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Association of Cardio-Ankle Vascular Index with Cardiovascular Disease Risk Factors and Coronary Heart Disease among Japanese Urban Workers and their Families

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Abstract

Purpose: Recently the cardio-ankle vascular index (CAVI) has been developed to represent the extent of arteriosclerosis in the artery from the aortic valve to the ankle. The aim of the study is to examine the association of CAVI scores with the established cardiovascular disease (CVD) risk factors and coronary heart disease (CHD).

Methods: Subjects were 9,881 men and 12,033 women of company employees and their families between 20 and 70 years of age and over who participated in CVD screening in Japan. The screening included measurements of CAVI, electrocardiogram, blood pressure, lipids, serum glucose, hemoglobin A1c, height, weight, and questions on smoking and drinking status. Persons having CHD were defined as those having history of CHD and/or having abnormal Q wave and/or ischemic change in ECG. After converting CAVI scores to binary variables (normal or abnormally high CAVI scores), logistic regression analysis was conducted.

Results: After adjusting for age, significant odds ratios (ORs) of abnormally high CAVI scores among men were found with diabetes mellitus (10.02, $p<0.001$), hypertension (8.37, $p<0.001$), triglycerides (2.76, $p<0.001$, for 150-199mg/dL and 2.85, $p<0.001$, for ≥200mg/dL, as reference:<150mg/dL), high density lipoprotein cholesterol (0.19, $p<0.001$, for 40-59mg/dL and 0.20, $p<0.001$ for ≥60mg/dL, as reference: <40mg/dL), body mass index (2.04, $p<0.001$, for <20, 2.31, $p<0.001$, for 28-29.9 and 3.37, $p<0.001$, for ≥30 as reference:20-22.9), and ex-smokers (1.20, $p<0.01$, as reference: non-smokers). Almost identical results were found among women, except a significant OR with current smokers (2.25, $p<0.001$). The significant association between CHD and abnormally high CAVI scores was found: OR=3.87, $p<0.001$ for men and 1.45, $p<0.01$ for women after adjusting for CVD risk factors.

Conclusions: Our results confirmed that CAVI scores are a reliable indicator of arteriosclerosis reflecting the extent of arterial stiffness and atherosclerosis in the major artery between the aortic valve and the ankle.

Keywords: Cardio-ankle vascular index; Arteriosclerosis; Arterial stiffness; Pulse wave velocity; Hypertension; Diabetes mellitus; Coronary heart disease

Abbreviations: CAVI: Cardio-Ankle Vascular Index; CVD: Cardiovascular Disease; CHD: Coronary Heart Disease; ORs: Odds Ratios; PWV: Pulse Wave Velocity; SD: Standard Deviation; TC: Total Cholesterol; TG: Triglycerides; HDL-C: High Density Lipoprotein Cholesterol; HbA1c: Glyco-Hemoglobin A1c; ECG: Electrocardiogram; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BMI: Body Mass Index; CI: Confidence Interval

Introduction

Several methods have been designed to assess arterial stiffness and arteriosclerosis. Among them, pulse wave velocity (PWV) [1-7], augmentation index [8], the stiffness parameter β [9,10], and carotid-femoral PWV [11] have been proposed as markers of arterial stiffness. In 2002, brachial-ankle PWV was proposed as a marker of vascular damage [12], and was reported to be a predictive factor of coronary artery disease [13]. However, PWV is known to depend on blood pressure at the time of measurement [14]. To overcome such a problem the cardio-ankle vascular index (CAVI) was developed with the objective to obtain an arterial stiffness index that is not affected by blood pressure at the time of measurement, and which reflects the stiffness or arteriosclerosis of a long artery from the aortic valve to the ankle [15].

Some researchers proposed to use CAVI scores as an indicator of atherosclerosis. Nakamura et al. found a strong association of CAVI with the presence of severity of coronary atherosclerosis based on their ordinal logistic regression analysis [16]. Kadota et al. suggested the use of CAVI as a screening tool for atherosclerosis based on their findings from the general population study of 1,014 adults showing strong significant associations of CAVI scores with carotid intima-media thickness and with homocysteine after adjustment for age and sex [17]. Thus, it is considered that CAVI scores reflect arterial stiffness, atherosclerosis and arteriosclerosis of which conditions are overlapping and inseparable. We use CAVI to represent the extent of arteriosclerosis in this paper but it is inclusive of arterial stiffness and atherosclerosis.

To practically use CAVI as a diagnostic tool for determining the

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extent of arteriosclerosis, Namekata et al. have recently published the baseline CAVI scores by age and gender among cardiovascular disease (CVD) risk-free persons, and then have found that the age- and sex-specific average CAVI scores were significantly greater among CVD high-risk persons than among CVD risk-free persons [18]. It implies that the extent of arteriosclerosis is more advanced among persons with CVD risk factors than among persons without such risk factors.

In our present study all CAVI scores were converted to categorical scores based on the baseline CAVI scores of the CVD risk-free persons in our previous study [18]. Such conversion enabled us to examine the association of CAVI categorical scores with CVD risk factors and with coronary heart disease (CHD) among Japanese urban workers and their families.

Methods

Study subjects

Subjects for the study were recruited from January 2006 to May 2009 through the screening program at Japan Health Promotion Foundation which has been conducting cardiovascular disease and cancer screening throughout major cities in Japan. Subjects were company employees and their family members: 9,881 men and 12,033 women between 20 and 70 years of age and over (Table 1). The study was approved by the Institutional Review Board and all subjects gave their consent to participate in the study.

Measuring cardio-ankle vascular index

CAVI, a stiffness and arteriosclerosis indicator of thorax, abdomen, common iliac, femoral and tibial arteries, is measured by VaSera VS-1000 manufactured by Fukuda-Denshi Company, LTD (Tokyo, Japan).

Figure 1 illustrates how PWV is measured [19]. The scale conversion from PWV to CAVI is performed by the following formula:

$$CAVI=a\{(2\rho/\Delta P) \times \ln(P_s/P_d)PWV^2\} + b$$

where P_s and P_d are systolic and diastolic blood pressure values, respectively, PWV is the pulse wave velocity between heart and ankle, ΔP is P_s-P_d, ρ is blood density, and a and b are constants. This equation was derived from Bramwell-Hill's equation [20] and stiffness parameter [21]. Scale conversion constants are determined so as to match CAVI with PWV by Hasegawa's method [22]. All these measurements and calculations are automatically made in VaSera VS-1000. More theoretical details of CAVI method are available elsewhere [15,19].

To examine the association of CAVI with CVD risk factors and CHD, CAVI scores of screening participants were stratified according to Table 2. These were constructed based on means and standard deviations in "Table 2 - Comparison of average cardio-ankle vascular index (CAVI) scores of CVD risk-free subjects by age and gender" from the paper by Namekata et al. [18]. All CAVI scores were converted to 1 for scores less than (mean – one standard deviation (SD)), 2 for scores between (mean – 1SD) and (mean - ½SD), 3 for scores between (mean - ½SD) and mean, 4 for scores between mean and (mean + ½SD), 5 for scores between (mean+ ½SD) and (mean + 1SD), and 6 for scores greater than (mean + 1SD). Based on distribution of CAVI scores by CHD status, there was a substantial increase in CHD cases from CAVI scores ≤5 to 6: prevalence of CHD corresponding to codes 1,2,3,4, 5 and 6 was 1.9%, 1.2%, 1.8%, 2.8%, 2.7% and 4.6%, respectively, among men and was 2.1%, 2.8%, 2.6%, 3.8%, 2.7% and 4.7%, respectively, among women.Thus, we coded CAVI scores as a binary variable: 1 for codes 1-5 combined and 2 for code 6 as abnormally high CAVI scores in order to conduct logistic regression analysis.

Clinical measurements

The methods to measure other clinical indicators were adopted based on the guidelines established by Japan Atherosclerosis Society, Japan Diabetes Society and Japan Society of Hypertension [23-25]. Blood was drawn from the subjects after a 12 hour-fast. The following measurements were made: total cholesterol (TC) and triglycerides (TG) by enzymatic assay; high density lipoprotein cholesterol (HDL-C) by modified enzymatic method; glucose by hexokinase glucose-6-phosphate dehydrogenate assay; and glyco-hemoglobin A1c (HbA1c) by latex agglutination. To identify subjects with ischemic changes, outputs from electrocardiogram (ECG) were classified by Minnesota code [26] which has been internationally and uniformly used in the epidemiology setting. Persons having CHD were defined as those having history of angina pectoris and/or myocardial infarction and/or as those who showed ECG codes: 1-1-1 to 1-1-3 (abnormal Q wave), and/or 4-1 to 4-3 (ischemic change). Persons having high blood pressure were defined as those taking hypertension drugs and/or as those whose systolic blood pressure (SBP) was higher than 160mmHg and/or diastolic blood pressure (DBP) was higher than 100mmHg. Persons with diabetes mellitus were defined as those who were previously diagnosed with diabetes mellitus, as those taking diabetes

Age in year	Males		Females	
	Number	Per cent	Number	Per cent
≤29	1066	10.8	905	7.5
30-39	2659	26.9	3089	25.7
40-49	2396	24.2	3127	26.0
50-59	2236	22.6	3578	29.7
60-69	1247	12.6	1148	9.5
≥70	277	2.8	186	1.5
Total	9881	100.0	12033	100.0

Table 1: Study participants by age and sex.

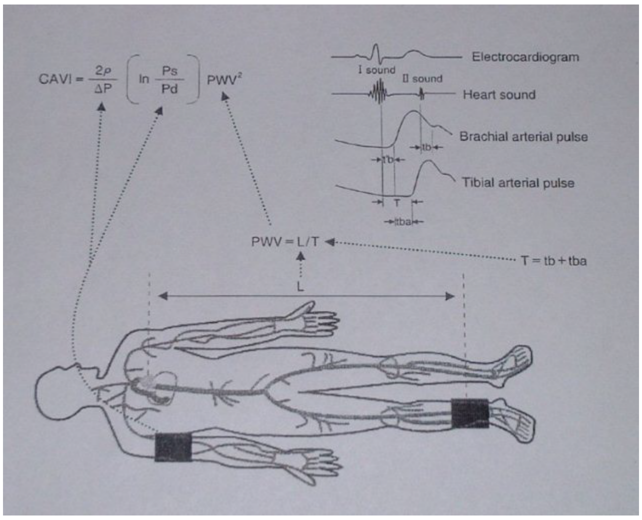

Figure 1: Illustration of CAVI measurement. A subject is placed in supine position and electrocardiogram and heart sound are monitored. PWV between heart and ankle is obtained by L/T where L is the distance from the aortic valve to the ankle, and T is the time during which PWV propagates from the aortic valve to the ankle (or the sum of tb and tba in place of t'b and tba, because t'b and tb are theoretically equal: tba is the time between the rise of the brachial pulse wave and the rise of the ankle pulse wave, tb is the time between the aortic valve's closing sound and the notch of the brachial pulse wave, and t'b is the time between the aortic valve's opening sound and the rise of the brachial pulse wave).

mellitus medication and/or as those whose serum glucose were higher than 126mg/dL and/or those whose HbA1c were higher than 6.2% in Japan Diabetes Society value. It is approximately equivalent to 6.6% in National Glycohemoglobin Standardization Program (NGSP) value.

Questionnaire

A short self-administered questionnaire was filled out by each subject during the screening. It contains questions on medical history and lifestyle factors such as smoking habit (non-smokers, ex-smokers, and current smokers) and frequency of alcohol consumption (not drinking, 1-2 times/week, 3-4 times/week, 5-6 times/week, and every day).

Statistical methods

In addition to the use of descriptive statistics, logistic regression method was used to examine the association of CAVI scores with CVD risk factors and CHD. Statistical Packages for Social Sciences version 18 was used for data analysis.

Results

Characteristics of study participants are shown in Table 3 for males and Table 4 for females. Means of CAVI scores among men increased from 6.38 for 29 years of age and younger to 9.43 for 70 years of age and older, while scores among women increased from 6.21 for 29 years of age and younger to 9.10 for 70 years of age and older. Differences in CAVI scores between genders ranged from 0.17 for 29 years of age and younger to 0.33 for 70 years of age and older, indicating that the average of CAVI scores for men advanced about five years faster than for women. It is observed that the means for both systolic and diastolic blood pressure linearly increased as ages advanced among women, while the same trend is seen for systolic blood pressure but not for diastolic blood pressure among men. Such an increasing trend with age was not observed in lipids, serum glucose and body mass index (BMI) among men, while an increasing trend in TC, TG, and serum glucose levels was observed among women as ages advanced. We observed that prevalence of CHD and diabetes linearly increased with advancing ages in both genders. We also observed that prevalence of abnormally high CAVI scores increased with advancing ages in women, while the highest prevalence of abnormally high CAVI scores (24.7%) appeared in 50-59 years of ages among men. Greater prevalence of drinkers and smokers was observed in men than in women. (Table 3, 4)

Table 5 shows odds ratios (ORs) of abnormally high CAVI scores for each CVD risk factor after making adjustment for age among men. Significantly high ORs were found in persons having hypertension, 8.37 (confidence interval: 7.32-9.56), and in persons with diabetes mellitus, 10.02 (CI: 8.74-11.49). All other CVD risk factors have significant ORs ranging 1.20 (CI: 1.05-1.36) in ex-smokers to 3.37 (CI: 2.72-4.18) in BMI≥30. Only HDL-C shows negative or protective ORs: 0.19 (CI: 0.17-0.23) for persons with 40-59mg/dL and 0.20 (CI: 0.17-0.24) in persons with ≥60mg/dL, as compared with the reference category of HDL-C<40mg/dL.

age		Mean(M)	SD	M-1SD	M-0.5SD	M+0.5SD	M+1SD
20-29	Males	6.69	0.70	5.99	6.34	7.04	7.39
	Females	6.57	0.66	5.91	6.24	6.90	7.23
30-39	Males	7.12	0.68	6.44	6.78	7.46	7.80
	Females	6.79	0.63	6.16	6.48	7.11	7.42
40-49	Males	7.59	0.70	6.89	7.24	7.94	8.29
	Females	7.29	0.66	6.63	6.96	7.62	7.95
50-59	Males	8.07	0.76	7.31	7.69	8.45	8.83
	Females	7.82	0.70	7.12	7.47	8.17	8.52
60-69	Males	8.73	0.81	7.92	8.33	9.14	9.54
	Females	8.26	0.72	7.54	7.90	8.62	8.98
70+	Males	9.35	1.00	8.35	8.85	9.85	10.35
	Females	8.71	0.75	7.96	8.34	9.09	9.46

Table 2: Baseline values of CAVI scores.

Variables	Age	≤29	30-39	40-49	50-59	60-69	≥70
CAVI scores	mean±SD	6.38±0.64	7.00±0.64	7.53±0.67	8.19±0.78	8.71±0.81	9.43±0.85
Systolic Blood Pressure	mean±SD	119±11	122±13	126±14	132±16	133±17	136±16
Diastolic Blood Pressure	mean±SD	69±9	74±10	79±11	83±11	81±10	79±11
Total Cholesterol(mg/dL)*	mean±SD	186±33	204±34	214±36	213±34	211±32	209±34
HDL-C(mg/dL)	mean±SD	62±15	59±16	60±17	61±18	63±18	62±18
Triglycerides(mg/dL)	mean±SD	95±77	135±103	158±169	147±113	126±72	122±81
Body Mass Index(kg/m^2)	mean±SD	22.3±3.5	24.0±3.7	24.2±3.2	24.0±2.9	23.7±2.8	23.5±3.0
Serum Glucose(mg/dL)*	mean±SD	84.6±12.6	87.7±13.2	92.4±20.8	99.3±27.5	99.1±24.7	99.9±25.1
Coronary Heart Disease	prevalence (%)	0.2	0.5	1.2	3.5	6.9	12.3
Diabetes Mellitus	prevalence (%)	0.2	1.7	4.0	9.5	12.0	15.2
Abnormally High CAVI	prevalence (%)	6.1	11.4	14.0	24.7	16.1	13.7
Drinkers	prevalence (%)	61.8	73.4	77.9	79.3	77.4	66.8
Ex-smokers	prevalence (%)	11.2	18.7	25.4	31.6	35.9	37.2
Smokers	prevalence (%)	55.4	51.9	48.4	41.2	28.5	18.1

Note: Number of persons having total cholesterol measurements was 5193 and number of persons having serum glucose measurements was 8705. Abnormally high CAVI scores were defined as CAVI scores greater than (mean + 1SD)

Table 3: Characteristics of study participants: Males.

Variables	Age	≤29	30-39	40-49	50-59	60-69	≥70
CAVI scores	mean±SD	6.21±0.57	6.74±0.60	7.21±0.64	7.87±0.71	8.41±0.77	9.10±0.80
Systolic Blood Pressure	mean±SD	109±10	113±12	119±14	127±16	130±16	135±16
Diastolic Blood Pressure	mean±SD	63±8	66±9	71±10	75±11	76±10	77±10
Total Cholesterol (mg/dL)*	mean±SD	180±28	194±32	209±34	233±36	236±35	233±42
HDL-C (mg/dL)	mean±SD	76±15	76±17	77±18	76±19	75±19	73±17
Triglycerides (mg/dL)	mean±SD	59±31	70±57	79±49	96±55	105±55	108±54
Body Mass Index (kg/m²)	mean±SD	20.4±3.0	20.9±3.1	21.7±3.2	22.2±3.2	22.3±3.0	22.9±3.6
Serum Glucose (mg/dL)*	mean±SD	82.2±7.6	83.2±7.4	86.1±9.9	88.9±15.1	90.4±15.9	91.0±12.0
Coronary Heart Disease	prevalence (%)	0.4	1.2	1.9	5.0	6.4	14.5
Diabetes Mellitus	prevalence (%)	0.2	0.4	1.3	3.1	4.4	6.5
Abnormally High CAVI	prevalence (%)	5.9	15.0	12.0	21.3	24.5	33.9
Drinkers	prevalence (%)	50.4	45.5	43.4	36.2	33.4	28.0
Ex-smokers	prevalence (%)	10.4	13.3	9.1	5.8	6.1	4.8
Smokers	prevalence (%)	22.8	15.6	11.7	8.5	5.7	3.8

Note: Number of persons having total cholesterol measurements was 9706 and number of persons having serum glucose measurements was 5955. Abnormally high CAVI scores were defined as CAVI scores greater than (mean + 1SD)

Table 4: Characteristics of study participants: Females.

CVD risk factors	Reference	Covariates	persons at risk	Odds ratio		lower CI	upper CI
Hypertension	No	Yes	755	8.37	***	7.32	9.56
Diabetes Mellitus	No	Yes	548	10.02	***	8.74	11.49
Total cholesterol	<200mg/dL	200-239	2128	1.01		0.87	1.18
		≥240	862	1.88	***	1.56	2.26
HDL-C	<40mg/dL	40-59	4859	0.19	***	0.17	0.23
		≥60	4369	0.20	***	0.17	0.24
Triglycerides	<150mg/dL	150-199	1319	2.76	***	2.43	3.14
		≥200	1609	2.85	***	2.53	3.22
Body Mass Index	20-22.9	<20	1012	2.04	***	1.72	2.41
		23-24.9	2453	0.94		0.82	1.08
		25-27.9	2205	0.90		0.78	1.04
		28-29.9	563	2.31	***	1.89	2.83
		≥30	429	3.37	***	2.72	4.18
Drinking	Non-drinkers	1-2 times/week	2151	1.12		0.96	1.31
		3-4 times/week	1183	1.81	***	1.53	2.14
		5-6 times/week	1216	1.87	***	1.58	2.21
		every day	2852	1.22	**	1.06	1.40
Smoking	Non-smokers	Current smokers	4457	1.05		0.94	1.19
		Ex-smokers	2481	1.20	**	1.05	1.36

Note: * p<0.05, **p<0.01, ***p<0.001, CI: Confidence Interval
Total number of persons at risk for total cholesterol is 5193

Table 5: Estimated risk for having abnormally high CAVI scores after making adjustment for age: Males.

Almost the same trend among females was found as shown in Table 6, except that significantly high ORs in both current smokers, 2.25 (CI: 1.98-2.56) and ex-smokers, 2.42 (CI: 2.11-2.79) when non-smokers were used as reference.

Table 7 shows crude and adjusted odds ratios (ORs) of coronary heart disease in association with abnormally high CAVI scores. We observed 26.79 of crude OR, 10.47 of OR adjusted for age and 3.87 of OR when making adjustment for other CVD risk factors including diabetes mellitus, hypertension, HDL-C, BMI, drinking and smoking among men, while women's ORs were 20.25 for crude, 3.70 for age-adjusted, and 1.45 for making other CVD risk factors adjusted. Because age is confounded with both CHD and CAVI scores, OR drastically decreased after age was included in logistic regression analysis. Adjusting for other CVD risk factors further made OR smaller, but it retained significance.

Discussion

In order to accept CAVI as a good indicator of arteriosclerosis, we need to achieve three objectives: (1) showing that age-sex-specific average CAVI scores are significantly higher in the CVD high-risk group than in the CVD risk-free group; (2) showing that CAVI scores are significantly associated with most of the established CVD risk factors; and (3) showing that CAVI scores are significantly associated with arteriosclerotic or atherosclerotic disease. We accomplished the first objective in the previous study [18] in which average CAVI scores in each of CVD high-risk groups (hypertension, hypercholesterolemia and hypertriglyceridemia, hyperglycemia, ischemic changes in ECG, retinal artery changes, and all high risk groups combined) were significantly higher than the baseline CAVI scores from the CVD risk-free group after 40 years of age in both genders. The second and third objectives were achieved by our present study and were shown in Tables 5, 6 and 7, respectively.

CVD risk factors	Reference	Covariates	persons at risk	Odds ratio		lower CI	upper CI
Hypertension	No	Yes	477	6.57	***	5.67	7.61
Diabetes	No	Yes	229	8.42	***	7.22	9.81
Total cholesterol	<200mg/dL	200-239	3793	1.13		0.99	1.29
		≥240	2276	1.33	***	1.15	1.54
HDL-C	<50	50-59	1667	0.47	***	0.38	0.57
		≥60	9722	0.33	***	0.28	0.39
Triglycerides	<150mg/dL	150-199	608	2.89	***	2.46	3.40
		≥200	402	4.30	***	3.60	5.14
Body Mass Index	20-22.9	<20	3992	1.43	***	1.28	1.60
		23-24.9	1677	1.17	*	1.01	1.35
		25-27.9	1091	0.98		0.82	1.17
		28-29.9	274	2.60	***	2.01	3.38
		≥30	272	2.45	***	1.87	3.20
Drinking	Non-drinkers	1-2 times/week	2473	1.05		0.93	1.19
		3-4 times/week	940	1.81	***	1.54	2.13
		5-6 times/week	654	2.50	***	2.10	2.99
		every day	884	2.06	***	1.75	2.41
Smoking	Non-smokers	Current smokers	1430	2.25	***	1.98	2.56
		Ex-smokers	1080	2.42	***	2.11	2.79

Note: * p<0.05, **p<0.01, ***p<0.001, CI: Confidence Interval
Total number of persons at risk for total cholesterol is 9706

Table 6: Estimated risk for having abnormally high CAVI scores after making adjustment for age: Females.

	Males				Females			
	odds ratio		confidence interval		odds ratio		confidence interval	
			lower	upper			lower	upper
(1) Crude	26.79	***	24.07	29.81	20.25	***	18.45	22.21
(2) Adjusted for age	10.47	***	8.93	12.27	3.70	***	3.18	4.31
(3) Adjusted for CVD risk factors	3.87	***	3.06	4.91	1.45	**	1.16	1.82

Note: (1) Only abnormally high CAVI scores were included as a covariate in logistic regression analysis.
(2) Age breakdowns (<50, 50-59, 60-69, ≥70 years of age) were added to logistic regression analysis.
(3) Other CVD risk factors (diabetes, hypertension, HDL-C, BMI, drinking, and smoking) were further added to logistic regression analysis.
* p<0.05, **p<0.01, ***p<0.001

Table 7: Crude and adjusted odds ratios of coronary heart disease in association with abnormally high CAVI scores among Japanese urban workers and their families.

Compared with non-diabetics, estimated risk of having abnormally high CAVI scores was 10 times higher among male diabetics and 8 times higher among female diabetics. The findings are consistent with significantly higher CAVI scores observed among diabetics [18,27] and significantly high odds ratios of abnormally high PWV values (5.65 among men and 2.47 among women) in association with diabetes mellitus reported by Namekata et al. [28].

Our results show that estimated risks of having abnormally high CAVI scores were 8 times higher among hypertensive men and 6.5 times higher among hypertensive women than among non-hypertensive persons. This is consistent with significant odds ratios of abnormally high PWV values (2.0 among men and 1.94 among women) in association with hypertension reported by Namekata et al. [28].

Hyperlipidemia per se does not immediately increase the stiffness of arterial wall. After accumulation of cholesterol in the lipid pool, oxidative stress generates oxysterol, which is strongly toxic and enhances inflammation, followed by the onset of atherosclerosis [19]. Our results show that higher concentrations of triglycerides (≥150mg/dL) were positively associated with abnormally high CAVI scores in both genders, while higher HDL-C levels (≥40mg/dL for men and ≥50mg/dL for women) were negatively associated with abnormally high CAVI scores, indicating that high HDL-C levels prevent advancement of arteriosclerosis. Namekata et al. reported that TC/HDL-C ratio ≥4.5 increased an estimated risk of having abnormally high PWV values to 1.32 among men and 1.98 among women [28]. Thus, persons with lipid abnormality possibly advance the extent of arteriosclerosis.

Visceral fat accumulation has been suggested to induce glucose intolerance, hypertension, and dyslipidemia such as low HDL-cholesterol and hypertriglyceridemia [29]. These conditions are believed to be due to insulin resistance. High CAVI scores are associated with obesity and metabolic syndrome [30]. Our study results show that the association between BMI and abnormally high CAVI scores was not linear but U-shape curve when 20-22.9 of BMI was used as the reference category. There is no doubt that the persons with BMI ≥28 have an elevated risk of having abnormally high CAVI scores in both genders, but it is important to recognize that the extremely slim persons (BMI <20) have significantly higher risk of having abnormally high CAVI scores in both genders of Japanese urban workers and their families. The impact of the slim population on cardiovascular disease cannot be ignored in Japan, because 10% of men and 30% of women fall in the slim category in our study sample.

Kubozono et al. [31] reported that CAVI was high in smoking subjects. Noike et al. [32] reported that smoking increases CAVI. Despite high prevalence of Japanese male smokers (45.1% in our study sample), odds ratio of abnormally high CAVI scores was not significant among male current smokers (OR=1.05) but was significant among ex-smokers (OR=1.20). Our results for women showed significantly high odds ratios of abnormally high CAVI scores in both current smokers (OR=2.25) and ex-smokers (OR=2.42). There might be gender difference in terms of effects of smoking on the cardiovascular system in the Japanese population.

Namekata et al. found significantly reduced odds ratios of having abnormally high PWV values for current drinkers and ex-drinkers of both genders, as compared to non-drinkers among Japanese Americans [28]. However, our present results showed elevated odds ratios of having abnormally high CAVI scores for persons drinking more than 3-4 times per week in both genders. The difference in such study results might be partly caused by the difference in length of artery measured between PWV method by Hasegawa [22] and CAVI method [15,19].

As seen in Table 7, we have shown that abnormally high CAVI scores were significantly associated with coronary heart disease, one of the atherosclerotic or arteriosclerotic diseases. Our findings are supported by Nakamura et al. report [16] that CAVI scores increases as the number of vessels with stenosis (>75%) increases. They also found that a stepwise ordinal logistic regression analysis including mean intima-media thickness, maximum intima-media thickness, plaque score and CAVI as independent variables identified only CAVI as the one significantly associated with the severity of coronary atherosclerosis.

A limitation of this study is that it is an observational and cross-sectional study. The strengths of this study are having the large sample size and including many clinical and behavioral factors as independent variables with enough statistical power.

In conclusion, our results show that CAVI scores were significantly associated with the established CVD risk factors and coronary heart disease, one of the arteriosclerotic diseases. We confirmed that CAVI scores are a reliable indicator of arteriosclerosis reflecting the extent of arterial stiffness and atherosclerosis in the major artery from the aortic valve to the ankle.

Authors' Contributions

TN, K. Suzuki and K. Shirai conceived and designed the study. K. Suzuki and NI acquired the data. TN and MN performed statistical analyses. TN drafted the manuscript, and all other authors revised critically and approved the final manuscript.

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