*Original Article*

# Relative low muscle mass and muscle strength is associated with the prevalence of metabolic syndrome in patients with type 2 diabetes

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(Received 15 November, 2021; Accepted 29 December, 2021; Released online in J-STAGE as advance publication 8 March, 2022)

**This cross-sectional study investigated the association of metabolic syndrome (MetS) with sarcopenia defined by absolute low muscle mass (aLMM) and absolute low muscle strength (aLMS), or sarcopenia defined by relative low muscle mass (rLMM) and relative low muscle strength (rLMS). The cut-off values for men and women were as follows: aLMM, appendicular muscle mass in kg/height$^2$ was <7.0 kg/m$^2$ and <5.7 kg/m$^2$; rLMM, appendicular muscle mass/body weight ×100 was <28.64% and <24.12%; aLMS, handgrip strength was <28 kg and <18 kg; and rLMS, handgrip strength/body weight ×100 was 51.26% and 35.38%. Among 207 men and 164 women, 41.5% men and 57.3% women had MetS, 14.0% men and 6.1% women had sarcopenia as defined by aLMM and aLMS, and 14.0% men and 22.0% women had sarcopenia defined by rLMM and rLMS. Compared with non-sarcopenia, adjusted OR of sarcopenia defined by aLMM and aLMS for the prevalence of MetS was 0.79 (95% CI 0.38–1.67), whereas that of sarcopenia defined by rLMM and rLMS for the prevalence of MetS was 20.6 (95% CI 7.81–54.3). Sarcopenia defined by rLMM and rLMS was associated with the risk of prevalence of MetS, whereas sarcopenia defined by aLMM and aLMS was not.**

***Key Words*: sarcopenia, muscle, obesity, metabolic syndrome, diabetes**

Metabolic syndrome (MetS), which is one of the global health problems, is reported to be associated with a high risk of cardiovascular disease.[1,2] It has been reported that several factors such as chronic inflammation, oxidative stress, and insulin resistance are associated with the mechanism for MetS.[3,4]

Sarcopenia, which is mainly characterized as absolute muscle mass, power, and function,[5] is now the focus because of higher risk of cardiovascular disease and mortality.[6–9] In patients with diabetes, declining insulin signaling and higher insulin resistance accelerate muscle catabolism[5] and resulting in accelerated reduction of muscle mass and strength.[10] Thus, it is an important target for treatment of diabetes, because the muscle is a major organ of glucose metabolism.[11] In fact, it has been reported that diets, including total energy, proteins, vitamins, and fatty acids, are associated with the sarcopenia in patients with diabetes.[12–14]

On the other hand, relative muscle mass loss, defined as weight-adjusted skeletal muscle mass index (SMI) (SM/Wt), has been described as a risk factor for type 2 diabetes (T2D)[15] and has been associated with insulin resistance.[16] In addition, we and other researchers revealed the relationship between relative muscle mass loss and nonalcoholic fatty liver disease (NAFLD)[17,18] or nonalcoholic steato-hepatitis (NASH)[19,20] which are closely related to MetS.[21] Furthermore, some studies revealed that there was a relationship between relative muscle mass loss and MetS.[22,23]

Previous studies have not revealed whether sarcopenia defined by absolute muscle mass and absolute muscle strength, or sarcopenia defined by the relative muscle mass and relative muscle strength is associated more with the prevalence of MetS. Hence, the objective of this cross-sectional study was to clarify the association of MetS with sarcopenia defined by absolute muscle mass and absolute muscle strength, or sarcopenia defined by relative muscle mass and relative muscle strength in patients with T2D.

## Materials and Methods

**Study participants.** We are conducting an ongoing cohort study KAMOGAWA-DM cohort study.[24] This ongoing study was approved by the research ethics committee of Kyoto Prefectural University of Medicine (No. RBMR-E-466-6) and was carried out in accordance with the Declaration of Helsinki, and informed consent was obtained from all the participants. We performed a post-hoc analysis of the previous cross-sectional study, and details of this study has been described previously.[25] All patients provided details of their demographics, including medication usage and medical history. We excluded patients who did not receive bioelectrical impedance analysis (BIA) and with no data on handgrip strength.

Patients were classified as non-smokers or smokers by a self-administered questionnaire. Patients were classified as non-exerciser or exerciser, performing any kind of physical activity at least once a week, by a self-administered questionnaire. Alcohol consumption was defined as ethanol over 20 g/day.[25]

**Biochemical analysis.** Serum triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were assessed using standard enzymatic methods. Hemoglobin A1c (HbA1c) was expressed as National Glycohemoglobin Standardization Program (NGSP) unit evaluated by high-performance liquid chromatography.

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doi: 10.3164/jcbn.21-152
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**Definition of metabolic syndrome.** Metabolic syndrome was diagnosed when patients fulfilled three or more of the following criteria were present:[26] abdominal obesity, waist circumference ≥90 cm in men and ≥80 cm in women; hypertension, a systolic blood pressure >130 mmHg and/or a diastolic blood pressure >85 mmHg and/or usage antihypertension medication; hypertriglyceridemia, triglycerides >1.7 mM and/or usage antihyperlipidemia medication; reduced HDL-C, HDL-C <1.03 mM in men and <1.29 mM in women; hyperglycemia, fasting plasma glucose >5.6 mM and/or under medical treatment (all patients had T2D in this study). Since waist measurements were not available for the study sample, we defined obesity as a percentage of body fat, i.e., >30% for men and >35% for women.[27] In addition, metabolic syndrome score was defined as the existence of each component of MetS (from 0 to 5).

**Definition of sarcopenia.** Using the multifrequency impedance body composition analyzer, Inbody 720 (InBody Japan, Tokyo, Japan), data on body weight (BW) (kg), appendicular muscle mass (kg), and body fat mass (kg) were obtained. Body mass index (BMI) was calculated as BW (kg)/height$^2$ (m$^2$). The height-adjusted SMI (SM/Ht$^2$) was calculated as follows: SM/Ht$^2$ = (appendicular muscle mass in kg)/(height in m$^2$).[28] The cut-off values for absolute low muscle mass (aLMM), defined as SM/Ht$^2$, were <7.0 kg/m$^2$ for men and <5.7 kg/m$^2$ for women.[28] The weight adjusted SMI (SM/Wt) was calculated as follows: SM/Wt = [(appendicular muscle mass in kg)/(BW in kg)] × 100.[29] The cut-off of relative low muscle mass (rLMM) was defined by a weight-adjusted SMI <28.64% for men and <24.12% for women.[29] Handgrip strength was measured two times with each hand by a handgrip dynamometer (Smedley, Takei Scientific Instruments Co., Ltd., Niigata, Japan), and the maximum value was used for the analysis. The cutoff points for absolute low muscle strength (aLMS) defined by handgrip strength was <28 kg for men and <18 kg for women.[28] Adjusted grip strength was calculated as follows: adjusted grip strength = [(handgrip strength in kg)/(BW in kg)].[29] The cut-off points for relative low muscle strength (rLMS) defined as adjusted grip strength was 51.26% for men and 35.38% for women.[29] Sarcopenia was defined as the presence of both aLMM and aLMS or both rLMM and rLMS.

**Statistical analysis.** The statistical analyses were performed using the JMP ver. 13.2. software (SAS Institute Inc., Cary, CA), figures were created by GraphPad Prism ver. 8.4.2 software (GraphPad Software, Inc., La Jolla, CA), and $p$ value <0.05 was considered statistically significant. Continuous variables were presented as mean (SD) and categorized variables were presented as percentage (number). The difference between groups was analyzed by Student's $t$ test or Chi-square test. The difference of SM/Ht$^2$, SM/Wt, handgrip strength, and adjusted grip strength between the presence of MetS were evaluated by Tukey honestly significant difference test and adjusted for age, sex, smoking, alcohol, and exercise. The difference of SM/Ht$^2$, SM/Wt, handgrip strength, and adjusted grip strength among metabolic syndrome score were evaluated by Kruskal-Wallis test and steel-dwass test. In addition, the participants were divided into four groups according to muscle mass and muscle strength stage: normal, aLMM only, aLMS only, or sarcopenia, defined by aLMM and aLMS; and normal, rLMM only, rLMS only, or sarcopenia, defined by rLMM and rLMS. Multivariate logistic regression analyses were performed to investigate the association of MetS with the presence of sarcopenia, the presence of aLMM, aLMS and sarcopenia, or the presence of rLMM, rLMS, and sarcopenia, adjusting for covariates, sex, age, smoking, alcohol, and exercise.

## Results

Initially, 383 patients with type 2 diabetes were included in the study. Among them, 12 patients were excluded based on the exclusion criteria (Fig. 1).

The clinical characteristics of 371 patients (207 men and 164 women) are shown in Table 1. Average age and duration of diabetes were 67.0 (11.0) years and 14.6 (9.6) years in men and 66.0 (10.3) years and 13.0 (10.6) years in women. Among them, 41.5% men and 57.3% women had MetS. In addition, 25.6% men and 25.0% women had aLMM, 17.4% men and 29.9% women had rLMM, 24.0% men and 25.0% women had aLMS, and 51.7% men and 48.8% women had rLMS.

The SM/Ht$^2$ of patients with MetS was higher than that of patients without both in men and women, whereas SM/Wt of patients with MetS was lower than that of patients without both in men and women. Moreover, handgrip strength of patients with MetS tended to be higher than that of patients without both in men and women, whereas adjusted grip strength of patients with MetS was lower than that of patients without both in men and women (Table 2).

Proportion of aLMM and sarcopenia, defined by aLMM and aLMS in patients with MetS, was lower than those of patients without MetS, and proportion of aLMS in patients with MetS was tended to be lower than that of patients without MetS (Fig. 2). On the other hand, proportions of rLMS, rLMM, and sarcopenia, defined by rLMM and rLMS, in patients with MetS

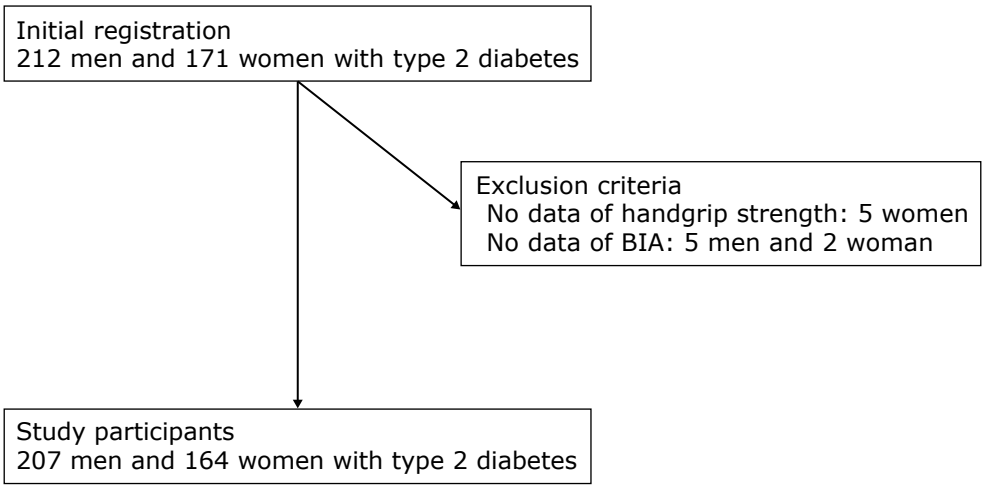


**Fig. 1.** Flow chart of inclusion and exclusion criteria. BIA, bioelectrical impedance analysis.


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**Table 1.** Clinical characteristics of study patients

| | Men $n = 208$ | Women $n = 165$ | $p$ |
|---|---|---|---|
| Age (years) | 67.0 (11.0) | 66.0 (10.3) | 0.339 |
| Duration of diabetes (years) | 14.6 (9.6) | 13.0 (10.6) | 0.137 |
| Systolic blood pressure (mmHg) | 133.4 (18.1) | 135.2 (19.7) | 0.353 |
| Diastolic blood pressure (mmHg) | 79.2 (10.9) | 78.7 (11.7) | 0.67 |
| Height (cm) | 167.1 (6.2) | 153.3 (5.6) | <0.001 |
| Body weight (kg) | 65.8 (10.8) | 60.3 (13.9) | <0.001 |
| Body mass index (kg/m$^2$) | 23.5 (3.6) | 25.7 (6.1) | <0.001 |
| Appendicular lean mass (kg) | 20.2 (3.5) | 16.1 (3.8) | <0.001 |
| SM/Ht$^2$ (kg/m$^2$) | 7.2 (1.0) | 6.8 (1.6) | 0.009 |
| SM/Wt (%) | 30.9 (4.1) | 26.9 (3.9) | <0.001 |
| Handgrip strength (kg) | 33.6 (7.7) | 21.0 (5.1) | <0.001 |
| Adjusted grip strength (%) | 51.9 (12.5) | 35.8 (9.2) | <0.001 |
| Regular exercises | 50.0% (104) | 44.2% (73) | 0.269 |
| Current smoker | 21.2% (44) | 6.1% (10) | <0.001 |
| Habitual alcohol consumption | 22.1% (46) | 0.6% (1) | <0.001 |
| Aspartate aminotransferase (IU/L) | 24.9 (11.4) | 22.1 (9.2) | 0.014 |
| Alanine aminotransferase (IU/L) | 25.6 (17.7) | 22.1 (15.2) | 0.046 |
| Gamma-glutamyltransferase (IU/L) | 40.2 (38.2) | 28.6 (19.7) | <0.001 |
| Triglycerides (mM) | 1.5 (1.0) | 1.4 (0.8) | 0.281 |
| HDL-C (mM) | 1.5 (0.4) | 1.6 (0.4) | 0.003 |
| HbA1c (%) | 7.4 (1.2) | 7.4 (1.4) | 0.923 |
| HbA1c (mM) | 57.1 (13.3) | 56.9 (15.1) | 0.923 |
| Usage of antihypertensive medications | 55.3% (115) | 52.7% (87) | 0.622 |
| Usage of antidyslipidemia medications | 46.6% (97) | 44.9% (74) | 0.731 |
| Usage of antidiabetic oral medications | 76.4% (159) | 75.8% (125) | 0.878 |
| Usage of GLP-1 analog | 13.9% (29) | 20.0% (33) | 0.119 |
| Usage of insulin | 22.6% (47) | 25.5 (42) | 0.52 |
| Obesity (%) | 31.7% (66) | 40.6% (67) | 0.076 |
| Hypertension (%) | 74.5% (155) | 72.7% (120) | 0.696 |
| Hypertriglycerides (%) | 36.5% (76) | 26.1% (43) | 0.031 |
| Low HDL-C (%) | 7.7% (16) | 21.8% (36) | <0.001 |
| Metabolic syndrome score | 2.5 (0.9) | 2.6 (.1.1) | 0.291 |
| Metabolic syndrome (%) | 53.9% (112) | 47.9% (79) | 0.252 |
| aLMM (%) | 8.7% (18) | 67.3% (111) | <0.001 |
| aLMS (%) | 24.0% (50) | 24.9% (41) | 0.856 |
| Sarcopenia defined by aLMM and aLMS (%) | 3.2% (1) | 18.6% (30) | <0.001 |
| rLMM (%) | 26.1% (43) | 23.0% (37) | 0.518 |
| rLMS (%) | 53.3% (88) | 47.8% (77) | 0.32 |
| Sarcopenia defined by rLMM and rLMS (%) | 17.6% (29) | 15.5% (25) | 0.619 |

Data are expressed as mean (SD) or % (number). The difference between groups was analyzed by Student's $t$ test or Chi-square test. SM/Ht$^2$, height-adjust skeletal muscle mass index; SM/Wt, weight-adjust skeletal muscle mass index; GLP-1, glucagon-like peptide-1; HDL-C, high-density lipoprotein cholesterol; aLMM, absolute low muscle mass; aLMS, absolute low muscle strength; rLMM, relative low muscle mass; rLMS, relative low muscle strength.

was higher than those of patients without MetS (Fig. 2).

Figure 3 shows the differences in SM/Ht$^2$, SM/Wt, handgrip strength, and adjusted grip strength among metabolic syndrome scores. Interestingly, SM/Ht$^2$ was increased in the order of metabolic syndrome scores, and handgrip strength tended to increase in the order of metabolic syndrome scores in both men and women, whereas SM/Wt and adjusted grip strength decreased in the order of metabolic syndrome scores in both men and women.

Table 3 shows the ORs of presence of sarcopenia and related factors for the prevalence of MetS. Compared with non-sarcopenia, adjusted OR of sarcopenia defined by aLMM and aLMS for the prevalence of MetS was 0.79 (95% CI 0.38–1.67, $p = 0.541$) and compared with normal, adjusted ORs of aLMS only, aLMM only, and sarcopenia were 0.83, 0.28, and 0.63, respectively. In contrast, compared with non-sarcopenia, adjusted OR of sarcopenia defined by rLMM and rLMS for the prevalence of MetS was 20.6 (95% CI 7.81–54.3, $p<0.001$) and compared with normal, adjusted ORs of rLMS only, rLMM only, and sarcopenia were 2.02, 7.02, and 31.2, respectively.


doi: 10.3164/jcbn.21-152
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**Table 2.** Unadjusted and adjusted difference of SM/Ht2, SM/Wt, handgrip strength and adjusted grip strength between the presence or absence of metabolic syndrome

| Men | Unadjusted | | | Adjusted | | |
|---|---|---|---|---|---|---|
| | MetS (–), *n* = 121 | MetS (+), *n* = 86 | *p* | MetS (–), *n* = 121 | MetS (+), *n* = 86 | *p* |
| SM/Ht$^2$ (kg/m$^2$) | 7.3 (0.8) | 7.8 (0.8) | <0.001 | 7.3 (7.1–7.5) | 7.8 (7.6–8.0) | <0.001 |
| SM/Wt (%) | 32.7 (3.5) | 30.0 (3.1) | <0.001 | 33.1 (32.3–33.8) | 30.3 (29.5–31.1) | <0.001 |
| Handgrip strength (kg) | 32.5 (7.2) | 35.2 (8.1) | 0.011 | 33.9 (32.4–35.5) | 35.2 (33.6–36.9) | 0.186 |
| Adjusted grip strength (%) | 52.4 (10.4) | 47.8 (9.5) | 0.001 | 54.4 (52.3–56.6) | 48.8 (46.4–51.2) | <0.001 |
| **Women** | **Unadjusted** | | | **Adjusted** | | |
| | MetS (–), *n* = 70 | MetS (+), *n* = 94 | *p* | MetS (–), *n* = 70 | MetS (+), *n* = 94 | *p* |
| SM/Ht$^2$ (kg/m$^2$) | 6.1 (0.7) | 6.6 (0.9) | <0.001 | 6.5 (5.7–7.3) | 6.9 (6.1–7.6) | 0.002 |
| SM/Wt (%) | 27.5 (2.3) | 24.3 (2.5) | <0.001 | 26.0 (23.3–28.6) | 22.8 (20.3–25.4) | <0.001 |
| Handgrip strength (kg) | 20.5 (4.8) | 21.3 (5.4) | 0.279 | 23.8 (19.1–28.5) | 23.6 (19.0–28.1) | 0.767 |
| Adjusted grip strength (%) | 39.5 (8.6) | 33.8 (8.3) | <0.001 | 39.5 (30.5–48.5) | 33.3 (24.6–42.0) | <0.001 |

SM/Ht$^2$, height-adjusted skeletal muscle mass index; SM/Ht, weight-adjusted skeletal muscle mass index; MetS, metabolic syndrome. Adjusted for age, smoking, exercise, and alcohol intake.

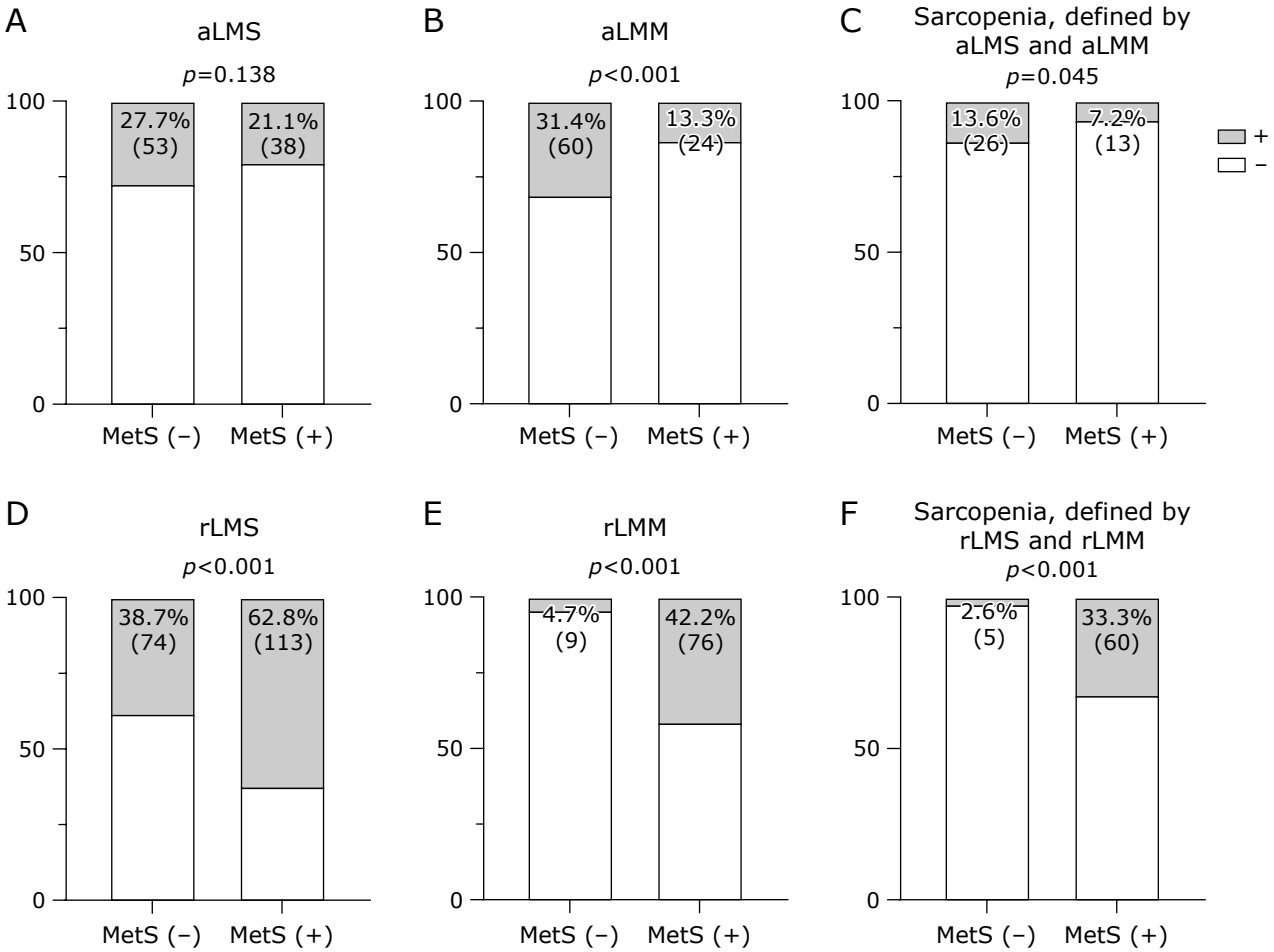


**Fig. 2.** Proportion of aLMS, aLMM, sarcopenia, defined by aLMM and aLMS, rLMS, rLMM and sarcopenia, defined by rLMM and rLMS in subjects without and with MetS tended to be lower than that of subjects without MetS. Chi-square tests were performed to evaluate the difference. (A) aLMS, absolute low muscle strength, (B) aLMM, absolute low muscle mass, (C) Sarcopenia, defined by aLMS and aLMM (D) rLMS, relative low muscle strength, (B) rLMM, relative low muscle mass, (C) Sarcopenia, defined by rLMS and rLMM.


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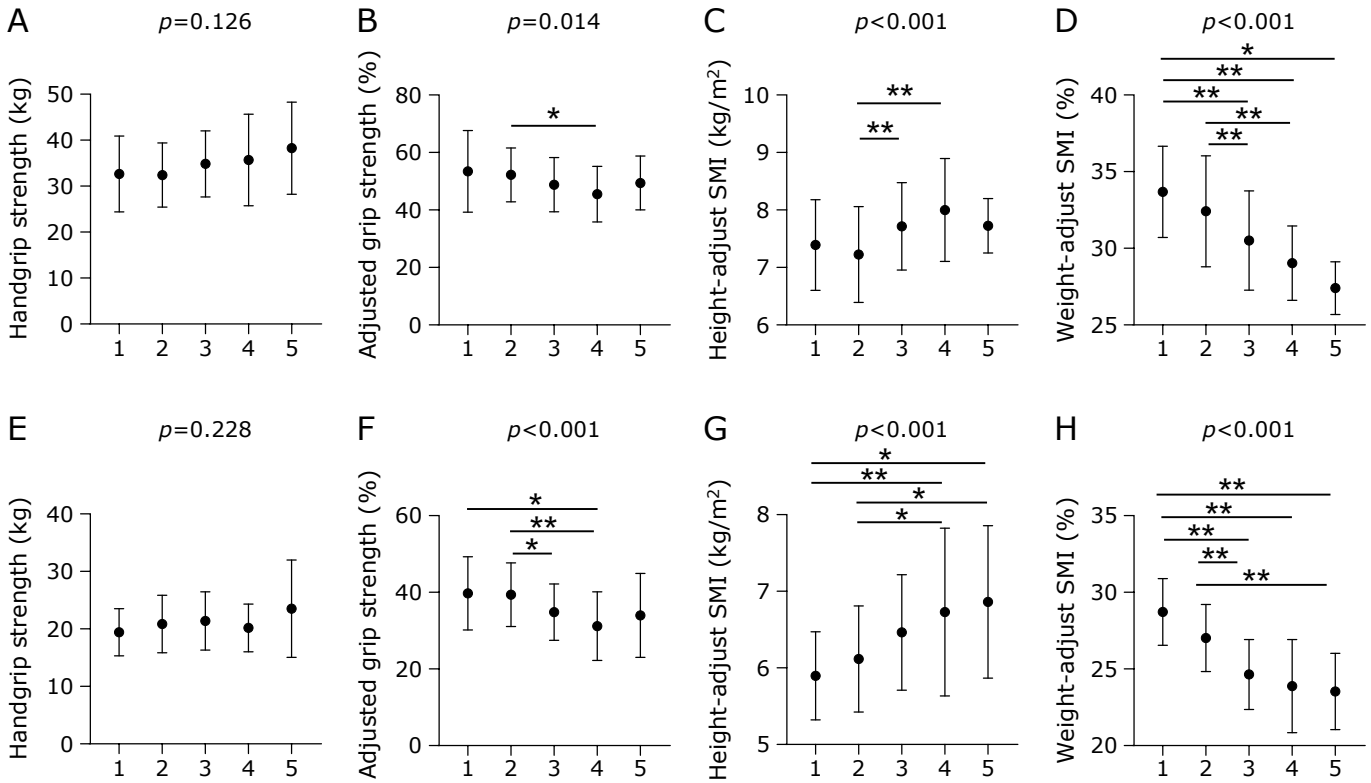


**Fig. 3.** The difference of height-adjusted skeletal muscle mass index, weight-adjusted skeletal muscle mass index, handgrip strength, and adjusted grip strength among metabolic syndrome scores. The differences were evaluated by Kruskal–Wallis test and steel-dwass test. (A) handgrip strength in men, (B) adjusted grip strength in men, (C) height-adjusted skeletal muscle mass index in men, (D) weight-adjusted skeletal muscle mass index in men, (E) handgrip strength in women, (F) adjusted grip strength in women, (G) height-adjusted skeletal muscle mass index in women, (F) weight-adjusted skeletal muscle mass index in women. *$p$<0.05 and **$p$<0.01.

**Table 3.** Odds ratios of sarcopenia and related factors for the prevalence of metabolic syndrome

| | Model 1 | | Model 2 | |
|---|---|---|---|---|
| | OR (95% CI) | $p$ | OR (95% CI) | $p$ |
| Normal ($n$ = 235) | Ref | — | Ref | — |
| aLMS only ($n$ = 52) | 0.84 (0.44–1.59) | 0.589 | 0.83 (0.43–1.58) | 0.569 |
| aLMM only ($n$ = 45) | 0.28 (0.13–0.60) | <0.001 | 0.28 (0.13–0.60) | <0.001 |
| Sarcopenia, defined by aLMS and aLMM ($n$ = 39) | 0.62 (0.29–1.33) | 0.22 | 0.63 (0.29–1.37) | 0.244 |
| Non-sarcopenia ($n$ = 332) | Ref | — | Ref | — |
| Sarcopenia ($n$ = 39) | 0.78 (0.37–1.63) | 0.504 | 0.79 (0.38–1.67) | 0.541 |
| | Model 1 | | Model 2 | |
| | OR (95% CI) | $p$ | OR (95% CI) | $p$ |
| Normal ($n$ = 164) | Ref | — | Ref | — |
| rLMS only ($n$ = 122) | 2.00 (1.20–3.34) | 0.008 | 2.02 (1.20–3.38) | 0.008 |
| rLMM only ($n$ = 20) | 6.87 (2.11–22.4) | 0.001 | 7.02 (2.14–23.0) | <0.001 |
| Sarcopenia, defined by rLMS and rLMM ($n$ = 65) | 30.3 (11.1–82.3) | <0.001 | 31.2 (11.4–85.6) | <0.001 |
| Non-sarcopenia ($n$ = 306) | Ref | — | Ref | — |
| Sarcopenia ($n$ = 65) | 20.3 (7.72–53.2) | <0.001 | 20.6 (7.81–54.3) | <0.001 |

aLMM, absolute low muscle mass; aLMS absolute low muscle strength; rLMM, relative low muscle mass; rLMS, relative low muscle strength. Model 1: Adjusted for age and sex. Model 2: Adjusted for age, sex, smoking, exercise, and alcohol intake.

## Discussion

This is the first study to investigate the relationship between MetS and sarcopenia in patients with T2D. We observed that handgrip strength and SM/Ht$^2$ of patients with MetS was higher than those without MetS, whereas adjusted grip strength and


doi: 10.3164/jcbn.21-152
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SM/Wt of patients with MetS was lower than those without MetS. In addition, sarcopenia defined by adjusted grip strength and SM/Wt was associated with the risk of prevalence of MetS, whereas sarcopenia defined by handgrip strength and SM/Ht$^2$ was not associated with the risk of prevalence of MetS.

Previous studies have revealed that rLMM is associated with impaired glucose tolerance,[15,16] NAFLD,[17,18,29] and NASH.[19,20,30]

It is well known that SM/Ht$^2$ and handgrip strength is used as a marker for sarcopenia.[28] However, heavier body weight is associated with more muscle mass, regardless of the fat mass.[17] Thus, there is a possibility that it is not the absolute muscle mass, but the relative muscle mass, which indicated proportion of muscle mass to body weight, is important for metabolic abnormal diseases, including MetS. Decrease in SM/Wt could indicate relative increase of visceral fat and relative decrease of muscle mass. In fact, SM/Wt is reported to be associated with incident diabetes,[15] incident MetS,[22,23] and progression of NAFLD.[31] In addition, previous studies have revealed that SM/Wt, but not SM/Ht$^2$ was associated with insulin resistance.[32–34] In this study, we demonstrated that rLMM, but not aLMM is important for MetS. This result was same as a previous study for NAFLD[35] which is a one of the phenotype of MetS.[21] In addition, we also revealed that low adjusted grip strength, which indicates rLMS but not low handgrip strength, is associated with the prevalence of MetS. Previous studies have revealed that low adjusted grip strength is associated with the prevalence of NAFLD[29] and incident diabetes.[36]

This study also showed that SM/Ht$^2$ increased in the order of metabolic syndrome score, whereas adjusted grip strength and SM/Wt decreased in the order of metabolic syndrome score. These results suggest that accumulation of metabolic abnormalities is associated with a decline in relative lower muscle mass and strength. Taking these findings into account, we should focus on relative low mass and strength in the clinical setting of MetS. Further studies are needed to understand the association between relative lower muscle mass and strength, and absolute lower muscle mass and strength.

The limitations of this study were as follows. First, this is a cross-sectional study; therefore, the causal relationship is unclear. Second, we did not use dual-energy X-ray absorptiometry, although the accuracy of the body composition analyzer has been previously validated.[37] Finally, this study included the Japanese population only; thus, the generalizability of this study to non-Japanese populations, especially non-Asian populations, is unclear.

## Conclusion

In conclusion, we discovered that sarcopenia defined by SM/Wt and adjusted grip strength was associated with the risk of prevalence of MetS, whereas sarcopenia defined by SM/Ht$^2$ and handgrip strength was not associated with the risk of prevalence of MetS. Our findings have potential clinical significance because the different definitions for sarcopenia could substantially influence study results, in relation to MetS.

## Author Contributions

Conceptualization, YH; data curation, MT, YH, AK, and RS; formal analysis, MT and YH; investigation, YH, MH, AK, RS, TOkamura, NK, TOsaka, HO, NN, SM, TS, EU, MA, MY, and MF; project administration, YH, MH, and EU; supervision, MF; visualization, YH; writing–original draft, MT; and writing–review and editing, YH, MH, AK, RS, TOkamura, NK, TOsaka, HO, NN, SM, TS, EU, MA, MY, and MF.


## Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing.


## Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.


## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.


## Conflict of Interest

YH reports grants from Asahi Kasei Pharma and personal fees from Sanofi K.K., Novo Nordisk Pharma Ltd., Daiichi Sankyo Co. Ltd., and Mitsubishi Tanabe Pharma Corp. outside the submitted work. Dr. Hamaguchi reports grants from Astellas Pharma Inc., Eli Lilly Japan K.K., Mitsubishi Tanabe Pharma Corp., Sanofi K.K., Asahi Kasei Pharma, Novo Nordisk Pharma Ltd., Takeda Pharma Co. Ltd., Kyowa Kirin Co. Ltd., Nippon Boehringer Ingelheim Co. Ltd., Daiichi Sankyo Co. Ltd., and Sumitomo Dainippon Pharma Co. Ltd. outside the submitted work. MA reports honoraria from AstraZeneca plc, Abbott Japan Co., Ltd., Novo Nordisk Pharma Ltd., Kowa Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., and Sumitomo Dainippon Pharma Co., Ltd. TOsaka reports grants from Combi Corp., and personal fees from Eli Lilly Japan K.K., Sumitomo Dainippon Pharma Co., Ltd., MSD K.K., Novo Nordisk Pharma Ltd., Daiichi Sankyo Co. Ltd., Takeda Pharma Co. Ltd., Nippon Boehringer Ingelheim Co. Ltd., Mitsubishi Tanabe Pharma Corp., Kyowa Kirin Co. Ltd., Kowa Pharma Co. Ltd., Ono Phama Co., Ltd., AstraZeneca plc, Toa Eiyo Corp., outside the submitted work. TS has received personal fees from Eli Lilly Japan K.K., Mitsubishi Tanabe Pharma Co., Kowa Pharma Co., Ltd., Astellas Pharma Inc., Takeda Pharma Co., Ltd., Sanofi K.K., Taisho Toyama Pharma Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Kissei Pharma Co., Ltd., MSD K.K., Novo Nordisk Pharma Ltd., Ono Pharma Co., Ltd. outside the submitted work. EU received grant support from the Astellas Foundation for Research on Metabolic Disorders and the Japanese Study Group for Physiology and Management of Blood Pressure, donated fund Laboratory of Diabetes therapeutics is an endowment department, supported with an unrestricted grant from Ono Pharma. Co., Ltd., and received personal fees from Kyowa Kirin Co. Ltd., AstraZeneca plc, Nippon Boehringer Ingelheim Co. Ltd., Daiichi Sankyo Co. Ltd., Astellas Pharma Inc., Kowa Pharma Co. Ltd., MSD K.K., Novo Nordisk Pharma Ltd., Takeda Pharma Co., Ltd., Mitsubishi Tanabe Pharma Corp., Sumitomo Dainippon Pharma Co. Ltd., and Taisho Toyama Pharma Co., Ltd. outside the submitted work. MY reports personal fees from Daiichi Sankyo Co. Ltd., AstraZeneca plc, MSD K.K., Kowa Pharma Co. Ltd., Ono Phama Co., Ltd., Takeda Pharma Co. Ltd., Kowa Pharma Co. Ltd., Sumitomo Dainippon Pharma Co. Ltd., and Kyowa Kirin Co. Ltd. outside the submitted work. MF received grants from Sanofi K.K., Daiichi Sankyo Co. Ltd., Mitsubishi Tanabe Pharma Corp., Astellas Pharma Inc., Kowa Pharma Co. Ltd., Kissei Phama Co. Ltd., Ono Pharma Co. Ltd., Takeda Pharma Co. Ltd., Eli Lilly Japan K.K., Sanwa Kagagu Kenkyusho Co., Ltd., Teijin Pharma Ltd., Novo Nordisk Pharma Ltd., Kyowa Kirin Co., Ltd., MSD K.K., Sumitomo Dainippon Pharma Co., Ltd., Nippon Chemiphar Co., Ltd., Terumo Corp., Abbott Japan Co., Ltd., Johnson & Johnson K.K. Medical Co., Taisho Pharma Co., Ltd., and Nippon Boehringer Ingelheim Co. Ltd. and received honoraria from Arkray Inc., Sanofi K.K., Daiichi Sankyo Co.



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Ltd., Takeda Pharma Co. Ltd., Abbott Japan Co., Ltd., Novo Nordisk Pharma Ltd., Teijin Pharma Ltd., Mitsubishi Tanabe Pharma Corp., Nipro Corp., MSD K.K., Medtronic Japan Co. Ltd., Kyowa Kirin Co. Ltd., Mochida Pharma Co. Ltd., Ono Pharma Co. Ltd., Kissei Pharma Co., Ltd., Sumitomo Dainippon Pharma Co. Ltd., Astellas Pharma Inc., Sanwa Kagaku Kenkyusho Co. Ltd., Kowa Pharma Co. Ltd., Taisho Pharma Co., Ltd., Bayer Yakuhin, Ltd., AstraZeneca plc, Eli Lilly Japan K.K., and Nippon Boehringer Ingelheim Co., Ltd. outside the submitted work. The other authors have nothing to disclose.

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doi: 10.3164/jcbn.21-152
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