in the serum ketone levels or free fatty acid levels, which reflect fat degradation.

Relationship between the baseline values of the parameters and the changes in the total fat mass and visceral fat area

An analysis was carried out to investigate the correlation of the changes in the total fat mass with the baseline factors, after luseogliflozin treatment (Table 5a). A decrease in the total fat mass at week 52 was significantly negatively correlated with the

Table 2 | Changes in the clinical parameters

		n	Baseline	Change from the baseline			
				Week 24		Week 52	
Glycemic control	FPG (mmol/L)	37	9.47 ± 2.47	−1.54 ± 1.58	***	−1.86 ± 1.70	***
	HbA1c (%)	37	7.74 ± 0.731	−0.514 ± 0.658	***	−0.549 ± 0.570	***
	F-IRI (pmol/L)	37	117 ± 110	−35.8 ± 86.0	**	−36.1 ± 71.7	***
	F-CPR (nmol/L)	37	0.777 ± 0.492	−0.124 ± 0.361	*	−0.159 ± 0.346	**
Serum lipids	HDL-C (mmol/L)	37	1.37 ± 0.381	0.0657 ± 0.272		0.0839 ± 0.254	**
	TG (mmol/L)	37	2.25 ± 2.25	−0.314 ± 2.37	*	−0.597 ± 2.01	***
	LDL-C (mmol/L)	37	3.19 ± 0.768	0.121 ± 0.649		0.161 ± 0.670	
	FFA (μmol/L)	37	602 ± 194	73.8 ± 268		64.3 ± 314	
Blood ketones	Acetoacetate (μmol/L)	37	36.5 ± 30.7	45.1 ± 112	***	50.2 ± 104	***
	β-hydroxybutyrate (μmol/L)	37	74.7 ± 78.9	124 ± 373	**	137 ± 338	***
pressure/pulse rate	SBP (mmHg)	37	134 ± 13.7	−2.19 ± 11.3		−2.16 ± 13.2	
	DBP (mmHg)	37	82.1 ± 10.9	−2.59 ± 10.0		−3.49 ± 9.70	*
	Pulse (beat/min)	37	76.5 ± 11.2	0.486 ± 11.0		0.595 ± 8.62	
Hematology	RBC ($\times 10^{12}$/L)	37	4.92 ± 0.400	0.200 ± 0.215	***	0.265 ± 0.259	***
	Hemoglobin (g/L)	37	148 ± 13.9	4.11 ± 7.91	***	6.32 ± 7.19	***
	Hematocrit (L/L)	37	0.441 ± 0.0396	0.0189 ± 0.0234	***	0.0235 ± 0.0227	***
Biochemistry	BUN (mmol/L)	37	4.52 ± 1.20	0.540 ± 0.936	**	0.521 ± 0.935	**
	Creatinine (μmol/L)	37	64.0 ± 17.0	0.0478 ± 5.77		−0.239 ± 5.64	
	eGFR (mL/min/1.73 m^2)	37	86.9 ± 21.2	−0.462 ± 9.10		−0.481 ± 8.92	
	AST (U/L)	37	28.6 ± 11.6	−4.14 ± 7.88	***	−3.73 ± 8.61	**
	ALT (U/L)	37	36.6 ± 18.8	−9.14 ± 13.3	***	−7.65 ± 15.8	***
	Adiponectin (mg/L)	37	5.74 ± 1.97	0.446 ± 1.34	**	0.151 ± 1.24	
Urinalysis	Urine albumin corrected by creatinine (mg/g Cr)	37	85.8 ± 193	−25.4 ± 111	*	−13.0 ± 67.9	
	Albumin excretion (g/24 h)	20†	0.106 ± 0.283	−0.0396 ± 0.105	**	0.0122 ± 0.116	
	Urine output (L/24 h)	20†	1.71 ± 1.04	0.430 ± 0.949	*	0.751 ± 1.68	*
	Urine glucose excretion (mmol/24 h)	20†	120 ± 161	402 ± 258	***	426 ± 273	***

†Baseline $n = 22$. For each clinical parameter, the baseline value and the mean changes from the baseline are presented with standard deviations. The change at each time-point was compared with the baseline value using the Wilcoxon signed-rank test and a significant difference is marked with ***$P < 0.001$, **$P < 0.01$ or *$P < 0.05$. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; DBP, diastolic blood pressure; F-CPR: fasting plasma C-peptide immunoreactivity; eGFR, estimated glomerular filtration rate; FFA, free fatty acid; F-IRI: fasting plasma insulin; FPG: fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RBC, red blood cells; SBP, systolic blood pressure; TG, triglyceride; Urine albumin, result obtained with morning urine and corrected by creatinine; Urine output, 24-h pooled urine (1/50 proportional sampling).

total fat mass at the baseline ($r = -0.350$, $P = 0.035$). In addition, the decrease in the total fat mass at week 52 showed a significant negative correlation with the extent of urine glucose excretion at the baseline ($r = -0.440$, $P = 0.045$).

Analyses were also carried out to investigate the correlation of the changes in the visceral fat area with various baseline factors. As shown in Table 5b and Figure 3, the changes in the visceral fat area at week 24, on an individual basis, showed a significant negative correlation with the extent of the visceral fat area at the baseline ($r = -0.399$, $P = 0.023$). In particular, the visceral fat area at week 24 was decreased in all the patients in whom the baseline visceral fat area was ≥187 cm^2.

The changes in the total fat mass and visceral fat area, both at weeks 24 and 52, did not show a significant correlation with the HbA1c levels, abdominal circumference or BMI.

Adverse events

The adverse events and adverse drug reactions observed in the present study are summarized in Table S7. During the study period, two patients were hospitalized due to serious adverse events, for which a causal relationship with the study drug was ruled out. Nine events of adverse drug reactions, possibly related to luseogliflozin use, were reported in eight patients (20.5%). All the adverse drug reactions were previously known and mild in severity. The serum ketones did not reach a dangerously high level.

DISCUSSION

In the present study, a decrease in the total fat mass was detected early in the treatment, at week 4. The time-course profile showed a rapid decrease in the first half of the treatment

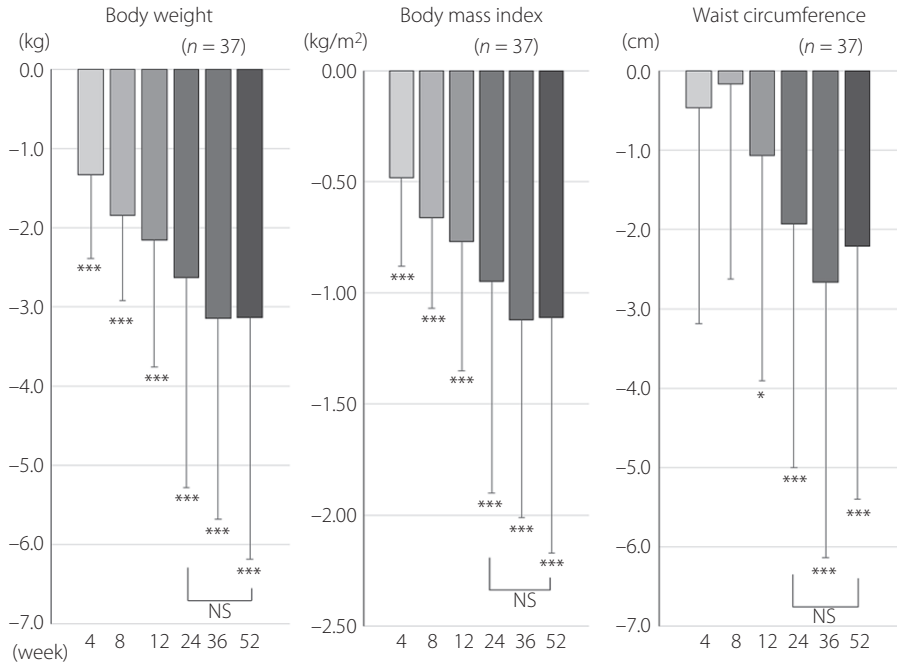

Figure 1 | Changes in the bodyweight, body mass index and abdominal circumference. Mean changes from the baseline (bodyweight 78.6 ± 13.3 kg, BMI 28.0 ± 3.4, abdominal circumference 94.4 ± 9.0 cm) are presented with standard deviations. The change at each time-point was compared with the baseline value, using the Wilcoxon signed-rank test, and a significant difference is marked with ***$P < 0.001$, **$P < 0.01$ or *$P < 0.05$. The change at week 24 was also compared with that at week 52 using the Wilcoxon signed-rank test, and an insignificant difference is marked with NS (not significant).

period, until week 24. In the first half, a decrease in the total fat mass was significantly correlated with an increase in the level of ketones, which are generated as a result of fat degradation. This suggests that a marked metabolic change occurred within the adipose tissues in the first half of the treatment, until week 24. A previous study with other SGLT2 inhibitors also reported decreases in the total fat mass and lean mass[1]. The present study determined the body composition using DXA, which involves less interference from body fluids than the bioimpedance method. In addition, the DXA method is capable of measuring the lean mass, focusing only on the limbs. Therefore, the SMI – which is based on the lean mass of the extremities – as measured using DXA, is a suitable indicator for the estimation of true skeletal muscle mass. The present study showed that the SMI decreased over the course of the treatment, but the degree of the change was small. To maintain adequate levels of skeletal muscle mass during type 2 diabetes treatment with SGLT2-i, further investigations are required, which focus on the type of diet therapy that is suitable in the early stages of treatment up to week 36, during which period drastic changes in the metabolism are followed by changes in the SMI.

Visceral fat accumulation is considered to have adverse metabolic and atherogenic effects. In the present study, the visceral fat area tended to decrease through the course of the treatment, though the change was not significant, and also showed a significant correlation with the change in the BW at weeks 24 and 52, and in the BMI. The present study was carried out to investigate the effect of SGLT2-i on the body composition of Japanese type 2 diabetes patients with a BMI between 20 and 35 kg/m^2, who were not deemed severely overweight. To date, studies carried out in the USA and European Union that investigated the changes in the body composition caused by SGLT2-i treatment focused predominantly on severely overweight patients with a BMI of 35 kg/m^2 or higher[9]. However, the present study evaluated patients with relatively lower body fat levels at the baseline, and did not detect a significant change in the visceral fat area during the course of treatment. This might be attributed to potential differences in the drug effectiveness as a result of the lower body fat levels at the baseline, when the study participants started taking SGLT2-i. In fact, the present study showed a significant negative correlation between the baseline visceral fat level and its change during treatment, as shown in Figure 3; the higher the baseline visceral fat level, the greater the decrease in the visceral fat. This is an important finding, in that it indicates the type of Japanese type 2 diabetes patients in whom this drug's use might be preferable.

Furthermore, we found that the change in the visceral fat area did not have a significant correlation with the change in the levels of triglyceride, high-density lipoprotein cholesterol or HbA1c. This could be attributed to the mechanism that the lowering of blood glucose levels through the use of SGLT2-i is

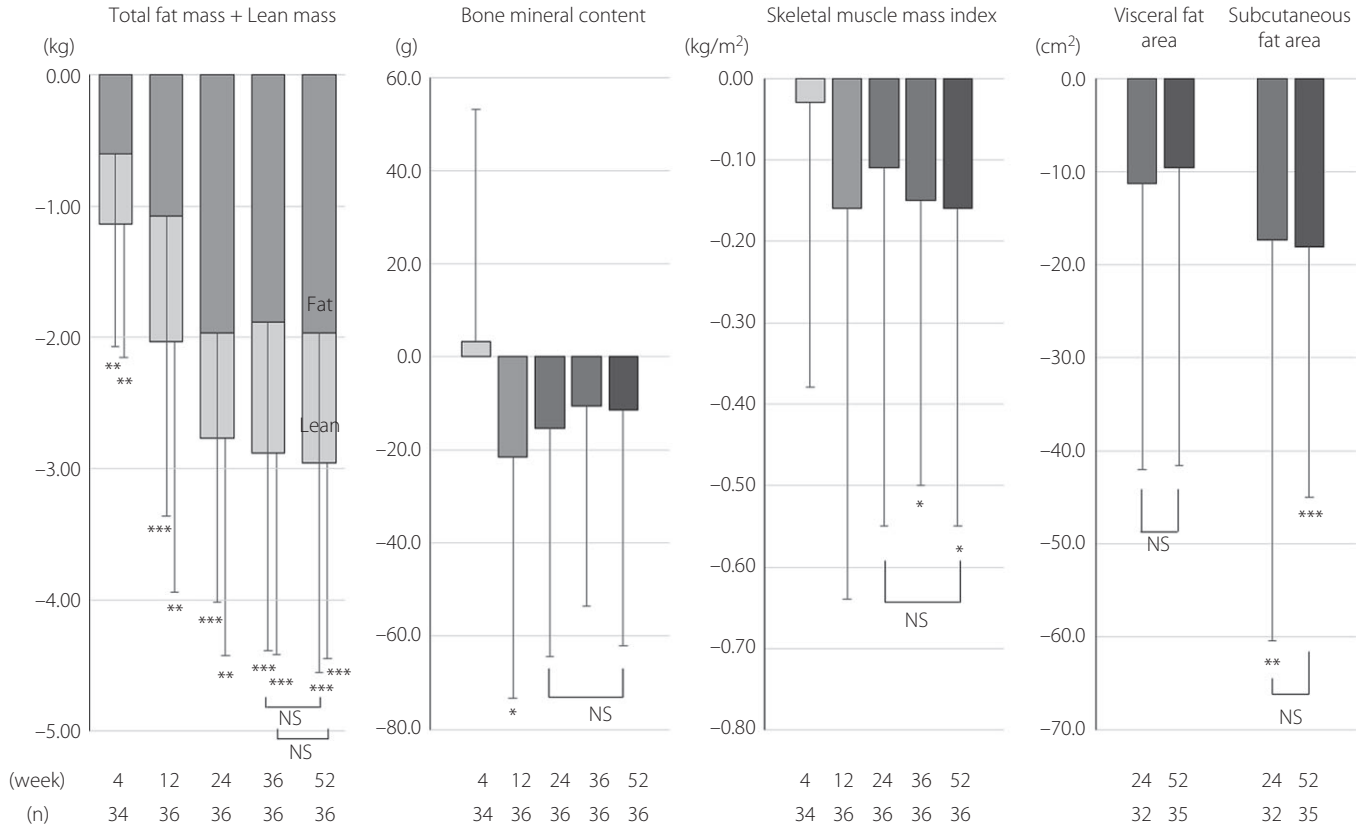

Figure 2 | Changes in the body components. Mean changes from the baseline (total fat mass 23.5 ± 5.9 kg, lean mass 53.1 ± 10.4 kg, skeletal muscle mass index 7.74 ± 1.23 kg/m^2, visceral fat area 161.6 ± 52.9 cm^2, subcutaneous fat area 214.7 ± 84.5 cm^2) are presented with standard deviations. In the graph of total fat mass + lean mass, the means of the total fat mass are shaded in gray and the means of the lean mass are shaded in light gray. The total fat mass and lean mass data were derived from DXA measurements, visceral fat area and subcutaneous area data were determined from abdominal computed tomography images, and skeletal muscle mass index data were calculated from dual-energy X-ray absorptiometry measurements. The change at each time-point was compared with the baseline value using the Wilcoxon signed-rank test, and a significant difference is marked with ***$P < 0.001$, **$P < 0.01$, or *$P < 0.05$. The change at week 24 was also compared with that at week 52 using the Wilcoxon signed-rank test and an insignificant difference is marked with NS (not significant).

mainly mediated by an increase in urinary glucose levels, but not directly associated with body fat mass reduction. As the mechanism of body fat mass reduction also involves an increase in the level of urinary glucose, which stimulates an increase in glyconeogenesis and the ultimate enhancement of lipolysis, the changes in the blood glucose and HbA1c levels do not necessarily correlate with the reduction of body fat.

In the present study, we confirmed that the total fat mass significantly decreased through the effect of luseogliflozin, which promotes fat degradation in the adipose tissues. However, we were unable to elaborate on the mechanism underlying the greater reduction in subcutaneous fat than visceral fat. However, because the decrease in the total fat mass was significantly correlated with the decrease in the abdominal circumference, monitoring the abdominal circumference in routine clinical practice is recommended for the estimation of fat mass changes. The present findings show that, unlike the visceral fat area at the baseline, BW, BMI, abdominal circumference and HbA1c levels at the baseline are not predictors of body fat reduction.

The present study had some limitations. First, because of its single-arm design, without a control group, this study was unable to compare the changes in the body composition that might be observed without SGLT2-i treatment. Additionally, the present study did not collect information on the compliance with diet therapy and exercise therapy. Due to a lack of information, we could not clarify why no correlation was observed between the changes in the visceral fat and HbA1c levels. Another concern is the potential effect of sex on metabolism; however, owing to the limited sample size, we were unable to carry out analyses by sex.

Except for glucose metabolism, significant changes were observed in the atherogenic factors, and triglyceride and high-density lipoprotein cholesterol levels, and a lowering of blood pressure was also observed. Although increases in low-density lipoprotein cholesterol levels were reported during the

Table 3 | Changes in the body components

	Baseline	Week 24	Week 52
Bodyweight (kg)			
Observed value	78.6 (74.1 to 83.0)	76.0 (71.5 to 80.4)	75.5 (71.1 to 79.8)
Difference from the baseline	–	−2.63 (−3.51 to −1.75)***	−3.13 (−4.15 to −2.11)***
BMI (kg/m^2)			
Observed value	28.0 (26.9 to 29.1)	27.1 (25.9 to 28.2)	26.9 (25.8 to 28.0)
Difference from the baseline	–	−0.946 (−1.26 to −0.629)***	−1.11 (−1.46 to −0.753)***
Abdominal circumference (cm)			
Observed value	94.4 (91.4 to 97.4)	92.4 (89.3 to 95.6)	92.2 (89.0 to 95.3)
Difference from the baseline	–	−1.93 (−2.96 to −0.910)***	−2.21 (−3.27 to −1.15)***
Total fat mass (kg)			
Observed value	23.5 (21.5 to 25.5)	21.2 (19.4 to 23.1)	21.2 (19.4 to 23.0)
Difference from the baseline	–	−1.97 (−2.66 to −1.28)***	−1.96 (−2.84 to −1.09)***
Lean mass (kg)			
Observed value	53.1 (49.6 to 56.6)	52.1 (48.6 to 55.6)	51.9 (48.3 to 55.5)
Difference from the baseline	–	−0.798 (−1.36 to −0.236)**	−0.992 (−1.50 to −0.486)***
Bone mineral content (g)			
Observed value	2,446 (2,274 to 2,617)	2,415 (2,245 to 2,584)	2,419 (2,250 to 2,588)
Difference from the baseline	–	−15.3 (−31.9 to 1.28)	−11.4 (−28.5 to 5.73)
Skeletal muscle mass index (kg/m^2)			
Observed value	7.74 (7.32 to 8.16)	7.59 (7.18 to 8.00)	7.53 (7.10 to 7.96)
Difference from the baseline	–	−0.113 (−0.261 to 0.0351)	−0.155 (−0.287 to −0.0237)*
Visceral fat area (cm^2)			
Observed value	162 (144 to 179)	150 (133 to 167)	151 (131 to 170)
Difference from the baseline	–	−11.2 (−22.3 to −0.132)	−9.59 (−20.6 to 1.38)
Subcutaneous fat area (cm^2)			
Observed value	215 (187 to 243)	204 (173 to 235)	200 (173 to 228)
Difference from the baseline	–	−17.3 (−32.8 to −1.75)**	−18.1 (−27.3 to −8.87)***

Data presented as mean (95% confidence interval): not applicable, *n* for each measurement. Refer to Table S8. ***$P < 0.001$, **$P < 0.01$ or *$P < 0.05$.

Table 4 | Correlation of the change in the (a) total fat mass during treatment with the clinical parameters, (b) Correlation of the change in the visceral fat area during treatment with the clinical parameters

		Correlation with the change in the total fat mass (Spearman's rank-order correlation analysis)					
		Week 24			Week 52		
		n	Correlation coefficient	*P*-value	*n*	Correlation coefficient	*P*-value
(a)							
Bodyweight (kg)		36	0.287	0.089	36	**0.442**	**0.006****
Abdominal circumference (cm)		36	**0.393**	**0.017***	36	**0.549**	**<0.001*****
BMI (kg/m^2)		36	**0.334**	**0.045***	36	**0.423**	**0.009****
Glucose metabolism	FPG (mmol/L)	36	−0.0287	0.868	36	0.264	0.120
	HbA1c (%)	36	0.0459	0.791	36	0.0966	0.577
	F-IRI (pmol/L)	36	−0.0646	0.710	36	0.130	0.453
	F-CPR (nmol/L)	36	0.133	0.440	36	0.268	0.114
Body component	Lean mass (kg)	36	−0.153	0.374	36	−0.0891	0.608
	SMI (kg/m^2)	36	−0.252	0.139	36	0.0831	0.632
	Visceral fat area (cm^2)	31	0.121	0.520	34	0.218	0.217
	Subcutaneous fat area (cm^2)	31	**0.491**	**0.004****	34	**0.540**	**<0.001*****
HDL-C (mmol/L)		36	−0.200	0.245	36	−0.149	0.388

Table 4 (*Continued*)

	Correlation with the change in the total fat mass (Spearman's rank-order correlation analysis)					
	Week 24			Week 52		
	n	Correlation coefficient	*P*-value	*n*	Correlation coefficient	*P*-value
TG (mmol/L)	36	−0.209	0.223	36	0.00103	0.995
FFA (μmol/L)	36	**0.363**	**0.028***	36	0.222	0.195
Acetoacetate (μmol/L)	36	**0.360**	**0.030***	36	0.0897	0.605
β-hydroxybutyrate (μmol/L)	36	**0.348**	**0.036***	36	0.100	0.563
Urine glucose excretion (mmol/24 h)	19	−0.0842	0.735	19	0.140	0.572

		Correlation with the change in the visceral fat area (Spearman's rank-order correlation analysis)					
		Week 24			Week 52		
		n	Correlation coefficient	*P*-value	*n*	Correlation coefficient	*P*-value
(b)							
Bodyweight (kg)		32	**0.400**	**0.022***	35	**0.390**	**0.020***
Abdominal circumference (cm)		32	0.190	0.299	35	0.259	0.133
BMI (kg/m^2)		32	**0.420**	**0.016***	35	**0.389**	**0.020***
Glucose metabolism	FPG (mmol/L)	32	0.283	0.117	35	0.103	0.557
	HbA1c (%)	32	0.330	0.064	35	0.0997	0.571
	F-IRI (pmol/L)	32	0.0942	0.610	35	0.136	0.440
	F-CPR (nmol/L)	32	0.215	0.240	35	0.170	0.331
Body component	Total fat mass (kg)	31	0.121	0.520	34	0.218	0.217
	Lean mass (kg)	31	0.224	0.228	34	0.149	0.404
	Fat/lean ratio	31	0.0597	0.751	34	0.126	0.479
	SMI (kg/m^2)	31	0.0968	0.607	34	0.00504	0.977
	Subcutaneous fat area (cm^2)	32	0.150	0.417	35	−0.0815	0.644
HDL-C (mmol/L)		32	−0.144	0.435	35	−0.182	0.296
TG (mmol/L)		32	0.223	0.222	35	0.0342	0.846
FFA (μmol/L)		32	0.311	0.083	35	0.330	0.052
Acetoacetate (μmol/L)		32	0.209	0.254	35	−0.0111	0.950
β-hydroxybutyrate (μmol/L)		32	0.196	0.285	35	−0.0210	0.905
Urine glucose excretion (mmol/24 h)		20	−0.144	0.548	20	−0.211	0.378

The correlation of the change from the baseline in the (a) total fat mass (dual-energy X-ray absorptiometry) or (b) visceral fat area (determined from computed tomography image) at each time-point with the changes in each clinical parameter was evaluated using Spearman's rank-order correlation. ***$P < 0.001$, **$P < 0.01$ or *$P < 0.05$. Significant difference at $P < 0.05$. Data with significant difference are shown in bold. F-CPR, fasting plasma C-peptide immunoreactivity; FFA, free fatty acid; F-IRI, fasting plasma insulin; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; SMI, skeletal muscle mass index; TG, triglyceride.

course of treatment with other SGLT2-i drugs,[11] the present study did not detect a significant change in the low-density lipoprotein cholesterol levels during the course of treatment. Furthermore, our study showed a significant increase in the blood adiponectin levels, which was a favorable outcome. It is of significance that, in Japanese type 2 diabetes patients with a moderate BMI, we observed a significant increase in the adiponectin level through SGLT2-i treatment, along with the observation of the time-course profile of the body composition. A significant decrease in urine albumin excretion was also observed, supporting a favorable effect on the kidney.[12]

In the present study, no new symptoms or serious symptoms were reported as adverse drug reactions, indicating favorable tolerability. In conclusion, combination therapy, involving the use of luseogliflozin and other oral hypoglycemic agents, in the treatment of Japanese type 2 diabetes patients is expected to provide better long-term glycemic control and improvements in the body composition and atherogenic factors, even in actual clinical practice.

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Table 5 | Correlation of the change in the (a) total fat mass during treatment with the clinical parameters at the baseline, (b) visceral fat area during treatment with the clinical parameters at the baseline

Baseline value		Correlation with the change in the total fat mass (Spearman's rank-order correlation analysis)					
		Change at week 24			Change at week 52		
		n	Correlation coefficient	*P*-value	*n*	Correlation coefficient	*P*-value
(a)							
Bodyweight (kg)		36	0.0555	0.750	36	–0.0915	0.598
Abdominal circumference (cm)		36	0.0417	0.810	36	–0.131	0.449
BMI (kg/m^2)		36	–0.113	0.514	36	–0.153	0.376
Glucose metabolism	FPG (mmol/L)	36	–0.000644	0.997	36	–0.116	0.504
	HbA1c (%)	36	–0.235	0.169	36	–0.217	0.204
	F-IRI (pmol/L)	36	–0.143	0.408	36	–0.0435	0.802
	F-CPR (nmol/L)	36	–0.241	0.158	36	–0.101	0.562
Body component	Total fat mass (kg)	36	–0.325	0.053	36	**–0.350**	**0.035***
	Lean mass (kg)	36	0.156	0.366	36	0.00180	0.991
	Fat/lean ratio	36	**–0.369**	**0.025***	36	–0.315	0.061
	SMI (kg/m^2)	36	0.131	0.450	36	–0.0716	0.680
	Visceral fat area (cm^2)	36	0.170	0.323	36	0.238	0.162
	Subcutaneous fat area (cm^2)	36	–0.178	0.300	36	**–0.351**	**0.035***
HDL-C (mmol/L)		36	0.220	0.198	36	0.254	0.136
TG (mmol/L)		36	0.287	0.090	36	0.0395	0.820
FFA (μmol/L)		36	0.0667	0.701	36	0.0189	0.913
Acetoacetate (μmol/L)		36	0.0463	0.789	36	0.0117	0.946
β-hydroxybutyrate (μmol/L)		36	–0.0669	0.700	36	–0.0422	0.808
Urine glucose excretion (mmol/24 h)		21	–0.174	0.455	21	**–0.440**	**0.045***

Baseline value		Correlation with the change in the visceral fat area (Spearman's rank-order correlation analysis)					
		Change at week 24			Change at week 52		
		n	Correlation coefficient	*P*-value	*n*	Correlation coefficient	*P*-value
(b)							
Bodyweight (kg)		32	0.0764	0.680	35	0.140	0.425
Abdominal circumference (cm)		32	–0.00294	0.987	35	0.177	0.312
BMI (kg/m^2)		32	0.0367	0.843	35	0.0961	0.585
Glucose metabolism	FPG (mmol/L)	32	–0.00220	0.990	35	0.107	0.545
	HbA1c (%)	32	0.203	0.267	35	0.164	0.350
	F-IRI (pmol/L)	32	–0.0663	0.720	35	0.113	0.520
	F-CPR (nmol/L)	32	–0.0729	0.694	35	0.0602	0.732
Body component	Total fat mass (kg)	31	0.0141	0.940	34	0.209	0.237
	Lean mass (kg)	31	0.0625	0.740	34	0.0576	0.748
	Fat/lean ratio	31	–0.0238	0.899	34	0.0735	0.681
	SMI (kg/m^2)	31	0.0194	0.918	34	0.00474	0.979
	Visceral fat area (cm^2)	32	**–0.399**	**0.023***	35	–0.183	0.296
	Subcutaneous fat area (cm^2)	32	0.110	0.550	35	0.318	0.062
HDL-C (mmol/L)		32	0.0228	0.902	35	0.232	0.182
TG (mmol/L)		32	–0.0381	0.837	35	–0.0228	0.897
FFA (μmol/L)		32	**–0.353**	**0.047***	35	**–0.498**	**0.002****
Acetoacetate (μmol/L)		32	–0.226	0.216	35	–0.265	0.124
β-Hydroxybutyrate (μmol/L)		32	**–0.458**	**0.007****	35	**–0.549**	**<0.001*****
Urine glucose excretion (mmol/24 h)		20	–0.281	0.233	20	–0.292	0.215

To investigate the baseline clinical parameters that correlate with the change in the total fat mass or visceral fat area, the change from the baseline in the (a) total fat mass or (b) visceral fat area at week 24 and week 52 was evaluated for the correlation with the baseline value of each clinical parameter, using Spearman's rank-order correlation. ***$P < 0.001$, **$P < 0.01$ or *$P < 0.05$. Significant difference at $P < 0.05$. Data with significant difference are shown in bold. BMI, body mass index; F-CPR, fasting plasma C-peptide immunoreactivity; F-CPR, fasting plasma C-peptide immunoreactivity; FFA, free fatty acid; F-IRI, fasting plasma insulin; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; SMI, skeletal muscle mass index; TG, triglyceride.

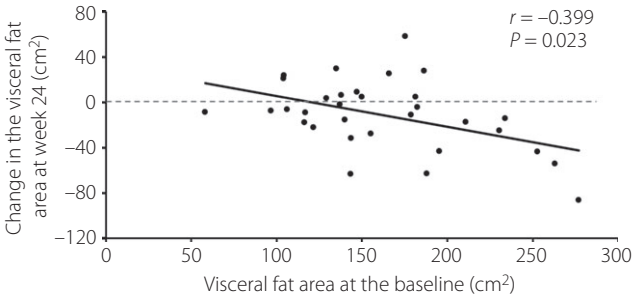

Figure 3 | Correlation of the individual changes in the visceral fat area with the visceral fat area at the baseline. The changes in the visceral fat area at week 24 in individual patients showed a significant negative correlation with the respective visceral fat area levels at the baseline ($r = -0.457$, $P = 0.0085$). In particular, the visceral fat area at week 24 was decreased in all the patients in whom the baseline visceral fat area was ≥187 cm^2.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 | Patient disposition.
Table S1 | List of participating institutions.
Table S2 | Key inclusion and exclusion criteria.
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