Associations between genetic loci related to lean mass and body composition in type 2 diabetes

Tatsuro Minohara, Shinsuke Nosō, Naru Babaya, Yoshihisa Hiromine, Yasunori Taketomo, Fumimaru Niwano, Yukako Makutani, Sawa Yoshida, Sara Yasutake, Shuzo Imamura and Hiroshi Ikegami

Department of Endocrinology, Metabolism and Diabetes, Kindai University Faculty of Medicine, Osaka, Japan

Correspondence
Dr. Shinsuke Nosō MD PhD, Department of Endocrinology, Metabolism and Diabetes, Kindai University Faculty of Medicine, 377-2 Ohno-higashi, Osaka-sayama, Osaka 589-8511, Japan.
Email: noso@med.kindai.ac.jp

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Aim: Several genetic loci related to lean mass have been identified in healthy individuals by genome-wide association studies; however, the contribution of these loci to body composition in type 2 diabetes remains to be investigated. Here, we aimed to clarify the genetic determinants of body composition in individuals with type 2 diabetes.

Methods: A total of 176 Japanese outpatients (70 women and 106 men) with type 2 diabetes were studied using a cross-sectional design. Body composition was measured using bioimpedance analysis with a commercially available device (InBody770). Single-nucleotide polymorphisms in IRS1 (rs2943656), HSD17B11 (rs9991501), VCAN (rs2287926), ADAMTSL3 (rs4842924) and FTO (rs93936385) were evaluated by genotyping. The contributions of single-nucleotide polymorphisms to body composition were examined, considering known clinical determinants.

Results: Sex, body composition and age were identified as clinical predictors. IRS1 rs2934656 was identified as an independent predictor of skeletal muscle mass ($\beta = 0.11$, $P = 0.026$), and ADAMTSL3 rs4842924 was an independent predictor of body fat mass ($\beta = 0.15$, $P = 0.0095$) and appendicular lean mass ($\beta = -0.13$, $P = 0.017$).

Conclusions: The findings clarified the contribution of genetic factors – IRS1 and ADAMTSL3 – to interindividual variation in body composition, independent of clinical factors, in type 2 diabetes patients. These data will contribute to the establishment of effective methods for the prediction, prevention, and intervention of sarcopenia and frailty in diabetes patients. Geriatr Gerontol Int 2021; 21: 932–938.

Keywords: ADAMTSL3, aging, body compositions, IRS1, type 2 diabetes.

Introduction

Lean body mass, consisting primarily of skeletal muscle and internal organs, is a component of the body composition calculated by subtracting fat and bone mass from the total body mass. Body composition is closely associated with glucose metabolism, because skeletal muscle is a major site for insulin-stimulated glucose uptake, and adipose tissue contributes to insulin resistance. Progressive changes in lean and fat mass are observed with aging in healthy individuals and in patients with diabetes, and often cause unfavorable metabolic changes in the elderly. In particular, the age-related loss of skeletal muscle mass (SMM) and strength could lead to functional impairment, physical disability, and even mortality, referred to as sarcopenia and frailty. We have recently shown that the diabetic state, as well as hyperglycemia, are correlated with reductions in SMM and strength, indicating a close relationship between glucose metabolism and lean mass. Additionally, sex is a well-known factor affecting body composition. Accordingly, age, sex and diabetic state are important clinical determinants of lean mass.

With respect to genetic factors for lean mass, family and twin studies have estimated a heritability of 0.52–0.60, suggesting that this trait is highly heritable in healthy adults. A large meta-analysis of genome-wide association studies supported the contribution of genetic factors to lean mass in healthy adults. However, the contributions of these loci to indices of body composition have not been fully elucidated in individuals with type 2 diabetes. Therefore, in the present study, we evaluated the contribution of genetic factors to body composition in type 2 diabetes, considering established clinical determinants.

Methods

Participants

A total of 176 consecutive Japanese ambulatory outpatients (70 women and 106 men) with type 2 diabetes were recruited from November 2016 to January 2018 at Kindai University Hospital, located in Japan, and studied using a cross-sectional design (Appendix S1. Supplementary methods). The clinical characteristics of participants are described in Table 1. The present study was approved by the appropriate ethics committee, and written informed consent was obtained from all participants.
Table 1 Clinical characteristics of participants with type 2 diabetes

| Characteristic                  | n = 176 |
|--------------------------------|---------|
| Sex (female/male)              | 70/106  |
| Age, years (range)             | 67.4 ± 9.5 (38–92) |
| Proportion of elderly participants (%) | 70.5    |
| Duration of diabetes (years)   | 15.2 ± 10.7 |
| BMI (kg/m²)                    | 24.9 ± 4.7 |
| HbA1c (%)                      | 8.7 ± 1.7 |
| Fasting plasma glucose (mg/dL) | 141.8 ± 38.3 |
| Serum albumin (g/dL)           | 4.0 ± 0.4 |
| cGFR (mL/min/1.73 m²)          | 69.1 ± 21.1 |
| NDR/SDR>pre-PDR (n)            | 131/20/25 |
| Treatment for diabetes (n)     | 104/67/23 |
| Insulin                        | 104     |
| Biguanide                      | 67      |
| DPP4 inhibitor                 | 62      |
| Sulfonylurea/glinide           | 35      |
| GLP-1 receptor agonist         | 29      |
| SGLT2 inhibitor                | 23      |
| Thiazolidine                   | 6       |

*Aged ≥65 years.

BMI, body mass index; DPP4, dipeptidyl peptidase-4; cGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; NDR, no diabetic retinopathy; PDR, proliferative diabetic retinopathy; SDR, simple diabetic retinopathy; SGLT2, sodium–glucose cotransporter 2.

Measurements of body composition

A bioelectrical impedance analysis (BIA) was carried out for the measurement of total and segmental body composition using a commercial device (InBody770, Inbody Japan, Tokyo, Japan; Appendix S1. supplementary methods). Total lean mass (TLM) was defined as the sum of the soft lean mass except for lipids and bone minerals in the whole body, and appendicular lean mass (ALM) was estimated as the sum of the soft lean mass of both arms and both legs. Body fat mass (BFM) was defined as the sum of the soft lean mass in the whole body. SMM was defined as the sum of the soft lean mass except for lipids and bone minerals in the whole body, and appendicular lean mass (ALM) was estimated as the sum of the soft lean mass of both arms and both legs. Body fat mass (BFM) was defined as the sum of the soft lean mass in the whole body. Body composition variables were estimated by direct counting.

Genetic analysis

Genomic DNA was extracted from peripheral leukocytes of participants using a standard phenol–chloroform method, after obtaining informed consent, and stored at 4°C at the Kindai University Faculty of Medicine, Osaka, Japan. Five single-nucleotide polymorphisms (SNPs) previously associated with lean mass were genotyped: rs2943656 in FTO, rs9991501 in HSD17B11, rs2287926 in VCAN, rs4842926 in ADAMTS13 and rs9936385 in FTO.* Genotyping was carried out using the TaqMan SNP genotyping assay according to the manufacturer’s instructions (Applied Biosystems, Tokyo, Japan; Appendix S1; supplementary methods). Allele frequencies were estimated by direct counting.

Statistical analysis

The relationship between body composition and other continuous variables was analyzed by a simple linear regression analysis (least squares method). A multiple linear regression analysis with the forward-backward stepwise selection method was carried out to identify variables that were independently associated with a change in indices of body composition. The χ²-test and Fisher’s exact probability test were used to determine the significance of differences in the distributions of the number of participants and alleles. Statistical significance was defined as *P < 0.05.

Results

Correlations between age and body compositions in type 2 diabetes patients

The relationships between indices of body composition and age are shown in Fig. 1. TLM (r = –0.24, P = 0.001), ALM (r = –0.24, P = 0.001) and SMM (r = –0.38, P = 1.8 × 10⁻²) were significantly negatively correlated with age (Table 2). BMI did not show a significant correlation with age (r = 0.005, P = 0.95, Appendix S2; supplementary results).

Correlations between clinical variables and body composition

To elucidate the clinical determinants of each body composition index other than age and sex, a simple regression analysis was carried out (Table 2). The duration of diabetes, hemoglobin A1c levels and serum albumin levels did not show significant correlations with any index of body composition (TLM, ALM and SMM). Body mass index (BMI) showed a highly significant correlation with body composition (TLM: r = 0.68, P = 1.6 × 10⁻²; ALM: r = 0.64, P = 1.3 × 10⁻²; SMM: r = 0.66, P = 3.1 × 10⁻²). BMI was significantly correlated with indices of body composition as independent predictors. With respect to medications for diabetes treatment, Dipeptidyl peptidase-4 (DPP4) inhibitor treatment was not correlated with TLM (β = 0.083, not significant [NS]), ALM (β = 0.086, NS) or SMM (β = 0.085, NS). Dipeptidyl peptidase-4 (DPP4) inhibitor treatment was not correlated with ALM (β = 0.069, NS). Glucagon-like peptide-1 (GLP-1) receptor agonist treatment was significantly correlated with BFM (β = 0.14, P = 0.025).

Multiple linear regression analysis of body composition with clinical variables, including diabetes medications

To further study the clinical determinants of body composition, including medications for diabetes treatment, a multiple linear regression analysis was carried out (Table S1). BMI was excluded as an independent variable owing to multicollinearity with body composition (tolerance <0.1). Sex, age and body composition indices (BFM for TLM/ALM/SMM and SMM for BFM) were significantly correlated with indices of body composition as independent predictors. With respect to medications for diabetes treatment, insulin/sulfonylurea/glinides, biguanide and thiazolidine were rejected as independent predictors for all indices of body composition. Sodium–glucose cotransporter 2 inhibitor treatment was not correlated with TLM (β = 0.083, not significant [NS]), ALM (β = 0.086, NS) or SMM (β = 0.085, NS). Dipeptidyl peptidase-4 (DPP4) inhibitor treatment was not correlated with ALM (β = 0.069, NS). Glucagon-like peptide-1 (GLP-1) receptor agonist treatment was significantly correlated with BFM (β = 0.14, P = 0.025).

Contribution of genetic loci and clinical parameters to lean mass

To determine the contribution of genetic loci to lean mass, including clinical determinants as independent variables, five loci (FTO, HSD17B11, VCAN, ADAMTS13 and FTO), previously identified by genome-wide association studies in healthy individuals, were genotyped for all participants (Table S2). No variants were observed for HSD17B11 rs9991501 in the study participants. Therefore, these four SNPs were included as independent variables that were independently associated with a change in indices of body composition. The χ²-test and Fisher’s exact probability test were used to determine the significance of differences in the distributions of the number of participants and alleles.
variables in a multiple regression analysis for body composition. Among the medications for diabetes treatment, insulin/SU/glinide, biguanide, and thiazolidine were excluded as independent variables based on the multiple linear regression analysis of the clinical determinants of body composition.

As the strongest determinant of body composition, sex showed a significant positive correlation with TLM ($\beta = 0.58$, $P = 2.4 \times 10^{-20}$), ALM ($\beta = 0.62$, $P = 3.6 \times 10^{-23}$) and SMM ($\beta = 0.58$, $P = 2.3 \times 10^{-22}$), indicating that the mass was higher in men than in women (Table 3). In contrast, sex showed a significant negative correlation with BFM ($\beta = -0.58$, $P = 3.6 \times 10^{-16}$), indicating that the mass was lower in men than in women. As the second strongest determinant, BFM showed a significant positive correlation with TLM ($\beta = 0.58$, $P = 2.4 \times 10^{-20}$).

Table 2  Simple regression analysis of indices for body compositions in type 2 diabetes patients

|                      | Total lean mass | Appendicular lean mass | Skeletal muscle mass | Body fat mass |
|----------------------|-----------------|------------------------|----------------------|--------------|
|                      | $r$             | $P$                    | $r$                  | $P$          |
| Age                  | $-0.24$         | $0.001$                | $-0.24$              | $0.001$      |
| Duration of diabetes | $0.018$         | NS                     | $0.024$              | NS           |
| BMI                  | $0.68$          | $1.6 \times 10^{-25}$  | $0.64$               | $1.3 \times 10^{-21}$ |
| HbA1c                | $0.029$         | NS                     | $0.029$              | NS           |
| Serum albumin        | $0.074$         | NS                     | $0.074$              | NS           |
| Total lean mass      | $-0.97$         | $3.8 \times 10^{-108}$ | $0.86$               | $6.3 \times 10^{-54}$ $0.41$ |
| Appendicular lean mass| $0.97$        | $3.8 \times 10^{-108}$ | $0.88$               | $6.1 \times 10^{-57}$ $0.35$ |
| Skeletal muscle mass | $0.86$          | $6.3 \times 10^{-54}$  | $0.88$               | $6.1 \times 10^{-57}$ $0.31$ |
| Body fat mass        | $0.41$          | $2.1 \times 10^{-8}$   | $0.35$               | $1.7 \times 10^{-6}$ $0.31$ |

Total $n = 176$.

BMI, body mass index; HbA1c, hemoglobin A1c; NS, not significant.
Table 3: Multiple regression analysis of indices of body composition in type 2 diabetes including genetic loci as independent variables

| Objective variables | Sex | Age | Body composition | Drug |
|--------------------|-----|-----|-----------------|------|
| | | | | 0: No | 1: Yes |
| Total lean mass | β | P | SMM | NS |
| Appendicular lean mass | β | P | SMM | NS |
| Lean mass index | β | P | SMM | NS |
| RSM | β | P | SMM | NS |
| SMM | β | P | SMM | NS |

**Multiple regression analysis of indices of body composition in type 2 diabetes including genetic loci as independent variables**

- **Objective variables**: Sex, Age, Body composition, Drug
- **Independent variables**: Sex, Age, Total lean mass, Appendicular lean mass, Lean mass index, SMM, RSM, SMM
- **Dependent variables**: Total lean mass, Appendicular lean mass, Lean mass index, SMM, RSM

As for the genetic determinants of body composition, **IRS1 rs2943656** showed a significant positive correlation with SMM (β = 0.11, P = 0.026), suggesting that participants with the G/G genotype had a higher mass than that of individuals with other genotypes. **ADAMTSL3 rs4842924** was significantly negatively correlated with ALM (β = 0.23, P = 0.008) and BFM (β = -0.26, P = 0.02) in non-elderly individuals (Table S3), but not in elderly individuals (Table S4); **ADAMTSL3 rs4842924** significantly correlated with the T/T genotype and showed a significant positive correlation with BMI (β = 0.15, P = 0.0095), suggesting that mass was higher in participants with the T/T genotype than in those with other genotypes. With respect to medications, GLP-1 receptor agonist (GLP-1ra) treatment showed a positive correlation with BMI (β = 0.14, P = 0.016).

To further evaluate the differences in genetic factors contributing to body composition, the participants were stratified by age (elderly: ≥65 years, non-elderly: <65 years) for multiple regression analysis. We observed that **IRS1 rs2943656** significantly correlated with SMM (β = 0.23, P = 0.008) and BMI (β = -0.26, P = 0.02) in non-elderly individuals (Table S3), but not in elderly individuals (Table S4); **ADAMTSL3 rs4842924** significantly correlated with the T/T genotype and showed a significant positive correlation with BMI (β = 0.15, P = 0.0095), suggesting that mass was higher in participants with the T/T genotype than in those with other genotypes. With respect to medications, GLP-1 receptor agonist (GLP-1ra) treatment showed a positive correlation with BMI (β = 0.14, P = 0.016).

**Difference in SMM between IRS1 rs2943656 genotypes**

To validate the observed associations between SNPs and body composition in type 2 diabetes patients, SMM, ALM, and BMI were evaluated in a stratified analysis (Fig. 2). For **IRS1 rs2943656** (A), the SMM was significantly higher in participants with the G/G genotype than in those with other genotypes (A/A + G/A genotypes) in women (8.6 ± 1.0 vs 8.0 ± 1.0 kg/m², P = 0.05) and men (9.8 ± 1.2 vs 9.2 ± 0.8 kg/m², P = 0.05). For **ADAMTSL3 rs4842924**, BMI (B) in women tended to be lower for the C/C + T/C genotypes than the T/T genotype (8.0 ± 3.9 vs 9.9 ± 4.6, P = 0.08), with no difference in men (6.9 ± 2.7 vs 7.1 ± 2.6, NS). When the BMI was divided by SMM for adjustment owing to the large standard deviation and strong correlation between these parameters, a similar pattern was observed (C; women: 0.94 ± 0.39 vs 1.13 ± 0.45, P = 0.08, men: 0.70 ± 0.26 vs 0.73 ± 0.24, NS). For **ADAMTSL3 rs4842924** (D), ALM did not differ significantly between participants with C/C + T/C genotypes and those with the T/T genotype in women (6.3 ± 1.0 vs 6.3 ± 1.0, NS) or men (7.5 ± 1.0 vs 7.3 ± 1.1, NS).

**Discussion**

To adjust for confounding factors in genetic association studies of body composition in type 2 diabetes patients, clinical determinants of lean mass, SMM, and BMI were analyzed by a multiple regression analysis in the present study. Among all independent predictors of body composition, the strongest determinant was sex and...
the second strongest was the body composition itself. Aging-related losses were consistently observed for TLM, ALM and SMM, but aging-related gain was observed for BFM.

With respect to medications for diabetes, only the GLP-1ra was positively correlated with BFM, suggesting that patients treated with GLP-1ra have a greater BFM. GLP-1ra induces a reduction in appetite and deceleration of gastric emptying, leading to a reduction in bodyweight.11 The positive correlation between GLP-1ra use and BFM, therefore, could be explained by the preferential administration of GLP-1ra to obese patients for the purpose of weight reduction. This speculation was supported by the observation of a higher BMI in participants treated with the GLP-1ra compared with those not having received this treatment (26.9 vs 24.5, \(P = 0.01\), Student’s t-test).

After the initial screening for clinical determinants of body composition, the contribution of genetic loci to body compositions was assessed by a multiple regression analysis. IRS1 rs2943656 was significantly correlated with SMM, but not with TLM, ALM or BFM. The allele for increased SMM (i.e. the G allele) was consistent with previous results for healthy individuals.12 A similar tendency was observed in the comparison of SMM between IRS1 rs2943656 genotypes. TLM consists of SMM and internal organs of the whole body, and ALM mainly consists of SMM of the arms and legs. A recent report showed that the SMM measured by BIA (InBody770) is closely correlated to the skeletal muscle index measured by computed tomography at the level of the third lumbar vertebra.13 Taken together, these observations suggest that there is a strong correlation between the IRS1 polymorphism and SMM in the body truncus, rather than that in the arms and legs. Insulin receptor substrate 1 (IRS1) is highly expressed in skeletal muscle and adipocytes, and is a key molecule in the insulin/insulin-like growth factor-1 signaling pathway, which plays a critical role in the induction of muscle hypertrophy, as well as in the blockade of muscle atrophy.14,15 The rs2943656 SNP is located within a regulatory region (promoter) of IRS1. A search for transcription factor binding sites predicted that the G allele of rs2943656 disrupts the binding motif for interferon regulatory factor 1 and MYB (MYB proto-oncogene, transcription factor), and creates an alternative binding motif for v-MYB (myeloblastosis viral oncogene homolog [Avian]). An expression quantitative trait loci analysis showed that rs2943656 affects the genotype-dependent

![Figure 2](image-url)

**Figure 2** Comparison of body composition among genotypes for lean mass. (a) Skeletal muscle mass index stratified by IRS1 rs2943656 genotypes (A/A + G/A vs G/G). (b) Body fat mass index stratified by ADAMTS3 rs4842924 genotypes (C/C + T/C vs T/T). (c) Body fat mass/skeletal muscle mass stratified by ADAMTS3 rs4842924 genotypes (C/C + T/C vs T/T). (d) Appendicular muscle mass stratified by ADAMTS3 rs4842924 genotypes (C/C + T/C vs T/T).
differences in the expression of IRS1, with the lowest expression for the G/G genotype in subcutaneous and omental adipose tissue (GTeX project, https://www.gtexportal.org/home/), suggesting that the polymorphism influences gene expression in skeletal muscle. In healthy individuals, a previous study reported that the lean mass-increasing allele of IRS1 rs2943656 (i.e., the G allele) is associated with a reduced BMI and fat mass. 12 The present data obtained from individuals with type 2 diabetes showed a similar tendency, with a significant correlation observed between IRS1 rs2943656 and BFM in non-elderly individuals (the G allele served as a fat mass-reducing allele; Table S3). The opposite effect of the G allele on muscle and fat mass suggests that IRS1 shows tissue-specific regulation. Despite the high expression of IRS1 in adipose tissue, we did not detect any evidence for a correlation between BFM and IRS1 rs2943656 in the multiple regression analysis. The degradation of the IRS1 protein by post-transcriptional modification has been observed in the adipose tissue in a mouse model of type 2 diabetes, but not in control mice, resulting in severe insulin resistance in type 2 diabetes. 16 In clear contrast to adipose tissue, the phosphorylation of IRS1 in skeletal muscle was not uniformly altered in patients with type 2 diabetes, despite the severe insulin resistance in skeletal muscle, suggesting that the post-transcriptional modification of IRS1 differs between adipose tissue and skeletal muscle in type 2 diabetes. 17

ADAMTSL3, a member of the ADAMTS (a disintegrin and metalloprotease with thrombospondin motifs)-like subfamily, is a component of the extracellular matrix and is ubiquitously expressed, including in adipose tissue and skeletal muscle. 18 Genetic association studies have consistently shown that ADAMTSL3 polymorphisms are associated with adult height 19,20 and lean mass 9,12 in humans. An animal study also reported that SNPs in the ADAMTSL3 are significantly correlated with body measurement traits, especially body size. 21 The multiple regression analysis in the present study showed that ADAMTSL3 rs4842924 was significantly correlated with BFM and ALM. However, the relationship was in the opposite direction; the T allele increased BFM and tissue, we did not detect any evidence for a correlation between BFM and IRS1 rs2943656 and BFM in non-elderly individuals (the G allele served as a fat mass-reducing allele; Table S3). The opposite effect of the G allele on muscle and fat mass suggests that IRS1 shows tissue-specific regulation. Despite the high expression of IRS1 in adipose tissue, we did not detect any evidence for a correlation between BFM and IRS1 rs2943656 in the multiple regression analysis. The degradation of the IRS1 protein by post-transcriptional modification has been observed in the adipose tissue in a mouse model of type 2 diabetes, but not in control mice, resulting in severe insulin resistance in type 2 diabetes. 16 In clear contrast to adipose tissue, the phosphorylation of IRS1 in skeletal muscle was not uniformly altered in patients with type 2 diabetes, despite the severe insulin resistance in skeletal muscle, suggesting that the post-transcriptional modification of IRS1 differs between adipose tissue and skeletal muscle in type 2 diabetes. 17

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Stratified analysis by age group showed that the contributions of IRS1 and ADAMTSL3 to body composition were concentrated in non-elderly individuals (Table S3), but not in elderly individuals (Table S4), suggesting that genetic factors predominantly correlate with body composition in younger individuals rather than elderly individuals with type 2 diabetes. As aging is one of the most significant factors affecting body composition, the contribution of genetic factors might be masked by aging-related factors in elderly individuals. These data in turn suggest that pharmacological and non-pharmacological interventions, such as resistance exercise and nutritional support, might improve body composition to help prevent sarcopenia and frailty in elderly individuals with type 2 diabetes.

The present study had some limitations. The BIA using InBody770 tended to overestimate the total and appendicular SMM in comparison with results obtained by dual-energy X-ray absorptiometry. 22 The genetic loci for lean mass, however, were identified by the assessment of body composition by either dual-energy X-ray absorptiometry or BIA. 9,12 Longitudinal studies might show alternative clinical variables, such as glycemic control and drugs for diabetes treatment, involved in changes in body composition in type 2 diabetes. 23 Further functional analyses of IRS1 and ADAMTSL3 are required to show a direct link between these genetic loci and phenotypes. The present study did not show the association of VCAN and FTO loci with body composition in type 2 diabetes patients, which might show the similarities (IRS1 and ADAMTSL3) and differences (VCAN and FTO) in genetic factors that contribute to lean mass between healthy individuals and individuals with type 2 diabetes; however, the further analysis might need to exclude the roles of VCAN and FTO loci for body compositions. In particular, our stratified age group analysis showed a significant correlation between VCAN and FTO loci for body compositions. In summary, the present study clarified the contribution of genetic factors, IRS1 and ADAMTSL3, to interindividual variation in body composition in type 2 diabetes patients, independent of key clinical variables, such as sex, age and body composition itself. These data improve our understanding of the etiology and determinants of sarcopenia and obesity in type 2 diabetes patients, facilitating the establishment of effective methods for the prediction, prevention, and intervention of sarcopenia and frailty in diabetes patients.

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Disclosure statement

The authors declare no conflict of interest.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher’s website:

Appendix S1 Supplementary methods
Appendix S2 Supplementary results
Table S1 Multiple regression analysis of indices for body compositions in type 2 diabetes patients including medications as independent variables.
Table S2 Genotype and allele frequencies of single-nucleotide polymorphisms in participants with type 2 diabetes.
Table S3 Multiple regression analysis of body composition indices in non-elderly individuals with type 2 diabetes.
Table S4 Multiple regression analysis of body composition indices in elderly individuals with type 2 diabetes.

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