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Original Article

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Clinical Significance of Cardio-Ankle Vascular Index as a Cardiovascular Risk Factor in Elderly Patients With Type 2 Diabetes Mellitus

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Abstract

Background: The cardio-ankle vascular index (CAVI) is a novel physiological marker of atherosclerosis that reflects systemic arterial stiffness. The aim of this study was to clarify the clinical significance of CAVI as a risk factor for cardiovascular diseases (CVDs) in elderly patients with type 2 diabetes mellitus.

Methods: This cross-sectional study enrolled 216 elderly (≥ 65 years) outpatients with type 2 diabetes mellitus who were undergoing antidiabetic treatment (96 males and 120 females; mean age, 75 ± 7 years (mean ± standard deviation)). Associations between CAVI and various clinical parameters were examined.

Results: CAVI was significantly higher in patients with a history of CVD than in those without a history of CVD (10.4 ± 1.4 vs. 9.5 ± 1.0, respectively, $P < 0.001$). There were significantly positive correlations between CAVI and various clinical parameters, such as skin autofluorescence ($r = 0.47$, $P < 0.001$), high-sensitivity cardiac troponin T levels ($r = 0.39$, $P < 0.001$), and reactive oxygen metabolite levels ($r = 0.28$, $P < 0.001$). Furthermore, multiple regression analyses revealed that these clinical parameters ((skin autofluorescence ($\beta = 0.30$, $P < 0.001$), high-sensitivity cardiac troponin T levels ($\beta = 0.18$, $P < 0.001$), reactive oxygen metabolite levels ($\beta = 0.15$, $P < 0.01$), and a history of CVD ($\beta = 0.19$, $P < 0.001$)) were independent variables when CAVI was used as a subordinate factor.

Conclusion: Findings of this study indicate that CAVI may be an important CVD risk factor in elderly patients with type 2 diabetes mellitus. Further investigations in a large number of prospective studies, including intervention therapies, are required to validate our results.

Keywords: Cardio-ankle vascular index; Cardiovascular risk factors; Skin autofluorescence; High-sensitivity cardiac troponin T; Oxidative stress; Elderly; Type 2 diabetes mellitus

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Introduction

Type 2 diabetes mellitus is one of the most important risk factors for cardiovascular diseases (CVDs). The population of elderly patients with type 2 diabetes mellitus has been increasing worldwide due to extended life expectancy [1-3]. Therefore, to prevent CVD, it is important to consider a diagnostic or therapeutic strategy for elderly patients with type 2 diabetes mellitus as well as for young-to-middle-aged patients with type 2 diabetes mellitus.

Arterial dysfunction is an important factor for CVD incidence. Among physiological markers of arterial function, the cardio-ankle vascular index (CAVI) is a novel marker of atherosclerosis, which reflects arterial stiffness in the aorta, femoral, and tibial arteries [4]. This stiffness parameter has been reported to be independent of blood pressure levels during measurements. Furthermore, some clinical studies have indicated that CAVI is significantly associated with macro- and microvascular complications in patients with type 2 diabetes mellitus [5, 6].

To the best of our knowledge, there are no reports regarding the clinical significance of CAVI as a CVD risk factor in elderly patients with type 2 diabetes mellitus. Therefore, this cross-sectional study attempts to clarify the clinical significance of CAVI as a risk factor for CVD in elderly patients with type 2 diabetes mellitus.

Materials and Methods

Patients

Patients in this study were enrolled between August 2015 and July 2017. The study population comprised 216 elderly outpatients (≥ 65 years) with type 2 diabetes mellitus, who were undergoing antidiabetic treatment at the Hitsumoto Medical Clinic. The patients included 96 (44.4%) males and 120 (55.6%) females, with a mean age of 75 ± 7 years (mean ± standard deviation). All participants provided informed consents, and the local Ethics Committee approved the study protocol.

CAVI measurement

CAVI was measured using a VaSera CAVI instrument (Fuku-

da Denshi, Tokyo, Japan) following the previously described methods [4]. Briefly, the brachial and ankle pulse waves were determined using inflatable cuffs with the pressure maintained between 30 and 50 mm Hg to ensure that the cuff pressure had a minimal effect on the systemic hemodynamics. Systemic blood and pulse pressures were simultaneously determined, with the participant in a supine position. CAVI was measured after the participants had rested for 10 min in a quiet room. The average coefficient of variation in CAVI has been shown to be less than 5%, which is small enough for clinical use and indicates that CAVI measurement has good reproducibility.

Estimation of cardiovascular risk factors

Various clinical parameters, such as classic CVD risk factors, blood glucose-related parameters, kidney function, brain natriuretic peptide (BNP) levels, high-sensitivity cardiac troponin T (hs-cTnT) levels, and oxidative stress were evaluated. Obesity was identified using body mass index, calculated as the weight (kg) divided by the squared height (m^2). Current smoking was defined as smoking at least one cigarette per day during the previous 28 days. The right brachial blood pressure was measured twice using a mercury sphygmomanometer, with participants in the sitting position. An average of two readings was used to determine the systolic and diastolic blood pressures. Hypertension was defined as a systolic blood pressure of ≥ 140 mm Hg, a diastolic blood pressure of ≥ 90 mm Hg, or any blood pressure value in those using antihypertensive medication. Blood samples were collected from the antecubital vein in the morning after 12 h of fasting. Total cholesterol and triglyceride levels were measured using standard enzymatic methods. Serum high-density lipoprotein cholesterol levels were measured by selective inhibition. Serum low-density lipoprotein cholesterol levels were calculated using the Friedewald equation [7]. Dyslipidemia was defined as low-density lipoprotein cholesterol levels of ≥ 140 mg/dL, high-density lipoprotein cholesterol levels of ≤ 40 mg/dL, triglyceride levels of ≥ 150 mg/dL, or on the basis of an ongoing treatment for dyslipidemia. Glucose and insulin levels were measured using the glucose oxidase method and an enzyme immunoassay, respectively. To measure insulin resistance, HOMA-IR was calculated using the following equation [8]: HOMA-IR = fasting glucose concentration (mg/dL) × fasting insulin concentration (μg/mL)/405. The hemoglobin A1c levels were expressed using the National Glycohemoglobin Standardization Program. Skin autofluorescence (AF), which reflects the accumulation of advanced glycation end products (AGEs) on the skin, was measured on the volar side of the forearm using a commercial instrument (AGE Reader™; DiagnOptics, Groningen, The Netherlands) as previously described [9]. Estimated glomerular filtration rate (eGFR) was calculated using the adjusted Modification of Diet in Renal Disease Study equation, which was proposed by the working group of the Japanese Chronic Kidney Disease Initiative [10]. BNP levels were measured using a commercial kit (SHIONOSPOT Reader; Shionogi & Co., Osaka, Japan), and hs-cTnT levels were also measured using a commercial kit (Roche Diagnostics, Switzerland) [11]. As a maker of oxidative stress *in vivo* [12], the reactive oxygen metabolites (d-ROMs) test was performed using a commercial kit (Diacron, Grosseto, Italy).

Table 1. Patient Characteristics

n (male/female)	216 (96/120)
Age (years)	75 ± 7
CVD, n (%)	73 (34)
Body mass index	23.5 ± 4.3
Current smoker, n (%)	46 (21)
Hypertension, n (%)	156 (72)
Systolic blood pressure (mm Hg)	141 ± 21
Diastolic blood pressure (mm Hg)	86 ± 13
Dyslipidemia, n (%)	130 (60)
Total cholesterol (mg/dL)	219 ± 42
LDL-cholesterol (mg/dL)	138 ± 38
Triglyceride (mg/dL)	145 ± 57
HDL-cholesterol (mg/dL)	49 ± 18
Fasting blood glucose (mg/dL)	134 ± 26
HOMA-IR	2.5 ± 1.3
Hemoglobin A1c (%)	7.2 ± 1.0
Skin autofluorescence (AU)	2.7 ± 0.6
eGFR (mL/min/1.73 m^2)	62.0 ± 19.5
Log-BNP (pg/mL)	1.7 ± 0.3
Log-hs-cTnT (ng/mL)	-2.1 ± 0.2
d-ROMs test (U. CARR)	365 ± 113
CAVI	9.8 ± 1.2
Medication	
Sulfonylurea, n (%)	151 (70)
Metformin, n (%)	43 (20)
DPP-4 inhibitor, n (%)	125 (58)
Insulin, n (%)	17 (8)
RAS inhibitor, n (%)	118 (55)
Statin, n (%)	95 (44)

Continuous values are mean ± SD. CVD: cardiovascular disease; LDL: low-density lipoprotein; HDL: high-density lipoprotein; HOMA-IR: homeostasis assessment insulin resistance; eGFR: estimated glomerular filtration rate; BNP: brain natriuretic peptide; hs- cTnT: high-sensitivity cardiac troponin T; d-ROMs: derivatives of reactive oxygen metabolites; CAVI: cardio-ankle vascular index; DPP: dipeptidyl peptidase; RAS: renin-angiotensin system.

Statistical analysis

A commercially available statistical software program (Stat View-J 5.0; HULINKS, Tokyo, Japan) was used for all statistical analyses. Data in the study are expressed as mean ± standard deviation. Between-group comparisons were performed using Student's *t*-test. Simple regression analysis was performed using the Spearman rank correlation, and a multi-

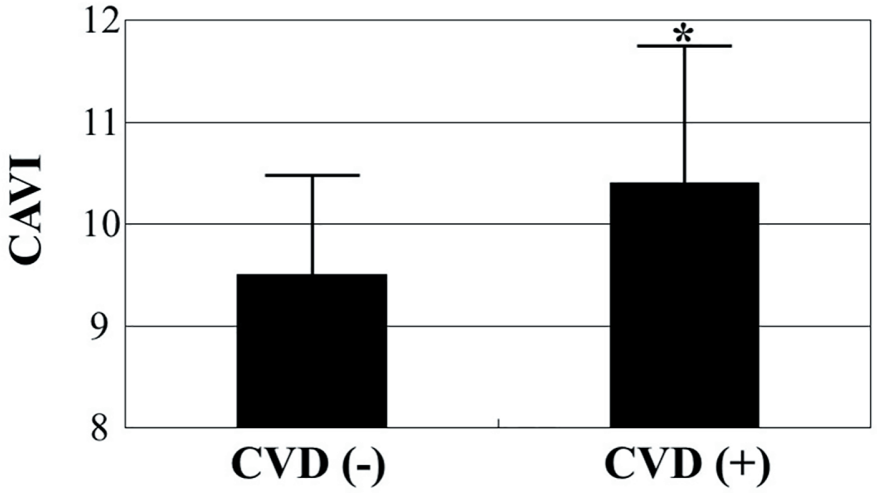

Figure 1. Comparisons of CAVI values between patients with and without CVD. CAVI was significantly higher in patients with CVD than in those without CVD (10.4 ± 1.4 vs. 9.5 ± 1.0, respectively, P < 0.001) even though mean age was similar between the two groups (76 ± 7 years vs. 75 ± 7 years, respectively). *P < 0.001 vs. CVD (-). CAVI: cardio-ankle vascular index; CVD: cardiovascular disease.

variate analysis was performed using multiple regression or multiple logistic regression analyses. A P-value of < 0.05 was considered statistically significant.

Results

Table 1 summarizes patient characteristics. In total, 73 (34%) patients had a history of CVD, such as coronary artery disease, cerebrovascular disease, or heart failure, upon admission. Mean CAVI level was 9.8 ± 1.2, ranging from 7.5 to 14.5. Figure 1 presents comparisons of CAVI levels between patients with CVD and those without CVD. CAVI was significantly higher in patients with CVD than in those without CVD (10.4 ± 1.4 vs. 9.5 ± 1.0, respectively, P < 0.001) even though mean age was similar between the two groups. Table 2 presents correlations between CAVI and various clinical parameters. Age, systolic blood pressure, HOMA-IR, skin AF, eGFR, BNP levels, hs-cTnT, and the d-ROMs test significantly correlated with CAVI.

Table 3 summarizes results of a multiple regression analysis with CAVI as a subordinate factor. Explanatory factors were selected by examining multicollinearity among the variables or by conducting a stepwise method. Skin AF, CVD, hs-cTnT, d-ROMs test, and age were identified as independent variables when CAVI was used as a subordinate factor. When coronary artery disease was used as an explanatory factor instead of CVD, coronary artery disease was also selected as an independent variable for CAVI as a subordinate factor (β = 0.14, P < 0.01). To illustrate the simple threshold of CAVI for detecting CVD or high hs-cTnT, participants were divided into three groups according to their CAVI values, and a multiple logistic regression analysis was performed (Fig. 2). Patients with a high CAVI (≥ 10) or a moderate CAVI (9.1 - 9.9) showed a significantly higher risk (OR, 7.3 (95% CI: 2.2 - 19.6), P < 0.001; OR, 2.2 (95% CI: 1.1 - 4.2), P < 0.05, respectively) of developing a CVD than those with a low CAVI (≤ 9). In contrast, patients with a high or moderate CAVI had a significantly higher risk (OR, 10.0 (95% CI: 2.3 - 29.4), P < 0.001; OR, 3.6 (95% CI: 1.3 - 9.6), P < 0.05, respectively) of having a high hs-cTnT level (≥ 0.014 ng/mL) than those with a low CAVI (≤ 9).

Discussion

Clinical studies have shown an association between CAVI and CVD including coronary artery disease [5, 13-15]. The results of this cross-sectional study also indicate that CAVI levels are higher in patients with CVD than in patients without CVD even when their mean age is similar. Furthermore, a history of CVD or coronary artery disease was identified as an independent variable for CAVI (as a subordinate factor), suggesting that CAVI is a considerable risk factor for CVD in elderly patients with type 2 diabetes mellitus.

Among glucose-related factors, only skin AF was independently associated with CAVI in our study. To the best of our knowledge, this is the first report of an independent association between skin AF and CAVI in patients with type 2 diabetes mellitus. Basic studies have reported that AGEs or their receptors can induce inflammation, oxidative stress, and calcification in vascular cells, such as endothelial or smooth muscle cells [16-18]. Moreover, clinical studies have also indicated a significant association between skin AF and physiological markers of arterial function [19, 20]. In contrast, AGEs are considered to be markers expressing "hyperglycemic memory" [21], and a study regarding the association between skin AF and HbA1c levels has reported that skin AF level was significantly associated with means of the last five and 10 HbA1c values [22]. Thus, taken together, all these results suggest that long-term glucose control is necessary to maintain arterial function in patients with type 2 diabetes mellitus.

Basic science and clinical studies support a role of oxidative stress in the pathogenesis of CVD in patients with un-

Table 2. Relationship Between CAVI and Various Clinical Parameters

	r	P value
Sex (female = 0, male = 1)	0.12	0.079
Age	0.19	< 0.001
Body mass index	0.04	0.566
Current smoker (no = 0, yes = 1)	0.11	0.105
Hypertension (no = 0, yes = 1)	0.13	0.059
Systolic blood pressure	0.30	< 0.001
Diastolic blood pressure	0.11	0.112
Dyslipidemia (no = 0, yes = 1)	0.08	0.288
Total cholesterol	-0.04	0.587
LDL-cholesterol	0.07	0.320
Triglyceride	-0.04	0.488
HDL-cholesterol	-0.10	0.139
Fasting blood glucose	0.11	0.105
HOMA-IR	0.14	< 0.05
Hemoglobin A1c	0.12	0.079
Skin autofluorescence	0.47	< 0.001
eGFR	-0.17	< 0.01
Log-BNP	0.13	< 0.05
Log-hs-cTnT	0.39	< 0.001
d-ROMs test	0.28	< 0.001
Sulfonylurea (no = 0, yes = 1)	0.03	0.501
Metformin (no = 0, yes = 1)	0.04	0.594
DPP-4 inhibitor (no = 0, yes = 1)	-0.06	0.320
Insulin (no = 0, yes = 1)	0.02	0.739
RAS inhibitor (no = 0, yes = 1)	-0.09	0.159
Statin (no = 0, yes = 1)	-0.10	0.142

r expressed correlation coefficient. CAVI: cardio-ankle vascular index; LDL: low-density lipoprotein; HDL: high-density lipoprotein; HOMA-IR: homeostasis assessment insulin resistance; eGFR: estimated glomerular filtration rate; BNP: brain natriuretic peptide; hs-cTnT: high-sensitivity cardiac troponin T; d-ROMs: derivatives of reactive oxygen metabolites; DPP: dipeptidyl peptidase; RAS: renin-angiotensin system.

derlying diabetes mellitus [23, 24]. Furthermore, there is a significant association between oxidative stress *in vivo* and various physiological markers of arterial function, including CAVI, in diabetic patients [25-29]. Our results also indicate that d-ROMs test (a marker of oxidative stress *in vivo*) is an independent factor for altered CAVI values in elderly patients with type 2 diabetes mellitus. Previous studies have reported that medications (antidiabetic, antihyperlipidemic, and antihypertension drugs) decrease oxidative stress *in vivo* [30-32], and improve CAVI values in these patients [25, 26, 33].

Additionally, a decrease in urinary 8-hydroxydeoxyguanosine (a marker of oxidative stress *in vivo*) showed a significant positive correlation with the decrease in CAVI values after an intervention therapy using statins or angiotensin receptor blockers in patients with type 2 diabetes mellitus [25, 26]. The results of this study indicate no significant correlation between the type of medication used and CAVI values; however, interventional studies are still required to examine the effectiveness of medications on oxidative stress and CAVI values in elderly patients with type 2 diabetes mellitus; we expect discoveries of new applications of antidiabetic, antihypertensive, and antihyperlipidemic drugs for the prevention of CVD.

Table 3. Multiple Regression Analysis for CAVI

Explanatory factor	β	P value
Skin autofluorescence	0.30	< 0.001
CVD	0.19	< 0.001
Log-hs-cTnT	0.18	< 0.01
d-ROMs test	0.15	< 0.01
Age	0.12	< 0.05
eGFR	-0.08	0.193
$R^2 = 0.32$		

CAVI: cardio-ankle vascular index; CVD: cardiovascular disease; hs-cTnT: high-sensitivity cardiac troponin T; d-ROMs: derivatives of reactive oxygen metabolites; eGFR: estimated glomerular filtration rate; β: standardized regression coefficient; R^2: coefficient of determination.

Hs-cTnT is a useful biomarker to evaluate myocardial injury in the clinical setting. In addition, epidemiological studies have reported that hs-cTnT is a predictor of CVD events in the general population and in patients with type 2 diabetes mellitus [34]. Clinical studies have indicated a significant association between physiological markers of arterial stiffness and hs-cTnT levels [35, 36]. Several studies have indicated that left ventricular dysfunction is significantly associated with myocardial injury [37]; furthermore, increases in aortic artery stiffness cause left ventricular dysfunction [38]. Therefore, we posit that the association between hs-cTnT levels and CAVI identified in this study reflects the presence of myocardial injury via left ventricular dysfunction due to an increased vascular resistance or afterload. Endothelial dysfunction plays a crucial role in the incidence of CVD. Increases in CAVI values may reflect endothelial dysfunction in patients with type 2 diabetes mellitus [39]. Endothelial dysfunction also causes left ventricular dysfunction or myocardial injury [40, 41]. Thus, the significant association between CAVI and hs-cTnT levels in this study may be partially explained by endothelial dysfunction following subclinical myocardial injuries.

It would be useful to set a target value for predicting CVD in the clinical setting. In this study, to clarify the clinical significance of CAVI measurements in elderly patients with type 2 diabetes mellitus, participants were divided into three groups on the basis of simple cut-off CAVI values and multiple logistic regression analysis was performed for detecting a correlation between CVD incidence and high hs-cTnT level (≥ 0.014 ng/mL), which has been reported to be the cut-off level for predictive CVD incidence rate [42]. Our results indicated that patients with CAVI values of ≥ 10 or 9.1 - 9.9 exhibited a significantly higher risk of CVD and higher hs-cTnT levels than those with CAVI values of ≤ 9. This result is consistent with a report that a CAVI value of ≥ 9 is a predictor of cardiovascular events in

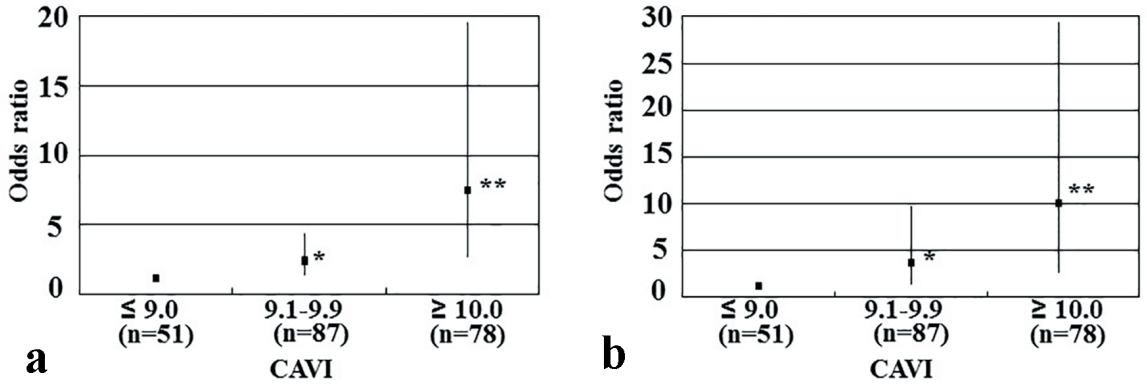

Figure 2. Results of multiple logistic regression analysis of CVD incidence or high hs-cTnT levels. (a) Subordinate factor is CVD incidence. Adjustment factors are skin autofluorescence, hs-cTnT, d-ROMs test, and age. (b) Subordinate factor is high hs-cTnT levels. High hs-cTnT was defined as hs-cTnT ≥ 0.014 ng/mL. Adjustment factors are skin autofluorescence, CVD, d-ROMs test, and age. *P < 0.05 vs. CAVI ≤ 9; **P < 0.001 vs. CAVI ≤ 9. CAVI: cardio-ankle vascular index; CVD: cardiovascular disease; hs-cTnT: high-sensitivity cardiac troponin T; d-ROMs: derivatives of reactive oxygen metabolites.

patients with type 2 diabetes mellitus [5]. Mean CAVI value in this study population was 9.8, and the results of this and other studies indicate that age is an independent factor for high CAVI values in patients with type 2 diabetes mellitus [43]. However, CAVI can be decreased by medication, and increasing physical activity is an independent factor for improving CAVI values in patients with diabetes mellitus [44]. Therefore, we believe that the risk of CVD incidence in elderly patients with type 2 diabetes mellitus can be reduced through interventions, such as the use of appropriate medications or an improvement in physical activity, with target CAVI values of > 9 - 10.

Limitations

This study has several limitations. First, medical treatments for diabetes mellitus, hypertension, and/or dyslipidemia may have affected the study results. Second, a substantial number of patients without CVD did not undergo modalities, such as angiography, computed tomography, magnetic resonance imaging, and echocardiography; therefore, asymptomatic CVD may have remained undetected. Third, the HOMA-IR has limitations as a marker of insulin resistance, particularly in patients with high blood glucose levels, and this study included patients with high fasting blood glucose levels. Therefore, additional studies using another accurate insulin resistance marker, such as a glucose clamp test, are warranted to evaluate the association between insulin resistance and CAVI. Finally, the study design was single-center cross-sectional study, and the sample size was relatively small. Additional prospective studies, including evaluations of interventional therapies, are required to clarify the clinical significance of CAVI as a risk factor for CVD in elderly patients with type 2 diabetes mellitus.

Conclusions

Findings of this study indicate that CAVI is a novel marker of arterial function, which may be an important CVD risk factor in elderly patients with type 2 diabetes mellitus. Further investigations in a large number of prospective studies, including intervention therapies, will be required to validate the results of this study.

Competing Interests

Author has no competing interests.

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Financial Disclosure

None.

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