Loss of skeletal muscle mass and its predictors in type 2 diabetes patients under a multifaceted treatment approach

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Received: 16 March 2017 / Accepted: 12 June 2017 / Published online: 13 July 2017
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Abstract

Background Weight loss, which is an effective method for reducing visceral fat, may cause a concomitant loss of skeletal muscle mass. The aim of this study was to elucidate the changes in visceral fat and skeletal muscle mass in response to diabetes treatment including weight control.

Methods For 6 months we observed the changes in the body compositions of 72 Japanese patients with type 2 diabetes who underwent multifaceted treatment including educational hospitalization. Visceral fat area (VFA) and appendicular skeletal muscle mass (ASM) were measured using a bioelectrical impedance method and dual-energy X-ray absorptiometry, respectively.

Results During the follow-up period, VFA reduced significantly whereas the average ASM did not change. Changes in ASM were strongly positively associated with changes in body weight ($r = 0.50$). Additionally, in an analysis of covariance, an above-median BMI (27 kg/m²) and above-median VFA (110 cm²) at baseline were found to be independent predictors of ASM reduction prevention. Of the 55 patients who lost weight, those who had a baseline VFA of ≥ 110 cm² had significantly greater reductions in VFA than those with a baseline VFA of < 110 cm² ($p < 0.01$). ASM reduced significantly in patients with a VFA of < 110 cm² ($p < 0.01$), but not in those with a VFA of ≥ 110 cm² ($p = 0.98$).

Conclusions Baseline accumulation of visceral fat may predict a preferential reduction of visceral fat rather than skeletal muscle during weight control programs in type 2 diabetes patients.

Keywords Visceral fat · Skeletal muscle mass · Type 2 diabetes · Weight loss

Abbreviations

VFA	Visceral fat area
ASM	Appendicular skeletal muscle mass
ADA	American Diabetes Association
BMI	Body mass index
DXA	Dual-energy X-ray absorptiometry
JDS	Japan Diabetes Society
HbA1c	Hemoglobin A1c
UCP	Urinary C-peptide
eGFR	Estimated glomerular filtration rate
SMI	Skeletal muscle index
SFA	Subcutaneous fat area

Background

In overweight or obese patients with type 2 diabetes, modest and sustained weight loss has been found to improve glycemic control and reduce glucose-lowering medications [1–3]. The American Diabetes Association (ADA) has recommended that Asian patients categorized as overweight or obese, defined as having a body mass index (BMI) of ≥ 23 kg/m², should attempt to lose 5% of their weight through lifestyle modification [4]. Weight reduction is a standard approach to improving visceral fat accumulation, which causes insulin resistance. However, there are serious concerns regarding concomitant loss of skeletal muscle during weight loss.

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Indeed, the Action for Health in Diabetes (Look AHEAD) trial has shown that intensive lifestyle intervention for 1 year reduces lean mass by 2.3 ± 0.1 kg and fat mass by 5.6 ± 0.2 kg [5]. Furthermore, although glucagon-like peptide-1 agonist, sodium-glucose cotransporter 2 inhibitor, and bariatric surgery are often used for weight control in obese patients with type 2 diabetes, they cause a considerable reduction in fat-free mass [6–9].

Loss of skeletal muscle decreases endurance and increases fatigability. These changes lead to physical inactivity and thus sarcopenia. Previously, Park et al. showed an association between type 2 diabetes and excessive loss of skeletal muscle [10]. Thus, weight reduction could increase the risk of sarcopenia in patients with type 2 diabetes. Furthermore, physical inactivity caused by loss of skeletal muscle may also lead to weight rebound and subsequent development of obesity along with sarcopenia. Decreased muscle mass and increased adiposity has also been associated with increased mortality [11]. Therefore, it is important to evaluate changes in skeletal muscle mass after hyperglycemia treatments including weight control in type 2 diabetes patients.

Additionally, some researchers have reported factors that can influence changes in skeletal muscle mass. Lee et al. reported that insulin sensitizers, such as biguanide and thiazolidinedione, are effective at preventing skeletal muscle loss in diabetes patients [12]. A Japanese cross-sectional study demonstrated that age, sex, weight, and visceral fat area are independent predictors of the skeletal muscle index (SMI) in healthy subjects [13]. However, there have been no studies of predictors of skeletal muscle mass changes in type 2 diabetic patients during weight loss intervention.

The primary aim of the present study was therefore to examine the changes in skeletal muscle mass concomitantly with those in visceral fat using bioelectrical impedance and dual-energy X-ray absorptiometry (DXA) in Japanese type 2 diabetes patients undergoing a multifaceted treatment consisting of diet, exercise, and hypoglycemic medication therapy, including educational hospitalization of diabetes. The secondary aim was to evaluate the associations between change in skeletal muscle mass and known factors that could affect skeletal muscle mass.

Methods

Patients

We recruited 72 Japanese patients with type 2 diabetes who were hospitalized at Tokyo Medical and Dental University Hospital to receive a diabetes educational program and

treatment. Patients with severe renal impairment—defined as those with an estimated glomerular filtration rate (eGFR) of <15 mL/min/1.73 m² or those undergoing renal replacement therapy—and those with a severe infection or serious trauma were excluded. The patients gave written informed consent to participate in this study and for the results of it to be published. Eligible participants (35–83 years old) were those with available data on measured visceral fat area (VFA), whole-body DXA, anthropometric parameters, and laboratory data at baseline and 6 months later. All patients received intensive medical therapy and underwent lifestyle modification, including caloric restriction and regular exercise. The components of the lifestyle guidance varied with the patient according to the plan discussed between the patient, dietician, and physician. Briefly, the patients were instructed to restrict their daily caloric intake to under 25–30 kcal per kg of ideal body weight, and to exercise for 30 min or more at least three times a week. After discharge, the participants continued to receive medical therapy and lifestyle guidance as an outpatient of the hospital. Type 2 diabetes was diagnosed according to the criteria of the Japan Diabetes Society (JDS) [14]. This study protocol was registered as a clinical trial in the University Hospital Medical Information Network (UMIN) system (UMINStudyID: UMIN000024401). The study complied with the principles laid down by the Declaration of Helsinki and was approved by the ethics committee of Tokyo Medical and Dental University (no. M2000-1573).

Clinical and biochemical analyses

Standardized questionnaires were used to obtain information on medication and past history. Hemoglobin A1c (HbA1c) levels were measured by the latex agglutination method and expressed in accordance with the National Glycohemoglobin Standardization Program recommended by the Japanese Diabetes Society [14]. Urinary C-peptide (UCP) levels were measured by chemiluminescent immunoassay. Glomerular filtration rate (GFR) was estimated using the following equation for Japanese people, as proposed by the Japanese Society of Nephrology [15]: $GFR = 194 \times SCr^{-1.094} \times age^{-0.287}$ [$\times 0.739$ if female], where SCr stands for serum creatinine in mg/dL, measured by an enzymatic method. Body weight and height were measured. BMI was calculated as the weight divided by the square of the height (kg/m²) to determine obesity. These data were collected at baseline and 6 months later.

Measurement of body composition

A whole-body DXA scan (Lunar iDXA, GE Healthcare, Madison, WI, USA) was performed for each patient to

evaluate total, trunk, and appendicular body composition. The Lunar iDXA is reported to provide excellent precision in body composition measurements, particularly for lean tissue mass; the precision error was CV 0.5% [16]. Appendicular skeletal muscle mass (ASM) (kg) was defined as the sum of the lean soft-tissue masses of the arms and legs, following the method of Heymsfield et al. [17]. SMI was calculated as the ASM divided by the square of the height (kg/m^2). According to the criteria for sarcopenia in Asia [18], low muscle mass was defined as SMI $<7.0 \text{ kg}/\text{m}^2$ in men and SMI $<5.4 \text{ kg}/\text{m}^2$ in women. The VFA and subcutaneous fat area (SFA) were measured at the level of the umbilicus by a dual bioelectrical impedance analyzer (DUALSCAN, Omron Healthcare Co., Kyoto, Japan). There was good agreement between the DUALSCAN and computed tomography measurements of the

intraabdominal fat area, with a correlation of 0.88 ($p < 0.001$) [19]. In addition, a high correlation was observed between changes in intraabdominal fat area (IAFA) observed by DUALSCAN and changes in IAFA seen on computed tomography during weight loss intervention [20]. These parameters were measured at baseline and 6 months later to permit a comparison of individual changes.

Statistical analysis

Statistical analysis was performed using programs available in the SPSS version 21.0 statistical software package (SPSS Inc., Chicago, IL, USA). Data are presented as values of mean $\pm$ SD or median with interquartile range (IQR) or as percentages, according to which is appropriate for the data distribution. Normality was tested using the Kolmogorov–Smirnov test. A paired-sample t test or Wilcoxon's signed-rank test was performed, as appropriate, to compare baseline and follow-up levels of laboratory and body-composition parameters. Pearson's correlation analysis was performed to investigate the relationships among change in body weight (Δ body weight), change in VFA (Δ VFA), and change in ASM (Δ ASM). Analysis of

Table 1 Clinical and metabolic characteristics of the study patients

Sex	
Men	51 (70.8)
Women	21 (29.2)
Age (years)	62 $\pm$ 12
Duration of diabetes (years)	9 [4, 16]
eGFR ($\text{ml}/\text{min}/1.73 \text{ m}^2$)	75.2 $\pm$ 24.7
UCP ($\mu\text{g}/\text{day}$)	70.5 [37.3, 101.0]
Prevalence of obesity	
BMI $\geq 23 \text{ kg}/\text{m}^2$	65 (90.3)
BMI $\geq 25 \text{ kg}/\text{m}^2$	50 (69.4)
Prevalence of visceral obesity	43 (59.7)
Prevalence of low muscle mass	24 (33.3)
SMI <7.0 in men	22 (43.1)
SMI <5.4 in women	2 (9.5)
Prevalence of hypertension	47 (65.3)
Prevalence of dyslipidemia	51 (70.8)
History of CVD	17 (23.6)
Medications during follow-up period	
DPP-4 inhibitor	28 (38.9)
GLP-1 receptor agonist	12 (16.7)
Biguanide	39 (54.2)
Sulfonylurea	5 (6.9)
Insulin	40 (55.6)
Thiazolidinedione	2 (2.8)
α -Glucosidase inhibitor	8 (11.1)
Glinide	6 (8.3)
SGLT2 inhibitor	3 (4.2)

Data are expressed as the mean $\pm$ standard deviation, the median [interquartile range], or the number (percentage)

eGFR estimated glomerular filtration rate, UCP urinary C-peptide, BMI body mass index, SMI skeletal muscle index, CVD cardiovascular disease, DPP-4 dipeptidyl peptidase-4 inhibitor, GLP-1 glucagon-like peptide-1, SGLT2 sodium-glucose cotransporter 2

Table 2 Laboratory, anthropometric, and body-composition parameters of the study patients at baseline and after 6 months

	Baseline	Follow-up	p value
HbA1c (%)	9.1 [8.3, 10.4]	7.2 [6.6, 8.2]	<0.001
Men	9.1 [8.3, 10.5]	7.2 [6.7, 8.4]	<0.001
Women	9.2 [8.2, 10.2]	6.9 [6.3, 7.9]	<0.001
Body weight (kg)	73.1 $\pm$ 13.5	70.3 $\pm$ 12.9	<0.001
Men	74.9 $\pm$ 12.3	72.4 $\pm$ 12.2	<0.001
Women	68.6 $\pm$ 15.4	65.3 $\pm$ 13.5	0.003
BMI (kg/m^2)	27.1 $\pm$ 4.2	26.0 $\pm$ 4.0	<0.001
Men	26.6 $\pm$ 3.6	25.5 $\pm$ 3.6	<0.001
Women	28.6 $\pm$ 5.3	27.2 $\pm$ 4.6	0.003
VFA (cm^2)	113.4 $\pm$ 47.0	92.6 $\pm$ 40.5	<0.001
Men	113.2 $\pm$ 47.2	91.1 $\pm$ 39.9	<0.001
Women	114.0 $\pm$ 47.5	96.4 $\pm$ 42.8	0.001
SFA (cm^2)	215.5 $\pm$ 75.6	190.8 $\pm$ 71.7	<0.001
Men	204.5 $\pm$ 70.4	179.2 $\pm$ 60.0	<0.001
Women	242.1 $\pm$ 82.9	219.1 $\pm$ 89.7	0.037
ASM (kg)	19.24 $\pm$ 3.82	19.27 $\pm$ 3.93	0.813
Men	20.64 $\pm$ 3.26	20.67 $\pm$ 3.41	0.826
Women	15.84 $\pm$ 2.87	15.85 $\pm$ 2.89	0.933

Data are presented as the mean $\pm$ SD or the median [interquartile range]. p values were obtained using the paired-sample t test or Wilcoxon's signed-rank test

BMI body mass index, VFA visceral fat area, SFA subcutaneous fat area, ASM appendicular skeletal muscle mass

Fig. 1 **a** Relationship between change in VFA (cm^2) and change in body weight (kg). **b** Relationship between change in ASM (kg) and change in body weight (kg). VFA visceral fat area, ASM appendicular skeletal muscle mass

covariance (ANCOVA) was used to investigate the association between ΔASM mass and the baseline characteristics of the participants (mean $\pm$ SE) in order to adjust $\Delta\text{body weight}$ accordingly. Differences were considered to be statistically significant when p was less than 0.05.

Results

Table 1 shows clinical and metabolic characteristics of the type 2 diabetic patients enrolled. They were 51 men and 21 women with a mean age of 62 ± 12 years. Most patients (90.3%) had BMI values of $\geq 23 \text{ kg/m}^2$, meaning that they were categorized as overweight or obese according to the ADA guideline [4]. Twenty-two males and two females (33.3%) had SMI values lower than the cutoff points for low muscle mass, as defined by the consensus report of the Asian Working Group for Sarcopenia [18]. Insulin, biguanide, and incretin agents were commonly used during the follow-up period. A small number of patients were treated with sulfonylurea ($n = 5$), thiazolidinedione ($n = 2$), α -glucosidase inhibitor ($n = 8$), glinide ($n = 6$), and sodium-glucose cotransporter 2 inhibitor ($n = 3$). Two patients who were treated with thiazolidinedione also used biguanide.

Table 2 shows the laboratory, anthropometric, and body-composition parameters at baseline and after 6 months. HbA1c, body weight, BMI, VFA, and SFA decreased significantly, whereas the average ASM did not change because a substantial proportion of the patients

showed increased ASM during the follow-up period even though their body weights decreased a little. Among the 55 patients who showed reductions in body weight during the follow-up period, 21 (38%) had increased ASM (Fig. 1b). Correlation analysis revealed significant positive associations of ΔVFA with $\Delta\text{body weight}$ ($r = 0.59$) (Fig. 1a) and ΔASM with $\Delta\text{body weight}$ ($r = 0.50$) (Fig. 1b). There was no correlation between ΔVFA and ΔASM ($p = 0.31$).

As $\Delta\text{body weight}$ was a strong determinant of ΔASM , ANCOVA analysis was performed to adjust $\Delta\text{body weight}$ so that the association between ΔASM and baseline characteristics which could affect the change in muscle mass could be assessed. Table 3 shows that patients with above-median BMI (27 kg/m^2) and above-median VFA (110 cm^2) at baseline were at significantly lower risk for a decrease in ASM after 6 months of treatment.

To evaluate the impact of baseline visceral fat on ΔASM in type 2 diabetes patients receiving multifaceted treatment, we classified the patients into four groups according to baseline VFA (below median vs. above median) and change in body weight (gain vs. reduction) (Table 4; Figs. 2, 3).

Among the 55 patients who showed reductions in body weight during the follow-up period, there was no statistical difference in mean $\Delta\text{body weight}$ between patients with VFA $< 110 \text{ cm}^2$ and those with VFA $\geq 110 \text{ cm}^2$ (-3.6 ± 2.7 vs. -5.3 ± 4.4 , $p = 0.09$), whereas ΔVFA was significantly smaller in VFA $< 110 \text{ cm}^2$ patients compared with VFA $\geq 110 \text{ cm}^2$ patients (-12.4 ± 23.0 vs. -36.9 ± 32.8 , $p < 0.01$) (Table 4). In patients with VFA $< 110 \text{ cm}^2$, mean

Table 3 ANCOVA analysis with change in ASM after 6 months of intensive treatment as the dependent variable in type 2 diabetes patients

Fixed factor	<i>n</i>	Estimated change	<i>p</i> value
Sex			
Men	51	0.012 ± 0.120	0.809
Women	21	0.065 ± 0.187	
Median age (65 years)			
Below median	37	0.088 ± 0.141	0.541
Above median	35	−0.037 ± 0.145	
Median baseline BMI (27 kg/m ²)			
Below median	36	−0.212 ± 0.140	0.021
Above median	36	0.266 ± 0.140	
Median baseline VFA (110 cm ²)			
Below median	36	−0.178 ± 0.140	0.045
Above median	36	0.232 ± 0.140	
Median baseline HbA1c (9.2%)			
Below median	37	−0.015 ± 0.144	0.678
Above median	35	0.072 ± 0.148	
Median SMI of men (7.25 kg/m ²)			
Below median	26	0.212 ± 0.178	0.157
Above median	25	−0.154 ± 0.182	
Median SMI of women (6.40 kg/m ²)			
Below median	10	0.075 ± 0.218	0.702
Above median	11	−0.043 ± 0.208	
Utilization of insulin			
No	32	−0.119 ± 0.150	0.196
Yes	40	0.144 ± 0.134	
Utilization of biguanide			
No	33	−0.095 ± 0.148	0.267
Yes	39	0.131 ± 0.136	

Covariate was Δbody weight

ASM appendicular skeletal muscle mass, BMI body mass index, VFA visceral fat area, SMI skeletal mass index

VFA significantly decreased (77.4 ± 24.7 vs. 65.0 ± 28.2 , $p < 0.01$), as did mean ASM (17.43 ± 3.29 vs. 17.10 ± 3.10 , $p = 0.01$) (Fig. 2a, c). In patients with VFA ≥ 110 cm², although mean VFA also significantly decreased (149.7 ± 30.6 vs. 112.8 ± 39.9 , $p < 0.01$), there was no significant change in mean ASM (20.50 ± 3.38 vs. 20.50 ± 3.46 , $p = 0.98$) (Fig. 2b, d). In other words, the change in ASM largely depended on the baseline VFA in patients who showed reductions in body weight.

Among the 17 patients who gained body weight during the follow-up period, no statistical difference in mean Δbody weight was observed between the two groups (3.6 ± 3.1 vs. 1.6 ± 2.0 , $p = 0.14$) (Table 4). In patients with VFA < 110 cm², both mean VFA (75.1 ± 25.0 vs. 84.8 ± 25.9 , $p = 0.13$) and mean ASM (18.97 ± 4.40 vs.

19.70 ± 3.88 , $p = 0.07$) tended to increase, but not statistically significantly (Fig. 3a, c). In patients with VFA ≥ 110 cm², mean VFA decreased significantly (151.3 ± 44.5 vs. 124.2 ± 31.5 , $p < 0.01$) whereas mean ASM tended to increase but not statistically significantly (21.23 ± 4.27 vs. 21.75 ± 5.06 , $p = 0.25$) (Fig. 3b, d). Despite gaining body weight, VFA reduced in the patients with VFA ≥ 110 cm² under the multifaceted intervention of this study (Fig. 3b).

The subgroups showed similar data for target energy intake and medications during the follow-up period. However, among the patients who showed a reduced body weight, biguanide was used more frequently in patients with VFA ≥ 110 cm² than in those with VFA < 110 cm² (Table 4).

Conclusions

In this study, we observed significant reductions in HbA1c, body weight, and body fat accumulation, but not in the amount of skeletal muscle mass lost. However, Δbody weight had strong positive associations with ΔASM and ΔVFA. Notably, after adjusting Δbody weight appropriately, higher BMI or VFA were found to be independent positive predictors of prevention of skeletal muscle mass loss. These observations could help to identify patients at a high risk of losing skeletal muscle mass after multifaceted diabetes treatment including lifestyle modification and weight control.

Visceral fat tends to decrease more rapidly than subcutaneous fat in response to diet therapy [21]. In this study, during weight reduction, there was a significant reduction in VFA without any change in ASM among patients with above-median baseline VFA (VFA ≥ 110 cm²), whereas ASM significantly decreased in parallel with a reduction in VFA among patients with below-median baseline VFA (VFA < 110 cm²). Collectively, these observations suggest that visceral fat is reduced more readily than skeletal muscle mass during weight loss in type 2 diabetes patients with excess visceral fat accumulation.

Among patients who showed reductions in body weight, ASM significantly reduced in patients with a low baseline VFA. In contrast, patients with a high baseline VFA were able to maintain their ASM, while their VFA decreased markedly compared with the VFA in the low-VFA group. These differences may be caused by the potential effect of body fat on the change in muscle mass. Several recent observational studies without weight loss intervention showed that body fat mass has a negative impact on skeletal muscle mass [13, 22–24]. In prospective studies, Kim et al. showed that baseline VFA is an independent negative predictor of ΔASM, whereas the association between baseline ASM and ΔVFA is not statistically

Table 4 Characteristics of the patients in each subgroup classified according to the changes in body weight and baseline VFA

	Weight loss			Weight gain		
	VFA <110 cm ² (n = 27)	VFA >110 cm ² (n = 28)	p value	VFA <110 cm ² (n = 9)	VFA >110 cm ² (n = 8)	p value
Sex (%men)	60	75	0.214	89	75	0.453
Age (years)	64 ± 12	61 ± 11	0.340	60 ± 14	59 ± 9	0.896
Baseline HbA1c (%)	8.7 [8.2, 9.7]	8.6 [8.1, 9.7]	0.966	11.6 [9.3, 12.8]	10.5 [9.9, 10.7]	0.531
ΔHbA1c	−1.6 [−2.5, −0.5]	−1.4 [−2.7, −0.2]	0.966	−3.9 [−5.3, −2.7]	−2.4 [−3.1, −0.6]	0.114
BMI (kg/m ²)	24.9 ± 2.4	30.0 ± 4.0	<0.001	23.5 ± 3.7	28.6 ± 2.5	0.005
Baseline BW (kg)	64.3 ± 8.0	81.9 ± 11.6	<0.001	65.0 ± 13.7	81.0 ± 10.5	0.018
ΔBW	−3.6 ± 2.7	−5.3 ± 4.4	0.092	3.6 ± 3.1	1.6 ± 2.0	0.142
Baseline VFA (cm ²)	77.4 ± 24.7	149.7 ± 30.6	<0.001	75.1 ± 25.0	151.3 ± 44.5	<0.001
ΔVFA	−12.4 ± 23.0	−36.9 ± 32.8	0.002	9.8 ± 17.5	−27.1 ± 21.4	0.001
Baseline SFA (cm ²)	166.6 ± 45.4	268.2 ± 72.6	<0.001	161.8 ± 52.4	256.0 ± 31.6	0.001
ΔSFA	−23.6 ± 38.6	−47.5 ± 43.6	0.036	30.5 ± 41.7	−9.9 ± 27.9	0.036
Baseline ASM (kg)	17.43 ± 3.29	20.50 ± 3.38	0.001	18.97 ± 4.40	21.23 ± 4.27	0.302
ΔASM	−0.33 ± 0.65	0.01 ± 1.02	0.151	0.69 ± 0.94	0.53 ± 1.34	0.707
Target energy intake (kcal/ IBW)	27.4 ± 1.7	26.6 ± 1.7	0.070	26.9 ± 1.4	26.3 ± 1.6	0.417
Medications (%)						
DPP-4 inhibitor	44	43	0.906	11	38	0.200
GLP-1 receptor agonist	11	18	0.478	22	25	0.893
Insulin	48	54	0.688	56	88	0.149
Biguanide	37	71	0.005	44	50	0.819

BMI body mass index, BW body weight, BMI body mass index, VFA visceral fat area, SFA subcutaneous fat area, ASM appendicular skeletal muscle mass, IBW ideal body weight

significant in nondiabetic subjects [22]. The authors proposed that chronic subclinical inflammation induced by adipokines may contribute to the loss of skeletal muscle mass. Body fat accumulation could accelerate the reduction of muscle mass through the release of proinflammatory adipokines—such as tumor necrosis factor- α and interleukin-6, which have catabolic effects on skeletal muscle—from visceral adipose tissue [25]. This being the case, the maintenance of ASM observed in patients with high VFA may have been caused by the considerable reduction in visceral fat induced by clinical intervention. In our case, a significant negative correlation between baseline VFA and Δ VFA was observed in our patients ($r = -0.52$, $p < 0.01$; data not shown). This correlation indicates that a large baseline VFA is associated with a significant decrease in VFA during a weight loss intervention program. It is therefore conceivable that those with visceral obesity are able to prevent muscle loss by attenuating the catabolic effect of proinflammatory adipokines produced in visceral fat during the process of decreasing the VFA. Further analysis is required to examine this hypothesis, as serum inflammatory cytokine levels were not evaluated in this study.

Insulin resistance is considered to be closely associated with sarcopenia [26]. Lee et al. reported that insulin sensitizers such as biguanide and thiazolidinedione are effective at attenuating skeletal muscle loss in diabetes patients [12]. In our study, ANCOVA analysis showed no significant association between the utilization of biguanide and Δ ASM. However, among the patients who reduced body weight in our study, patients with VFA ≥ 110 cm² were administered biguanide more frequently than those with VFA <110 cm². Therefore, there is a possibility that potential effects of biguanide contributed to the maintenance of skeletal muscle.

Skeletal muscle mass loss is one of the components of frailty. Recently, frailty has been recognized as a risk factor for mortality and hypoglycemia in older people with type 2 diabetes [27]. On the other hand, weight loss is effective at improving glycemic control, and ADA has recommended that Asian diabetes patients with a BMI of ≥ 23 kg/m² should attempt to lose 5% of their weight [4]. Therefore, evaluating the changes in muscle mass during weight loss intervention is an important tool for improving total clinical outcomes for aging patients with type 2 diabetes who are at high risk for frailty.

Fig. 2a–d Differences in changes in VFA and ASM among the patients showing weight loss. The patients were divided into two groups according to whether they were below or above median baseline VFA: **a, c** VFA <110 cm² and **b, d** VFA ≥110 cm². VFA visceral fat area, ASM appendicular skeletal muscle mass

In our study, body weight reduced significantly after multifaceted diabetes treatment, whereas ASM did not change. These findings are different from the results of previous reports on the changes in skeletal muscle mass during various diabetes treatments, including weight loss [5–9]. As our research was a single-arm, small-scale study, it is unclear which factor in our multifaceted intervention had a decisive impact on the maintenance of ASM. However, our findings may imply that multifaceted treatment including educational hospitalization has unexpected effects on preventing skeletal muscle loss for patients with severe type 2 diabetes. Furthermore, our results suggest that changes in muscle mass differ greatly among individuals and that baseline VFA may predict muscle mass loss in patients receiving diabetes treatments that include weight loss. These findings may help to identify the target weight for diabetes treatment, especially in aging patients.

Some limitations of our study should be considered. First, physical activity during the follow-up period was not

evaluated. Castaneda et al. reported positive effects of resistance training in that it increased lean mass in older adults with type 2 diabetes [28]. Although our patients were instructed to perform only moderate-intensity aerobic exercises, the level of resistance training performed by the patient may be a confounding factor. Second, data about nutrition intake were not available. Considering the effects of nutrients such as vitamin D and amino acids on muscle mass [29, 30], differences among the patients in diet may have affected the outcome. Third, we were unable to determine the prevalence of sarcopenia because we had no information on muscle strength and physical performance. Fourth, the number of study patients was not large enough to allow multiple regression analyses to be performed in order to eliminate the influence of confounding factors. Therefore, more important predictors for Δ ASM could exist. Finally, the participants in this study were all hospitalized patients at baseline. Therefore, the ability to generalize our findings might be limited.

Fig. 3a–d Differences in changes in VFA and ASM among the patients showing weight gain. The patients were divided into two groups according to whether they were below or above median baseline VFA: **a, c** VFA <110 cm² and **b, d** VFA ≥110 cm². VFA visceral fat area, ASM appendicular skeletal muscle mass

In summary, no significant reduction in the amount of skeletal muscle mass was observed in Japanese type 2 diabetes patients receiving multifaceted treatment. Additionally, change in body weight and high visceral fat accumulation at baseline were associated with the change in skeletal muscle mass. These results suggest that in type 2 diabetes patients with visceral obesity, visceral fat may be preferentially reduced relative to skeletal muscle mass during weight control programs. For type 2 diabetes patients without visceral fat accumulation, especially the elderly group, intensive lifestyle intervention that includes a resistance training program may be recommended to prevent loss of muscle mass and subsequent development of frailty when considerable weight loss has been observed.

Acknowledgements This work was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan [Grant Number 25860403].

Compliance with ethical standards

Conflict of interest None of the authors have any conflicts of interest associated with this research.

Ethical standards This study was carried out in accordance with the Declaration of Helsinki of 1964 and later versions and approved by the ethics committee of Tokyo Medical and Dental University (approval no. M2000-1573, approval date: 23 July 2013).

Informed consent The patients gave their written informed consent to participate in this study and for its results to be published.

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