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Significance of body mass index for diagnosing sarcopenia is equivalent to slow gait speed in Japanese individuals with type 2 diabetes: Cross-sectional study using outpatient clinical data

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ABSTRACT

Aims/Introduction: This study examined the association between body mass index (BMI) and the risk of sarcopenia in Japanese type 2 diabetes patients.

Materials and Methods: Patients with type 2 diabetes who visited an outpatient clinic comprised the study's participants. Sarcopenia was defined using the definition of the Asian Working Group for Sarcopenia 2014. The area under the curve was examined for the presence of sarcopenia based on the receiver operating characteristic curve of BMI.

Results: Among 1,137 patients, 210 were diagnosed with low grip strength, 78 with slow gait speed, 444 with low muscle mass and 142 with sarcopenia. The optimal cut-off point of BMI level for risk of sarcopenia was 24.4 kg/m^2 (area under the curve 0.729, 95% confidence interval 0.688–0.770, sensitivity 0.587, specificity 0.789). Furthermore, the receiver operating characteristic curve of BMI for sarcopenia did not significantly differ ($P = 0.09$) from that of gait speed, an established marker of sarcopenia. In both the male and female groups, there was no difference between the receiver operating characteristic curves of BMI and gait speed for sarcopenia. ($P = 0.23$ and $P = 0.40$, respectively).

Conclusions: These results suggest that a BMI <24 kg/m^2 among Japanese patients with type 2 diabetes could increase their risk of sarcopenia, the extent of which is equivalent to the risk for sarcopenia from slow gait speed in this study. Further prospective investigation, however, is required.

INTRODUCTION

Sarcopenia is a geriatric syndrome associated with aging. It is characterized by loss of muscle mass, decrease in muscle strength and decline in physical performance[1]. Sarcopenia not only affects the daily activities of individuals, resulting in a decline of quality of life, but also can result in the acceleration of the progression of metabolic diseases.

The definition and diagnostic criteria of sarcopenia proposed by the Asian Working Group for Sarcopenia[1] adequately cover the specific and varied body compositions, genetic backgrounds, and ethnicity of Asian peoples. Sarcopenia in these criteria is a composite phenotype defined by a combination of excessive loss of muscle mass, weakening of muscle strength and decline of physical function, characterized by weak handgrip or slow usual gait speed, as well as low skeletal muscle index (SMI)[1]. Prospective studies have shown consistent associations between low muscle strength[2], low muscle mass[3–6] and mortality risk.

Patients with type 2 diabetes mellitus are recognized as being at high risk for sarcopenia[7]. Changes in muscle fiber in patients with type 2 diabetes might occur as a result of diabetic complications and insulin resistance. The frequency of sarcopenia diagnosis has been reported to increase in a linear fashion with glycated hemoglobin (HbA1c) level[8]. Accordingly, it is important to diagnose sarcopenia among

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patients with type 2 diabetes, because an important goal for diabetes patients is to secure years of healthy life by managing the disorder and keeping glucose levels under control, thereby maintaining a quality of life equivalent to that of their healthy counterparts[9].

Body mass index (BMI) is commonly used worldwide as a measure for evaluating obesity[10]. BMI is also a simple measure that is inexpensive to use. Several studies suggested that patients in a group defined as having sarcopenia had a lower BMI compared with that of the general public[11] or patients with type 2 diabetes[12] in a Japanese population, indicating that loss of weight might cause loss of muscle mass at the same time. Accordingly, BMI might prove to be a useful marker for screening of sarcopenia in patients with type 2 diabetes. However, no report has verified the significance of BMI in the diagnosis of sarcopenia, in terms of cut-off points, in Japanese patients with type 2 diabetes.

In the present cross-sectional study, BMI was hypothesized to be an appropriate screening marker for the diagnosis of sarcopenia in Japanese participants with type 2 diabetes. To clarify this hypothesis, among Japanese patients with type 2 diabetes, three markers for diagnosis of sarcopenia were compared. Additionally, the study compared BMI receiver operating characteristic (ROC) curves and estimated BMI cut-off points for diagnosis of sarcopenia.

METHODS

Study population and patient selection

Patients eligible for participation in the present study were those who were diagnosed with type 2 diabetes, regularly visited the diabetes outpatient clinic at Iwamoto Medical Clinic and were aged at least 65 years. Patients who had finished a physical performance test required for diagnosis of sarcopenia and whose clinical data were available, including disease histories, treatment regimens and plasma levels of glycemic parameters, were recruited to participate in the study from May 2017 to April 2018. Among the total of 1,562 patients, 425 patients with active retinopathy, end-stage renal disease, steroid use, difficulties in carrying out the examination for assessment of sarcopenia due to orthopedic reasons, stroke or other impairments and those deemed to be inappropriate for assessment by the attending physician were excluded. Data collection for variables, such as type of medication, duration of diabetes and biochemical data, were carried out at the same time as the assessment of sarcopenia. BMI was calculated as weight in kilograms divided by the square of height in meters.

The ethics committee of Kawasaki Medical School (No. 3549) and the ethics committee of the Kagawa Medical Association (No. KAI2018-5) approved the study protocol. Information pertaining to the study was provided to the public through the internet, instead of informed consent being obtained from each individual patient, based on the 2013 Declaration of Helsinki.

Assessment of sarcopenia

Sarcopenia was diagnosed based on the Asian Working Group for Sarcopenia, which defined the disorder as being marked by low muscle mass with low muscle strength and/or low physical performance[1]: weak handgrip (<26 kg for men, <18 kg for women) or slow usual gait speed (<0.8 m/s) and low SMI (<7.0 kg/m^2 for men, <5.7 kg/m^2 for women).

Grip strength with each hand was measured using a standard handgrip dynamometer (Smedley; Matsumiya Ika Seiki Seisakujo, Tokyo, Japan). Measurements were taken twice in a sitting position with the measured arm positioned horizontal to the ground. The participants were instructed to adjust the handle of the dynamometer to ensure a position under the second phalanx when gripped. Mean values were used for analysis. Measurements for usual gait speed were carried out and obtained by an accompanying medical staff using a digital timer. SMI was estimated using bioimpedance analysis devices (InBody770; InBody Japan, Tokyo, Japan). The validity and reproducibility of appendicular lean mass and fat mass measurements by segmental multiple-frequency bioelectrical impedance analysis were reported to be comparable to dual-energy X-ray absorptiometry[13–16] and hydrostatic weighing[14]. SMI was obtained by dividing appendicular lean mass by squared body height[16].

Statistical analysis

Categorical variables were expressed as numerals and percentages. Continuous variables were expressed as the mean and standard deviation, or median and interquartile ranges. The χ^2-test was used for testing associations between categorical variables. Continuous variables were compared using analysis of covariance (ANCOVA) for comparisons with categories, after adjustment for age and sex. Logistic regression analysis, which was used for diagnosis of sarcopenia (1 = having sarcopenia, 0 = no sarcopenia) as a dependent variable, was carried out to clarify the effect of BMI. These analyses were also carried out among participants divided into quartiles of BMI based on participant number (<22.49, 22.50–24.71, 24.72–27.03 and >27.04 kg/m^2 in BMI). Participant numbers were 284, 284, 285 and 284, respectively. In addition, to compare the effect of BMI on the diagnosis of sarcopenia, the study constructed ROC and determined the area under the curve (AUC), and compared the curves using EZR[17] (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (the R Foundation for Statistical Computing, Vienna, Austria). More precisely, EZR is a modified version of R Commander, designed to incorporate statistical functions frequently used in biostatistics. Statistical comparisons were carried out for men and women separately, in addition to all participants combined, because cut-offs of grip strength and SMI for diagnosis of sarcopenia differ between men and women. Other statistical analyses were carried out using JMP software (version 13.2 for Windows; SAS Institute, Cary, NC, USA). *P*-values of <0.05 were considered to show statistical significance.

RESULTS

Clinical characteristics of study participants

The mean age, HbA1c and BMI for all participants were 73.7 ± 6.3 years, 7.0 ± 0.9% and 24.9 ± 3.7 kg/m^2, respectively. Among the 1,137 study participants, 142 individuals were diagnosed with sarcopenia. Table 1 indicates the clinical characteristics of patients in the two categories with and without sarcopenia. The patients with sarcopenia showed significantly higher HbA1c and lower BMI adjusted for age and sex than those without sarcopenia ($P = 0.018$ and $P = 0.0001$, respectively).

Association between sarcopenia and BMI

After adjustment was carried out for age, sex, duration of type 2 diabetes and HbA1c level, logistic regression analyses were carried out to understand the effect of BMI on the diagnosis of sarcopenia. As a result, the adjusted odds ratio of BMI as an independent factor for diagnosis of sarcopenia was 0.746 (95% confidence interval [CI] 0.696–0.801, $P < 0.0001$) among all participants. In addition, the adjusted odds ratios of BMI among men and women were 0.681 (95% CI 0.603–0.770, $P < 0.0001$) and 0.783 (95% CI 0.717–0.854, $P < 0.0001$), respectively. After dividing by quartiles according to BMI, the odds ratios of BMI were still significant for diagnosing sarcopenia among patients in the lowest and the lower quartiles. These significances were confirmed before adjustment, as described in Table 2. Accordingly, BMI was likely a negative risk factor for sarcopenia, especially among patients with a BMI <24 kg/m^2 in the present study.

According to the ROC analysis, the optimal cut-off point of BMI level for the presence of sarcopenia was 24.4 kg/m^2 (AUC 0.729, 95% CI 0.688–0.770, sensitivity 0.587, specificity 0.789) among all participants. In addition, the optimal cut-off point of BMI level for the presence of sarcopenia was 24.3 kg/m^2 (0.783, 95% CI 0.729–0.836, sensitivity 0.601, specificity 0.860) and 24.5 kg/m^2 (0.683, 95% CI 0.625–0.741, sensitivity 0.555, specificity 0.753) for men and women, respectively (Figure 1). Accordingly, the optimal cut-off point of BMI for the screening of sarcopenia was less than approximately 24 kg/m^2.

Differences in AUC among grip strength, gait speed, SMI and BMI for diagnosis of sarcopenia

To validate the significance of BMI for the diagnosis of sarcopenia among patients with type 2 diabetes, ROC analyses were carried out to compare the ROC of BMI with three ROCs

Table 1 | Clinical characteristics among patients with and without sarcopenia

	Without sarcopenia	Sarcopenia	*P*
Male/female (*n*)	604/391	57/85	
Age (years)	73.1 ± 5.8	79.4 ± 7.2	0.0001
Duration of type 2 diabetes (years)	16.3 ± 10.0	17.2 ± 10.3	0.0908
BMI	25.3 ± 3.6	22.5 ± 2.7	0.0001
HbA1c	7.0 ± 0.9	7.2 ± 1.3	0.0179
SMI (kg/m^2)	6.8 ± 1.0	5.5 ± 0.7	0.0001
Low SMI (male/female)	184/118	57/85	
Handgrip strength (kg)	30.4 ± 8.9	17.2 ± 5.8	0.0001
Low grip strength (male/female)	33/47	49/81	
Usual gait speed (m/s)	1.33 ± 0.28	0.99 ± 0.32	0.0001
Slow gait speed (N)	31	47	
SBP (mmHg)	129.0 ± 15.2	131.5 ± 19.7	0.4712
DBP (mmHg)	70.4 ± 9.4	68.3 ± 10.4	0.7633
AST (IU/L)	24.6 ± 9.1	24.1 ± 17.1	0.8869
ALT (IU/L)	22.5 ± 12.7	18.0 ± 9.6	0.0796
Cr (mg/dL)	0.8 ± 0.4	0.8 ± 0.3	0.0136
TG (mg/dL)	160.7 ± 109.2	129.0 ± 62.7	0.0052
HDL-C (mg/dL)	53.5 ± 14.0	55.5 ± 14.6	0.1961
LDL-C (mg/dL)	108.2 ± 25.3	109.1 ± 24.6	0.4896
Treatment for hypertension (%)	667 (67.0%)	94 (66.2%)	
Treatment for dyslipidemia (%)	526 (52.9%)	69 (48.6%)	
Treatment for diabetes (*n*)			
Insulin/SU/glinides/TZD	453/225/187/54	77/32/37/8	
BG/α-GI/DPP-4I	362/128/703	38/24/99	
SGLT2I/GLP-1RA	158/68	15/13	

Data are shown as the mean ± standard deviation. *P*-value was expressed after adjustment for age and sex, except age. α-GI, α-glucosidase inhibitor; ALT, alanine transaminase; AST, aspartate transaminase; BG, biguanide; BMI, body mass index; Cr, creatinine; DBP, diastolic blood pressure; DPP-4I, dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SGLT2I, sodium–glucose linked transporter 2 inhibitor; SMI, skeletal muscle index; SU, sulfonylureas; TG, triglyceride; TZD, thiazolidinedione.

Table 2 | Logistic regression analysis of body mass index for diagnosing sarcopenia

	β	Standard error	Wald	*P*-value	OR (95% CI)
Among all patients (*n* = 1,137)					
Crude	−0.2630	0.0317	68.7310	<0.0001	0.769 (0.722–0.818)
Adjusted	−0.2925	0.0360	66.1254	<0.0001	0.746 (0.696–0.801)
Among men (*n* = 661)					
Crude	−0.3559	0.0555	41.1548	<0.0001	0.701 (0.628–0.781)
Adjusted	−0.3840	0.0625	37.6900	<0.0001	0.681 (0.603–0.770)
Among women (*n* = 476)					
Crude	−0.1922	0.0374	26.4599	<0.0001	0.825 (0.767–0.888)
Adjusted	−0.2452	0.0445	30.3988	<0.0001	0.783 (0.717–0.854)
Among patients in lowest quartile (*n* = 284)					
Crude	−0.1928	0.0912	4.4720	0.0345	0.825 (0.690–0.986)
Adjusted	−0.2165	0.1056	4.2022	0.0404	0.805 (0.655–0.991)
Among patients in lower quartile (*n* = 284)					
Crude	−0.5724	0.2608	4.8176	0.0282	0.564 (0.338–0.941)
Adjusted	−0.5858	0.2949	3.9469	0.0470	0.557 (0.312–0.992)
Among patients in higher quartile (*n* = 285)					
Crude	0.1276	0.3245	0.1545	0.6943	1.136 (0.601–2.146)
Adjusted	0.2038	0.3683	0.3062	0.5800	1.226 (0.596–2.524)
Among patients in highest quartile (*n* = 284)					
Crude	−0.5733	0.3692	2.4106	0.1205	0.564 (0.273–1.162)
Adjusted	−0.7019	0.4063	2.9843	0.0841	0.496 (0.224–1.099)

Multivariate logistic analysis was used for age, sex, duration of diabetes, glycated hemoglobin and body mass index as independent factors among all patients or quartiles. Multivariate logistic analysis was used for age, duration of diabetes, glycated hemoglobin and body mass index as independent factors among men or women. β, Regression coefficient; CI, confidence interval; OR, odds ratio; Wald, Wald χ^2 value.

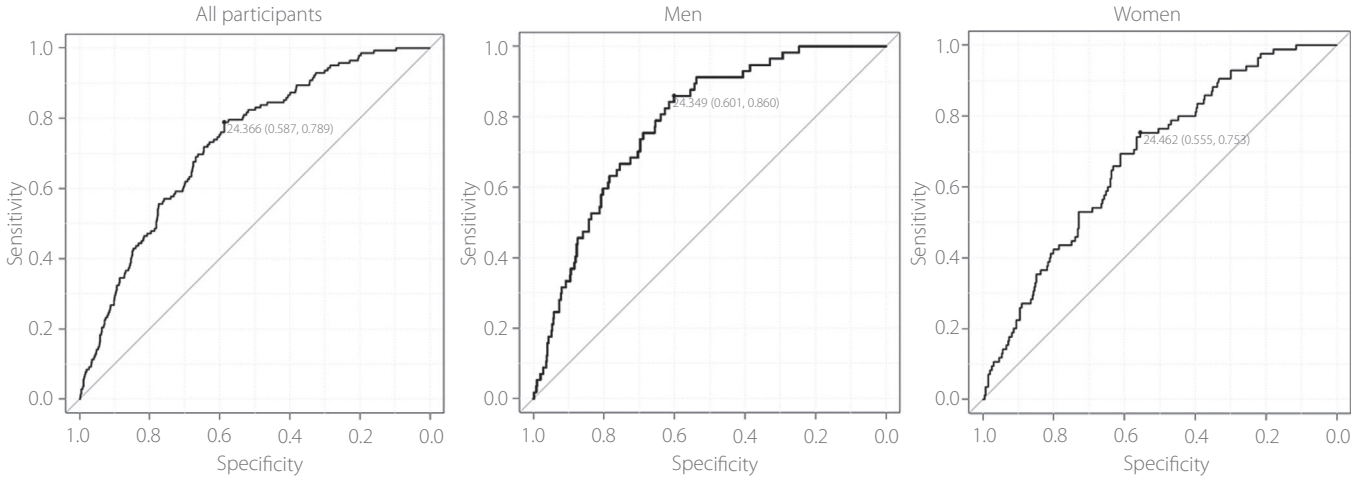

Figure 1 | Receiver operating characteristic curves for diagnosis of sarcopenia. The optimal cut-off points of body mass index levels for sarcopenia, sensitivities and specificities are presented.

of three diagnostic factors for sarcopenia: grip strength, gait speed and SMI. Among all participants, the AUCs of grip strength, gait speed and SMI were 0.895 (95% CI 0.869–0.921), 0.781 (95% CI 0.741–0.822) and 0.862 (95% CI 0.836–0.889), respectively. The ROC of BMI was significantly low in terms of AUC compared with those of grip strength ($P < 0.0001$) and SMI ($P < 0.0001$). However, the ROC of BMI did not differ in terms of AUC from the ROC of gait speed ($P = 0.09$; Figure 2a). Similarly, among men, the AUCs of grip strength, gait speed and SMI were 0.944 (95% CI 0.916–0.971), 0.830 (95% CI 0.775–0.885) and 0.924 (95% CI 0.900–0.948), respectively. The ROC of BMI was significantly low in terms of AUC

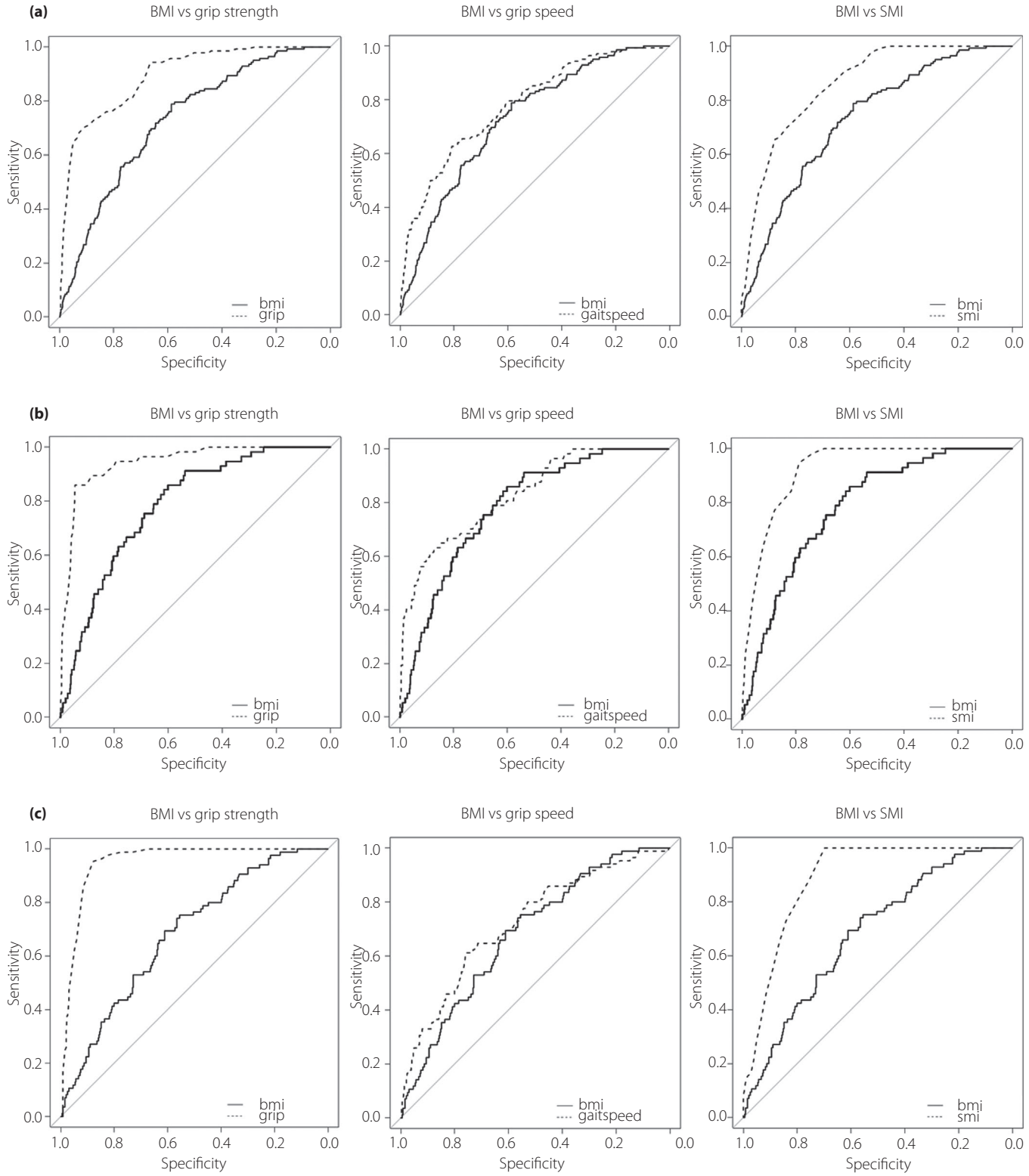

Figure 2 | Comparisons of receiver operating characteristic curves among body mass index (BMI) and three components for the diagnosis of sarcopenia. The solid line is the curve for BMI. The dotted lines are curves for grip strength on the left, usual gait speed in the middle and skeletal muscle index (SMI) on the right. (a) Curves in all participants. (b) Curves in men. (c) Curves in women.

compared with those of grip strength ($P < 0.0001$) and SMI ($P < 0.0001$). However, the ROC of BMI did not differ in terms of AUC from the ROC of gait speed ($P = 0.23$; Figure 2b). Finally, among women, the AUCs of grip strength, gait speed and SMI were 0.951 (95% CI 0.932–0.969), 0.722 (95% CI 0.662–0.782) and 0.887 (95% CI 0.858–0.916), respectively. The ROCs of BMI were significantly low in terms of AUC compared with those of grip strength ($P < 0.0001$) and SMI ($P < 0.0001$). However, the ROC of BMI did not differ in terms of AUC from the ROC of gait speed ($P = 0.40$; Figure 2c). Accordingly, the present study suggests that BMI is likely a practical marker in the screening of sarcopenia that is as important as usual gait speed in this study.

DISCUSSION

This single-center, cross-sectional study clarified the significance of BMI as a marker for screening of sarcopenia in Japanese patients with type 2 diabetes. It was also found that the optimal cut-off point was as high as 24 kg/m^2, and the effect of BMI with respect to diagnosis of sarcopenia was comparable to that of usual gait speed. These results suggest that even patients of normal bodyweight among Japanese patients with type 2 diabetes should be eligible for screening of sarcopenia, and that BMI could serve as a surrogate, to a certain extent, for gait speed in sarcopenia diagnosis.

Sarcopenia has been defined as an age-related, involuntary loss of skeletal muscle mass and strength. The present study clarified the association between high HbA1c and low BMI among type 2 diabetes patients with sarcopenia compared with type 2 diabetes patients without sarcopenia. This finding shows that low BMI was not necessarily desirable for patients with type 2 diabetes in cases of sarcopenia, because low BMI is typically associated with low muscle mass. Accordingly, the study results are plausible, because skeletal muscle as energy-consuming tissue is one of the important targets for insulin action, alongside liver and adipose tissue[18]. In addition, the optimal cut-off point of >24 kg/m^2 for diagnosis of sarcopenia in this study regardless of sex is recognized as being in the normal range for BMI, according to World Health Organization criteria[19]. These results suggest that we should bear in mind the possibility that not only underweight patients with type 2 diabetes, but also those with normal bodyweight might also be at risk for sarcopenia.

The cut-off point of 24 kg/m^2 of BMI found in the present study might be suggestive. The mortality rate among Japanese patients with type 2 diabetes was reported to be lowest among patients with a BMI of 18.5–24.9 kg/m^2[20]. The Japan Diabetes Society recently revised its calculation of appropriate caloric intake for diet therapy[21] from an ideal bodyweight calculated on the basis of a BMI of 22 to a targeted bodyweight calculated on the basis of BMI of between 22 and 25 kg/m^2 among elderly type 2 diabetes patients aged >65 years. Considering the results of this study, these changes in targets might prove to be beneficial for the prevention of sarcopenia in type 2 diabetes patients. In addition, a study based on 132 Chinese participants with type 2 diabetes[22] reported that the prevalence of sarcopenia at a BMI of at least 24 was approximately 14%, with the prevalence in those with a BMI of <24 being approximately 57%. With the aforementioned in mind, considering a BMI of 24 kg/m^2 as a cut-off point for sarcopenia screening could be beneficial, especially among Asian populations.

Both obesity and sarcopenia are critical concerns in an aging society. Obesity-mediated factors and pathways might directly or indirectly aggravate sarcopenia. For example, in obese adipose tissue, accumulation of pro-inflammatory macrophages and other immune cells, as well as dysregulated production of various adipokines together with the immune cell-released cytokines, create a local pro-inflammatory status[23]. In addition, obese adipose tissue is characterized by excessive production and disturbed capacity to store lipids, which accumulate ectopically in skeletal muscle[24]. These intramuscular lipids and their products can bring about mitochondrial dysfunction[24] and enhanced secretion of certain pro-inflammatory myokines with the potential to induce muscle dysfunction. In turn, these myokines might exacerbate adipose tissue inflammation, and support chronic and systemic inflammation in a paracrine manner, overall inducing a detrimental vicious cycle marked by preservation of adipose tissue and inflammation of skeletal muscle. In this way, such mechanisms might explain the development of sarcopenic obesity[23]. Sarcopenic obesity might be more insulin resistant, because increased bodyweight, as well as low muscle mass and strength, might relate to lack of physical exercise, slow walking speed, low amount of daily activity and longer sedentary duration. Accordingly, patients with type 2 diabetes might be recognized as having a higher risk of sarcopenia than healthy individuals, even if those same patients present a normal bodyweight, at least as found in the present study.

We surprisingly found that BMI was comparable with usual gait speed for diagnosis of sarcopenia, whereas grip strength and SMI were, as expected, significantly more important determinants than BMI in the present study. In everyday clinical practice, information about BMI is typically available for each patient, but information about gait speed is not. In addition, the measurement of BMI is much easier than the assessment of gait speed, added to which is the problem of imprecise information about gait speed obtained from each patient. Substitution of BMI for gait speed in screening of sarcopenia, as a first step, should therefore enable clinicians to make a judgement more easily regarding selection of candidates for screening of sarcopenia. Both gait speed and grip strength are measures used to assess muscle strength. From the viewpoint of muscle strength, the aspect of fast gait speed, which requires greater limb acceleration generated by muscular force, might be a more sensitive measure of physical and biological indicators of accelerated aging rather than habitual gait speed, which was confirmed in one study among middle-aged participants[25]. In another study[26], because neither habitual nor maximal gait

speed could determine age-related differences in functional capacity, both shorter gait speed tests were thought to suffer from a ceiling effect in the assessment of healthy older adults, with longer extended tests recommended for assessment of gait speed. The association between BMI and gait speed found in our study might have been different if fast or extended gait speed had been used, instead of usual gait speed for assessment of muscle strength. Further prospective investigation is thus required.

In the present study, the prevalence of sarcopenia was 12.5% among 1,137 patients, and the patients with sarcopenia had higher HbA1c than the patients without sarcopenia. In contrast, another report showed the prevalence of 18.7% among 267 Japanese patients with type 2 diabetes, whereas a study among Chinese and European patients with type 2 diabetes reported the prevalence of sarcopenia to be 28.8%[22] and 21%[27], respectively. HbA1c level did not differ between those with and without sarcopenia[12,27]. The patients with sarcopenia in the present study were at relatively advanced ages compared with these studies[12,22,28], and were overweight, had weak grip strength, low usual gait speed and low SMI compared with the other Japanese study[12]. These differences imply that the participants of the present study were more likely to have been categorized as having sarcopenic obesity than in previous studies. Accordingly, the results from our study might be difficult to use more broadly, because the participants with sarcopenia might have been relatively extreme cases.

The present study had several limitations other than those aforementioned. First, it was a single-center study with a cross-sectional design and a limited participant population. Accordingly, it was difficult to generalize the results, and distinguish cause and effect. Second, prescribed diabetes medications were not considered, because no statistical differences in variations of medications existed between the two categories (Table 1). However, the doses of medications used were likely increased in patients with high HbA1c levels. In addition, having sarcopenia might have affected the selection of medication, including sodium–glucose linked transporter 2 inhibitors. Finally, the study did not consider lifestyle habits and comorbidity factors, such as daily activities, smoking, cognitive function and frailty. In particular, exercise and nutritional status were crucial confounders for concluding the results of this study. Further prospective study on this topic is necessary.

In conclusion, the presence of sarcopenia was strongly associated with poor glycemic control in Japanese individuals with type 2 diabetes. In addition, the possibility should be considered that patients with type 2 diabetes are more likely to have sarcopenia, even with BMIs within what is considered a normal range. Finally, and interestingly, the significance of BMI in the diagnosis of sarcopenia was found to be comparable to slow gait speed, an established marker of sarcopenia, suggesting that BMI might possibly serve as a screening marker for sarcopenia.

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