ORIGINAL ARTICLE

TITLE: Arterial stiffness is associated with low skeletal muscle mass in Japanese community-dwelling older adults

RUNNING TITLE: Arterial stiffness and low SMI in older adults

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ABSTRACT

Aim: To examine whether arterial stiffness, measured by the cardio-ankle vascular index (CAVI), is associated with skeletal muscle mass index (SMI) in Japanese community-dwelling older adults.

Methods: Data were collected from 175 participants through questionnaires and specific tests; the data included demographic, lifestyle and health characteristics, body mass index (BMI), and body composition features determined by the bioelectrical impedance analysis, ankle-brachial index, the Mini-Nutritional Assessment, handgrip strength (GS), walking speed and shuttle walking tests (SW), and arterial stiffness determined by the CAVI. Absolute SMI was dichotomized according to the first quintile, which determined low (n=35) and normal (n=140) SMI.

Results: Participants with low SMI were older ($P = 0.01$), had more polypharmacy ($P = 0.01$), a lower BMI ($P < 0.001$), and fat mass index ($P = 0.02$), and had a greater risk of malnutrition ($P < 0.001$) than the normal group. Additionally, they showed poorer physical performance (GS and SW, $P = 0.007$ and 0.01, respectively) than the normal group. Furthermore, CAVI was associated with SMI even after adjustments (OR 1.82, 95% CI 1.14–2.90, $P = 0.01$).

Conclusions: Our data showed that arterial stiffness is associated with low SMI in community-dwelling older adults, even when adjusting by multiple factors, showing a close interaction of vascular aging and muscle mass decline.

Keywords: arterial stiffness, cardio-ankle vascular index, older adults, sarcopenia, skeletal muscle mass.

INTRODUCTION

The progressive loss of skeletal muscle mass is the primordial factor to determine sarcopenia, a syndrome that combines low skeletal muscle mass and strength and may lead to adverse health outcomes, such as physical disability, poor quality of life and mortality.[1] In addition, the elderly might experience several adverse health outcomes as a result of vascular aging, such as increased arterial stiffness, which can contribute to the development of cardiovascular and cerebrovascular diseases.[2] It is known that both the loss of skeletal muscle mass and arterial stiffness worsen with age, and that some of the predisposing factors and mechanisms underlying low muscle mass and sarcopenia; for example, oxidative stress,[3] inflammation,[4] and insulin resistance,[1] are also associated with atherosclerosis.[5] However, only a few studies have been carried out to verify such associations.[5~8] A study showed that arterial stiffness is associated with an increase in the loss of muscle mass index over time independent of age, body fat, peripheral arterial disease, chronic inflammation, and cardiac disease.[6] Other studies have verified the associations of peripheral lean mass and visceral fat mass with atherosclerosis,[7] and the relationships between regional fat and lean mass and large artery properties in young men and women.[8]

A novel measurement tool to assess arterial stiffness is the cardio-ankle vascular index (CAVI), which reflects the stiffness of the aorta, femoral artery and tibial artery, and involves the measurement of the brachial-ankle pulse wave velocity (baPWV) and blood pressure (BP). The most important feature of CAVI is its independence from BP during examination,[2,9,10] which shows that it is a useful tool to assess those who are subject to variation in blood pressure at different times of the day, suffer from masked hypertension or are taking antihypertensive medications.[11]

Therefore, the objective of the present study was to examine whether arterial stiffness, measured by CAVI, is associated with skeletal muscle mass index (SMI) in Japanese community-dwelling older adults. We hypothesized that arterial stiffness is associated with a low SMI independent of sex, nutritional status, and physical performance in community-dwelling older adults.

METHODS

The present study had a cross-sectional design.

Participants

The participants of the present study were community-dwelling Japanese older adults (n=175; male=84, female=91) recruited through local press announcements requesting healthy volunteers. Recruited participants were 65 years-of-age or older, and were able to carry out the activities of daily living (ADL) and answer the proposed questionnaires. The exclusion criteria at the first screening were the following: (i) moderate cognitive impairment (i.e. Mini-Mental State Examination score ≤ 21 points); (ii) uncontrolled cardiovascular, pulmonary or metabolic diseases; (iii) any orthopedic conditions that could restrain the ADL; and (iv) comorbidities associated with a greater risk of falls (e.g. Parkinson's disease and stroke). Additionally, in the present study, none of the participants had peripheral artery disease as evidenced by an ankle-brachial index (ABI) of less than 0.9. All participants were informed of the purpose and procedures of the study, and signed a written consent. The data were collected in November 2012. The study protocol was approved by the Kyoto University Graduate School of Medicine Ethics Committee (No. E1245, E1583).

Assessments

The participants answered a self-administered questionnaire about demographic, lifestyle and health characteristics, including age, regular physical activity engagement, alcohol consumption, smoking, current number of medications and morbidities (i.e. diabetes, hypertension, hyperlipidemia and coronary artery disease; determined by the assumption that the prescribed medications they reported in the analysis were being used for the morbidity).

Additional relevant health indicators, such as (i) body mass index (BMI), (ii) body composition features determined by bioelectrical impedance analysis (Inbody 430; Biospace, Seoul, Korea), (iii) ABI; and (iv) the Mini-Nutritional Assessment short-form (MNA)[12] were also collected.

The bioelectrical impedance instrument made use of octapolar tactile electrodes, two in contact with the palm and thumb of each hand, and two with the anterior and posterior aspects of the sole of each foot. The participants were instructed to stand with their soles in contact with the foot electrodes and to grasp the hand electrodes. The resistance of the arms, trunk, and legs was measured at frequencies of 5, 50, and 250 kHz. The participants' ID number, height (measured with a standard stadiometer), age and sex were also inserted in the analyzer. Then,

body mass and consequently BMI were automatically measured by the "InBody". For classification purposes, the BMI cut-offs used were those proposed by the Japan Society for Study of Obesity (i.e. underweight, BMI <18.5 kg/m^2, normal weight, BMI 18.5–25 kg/m^2, and obese, BMI $\geq$25 kg/m^2).[13] The bioelectrical impedance examination provided values for absolute skeletal muscle mass, body fat percentage, absolute fat mass, and segmental muscle mass (right and left arms/legs and trunk). From these measurements, absolute skeletal muscle mass and absolute fat mass were posteriorly adjusted by height to determine the SMI and fat mass index (FMI), respectively. The "InBody" system uses direct segmental multifrequency technology, and had previously been validated as having a strong correlation to muscle volume and fat mass as measured by dual energy X-ray absorptiometry.[14,15]

Physical performance was investigated by the following: (i) handgrip strength (GS), (ii) walking speed (WS); and (iii) shuttle walking tests (SW).[16,17]

GS was collected with a standard handgrip dynamometer (Smedlay's Dynamo Meter, TTM, Tokyo, Japan). The participants were asked to stand up and hold the dynamometer with their arms parallel to their bodies without touching their bodies. GS was measured once for each hand, and the higher value was used to characterize his/her maximum muscle strength. GS was expressed in kilograms (kg).

In the WS test, outside marks of 12 m in length were clearly placed on the ground. Inside this distance, another 10 m long delimitation was marked. The participants were asked to walk the entire distance at their usual pace, but only the time to complete the inner 10 m distance was measured. Such measurement was intended to avoid the acceleration and deceleration stages of the participant's walking.

Finally, the SW test was carried out; two cones were placed 10 m apart. The participants were instructed to walk around the cones without stopping at a pace set by a timed signal played on a CD player. The SW test consists of 102 shuttles divided into 12 levels, each lasting approximately 1 min. The first level consists of three shuttles with a subsequent one-shuttle (i.e. 10 m) increase at each following level. At each level, the speed is increased by 0.17 m/s, with an initial speed of 0.5 m/s rising to a maximum speed of 2.37 m/s.[16,17] The test ended if the participant was unable to continue (due to breathlessness or any other reason) or was unable to reach the next cone before the timer sounded. If none of these mentioned factors occurred, we stopped the test at shuttle 50 (or 500 m, half of the total) to assure the

participants' safety due to fatigue issues. Then, the values in meters were included in the analysis. A resting time of at least 3 minutes was provided between each assessment, and a longer time was provided if the participant claimed fatigue.

Cardio-ankle Vascular Index

CAVI was determined using VaSera1500 (Fukuda Denshi, Tokyo, Japan). The procedures started with the participants resting for 5 min in a sitting position. Afterwards, they were placed supine in a standard stretcher. Cuffs were wrapped around both arms and ankles to detect the brachial and ankle pulse waves. An electrocardiogram was performed, and the heart sound was monitored. The pulse wave velocity (PWV) from the heart to the ankle was determined by measuring the length from the aortic valve to the ankle divided by time, according to the heart sound and the rise of the brachial and ankle pulse wave. The BP was measured at the four limbs alternately, first at the right arm and ankle and then at the left arm and ankle. This procedure is important not only because it reduces the burden of the examinees, but also because it enables a more accurate measurement. Finally, a scale conversion was carried out using the following formula: $CAVI = a\{(2\rho/\Delta P) \times In(Ps/Pd)PWV^2\} + b$ (no unit), in which "ρ" is blood density, "Ps" is systolic blood pressure, "Pd" is diastolic blood pressure, "ΔP" is Ps - Pd, "PWV" is pulse wave velocity, and "a" and "b" are specific constants. This procedure has also been detailed in previous studies.[2,10]

This measurement was carried out once for each participant, and the mean of the right and left values of CAVI for each participant was used for analytical purposes.[18] The validity, reproducibility, and blood pressure-independent nature of this system has been widely documented by other researchers.[2,9,10]

STATISTICAL ANALYSIS

The Kolmogorov-Smirnov test was carried out to determine the normality of the data. Absolute SMI was dichotomized according to the first quintile for males (8.81 kg/m^2) and females (7.57 kg/m^2). Then, we arbitrarily assumed that those in the first quintile had a low SMI (n=35), coded 1, and the others were considered normal SMI (n=140), coded 0.

We analyzed the relationship between the two groups using the unpaired *t*-test for the age, BMI, body fat percentage, FMI, and ABI variables, and the Mann Whitney *U*-test for the

SMI, CAVI, GS, WS, and SW tests. Furthermore, the chi-square test was used for sex, regular physical activity engagement, alcohol consumption, smoking, number of medications, morbidities, and malnutrition. In addition, a univariate logistic regression was carried out to verify the association of each variable and the muscle mass condition, except for the number of medications as a result of missing values in the variable; then, a stepwise multivariate logistic regression was carried out to investigate whether CAVI was associated with low SMI. We assigned the status of muscle mass as the dependent variable, CAVI as the main covariate, and sex, age, BMI, MNA, GS, and SW as adjusted covariates. Differences were considered statistically significant at $P < 0.05$. All analyses were carried out using the Statistical Package for the Social Sciences software (SPSS; IBM, Chicago, IL, USA) version 20.0.

RESULTS

A total of 175 subjects participated in the present study; we divided them into two groups: low SMI older adults (n=35) and normal SMI (n=140) participants. The participants in the first group were older and had more polypharmacy (four or more concurrent medications) than the normal participants. No significant differences were found for the lifestyle characteristics or morbidities (Table 1).

Table 1. Bivariate comparisons of the participants' demographic and lifestyle characteristics

Variables	Normal (n=140)	Low SMI (n=35)	P
Age (years)	73 [70 - 76.7]	76 [71 - 78]	0.01
Females	52.1 (73)	51.4 (18)	0.94
Regular physical activity[a]	65.4 (83)	63.3 (19)	0.83
Alcohol consumption[b]	39.4 (52)	36.7 (11)	0.78
Smoking[b]	9.1 (12)	6.7 (2)	1.00
No. medications[c]	76.6 (95)	52 (13)	0.01
	23.4 (29)	48 (12)	
Morbidities[b]			
Diabetes	12.1 (16)	10 (3)	1.00
Hypertension	42.4 (56)	36.7 (11)	0.56

Hyperlipidemia	14.4 (19)	20 (6)	0.41
Coronary artery disease	7.6 (10)	10 (3)	0.71

[a]n=157; [b]n=162; [c]n=149; values are expressed as medians [interquartile range] or valid percentages (n).

The results of the health indicators showed that low SMI participants had a lower BMI and FMI, and were at a higher risk of malnutrition than the normal group. Additionally, they presented with poorer physical functioning, such as low muscle strength and lower SW test scores. Regarding the CAVI results, the low SMI older adults had higher CAVI (Table 2).

Table 2. Bivariate comparisons of the participants' health indicators

Variables	Normal (n=140)	Low SMI (n=35)	P
BMI (kg/m^2)	23.6 ± 2.71	20.7 ± 2.61	<0.001
SMI (kg/m^2)	9.00 [8.20 - 9.81]	7.54 [7.39 - 8.43]	<0.001
Body fat percentage	29.0 ± 7.72	28.1 ± 8.80	0.56
FMI (kg/m^2)	7.06 ± 2.37	6.03 ± 2.42	0.02
ABI	1.10 ± 0.07	1.08 ± 0.07	0.10
MNA at risk	20 (28)	51.4 (18)	<0.001
Handgrip strength (kg)	28.7 [25 - 35]	24.5 [22.5 - 31]	0.007
Walking speed (m/s)	1.39 [1.25 - 1.50]	1.39 [1.22 - 1.48]	0.48
Shuttle walking (m)	400 [360 - 470]	360 [300 - 440]	0.01
CAVI	9.13 [8.52 - 9.71]	9.57 [8.93 - 10.4]	0.008

Values are means ± SD, medians [interquartile range] or valid percentages (n). ABI, ankle-brachial index; BMI, body mass index; CAVI, cardio-ankle vascular index; FMI, fat mass index; MNA, mini-nutritional assessment; SMI, skeletal muscle mass index.

The findings of the multivariate logistic regression showed that females were less likely to have low SMI than males. Similar conditions were verified in the participants with higher BMI and GS. Additionally, CAVI showed an independent association with SMI, even when adjusted for age, sex, BMI, MNA, GS, and SW. Thus, a higher CAVI was associated with low

a SMI in older adults (Table 3).

Table 3. Stepwise multivariate logistic regression considering skeletal muscle mass index (normal or low condition) as dependent variable and cardio-ankle vascular index, age, sex, body mass index, Mini-nutritional Assessment, handgrip strength, and shuttle walking as covariates

Variables	OR (95% CI)	P
Sex		
Female	0.23 (0.61 – 0.90)	0.03
BMI	0.71 (0.59 – 0.85)	<0.001
Handgrip strength	0.83 (0.74 – 0.94)	0.002
CAVI	1.82 (1.14 – 2.90)	0.01

Values are odds ratio (95% confidence interval). BMI, body mass index; CAVI, cardio-ankle vascular index; SMI, skeletal muscle mass index.

DISCUSSION

The present study supported the hypothesis that arterial stiffness (assessed by CAVI) is associated with low SMI in community-dwelling older adults. Other studies have been carried out to ascertain this association;[5~8] however, none of them considered arterial stiffness as measured by CAVI, a non-invasive and BP-independent tool.

A previous study investigated the occurrence of a specific association between arterial stiffening (analyzed by baPWV) and peripheral skeletal muscle mass, and concluded that arterial stiffness was associated with a higher loss of muscle mass index over time independent of age, total body fat, peripheral arterial disease, chronic inflammation, or cardiac disease.[6] Ochi et al. hypothesized that age-related decline of muscle mass and atherosclerosis share common pathological processes and interact with each other. In fact, the authors verified a direct association with baPWV and thigh muscle sarcopenia in men, but that association was not confirmed in women.[5] Furthermore, Kohara et al. found that men with sarcopenic obesity had higher baPWV than normal, sarcopenic, or obese men.[19] In theory, changes in arterial stiffness might mediate the association between body composition and cardiovascular risk.[8]

However, it is unclear how arterial stiffness and the loss of muscle mass relate to each other. Authors suggested that because basal limb blood flow declines with aging, in part due to arterial stiffening, dysfunction in blood vessel dynamics could have a predictive role in muscle mass decline.[6]

Some researchers have linked the higher prevalence of low muscle mass in men[20] to their findings of arterial stiffness in men and not women.[5,19] To examine any sex effect on CAVI, we carried out further analysis and verified that men had higher CAVI than women (data not shown). However, in our fully adjusted analysis, we verified the association of CAVI and low SMI independent of sex.

Regarding physical performance, those with normal muscle mass presented better physical functioning, such as a higher GS, higher SW test scores, and a lower CAVI, than the group with low SMI. GS is a representative measure of strength and is an important screening tool for sarcopenia,[1] whereas SW represents aerobic capacity.[16,17] Regarding SW, a previous study showed that endurance-trained older men demonstrated lower arterial stiffness than their sedentary age peers despite similar systolic blood pressures, suggesting that age-associated augmentation of arterial stiffness might be mitigated by regular aerobic exercise.[21]

Furthermore, polypharmacy was observed more frequently among participants in the low SMI group. Although we did not deeply investigate the classes of medications to which they were exposed, our results were in agreement with previous studies that identified the association of concomitant medications and impaired physical functioning in older adults.[22]

Based on the present results, we would like to emphasize the importance of physical activity, mainly the combination of progressive resistance exercise and aerobic exercise,[23] in accordance with well-balanced nutrition in relation to low SMI and arterial stiffness, especially because the participants with low SMI in the present study had lower physical performance, lower BMI and a higher risk for malnutrition. Nutritional status is widely known to be associated with both muscular and vascular health. Thus, aiming to reverse low muscle mass, Yamada et al. verified that a diet rich in proteins and vitamin D in combination with resistance exercise was more effective at improving muscle mass than resistance exercise alone.[24] In addition, evidence showed that lower levels of 25-hydroxyvitamin D (25-OH D), an established marker of vitamin D status, are associated with abnormalities in the indices of arterial stiffness.[25]

Although the low SMI participants had lower BMI and FMI than the normal group, both groups presented similar results for body fat percentage. This result might show that lean body mass is lost, and fat could be preserved or even increased in people with low muscle mass or sarcopenia. As intramuscular and visceral fat increase, and subcutaneous fat decreases with age,[1),4)] the association with muscle mass decline and arterial stiffness might also be perceived from the standpoint of the relationship between fat mass and cardiovascular risks.

Some limitations of the present study should be mentioned: (i) its cross-sectional design did not permit the determination of a cause-effect relationship between CAVI and the low SMI condition; and (ii) the small number of participants limited further group subdivision (i.e. to differentiate pre-sarcopenic and sarcopenic older adults) as a result of the low statistical power achieved when further dividing the groups. However, the present study showed that a relationship between CAVI and low SMI does exist, and might serve as a basis for further studies with a larger sample size, analyzing the time effect on muscle, and physical performance decline, and also investigating the role of sex on such an association.

To our knowledge, this is the first study to verify the interaction of CAVI and total SMI in Japanese older adults. The main clinical advantage of the present study was that it clearly showed the important relationship between arterial stiffness and low SMI in community-dwelling older adults as measured by CAVI, a non-invasive reliable method and blood pressure independent measure. It would be useful to perform further health analyses in older adults with arterial stiffness, including body composition features and physical performance measurements, to aid in the early detection of people with the risk of developing sarcopenia; and also to verify arterial stiffness in older adults already in a progressive muscle loss condition. We believe that a suitable intervention for the promotion of improvements in vascular and muscular parameters would be aimed at increasing physical fitness levels and improving nutrition; this combined intervention might reduce the probability of a person developing systolic hypertension and the associated risk of cardiovascular events, and could help maintain a SMI and function, especially in older adults.

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