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Longitudinal association among endothelial function, arterial stiffness and subclinical organ damage in hypertension☆

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ABSTRACT

Objectives: To examine the longitudinal mutual association between endothelial dysfunction and arterial stiffness, and also to determine which of the two variables was more closely associated with the progression of subclinical organ damage.
Methods: The brachial-ankle pulse wave velocity (baPWV), carotid intima-media thickness (CIMT), estimated glomerular filtration rate, microalbuminuria and flow-mediated vasodilatation of the brachial artery (FMD) were measured three times at 1.5-year intervals in 674 Japanese patients receiving antihypertensive treatment.
Results: The change of the baPWV during the study period was larger in the subjects with baseline FMD values in the lowest tertile as compared to those with baseline FMD values in the highest tertile. The change of the CIMT was smaller in the subjects with baseline baPWV values in the lowest tertile than in those with baseline baPWV values in the highest tertile. After the adjustment, the FMD value at the baseline was inversely associated with the baPWV at the end of the study period (beta = −0.07, $p = 0.01$), although, the reverse association was not significant. The baPWV, but not the FMD value, at the baseline was associated with the CIMT (beta = 0.06, $p = 0.04$) measured at the end of the study period.

Abbreviations: FMD, flow-mediated vasodilatation of the brachial artery; baPWV, brachial-ankle pulse wave velocity; CIMTmean, the mean intima-media thickness of the common carotid artery; CIMTmax, the maximum intima-media thickness of the common carotid artery; eGFR, the estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; T 1, 2, 3, three tertiles (tertile 1 [T1] = lowest and tertile 3 [T3] = highest).

☆ "All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation".

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Conclusions: In hypertension, endothelial dysfunction was associated with the progression of arterial stiffness, although the reverse association was not confirmed. The increased arterial stiffness rather than endothelial dysfunction may be more closely associated with the progression of atherosclerotic vascular damage, and the endothelial dysfunction-arterial stiffness-atherosclerosis continuum may be important in hypertension.

1. Introduction

For the prevention of cardiovascular disease in patients with hypertension, prevention of the progression of subclinical organ damage is crucial [1,2]. Vascular dysfunction is thought to contribute to the progression of subclinical organ damage [3]. In clinical settings, FMD, a marker of endothelial function, and PWV, a marker of arterial stiffness, which is affected by abnormalities of the intima and media, have been used for the assessment of vascular function, and both are known to be independent predictors of future cardiovascular events [4,5,6]. Endothelial dysfunction is thought to be associated with the progression of arterial stiffness, atherosclerosis and renal damage [4,7,8,9,10,11]. On the other hand, arterial stiffness is also thought to augment endothelial dysfunction [12] and to be associated with the progression of atherosclerosis and renal damage, even via mechanisms other than endothelial dysfunction [4,7,13,14,15,16]. However, the significances of these associations have not yet been fully clarified. The present multicenter prospective observational study was conducted to examine whether progression of endothelial dysfunction and progression of arterial stiffness are mutually associated, and also to determine which of the two variables is more closely associated with the progression of atherosclerotic vascular damage as assessed by carotid ultrasound examination and/or renal damage.

2. Methods

The study design has been reported elsewhere [17]. The study was conducted in conformity with the principles of the Declaration of Helsinki, and with the approval of the Ethics Committee of Tokyo Medical University (the core center of the FMD-J study) (No. 2456) as well as of the Ethics Committee of each of the other participating institutions. Written informed consent was obtained from each of the study participants prior to their participation in the FMD-J study. The details of the study subjects, study protocol and measurement are described in the supplementary file.

2.1. Study subjects

The subjects enrolled were hypertensive patients receiving antihypertensive treatment, with a blood pressure of <150/95 mm Hg, who had been under follow-up at any of the participating centers for at least 6 months [17]. As shown in Supplementary Fig. 1, all the analyses were successfully completed in 674 patients.

2.2. Study protocol

This multicenter prospective observational study was conducted with the participation of 17 university hospitals in Japan, from June 2010 to October 2015. Measurements of the FMD, brachial-ankle PWV (baPWV), markers of subclinical organ damage and blood parameters to assess the conventional risk factors for CVD were conducted a total of three times until the end of the 3-year study period {i.e., at the start of the study (baseline), at 1.5 years after the start of the study, and at 3 years after the start of the study (end of the study period)} [17].

2.3. Measurements

2.3.1. Flow-mediated vasodilatation of the brachial artery

FMD was measured from A-mode images of the brachial artery as a signal of the intima-media complex (EF, Unex Co. Ltd., Nagoya, Japan) [17,18]. The FMD assessment at each of the participant institutions was conducted in a blinded manner. In our previous study, we determined the correlation coefficient between the FMD values measured at each institution and the FMD value measured at a core laboratory ($n = 880$), and found a good correlation coefficient ($R = 0.838$; $P < 0.001$) [18].

2.3.2. Ultrasonographic examination of the carotid arteries

The records of the carotid artery obtained at each institution were uploaded as JPEG files to the website of the FMDJ-study [17,19], and the measurements were then conducted at a core laboratory (University of Tsukuba). A single expert analyst who was blinded to clinical information about the participants measured the mean intima-media thickness of the common carotid artery (CIMTmean) and the maximum intima-media thickness of the common carotid artery (CIMTmax) in all the subjects, using an automatic IMT measurement software (Vascular Research Tools 5, Medical Imaging Applications) [20].

2.3.3. Pulse wave velocity

The baPWV was measured using a volume-plethysmographic apparatus (Form/ABI, Omron Health Care Co. Ltd., Kyoto, Japan), in accordance with a previously described method [21]. The instrument that was used to measure the baPWV was also used to measure the ankle-brachial pressure index (ABI). Patients with ABI values of <0.90 and/or atrial fibrillation were excluded from the analyses, because the measured baPWV values in such patients are known to be unreliable. No facility for baPWV measurement was available at 2 institutions.

2.3.4. Laboratory measurements

Fasting blood samples (5 ml) for laboratory measurements were collected from the subjects on the day of the FMD measurement. The estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR) were calculated.

2.4. Statistical methods

We have described our method for estimating the sample size for the present study in a previously published report [17,22]. It was determined that a total of 598 subjects would be needed to obtain at least 80% statistical power at a 2-sided significance level of 0.05 to detect a significant difference of the CIMTmean between the 2 groups, and a total of 642 subjects would be needed to detect a significant difference of the UACR between the 2 groups [17,23].

Differences in the measured values between each variable were assessed using the paired *t*-test for continuous variables and McNemar's non-parametric test for categorical variables. The subjects were divided into tertiles of the baPWV and FMD values recorded at the study baseline. Then, the differences in the changes between subject groups with values in the lowest and highest tertiles were compared using a general linear model (GLM) analysis model with and without adjustments. The relationships among the variables were assessed by measuring the Pearson's correlation coefficients and by multivariate linear regression analysis with adjustments.

For the adjustments, the covariates in Model 1 were the age, gender, body mass index, systolic blood pressure, smoking status (current smoker = 1; non-current smoker = 0), daily alcohol intake (ethanol g/day), daily exercise level (Mets/day), LDLC, HDLC, TG and Crnn, presence/absence of diabetes mellitus, history of medication use (statins, renin-angiotensin system blockers, and calcium channel blockers [not receiving medication = 0; receiving medication = 1 for each medication]).

All the other analyses were conducted using the SPSS software (version 24.0; IBM/SPSS Inc., Armonk, NY, USA). $P < 0.05$ was considered to indicate a statistically significant difference in all the statistical tests.

3. Results

The numerical data that were available for completion of all the analyses in this study are summarized in Supplementary Fig. 1. The clinical characteristics of the subjects in whom all the analyses could be completed are summarized in Table 1. The CIMTmean, CIMTmax and UACR showed significant increase, while the diastolic blood pressure and eGFR showed significant decrease during the study period (Table 1).

Fig. 1 and Fig. 2 show the changes in the markers of vascular function, vascular damage and renal damage during the study period {i.e., from the baseline to 1.5 years after the start of the study (filled circles) and from the baseline to the end of the study period (clear circles)} in the study subjects divided into three groups according to the tertile ranges (tertile 1 [T1] = lowest and tertile 3 [T3] = highest) of the baPWV and FMD values measured at the study baseline (the T1-baPWV to T3-baPWV groups and the T1-FMD to T3-FMD groups, respectively).

Table 1
Clinical characteristics of the study subjects at the baseline and their changes during the study period.

Parameter	Baseline	1.5 years	3 years
Number	674		
Age	62 ± 9		
Gender (m/f)	382/292		
BMI	24.7 ± 3.6	24.7 ± 3.7	24.6 ± 3.8
SBP (mm Hg)	134 ± 14	133 ± 14	133 ± 15
DBP (mm Hg)	80 ± 10	79 ± 10*	78 ± 10*
BP controlled (%)	448 (67)	441 (65)	444 (66)
Smoking# (%)	75/663 (11)	68/664 (10)	67/672 (10)*
Alcohol# (%)	309/663 (44)	288/632 (45)	283/641 (44)
Ethanol g	15 ± 22	14 ± 21	14 ± 22
Exercise habit# (%)	365/647 (56)	368/617 (60)*	382/631 (61)*
Mets/day	608 ± 1213	634 ± 927	654 ± 930
LDLC (mmol/L)	3.01 ± 0.76	2.92 ± 0.74*	2.89 ± 0.75*
HDLC (mmol/L)	1.51 ± 0.40	1.53 ± 0.40*	1.53 ± 0.40*
TG (mmol/L)	1.47 ± 0.86	1.44 ± 0.82	1.37 ± 0.73*
FPG (mmol/L)	5.83 ± 1.04	5.80 ± 1.12	5.81 ± 1.18
Diabetes (%)	115 (17)	104 (15)	123 (18)
Crnn (μmol/L)	68 ± 18	69 ± 19*	71 ± 25*
CRP (mg/L)	0.76 ± 0.20	0.78 ± 0.22*	0.80 ± 0.29*
FMD (%)	4.89 ± 2.77	5.02 ± 2.97	5.00 ± 3.08
BRdia (mm)	4.13 ± 0.65	4.15 ± 0.62	4.10 ± 0.65
CIMTmean (mm)	0.77 ± 0.15	0.77 ± 0.15	0.78 ± 0.16*
CIMTmax (mm)	1.06 ± 0.26	1.06 ± 0.27	1.07 ± 0.27*
baPWV (cm/s)	1621 ± 295	1603 ± 357	1625 ± 293
eGFR (ml/min/1.73 m^2)	74 ± 17	72 ± 17	70 ± 17*
UACR (mg/g creatinine)	26 ± 118	33 ± 218	38 ± 274*
FRSscore	10 ± 7 (n = 653)	10 ± 7 (n = 659)	10 ± 7 (n = 661)
Medications			
CCBs (%)	431 (64)	424 (63)	441 (65)
RAbs (%)	439 (65)	421 (63)	436 (65)
BBs	116 (17)	127 (19)	134 (20)*
Diuretics	177 (26)	149 (22)*	136 (20)*
Others	46 (7)	60 (9)	53 (8)
Medication for DM	70 (10)	67 (10)	80 (12)
Statins	203 (30)	214 (32)*	238 (35)*

Abbreviations: Data are expressed as means ± standard deviation; Baseline = at the study baseline; 1.5 years = 1.5 years after the start of the study; 3 years = 3 years after the start of the study; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; BP controlled = number of subjects in whom the BP was controlled to ≤ 140/90 mm Hg; Smoking# = number of current smokers; Alcohol# = number of current drinkers; ethanol = daily ethanol intake; Exercise habit# = number of subjects engaging in habitual exercise; Mets/day = daily exercise level expressed in Mets; # = data for smoking, alcohol intake, and habitual exercise were not available for some cases (the denominators show the number of subjects for whom the data were available); TC = serum levels of total cholesterol; LDLC = serum level of low-density lipoprotein cholesterol calculated by the Friedewald formula; HDLC = serum level of high-density lipoprotein cholesterol; TG = serum level of triglycerides; FPG = fasting plasma glucose level; Diabetes = number of subjects diagnosed as having diabetes mellitus; Crnn = serum level of creatinine; CRP = serum level of C-reactive protein; FMD = flow-mediated dilatation of the brachial artery; BRdia = baseline diameter of the brachial artery; CIMTmean = mean intima-media thickness of the common carotid artery; CIMTmax, maximum intima-media thickness of the common carotid artery; Cdia = diameter of the common carotid artery; baPWV = brachial-ankle pulse wave velocity; eGFR = estimated glomerular filtration rate; UACR = urinary albumin/creatinine ratio; FRS = Framingham risk score; n = number of patients in whom the FRS had been calculated; CCB = number of subjects taking calcium channel blockers; RAb = number of subjects taking renin-angiotensin system blockers; BB = number of subjects taking beta-blockers; Diuretics = number of subjects taking diuretics; Others = number of subjects taking antihypertensive medication(s) other than a CCB, RAb, BB or diuretic; Medication for DM = number of subjects taking medication(s) for diabetes mellitus; Statin = number of subjects taking statins; *, $p < 0.05$ vs. baseline.

As shown in Fig. 1, the change of the baPWV from the baseline to the end of the study period was lower in the T3-FMD group than in the T1-FMD group. This difference remained significant even after adjustments for the covariates in Model 1 plus the baPWV at the baseline. While the crude value of the change of the FMD from the baseline to the end of the study period was higher in the T3-baPWV group and then in the T1-baPWV group, this difference was no longer significant after adjustments for the covariates in Model 1 plus the FMD at the baseline.

The change of the CIMTmean from the baseline to the end of the study period was higher in the T2- and T3-baPWV groups than in the T1-baPWV group, even after adjustments for model 1 covariates plus the CIMTmean at the study baseline (Fig. 1). The crude value of the change of the CIMTmean from the baseline to 1.5 years after the start of the study was higher in the T3-FMD group than in the T1-FMD group. However, this difference was no longer significant after adjustment for the covariates in Model 1 plus the CIMTmean at the baseline (Fig. 1). On the other hand, the crude value of the change of the CIMTmax from the baseline to the end of the study period was similar among the three tertile range groups (Fig. 1). In the assessment of the relationships among the changes in the vascular biomarkers from the baseline to the end of study period, the change of the baPWV showed a significant correlation with the change of the FMD ($R = -0.09$, $p = 0.036$), but not with that of the CIMTmean ($R = -0.06$, $p = 0.148$).

As shown in Fig. 2, the crude value of the change of the eGFR from the baseline to 1.5 years after the start of the study was higher in the T3-baPWV group than in the T1-baPWV group, and the crude value of the change of the eGFR from the baseline to the end of the study was lower in the T3-FMD group than in the T1-FMD group. However, these differences were no longer significant after adjustments for the covariates of model 1 plus the baseline eGFR value. The change of the UACR from the baseline to the end of the study period was similar among the T1 to T3-FMD groups as well as among the T1- to T3-baPWV groups.

The clinical characteristics at the baseline of the subjects divided into three groups according to the tertile ranges of the baPWV and FMD values measured at the study baseline are described in Supplementary Table 1.

Table 2 summarizes the relationship of the FMD and baPWV values measured at the baseline with their opponent variable, CIMT, eGFR and UACR measured at the end of the study period. Even after adjustments for covariates of model 1 plus the baseline value of the outcome variable, the FMD value measured at the baseline showed a significant inverse association with the baPWV measured at the end of the study period. On the other hand, the reverse association could not be confirmed, namely, the baPWV measured at the baseline showed no significant inverse association with the FMD value measured at the end of the study period. Furthermore, the baPWV, but not the FMD, value measured at the baseline showed a significant association with the CIMTmean, but not the CIMTmax, measured at the end of the study period. Neither the FMD value nor the baPWV measured at the baseline showed any significant relationship with the eGFR or UACR measured at the end of the study period (Table 2).

4. Discussion

The novel findings of the present study were that a lower FMD value at the baseline was associated with a higher longitudinal increase of the baPWV. In addition, a higher value of the baPWV, but not lower value of the FMD, at the baseline was associated with a higher longitudinal increase of the CMIT; no such association was observed with the changes of the UCAR/eGFR. Thus, one-way relationships of the FMD with the baPWV (lower the FMD value at the baseline, higher the longitudinal increase of the baPWV) and of the baPWV with the CIMT (higher the baPWV at the baseline, higher the longitudinal increase of the CIMT) were observed in the present study.

4.1. Flow-mediated vasodilatation and arterial stiffness

Several experimental studies have reported that imbalances of vasoactive substances derived from the endothelium, such as nitric oxide or endothelin, can cause functional increase of the arterial stiffness via changing the arterial tone, and also structural increase of the arterial stiffness via inducing abnormal medial vascular smooth muscle cell behaviors and altering the medial extracellular matrix composition and

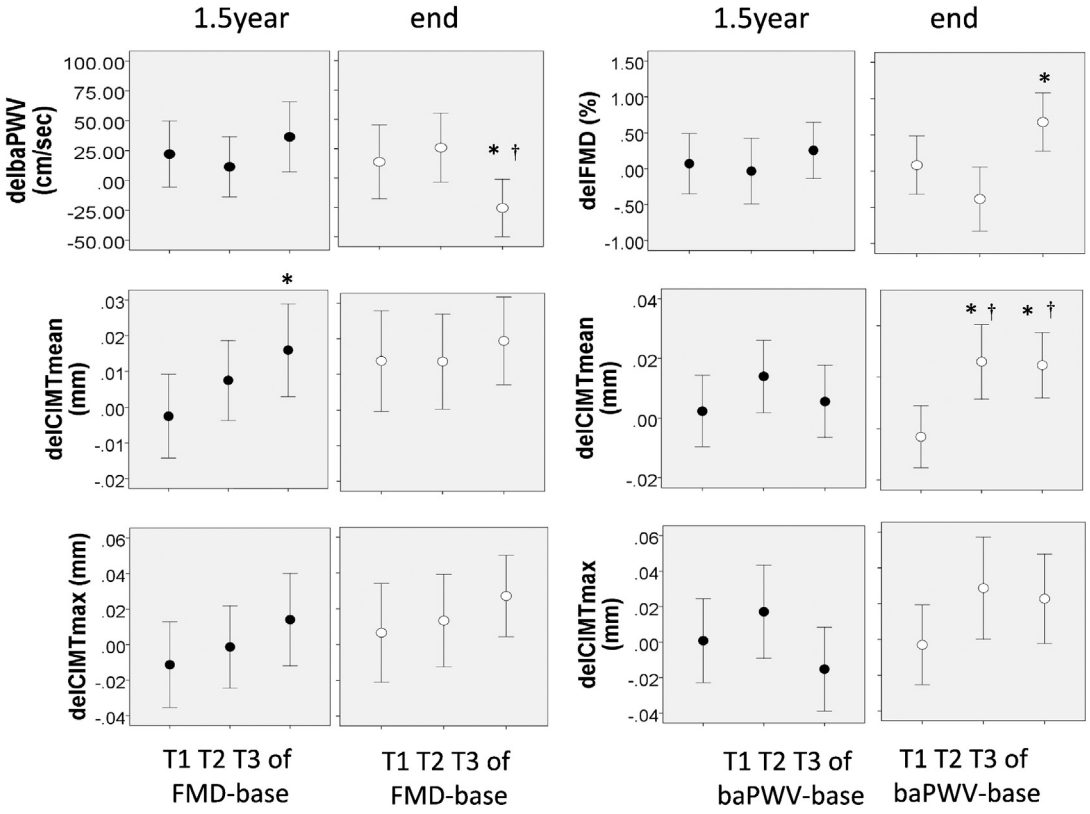

Fig. 1. Changes in the markers of vascular function and vascular damage during the study period in the subjects divided into three groups according to the tertile range of the baPWV or FMD values at the study baseline. Abbreviations: FMD = flow-mediated vasodilatation of the brachial artery; baPWV = brachial-ankle pulse wave velocity; CIMTmean = mean intima-media thickness of the common carotid artery; CIMTmax = maximum intima-media thickness of the common carotid artery; T1 = lowest tertile; T2 = intermediate tertile; T3 = highest tertile; del = delta change of variable; −base = at the baseline; 1.5 year = delta change from the baseline to the measurement at 1.5 years; end = delta change from the baseline to the end of the study period; * = $p < 0.05$ vs. T1 without adjustments; † = $p < 0.05$ vs. T1 after adjustments; adjustment = adjusted for covariates of Model 1 plus the value of the outcome variable at the baseline;

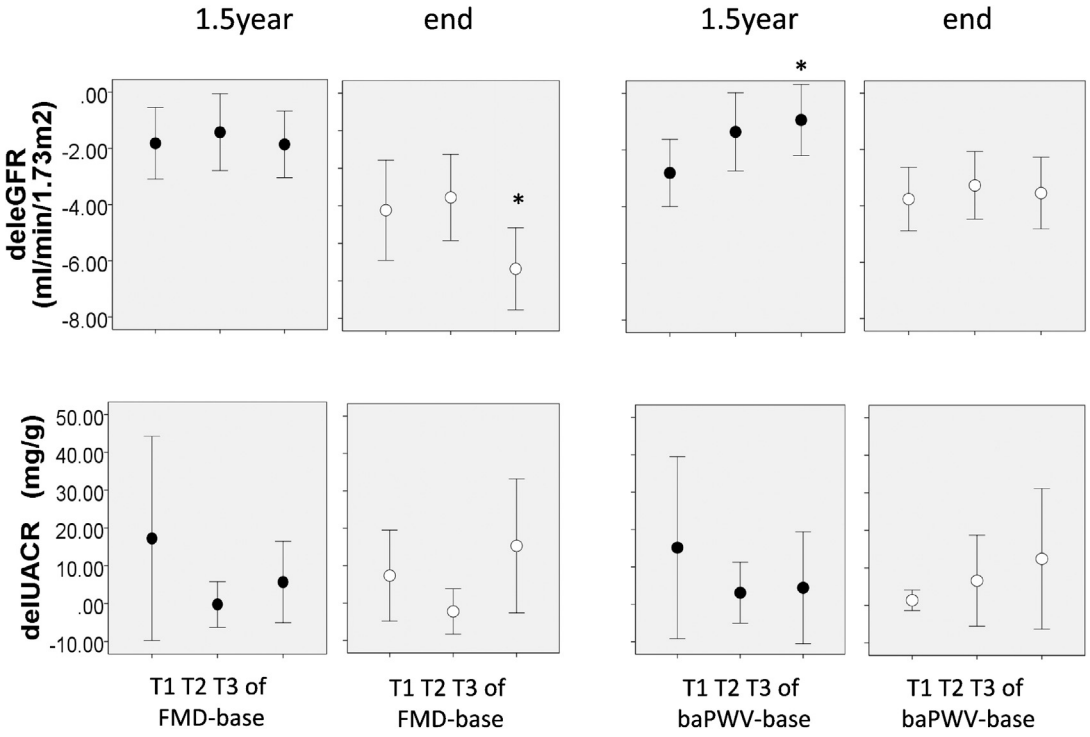

Fig. 2. Changes in the markers of renal damage during the study period in the subjects divided into three groups according to the tertile range of the baPWV or FMD values at the study baseline. Abbreviations: eGFR = estimated glomerular filtration rate; UACR = urinary albumin/creatinine ratio; for the eGFR, crnn was excluded as a covariate for adjustment; other abbreviations are as described in the figure legend for Fig. 1.

Table 2
Relationships of the flow-mediated vasodilation and brachial-ankle pulse wave velocity values at the first examination with the values of their opponent variables and markers of subclinical organ damage at the third examination.

	Pearson's correlation		Multivariate analysis		
Outcome	R	*P*-value	B	Beta	P-value
Explained variable = FMD at the baseline of study period					
baPWV-e	−0.13	<0.01	−7.43	−0.07	0.01
IMTmean-e	−0.07	0.09	0.01	0.01	0.55
IMTmax-e	−0.05	0.26	–	–	–
eGFR-e	−0.07	0.09	−0.14	−0.02	0.27
UACR-e	−0.02	0.63	–	–	–
Explained variable = baPWV at the baseline of study period					
FMD-e	−0.03	0.43	–	–	–
IMTmean-e	0.28	<0.01	0.01	0.06	0.04
IMTmax-e	0.25	<0.01	0.01	0.04	0.21
eGFR-e	0.02	0.54	–	–	–
UACR-e	−0.13	<0.01	0.02	0.04	0.35

Abbreviations: outcome = outcome variable; −e = at the end of the study period; R = Pearson's correlation coefficient; B = non-standardized coefficient in multivariate analysis; beta = standardized coefficient in multivariate analysis; adjustment = adjusted Model 1 plus the value of the outcome variable at the baseline added as a covariate (for eGFR, crnn was excluded as a covariate); other abbreviations are as described in the footnote for Table 1.

organization [7]. However, in clinical settings, while cross-sectional studies have reported the existence of a significant association between endothelial dysfunction and increased arterial stiffness [24], the present study is the first prospective clinical study to demonstrate a significant association of endothelial dysfunction (assessed by FMD) with the longitudinal progression of the arterial stiffness (assessed by the baPWV). As this association was significant even after adjustment for blood pressure, it is reasonable to assume that endothelial dysfunction may contribute to the progression of structural arterial stiffness. In addition, the baPWV also decreased significantly from the baseline to the end of the study period in the subject group with baseline FMD values in the highest tertile. While arterial stiffness has been demonstrated as an independent risk factor for future cardiovascular events [19], no strategy for de-stiffening of the arteries has been established yet. The results of the present study serve to emphasize that maintenance of a healthy endothelium and/or improvement of endothelial dysfunction are important to counteract the progression of arterial stiffness.

On the other hand, increased arterial stiffness causes greater exposure of the endothelium to hemodynamic load [12], which has been speculated to augment endothelial dysfunction via reducing NO bioavailability and increasing oxidative stress [25]. However, in the present study, the baPWV measured at the baseline was not found to be associated with the FMD measured at the end of the study period. Furthermore, there were no significant differences in the delta-change of FMD during the study period among subjects with baseline baPWV values in the lowest, intermediate and highest tertiles (T1, T2 and T3). Thus, we could not confirm augmentation of endothelial dysfunction by increased arterial stiffness in the present study.

4.2. Vascular function and subclinical organ damage

Several experimental studies have demonstrated that not only endothelial dysfunction, but also abnormal medial vascular smooth muscle cell behaviors and/or alterations of the medial extracellular matrix composition and organization contribute to atherosclerosis [26,27]; these pathophysiological abnormalities of the intima and media also contribute to arterial stiffness [7]. Among the risk factors for cardiovascular disease, hypertension is known as a major determinant of arterial stiffness [28]; therefore, the combination of endothelial dysfunction with pathophysiological abnormalities of the media may contribute to the progression of atherosclerosis in hypertension. Therefore, as compared to endothelial dysfunction (assessed by FMD), arterial stiffness (assessed by the baPWV) may show a closer association with the progression of atherosclerotic vascular damage (assessed by CIMT) in subjects with hypertension under antihypertensive medication. In addition, the CIMTmean is actually a measure of arterial wall hypertrophy, which determines the arterial stiffness to some extent. That may serve as a plausible explanation for why the baPWV was associated with the changes of the CIMTmean, but not with those of the CIMTmax.

In two previous prospective studies, the FMD value measured at the study baseline was found to be an independent predictor of the progression of carotid atherosclerosis during the study period [8,9]. However, FMD is also known to show intra-subject variability [29], and the longitudinal intra-subject variations of the control status of the cardiovascular risk factors also affect the FMD value [4]. However, in the present longitudinal study, no longitudinal association could be confirmed between the FMD and CIMT. A plausible explanation for these conflicting findings is as follows; the MESA study has reported that the use of antihypertensive medication(s) was associated with slower progression of the CIMT [30]; the discrepant findings between our studies and the two aforementioned studies could be attributable to the fact that <50% of the study participants in the two previous studies were under antihypertensive medication [8,9].

Several cross-sectional studies have reported the existence of an association between FMD and eGFR decline/microalbuminuria in patients with diabetes mellitus and/or hypertension [10,11]. The PWV has been reported to be a significant predictor of eGFR decline and/or microalbuminuria [15,16]. However, in the present study, we could not confirm any significant longitudinal relationship of either FMD or baPWV with eGFR decline/microalbuminuria. The plausible explanations for these findings are as follows; 1) Antihypertensive medications, especially renin-angiotensin system blockers (RAS blockers), exert beneficial effects on the FMD, PWV, eGFR and microalbuminuria [3,4,31]; 2) Microalbuminuria and reduced glomerular filtration rate are observed even in subjects with preclinical hypertension (i.e., prehypertension/high normal blood pressure) [32,33]. These aspects of renal damage are mainly a consequence of arteriolar lesions, and usually precede stiffness or other functional abnormalities of the large arteries. Further longitudinal studies are needed to clarify the associations among endothelial function, arterial stiffness and renal function decline in patients with early-stage hypertension and also in those under antihypertensive medication, especially RAS blockers.

4.3. Study strengths and limitations

The strengths of the present study were as follows: all steps were taken in the study to reduce any measurement bias (i.e., acceptable reliability of the FMD assessment at individual participating institutions was ensured [18], and the CIMTs were analyzed at a core laboratory [19]). The study limitations were as follows: 1) a clear FMD image could not be obtained in 10% of the study subjects, and the 3-year follow-up could not be completed in 20% of the study subjects. However, the clinical characteristics of the subjects included in and excluded from the analyses were mostly similar (Supplementary Table 2); 2) the change in the shear rate before and after hyperemia is thought to affect the measured value of FMD, and normalization of the FMD value by the change in the shear rate has been proposed [34]; however, in this study, we did not measure this normalized FMD value; 3) nitroglycerine-induced vasodilatation was not employed in the present study; 4) further study is proposed to confirm the significance of the endothelial dysfunction-arterial stiffness-atherosclerosis continuum in subjects with risk factors for cardiovascular diseases other than hypertension; 5) we did not examine the effects of antioxidant vitamin intake on the FMD and PWV values [35]; 6) we did not examine the association of vascular dysfunction with hypertensive cardiac abnormalities (i.e., left ventricular hypertrophy and/or cardiac diastolic dysfunction).

5. Conclusions

Endothelial dysfunction (assessed by FMD) was associated with the longitudinal progression of arterial stiffness, although the reverse association was not confirmed. In subjects with lower FMD values at the baseline, the arterial stiffness increased during the study period. Increased arterial stiffness, which is affected to a greater extent by intimal and medial abnormalities than by endothelial dysfunction, was more closely associated with the progression of atherosclerosis, although no such association was found with the progression of renal damage. Finally, the endothelial dysfunction-arterial stiffness-atherosclerosis continuum may be important in hypertension.

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Conflict of interest/disclosure

None.

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