Association between Arterial Stiffness and Estimated Glomerular Filtration Rate in the Japanese General Population

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Aim: Chronic kidney disease (CKD) is associated with an increased risk of cardiovascular disease, although it has yet to be established whether CKD is an independent risk factor for arterial stiffness in community residents. The purpose of this study was to determine the correlation between the cardio-ankle vascular index (CAVI) and estimated glomerular filtration rate (eGFR) in the general population.

Methods: We studied 881 consecutively enrolled subjects undergoing health checkups. CAVI was calculated automatically from the pulse volume record, blood pressure and the vascular length from the heart to the ankle. CKD was evaluated by the eGFR.

Results: The distribution of eGFR was as follows: 241 with eGFR (mL/min/1.73m2) ≥ 90; 572 with eGFR 60–89; 65 with eGFR 30–59; 3 with eGFR 15–29; 0 with eGFR < 15. Linear regression analysis showed that CAVI was negatively correlated significantly with eGFR, while multiple regression analysis using CAVI as an objective variable, adjusted for conventional atherosclerotic risk factors and eGFR as explanatory variables, demonstrated that CAVI was an independent determinant of eGFR. We also showed that stepwise increments of CAVI occurred with progressive deterioration of CKD.

Conclusion: CAVI was independently correlated with eGFR indicating that CKD is associated with arterial stiffness in the general population.


Key words: Cardio-ankle vascular index, Chronic kidney disease, Arterial stiffness
with systolic BP (SBP) than with brachial-ankle PWV (baPWV) and was not affected by changes in BP during measurement\(^9\). There is also evidence that CAVI is associated significantly with the presence and severity of coronary atherosclerosis\(^10\).

While it has been reported that PWV correlates negatively with eGFR in community residents\(^11\), it has not yet been determined whether CAVI correlates with eGFR in the general population. The purpose of this study was therefore to determine the correlation between CAVI and eGFR in the general Japanese population.

**Methods**

**Subjects**

The study group consisted of 881 consecutively enrolled subjects (488 males and 393 females, mean age: 52±14 years, range: 18–80 years) who underwent routine health checkups at JA Kagoshima Kouseiren Medical Health Care Center. Personal interviews showed that 112 subjects were receiving treatment for hypertension, 10 for diabetes mellitus and 36 for hyperlipidemia. Five subjects had a history of ischemic heart disease and 10 had a history of stroke. Information on smoking history was obtained by means of a self-administered questionnaire.

The protocol used for the present study was approved by the institutional review board of Kagoshima University. Informed consent was obtained from all volunteers.

**Biochemical Measurements**

Blood samples were collected after the subjects had fasted overnight. The serum concentrations of total cholesterol (TC), triglyceride (TG) and high density lipoprotein (HDL)-cholesterol were measured by standard laboratory procedures, while low density lipoprotein (LDL)-cholesterol was calculated by the Friedewald equation. Eight subjects with a serum TG concentration of 400 mg/dL or higher did not have LDL-cholesterol calculated as the Friedewald equation is unsuitable for TG values above this level.

**Measurements of Proteinuria**

Dipstick urinalysis for proteinuria was performed on spontaneously voided fresh urine samples. The test results were interpreted by physicians and recorded as −, +, 1+, 2+, 3+ or 4+. Results recorded as − and ± were classified as the absence of proteinuria and the others were classified as the presence of proteinuria.

**Measurements of Estimated GFR**

CKD was evaluated by eGFR using the equation of the Japanese Society of Nephrology: $eGFR = 194 \times Cr^{-1.094} \times age^{-0.287}$ (mL/min/1.73 m\(^2\)). For women, the eGFR was multiplied by a correction factor of 0.739. eGFR was classified using the following five categories provided by the Kidney Disease Outcomes Quality Initiative (K/DOQI)\(^12\): stage 1: eGFR ≥90 mL/min/1.73 m\(^2\); stage 2: eGFR 60 to 89 mL/min/1.73 m\(^2\); stage 3: eGFR 30 to 59 mL/min/1.73 m\(^2\); stage 4: eGFR 15 to 29 mL/min/1.73 m\(^2\); stage 5 eGFR <15 mL/min/1.73 m\(^2\).

In 2002, the National Kidney Foundation published clinical practice guidelines on evaluation, classification and risk stratification in CKD. In these guidelines, CKD is defined as either kidney damage for ≥3 months, as confirmed by kidney biopsy or markers of kidney damage, with or without a decrease in GFR; or GFR <60 mL/min/1.73 m\(^2\) for ≥3 months, with or without kidney damage\(^12\).

**Measurements of CAVI**

CAVI was measured using a Vasera VS-1000 (Fukuda Denshi, Tokyo, Japan) as reported previously\(^8,10\). Briefly, cuffs were applied to the four extremities and electrocardiographic electrodes were attached to the upper arm. A microphone was placed on the sternal angle for phonocardiography. The subjects then rested in the supine position for 5 min.

PWV was calculated by dividing the distance from the aortic valve to the ankle artery by the sum of the difference between the time the pulse waves were transmitted to the brachium and the time the same waves were transmitted to the ankle, and the time difference between the second heart sound on the phonocardio gram and the notch of the brachial pulse waves\(^9\). To minimize cuff inflation effects on blood flow dynamics, pulse waves were measured with the cuffs inflated to lower than diastolic BP (DBP) (50 mmHg). Extremity blood pressure was then measured by oscillometry. SBP, DBP and pulse pressure (PP) were obtained by measuring blood pressure at the right brachial artery. In this study, there were no patients with peripheral artery disease with an ankle brachial index less than 0.9.

CAVI was calculated by the following equation: $CAVI = a \times \left[\frac{\{2 \rho \times 1/(SBP-DBP)\}}{\ln \left(\frac{SBP}{DBP}\right) \times PWV^2}\right] + b \left(\rho: \text{density of blood, a and b: constants}\right)^9,10,13$.

**Statistical Analysis**

Data are expressed as the mean ± SD. Differences between the mean values of the two groups were analyzed by unpaired t tests. The relationship between
continuous variables was analyzed by linear regression analysis. The independence of the association between variables was tested with multiple regression analysis. Statistical analyses were performed with Stat View, version 5.0. P values less than 0.05 were considered significant.

Results

Background of Subjects

The clinical characteristics of the subjects are summarized in Table 1. The mean age was 52 ± 14 years (range, 18 to 80 years). The mean value of eGFR was 81 ± 16 mL/min/1.73 m², with the distribution of eGFR and CKD stages as follows: stage 1, \( n = 241 \); stage 2, \( n = 572 \); stage 3, \( n = 65 \); stage 4, \( n = 3 \); stage 5, \( n = 0 \). The mean value of CAVI was 8.5 ± 1.3.

Relationship between CAVI and Risk Factors

Linear regression analysis showed that CAVI correlated significantly with age, LDL cholesterol, TG, HDL cholesterol, FBS, HbA1c, BUN, serum creatinine, SBP, DBP and PP (Table 2). In addition, there was a significant negative correlation between CAVI and eGFR (Fig. 1).

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**Table 1.** Characteristics of the subjects \((n = 881)\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52 ± 14</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.0 ± 3.3</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>488/393</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>110 ± 73</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>58 ± 15</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>124 ± 30</td>
</tr>
<tr>
<td>FBS (mg/dL)</td>
<td>103 ± 21</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>5.2 ± 0.6</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>15.4 ± 4.2</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.7 ± 0.2</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>127 ± 17</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>82 ± 12</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>99 ± 15</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>45 ± 10</td>
</tr>
<tr>
<td>Smoking history (%)</td>
<td>50</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>81 ± 16</td>
</tr>
<tr>
<td>CAVI</td>
<td>8.5 ± 1.3</td>
</tr>
</tbody>
</table>

BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; FBS, fasting blood sugar; BUN, blood urea nitrogen; BP, blood pressure; eGFR, estimated glomerular filtration rate; CAVI, cardio-ankle vascular index.

**Table 2.** Linear regression analysis between CAVI and other variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>( r )</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.699</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.025</td>
<td>0.47</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.131</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-0.114</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.155</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FBS</td>
<td>0.247</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>0.196</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BUN</td>
<td>0.308</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.170</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.402</td>
<td>&lt;0.0001</td>
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<tr>
<td>Diastolic BP</td>
<td>0.359</td>
<td>&lt;0.0001</td>
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<tr>
<td>Mean BP</td>
<td>0.443</td>
<td>&lt;0.0001</td>
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<tr>
<td>Pulse pressure</td>
<td>0.266</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR</td>
<td>-0.383</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; FBS, fasting blood sugar; BUN, blood urea nitrogen; BP, blood pressure; eGFR, estimated glomerular filtration rate.

**Fig. 1.** Relationship between CAVI and eGFR in the general population.
CAVI, cardio-ankle vascular index; eGFR, estimated glomerular filtration rate.

**Multiple Regression Analysis between CAVI and Other Clinical Variables**

Multiple regression analysis was performed using CAVI as an objective variable, adjusted for conventional atherosclerotic risk factors that included age, gender, SBP, LDL cholesterol, hemoglobin A1c and eGFR, as explanatory variables. This analysis demonstrated that CAVI correlated independently with age, hemoglobin A1c, SBP, history of smoking and eGFR.
Comparison of CAVI in Stage of CKD

We analyzed the correlation between CAVI and CKD stages and showed that stepwise increments in CAVI occurred with deterioration in CKD from stage 1 to 4 (stage 1: 7.8 ± 1.2, stage 2: 8.7 ± 1.3, stage 3–4: 9.5 ± 1.3) (Fig. 2).

Relationship between CAVI and Proteinuria

We collected urinalysis data on 872 subjects and investigated the relationship between the prevalence of proteinuria and CAVI. Proteinuria was absent in 842 subjects and present in 30 subjects. CAVI in subjects without proteinuria was significantly higher than that measured in subjects with proteinuria (Fig. 3).

Discussion

In this study, we analyzed the association between CAVI and eGFR in the general Japanese population. Linear regression analysis demonstrated a significant correlation between CAVI and eGFR. Furthermore, multiple regression analysis using CAVI as an objective variable, adjusted for conventional atherosclerotic risk factors and eGFR as explanatory variables, revealed that CAVI was independently correlated with eGFR. In addition, there was a stepwise increase in CAVI that corresponded to increasing severity in CKD from stage 1 to 4.

A lower eGFR is associated with greater arterial stiffness and enhanced urinary albumin excretion, even at levels below those classified as microalbuminuria. Measurement of baPWV has been used as a noninvasive clinical index of arterial stiffness, and has also been shown to predict the presence of coronary artery disease, and correlate with abdominal aortic calcification and carotid intima-media thickness. We have reported previously that baPWV correlates with age in healthy subjects, a finding suggesting that the index reflects age-related changes in vascular stiffness. It has also been reported that eGFR is associated significantly with baPWV in Japanese patients, independent of traditional risk factors for cardiovascular disease. In addition, Kawamoto et al. reported that PWV increased progressively with decreases in eGFR in community residents.

Several reports have shown the usefulness of...
CAVI for the detection of atherosclerotic diseases. Ichihara et al. reported that CAVI reflects histological arterial fibrosis in hemodialysis patients and is a useful clinical marker for evaluating arterial stiffness in patients with kidney failure treated by hemodialysis; however, there are no reports on the correlation between CAVI and eGFR in community residents and, to the best of our knowledge, this is the first report demonstrating that CAVI negatively correlates independently with eGFR in the general population.

The reason why CAVI showed a negative relationship with GFR warrants discussion. Renal changes may directly affect the viscoelastic arterial properties of arteries. In addition, if a common factor interacts between large muscular-elastic arteries and the kidney, it seems likely that the extracellular matrix of vascular and renal cells is primarily involved. These changes may obviously affect several pathways that control sodium and water balance, the renin-angiotensin-aldosterone system, calcium-phosphate metabolism, and even vasoactive factors, such as nitric oxide, endothelin, and other compounds of endothelial origin.

There are several limitations when measuring CAVI as it cannot be measured accurately in patients with aortic stenosis, peripheral arterial disease or atrial fibrillation. An ankle-brachial pressure index (ABI) <0.95 has been reported to be the cut-off value for diminished accuracy of baPWV measurements, and accordingly, CAVI cannot be measured accurately if the ABI is less than 0.95. In addition, there is no evidence that CAVI predicts mortality and morbidity in cardiovascular diseases. At present, this is also one of the limitations when assessing CAVI. Further studies are needed to evaluate the clinical value of CAVI.

In conclusion, we showed that the new arterial stiffness index, CAVI, negatively correlated with eGFR independently, indicating that CKD in the general Japanese population is associated with increased arterial stiffness.

References

14) Hermans MM, Henry R, Dekker JM, Kooman JP,