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Original Study

Glycemic Control and Insulin Improve Muscle Mass and Gait Speed in Type 2 Diabetes: The MUSCLES-DM Study

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A B S T R A C T

Objectives: Type 2 diabetes is a risk factor for sarcopenia. Evidence on the prevention of sarcopenia using blood glucose–lowering therapy is limited. We aimed to examine the relationship between changes in glycemic control and sarcopenia and the effect of antidiabetic agents against sarcopenia in patients with type 2 diabetes.
Design: We conducted an observational longitudinal study.
Setting and Participants: In total, 588 Japanese patients with diabetes of an ongoing multicenter study completed 1-year follow-up measurements for sarcopenia and clinical data.
Methods: The data set of the Multicenter Study for Clarifying Evidence for Sarcopenia in patients with Diabetes Mellitus (the MUSCLES-DM study) was analyzed.
Results: During the follow-up period, the frequency of sarcopenia marginally increased, and the means of skeletal muscle mass index (SMI), handgrip strength, and gait speed did not show any changes. However, on dividing into 5 groups depending on the degree of changes in glycated hemoglobin (HbA_{1c}) value, the patients with a decrease of $\geq$1% in HbA_{1c} exhibited a significant increase in SMI. Our analysis revealed similar results for gait speed but not handgrip strength. Using the multiple linear regression model, we identified that a $\geq$1% decrease in HbA_{1c} value was an independent determinant of the changes in SMI and gait speed. We also determined that insulin use at baseline was an independent factor for the changes in SMI.
Conclusions and Implications: Correction of poor glycemic control and use of insulin were significantly associated with the increase in skeletal muscle mass or gait speed in Japanese patients with type 2 diabetes. The current finding increases our understanding of the importance of glycemic control for the prevention of cardiovascular diseases and sarcopenia.

The primary goal in the treatment of type 2 diabetes is to prevent diabetic complications and ensure a life span similar to that of nondiabetic individuals. However, in older people, unless appropriate measures are adopted against geriatric syndrome (eg, falls or frailty), biological life expectancy can be extended but not healthy life expectancy. Type 2 diabetes is a well-known risk factor for geriatric syndrome, including depressive symptoms, cognitive dysfunction, and

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sarcopenia.[1,2] Sarcopenia is a muscle disease defined by a combination of low muscle mass, weak muscle strength, and declining physical function.[3] We previously reported a linear positive association between glycated hemoglobin (HbA_{1c}) levels and frequency of sarcopenia in middle-aged to older patients with type 2 diabetes (age range: 38-96 years).[4] Another study in older patients with diabetes also reported HbA_{1c} ≥8.0% (64 mmol/mol) as a risk factor for the decline in muscle quality, independent of the duration of diabetes.[5] Additionally, a few studies found that blood glucose–lowering therapy with insulin sensitizers could prevent loss of muscle mass.[6] However, limited evidence is available because only a few studies have investigated this issue.[7,8]

Given this background, we conducted an observational study that aimed to answer the research question of whether glucose-lowering therapy prevents longitudinal decline of the components of sarcopenia, namely, skeletal muscle index (SMI), handgrip strength, and gait speed, in ambulatory patients with type 2 diabetes. In addition, we investigated the class effect of antidiabetic agents, as some of them are reported to be prophylactic against the decline of muscle mass and function.

Methods

Study Participants

This longitudinal study analyzed a data set of the ongoing multicenter study for clarifying evidence for sarcopenia in patients with diabetes mellitus (the MUSCLES-DM study). We included a total of 860 independent ambulatory patients with stable type 2 or type 1 diabetes who were aged 40 years or older at recruitment. Participants were recruited between May 2016 and December 2017 from the list of patients under treatment and regularly visited the 3 university hospitals and 2 general clinics. Among a total of 799 patients with type 2 diabetes, we finally analyzed 588 patients who finished 1-year follow-up measurements of physical performance required for the diagnosis of sarcopenia and whose clinical data on various characteristics, including regular exercise habit, treatment regimens, and plasma levels of glycemic traits, were available. We used only HbA_{1c} as the index representing insulin resistance, insulin secretion, and therapeutic effect. No other glycemic parameters such as plasma glucose and insulin levels were used because all the study participants were taking oral antidiabetic medications or insulin therapy. All the measurements were performed at baseline and after 1 year.

All study procedures were approved by the ethics committee of the 3 universities (the procedures in the 2 general clinics were approved by the ethics committee of one university), and written informed consent was obtained from all participants.

Assessment of Sarcopenia

Sarcopenia was defined using the revised definition according to the Asian Working Group for Sarcopenia (AWGS, 2019),[3] using 2 of the following parameters: (A) low SMI (men: <7.0, women: <5.7) and (B) weak handgrip strength (men: <28 kg, women: <18 kg) or (C) low physical performance (slow gait speed: <1 m/s), that is, either A and B, A and C, or A and B and C.

The appendicular lean mass was estimated using a bioelectrical impedance analysis device (MC-780A; Tanita Co, Tokyo, Japan). SMI was determined using the following formula[3]:

$$\mathrm{SMI} = \frac{\text{appendicular lean mass (kg)}}{\text{body height (m}^2\text{)}}.$$

Grip strength of the dominant hand was measured using a standard digital grip dynamometer (Grip-D; Takei Scientific Instrument Co, Ltd, Japan). Measurements were taken twice in the sitting position with the arm positioned horizontal to the ground. The participants were instructed to adjust the handle of the dynamometer so that it would be under the second phalanx when gripped. The mean values of all measurements were used for analysis.

Usual gait speed measurement was conducted using a 2.44-m or 4-m walkway with a 1-m approach way. An accompanying person measured and calculated the gait speed using a digital timer. Measurements were taken twice, and the average value was used for the analysis. The gait speeds measured during the different walking distances were adjusted using equations previously described[4] to avoid potential misclassification.

Exercise Habit

The exercise habit of each patient was determined using a yes-no question: Are you in a habit of doing exercise to sweat lightly for over 30 minutes a time, 2 times weekly, for over a year?

Statistical Analysis

Calculated values were presented as mean ± standard deviation (SD) or frequency. Changes in clinical values between the baseline and follow-up investigations were assessed using the paired *t* test or McNemar test. We assessed the group differences in longitudinal changes in the 3 components of sarcopenia by the degree of change in HbA_{1c} levels using analysis of variance. Dunnett test was used for post hoc analysis. Factors independently associated with SMI and gait speed at the follow-up investigation were assessed by linear regression analysis. All statistical analyses were performed using JMP statistical software (JMP Pro, version 15.1.0; SAS Institute, Cary, NC). A *P* value of <.05 was considered statistically significant.

Results

Table 1 summarizes the clinical characteristics of the study participants at the baseline and follow-up investigations. During the follow-up period of 382 ± 53 days, the HbA_{1c} levels decreased significantly, irrespective of the slight increases in body mass index and waist circumference. No marked changes were observed in the frequencies of prescribed antihyperglycemic drug classes.

During the follow-up period, the frequency of sarcopenia increased slightly (Table 1) although the difference did not reach statistical significance ($P = .12$). The percentage of changes in the 3 components of sarcopenia exhibited normal distribution (Supplementary Table 1), and the differences between their means at baseline and follow-up were not statistically significant. However, when we subdivided the participants into 5 groups by the degree of changes in their HbA_{1c} values (mean ± SD: −0.12% ± 0.87%), SMI significantly increased only in the subgroup with a decrease in HbA_{1c} value by ≤1.0% (more than 1 SD) (Figure 1). We observed similar results in the analysis for gait speed but not for handgrip strength (Figure 1). The baseline HbA_{1c} value of the patients with ≥1% decrease (9.3% ± 1.5%, 78 ± 17 mmol/mol) was higher than that of the other patients (7.1% ± 0.9%, 54 ± 10 mmol/mol, $P < .001$). However, the results of the multivariate analysis adjusting for baseline HbA_{1c} value indicated that ≥1% decrease in the HbA_{1c} value was an independent determinant of the percentage changes in SMI and gait speed, during the follow-up period (Table 2). In addition, we identified insulin use at baseline as an independent factor for the changes in SMI in either simple comparison (Figure 2) or the multivariate analysis (Table 2), whereas the use of antihyperglycemic drugs was not associated with changes in handgrip strength and gait speed (Figure 2).

Table 1
Clinical Characteristics of Study Patients (n = 588)

	Baseline	1-y Follow-up	*P* Value
Age (y)	70.0 ± 8.9	71.0 ± 8.9	
Sex, male (%)	58.8		
Body weight (kg)	63.4 ± 12.0	63.5 ± 12.0	.84
BMI	24.7 ± 4.0	24.8 ± 3.9	.002
Waist circumference (cm)	90.5 ± 10.2	91.2 ± 10.1	<.001
Creatinine (mg/dL)	0.8 ± 0.3	0.9 ± 0.3	.003
HbA_{1c} (%)	7.3 ± 1.2	7.1 ± 1.0	.001
HbA_{1c} (mmol/mol)	55.8 ± 12.7	54.5 ± 10.5	.001
Regular exercise habit (%)	55.6	56.5	.68
Antihyperglycemic treatment			
Sulfonylureas (%)	28.1	27.4	.49
Glinides (%)	9.5	10.4	.32
Biguanides (%)	39.1	41.8	.014
Thiazolidinediones (%)	15.3	16.3	.32
DPP-4 inhibitors (%)	61.6	62.4	.52
SGLT-2 inhibitors (%)	12.8	15.3	.019
α-Glucosidase inhibitor (%)	14.7	16.7	.028
Number of oral drugs	1.8 ± 1.3	1.9 ± 1.3	<.001
GLP-1 analogs (%)	4.6	4.8	.81
Insulin (%)	25.9	26.5	.47
Muscle mass and function			
SMI	7.5 ± 1.2	7.5 ± 1.2	.80
Handgrip strength (kg)	28.4 ± 9.3	28.3 ± 9.4	.40
Gait speed (m/s)	1.18 ± 0.25	1.17 ± 0.25	.11
Sarcopenia (%)	6.3	7.8	.12

BMI, body mass index; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA_{1c}, glycated hemoglobin A_{1c}; SGLT-2, sodium-glucose cotransporter-2.
Values are mean ± standard deviation or frequency. Statistical significance was assessed by paired *t* test or McNemar test.

Exercise was associated with stronger handgrip strength (29.3 ± 8.5 kg vs 27.3 ± 10.0 kg, $P = .007$) and faster gait speed (1.22 ± 0.23 m/s vs 1.13 ± 0.27 m/s, $P < .001$), but not with SMI (7.5 ± 1.2 vs 7.5 ± 1.2, $P = .75$) at baseline, though no significant association was observed with handgrip strength in the follow-up investigation (Table 2). During the follow-up period, 76 patients started exercising, whereas 71 patients discontinued it. However, changes in the habit did not affect percentage changes in SMI, handgrip strength, and gait speed (Supplementary Table 2).

Discussion

We longitudinally observed the relationship between glycemic control and sarcopenia and its components (muscle mass, handgrip strength, and gait speed) over 1 year. SMI and gait speed increased significantly in the subgroup in which the HbA_{1c} value decreased by 1% or more. Our study is the first to report that better glycemic control exerted favorable effects on muscle mass and physical functions. In addition, insulin use at baseline showed an independent and positive correlation with the changes in SMI, considering age, sex, body mass index, and other covariates. Several diabetes specific (eg, glycemic levels and medication) and nonspecific (eg, age, body composition, and nutritional status) factors have been identified as risk factors for sarcopenia.[5–8] However, there is insufficient evidence regarding the usefulness of any improvement of these risk factors, particularly blood glucose–lowering interventions, in the prevention of sarcopenia. Our findings attempt to fill the gap in the diabetes-sarcopenia interrelationship.

Previous studies demonstrated that insulin resistance and chronic inflammation caused by hyperglycemia led to muscle wasting through the pathways involving serine-threonine kinase Akt (protein kinase B)[9] or transcription factor forkhead box O.[10] Additionally, the accumulation of advanced glycation end products, whose levels partially reflect long-term glycemic profiles,[8] led to a decline in muscle mass[11] through its receptor-mediated downregulation of the Akt signaling pathway.[12] The existence of direct molecular pathways indicates that the favorable effects on sarcopenia due to reduction in HbA_{1c} values were not just an epiphenomenon of unmeasurable effects of potential confounding factors.

Poor glycemic control in patients with type 2 diabetes was reported to be a risk factor for sarcopenia.[8] In addition, a longitudinal study in a Korean population revealed that a high glycemic level

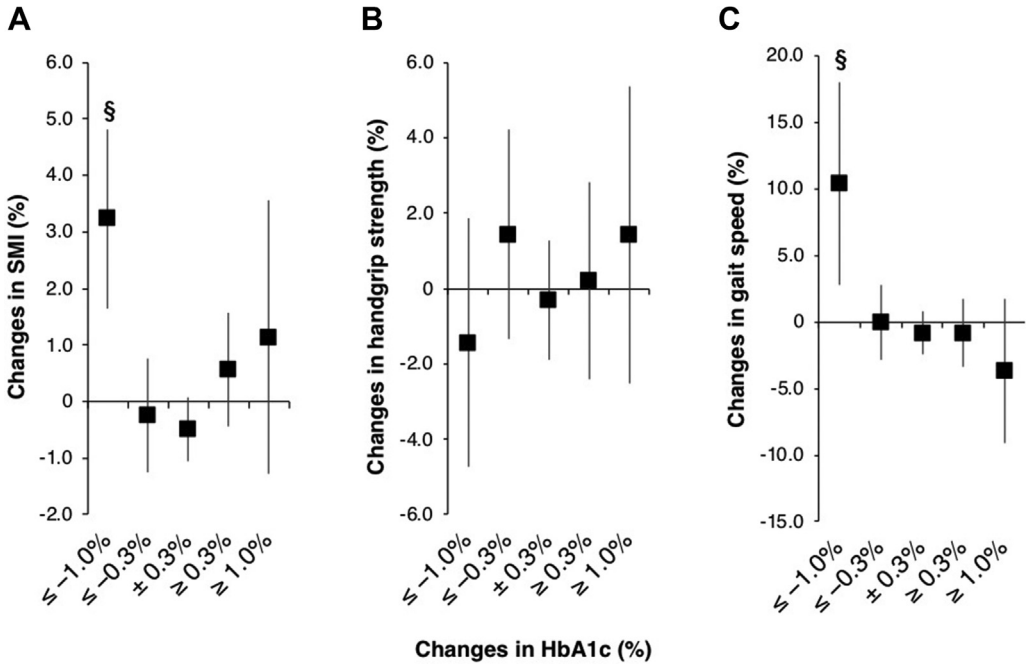

Fig. 1. Association of changes in HbA1c level during the follow-up period with SMI, grip strength, and gait speed. Change. Values are mean percentage change and 95% confidence interval of (A) SMI, (B) hand grip strength, and (C) gait speed. Statistical significance was assessed by Dunnett test considering the subgroup of HbA1c change ±0.3% as a reference (§$P < .001$). Number of patients in each group was as follows: ≥1.0% decrease: 53, ≥0.3% decrease: 119, ±0.3%: 279, ≥0.3% increase: 106, and ≥1.0% increase: 31.

Table 2
Linear Regression Analysis of Percentage Changes in SMI, Handgrip Strength, and Gait Speed During the Follow-up Period

	Percentage Change During Follow-up Period					
	SMI		Handgrip Strength		Gait Speed	
	β	*P* Value	β	*P* Value	β	*P* Value
Age (years)	−0.021	.638	−0.178	<.001	−0.236	<.001
Sex (men)	0.183	.006	0.336	<.001	0.027	.490
BMI	0.173	.012	0.024	.574	−0.085	.033
Baseline SMI	−0.341	<.001				
Baseline handgrip strength (kg)			−0.439	<.001		
Baseline gait speed (m/s)					−0.421	<.001
HbA_{1c} (%)	−0.003	.966	−0.096	.093	−0.067	.210
HbA_{1c} (≥1% decrease)	0.113	.027	−0.005	.914	0.145	.002
Regular exercise habit	0.015	.719	0.081	.054	0.050	.208
Antihyperglycemic drug use						
Insulin	0.115	.022				
DPP-4 inhibitors	−0.073	.104				
SGLT-2 inhibitors	−0.069	.125				
α-Glucosidase inhibitor	−0.068	.094				

β, standardized regression coefficient; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; HbA_{1c}, glycated hemoglobin A_{1c}; SGLT-2, sodium-glucose cotransporter-2.
Measurement site was included in the regression model as dummy variables.

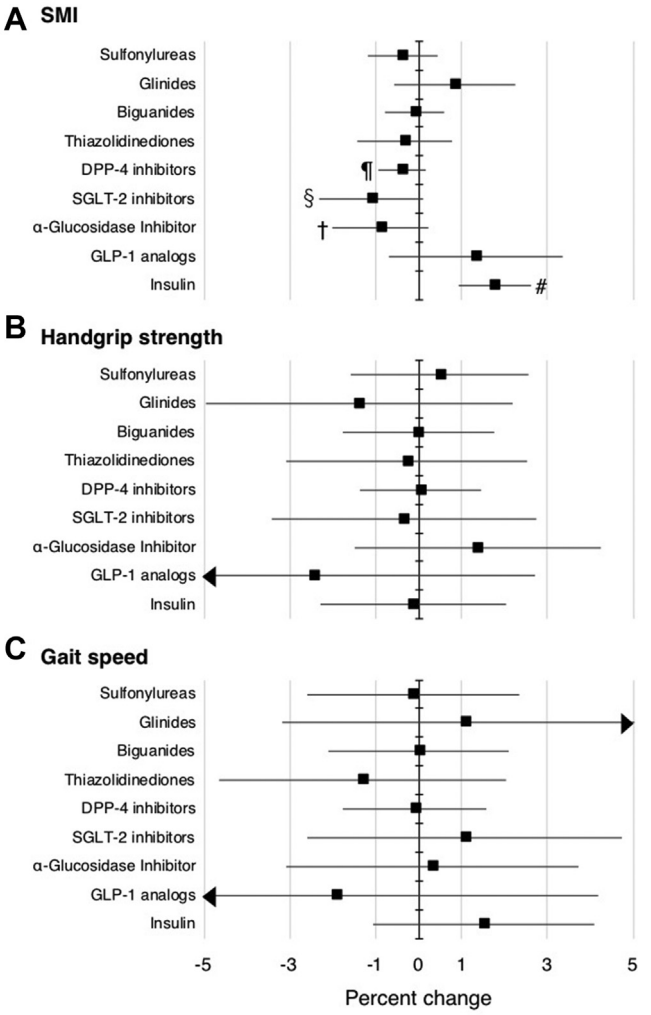

Fig. 2. Associations between antihyperglycemic drug use at baseline and changes in SMI, grip strength, and gait speed during the follow-up period. Values are mean percentage changes and 95% confidence interval of (A) SMI, (B) hand grip strength, and (C) gait speed in patients taking each class of antihyperglycemic drugs. Differences in the values between patients using and not using each drug were assessed by analysis of variance (#$P < .001$, ¶$P = .002$, §$P = .029$, †$P = .046$).

($HbA_{1c} \geq 8.5\%$ or 69 mmol/mol) in older patients with diabetes was associated with low muscle mass and muscle quality.[13] Furthermore, postprandial hyperglycemia, assessed by blood glucose self-monitoring, was suggested to be an independent risk factor for low muscle mass, weak handgrip strength, and slow gait speed.[14] However, a cross-sectional study reported conflicting results in patients with diabetes with a mean HbA_{1c} value of 7.0% (53 mmol/mol).[15] This discrepancy might be due to different glycemic levels in the study population. In particular, a high HbA_{1c} value, approximately ≥8.0% (64 mmol/mol), in patients with type 2 diabetes should be considered as a risk factor for sarcopenia. Therefore, correcting glycemic control in such patients may have a greater effect on skeletal muscle phenotypes. In this regard, our results strongly support that blood glucose–lowering interventions are effective against sarcopenia.

In this study, we enrolled patients when they were being treated by primary physicians according to the standards of medical care in type 2 diabetes, including proper diet, exercise, and medications. Therefore, these factors needed to be considered when investigating the blood glucose–lowering effects on the indices of sarcopenia. Multivariate analysis showed that a ≥1% decrease in the HbA_{1c} value was a factor influencing the improvement in SMI and gait speed, independent of exercise habit (Figure 2). From these results, we deduce that the changes in glycemic control have an important effect on SMI and gait speed independent of the changes in exercise habits.

Resistance training was effective for improving the size and strength of muscles and metabolic health in older adults with type 2 diabetes.[16] However, a study reported that adhering to exercise was difficult for patients with diabetes because of improving glycemic control.[17] Therefore, we consider that a combination intervention of antihyperglycemic treatment and exercise might be better than exercise intervention alone to maintain muscle mass or physical functions. However, further investigations will be needed to clarify the beneficial effects of correction of hyperglycemia on preventing the decline of muscle mass or physical functions because this study was observational and did not have detailed information on exercise habits (intensity, time, duration, etc).

In this study, skeletal muscle mass was maintained or increased in patients using insulin. As insulin is an anabolic hormone[18] and a subcutaneous injection acts on skeletal muscle and adipose tissue prior to liver, theoretically, insulin use could positively function on skeletal muscle. However, a study reported that supraphysiological hyperinsulinemia is necessary to stimulate muscle protein synthesis and anabolic signaling in older individuals because of the existence of age-related insulin resistance.[19] Moreover, a meta-analysis investigating the role of insulin in the regulation of human skeletal muscle protein synthesis and breakdown demonstrated that insulin has a permissive role in muscle protein synthesis in the presence of elevated amino acid levels. Additionally, it plays a definite role in reducing muscle protein breakdown independent of amino acid availability.[20] Therefore, insulin use contributes to maintaining muscle mass and prevents the incidence or progression of sarcopenia in patients with diabetes.

According to a review summarizing the effects of antidiabetic drugs on skeletal muscle, insulin, thiazolidine drugs, glucagon-like peptide-1 (GLP-1) analogs, and dipeptidyl peptidase-4 (DPP-4) inhibitors might be useful or have no impact on the maintenance of the skeletal muscle mass, whereas the effects of biguanides and sodium-glucose cotransporter-2 (SGLT2) inhibitors are unknown, and sulfonylureas and glinides might be unfavorable.[21] In this study, muscle

mass tended to decrease in patients using SGLT2 inhibitors. In contrast, it is reported that SGLT2 inhibitors suppressed the decline of muscle mass by lowering blood glucose level in diabetic model mice.[22] Thus, further clinical investigations are needed to explore the effects of SGLT2 inhibitors on muscle mass or function.

Our study has several limitations. The number of patients was relatively small, and the follow-up duration of 1 year was short. However, no studies have examined the association of the changes in glycemic control or the use of hypoglycemic agents with the changes in indices of sarcopenia in 588 patients with type 2 diabetes. Our current findings are noteworthy in suggesting the importance of glycemic control in preventing or suppressing the progression of sarcopenia. In this study, we did not consider the nutritional status, especially the protein intake, which may modulate the relationship between diabetes and sarcopenia. We did not examine the dosages of antihyperglycemic agents and insulin. Regarding insulin use, we did not have data for the type of insulin, such as short-acting, long-acting, or premixed, used by the patients. However, 81.2% of insulin users also had basal-supported oral therapy in this study. This means that most of the insulin users received long-acting insulin. Finally, we did not evaluate the level of physical activity but only gathered data about the frequency and duration of exercise habit. The level of physical activity can affect changes in muscle mass and strength. A meta-analysis revealed that low-intensity exercise was enough to induce substantial gains in muscle strength in older adults if a sufficient number of exercise repetitions was performed.[23] Collecting the data on the intensity of physical training should be considered in our further study. Despite the limitations, our findings could provide suggestions for establishing new strategies for the management of older patients with type 2 diabetes, especially for those who have a risk for sarcopenia.

Conclusions and Implications

In summary, the correction of poor glycemic control and the use of insulin were significantly associated with increase in skeletal muscle mass or gait speed independent of possible covariates, including exercise habit, in Japanese patients with type 2 diabetes. The current finding increases our understanding of the importance of glycemic control for the prevention of cardiovascular diseases and sarcopenia.

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Supplementary Table 1
Distribution of Changes in SMI, Handgrip Strength, and Gait Speed During the Follow-up Period (n = 588)

Percent change during the Follow-up Period	SMI, %	Handgrip Strength, %	Gait Speed, %
≤−20	0	5.4	6.3
≤−15	0.5	3.9	7.7
≤−10	2.0	7.7	10.5
≤−5	10.4	15.0	13.9
±5	72.4	38.4	30.1
≥5	9.7	11.6	10.4
≥10	3.4	6.8	6.6
≥15	1.4	4.6	4.4
≥20	0.2	6.6	10.0

SMI, skeletal muscle mass index.

Supplementary Table 2
Associations Among Changes in Exercise Habit, SMI, Handgrip Strength, and Gait Speed During Follow-up Period

Change in Exercise Habit	n	Percent Changes in Components of Sarcopenia					
		SMI		Handgrip Strength		Gait Speed	
			P Value		*P* Value		*P* Value
Discontinued	71	0.55 ± 5.7	.92	1.11 ± 14.0	.62	0.18 ± 16.7	.51
Continued	256	0.08 ± 4.8		0.68 ± 13.0		−0.49 ± 14.6	
Started	76	0.01 ± 4.2		−0.56 ± 13.7		2.71 ± 17.0	
None	185	0.21 ± 6.2		−0.77 ± 14.2		0.09 ± 17.6	

SMI, skeletal muscle mass index.
Statistical significance was assessed by analysis of variance.