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ARTICLE

Clinical significance of an elevated ankle-brachial index differs depending on the amount of appendicular muscle mass: the J-SHIPP and Nagahama studies

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Abstract

Clinical implication of a high ankle-brachial index (ABI) is not well known. Based on our previous study, we suspected that body composition may be a determinant of a high ABI and may consequently modulate the clinical significance of a high ABI. Datasets of two studies with independent cohorts, the anti-aging study cohort ($n = 1765$) and the Nagahama study cohort ($n = 8{,}039$), were analyzed in this study, in which appendicular muscle mass was measured by computed tomography and bioelectrical impedance analysis, respectively. Brachial and ankle blood pressures were measured using a cuff-oscillometric method. In the anti-aging study cohort, thigh muscle area ($\beta = 0.387$, $p < 0.001$), but not fat area, showed a strong positive association with the ABI independent of the body mass index ($p = 0.662$) and other possible covariates, including systolic brachial blood pressure ($p = 0.054$), carotid hypertrophy ($p = 0.559$), and arterial stiffness ($\beta = 0.102$, $p = 0.001$). This positive association was replicated in the Nagahama cohort. When the subjects were subdivided by the 75th percentiles of the ABI and appendicular muscle mass, multinomial logistic regression analysis identified insulin resistance as an independent determinant of an elevated ABI in subjects with normal muscle mass (coefficient = 0.134, $p = 0.010$), whereas insulin resistance was inversely associated with an elevated ABI in subjects with high muscle mass (coefficient = −0.268, $p = 0.001$). Appendicular muscle mass was a strong determinant of the ABI. The clinical background, particularly insulin resistance, of individuals with an elevated ABI may differ based on the amount of muscle mass.

Introduction

A low ankle-brachial index (ABI), a ratio of ankle systolic blood pressure (SBP) to brachial SBP, is associated with cardiovascular risk factors [1] as well as the incidence of cardiovascular diseases and mortality [2]. An ABI of 0.9 is usually adopted as a lower cut-off point to discriminate at-risk individuals; however, a recent large-scale meta-analysis by the Ankle Brachial Index Collaboration revealed increased risks for total and cardiovascular morbidity and mortality even in individuals with a low-normal ABI ($0.9 \leq$ ABI < 1.0) [3]. In contrast, the clinical implication of a high ABI is less understood. Several cross-sectional studies have reported that a high ABI, usually defined as an ABI greater than 1.4, was associated with left ventricular hypertrophy [4], increased coronary artery calcium scores [5], and chronic kidney disease [6] in general [4, 5] and high-risk populations [6]. Furthermore, a high ABI has been suggested to have prognostic significance for the incidence of

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coronary artery disease [6–8] as well as cardiovascular [9] and total mortality [9, 10], although the results were not always consistent across studies. The inconsistencies may be due to different population characteristics and a particularly low frequency of individuals with a high ABI (1.1 to 4.9%), although the Strong Heart Study with high-risk individuals showed a greater frequency (9.2%) of a high ABI [9].

We previously reported that muscle mass, but not fat mass, in the lower extremities measured directly from computed tomography (CT) images was significantly and positively associated with the ABI in a general population [11]. This finding suggested that in addition to medial arterial calcification, which is known to increase ankle BP [12], incompressibility of the tibial artery due to high appendicular muscle mass may be a cause of a spuriously high ABI. Consistent characteristics among high ABI populations in previous studies, namely, a large body mass index (BMI) [5, 6, 8, 10, 13–15] and a higher frequency of men [4, 6–8, 10, 13, 14], support the involvement of lower extremity composition in increasing the ABI because body weight and male sex are strong determinants of skeletal muscle mass. Absence of an association between total arterial compliance and a high ABI [14] also supports the hypothesis.

In addition to the muscle involvement hypothesis, other common characteristics of individuals with a high ABI, namely, non-smoking [5, 6, 8, 10, 13, 14], relatively low brachial BP [5, 7, 9, 10, 13, 14], and good plasma lipid profiles [4, 5, 7, 10, 14], further support the hypothesis that a high ABI may not always represent poor arterial properties, and the clinical implication of a high ABI may differ according to the amount of appendicular muscle mass.

Here, we performed an extended analysis of our preceding study that first reported a positive relationship between thigh muscle mass and the ABI [11] and performed an additional analysis in a large cohort to test these hypotheses.

Methods

Study participants

The present study incorporated datasets from two Japanese general populations.

The Shimanami Health Promoting Program (J-SHIPP study) is a longitudinal study conducted by Ehime University Graduate School of Medicine evaluating factors related to cardiovascular disease (CVD), dementia, and death among several cohorts from the general population in Ehime Prefecture, Japan. Here, we analyzed a dataset from the Anti-Aging Study Cohort (AASC) [16–19]. The AASC includes apparently healthy, middle-aged to elderly participants in the medical check-up program at the Ehime University Hospital Anti-aging Center. This medical check-up program was offered to general residents of Ehime Prefecture and was specifically designed to evaluate age-related disorders, such as atherosclerosis, CVD, physical dysfunction, and cognitive impairment. From a total of 2034 individuals who participated from February 2006 to December 2016, we analyzed a dataset of participants for whom relevant clinical data, including thigh muscles mass, were available and those with a normal ABI (>0.9) in both legs ($n = 1765$). Because an ABI less than 0.9 is usually used as a cut-off point to discriminate potential peripheral arterial disease, we excluded individuals with an ABI less than 0.9 in this study to clarify the effect of appendicular muscle mass on the ABI.

The Nagahama Prospective Cohort for Comprehensive Human Bioscience (the Nagahama Study) is a community-based prospective cohort study in which participants were recruited between 2008 and 2010 from 30- to 74-year-old residents in Nagahama City ($n = 9764$). The participants in the Nagahama cohort were invited to a follow-up assessment that was conducted from 2013 to 2015, 5 years after the baseline evaluations, respectively. Among the 8289 participants in the follow-up investigation, individuals who met the following criteria were excluded from the analysis: pregnant women ($n = 24$), those with implanted pacemakers ($n = 12$), those undergoing hemodialysis therapy ($n = 5$) or insulin therapy ($n = 45$), those with incomplete or wide deviations in clinical values required for the present study ($n = 85$), and those with an ABI lower than 0.9 in either leg ($n = 79$). Details of the Nagahama study participants are described elsewhere [20, 21].

All study procedures were approved by the ethics committee of Ehime University Graduate School of Medicine (the AASC cohort) or that of Kyoto University Graduate School of Medicine and the Nagahama Municipal Review Board (the Nagahama cohort). Written informed consent was obtained from all participants.

Thigh muscle and fat mass measurements (the AASC cohort)

CT of the abdomen and mid-thigh was performed as an optional examination upon request. Cross-sectional areas (CSAs) of the cortical bone and thigh muscle, including the quadriceps, adductors, and hamstrings, were measured from a CT image (LightSpeed VCT; GE Healthcare, Tokyo, Japan) at the midpoint of the lower margin of the femoral condyles and the upper margin of the greater trochanter. The CSA (cm^2) was computed using OsiriX software [22] with an attenuation range of 0–1000 Hounsfield units for cortical bone CSA and 0–100 Hounsfield units for muscle

CSA. The area of subcutaneous thigh fat was also measured from the same image [total CSA (−200 to 100 Hounsfield units) − muscle CSA − bone CSA (cortical bone, trabecular bone, and bone marrow area)]. CT images were obtained at a minimal slice width of 5 mm.

Estimation of lean mass (the Nagahama cohort)

Appendicular lean mass (ALM) was estimated by bioelectrical impedance analysis (InBody 430, InBody Co., Ltd, Seoul, Korea). A device measures the resistance and reactance of the arms, trunk, and legs separately at three frequencies (5, 50, and 250 kHz) of alternating current of 250 A using a tetrapolar, eight-point tactile electrode system. Total body water was estimated using the sum of five segmental impedances and then fat-free mass was calculated based on the assumption that the hydration of fat-free mass is 73.2%. Lean mass was estimated by subtracting the bone mass calculated using a prediction equation based on dual-energy X-ray absorptiometry (DXA) measurement from the fat-free mass [23, 24]. The skeletal muscle mass index (SMI) was obtained by dividing the ALM by body height squared [25]. The validity and reproducibility of ALM and fat mass measurements by the segmental multiple-frequency BIA (SMF-BIA) method have been reported compared to those of measurements obtained by DXA [23, 24, 26–28] and hydrostatic weighing [23], although fat mass estimation in obese subjects may be susceptible to measurement errors [25–28].

ABI and pulse wave velocity

Brachial and ankle BPs were measured in the supine position. Cuffs were attached to the brachia and ankles, and BPs were measured simultaneously using the cuff-oscillometric method (AASC cohort: PWV/ABI, Omron Healthcare, Co., Ltd, Kyoto, Japan; Nagahama cohort: Vasera-1500, Fukuda Denshi Co., Ltd, Tokyo, Japan). The ABI was calculated as the ratio of ankle SBP to brachial SBP. The mean of the right-side and left-side ABI values was used in the analysis as a representative value.

Pulse volume waveforms were also recorded simultaneously using a plethysmographic sensor connected to the cuffs. Brachial-to-ankle pulse wave velocity (baPWV) was calculated from the time interval between the wave fronts of the brachial and ankle waveforms (ΔT_{ba}) by the following formula: baPWV $= (L_a - L_b)/\Delta T_{ba}$, where L_b and L_a indicate the path lengths from the suprasternal notch to the brachium [$L_b = 0.2195 \times$ body height (cm)–2.0734] and to the ankle [$L_a = 0.8129 \times$ body height (cm)–12.328], respectively [29]. The collinearity of baPWV with carotid-to-femoral PWV, a standard measure of arterial stiffness, has been reported elsewhere [30, 31].

Carotid ultrasonography

The intima-media thickness (IMT) of the carotid artery was measured as an index of atherosclerosis. In the AASC cohort, ultrasonography of the common carotid artery was performed using an SSD-3500SV or α10 ultrasonograph (Aloka Co., Ltd, Tokyo, Japan) with a 7.5-MHz probe. After a few minutes of rest in the supine position, optical visualization of the bilateral carotid arteries was obtained with the subject's head tilted slightly upward in the mid-line position. The IMT of the far wall was measured from B-mode images using built-in computerized software, which simultaneously measured the IMT at three points at 1-cm intervals. Nine IMT measurements of the far wall were obtained at 1-cm intervals proximal to the bulb from the anterior, lateral, and posterior directions. The mean IMT calculated from the nine measurements was used in the analysis. No measurements were taken at the level of a discrete plaque. In the Nagahama cohort, carotid IMT was measured using a Prosound 2 (Aloka), SSD-3500SV (Aloka), or XARIO SSA-660A (Toshiba Medical Systems Corporation, Tochigi, Japan) ultrasonograph with a 7.5-MHz probe. After a few minutes of rest in the supine position, IMT measurements of the far wall were manually (Aloka) or automatically (Toshiba) obtained from B-mode images at 1-cm intervals proximal to the bulb from the lateral direction. The mean IMT calculated from the three readings was used in the analysis.

Basic clinical parameters

The basic clinical parameters used in this study were obtained from the subjects' personal health records from the baseline examination. Brachial BP was measured in a sitting position after a few minutes of rest using a cuff-oscillometric device (HEM9000-AI; Omron Healthcare). Plasma markers were measured using peripheral blood samples. In the AASC cohort, the low-density lipoprotein (LDL) cholesterol level was calculated using the Friedewald equation [total cholesterol − high-density lipoprotein (HDL) cholesterol − triglyceride/5], and in the Nagahama cohort, it was measured directly using a selective solubilization assay (MetaboLead LDL-C; Kyowa Medix, Co., Ltd, Tokyo, Japan). Insulin resistance was assessed using the homeostasis model assessment index for insulin resistance {HOMA-IR: [insulin (μU/ml) × glucose (mg/dl)]/405}. Because blood samples from some of the Nagahama cohort participants were collected under non-fasting (<5 h, 5.7%) or near-fasting (5–11 h, 21.7%) conditions, the elapsed time after the last meal (fasting time) was included in the regression analysis as a covariate. Information regarding medication history and smoking habits was obtained using a structured questionnaire.

Statistical analysis

The values are expressed as the mean ± standard deviation. The quartiles of thigh CSA and the SMI were calculated within sex and then combined to avoid potential sex differences. Group differences in numeric variables were assessed by analysis of variance, and a post hoc analysis was performed using Dunnett's test. Factors independently associated with subgroups defined by the ABI and SMI were identified using a multinomial logistic regression model. Statistical analyses were performed using commercially available statistical software (JMP ver. 12.2.0; SAS Institute, Cary, NC, USA). Null hypotheses were rejected at a $p < 0.05$ level of significance.

Results

The clinical characteristics of the study participants in both cohorts are shown in Table 1. The mean age of the AASC

Table 1 Clinical characteristics of study subjects

	AASC		Nagahama	
	Men	Women	Men	Women
	707	1058	2557	5482
Age (years)	65.7 ± 9.9	65.1 ± 9.0	60.5 ± 13.2	57.4 ± 12.7
BMI (kg/m^2)	24.0 ± 2.9	22.7 ± 3.1	23.2 ± 3.1	21.7 ± 3.3
Current smoking (%)	13.3	2.2	23.0	4.4
Brinkman index	525 ± 638	25 ± 108	399 ± 424	25 ± 95
CT				
Thigh muscle CSA (cm^2)	134.9 ± 19.2	95.4 ± 13.4		
Thigh fat CSA (cm^2)	46.7 ± 18.5	78.0 ± 26.5		
Thigh circumference (cm)	49.6 ± 3.9	48.3 ± 4.2		
BIA				
Appendicular lean mass (kg)			21.8 ± 3.2	15.0 ± 2.2
SMI (kg/m^2)			7.7 ± 0.7	6.2 ± 0.6
Systolic BP (mmHg)	136 ± 19	132 ± 20	131 ± 17	122 ± 18
Diastolic BP (mmHg)	78 ± 11	75 ± 11	76 ± 11	70 ± 10
Antihypertensive treatment (%)	34.4	25.9	32.2	21.1
Total cholesterol (mg/dl)	205 ± 34	225 ± 36	197 ± 33	207 ± 34
HDL cholesterol (mg/dl)	59 ± 16	71 ± 17	60 ± 16	71 ± 17
LDL cholesterol (mg/dl)	123 ± 31	134 ± 33	115 ± 29	119 ± 29
Triglyceride (mg/dl)	118 ± 64	101 ± 55	112 ± 78	85 ± 49
Antihyperlipidemic treatment (%)	17.5	25.6	19.4	21.6
Glucose (mg/dl)	107 ± 19	100 ± 16	93 ± 18	86 ± 11
HbA1c (%)	5.9 ± 0.7	5.9 ± 0.6	5.7 ± 0.6	5.5 ± 0.4
Insulin (μU/ml)	6.3 ± 4.0	5.5 ± 3.4	4.3 ± 4.4	3.6 ± 3.1
HOMA-IR	1.69 ± 1.22	1.40 ± 1.00	1.05 ± 1.38	0.79 ± 0.84
Antihyperglycemic treatment (%)	7.8	4.1	8.2	2.9
CRP (mg/dl)	0.18 ± 0.64	0.11 ± 0.27	0.13 ± 0.49	0.08 ± 0.28
Carotid IMT (mm)	0.80 ± 0.15	0.77 ± 0.15	0.74 ± 0.19	0.68 ± 0.15
baPWV (cm/s)	1631 ± 321	1543 ± 327	1,370 ± 253	1,274 ± 238
ABI				
Mean	1.18 ± 0.07	1.14 ± 0.07	1.12 ± 0.06	1.10 ± 0.06
>1.4 in either leg (n)	7	1	3	0
>1.3 in either leg (n)	61	20	32	18

Values are mean ± standard deviation.

BMI body mass index, *CT* computed tomography, *CSA* cross-sectional area, *BIA* bioelectrical impedance analysis, *CRP* high-sensitive C-reactive protein, *IMT* intima-media thickness, *baPWV* brachial-to-ankle pulse wave velocity, *ABI* ankle-brachial index

Skeletal muscle index (SMI) was calculated by dividing appendicular lean mass by squared body height. Insulin resistance was assessed using the homeostasis model assessment index for insulin resistance {HOMA-IR: [insulin (μU/ml) × glucose (mg/dl)]/405}

participants was slightly higher than that of the Nagahama cohort participants.

Scatter plots of the thigh muscle CSA and ABI in the AASC cohort (Fig. 1a) indicated a significant positive association between these parameters. Because apparent sex differences in the ABI were observed ($p < 0.001$), particularly in the muscle CSA ($p < 0.001$), the participants were subdivided into quartiles within sex and then group differences in the ABI were analyzed (Fig. 1b). The results clarified a sex-independent positive association between muscle CSA and the ABI, whereas the ABI in the high-fat CSA subgroup was slightly lower than that in the low-fat CSA subgroup (Fig. 1c). Although BMI was another strong determinant for thigh muscle CSA (men, $r = 0.555$; women, $r = 0.594$), multiple linear regression analysis identified muscle CSA ($\beta = 0.387$, $p < 0.001$), but not BMI ($p = 0.662$), as a strong positive determinant of the ABI independent of possible covariates, including age ($\beta = 0.052$, $p = 0.080$), the Brinkman index ($\beta = -0.065$, $p = 0.009$), systolic BP ($\beta = 0.055$, $p = 0.054$), triglyceride level ($\beta = -0.094$, $p < 0.001$), HDL cholesterol level ($\beta = -0.005$, $p = 0.847$), LDL cholesterol level ($\beta = -0.052$, $p = 0.023$), HOMA-IR ($\beta = -0.060$, $p = 0.023$), baPWV ($\beta = 0.102$, $p = 0.001$), and carotid IMT ($\beta = -0.016$, $p = 0.559$), whereas thigh fat CSA was identified as an inverse determinant ($\beta = -0.253$, $p < 0.001$). When both muscle and fat CSAs were included in the same regression model, muscle CSA ($\beta = 0.348$, $p < 0.001$, variation inflation factor (VIF) = 2.78), but not fat CSA ($\beta = -0.058$, $p = 0.087$, VIF = 2.32), was identified as an independent determinant of the ABI. In these regression analyses, we did not include sex in the model because of moderate collinearity with muscle CSA. However, even in a regression model including sex (women: $\beta = -0.087$, $p = 0.055$, VIF = 4.19), muscle CSA was identified as an independent determinant of the ABI ($\beta = 0.286$, $p < 0.001$, VIF = 4.87).

A similar positive association between muscle mass and the ABI was observed in the Nagahama dataset regardless of the method of muscle mass measurement (Fig. 2). To clarify whether the clinical background of the elevated ABI subgroup differed according to the amount of SMI, we subdivided the participants by the 75th percentiles of the ABI (men ≥ 1.16; women ≥ 1.14) and SMI (men ≥ 8.14; women ≥ 6.56) because few individuals showed an ABI ≥ 1.4 (Table 1) and analyzed group differences in clinical parameters (Table 2). Compared with the control group, the elevated ABI with a normal SMI subgroup and the elevated ABI with a high SMI subgroup showed significantly different values for several parameters (Table 2). A multinomial logistic regression analysis was then performed to identify factors characterizing the elevated ABI subgroups (Table 3). The results indicated that the determinant with the greatest difference between the subgroups was the HOMA-IR, with coefficients that contrasted significantly according to the SMI. Similar results were also observed in a regression model including sex [ABI (Q4) – SMI (Q1–Q3): coefficient = 0.154, $p = 0.004$; ABI (Q4) – SMI (Q4): coefficient = –0.247, $p = 0.003$]. Figure 3 depicts the

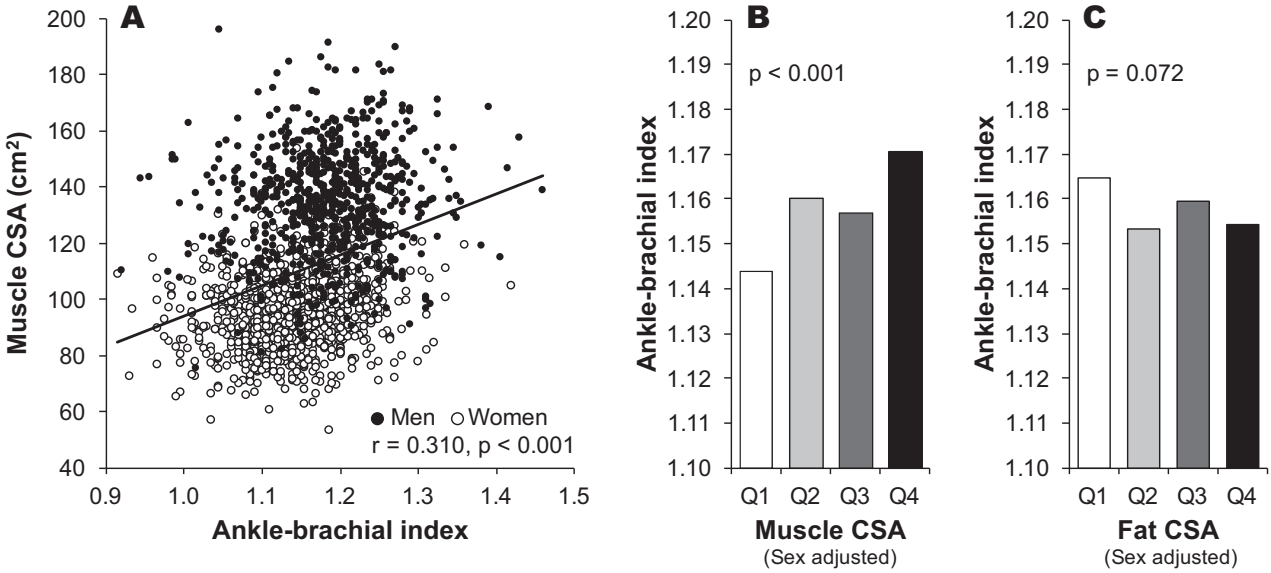

Fig. 1 Association between thigh muscle CSA and the ABI in the AASC cohort. **a** The scatter plot is depicted according to sex, whereas the correlation coefficient was calculated using the total population. **b**, **c** Quartiles of thigh muscle CSA and fat CSA were defined according to sex and then combined to avoid potential sex differences. The numbers of subjects in the subgroups were as follows: muscle CSA: Q1 = 441, Q2 = 438, Q3 = 444, and Q4 = 442; fat CSA: Q1 = 438, Q2 = 443, Q3 = 443, and Q4 = 441. Statistical significance was assessed by analysis of variance

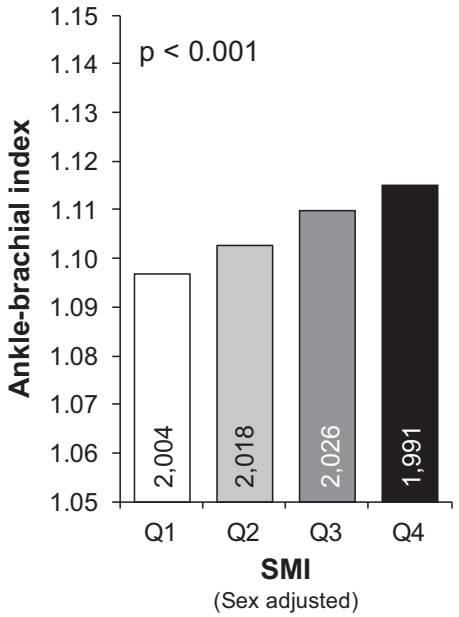

Fig. 2 Association between the SMI and ABI in the Nagahama cohort. The skeletal muscle index (SMI, kg/m^2) was calculated by dividing appendicular lean mass by body height squared. The quartiles of the SMI were calculated within sex and then combined. The number of study participants in each subgroup is shown in the columns. Statistical significance was assessed by analysis of variance

differences in the HOMA-IR among the subgroups. Individuals with both higher ABI and SMI values showed a significantly lower HOMA-IR in the adjusted analysis, suggesting that a clinical profile of an elevated ABI may not be deleterious when associated with a higher SMI. The SMI was inversely associated with the HOMA-IR ($\beta = -0.236$, $p < 0.001$) even after adjustments for age ($\beta = -0.022$, $p = 0.027$), sex ($\beta = 0.155$, $p < 0.001$), and BMI ($\beta = 0.658$, $p < 0.001$).

Discussion

In this cross-sectional analysis of two different general populations, we verified that appendicular muscle mass was a strong determinant of the ABI. The clinical implication of an elevated ABI, particularly in the context of insulin resistance, may differ based on the amount of muscle mass.

In our previous study [11], we reported that thigh muscle mass was a significant positive determinant of the ABI in part of the AASC population ($n = 407$). The reproducibility of the previous findings in this extended analysis and in the independent population sample strongly supports the involvement of muscle mass in measurement of the ABI. Common characteristics of individuals with a high ABI in various studies, namely, larger body size and a higher frequency of men, may reflect potentially greater appendicular muscle mass.

Thigh fat CSA was inversely associated with the ABI. Furthermore, a regression analysis including both fat CSA and muscle CSA identified only muscle CSA as a determinant of the ABI. These results strongly suggested that the composition but not the size of the lower extremity is a determinant of the ABI. Although we found a strong difference in muscle mass based on the sex of the participants, we did not perform a sex-specific analysis because a sex-specific analysis could obscure a true relationship between muscle mass and the ABI by dichotomizing the correlation according to sex. However, as the association remained significant in a regression analysis adjusted for sex, the involvement of muscle mass in the ABI may not be a false-positive finding caused by combining the results of men and women in the present study.

In a subgroup analysis of the Nagahama population, the HOMA-IR was identified as a positive determinant of an elevated ABI in subjects with a normal SMI. The positive association of insulin resistance with the ABI was consistent with previous findings in epidemiological studies that reported a significantly higher frequency of type 2 diabetes in high ABI sub-populations [4–7, 14, 32]. Furthermore, the incidence of a high ABI in a general population in a 4-year follow-up period has also been reported to be associated with type 2 diabetes [33]. A high ABI is generally believed to be due to arterial calcification [2]. Arterial calcification reflects two distinct vascular changes [34], namely, intimal calcification, which is associated with atherosclerosis caused mainly by lipid accumulation, inflammation, and fibrosis, and medial calcification due to structural changes in the arterial wall. Because insulin resistance is an established risk factor for atherosclerosis, with possible mechanisms of decreased insulin-mediated vasodilation and increased smooth muscle cell proliferation and enzymatic glycosylation of structural proteins such as collagen, these pathological changes may be factors in the positive relationship between the HOMA-IR and a high ABI.

In contrast, the HOMA-IR showed an inverse association with an elevated ABI in the high SMI subgroup, possibly due to insufficient compression of the tibial artery by the appendicular muscles rather than structural changes in large arteries. Another reason may be the inverse association between the SMI and the HOMA-IR. The clinical implication of an elevated ABI may consequently differ based on the amount of muscle mass. Because previous longitudinal studies on cardiovascular outcomes did not consider the amount of muscle mass, the results of these studies may underestimate the true prognostic significance of a high ABI in poor cardiovascular outcomes. Since the present study used a cross-sectional design, we could not investigate the possibility that appendicular muscle mass may modulate the prognostic significance of a high ABI. The small number of individuals with an ABI > 1.4 was also a limitation for

Table 2 Differences in clinical parameters by ABI and SMI subgroups in the Nagahama cohort

	Control	Elevated ABI			
ABI quartiles	Q1–Q3	Q4		Q4	
SMI quartiles	Q1–Q3	Q1–Q3		Q4	
	(5917)	(1504)		(618)	
	Mean ± SD	Mean ± SD	*p*	Mean ± SD	*p*
Age (years)	58.0 ± 13.2	60.8 ± 12.0	**<0.001**	57.0 ± 11.8	0.152
BMI (kg/m^2)	22.1 ± 3.3	21.4 ± 2.4	**<0.001**	25.3 ± 3.2	**<0.001**
Brinkman index	150 ± 314	123 ± 277	**0.005**	138 ± 290	0.602
Systolic BP (mmHg)	125 ± 18	124 ± 17	0.205	127 ± 17	**0.028**
Diastolic BP (mmHg)	72 ± 11	71 ± 10	**0.003**	74 ± 11	**<0.001**
HDL cholesterol (mg/dl)	67 ± 17	69 ± 17	**<0.001**	62 ± 16	**<0.001**
LDL cholesterol (mg/dl)	118 ± 29	117 ± 28	0.214	118 ± 29	0.919
Triglyceride (mg/dl)	93 ± 60	89 ± 55	**0.045**	107 ± 81	**<0.001**
Glucose (mg/dl)	88 ± 14	88 ± 15	0.215	90 ± 14	**<0.001**
HbA1c (%)	5.6 ± 0.5	5.6 ± 0.5	0.658	5.7 ± 0.5	**<0.001**
HOMA-IR	0.87 ± 1.03	0.83 ± 1.13	0.367	1.09 ± 0.99	**<0.001**
CRP (μg/ml)	0.98 ± 3.78	0.88 ± 2.53	0.601	1.11 ± 4.15	0.612
Carotid IMT (mm)	0.70 ± 0.17	0.70 ± 0.16	0.214	0.71 ± 0.15	0.376

Values are mean ± standard deviation

Study participants were subdivided by quartiles of ankle-brachial index and high skeletal muscle index. The quartiles were defined by each sex separately: ABI: men, ≥1.16, women, ≥1.14; SMI: men, ≥8.14, women, ≥6.56. *P* values reached statistical significance are shown in bold

Differences in clinical parameters with the control group were assessed by Dunnett's test

Table 3 Multinomial logistic regression analysis in the Nagahama cohort

ABI quartiles	Q4			Q4		
SMI quartiles	Q1–Q3			Q4		
	Coefficient	SE	*p*	Coefficient	SE	*p*
Age (years)	0.028	0.003	**<0.001**	0.002	0.005	0.606
BMI (kg/m^2)	−0.083	0.013	**<0.001**	0.280	0.015	**<0.001**
Brinkman index (per 100)	−0.025	0.010	**0.017**	−0.040	0.016	**0.013**
Systolic BP (mmHg)	−0.005	0.002	**0.015**	−0.001	0.004	0.706
HDL cholesterol (mg/dl)	0.003	0.002	0.091	−0.002	0.003	0.500
Triglyceride (mg/dl)	<0.001	0.001	0.930	<0.001	0.001	0.630
baPWV (cm/s)	<0.001	<0.001	0.200	−0.001	<0.001	**0.007**
HOMA-IR (log normalized)	0.146	0.053	**0.006**	−0.235	0.083	**0.005**

Multinomial logistic regression analysis with further adjustment for fasting time was performed using the control group (ankle-brachial index: Q1–Q3 and skeletal muscle index: Q1–Q3) as a reference. The quartiles were separately defined by each sex: ABI: men, ≥1.16, women, ≥1.14; SMI: men, ≥8.14, women, ≥ 6.56. *P* values reached statistical significance are shown in bold

clarifying this issue. Although ethnic differences in arterial properties may partly account for the small number of individuals with a high ABI in our population, differences in body size and composition may be more plausible explanations for the lower frequency since the body size of Asians is known to be smaller than that of Europeans [35]. Another Japan-based study also reported a small number of individuals with a high ABI ($n = 2$) in a population of approximately 3000 [36].

An important limitation of this study warranting discussion was measurement of the ABI using an oscillometric method rather than a standard method using continuous wave Doppler ultrasound [37]. Although the reliability of oscillometric determination of the ABI has

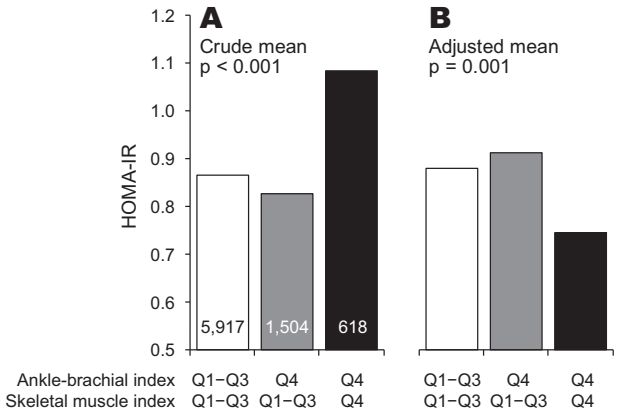

Fig. 3 Differences in the HOMA-IR among subgroups according to the ABI and SMI. The values are the crude (**a**) and adjusted (**b**) means. The adjusted factors were age, body mass index, Brinkman index, systolic blood pressure, HDL cholesterol, triglycerides, and baPWV. Statistical significance was assessed by analysis of variance (**a**) or a linear regression model (**b**). The number of study participants in each subgroup is shown in the columns

been confirmed [37, 38], a poor correlation with intra-arterial BP was also reported in obese individuals even when an appropriate cuff size was used [39]. In addition, we did not directly measure appendicular muscle mass in the Nagahama cohort. However, lean mass estimation using the SMF-BIA method has been found to be suitable for evaluating ALM [23, 24, 26–28].

In summary, we confirmed that appendicular muscle mass is a strong determinant of the ABI and may modulate the clinical significance of an elevated ABI. Careful attention is warranted in epidemiological studies of the ABI, particularly in those with obese individuals as well as muscular individuals and subjects with large body sizes.

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Compliance with Ethical Standards

Conflict of interest :The authors declare that they have no conflict of interest.

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