Original Article

Lipid Parameters are Independently Associated with Cardio−Ankle Vascular Index (CAVI) in Healthy Japanese Subjects

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Aim: To investigate the associations of conventional lipid parameters with arterial stiffness assessed by cardio−ankle vascular index (CAVI).

Methods: A retrospective cross-sectional study was conducted in 23,257 healthy Japanese subjects (12,729 men and 10,528 women, aged 47.1 ± 12.5 years, body mass index (BMI) 22.9 ± 3.4 kg/m^2) who underwent health screening between 2004 and 2006 in Japan.

Results: Male subjects had significantly higher BMI, CAVI and triglycerides (TG), and lower high-density lipoprotein cholesterol (HDL-C) compared to female subjects. After adjusting for confounders, including gender, age, systolic blood pressure and BMI identified by multiple regression analysis, adjusted CAVI was lower in normolipidemic than in dyslipidemic subjects. Among dyslipidemic subjects, those with hypertriglyceridemia had higher adjusted CAVI. A trend test detected linear relations between adjusted CAVI and all the conventional lipid parameters throughout the entire range of serum levels. After adjusting for confounders, logistic regression models showed that all lipid parameters contributed independently to high CAVI ($\geq$ 90th percentile). Receiver−operating−characteristic analysis determined reliable cut-off values of 93 mg/dl for TG (area under the curve, AUC= 0.735), 114 mg/dl for low-density lipoprotein cholesterol (AUC=0.614) and 63 mg/dl for HDL-C (AUC=0.728) in predicting high CAVI. These cut-off values were confirmed to independently predict high CAVI in a bivariate logistic regression model.

Conclusion: The present study demonstrated independent contribution of conventional lipid parameters to CAVI, indicating a possible association of lipid parameters with early vascular damage.

Key words: Lipid, Cardio-ankle vascular index (CAVI), Arterial stiffness

Introduction

Dyslipidemia is characterized by elevated triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C) as well as decreased high-density lipoprotein cholesterol (HDL-C) levels, and has been recognized as an independent risk for cardiovascular diseases (CVD)[1-5]. Moreover, it is common knowledge that atherogenesis is accelerated in patients with dyslipidemia compared to that of the healthy general population[6]. From the perspective of prevention and treatment of CVD, LDL-C level of 140 mg/dl is proposed to be the reference value when screening Japanese individuals for hyper-LDL cholesterolemia. Furthermore, targeting a TG level <150 mg/dl and an HDL-C level ≥40 mg/dl is recommended[7]. The progression of atherosclerosis may be decelerated, stopped or even reversed by intensive treatment targeting the main cardiovascular risk factors, primarily dyslipidemia[8, 9]. On the other hand, even if adequate control of dyslipidemia is achieved, residual cardiovascular risk is not completely eliminated[10], suggesting that achieving the current target lipid levels is inadequate. Additionally, the pathophysiological relationship between the vascular composition and individual lipid parameters have not been clarified.

In the management of CVD risks, early detection of atherosclerosis using simple, quantitative and non-invasive assessments is needed to initiate early treatment and prevent further complications and cardiovascular events. Several studies have reported that increased arterial stiffness is associated with increased morbidity and mortality of CVD[11, 12]. Cardio−ankle vascular index (CAVI) determination is a non-invasive method for detecting preclinical condition of systemic arterial stiffness. CAVI has been reported to be essentially independent of blood pressure (BP) and based on a stiffness parameter beta[13-16]. This parameter has adequate reproducibility for clinical use[17-22] and is associated with a number of risk factors and severity of CVD[23-28]. Furthermore, CAVI has also been reported to be an independent predictor of major adverse cardiovascular events[29, 30]. These reports suggest that analyzing arterial stiffness based on CAVI may be helpful for identifying subjects with greater cardiovascular risks.

Some of the traditional arterial stiffness markers except CAVI were reported to be associated with dyslipidemia. However, in most of them, just linear correlations between lipid profiles and arterial stiffness were observed. In fact, none is established as the threshold of each lipid parameter for change in arterial stiffness. On these premises, the primary aim of this cross-sectional study was to investigate the highly-detailed relationship of the lipid profile with arterial stiffness assessed by CAVI in healthy Japanese subjects. Furthermore, we also attempted to explore the thresholds of individual lipid parameters for change in CAVI.

Subjects and Methods

Design

This retrospective cross-sectional study was approved by the Institutional Review Board and Ethics Committee of the Sakura Hospital, School of Medicine, Toho University (No. S17013). Written informed consent was obtained from the participants.

Data Collection and Laboratory Assay Methods

The population-based sample used in the present analysis comprised 23,257 healthy Japanese subjects residing in the major cities nationwide, who were not taking any medication and had no history of heart disease, hypertension, stroke, diabetes, nephritis or gout. They participated in the CVD and cancer screening program organized by the Japan Health Promotion Foundation between 2004 and 2006. Participants were volunteers who were not paid and were not recruited for this study as in the case of a clinical trial.

Obesity was defined as body mass index (BMI) ≥25 kg/m², according to the Examination Committee of Criteria for Obesity Disease in Japan[31]. Blood was collected from the antecubital vein in the morning after 12-h fasting to determine glutamate-oxaloacetate transaminase (GOT), glutamate-pyruvate transaminase (GPT), γ-glutamyltranspeptidase (γ-GTP), fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c), total cholesterol (TC), TG, HDL-C and creatinine. All the blood levels were measured according to standard procedures. Non-HDL-C was defined as the difference in level between total cholesterol and HDL-cholesterol. LDL-C was calculated using Friedewald's formula: LDL-C=(TC)−(HDL-C)−(TG/5). This formula is not valid for patients with TG ≥400 mg/dl[32]. Therefore, subjects with TG ≥400 mg/dl (N=361, 1.55%) were excluded from the analysis of LDL-C only. HbA1c (%) measured by the Japan Diabetes Society (JDC) method was converted to NGSP value (%) using the following formula: HbA1c (NGSP) (%)=HbA1c (JDS) (%)+0.4%[33]. Impaired fasting glucose (IFG) was defined as FPG ≥110 mg/dl[34].

Exclusion criteria were current medication use and a history of cardiovascular disease, hypertension, stroke, diabetes and nephritis. However, one or more cardiovascular risk factors such as dyslipidemia, hypertension and glucose tolerance were newly detected in some participants.

Measurement of CAVI and BP

CAVI was obtained by measuring BP and pulse wave velocity (PWV) according to the following formula: CAVI=a{(2ρ/ΔP) × ln(Ps/Pd)PWV2} + b, where Ps is systolic BP, Pd is diastolic BP, ΔP is Ps−Pd, ρ is blood density, and a and b are constants. CAVI originates from the stiffness parameter β =ln(Ps/Pd) × (D/ΔD). D/ΔD is calculated from PWV of some length of the artery and ΔP in place of diameter change (D/ΔD). As for the application of BP of the upper brachial artery in the calculation of the CAVI equation, there is an assumption that BP at the upper brachial artery is nearly the mean of the BP from the origin of the aorta to the tibial artery at the ankle. Therefore, in cases where the BP at the aorta and the femoral artery were remarkably changed, such as in the case of femoral arterial arteriosclerosis obliterans (ABI <0.9), the CAVI value is invalid. Also, it is wrong to measure CAVI in the standing position. In this case, BP at the ankle and brachial artery is quite different. The details of CAVI and the measurement have been described previously[13].

In the present study, CAVI was measured using a VaSera VS-1000 (Fukuda Denshi Co Ltd, Tokyo, Japan). Cuffs were applied to bilateral upper arms and ankles, with the subject lying supine and the head held in midline position. After resting for 10 min, the exami-

Table 1. Clinical and biochemical characteristics of male and female participants

Variable	All	Male	Female	P value[*]
Number of subjects	23,257	12,729	10,528	−
Age (years)	47.1 ± 12.5	47.0 ± 13.0	47.1 ± 12.0	0.692
Height (cm)	163 ± 9	169 ± 6	156 ± 6	< 0.001
Body weight (kg)	61.6 ± 12.2	68.4 ± 10.5	53.3 ± 8.4	< 0.001
BMI (kg/m²)	22.9 ± 3.4	23.9 ± 3.2	21.7 ± 3.3	0.003
CAVI	7.84 ± 1.07	7.96 ± 1.14	7.69 ± 0.97	< 0.001
sBP (mmHg)	124 ± 16	124 ± 16	123 ± 16	< 0.001
dBP (mmHg)	76 ± 12	76 ± 12	75 ± 11	< 0.001
GOT (IU/l)	23 ± 12	23 ± 12	23 ± 11	0.783
GPT (IU/l)	24 ± 20	24 ± 20	24 ± 20	0.524
γ-GTP (IU/l)	43 ± 56	43 ± 52	44 ± 60	0.415
FPG (mg/dl)	91 ± 18	91 ± 18	91 ± 18	0.465
HbA1c (NGSP, %)	5.3 ± 0.6	5.3 ± 0.6	5.3 ± 0.6	0.086
TC (mg/dl)	209 ± 37	210 ± 37	208 ± 36	0.002
TG (mg/dl)	113 ± 95	117 ± 100	108 ± 89	< 0.001
Log$_e$TG	4.53 ± 0.60	4.55 ± 0.60	4.50 ± 0.59	< 0.001
HDL-C (mg/dl)	66 ± 19	65 ± 18	67 ± 19	< 0.001
LDL-C (mg/dl)	121 ± 34	122 ± 34	120 ± 33	< 0.001
Non-HDL-C (mg/dl)	144 ± 39	145 ± 39	142 ± 38	< 0.001
Creatinine (mg/dl)	0.71 ± 0.15	0.80 ± 0.13	0.62 ± 0.10	0.055

Data are presented as mean ± standard deviation. [*]Student's t-test was used to compare male and female subjects.
BMI, body mass index; CAVI, cardio-ankle vascular index; sBP, systolic blood pressure; dBP, diastolic blood pressure; GOT, glutamate-oxaloacetate transaminase; GPT, glutamate-pyruvate transaminase: γ-GTP, γ-glutamyl transpeptidase; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.

nations were performed. To detect the brachial and ankle pulse waves with cuffs, a low cuff pressure of 30−50 mmHg was used to minimize the effect of cuff pressure on the hemodynamics. Thereafter, BP was measured. Hypertension was defined as systolic BP (sBP) ≥ 140 mmHg and/or diastolic BP (dBP) ≥ 90 mmHg[35]. BP was measured from the cuff of the upper arm. PWV was obtained by dividing the vascular length by the time for which the pulse wave propagated from the aortic valve to the ankle, and was measured using cuffs at the upper arms and ankles. All the measurements and calculations were performed automatically. Subjects with ankle-brachial indices lower than 0.90 were excluded because patients with severe arterial occlusive diseases may falsely give low CAVI[13]. The mean coefficient of variation of CAVI measured by this method is < 5%, which is sufficiently small for clinical usage and indicates that CAVI has good reproducibility[19].

Statistical Analysis

All data are expressed as mean ± standard deviation (SD). The IBM SPSS software (version 11.5, Chicago, IL, USA) was used for statistical processing. Student's t-test or Fisher's exact test was performed to examine gender difference in clinical variables or prevalence of major cardiovascular risks. The relationship between CAVI and clinical variables was analyzed using multiple regression analysis, and the results were used to adjust CAVI in subsequent analyses. The relationship of CAVI with each lipid parameter was analyzed using ANOVA after adjusting for confounders of CAVI, followed by trend analysis. Logistic regression analysis was used to identify contributors to high CAVI (≥ 90th percentile) and expressed as odds ratio (OR) with 95% confidence interval (CI). Sensitivity and specificity with respect to high CAVI were analyzed using conventional receiver−operating−characteristic (ROC) curves. In all comparisons, P values less than 0.05 were considered statistically significant.

Results

Clinical and Biochemical Characteristics of Male and Female Participants

In this study, a total of 23,257 Japanese urban residents (12,729 men and 10,528 women) aged from 20 to 74 (mean 47.1 ± 12.5) years were screened. **Table 1** compares the clinical characteristics of male

Table 2. Prevalence of major cardiovascular risk factors

Variable	All	Male	Female	*P* value[**]
Older age (Age ≥65)	9.2%	9.2%	6.6%	<0.001
Obesity (BMI ≥25)	24.9%	32.9%	15.4%	<0.001
Hypertension (BP ≥140/90)	15.3%	16.1%	14.3%	<0.001
IFG (FPG ≥110)	10.1%	10.2%	10.0%	0.498
Hypo-HDL cholesterolemia (HDL-C <40)	5.0%	5.3%	4.7%	0.058
Hypertriglyceridemia (TG ≥150)	24.8%	25.9%	23.5%	<0.001
Hyper-LDL cholesterolemia (LDL-C ≥140)	20.1%	21.6%	18.3%	<0.001

[**]Fisher's exact test was used to compare male and female subjects.
BMI, body mass index; BP, blood pressure; IFG, Impaired fasting glucose; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein-cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein-cholesterol.

Table 3. Correlation of CAVI with clinical variables analyzed by multiple regression model

Variable	β coefficient	SE	*P* value
Male	0.149	0.125	<0.001
Age	0.584	0.017	<0.001
BMI	−0.119	0.003	<0.001
sBP	0.139	17.105	<0.001
γ-GTP	0.004	0.538	<0.001
HbA1c	−0.003	0.015	0.712
HDL-C	−0.181	0.001	<0.001
Non-HDL-C	0.107	<0.001	0.542
Creatinine	0.012	1.470	0.142

Model: $r^2 = 0.598$, $P < 0.001$.
CAVI, cardio-ankle vascular index; SE, standard error; BMI, body mass index; BP, blood pressure; sBP, systolic blood pressure; IFG, Impaired fasting glucose; γ-GTP, γ-glutamyl transpeptidase; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein-cholesterol.

and female participants. Compared with women, men had significantly and markedly higher BMI and CAVI (7.96 ± 1.14 vs. 7.69 ± 0.97, $P < 0.001$). Furthermore, slightly higher TG and lower HDL-C were observed in male subjects.

Prevalence of Major Cardiovascular Risk Factors

The prevalence of conventional cardiovascular risks in participants is shown in **Table 2**. The proportions of older age (defined as age ≥65 years), obesity (defined as BMI ≥25 kg/m²), hypertension, hypertriglyceridemia (defined as TG ≥150 mg/dl) and hyper-LDL cholesterolemia (defined as LDL-C ≥140 mg/dl) were significantly higher in men than in women, whereas those of IFG and hypo-HDL cholesterolemia (defined as HDL-C <40 mg/dl) were not different.

Correlation of CAVI with Clinical Variables Analyzed by Multiple Regression Model

Next, we examined the factors associated with CAVI. **Table 3** summarizes the results of a multiple regression analysis of the correlation of CAVI with clinical variables. GOT and GPT were omitted because of intraclass correlation with γ-GTP. TG was also omitted because of intraclass correlation with HDL-C, and non-HDL-C was added instead. Age was a major independent predictor of CAVI (β coefficient = 0.584, $P < 0.001$). Additionally, a weak correlation between CAVI and male gender ($\beta = 0.149$, $P < 0.001$), BMI ($\beta = -0.119$, $P < 0.001$), sBP ($\beta = 0.139$, $P < 0.001$) or HDL-C ($\beta = 0.107$, $P < 0.001$) was observed. These confounders, except HDL-C, were used to adjust CAVI in subsequent analyses as shown in **Fig. 1** and **2**.

Comparison of Adjusted CAVI between Types of Dyslipidemia

We classified the participants into four groups according to the presence of hypertriglyceridemia and/or hyper-LDL cholesterolemia. **Fig. 1** compares adjusted CAVI between normolipidemic and dyslipidemic subjects. Adjusted CAVI was lower in normolipidemic subjects compared to all three groups of dyslipidemic
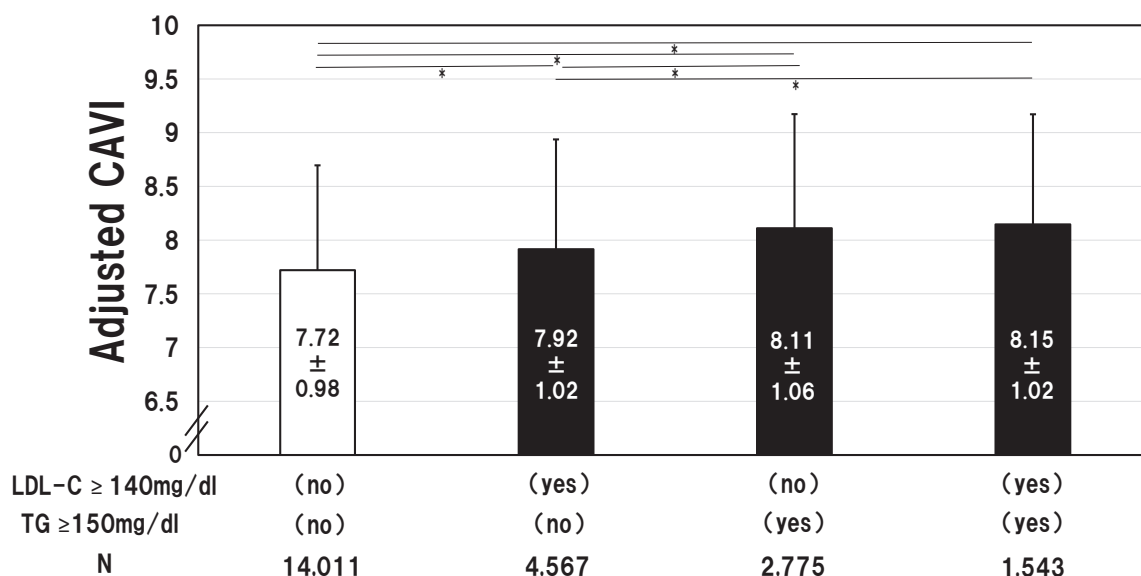
Fig. 1. Comparison of adjusted CAVI between three types of dyslipidemia.

CAVI was adjusted by gender, age, sBP and BMI. Data are presented as mean ± SD. *$P < 0.01$: one-way ANOVA followed by Bonferroni multiple comparison test. CAVI, cardio-ankle vascular index; sBP, systolic blood pressure; BMI, body mass index; LDL-C, low-density lipoprotein-cholesterol; TG, triglycerides; SD, standard deviation.

subjects. Among subjects with hyper-LDL cholesterolemia, those with concurrent hypertriglyceridemia had higher adjusted CAVI.

Relationship between Adjusted CAVI and Lipid Parameters

Fig. 2 shows the relationship of adjusted CAVI with serum level profiles of TC, TG, HDL-C, non-HDL-C and LDL-C. A trend test after ANOVA detected a positive linear relationship of adjusted CAVI with TC, TG, non-HDL-C or LDL-C, and a negative relationship with HDL-C for the entire range of serum levels. In addition, trend tests yielded relatively large variances for TG ($F = 196.11$), HDL-C ($F = 329.27$) and non-HDL-C ($F = 191.18$).

Odds Ratios for High CAVI (≥ 90th Percentile) Per 1-SD Increment of Lipid Parameters Analyzed by Logistic Regression Models

Furthermore, we examined the contribution of each lipid parameter to high CAVI in all participants using multivariate logistic regression models (**Table 4**). High CAVI was conveniently defined as higher than or equal to the 90th percentile of CAVI (≥ 9.40 in males, ≥ 9.00 in females) because CAVI above 9 corresponds substantially to the cut-off value for the presence of coronary artery stenosis[20].

ORs for high CAVI per 1-SD increment were calculated using the actual serum levels of individual lipid parameters (continuous model). Only TG was converted to logarithmic scale to curb departure from normality.

After adjusting for dichotomous confounders including gender, older age, obesity, hypertension and IFG, the ORs (95% CI) of high CAVI were 1.24 (1.19–1.31) for TC, 1.90 (1.81–1.99) for Log_eTG, 0.444 (0.417–0.472) for HDL-C, 1.63 (1.55–1.70) for non-HDL-C and 1.30 (1.24–1.37) for LDL-C.

Discriminatory Powers of Lipid Parameters for High CAVI

The ROC curves and Youden's J Index, which represents the maximum of sensitivity + specificity − 1 for all cutoff points in the ROC curve[36], were generated to evaluate the discriminatory powers and cut-off values of lipid parameters for high CAVI (**Fig. 3**). The diagnostic accuracy of each lipid parameter (area under curve, 95% CIs) for high CAVI was 0.591 (0.579–0.603) for TC, 0.735 (0.725–0.745) for TG, 0.728 (0.718–0.738) for HDL-C, 0.692 (0.682–0.702) for non-HDL-C, and 0.614 (0.602–0.625) for LDL-C. Additionally, ROC curve analysis identified the cut-off values of lipid parameters in predicting high CAVI as follows: 209 mg/dl for TC, 93 mg/dl for TG, 63 mg/dl for HDL-C, 143 mg/dl for non-HDL-C, and 114 mg/dl for LDL-C (**Table 5**).

Bivariate Logistic Regression Model for Factors Predicting High CAVI (≥ 90th Percentile)

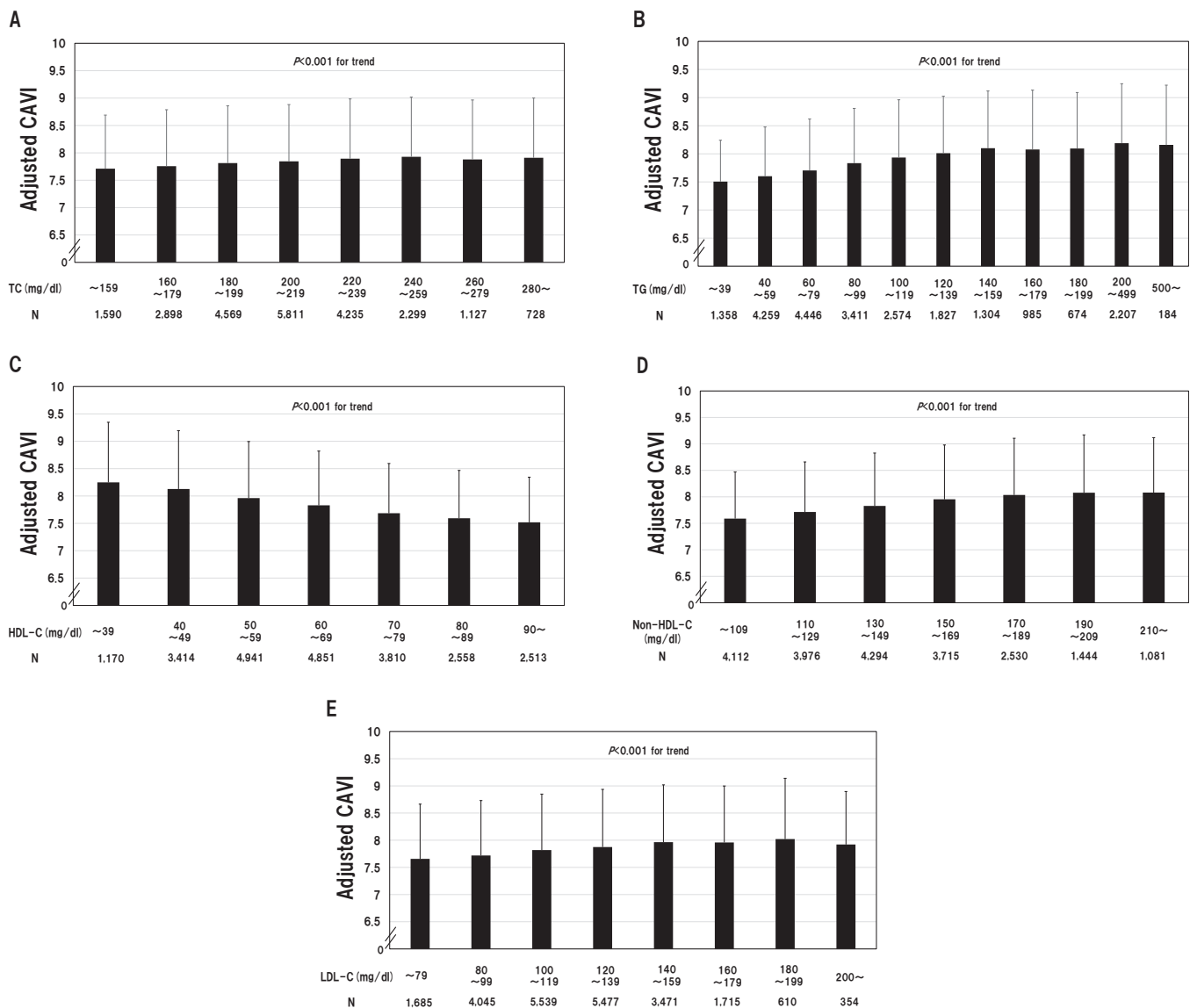Furthermore, we examined the factors associated

Fig. 2. Relationship between adjusted CAVI and lipid parameters: (A) TC, (B) TG, (C) HDL-C, (D) Non-HDL-C and (E) LDL-C.
CAVI was adjusted by gender, age, sBP and BMI. Data are presented as mean ± SD. A significant linear trend ($P < 0.001$ for all parameters. $F = 22.46$ in [A], $F = 196.11$ in [B], $F = 329.27$ in [C], $F = 191.18$ in [D] and $F = 62.52$ in [E]) was observed for the whole range of serum levels. CAVI, cardio-ankle vascular index; sBP, systolic blood pressure; BMI, body mass index; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; SD, standard deviation.

with high CAVI using multivariate logistic regression analysis with dichotomous variables (**Table 6**). Gender and major cardiovascular risks were entered into the model as identified in **Table 2**. TG, HDL-C and LDL-C were adopted using binary cut-off thresholds identified in the analysis shown in **Table 5**. Because we adopted LDL-C that was calculated using Friede-wald's formula in this model, subjects with TG ≥400 mg/dl ($N = 361$, 1.55%) were excluded.

The analysis identified the following variables to be positively associated with high CAVI: male gender

(OR, 95% CI: 2.25, 2.01−2.53), older age (12.7, 11.3−14.4), hypertension (1.85, 1.63−2.09), TG ≥93 mg/dl (2.43, 2.14−2.75), HDL-C <63 mg/dl (2.60, 2.29−2.94), and LDL-C ≥114 mg/dl (1.48, 1.32−1.67). Interestingly, obesity correlated negatively with high CAVI (OR: 0.817, 95% CI: 0.723−0.924). IFG was not a significant independent predictor of high CAVI.

Discussion

This cross-sectional study in 23,257 healthy mid-

Table 4. Odds ratios [95% confidence intervals (CIs)] for high CAVI (≥90th percentile) per 1-SD increment of each lipid parameter analyzed by logistic regression models

Parameters	OR	95% CI	P value
TC	1.24	1.19−1.31	<0.001
Log_e TG	1.90	1.81−1.99	<0.001
HDL-C	0.444	0.417−0.472	<0.001
Non-HDL-C	1.63	1.55−1.70	<0.001
LDL-C	1.30	1.24−1.37	<0.001

The actual values of lipid parameters were entered as continuous variables to calculate ORs per 1-SD increment of lipid parameters adjusted for gender, older age, obesity, hypertension and IFG.
SD, standard deviation; CAVI, cardio-ankle vascular index; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; IFG, impaired fasting glucose.

dle-aged Japanese subjects showed that gender, age, BMI and sBP were major independent confounders for CAVI. After adjusting for these variables, CAVI increased progressively with increasing levels of TC, TG, non-HDL-C and LDL-C, and decreased with increasing level of HDL-C. Interestingly, the increase or decrease in adjusted CAVI was observed spanning the whole range of serum levels (from the lowest to the highest) for all lipid parameters. In continuous models adjusted for confounders, every 1-SD increment of each lipid parameter was independently associated with high CAVI (≥90th percentile). Furthermore, the cut-off values of lipid parameters to predict high CAVI calculated by ROC analysis were different from the current target levels. In this study, we obtained cutoff values of TG, HDL-C and LDL-C for independent discrimination of high CAVI, while also identified male gender, older age, obesity and hypertension to be independent predictors.

Atherogenic dyslipidemia, which refers to the condition of hypertriglyceridemia combined with hypo-HDL cholesterolemia, has emerged as an important risk factor for CVD, along with hyper-LDL cholesterolemia. However, a lack of correlation between individual lipid parameters and existing arterial stiffness markers such as PWV and augmentation index has been noted in previous studies[37, 38], indicating that these traditional lipid parameters may not be robust enough to predict CVD risk in individuals. Recently, many studies have suggested that analyzing the structure and function of apolipoproteins is imperative in the management of atherosclerosis-related diseases. In contrast, our population-based study clearly demonstrated the relationship between CAVI and individual lipid parameters. Therefore, as shown in the present study, conventional lipid parameters may now be used reliably to manage vascular health.

Increase or decrease in adjusted CAVI was
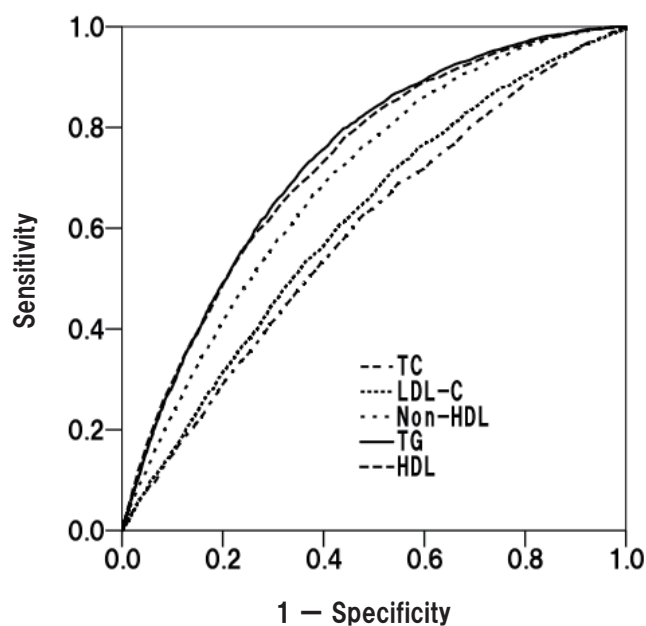
Fig. 3. Discriminatory powers of lipid parameters for high CAVI (≥90th percentile).

Curves represent ROC analyses for discriminating the probability of high CAVI. ROC, receiver−operating−characteristics; CAVI, cardio-ankle vascular index; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

observed linearly from the lowest to the highest serum levels for all lipid parameters. Accordingly, the lowest levels of TC, TG, non-HDL-C and LDL-C, and the highest level of HDL-C would reflect the most desirable state of arterial stiffness expressed as the lowest CAVI, at least in this study population. Furthermore, cut-off values of TC, TG, non-HDL-C and LDL-C for predicting high CAVI were lower, and that of HDL-C was higher compared to current targets of lipid levels for primary prevention of CVD in Japan.

Table 5. Cut-off values of lipid parameters and area under the receiver-operating-characteristic curves (AUC) for high CAVI (≥90th percentile)

Parameter	Cut-off value	Sensitivity	Specificity	AUC (SE)	*P* value
TC	209 mg/dl	63%	48%	0.591 (0.006)	<0.001
TG	93 mg/dl	78%	57%	0.735 (0.005)	<0.001
HDL-C	63 mg/dl	78%	54%	0.728 (0.005)	<0.001
Non-HDL-C	143 mg/dl	75%	47%	0.692 (0.005)	<0.001
LDL-C	114 mg/dl	72%	55%	0.614 (0.006)	<0.001

The Youden Index was used in conjunction with the receiver-operating-characteristic (ROC) analysis shown in Fig. 3 to select the optimum cut-off points of lipid parameters for high CAVI.
CAVI, cardio-ankle vascular index; AUC, area under the ROC curve; SE, standard error; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.

Therefore, it may be beneficial to re-examine the target value of each lipid parameter according to vascular stiffness in daily clinical practice.

Meanwhile, whether each lipid parameter is a pathogenic mediator or just a marker of atherosclerosis remains uncertain. Our data demonstrates that TG, HDL-C and LDL-C independently influence CAVI, which may suggest the intrinsic effect of each form of lipid. Serum LDL-C is the lipoprotein most commonly associated with coronary heart disease[39]. On the other hand, CAVI may be less closely related to hypercholesterolemia compared to diabetes mellitus. Several studies have reported that CAVI is not necessarily high in heterozygous familial hypercholesterolemic patients[40, 41]. However, some reports have shown that CAVI is related to dyslipidemia, especially elevated LDL-C serum level and LDL-C/HDL-C ratio[42-44]. Initial lipidosis induced by infiltration of LDL may soften the arterial wall. CAVI may increase subsequent to the occurrence of a complicated lesion. In addition, cholesterol-lowering agents such as pitavastatin[45] and ezetimibe[46] have been reported to decrease CAVI. The pathological processes in the early phase of atherogenesis are initiated by accumulation of modified forms of LDL, followed by cellular infiltration and foam cell formation[47]. Furthermore, we have reported that CAVI may be a marker related to endothelial function in subjects with coronary risks[48]. Together, these findings suggest that CAVI may reflect endothelial dysfunction associated with increased serum LDL-C, as shown in this study.

A study has suggested that elevated serum TG and decreased HDL-C are secondary to resistance to insulin-stimulated glucose uptake[49]. Furthermore, inflammation and oxidative stress involved in insulin resistance play a central role its pathogenesis. We have reported that high CAVI may reflect insulin resistance and can be decreased by insulin-sensitizing therapeutic approaches[50-53]. Additionally, Satoh *et al.*[42] have reported that the severity of metabolic syndrome correlates positively with CAVI, probably due to insulin resistance. Therefore, both TG and HDL-C are considered to be surrogate markers to help detect insulin resistance. However, they are also mediators associated with inflammation and atherosclerosis in metabolic syndrome. HDL appears to act as a vasoprotective mediator, and is recognized for its ability to shuttle excess cholesterol from peripheral tissues to the liver for excretion in the process of reverse cholesterol transport, likely contributing to the well-known inverse relationship between HDL-C and CVD. Additional cardioprotective roles of HDL have been identified, including anti-inflammatory, antioxidative and anti-apoptotic properties in vascular endothelial cells[54-56]. The inverse relationship of CAVI with serum HDL-C shown in this study may reflect the favorable effect of HDL on arterial stiffness. In contrast, there is no evidence supporting the hypothesis that TG per se is a culprit in the atherogenic process. However, recently published works have confirmed that TG-rich lipoproteins and their remnants seen in metabolic syndrome are also predictors of arterial stiffening evaluated by CAVI and intima-media thickness[57, 58]. Remnant cholesterol can be taken up into the subendothelial space by scavenger receptors of resident macrophages, thus promoting foam cell formation[59]. In fact, many studies have shown that TG-lowering medications exert vasoprotective effects. Fibrate is a widely used class of lipid-regulating agents that affects lipoprotein metabolism, attenuates postprandial lipemia and reduces TG-rich lipoprotein[60, 61]. Fibrate was reported to improve endothelial function as assessed by flow-mediated dilation[62, 63]. In addition, Satoh *et al.*[64] have reported that eicosapentaenoic acid, an n-3 polyunsaturated fatty acid that lowers TG, decreases CAVI accompanied by decreases in TG and oxidized LDL. On the other hand, our finding may support the notion of "lower is better" for serum TG with respect to the relationship with arterial stiffness. Consequently,

Table 6. Bivariate logistic regression model for high CAVI (≥ 90th percentile)

Variable	OR	95% CI	*P* value
Gender (Male; 1, Female; 0)	2.25	2.01−2.53	< 0.001
Older age (Age ≥65; 1, <65; 0)	12.7	11.3−14.4	< 0.001
Obesity (BMI ≥25; 1, <25; 0)	0.817	0.723−0.924	< 0.001
Hypertension (+; 1, −; 0)	1.85	1.63−2.09	< 0.001
IFG (FPG ≥110; 1, <110; 0)	0.921	0.820−1.03	0.158
TG ≥93 mg/dl	2.43	2.14−2.75	< 0.001
HDL-C <63 mg/dl	2.60	2.29−2.94	< 0.001
LDL-C ≥114 mg/dl	1.48	1.32−1.67	< 0.001

Akaike's Information Criterion: 9940.6, residual deviance: 9922.6, $P<0.001$. Subjects with TG ≥400 mg/dl ($N=$ 361, 1.55%) were excluded.

OR, odds ratio; CI, confidence interval; CAVI, cardio-ankle vascular index; IFG, Impaired fasting glucose; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.

more intensive TG-lowering therapy may be appropriate, although it remains controversial whether adherence to the current guideline for hypertriglyceridemia contributes to CVD prevention.

In 2002, brachial−ankle PWV (baPWV) was proposed to be a marker of vascular damage and was reported to be a predictive marker of CVD[65, 66]. Furthermore, baPWV correlates strongly with aortic (carotid−femoral) PWV, an established index of central arterial stiffness[67], and is proposed as the gold standard method by the European Society of Hypertension/European Society of Cardiology guidelines[68]. However, PWV, unlike CAVI, is known to strongly depend on BP at the time of measurement, and to have inadequate reproducibility. When the selective β1-blocker metoprolol was administered to Japanese men, systolic and diastolic BP decreased for 6 h[14]. During this time, baPWV significantly decreased, whereas CAVI did not change. This phenomenon could be explained as follows: CAVI does not change because metoprolol does not affect the contracture of arterial wall smooth muscle cells, whereas baPWV decreases because PWV has the property to decrease according to a decrease in BP. Therefore, the validity of PWV in reflecting actual arterial stiffness is controversial, and this parameter is unsuitable for evaluating the effect of antihypertensive drugs on the arterial wall. On the other hand, unlike PWV, CAVI is not affected by BP at the time of measurement, which makes it more precise and reproducible than PWV as an index of arterial stiffness, although its predictive value of cardiovascular events has not been established adequately[69]. Moreover, a multiple regression analysis revealed that CAVI was superior to baPWV as a predictor of carotid and coronary arteriosclerosis[24, 70-72].

The inverse relationship of CAVI with BMI shown in this report (**Tables 3** and **6**) may seem inconsistent with previous reports showing that CAVI increases reversibly according to abdominal obesity/metabolic syndrome[51]. We previously reported a negative relationship between CAVI and BMI in healthy middle-aged Japanese subjects, suggesting that the systemic accumulation of adipose tissue per se may lead to a linear decrease of arterial stiffness in nonobese and obese subjects without metabolic disorders[73]. If the study was conducted in obese subjects with metabolic disorders, the results might have been markedly different. We speculate that adipose tissue-derived cytokines may explain the paradox in arterial stiffness observed in the present study. Shiba *et al.*[74] reported that intravitreal injection of antivascular endothelial growth factor (anti-VEGF) drugs decreased CAVI and carotid intima−media thickness, probably due to decreased vasa vasorum flow and improved kidney function. Inhibition of angiogenesis inducers such as VEGF may therefore result in a decrease in arterial stiffness. On the other hand, tenomodulin (TNMD), a putative angiogenesis inhibitor, has been shown to be highly expressed in human adipose tissue, especially in obese subjects[75]. Furthermore, a recent study suggests that TNMD acts as a protective factor in visceral adipose tissue to alleviate insulin resistance in obesity[76]. We have previously reported that improved insulin resistance may contribute to decreased CAVI in obese and type 2 diabetic patients[51-53]. These reports suggest that adipose tissue may affect systemic vascular function through expression of antiangiogenic factors such as TNMD. For the metabolically healthy overweight/obese individuals only, these various protective cytokines and neuroendocrine profiles may contribute to a decrease in arterial stiffness. Further elucidation of the cause−effect relationship between accumulation of adipose tissue and regulation of arterial pathophysiology is required.

The limitations of this study include the lack of data on some potential confounders such as proteinuria[77], alcohol consumption, menopause, and smoking status. In addition, the cross-sectional nature of this study does not allow determination of the time course for the causal relationship between lipid profiles and the risk of arterial stiffness. Therefore, it was not possible to establish the exact pathophysiology linking each lipid parameter with CAVI. From these viewpoints, longitudinal cohort studies are needed to clarify the change in relationship between lipid parameters and arterial stiffness during the evolution of cardiovascular risks.

Conclusion

The present study demonstrated the independent contribution of conventional lipid parameters to CAVI, indicating a possible association of lipid parameters with early vascular damage.

Declaration of Conflicting Interests

The author(s) declare no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Author Contributions

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