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Relationships of Skeletal Muscle Mass and Visceral Fat with Atherosclerosis Risk Factors in Middle-aged Japanese People: An Assessment Using Accurate, Simple Bioelectrical Impedance Methods

Tetsuya Sato[1,3], Kenji Kanaji[2], Hiroyuki Nishikawa[2], Takashi Miyawaki[1,2]

Abstract

Objective: Recently, a decrease in skeletal muscle mass was found to be related to atherosclerosis risk. We investigated the relationship between skeletal muscle mass and atherosclerosis risk factors according to visceral fat accumulation status, using accurate, simple bioelectrical impedance methods.

Methods: The study included 1,161 middle-aged Japanese people (998 men and 163 women). The skeletal muscle was assessed using a bioelectrical impedance method between the upper and lower limbs, and visceral fat area (VFA) was measured using a dual bioelectrical impedance method. The subjects were divided into two groups according to VFA (VFA ≥100 cm^2 and VFA <100 cm^2) by sex and the relationship between percentage of skeletal muscle of body weight (PSM) and the number of atherosclerosis risk factors in each group was investigated. Multiple linear regression analysis was performed to determine the relative contribution of explanatory variables (age, VFA, subcutaneous fat area, and PSM) to the response variable (number of risk factors).

Results: The mean PSM significantly decreased as the number of risk factors increased in both men and women. In men with VFA <100 cm^2, the number of risk factors was significantly correlated with PSM (B = -0.164, $p < 0.001$), whereas in men with VFA ≥100 cm^2, there was no correlation. In women, the number of risk factors was not correlated with PSM irrespective of VFA.

Conclusions: Skeletal muscle mass assessed using the present accurate, simple bioelectrical impedance methods may be a new index for assessing the possibility of atherosclerosis risk factors in men.

Keywords skeletal muscle mass, bioelectrical impedance, atherosclerosis risk, visceral fat

Sarcopenia refers to age-related loss of skeletal muscle mass and muscle strength[1], and is a marker of frailty and poor prognosis among the elderly. In addition, it is known that sarcopenia is related to metabolic disorders. Insulin resistance has a stronger association with sarcopenic obesity, which is the combination of sarcopenia and obesity, than with sarcopenia or obesity alone in elderly people[2,3]. Additionally, a decrease in muscle mass may be a risk factor for atherosclerosis in middle-aged people[4] and young adults[5].

It is well known that metabolic syndrome (MS) is closely associated with atherosclerosis risk. MS is a cluster of atherosclerosis risk factors including visceral fat accumulation, hypertension, dyslipidemia, and diabetes[6]. Visceral fat accumulation increases the risk of atherosclerosis, and previous studies have shown that visceral fat accumulation is related to insulin resistance[7,8]. In addition, the coexistence of a decrease in muscle mass and MS increases the risk of cardiovascular diseases[9]. Thus, measurements of both visceral fat and muscle mass may be important for assessing the possibility of atherosclerosis risk factors.

The gold standard methods for the assessment of visceral fat and skeletal muscle are computed tomography (CT)[10] and magnetic resonance imaging (MRI)[1], respectively. In Japan, visceral fat accumulation is defined as visceral fat area (VFA) of ≥100 cm^2 using CT and MRI, both in men and women[6]. However, CT involves radiation exposure, and both of these methods are complex, costly, and time-consuming. Additionally, they are not suitable for body composition screening. Although dual energy X-ray absorptiometry (DXA) is an accu-

[1] Graduate School of Home Economics, Kyoto Women's University ; [2] Health Administration Center, Rakuwakai Toji-Minami Hospital ; [3] Omron Healthcare Co., Ltd.
Contact : Tetsuya Sato, Graduate School of Home Economics, Kyoto Women's University, 35, Kitahiyoshi-cho, Imakumano, Higashiyama-ku, Kyoto 605–8501, Japan. Tel : +81–75–925–2224 ; Fax : +81–75–925–2044 ; E-mail : k5420351@kyoto-wu.ac.jp

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rate method for measuring body composition, it also involves radiation exposure and is complex, and the assessment is influenced by body thickness[11].

Recently, two simple, highly accurate bioelectrical impedance methods for measuring VFA, subcutaneous fat area (SFA), and percentage of skeletal muscle of body weight (PSM) have been developed[12,13,14]. In this study, we investigated the relationship between skeletal muscle mass and atherosclerosis risk factors according to visceral fat accumulation status, using accurate, simple bioelectrical impedance methods, in middle-aged Japanese people.

Subjects and Methods

Subjects

We initially enrolled 1,441 adults (1,250 men and 191 women; mean age, 50.3±7.2 (SD) and 49.3 ± 8.8 (SD) years, respectively) who underwent an annual medical check-up at a health check-up center in the Kinki area of Japan between February 2012 and April 2015. We excluded 252 men and 28 women who were taking antihypertensive agents, antidiabetic agents, and lipid-lowering agents, and/or had dehydrative or edematous diseases. The study finally included 1,161 adults (998 men and 163 women; mean age, 49.4 ± 7.4 (SD) and 48.2 ± 8.9 (SD) years, respectively).

Anthropometric and atherosclerosis risk factor assessments

In the morning, the body weight of each subject was measured to the nearest 0.1 kg, with the subject in light clothes, and the height was measured to the nearest 0.1 cm. The waist circumference was measured to the nearest 0.5 cm at the umbilical level in the late exhalation phase while standing, by a well-trained examiner. Blood pressure measurements were obtained in the morning while the subjects were resting in a seated position. Blood samples were collected after an overnight fast for assessment of fasting plasma glucose, triglyceride, and high-density lipoprotein (HDL)-cholesterol levels.

Diagnosis of atherosclerosis risk factors

The diagnosis of atherosclerosis risk factors was in accordance with the definitions of the Examination Committee of Criteria for the Metabolic Syndrome in Japan[7,15]. Hypertension was defined as systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg, diabetes was defined as a fasting plasma glucose level ≥ 110 mg/dL, and dyslipidemia was defined as a triglyceride level ≥ 150 mg/dL and/or HDL-cholesterol level ≤ 40 mg/dL.

Body composition (PSM, VFA, and SFA) measurements

Measurement of PSM

Skeletal muscle mass was measured with the HBF-354 prototype (Omron Healthcare Co. Ltd., Kyoto, Japan), which used bioelectrical impedance between the upper and lower limbs[14].

Bioelectrical impedance was determined by measuring the voltage induced by applying a current to electrodes fixed on bilateral palms and soles while shorting each of the current and voltage electrodes fixed on each palm and sole, in the standing position with bilateral upper limbs extended forward. A constant current of 500 μA at 50 kHz was applied. The impedance measured using this method was whole-body impedance (Zw). Skeletal muscle mass was calculated using the BI index (height^2/Zw), the body surface area (BSA), sex, and age, using the following formula:

Skeletal muscle mass (kg) = (0.147 × BI index) + (1.625 × BSA) + (− 0.056 × age) + (− 2.098 × sex) − 2.282

The reference skeletal muscle mass was obtained using MRI performed in the supine position, every 20 mm from the hand to the foot. There was a good correlation between the skeletal muscle mass determined using the HBF-354 prototype and that measured using MRI ($r = 0.959$, $p < 0.001$).

Measurement of VFA and SFA

VFA and SFA were measured with HDS-2000 (DUALSCAN®, Omron Healthcare Co. Ltd., Kyoto, Japan), which used a dual bioelectrical impedance method[12,13]. Bioelectrical impedance was measured by applying a constant current of 500 μA at 50 kHz between the upper and lower limbs and the surface of the abdominal area in the supine position.

DUALSCAN (DS) calculates the cross-sectional area of visceral fat at the umbilical level based on a dual bioelectrical impedance method. DS uses two components (Zt: fat free area, Zs: subcutaneous fat area) to measure two kinds of bioelectrical impedance, and the width (A) and height (B) of a cross-sectional area of the abdomen. Using DS, the VFA was calculated according to the following formula:

$VFA = a_1 A + a_2 B^2 - a_3 (A^2 + B^2)^{1/2} Zs - a_4 / Zt + a_5$

a_1, a_2, a_3, a_4, and a_5 are constants

Reference VFA and SFA values were obtained using CT. There were good correlations between VFA determined using DS and that measured using CT ($r = 0.888$, $p < 0.001$)[13], and between SFA determined using DS and that measured using CT ($r = 0.887$, $p < 0.001$).

With the bioelectrical impedance method, as there is intra-day variability in body composition measurements[14], skeletal muscle mass, VFA, and SFA were measured after an overnight fast.

Statistical analysis

We divided the subjects into two groups according to visceral fat accumulation, and analyzed the relationship between PSM and the number of risk factors. Visceral fat accumulation was defined as VFA ≥ 100 cm^2 according to the Japanese guidelines for obesity treatment of the Japan Society for the Study of Obesity[6].

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We used PSM, the percentage of skeletal muscle mass of body weight, for the evaluation of skeletal muscle.

Data are presented as mean ± standard deviation. We used the Mann-Whitney U test to assess significant differences between the groups, and Spearman's correlation coefficient to assess the relationship between each atherosclerosis risk factor and PSM. We determined the relationship between the number of risk factors and PSM, using the Jonckheere-Terpstra trend test. Multicollinearity analysis was performed on BMI, age, VFA, SFA, and PSM. Explanatory variables with a low contribution rate were excluded and multiple linear regression analysis was performed to determine the relative contribution of explanatory variables to the response variable (number of risk factors), grouped by presence or absence of visceral fat accumulation. All statistical analyses were performed using SPSS Statistics version 21 for Windows (IBM Corp., Armonk, NY). Statistical significance was set at $p < 0.05$.

Ethical statement

Informed consent was obtained from each study subject, and this study was approved by the Research Ethics Committee of Kyoto Women's University (Approval number 25–26).

Results

The subjects' characteristics are presented in **Table 1**. The mean height, body weight, BMI, waist circumference, VFA, skeletal muscle mass, and PSM were significantly higher in men than in women. There were no significant differences in the mean age or SFA between men and women.

The mean PSM significantly decreased with aging in both men and women (p for trend < 0.001). PSM significantly decreased as VFA increased in both men ($r = -0.59$, $p < 0.001$) and women ($r = -0.58$, $p < 0.001$).

Table 1. Clinical Characteristics of Study Subjects

		Men	Women	*p* value
Number		998	163	
Age (years)		49.4 ± 7.4	48.2 ± 8.9	0.216
Height (cm)		171.4 ± 5.8	158.7 ± 5.2	<0.001
Weight (kg)		68.9 ± 9.1	57.3 ± 8.7	<0.001
BMI (kg/m^2)		23.4 ± 2.7	22.7 ± 3.3	<0.001
Waist circumference (cm)		84.0 ± 7.5	79.7 ± 8.9	<0.001
VFA (cm^2)		72.8 ± 30.9	48.9 ± 23.1	<0.001
SFA (cm^2)		148.2 ± 49.5	158.1 ± 72.5	0.541
Skeletal muscle mass (kg)		21.9 ± 2.8	14.6 ± 1.9	<0.001
PSM (%)		31.8 ± 1.9	25.6 ± 2.1	<0.001
SBP (mmHg)		122.9 ± 15.6	112.6 ± 17.0	<0.001
DBP (mmHg)		78.3 ± 10.0	70.9 ± 11.0	<0.001
FPG (mg/dL)		102.9 ± 10.8	99.7 ± 10.0	<0.001
TG (mg/dL)		125.6 ± 102.1	85.7 ± 54.6	<0.001
HDL-C (mg/dL)		60.2 ± 14.6	67.8 ± 14.5	<0.001
number of risk factors	0	431	118	
	1	373	33	
	2	160	9	
	3	34	3	
			mean ± SD	

VFA: visceral fat area, SFA: subcutaneous fat area, PSM: percentage of skeletal muscle mass of body weight, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, TG: triglyceride, HDL-C: HDL-cholesterol

Table 2. Relationship between Risk Factors and PSM

	Men		Women	
	r	*p* value	r	*p* value
SBP (mmHg)	-0.319	<0.001	-0.440	<0.001
DBP (mmHg)	-0.354	<0.001	-0.425	<0.001
FPG (mg/dL)	-0.255	<0.001	-0.322	<0.001
TG (mg/dL)	-0.366	<0.001	-0.336	<0.001
HDL-C (mg/dL)	0.211	<0.001	0.229	0.003

PSM: percentage of skeletal muscle mass of body weight, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, TG: triglyceride, HDL-C: HDL-cholesterol

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Table 2 shows the relationship between atherosclerosis risk factors and PSM in both men and women. Systolic blood pressure, diastolic blood pressure, fasting plasma glucose level, and triglyceride level had significant negative correlations with PSM in both men ($p < 0.001$) and women ($p < 0.001$), while the HDL-cholesterol level had a significant positive correlation with PSM in both men ($p < 0.001$) and women ($p = 0.003$).

Fig. 1 shows the relationship between the number of atherosclerosis risk factors and PSM. The mean PSM significantly decreased as the number of risk factors increased in both men and women (p for trend < 0.01).

Table 3 shows the results of multiple linear regression analysis on the relationship between the number of atherosclerosis risk factors and age, VFA, SFA, and PSM. There was multicollinearity between BMI and SFA, and the contribution rate of BMI was lower than that of SFA and therefore, BMI was excluded. In men with VFA <100 cm^2, the number of risk factors was significantly correlated with PSM (B = -0.164, $p < 0.001$), whereas in men with VFA ≥ 100 cm^2, the number of risk factors was significantly correlated with VFA (B = 0.182, $p = 0.031$). In women with VFA <100 cm^2, the number of risk factors was significantly correlated with VFA (B = 0.259, $p = 0.006$); however, in women with VFA ≥ 100 cm^2, there was no significant correlation between the number of risk factors and any of the variables.

Discussion

The number of risk factors was negatively correlated with PSM only in men with VFA<100cm^2 (B=-0.164, $p<0.001$), and positively correlated with VFA both in men (VFA<100cm^2 B=-0.189, $p<0.001$, VFA >100cm^2 B=0.182, $p=0.031$) and women with VFA<100cm^2 (B=0.259, $p=0.006$). No such relationships were seen between SFA and number of risk factors. To our knowledge, this is the first study to investigate the relationship between skeletal muscle mass and cardiovascular risk factors according to visceral fat accumulation using accurate, simple bioelectrical impedance methods.

Skeletal muscle, which accounts for the largest amount of tissue in the human body, plays important roles in energy metabolism, uptake of glucose, and physical activity. Approximately 15% of the circulating blood volume is supplied to skeletal muscle at rest,

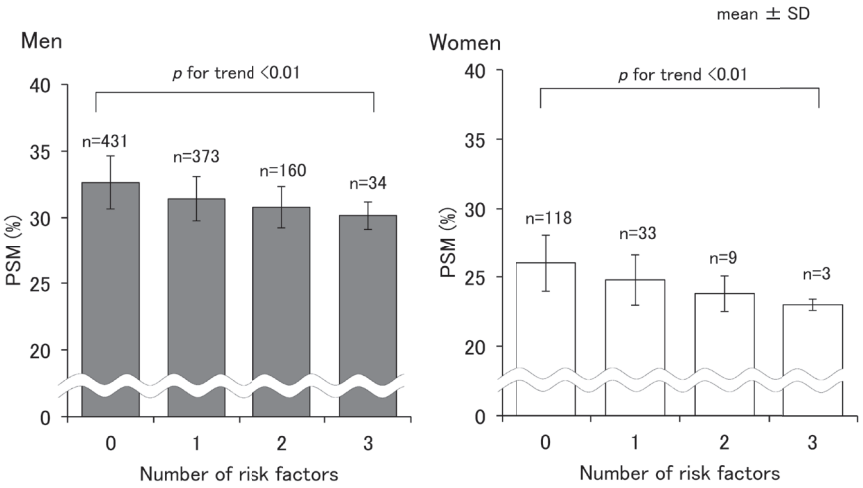

Fig. 1. Relationship between Number of Risk Factors and PSM
PSM: percentage of skeletal muscle mass of body weight

Table 3. Results of Multiple Linear Regression Analysis on Relationship between Number of Risk Factors and Age, VFA, SFA, and PSM

	Men				Women			
	VFA <100cm^2 (n=810)		VFA ≥ 100cm^2 (n=188)		VFA <100cm^2 (n=156)		VFA ≥ 100cm^2 (n=7)	
	B	p value	B	p value	B	p value	B	p value
Age	0.158	<0.001	0.129	0.113	0.212	0.015	0.803	0.349
VFA	0.189	<0.001	0.182	0.031	0.259	0.006	0.098	0.906
SFA	0.058	0.234	0.171	0.071	-0.011	0.922	-0.322	0.679
PSM	-0.164	<0.001	0.103	0.233	-0.104	0.408	-0.376	0.672

Objective variable: number of risk factors, Explanatory variables: age, VFA, SFA, and PSM, B: standardized partial regression coefficient, VFA: visceral fat area, SFA: subcutaneous fat area, PSM: percentage of skeletal muscle mass of body weight

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and approximately 20% of the oxygen used in the body is consumed by skeletal muscle. Glucose in the blood is carried to skeletal muscle, and metabolized with oxygen[16]. Sarcopenia has been shown to aggravate impaired glucose tolerance[4]. A previous study showed that among older adults, muscle mass and muscle strength were lower in those with type 2 diabetes than in those without diabetes[17] and another study found that in Japanese patients with type 2 diabetes, the muscle mass of the lower limbs was significantly decreased[18].

The exact mechanism by which atherosclerosis risk factors develop with a decrease in muscle mass is not yet fully understood. It is considered that insulin resistance due to a decrease in skeletal muscle mass leads to atherosclerosis risk factors such as diabetes, dyslipidemia, and hypertension[3]. Skeletal muscle is responsible for a major part of insulin-stimulated whole-body glucose disposal and therefore plays an important role in the pathogenesis of insulin resistance. Previous studies revealed that a decrease in skeletal muscle mass caused a decline in and hypofunction of mitochondria in skeletal muscle[19,20]. Skeletal muscle mitochondrial dysfunction is involved in the accumulation of intra-myocellular lipid metabolites and therefore, the fatty acid in skeletal muscle is not metabolized, and becomes a factor of insulin resistance[19–21].

An exercise-induced transient increase in interleukin-6 (IL-6), a myokine derived from skeletal muscle contraction, stimulates glucose uptake and fatty-acid oxidation[22]. Although exercise levels were not examined in this study, a relative decrease in the contraction of skeletal muscle in subjects with low PSM might be associated with insulin resistance. Further studies are required to explore the molecular mechanisms associated with the development of atherosclerosis risk factors with decreasing skeletal muscle mass.

The results of multiple regression analysis suggested that VFA had the strongest association with atherosclerosis risk factors in men without visceral fat accumulation, and PSM was the second largest contributing factor next to VFA, but not to SFA or age, while in women, the number of risk factors was not significantly correlated with PSM. One of the reasons for the gender difference might be that the volume of muscle mass in women is relatively smaller than that in men, and therefore the contribution of muscle mass is lower in women than in men. Another might be the influence of sex hormones. The male hormone testosterone has been shown to induce skeletal muscle protein anabolism and have an influence on muscle size and muscle strength[23]. On the other hand, estrogen, a female hormone, is probably associated with a protective effect against atherosclerosis risks and an increasing effect with respect to subcutaneous fat[24]. Taken together, in men, a measurement not only of VFA, but also of the volume of muscle, an organ related to energy metabolism in humans, might be required for an assessment of the possibility of atherosclerosis risk factors.

In the present study, we used simple, highly accurate bioelectrical impedance methods to measure PSM, VFA, and SFA. Skeletal muscle mass, VFA, and SFA can be measured with the two bioelectrical impedance methods used in this study. One of them involves bioelectrical impedance between the upper and lower limbs, and has been shown to be highly accurate for measurement of skeletal muscle mass when compared with MRI in two previous studies ($r = 0.92$, $p < 0.001$ and $r = 0.85$, $p < 0.001$, respectively)[25,26]. The other method involves dual bioelectrical impedance, and has been shown to be accurate for measurement of VFA when compared with CT ($r = 0.821$, $p < 0.0001$)[13,27]. Results for both methods in clinical application are available[27–35].

Various indices are used for the assessment of skeletal muscle, such as skeletal muscle mass, appendicular skeletal muscle mass (ASM), and the skeletal muscle index (SMI), which involves dividing appendicular muscle mass by the square of height[1,36]. In the present study, we used PSM to assess skeletal muscle because it allows a relative assessment of body composition to be made, and the percentage of body fat and muscle mass (fat free mass) do not increase linearly with an increase in weight, although findings have suggested that the increase in fat mass is almost linear[37]. Additionally, there may be a good correlation between PSM and insulin resistance[38], which may be related to arteriosclerosis risk with a decrease in muscle mass.

The present study has several limitations. First, we did not measure each segment of skeletal muscle in the lower or upper limbs. In a previous study, the rate of decrease in skeletal muscle mass and the percentage of skeletal muscle mass were higher in the lower limbs than in the upper limbs[23,39]. Additionally, metabolic parameters were more closely associated with sarcopenia defined as ASM/Weight than with sarcopenia defined as ASM/square height[3]. Kim, *et al.*[5] reported that a lower muscle mass estimated using DXA was significantly associated with MS and its components only in men and women who were not obese. Therefore, further studies on the relationship of each segment of skeletal muscle assessed using bioelectrical impedance and atherosclerosis risk should be performed. Second, we could not evaluate functional aspects of skeletal muscle, such as muscle strength. It has been reported that training to increase muscle strength reduced the risk of MS[40]. Finally, we did not evaluate humoral factors such as insulin, myokines, and sex hormones, for which findings have suggested a relationship with the mechanisms of

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arteriosclerosis risk with a decrease in muscle mass.

In conclusion, the present study showed that a decrease in PSM is related to an increase in the number of atherosclerosis risk factors in middle-aged Japanese men without visceral fat accumulation. Measurement of muscle mass with the accurate, simple bioelectrical impedance methods used in this study may be useful for assessing the possibility of atherosclerosis risk factors.

Conflict of Interest Statement

Tetsuya Sato is an employee of OMRON HEALTHCARE Co., Ltd. The other authors declare no conflict of interest.

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