

Low skeletal muscle mass is associated with the risk of all-cause mortality in patients with type 2 diabetes mellitus

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Abstract

Background: Patients with type 2 diabetes mellitus (T2DM) have an increased risk of muscle mass reduction. However, the association between muscle mass and mortality in T2DM remains unknown.

Methods: This was a historical cohort study with the endpoint of all-cause mortality. This study included 163 Japanese men and 141 postmenopausal women with T2DM whose body compositions were evaluated using dual-energy X-ray absorptiometry. Low muscle mass was defined as a skeletal muscle mass index (SMI) of $<7.0 \text{ kg/m}^2$ for men and $<5.4 \text{ kg/m}^2$ for women.

Results: During the 6-year follow-up period, 32 men and 14 women died. In a Cox regression analysis adjusted for age, T2DM duration, glycosylated hemoglobin, serum creatinine, fasting C-peptide, body mass index, and lean body mass were associated with the risk of mortality in men [hazard ratio (HR) = 1.81, 95% confidence interval (CI) = 1.00–3.28 per standard deviation (SD) decrease, $p = 0.049$] and women (HR = 4.53, 95% CI = 1.14–17.96 per SD decrease, $p = 0.032$). Neither fat mass nor bone mineral content was associated with mortality. Low SMI was associated with increased mortality in women (HR = 5.97, 95% CI = 1.04–34.37, $p = 0.045$), while the association between low SMI and mortality was marginal in men (HR = 2.38, 95% CI = 0.92–6.14, $p = 0.074$).

Conclusions: Low muscle mass was independently associated with all-cause mortality in patients with T2DM. The preservation of skeletal muscle mass is important to protect patients with T2DM from increased mortality risk.

Keywords: mortality, muscle mass, sarcopenia, skeletal muscle mass index, type 2 diabetes mellitus

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Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is increasing in the elderly population, and the management of elderly patients with T2DM is a critical issue. In the ageing population, sarcopenia is a serious complication related to the progressive loss of skeletal muscle mass and function as it causes frailty that results in elderly patients becoming bedridden.¹ Accumulating evidence has shown that patients

with T2DM are at an increased risk of sarcopenia.^{2–4} Although the pathophysiological mechanism underlying T2DM-associated sarcopenia remains unclear, the dysfunction of insulin and insulin-like growth factor 1, as well as advanced glycation end products, which are generated by the sequential nonenzymatic chemical glycation of proteins⁵ and are increased in patients with T2DM,⁶ may be associated with the mechanism of T2DM-associated sarcopenia.^{7–9} Moreover,

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skeletal muscle is an important tissue involved in insulin action and glucose metabolism. Thus, the disturbance of glucose metabolism in T2DM may lead to the loss of skeletal muscle and vice versa. Therefore, sarcopenia has recently been recognized as a diabetic complication.

T2DM reduces the life expectancy of patients.¹⁰ The adjusted relative risk of death has been reported to be almost twice as high in patients with diabetes mellitus compared with that in age-matched controls.¹¹ Furthermore, the presence of T2DM increases the risks of cardiovascular diseases,¹⁰ infections,¹² cancer,¹³ and fractures,¹⁴ all of which are associated with increased mortality. However, whether other diabetic complications contribute to the increased mortality in patients with T2DM remains unclear. Studies have demonstrated that low skeletal muscle mass is associated with an increased risk of all-cause mortality in the elderly population.¹⁵ Therefore, we hypothesized that low skeletal muscle mass is associated with mortality in patients with T2DM. Thus far, no study has focused on the association between muscle mass and mortality risk in patients with T2DM. Therefore, this study aimed to examine the association of body composition, skeletal muscle mass index (SMI), and all-cause mortality in patients with T2DM.

Materials and methods

Patients

In this historical cohort study, we investigated the association between lean body mass (LBM) and the endpoint of all-cause mortality in patients with T2DM. Patients admitted to Shimane University Hospital, Japan, for the treatment of T2DM, except those with malignant diseases, infections, necessity of surgery, and other special conditions, from 1997 to 2009 were screened. According to hospital records, 843 men and 667 women were admitted. We investigated patient survival or mortality based on medical records and telephone surveys from 2013 to 2014. Based on the data, the body composition was evaluated using whole-body dual-energy X-ray absorptiometry (DXA) at the baseline, and a survey of life and death was available for 163 men and 141

postmenopausal women with T2DM. The median follow-up periods were 5.9 and 6.2 years in men and women, respectively. This study was approved by the institutional review board (IRB) of the Faculty of Medicine at Shimane University (IRB approval number 2958). The requirement for informed patient consent was waived because no interventions or further examinations were performed.

Anthropometric and biochemical measurements

Body height (cm) was measured using the Martin metal anthropometer to the nearest 0.1 cm according to standard techniques, and body weight (kg) was measured using a medical electronic scale and recorded with 0.05-kg precision with the patient wearing lightweight clothes. Body mass index (BMI; kg/m²) was calculated using the following formula: BMI = (weight in kg)/[(height in m)²]. After overnight fasting, blood and urine samples were collected the day after admission. Hemoglobin A1c (HbA1c), serum fasting C-peptide, and serum creatinine levels were measured using standard biochemical methods, as previously reported.^{7,8} HbA1c values were determined by high-performance liquid chromatography and were estimated as the National Glycohemoglobin Standardization Program equivalent values calculated using the formula: HbA1c (%) = HbA1c (Japan Diabetes Society; %) + 0.4%.

Radiography

Body composition was assessed using whole-body DXA (QDR-4500, Hologic Co., Bedford, MA, USA). Fat mass (FM), bone mineral content (BMC), and LBM were expressed in kilograms. LBM of the arms and legs and appendicular skeletal muscle mass (ASM) was evaluated. SMI was calculated using the following formula: SMI = (ASM in kg)/[(height in m)²], as previously described.^{7,8} Low SMI was defined as <7.0 kg/m² for men and <5.4 kg/m² for women, which are used for the diagnosis of sarcopenia in Asian individuals.¹⁶

Statistical analysis

Data were expressed as means ± standard deviations (SDs). The statistical significance between

the two groups was determined using Student's *t* test and Chi-square tests. Kaplan–Meier curves, log-rank tests, and Cox proportional hazard regression analyses were used to estimate the associations among body composition, SMI, and the risk of mortality after adjusting for confounding factors such as age, duration of diabetes, HbA1c, serum creatinine, fasting C-peptide, and BMI. All analyses were performed using StatView (Abacus Concepts, Berkeley, CA, USA). A *p* value <0.05 was considered statistically significant.

Results

Baseline characteristics of the patients and comparison between dead and surviving patients

Baseline characteristics of the patients (163 men and 141 women) and a comparison between survivors (131 men and 32 women) and dead patients (32 men and 14 women) are shown in Table 1. Among men, dead patients were significantly older than survivors ($p < 0.001$). The BMC, LBM, and SMI of dead patients were significantly lower than those of survivors ($p = 0.002$, $p < 0.001$, and $p = 0.004$, respectively). Among women, dead patients were significantly older ($p < 0.001$) and had longer durations of T2DM ($p = 0.021$). BMI, fasting C-peptide, FM, BMC, LBM, and SMI of dead patients were significantly lower than those of survivors ($p = 0.011$, $p = 0.005$, $p = 0.008$, $p = 0.015$, $p < 0.001$, and $p = 0.037$, respectively). The numbers of patients who received insulin, sulfonylurea, metformin, and thiazolidine were 26, 56, 22, and 19 men, respectively, and 41, 47, 27, and 12 women, respectively. The numbers of patients with a history of cardiovascular disease and stroke were 19 and 12 men, respectively, and 11 and 14 women, respectively.

Association between body composition and all-cause mortality

In the unadjusted Cox regression analysis, LBM was significantly and inversely associated with all-cause mortality in men [hazard ratio (HR) = 2.19, 95% confidence interval (CI) = 1.49–3.22 per SD decrease, $p < 0.001$] and

women (HR = 4.95, 95% CI = 2.10–11.67 per SD decrease, $p < 0.001$) (Table 2). After adjustment for age, duration of T2DM, HbA1c, serum creatinine, and serum fasting C-peptide (Model 1), LBM was significantly associated with mortality in men (HR = 1.73, 95% CI = 1.10–2.72 per SD decrease, $p = 0.018$) and in women (HR = 3.06, 95% CI = 1.17–8.02 per SD decrease, $p = 0.023$). Moreover, after additional adjustments for BMI (Model 2), LBM was still significantly associated with mortality in men (HR = 1.81, 95% CI = 1.00–3.28 per SD decrease, $p = 0.049$) and women (HR = 4.53, 95% CI = 1.14–17.96 per SD decrease, $p = 0.032$). In contrast, in the unadjusted analysis, lower FM and lower BMC values were associated with increased mortality in men and women, whereas the association became insignificant after adjustment (Models 1 and 2).

Association between SMI and all-cause mortality

Next, the background characteristics were compared between patients with and without low SMI (Table 3). In men, patients with low SMI (<7.0 kg/m²) had significantly lower BMI and lower serum fasting C-peptide levels than those without low SMI ($p < 0.001$ and $p = 0.021$, respectively). In women, patients with low SMI (<5.4 kg/m²) had significantly lower BMI than those without low SMI ($p < 0.001$).

Unadjusted survival analyses indicated that patients with low SMI had higher mortality than those with high SMI, both in men and women ($p = 0.008$ and $p = 0.014$, respectively; Figure 1 and Table 4). In the Cox regression analysis adjusted for age, duration of T2DM, HbA1c, serum creatinine, and serum fasting C-peptide (Model 1), low SMI was significantly and positively associated with mortality in men (HR = 2.46, 95% CI = 1.13–5.37, $p = 0.023$) and women (HR = 6.20, 95% CI = 1.46–26.28, $p = 0.013$). The association remained significant even after adjusting for BMI (Model 2) in women (HR = 5.97, 95% CI 1.04–34.37, $p = 0.045$), but the association became marginal in men (HR = 2.38, 95% CI 0.92–6.14, $p = 0.074$).

Table 1. Baseline characteristics and comparison between dead patients and survivors.

	Men			Women		
	Total	Survivors	Dead patients	Total	Survivors	Dead patients
Age (years)	64.4 ± 9.3	63.0 ± 9.1	70.4 ± 7.4	66.1 ± 9.9	65.1 ± 9.6	75.1 ± 8.9
Duration of diabetes (years)	10.6 ± 9.9	10.7 ± 9.8	10.5 ± 10.8	11.6 ± 10.2	10.9 ± 9.8	17.7 ± 10.18
BMI (kg/m ²)	23.0 ± 3.2	23.2 ± 3.1	22.3 ± 3.3	24.7 ± 4.5	24.9 ± 4.4	22.7 ± 4.9
HbA1c (%)	8.9 ± 2.1	8.8 ± 2.1	9.0 ± 2.3	8.9 ± 2.2	8.8 ± 2.2	9.5 ± 2.4
Serum creatinine (mg/dl)	0.80 ± 0.23	0.78 ± 0.22	0.87 ± 0.27	0.65 ± 0.29	0.66 ± 0.30	0.57 ± 0.13
Fasting C-peptide (ng/ml)	1.7 ± 1.0	1.7 ± 1.0	1.6 ± 1.0	1.7 ± 0.8	1.7 ± 0.8	1.1 ± 0.5
FM (kg)	12.3 ± 4.5	12.6 ± 4.3	11.0 ± 4.8	17.1 ± 6.4	17.6 ± 6.25	12.8 ± 6.6
BMC (kg)	2.2 ± 0.4	2.2 ± 0.4	2.0 ± 0.3	1.5 ± 0.3	1.6 ± 0.3	0.4 ± 0.4
LBM (kg)	46.1 ± 5.9	46.9 ± 5.6	42.8 ± 5.9	36.6 ± 5.1	37.2 ± 5.0	3.1 ± 3.1
SMI (kg/m ²)	7.14 ± 0.86	7.23 ± 0.83	6.74 ± 0.89	6.40 ± 0.88	6.47 ± 0.85	5.76 ± 0.93
Insulin	26	20	6	41	36	5
Sulfonylurea	56	45	11	47	42	5
Metformin	22	20	2	27	26	1
Thiazolidine	19	14	5	12	11	1
Statin	27	22	5	52	48	4
ACEi/ARB	24	20	4	48	45	2
Calcium antagonists	26	20	6	42	40	2
Anti-platelet drugs	35	27	8	28	28	0
CVD	19	13	6	11	11	0
Stroke	12	11	1	14	13	1

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMC, bone mineral content; BMI, body mass index; CVD, cardiovascular disease; FM, fat mass; HbA1c, glycated hemoglobin; LBM, lean body mass; SMI, skeletal muscle mass index.

Table 2. Association between body composition and mortality.

	Men			Women		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
LBM						
Crude	2.19	1.49–3.22	<0.001	4.95	2.10–11.67	<0.001
Model 1	1.73	1.10–2.72	0.018	3.06	1.17–8.02	0.023
Model 2	1.81	1.00–3.28	0.049	4.53	1.14–17.96	0.032
FM						
Crude	1.69	1.10–2.62	0.018	2.82	1.38–5.75	0.005
Model 1	1.53	0.92–2.56	0.104	1.74	0.69–4.37	0.238
Model 2	1.47	0.70–3.08	0.309	1.42	0.27–7.43	0.679
BMC						
Crude	1.76	1.24–2.48	0.001	1.99	1.09–3.60	0.024
Model 1	1.45	0.94–2.24	0.095	1.16	0.56–2.44	0.688
Model 2	1.37	0.86–2.16	0.182	0.96	0.42–2.16	0.912

Cox proportional hazard regression models were performed with all-cause mortality as a dependent variable and SMI as an independent variable.
Model 1; adjusted for age, duration of diabetes, HbA1c, serum creatinine, and fasting C-peptide Model 2; adjusted for model 1 plus BMI.
Unit of change; standard deviation per decrease.
BMC, bone mineral content; BMI, body mass index; CI, confidential interval; FM, fat mass; HbA1c, glycated hemoglobin; HR, hazard ratio; LBM, lean body mass; SMI, skeletal muscle mass index.

Table 3. Comparison of various parameters between patients with and without low SMI.

	Men			Women		
	>7.0 kg/m ²	<7.0 kg/m ²	<i>p</i>	>5.4 kg/m ²	<5.4 kg/m ²	<i>p</i>
Number of patients	94	69		124	17	
Age (years)	63.9 ± 9.8	65.2 ± 8.4	0.402	66.2 ± 10.0	65.6 ± 9.6	0.840
Duration of diabetes (years)	10.7 ± 10.0	10.6 ± 9.9	0.972	11.3 ± 9.6	13.3 ± 13.6	0.460
BMI (kg/m ²)	24.6 ± 2.6	20.8 ± 2.5	<0.001	25.3 ± 4.4	20.1 ± 2.4	<0.001
HbA1c (%)	8.6 ± 2.0	9.2 ± 2.3	0.131	8.9 ± 2.2	8.7 ± 2.2	0.726
Serum creatinine (mg/dl)	0.80 ± 0.23	0.80 ± 0.24	0.858	0.61 ± 0.14	0.66 ± 0.30	0.483
Fasting C-peptide (ng/ml)	1.8 ± 1.1	1.4 ± 0.7	0.021	1.7 ± 0.8	1.5 ± 0.6	0.342
SMI (kg/m ²)	7.72 ± 0.57	6.35 ± 0.47	<0.001	6.59 ± 0.74	4.99 ± 0.41	<0.001
Insulin	13	13	0.408	36	5	0.990

(Continued)

Table 3. (Continued)

	Men			Women		
	>7.0 kg/m ²	<7.0 kg/m ²	p	>5.4 kg/m ²	<5.4 kg/m ²	p
Sulfonylurea	25	21	0.344	42	5	0.701
Metformin	16	6	0.120	27	0	-
Thiazolidine	12	7	0.592	11	1	0.675
Statin	18	9	0.289	50	2	0.035
ACEi/ARB	12	12	0.571	45	2	0.059
Calcium antagonists	15	11	0.743	40	2	0.098
Anti-platelet drugs	18	17	0.400	26	2	0.380
CVD	13	6	0.295	9	2	0.520
Stroke	7	5	0.931	14	0	-

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CVD, cardiovascular disease; HbA1c, glycated hemoglobin; SMI, skeletal muscle mass index.

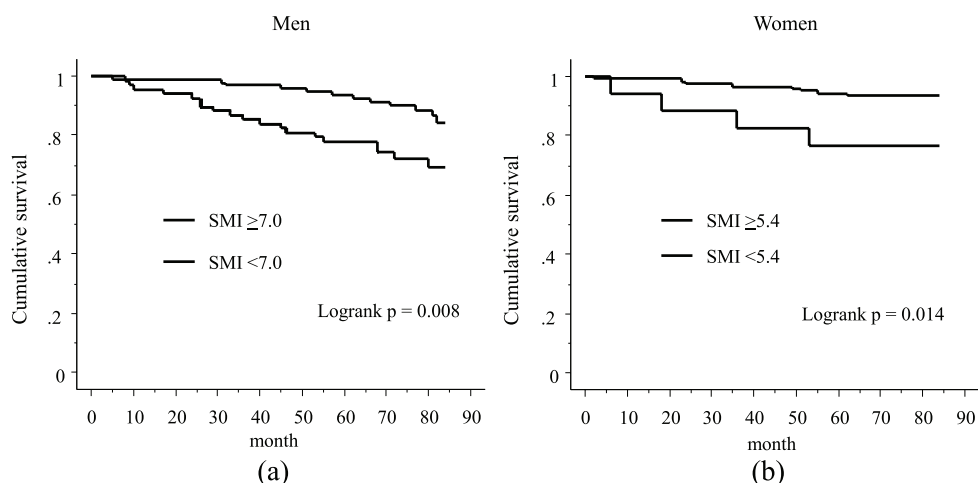


Figure 1. Survival curves of high and low SMI in men (a) and women (b) with type 2 diabetes mellitus. SMI, skeletal muscle mass index.

Table 4. HRs stratified by low SMI.

	Men			Women		
	HR	95% CI	p value	HR	95% CI	p value
Crude	2.58	1.25–5.32	0.010	4.00	1.20–13.30	0.024
Model 1	2.46	1.13–5.37	0.023	6.20	1.46–26.28	0.013
Model 2	2.38	0.92–6.14	0.074	5.97	1.04–34.37	0.045

Cox proportional hazard regression models were performed with all-cause mortality as a dependent variable and SMI as an independent variable.
 Model 1; adjusted for age, duration of diabetes, HbA1c, serum creatinine, and fasting C-peptide.
 Model 2; adjusted for model 1 plus BMI.
 BMI, body mass index; CI, confidential interval; HbA1c, glycated hemoglobin; HR, hazard ratio; SMI, skeletal muscle mass index.

Discussion

Previous studies have demonstrated that low muscle mass is associated with an increased risk of mortality.^{15,17–19} However, to date, no study has examined the association between muscle mass and mortality in patients with T2DM. Therefore, this is the first study to reveal that LBM is inversely associated with the risk of all-cause mortality in Japanese patients with T2DM and that low SMI based on the criteria of the Asian Working Group for Sarcopenia is associated with mortality risk. Moreover, the association was independent of age, duration of T2DM, HbA1c, serum creatinine, serum C-peptide, and BMI. Therefore, muscle mass reduction is an important predictor of all-cause mortality in patients with T2DM.

The present study revealed that low LBM was associated with increased mortality even after adjusting for BMI. Chuang and colleagues previously reported that the lowest quartile of SMI was associated with the highest all-cause mortality in the elderly Chinese population after adjusting for various confounding factors, including BMI.¹⁵ Moreover, weight loss is a risk factor for poor prognosis among elderly individuals. In this study, LBM was independently associated with mortality risk, whereas FM was not associated with mortality risk. These findings suggest that muscle mass reduction, but not FM, may be the cause of increased mortality in patients with T2DM.

In this study, the association between low muscle mass and increased mortality was more prominent in postmenopausal women than in men. Batsis and colleagues showed that women with sarcopenia, which is defined by magnetic resonance imaging-measured skeletal mass, had a higher mortality risk than those without sarcopenia, whereas the presence of sarcopenia was not associated with mortality in men.¹⁷ Chuang and colleagues also reported that low SMI appeared to be more tightly associated with high mortality in women than in men.¹⁵ Thus, our findings are consistent with those of previous studies. The underlying mechanism of muscle mass reduction may differ between men and women. In this study, we did not examine sex hormones and binding proteins, which might be involved in the difference in sex. Furthermore, the causes of death could be different between men and women with T2DM. The causes of death, such as cardiovascular conditions, infections, and malignant diseases, were not available in this study because the information was obtained from hospital records and telephone surveys. Further investigations should be performed

to assess the relationship between muscle mass and cause of death in men and women with T2DM in the future.

However, muscle quality has recently been considered important, especially in patients with T2DM. Park and colleagues showed that muscle quality, defined as muscle strength per unit of regional muscle mass, was significantly lower in patients with T2DM, although patients with T2DM had greater muscle mass than healthy people because they had a larger body size.² Moreover, leg muscle quality declined more rapidly in patients with T2DM than in healthy people.¹⁸ In this study, muscle functions such as handgrip and gait speed were not evaluated. Further studies should be performed to clarify whether muscle function and quality are associated with an increased all-cause mortality risk in men and women with T2DM.

The present study had several limitations. First, the sample size was not large enough to make definite conclusions. Because we could not follow up several patients, some patients lost to follow up may have died. Second, we examined only those patients who visited Shimane University Hospital, a tertiary center for the evaluation or treatment of T2DM. Therefore, the patients enrolled in this study might have relatively severe diseases. Third, the retrospective study design was an important limitation. Although several potential confounders were adjusted for, selection bias could affect the present findings. Moreover, comorbidities could be associated with muscle mass reduction and mortality. Because of the small number of patients with a history of cardiovascular or stroke, these comorbidities could not be included in the analysis. Further large-scale prospective studies are necessary to confirm the independent association between muscle mass reduction and mortality risk. Fourth, data such as those regarding HbA1c during the follow-up period were lacking. Finally, nondiabetic controls were not examined in this study. Therefore, we could not compare the contribution of muscle mass reduction to mortality between patients with T2DM and nondiabetic people. Conversely, we evaluated the association between not only LBM but also FM and all-cause mortality risk. Moreover, we examined the BMI-independent association between muscle mass and mortality. Thus, we should consider body composition rather than BMI when assessing the life expectancy of patients with T2DM. Furthermore, we used the cut-off value of SMI according to

the criteria of the Asian Working Group for Sarcopenia.¹⁶ The findings of our study indicate that SMI might be useful not only for defining sarcopenia but also for predicting the all-cause mortality risk in patients with T2DM.

In conclusion, the present study showed that lower LBM and lower SMI were associated with increased all-cause mortality independent of age, duration of T2DM, HbA1c, renal function, insulin secretion, and BMI in patients with T2DM. Therefore, the preservation of skeletal muscle mass is an important factor in the protection of patients with T2DM from increased mortality risk.

Authors' note

HM researched data and wrote manuscript. IK researched data and wrote/reviewed/edited manuscript. K-iT and TS contributed to discussion and reviewed/edited manuscript.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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