Original Article
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Clinical Significance of the Cardio-Ankle Vascular Index in Postmenopausal Women With Hypercholesterolemia

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Abstract

Background: The cardio-ankle vascular index (CAVI) is a physiological indicator of arterial elasticity. However, limited information regarding the clinical significance of the CAVI in patients with hypercholesterolemia is available. This cross-sectional study aimed to elucidate the clinical significance of the CAVI for the primary prevention of cardiovascular disease (CVD) among postmenopausal women with hypercholesterolemia.

Methods: A total of 168 untreated postmenopausal hypercholesterolemic women (low-density lipoprotein cholesterol levels ≥ 140 mg/dL, mean age ± standard deviation, 63 ± 10 years) with no history of CVD events were enrolled. The CAVI was measured using commercial devices, after which, its relationships with various clinical parameters, such as carotid artery ultrasonography findings and CVD biomarkers, were examined.

Results: A significant positive correlation was observed between the CAVI and maximum intima-media thickness of the common carotid artery (max-C-IMT), which was evaluated using carotid artery ultrasonography (r = 0.49, P < 0.001). Regarding CVD biomarkers, the CAVI was significantly correlated with estimated glomerular filtration rate (r = -0.18, P < 0.001), high-sensitivity C-reactive protein (r = 0.36, P < 0.001), whole blood passage time as a marker of blood rheology (r = 0.41, P < 0.001), and skin autofluorescence as a marker of advanced glycation end products in tissues (r = 0.46, P < 0.001), although no significant correlation was noted between serum lipid parameters and the CAVI. Multiple regression analysis identified max-C-IMT (β = 0.35, P < 0.001), whole blood passage time (β = 0.18, P = 0.007), skin autofluorescence (β = 0.17, P = 0.011), and age (β = 0.16, P = 0.018) as variables independently associated with CAVI.

Conclusion: The present study indicated that the CAVI is an essential CVD risk factor among postmenopausal women with hypercholesterolemia. Moreover, impaired blood rheology and increase of skin autofluorescence were associated with elevated CAVI in such patients.

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Introduction

Hypercholesterolemia, especially increased low-density lipoprotein cholesterol (LDL-C), has been known as one of the most important risk factors for cardiovascular disease (CVD) [1-3]. Moreover, previous studies have reported that blood cholesterol levels increase progressively in postmenopausal-stage women [4]. However, several clinical studies on primary CVD events have indicated that cholesterol-lowering therapy is not always effective in women [5, 6]. In fact, several healthy elderly women have exhibited hypercholesterolemia alone without a history of CVD events in daily clinical practice. Thus, novel therapeutic strategies, apart from lowering LDL-C levels, should be considered to prevent primary CVD events in postmenopausal women with hypercholesterolemia.

The cardio-ankle vascular index (CAVI) is a physiological indicator of arterial elasticity [7]. Recent clinical studies have emphasized the clinical importance of the CAVI as a CVD risk factor [8-11]. Moreover, several researchers have reported associations between serum lipid parameters, including LDL-C levels, and the CAVI [12-14]. However, limited information regarding the clinical significance of the CAVI in patients with hypercholesterolemia has been available. Therefore, the present study sought to elucidate the clinical significance of the CAVI for primary CVD prevention in postmenopausal women with hypercholesterolemia.

Materials and Methods

Patients

Between January 2017 and December 2019, this study enrolled 168 untreated, postmenopausal, hypercholesterolemic women (LDL-C levels ≥ 140 mg/dL; mean age: 63 ± 10 years) without history of CVD, such as coronay artery disease, stroke, peripheral artery disease, and heart failure, who visited the Hitsumoto Medical Clinic. Previous studies have reported that various antihypertensive and antidiabetic drugs can affect

CAVI [15-18]. Thus, subjects receiving such medications were also excluded. This study was approved by the Ethics Committee of the Hitsumoto Medical Clinic (approval number: HMCR-2017-1) and was conducted in accordance with the ethical standards of the responsible agency for humans and the Declaration of Helsinki.

Measurement of the CAVI

CAVI was measured using commercially available medical equipment (VaSera CAVI device, Fukuda Denshi Co., Ltd, Tokyo, Japan), which have been reported in previous papers [7, 19]. In brief, CAVI is calculated using blood pressure and pulse wave velocity, basing its concept on the stiffness parameter β and Bramwell-Hill equations which is taken after lying on one's back for about 10 min in a quiet room [7]. In this study, the higher CAVI value on the left or right side was selected as the measurement, and patients with arteriosclerosis obliterans (ankle-brachial blood pressure ratio < 0.9) and/or chronic atrial fibrillation were excluded due to unstable measurements. A previous study indicated that the average coefficient of variation for CAVI was 3.8%, which is sufficiently small for clinical use, indicating good reproducibility [7].

Carotid artery ultrasonographic examination

Carotid ultrasonography was performed using a commercial device, the 3.0 MHz convex array probe (HI VISION Avius, Hitachi Medical Corporation, Tokyo, Japan). The maximum intima-media thickness (max-C-IMT) of the common caroditd artery (CCA), defined as the largest IMT measured at the CCA, was used as the surrogate marker for CVD events in this study since reports have indicated its use as a predictor of CVD events [20]. All measurements were performed by same experienced physician who was blinded to the other data of the subjects.

Evaluation of CVD risk factors

The degree of obesity was evaluated using body mass index, and a smoker was defined somone who smoked within the past month. Blood samples were collected after fasting for 12 h or more, wherein serum lipid, blood glucose, hemoglobin A1c (HbA1c), creatinine, high-sensitivity C-reactive protein (hs-CRP) levels, and whole blood passage time (WBPT) were measured using standard laboratory procedures. For lipid profiling, serum LDL-C concentrations were evaluated using the Friedewald formula [21], excluding subjects with serum triglyceride concentrations of ≥ 400 mg/dL given the formula's lack of reliability for these levels. Meanwhile, non-HDL-C levels were determined using this indicated formula (total cholesterol levels - HDL-C levels), and the triglyceride-glucose index (ln (fasting triglycerides (mg/dL) × fasting plasma glucose (mg/dL)/2)) was calculated as an insulin resistance marker [22]. Moreover, the estimated glomerular filtration rate (eGFR) was calculated using the Japanese diagnostic method [23]. In particular, blood rheology was measured using commercially available medical devices (MC-FAN HR300 rheometer, MCLaboratory Inc., Tokyo, Japan; width: 7.5 µm, depth 4.5 µm, length 30 µm), wherein themicrochannel transit time of 100 µL saline was first measured as a control before measuring the same parameters of the same volume of the patient's whole blood treated with 5% heparin [24, 25]. The subjects' WBPT was then determined after saline transit time correction, which previous reports have described as having good reproducibility [24]. Skin autofluorescence (AF), which reflects the amount of advanced glycation end products (AGEs) *in vivo* and is expressed as the average light internsity per nanometer of 300 - 420 nm, was also measured using commercially available medical devices given its reliability (AGEReader™; DiagnOptics, Groningen, The Netherlands) [19, 26]. With the patient seated, measurements were taken on the volar side of the lower arm, about 10 - 15 cm below the elbow. Of note, pentosidine, one of the major AGEs components obtained from major skin biopsies, has been reported to significantly correlate with skin AF [27].

Statistical analysis

Statistical processing was performed using MedCalc for Windows (version 14.8.1; MedCalc Software, Ostend, Belgium) and StatView J5.0 (HULINKS, Tokyo, Japan). Correlation coefficients were evaluated using the Pearson or Spearman rank-order correlation analysis, and multiple regression analysis was performed with CAVI or max-C-IMT as the dependent variable. For the explanatory variables, eight significant factors in the univariate analysis were selected (age, smoker, HbA1c, eGFR, hs-CRP, WBPT, skin AF, max-C-IMT) for CAVI, while seven explanatory variables (age, smoker, eGFR, hs-CRP, WBPT, skin AF, CAVI) for max-IMT were inserted and analyzed. A P-value of < 0.05 was judged to be statistically significant.

Results

Clinical characteristics

Table 1 summarizes the patients' clinical characteristics. Accordingly, they had a mean LDL-C of 165 ± 21 mg/dL, ranging from 140 to 271 mg/dL (median value: 159 mg/dL), but the CAVI had a mean value of 8.4 ± 1.2, ranging from 6.7 to 11.8 mg/dL (median value: 8.2).

Correlations between the CAVI and various clinical parameters

Table 2 summarizes the correlations between CAVI and various clinical parameters. CAVI had a significant positive correlation with max-C-IMT and with CVD risk factors including age, smoking habits, HbA1c, hs-CRP, WBPT, and skin AF. However, a significant negative correlation was observed between CAVI and eGFR. Accordingly, no significant correla-

Table 1. Baseline Clinical Characteristics of the Patients

n	168
Age (years)	63 ± 10
Body mass index (kg/m^2)	21.8 ± 4.0
Smoker, n (%)	12 (7)
Systolic blood pressure (mm Hg)	122 ± 12
Diastolic blood pressure (mm Hg)	75 ± 9
Pulse rate (/min)	68 ± 10
Total cholesterol (mg/dL)	258 ± 25
LDL-cholesterol (mg/dL)	165 ± 21
Triglyceride (mg/dL)	99 ± 52
HDL-cholesterol (mg/dL)	73 ± 13
Non-HDL-cholesterol (mg/dL)	185 ± 24
LDL-cholesterol/HDL-cholesterol	2.3 ± 0.6
Triglyceride/HDL-cholesterol	1.5 ± 0.9
Fasting blood glucose (mg/dlL)	91 ± 22
Hemoglobin A1c (%)	5.6 ± 0.9
Triglyceride-glucose index	8.2 ± 0.6
eGFR (mL/min/1.73 m^2)	67 ± 21
hs-CRP (mg/dL)	0.050 (0.020, 0.110)
Log-hs-CRP (mg/dL)	-1.4 ± 0.7
WBPT (s)	56 ± 13
Skin autofluorescence (AU)	2.4 ± 0.7
Max-C-IMT (mm)	0.9 ± 0.4
CAVI	8.4 ± 1.2

Continuous values are mean ± SD. hs-CRP levels are presented as the median (25%, 75%). LDL: low-density lipoprotein; HDL: high-density lipoprotein; eGFR: estimated glomerular filtration rate; hs-CRP: high-sensitivity C-reactive protein; WBPT: whole blood passage time; AU: arbitrary unit; Max-C-IMT: maximum intima-media thickness in the common carotid artery; CAVI: cardio-ankle vascular index.

tions were noted between CAVI and serum lipid parameters including LDL-C levels.

Multiple regression analysis

Table 3 shows the results of multiple regression analyses for CAVI and max-C-IMT. For the dependent variable CAVI, four explanatory variables (max-C-IMT, WBPT, skin AF, age) were selected as independent contributors (Table 3, section A). Meanwhile, for max-C-IMT as the dependent variable, three explanatory variables (CAVI, skin AF, age) were selected (Table 3, section B).

Discussion

The present study elucidated the clinical significance of the CAVI as a risk factor for CVD among postmenopausal women with hypercholesterolemia. Notably, the results of this study showed a close relationship between the CAVI and carotid atherosclerosis, with novel CVD risk factors, such as WBPT and skin AF, being independently associated with the CAVI. Nevertheless, no relationship had been observed between CAVI and serum lipid parameters including LDL-C.

Several clinical studies have reported that carotid atherosclerosis, which is evaluated through carotid artery ultrasonography, can indicate systemic atherosclerosis and be used as a predictor of CVD events [20, 28, 29]. However, several researchers have indicated significant associations between the CAVI and parameters of carotid artery ultrasonography [30-32]. The findings of the present study also indicated that the max-C-IMT, one of the parameters for carotid atherosclerosis, was significantly associated with the CAVI. Kokubo et al, who examined the relationships between three carotid atherosclerosis parameters (mean IMT, max-IMT, and max-C-IMT) and primary CVD events in a Japanese cohort, reported that the max-C-IMT was the most useful parameter for predicting CVD events, such as both ischemic heart disease and stroke [20]. Thus, the independent association between the CAVI and

Table 2. Correlations Between CAVI and Various Clinical Parameters

	r	P value
Age	0.33	< 0.001
Body mass index	0.01	0.902
Smoker (no = 0, yes = 1)	0.29	< 0.001
Systolic blood pressure	0.14	0.067
Diastolic blood pressure	-0.10	0.194
Pulse rate	0.08	0.256
Total cholesterol	0.00	0.949
LDL cholesterol	0.06	0.408
Triglyceride	0.00	0.980
HDL cholesterol	-0.09	0.236
Non-HDL cholesterol	0.06	0.449
LDL cholesterol/HDL cholesterol	0.08	0.257
Triglyceride/HDL cholesterol	0.00	0.954
Fasting blood glucose	0.11	0.142
Hemoglobin A1c	0.33	< 0.001
Triglyceride-glucose index	0.07	0.344
eGFR	-0.18	0.017
Log-hs-CRP	0.36	< 0.001
WBPT	0.41	< 0.001
Skin autofluorescence	0.46	< 0.001
Max-C-IMT	0.49	< 0.001

r expressed correlation coefficient. LDL: low-density lipoprotein; HDL: high-density lipoprotein; eGFR: estimated glomerular filtration rate; hs-CRP: high-sensitivity C-reactive protein; WBPT: whole blood passage time; Max-C-IMT: maximum intima-media thickness in the common carotid artery; CAVI: cardio-ankle vascular index.

Table 3. Multiple Regression Analyses for CAVI and Max-C-IMT

Explanatory factor	β	P value
A		
Max-C-IMT	0.35	< 0.001
WBPT	0.18	0.007
Skin autofluorescence	0.17	0.011
Age	0.16	0.018
Hemoglobin A1c	0.13	0.064
Log-hs-CRP	0.11	0.073
Smoker	0.06	0.319
eGFR	-0.05	0.503
B		
CAVI	0.45	< 0.001
Skin autofluorescence	0.17	0.023
Age	0.16	0.040
WBPT	0.14	0.092
eGFR	-0.13	0.124
Smoker	0.11	0.176
Log-hs-CRP	0.07	0.412

For section A: subordinate factor is CAVI. $R^2 = 0.48$, $P < 0.001$. For section B: subordinate factor is Max-C-IMT. $R^2 = 0.30$, $P < 0.001$. Explanatory factors were selected by significant variables in univariate analysis. Max-C-IMT: maximum intima-media thickness in the common carotid artery; WBPT: whole blood passage time; hs-CRP: high-sensitivity C-reactive protein; eGFR: estimated glomerular filtration rate; β: standardized regression coefficient; CAVI: cardio-ankle vascular index; R^2: coefficient of determination.

max-C-IMT observed herein suggests that the CAVI is an essential predictor for primary CVD events, such as ischemic heart disease and stroke, among postmenopausal women with hypercholesterolemia.

The association between the CAVI and LDL-C remains controversial. Several researchers have reported that the CAVI was significantly associated with LDL-C [12, 33, 34]. However, Homma et al reported that the CAVI was inversely associated with LDL-C among patients with early-stage atherosclerosis [35]. Conversely, other reports, including the present study, indicated no association between CAVI and LDL-C [36, 37]. Several studies have emphasized the importance of serum lipid parameters, apart from LDL-C, in the occurrence of CVD events [38-40]. However, the results presented herein indicated no significant association between various serum lipid parameters and the CAVI. Thus, the present study suggests the need for considering other factors contributing to arterial stiffness, aside from serum lipid parameters, among postmenopausal women with hypercholesterolemia.

Hemorheological impairments have been considered an essential factor in the incidence of CVD events, as well as the progression of atherosclerosis [41-43]. Moreover, recent clinical studies have elucidated that the WBPT estimated using the MC-FAN can be a considerable CVD risk factor [25, 43, 44]. However, several researchers have highlighted the importance of vasa vasorum flow in arterial function [45, 46]. Given that the microchannel formation of MC-FAN was 7 µm wide and 4.5 µm deep, the WBPT may perhaps have the ability to reflect capillary flow, including that within the vasa vasorum. To what extent collected peripheral venous blood represents vasa vasorum flow in the arterial wall remains unknown. One reason for the significant association between the WBPT and CAVI may be the increased arterial stiffness due to hemorheological impairment in the vasa vasorum. Several clinical studies have emphasized that smoking is one of the essential factors for increased WBPT [47, 48]. Moreover, smoking habits and their cessation have been reported to be associated with the CAVI [19, 49]. Although the number of smokers included herein was relatively low (7%), smoking habits were not identified as independent variables for the CAVI. Nevertheless, postmenopausal women with hypercholesterolemia who engage in smoking habits should be advised to cease the same from the perspective of blood rheology and arterial elasticity.

Basic studies have reported that AGEs or their receptors are associated with calcification and proliferation in vascular cells [50-52]. Moreover, the independent association between skin AF and the CAVI observed herein may have been attributed to the crucial role AGEs play in the progression of arterial stiffness among postmenopausal women with hypercholesterolemia. Several studies have reported that lifestyle habits, such as physical activity, smoking habits, and diet contents, were closely associated with skin AF [19, 53, 54]. Hence, healthy lifestyle habits are essential for maintaining low skin AF and arterial function. However, several reports have elucidated that statin, one of the antilipidemic agents, inhibits AGEs-induced vascular dysfunction [55, 56]. Thus, statins may be used for hypercholesterolemic patients with high skin AF, which can consequently decrease the risk for primary CVD events.

Limitations

Several limitations of this study should be acknowledged. First, a significant number of patients did not undergo definitive examinations for the diagnosis of CVDs, such as angiography, computed tomography, magnetic resonance imaging, and echocardiography, possibly missing asymptomatic CVD patients. Second, this was a single-center, cross-sectional study with a relatively small sample size. Large-scale studies, including interventional therapies, are desired to elucidate the clinical importance of CAVI as a risk factor for CVD in postmenopausal, hypercholesetrolemic women.

Conclusions

The present study indicated that the CAVI is an essential risk factor for CVD among postmenopausal women with hypercholesterolemia. Moreover, impaired blood rheology and increase of skin AF were closely associated with elevated CAVI among the same patients. Nevertheless, further large-scale prospective investigations that include intervention therapies are required to validate the results of the present study.

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None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Informed consent was obtained from all participants in this study.

Author Contributions

The author was involved in preparing the study design as well as in the acquisition, analysis, and interpretation of data.

Data Availability

The author declares that data supporting the findings of this study are available within the article.

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