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 (CA VI) is a novel physiological marker of atherosclerosis that reflects systemic arterial stiffness. The aim of this study was to clarify the clinical significance of CA VI 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 anti-diabetic treatment (96 males and 120 females; mean age, 75 ± 7 years (mean ± standard deviation)). Associations between CA VI and various clinical parameters were examined.

Results: CA VI 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 CA VI 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 (β = 0.30, P < 0.001), high-sensitivity cardiac troponin T levels (β = 0.18, P < 0.001), reactive oxygen metabolite levels (β = 0.15, P < 0.01), and a history of CVD (β = 0.19, P < 0.001)) were independent variables when CA VI was used as a subordinate factor.

Conclusion: Findings of this study indicate that CA VI 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

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 (CA VI) 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 CA VI 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 CA VI 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 CA VI 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-
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 (m²). 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.

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-
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 (76 ± 7 years vs. 75 ± 7 years, respectively). *P < 0.001 vs. CVD (-). CAVI: cardio-ankle vascular index; CVD: cardiovascular disease.

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.

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-
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 and improve CAVI values in these patients [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 2. Relationship Between CAVI and Various Clinical Parameters

| Explanatory factor | β     | 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   |

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; R²: coefficient of determination.

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   |

R² = 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; R²: coefficient of determination.

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 levels (≥ 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...
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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None.

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