Inverse relationship of cardioankle vascular index with BMI in healthy Japanese subjects: a cross-sectional study

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Objective: The objective of this study is to investigate the association of body mass index (BMI) with arterial stiffness assessed by cardioankle vascular index (CAVI).

Subjects and methods: A retrospective cross-sectional study was conducted in 23,257 healthy Japanese subjects (12,729 men and 10,528 women, aged 47.1 ± 12.5 years, BMI 22.9 ± 3.4 kg/m2) who underwent health screening between 2004 and 2006 in Japan. Exclusion criteria were current medication use and a past history of cardiovascular disease, hypertension, stroke, diabetes, and nephritis.

Results: Male subjects showed significantly higher BMI, CAVI, and triglycerides and lower high-density lipoprotein (HDL)-cholesterol compared with female subjects. Next, the subjects were divided into tertiles of BMI: lower, middle, and upper, in a gender-specific manner. After adjusting for confounders including age, systolic blood pressure, and HDL-cholesterol identified by multiple regression analysis, the mean CAVI decreased progressively as BMI tertile increased in both genders. Furthermore, a negative inverse relationship between BMI and adjusted CAVI was observed throughout the BMI distribution. Multivariate logistic regression model for contributors of high CAVI (90th percentile) identified obesity (odds ratio: 1.204 (0.720–1.999), older age [15.6 (14.0–17.4)], male gender [2.26 (2.03–2.51)], hypertension [2.28 (2.06–2.54)], impaired fasting glucose [1.17 (1.01–1.37)], and low HDL-cholesterol [0.843 (0.669–1.060)] as independent factors.

Conclusion: We demonstrated an inverse relationship between CAVI and BMI in healthy Japanese subjects, suggesting that systemic accumulation of adipose tissue per se may lead to a linear decrease of arterial stiffness in nonobese and obese subjects without metabolic disorders.

Keywords: BMI, cardioankle vascular index, arterial stiffness

Introduction
Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health1 and have been reported to be associated with glucose in tolerance, dyslipidemia, and hypertension, thus increasing cardiovascular risks.2,3 Furthermore, cardiovascular disease (CVD) is the leading cause of death worldwide.4 On the other hand, underweight is also associated with increased all-cause mortality compared to normal weight after adjustment for covariates.5–8 It is an obvious fact that body fat distribution influences morbidity and mortality. Thus, healthy ranges for percentage body fat (%BF) should be considered in the management of intensive therapeutic approaches for obesity.9–11 The most commonly used surrogate marker of %BF is body mass index (BMI), which is calculated from a person’s height and weight. BMI
is reliable and provides a fair indication of body fat level but
is not a perfect system for measuring body fat.12–14 A BMI <18.5 kg/m² is defined as underweight and a BMI >25 kg/m²
as overweight. Actually, numerous studies have documented
a U- or J-shaped association between BMI and mortality
and an association of increased mortality rate with relatively
low or high BMI.15,16 In Japan, the ideal body weight that is
associated with the lowest mortality corresponds to a BMI
of 22 kg/m² in both men and women.17 Arterial stiffness is a
significant surrogate marker of subclinical atherosclerosis,
and increased arterial stiffness is independently associated
with an increased risk of major adverse cardiovascular events
(MACEs).18,19
Recently, a novel arterial stiffness diagnostic parameter
called cardioankle vascular index (CAVI) has been de-
veloped in Japan, which allows quantification of the stiffness
parameter beta independent of blood pressure (BP).20–22 This
stiffness parameter has adequate reproducibility for clinical
use23–27 and is associated with a number of risk factors and
severity of CVD.28–33 CAVI has also been reported to be an
independent predictor of MACE.34,35 Moreover, an increase
in the number of risk factors for metabolic syndrome cor-
relates positively with increased CAVI, probably due to
insulin resistance.36 Weight gain most likely contributes to
the risk of increase in arterial stiffness. Nevertheless, the
relationship between BMI and arterial stiffness has not been
fully elucidated.

The aim of this cross-sectional study was to investigate
whether BMI is associated independently with arterial stiff-
ness assessed by CAVI after adjustment for covariates in
healthy Japanese subjects. Additionally, gender difference in
the relationship between BMI and CAVI was also examined.

Subjects and methods

Design

This retrospective cross-sectional study was approved by the
Institutional Review Board and Ethics Committee of Sakura
Hospital, School of Medicine, Toho University (no S16002).
Written informed consent was obtained from the participants.

Data collection and laboratory assay methods

A total of 23,257 Japanese urban residents (12,729 men and
10,528 women) residing in major cities nationwide, who
participated in the CVD and cancer screening program provided
by the Japan Health Promotion Foundation between 2004
and 2006, were studied. Subjects were excluded if they were
taking any medication or had a past history of heart disease,
hypertension, stroke, diabetes, nephritis, or gout. Height
and body weight were measured, and BMI was calculated
[weight (kg) divided by square of height (m²)]. Obesity was
defined as BMI ≥25 kg/m², which is the definition for obesity
in adult Japanese population according to the Examination
Committee of Criteria for Obesity Disease in Japan.37 Blood
was collected from the antecubital vein in the morning after
12-hour fasting to determine γ-glutamyl transpeptidase
(γ-GTP), fasting plasma glucose (FPG), glycosylated hemoglo-
bain (HbA1c), total cholesterol (TC), triglycerides (TGs),
high-density lipoprotein-cholesterol (HDL-C), creatinine,
and uric acid. All the blood levels were measured accord-
ing to standard procedures. Non-HDL-C was defined as the
difference between total and HDL-cholesterol. HbA1c (%) measured by the Japan Diabetes Society (JDC) method was
converted to NGSP value (%) using the following formula:
HbA1c (NGSP) (%) = HbA1c (JDS) (%) + 0.4%.38 Impaired
fasting glucose (IFG) was defined as fasting glucose levels
of 100 to 125 mg/dL.39

Measurement of CAVI and BP

CAVI was measured using a VaSera VS-1000 (Fukuda Denshi
Co Ltd, Tokyo, Japan) by the methods described previously.20
Cuffs were applied to bilateral upper arms and ankles, with
the subject lying supine and the head held in midline posi-
tion. After resting for 10 minutes, the examinations were
performed. To detect the brachial and ankle pulse waves with
cuffs, a low cuff pressure from 30 to 50 mmHg was used to
ensure minimal effect of cuff pressure on hemodynamics.
Furthermore, BP was measured thereafter. Hypertension
was defined as systolic BP (sBP) ≥140 mmHg and/or dia-
ostolic BP (dBP) ≥90 mmHg.40 Finally, for the convenience
of comparison with the pulse wave velocity (PWV), scale
conversion was performed. CAVI was calculated by the fol-
lowing formula:

\[
CAVI = a \left( \frac{2\rho \Delta P}{\ln(Ps/Pd)PWV^2} \right) + b,
\]

where \( Ps \) is sBP, \( Pd \) is dBP, \( \Delta P \) is \( Ps - Pd \), \( \rho \) is blood density,
and \( a \) and \( b \) are constants. BP was measured from the cuff of
the upper arm. PWV was obtained by dividing the vascular
length by the time for which the pulse wave propagated from
the aortic valve to the ankle and was measured using cuffs
at the upper arms and ankles. All the measurements and
calculations were performed automatically by the VaSera.
Subjects with ankle–brachial indices <0.90 were excluded,
because patients with severe arterial occlusive diseases may
give falsely low CAVI.20 The mean coefficient of variation of
CAVI measured by this method is <5%, which is sufficiently
small for clinical usage and indicates that CAVI has good
reproducibility.25
Statistical analysis
All data are expressed as mean ± standard deviation. The SPSS software (version 11.5; SPSS Inc, Chicago, IL, USA) was used for statistical processing. Student’s t-test was performed to examine gender difference in clinical variables. The relationship between CAVI and clinical variables was analyzed using multiple regression analysis. The relationship of CAVI with BMI was analyzed using analysis of variance (ANOVA) after adjusting for confounders of CAVI, together with trend analysis. Logistic regression analysis was used to identify contributors of high CAVI (≥90th percentile) and expressed as odds ratio (OR) with 95% confidence interval (CI). In all comparisons, P values <0.05 were considered statistically significant.

Results
Characteristics of male and female participants
In this study, a total of 23,257 Japanese urban residents (12,729 men and 10,528 women) aged from 20 to 74 (mean 47.1 ± 12.5) years were screened. Table 1 compares the clinical characteristics of male and female participants. Compared with men, women had significantly and markedly higher BMI (23.9 ± 3.2 vs. 21.7 ± 3.3 kg/m², P = 0.003) and CAVI (7.96 ± 1.14 vs. 7.69 ± 0.97, P < 0.001).

Table 1 Characteristics of male and female participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All</th>
<th>Male</th>
<th>Female</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>23,257</td>
<td>12,729</td>
<td>10,528</td>
<td>–</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.1 ± 12.5</td>
<td>47.0 ± 13.0</td>
<td>47.1 ± 12.0</td>
<td>0.692</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163 ± 9</td>
<td>169 ± 6</td>
<td>156 ± 6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>61.6 ± 12.2</td>
<td>68.4 ± 10.5</td>
<td>53.3 ± 8.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.9 ± 3.4</td>
<td>23.9 ± 3.2</td>
<td>21.7 ± 3.3</td>
<td>0.003</td>
</tr>
<tr>
<td>CAVI</td>
<td>7.84 ± 1.07</td>
<td>7.96 ± 1.14</td>
<td>7.69 ± 0.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sBP (mmHg)</td>
<td>124 ± 16</td>
<td>124 ± 16</td>
<td>123 ± 16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>dBP (mmHg)</td>
<td>76 ± 12</td>
<td>76 ± 12</td>
<td>75 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>γ-GTP (IU/L)</td>
<td>43 ± 56</td>
<td>43 ± 52</td>
<td>44 ± 60</td>
<td>0.415</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>91 ± 18</td>
<td>91 ± 18</td>
<td>91 ± 18</td>
<td>0.465</td>
</tr>
<tr>
<td>HbA1c (NGSP, %)</td>
<td>5.3 ± 0.6</td>
<td>5.3 ± 0.6</td>
<td>5.3 ± 0.6</td>
<td>0.086</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>209 ± 37</td>
<td>210 ± 37</td>
<td>208 ± 36</td>
<td>0.002</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>113 ± 95</td>
<td>117 ± 100</td>
<td>108 ± 89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>66 ± 19</td>
<td>65 ± 18</td>
<td>67 ± 19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>144 ± 39</td>
<td>145 ± 39</td>
<td>142 ± 38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.71 ± 0.15</td>
<td>0.80 ± 0.13</td>
<td>0.62 ± 0.10</td>
<td>0.055</td>
</tr>
</tbody>
</table>

Notes: Data are presented as mean ± standard deviation. *Student’s t-test was used to compare male and female subjects.

Prevalence of major cardiovascular risk factors
The prevalence of traditional cardiovascular risks in participants is shown in Table 2. The proportions of older age, obesity, and hypertension were significantly (P < 0.001) higher in men than in women, whereas the proportions of IFG and low HDL-cholesterol (defined as HDL-C <40 mg/dL) were not significantly different (Table 2).

Correlation of CAVI with clinical variables analyzed by multiple regression model
Next, we examined the factors associated with CAVI. Table 3 summarizes the results of a multiple regression analysis for the correlation between CAVI and clinical variables. TG was also omitted because of intraclass correlation with HDL-C, and non-HDL-C was added instead. Age was a major independent predictor of CAVI (β coefficient = 0.584, P < 0.001). Additionally, a low correlation between CAVI and gender

Table 2 Prevalence of major cardiovascular risk factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (%)</th>
<th>Male (%)</th>
<th>Female (%)</th>
<th>P value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>9.2</td>
<td>9.2</td>
<td>6.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(age ≥65; 1, &lt;65; 0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>24.9</td>
<td>32.9</td>
<td>15.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(BMI ≥25; 1, &lt;25; 0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (BP ≥140/90; 1, &lt;140/90; 0)</td>
<td>15.3</td>
<td>16.1</td>
<td>14.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IFG (FPG ≥110; 1, &lt;110; 0)</td>
<td>10.1</td>
<td>10.2</td>
<td>10.0</td>
<td>0.498</td>
</tr>
<tr>
<td>Low HDL-C (HDL-C &lt;40; 1, ≥40; 0)</td>
<td>5.0</td>
<td>5.3</td>
<td>4.7</td>
<td>0.058</td>
</tr>
</tbody>
</table>

Notes: **Fisher’s exact test was used to compare male and female subjects.

Abbreviations: BMI, body mass index; BP, blood pressure; IFG, impaired fasting glucose; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein-cholesterol.

Table 3 Correlation of cardioankle vascular index with clinical variables analyzed by multiple regression model

<table>
<thead>
<tr>
<th>Variable</th>
<th>β coefficient</th>
<th>SE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male; 1, female; 0)</td>
<td>0.149</td>
<td>0.125</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.584</td>
<td>0.017</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>–0.119</td>
<td>0.003</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sBP (mmHg)</td>
<td>0.139</td>
<td>17.105</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>γ-GTP (IU/L)</td>
<td>0.004</td>
<td>0.538</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>–0.003</td>
<td>0.015</td>
<td>0.712</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>–0.181</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>0.107</td>
<td>0.001</td>
<td>0.542</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.012</td>
<td>1.470</td>
<td>0.142</td>
</tr>
</tbody>
</table>

Notes: Model: r² = 0.598, P < 0.001.

Abbreviations: SE, standard error; BMI, body mass index; sBP, systolic blood pressure; γ-GTP, γ-glutamyl transpeptidase; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein-cholesterol.
Table 4 Characteristics of male and female participants stratified by tertile of body mass index

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tertile of body mass index</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower (T1)</td>
<td>Middle (T2)</td>
</tr>
<tr>
<td>Male subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td>4,181</td>
<td>4,365</td>
</tr>
<tr>
<td>Age (years)</td>
<td>45.2 ± 13.8</td>
<td>48.4 ± 12.6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169 ± 6</td>
<td>169 ± 6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23 ± 1.3</td>
<td>23 ± 0.8</td>
</tr>
<tr>
<td>Middle tertile</td>
<td>(≤22.2)</td>
<td>(22.3–24.9)</td>
</tr>
<tr>
<td>CAVI</td>
<td>4.10 ± 1.3</td>
<td>7.51 ± 1.2</td>
</tr>
<tr>
<td>Adjusted CAVI***</td>
<td>8.16 ± 0.87</td>
<td>7.97 ± 0.84</td>
</tr>
<tr>
<td>sBP (mmHg)</td>
<td>123 ± 15</td>
<td>127 ± 15</td>
</tr>
<tr>
<td>dBP (mmHg)</td>
<td>75 ± 11</td>
<td>79 ± 11</td>
</tr>
<tr>
<td>γ-GTP (IU/L)</td>
<td>47 ± 68</td>
<td>58 ± 69</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>91 ± 18</td>
<td>94 ± 21</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.6 ± 0.6</td>
<td>5.7 ± 0.7</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>197 ± 34</td>
<td>209 ± 36</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>103 ± 79</td>
<td>138 ± 109</td>
</tr>
<tr>
<td>Non HDL-C (mg/dL)</td>
<td>65 ± 17</td>
<td>58 ± 15</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.79 ± 0.11</td>
<td>0.82 ± 0.29</td>
</tr>
<tr>
<td>Female subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td>3,585</td>
<td>3,462</td>
</tr>
<tr>
<td>Age (years)</td>
<td>43.1 ± 12.0</td>
<td>47.4 ± 11.4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>157.7 ± 5.4</td>
<td>156.4 ± 5.5</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>46.5 ± 4.1</td>
<td>52.1 ± 3.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>18.6 ± 1.1</td>
<td>21.2 ± 0.7</td>
</tr>
<tr>
<td>Middle tertile</td>
<td>(≤20.0)</td>
<td>(20.1–22.5)</td>
</tr>
<tr>
<td>CAVI</td>
<td>7.61 ± 0.94</td>
<td>7.70 ± 0.96</td>
</tr>
<tr>
<td>Adjusted CAVI***</td>
<td>7.89 ± 0.76</td>
<td>7.70 ± 0.71</td>
</tr>
<tr>
<td>sBP (mmHg)</td>
<td>114 ± 14</td>
<td>119 ± 15</td>
</tr>
<tr>
<td>dBP (mmHg)</td>
<td>68 ± 10</td>
<td>71 ± 10</td>
</tr>
<tr>
<td>γ-GTP (IU/L)</td>
<td>21 ± 18</td>
<td>24 ± 25</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>84 ± 8</td>
<td>86 ± 9</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.6 ± 0.4</td>
<td>5.6 ± 0.5</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>202 ± 36</td>
<td>212 ± 37</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>65 ± 34</td>
<td>80 ± 52</td>
</tr>
<tr>
<td>Non HDL-C (mg/dL)</td>
<td>80 ± 18</td>
<td>75 ± 17</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.61 ± 0.14</td>
<td>0.61 ± 0.08</td>
</tr>
</tbody>
</table>

Notes: ***CAVI was adjusted by age, sBP, and HDL-C. Data are presented as mean ± standard deviation. P value for trend by ANOVA.

Abbreviations: BMI, body mass index; CAVI, cardioankle vascular index; sBP, systolic blood pressure; dBP, diastolic blood pressure; γ-GTP, γ-glutamyl transpeptidase; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; ANOVA, analysis of variance.

Characteristics of male and female participants stratified by tertiles of BMI

Participants were divided into men and women, and each gender group was stratified by BMI tertiles into the following three groups: lower (T1), middle (T2), and upper tertile (T3). Among 12,729 men, 4,181 were stratified into T1 (BMI ≤22.2 kg/m²), 4,365 into T2 (22.3–24.9 kg/m²), and 4,183 into T3 (≥25.0 kg/m²). Among 10,528 women, 3,585 were stratified into T1 (≤20.0 kg/m²), 3,462 into T2 (20.1–22.5 kg/m²), and 3,481 into T3 (≥22.6 kg/m²). Table 4 compares their clinical characteristics. CAVI was adjusted for confounders identified in the multiple regression model as shown in Table 3. In both genders, sBP, dBP, γ-GTP, FPG, HbA1c, TC, TG, and non-HDL-C increased, while adjusted CAVI and HDL-C decreased progressively with increasing BMI tertile.

ORs (95% CIs) for high CAVI (≥90th percentile)

Furthermore, we examined the factors associated with high CAVI using multivariable logistic regression model with dichotomous variables (Table 5). High CAVI was defined as ≥90th percentile of CAVI (9.20 in all participants). Gender and major cardiovascular risks were entered into the model as shown in Table 2. The analysis identified the following factors to be independently associated with high CAVI: male gender (OR: 2.26, P < 0.001), older age (OR: 15.6, P < 0.001), hypertension (OR: 2.28, P < 0.001), and IFG (OR: 1.17, P = 0.0428). Interestingly, obesity correlated negatively with high CAVI (OR: 0.804, P < 0.001). Low HDL-cholesterol was not a significant independent predictor of high CAVI.

Relationship of adjusted CAVI with BMI in men and women

Figure 1 shows the relationship of adjusted CAVI with BMI in men (Figure 1A) and women (Figure 1B). In both genders, a trend test after ANOVA detected an inverse linear relationship (P < 0.001) between adjusted CAVI and BMI throughout the entire BMI distribution.

Discussion

In this cross-sectional study, gender, age, BMI, BP, and HDL-cholesterol were major independent variables associated with...
CAVI in 23,257 healthy Japanese subjects. After adjusting for confounders, CAVI correlated negatively with BMI in both genders. Furthermore, obesity was identified as an independent negative predictor of high CAVI (≥90th percentile), while male gender, hypertension, and IFG were found to be independent positive predictors. Consequently, the present study is the first report to demonstrate an inverse relationship between CAVI and BMI in healthy middle-aged subjects. Note that most of the participants in the present study were nonobese subjects without metabolic disorders. If the study was conducted in obese subjects with metabolic disorders, the results might have been markedly different.

Weight gain has been associated with vascular remodeling and increased cardiovascular mortality. CAVI has been shown to be high in the abdominal obesity/metabolic syndrome and decrease by body weight reduction. Insulin resistance, a consequence of weight gain, has been recognized as an independent predictor of vascular stiffening and other elements of diabetic vasculopathy. Our finding of an inverse relationship between CAVI and BMI might seem inconsistent with previous reports. However, the interaction of weight gain with insulin resistance in the regulation of vascular pathophysiology involves complex mechanisms that are not fully understood. Thus, the mechanism of vascular adaptation...
to fat accumulation remains controversial. In fact, a negative association of obesity with vascular stiffening has been reported in children and adolescents, but not in older adults or the elderly. We therefore stratified the participants in this study by age into tertiles: lower (33.1 ± 5.0 years, n = 7,878), middle (47.1 ± 3.8 years, n = 7,577), and upper (61.0 ± 7.5 kg/m²) Japanese subjects with metabolic disorders. In this study, mean CA VI was higher in men (7.96 ± 1.2 years, n = 7,802) and investigated the contribution of BMI to CA VI in each group using logistic regression analysis. We found approximately equal degree of inverse relationship between CAVI and BMI in all three tertiles (data not shown). However, these data do not imply a similar inverse relationship between CAVI and BMI in elderly subjects. While weight gain is a risk factor for CVD, an inverse relationship between BMI and CAVI in each tertile using logistic regression analysis. The OR value for high cardioankle vascular index (≥90th percentile) was 2.26 for gender, 1.56 for age, 0.804 for hypertension, 2.28 for IFG, and 0.843 for low HDL-C. The P value was <0.001 for gender, age, and hypertension, <0.001 for IFG, and 0.001 for low HDL-C. The note indicates that the Akaike's Information Criterion: 12,166, residual deviance: 12,152, P < 0.0001.

**Table 5 OR (95% CI) for high cardioankle vascular index (≥90th percentile)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>2.26</td>
<td>2.03–2.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Older age, years (age ≥65; 1, &lt;65; 0)</td>
<td>15.6</td>
<td>14.0–17.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity (BMI ≥25; 1, &lt;25; 0)</td>
<td>0.804</td>
<td>0.720–0.899</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (≥1, &lt;0)</td>
<td>2.28</td>
<td>2.06–2.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IFG (FPG ≥110; 1, &lt;110; 0)</td>
<td>1.17</td>
<td>1.01–1.37</td>
<td>0.0428</td>
</tr>
<tr>
<td>Low HDL-C (HDL-C &lt;40; 1, ≥40; 0)</td>
<td>0.843</td>
<td>0.669–1.06</td>
<td>0.145</td>
</tr>
</tbody>
</table>

Note: OR, odds ratio.

**Abbreviations:** CI, confidence interval; BMI, body mass index; IFG, impaired fasting glucose; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein-cholesterol.

What is the clinical efficacy of our findings? We hypothesized that CAVI might be useful to exclude “malignant obesity”, which means normal metabolic features despite increased adiposity, and they may be allowed a period of grace for atherogenesis. Of course, metabolicically healthy overweight/obese individuals may be needed to receive permanent medical follow-up because of increased risk of adverse long-term outcomes after all.

Gender difference in CAVI has been reported previously. Similarly, in this study, mean CAVI was higher in men (7.96 ± 1.14) than in women (7.69 ± 0.97), despite almost the same age in both groups (47.0 ± 13.0 in men and 47.1 ± 12.0 years in women). The mechanism of this gender difference in CAVI remains uncertain, although gender-related differences in body fat distribution may partly explain the phenomenon.

In 2002, brachial–ankle PWV (baPWV) was proposed to be a marker of vascular damage and was reported to be a
predictive marker of CVD. Furthermore, baPWV correlates strongly with aortic (carotid–femoral) PWV, an established index of central arterial stiffness. However, PWV is known to depend on BP at the time of measurement. Therefore, the validity of PWV in reflecting actual arterial stiffness is controversial, and this parameter is unsuitable for evaluating the effect of antihypertensive drugs on the arterial wall. On the other hand, CAVI is independent of BP, which makes it more precise and reproducible than PWV as an index of arterial stiffness, whereas its predictive value of cardiovascular events has not been established adequately. Additionally, a multiple logistic analysis revealed that CAVI, but not baPWV, was associated with the presence of carotid and coronary arteriosclerosis.

The limitations of this study include the lack of data on some potential confounders such as proteinuria, alcohol consumption, menopause, and smoking status. In addition, the cross-sectional nature of this study does not allow determination of the time course for the development of vascular changes. Therefore, it was not possible to establish the exact pathophysiology linking BMI with CAVI. From these viewpoints, longitudinal cohort studies are needed to clarify the change in relationship between body composition and arterial stiffness during the development of cardiovascular risks.

**Conclusion**

We demonstrated an inverse linear relationship between CAVI and BMI in healthy Japanese subjects, suggesting that systemic accumulation of adipose tissue per se may lead to a proportionate decrease in arterial stiffness in nonobese subjects and obese subjects without metabolic disorders.

**Acknowledgments**

We are grateful to Dr. Kenji Suzuki, Japan Health Promotion Foundation, for making enormous contribution in this study, and we gratefully acknowledge the investigators, their coinvestigators, study coordinators, and the patients who participated in this study.

**Author contributions**

Kohji Shirai contributed to concept/design. Daiji Nagayama contributed to data analysis and interpretation. Ichiro Tatsuno contributed to critical revision of article. Haruki Imamura, Yuta Sato, Takashi Yamaguchi, Noriko Ban, Hitodoshi Kawana, Masahiro Ohira, and Atsuhito Saiki contributed to data interpretation. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**


