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Original Article

Relationships of Age and Gender with Ankle-brachial Systolic Pressure Index and Cardio-ankle Vascular Index in Patients with Diabetes Mellitus

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SUMMARY

Background: Cardio-ankle vascular index (CAVI) and ankle-brachial systolic pressure index (ABI) are used as indicators of atherosclerotic progression, which is more prominent in the elderly than in the young. The relationships of age and gender with these indicators were investigated in patients with diabetes mellitus.
Methods: Subjects were outpatients with type 2 diabetes (113 men and 53 women). CAVI and ABI were simultaneously measured at rest. ABI was also measured after leg exercise. Patients with ABI higher than 1.3 were excluded from the subjects.
Results: CAVI and ABI were significantly higher in men than in women, while % decrease in ABI after exercise was not significantly different in men and women. Both in men and women, CAVI was not significantly correlated with ABI and % decrease in ABI. Both in men and women, there were significant correlations between age and CAVI (men, $r = 0.497$ [$p < 0.01$]; women, $r = 0.480$ [$p < 0.01$]). In men, age did not show significant correlations with ABI ($r = -0.167$) and % decrease in ABI after exercise ($r = 0.129$). In women, age showed a significant correlation with ABI ($r = -0.280$ [$p < 0.05$]) but not with % decrease in ABI after exercise ($r = 0.020$).
Conclusion: In male and female patients with diabetes, ABI was not associated with CAVI. Age was related more strongly with CAVI than with ABI. Thus, CAVI is thought to be a more reliable marker than ABI for atherosclerotic progression in patients with diabetes.

1. Introduction

Age and gender are destined risk factors for atherosclerosis, which is accelerated by aging but is retarded in premenopausal women, compared with that in men at the same ages, by the actions of sex hormones.[1] However, diabetes has been shown to modify the relationship between atherosclerotic risk and gender: the associations of diabetes with the risks of coronary heart disease and ischemic stroke were shown to be stronger in women than in men in a meta-analysis.[2] In addition, an adverse cardiometabolic risk profile, including abdominal obesity, hypertension, dyslipidemia and metabolic syndrome, was shown to be more prevalent in women with diabetes than in men with diabetes.[3–5]

The risk of peripheral arterial disease (PAD), which is due to atherosclerosis in lower extremity arteries, is also greatly increased by the presence of diabetes.[6] The ankle-brachial systolic pressure index (ABI) is a standard diagnostic tool for patients with PAD. However, patients with diabetes are prone to have calcium deposition in the media of arteries, especially in that of ankle arteries,[7] and this causes arterial wall stiffness, resulting in high blood pressure in the ankle and thus a high ABI.[8] Therefore, it has been pointed out that ABI underestimates the prevalence of PAD in diabetic patients at high risk for arterial disease, and patients with high ABI (> 1.3) as well as those with low ABI (< 0.9) are considered to be at high risk for PAD.[8] It remains to be determined whether ABI

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can be used to evaluate ischemia in lower limb arteries of patients with diabetes.

Aortic stiffness results from a degenerative process affecting mainly the extracellular matrix of elastic arteries and causes reduction of the capability of an artery to expand and contract in response to pressure changes.[9,10] Stiffness of large arteries is increased in the presence of atherosclerosis, but the inter-relationship between atherosclerosis and arterial stiffness is complex and the nature of the possible link between them is not clearly established.[10] In diabetes mellitus, advance glycation endproducts (AGEs) and nitric oxide dysregulation play critical roles in the pathogenesis of arterial stiffness.[11]

Cardio-ankle vascular index (CAVI)[12] and ABI are conventional non-invasive methods for evaluation of arterial stiffness in the aorta and leg arterial flow, which reflect degrees of atherosclerosis in the aorta and leg artery, respectively. There is a merit that CAVI and ABI can be measured simultaneously using an automatic device (VaSera VS-3000, Fukuda Denshi, Tokyo, Japan). The purpose of this study was to elucidate the relationships of atherosclerosis with age and gender using measurements of CAVI and ABI, different indicators of atherosclerotic progression, in patients with diabetes.

2. Subjects and methods

2.1. Subjects

The subjects of this study were 115 male and 55 female outpatients who had been diagnosed as having type 2 diabetes mellitus. Patients with ABI higher than 1.3 (2 men and 2 women) were excluded from the subjects because of possible calcification of ankle arteries. This study was approved by the ethics committees of Kobe Tokushukai Hospital (number: TGE00313-014) and Hyogo College of Medicine (number: 1766). Individual histories of illness, medication and cigarette smoking were surveyed by questionnaires.

2.2. Measurements

Height and body weight were measured with light clothes at the health checkup. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Fasted blood and urine were sampled from each subject in the morning. Serum HDL cholesterol and LDL cholesterol concentrations were measured by enzymatic methods using commercial kits, HDL-EX and LDL-EX(N) (DENKA SEIKEN CO., LTD. Tokyo, Japan), respectively. Serum C-reactive protein (CRP) concentration was measured by the latex agglutination immunophotometric assay using a commercial kit (CRP-latex X2, Denka Seiken Co.,Ltd, Gosen, Niigata, Japan). Hemoglobin A1c was measured by using an automatic glycol-hemoglobin analyzer based on high-performance liquid chromatography (ADAMS A1c HA-8181, ARKRAY, Inc. Kyoto, Japan). Since the standards of hemoglobin A1c used for measurement are different in the NGSP (National Glycohemoglobin Standardization Program) method and the JDS (Japan Diabetes Society) method, hemoglobin A1c values were calibrated by using a formula proposed by the JDS: hemoglobin A1c (NGSP) (%) $=$ 1.02 x hemoglobin A1c (JDS) (%) $+$ 0.25%. Subjects with diabetes were defined as those receiving drug therapy for diabetes and/or those showing high hemoglobin A1c levels ($\geq$ 6.5%), according to the criteria for diagnosis of diabetes by the American Diabetes Association.[13] Blood glucose was measured by using an automatic glucose analyzer based on the GOD/hydrogen peroxide electrode method (ADAMS Glucose GA-1171, ARKRAY, Inc. Kyoto, Japan). Urine protein concentrations were measured by the Pyrogallol Red method, using a commercial kit (Protein Assay BCA Kit, Wako Pure Chemical Industries, Ltd, Osaka, Japan).

After each subject had rested in the supine position, ABI and CAVI were measured by an oscillometric method using an automatic device (VaSera VS-3000, Fukuda Denshi, Tokyo, Japan). ABI was also measured after stress loading. For load stress to the legs, fatigue in the gastrocnemius and soleus muscles was induced by an isotonic ankle plantar flexion exercise using a leg loader (VSL-100A, Fukuda Denshi, Tokyo, Japan) as reported previously.[14] Lower and higher values measured at the right or left legs were used for analysis of ABI and % decrease in ABI after stress loading, respectively. Leg exercise results in increases in systolic pressures of the left ventricle and central circulation, while systolic pressure decreases at the ankle owing to vasodilation in exercising muscle, leading to a mild decrease in ABI when measured immediately after exercise cessation. In patients with PAD, ankle pressure decreases more during exercise compared with that in individuals without PAD.[15] The cut-off value used for low ABI was 0.9. Arterial pressure of the right brachial artery was also recorded using CAVI-VaSera VS-3000. Mean arterial pressure was defined as systolic blood pressure $+1/3$ x (systolic blood pressure $-$ diastolic blood pressure). CAVI was calculated as reported previously,[12] and the normal range of CAVI was defined as $<$ 10.0 m/sec.

2.3. Statistical analysis

Statistical analyses were performed using a computer software program (SPSS version 16.0 J for Windows, Chicago IL, USA). Data are presented as means $\pm$ standard deviations or errors for variables showing normal distributions and medians with 25 and 75 percentile values for variables (% decrease in ABI after exercise) not showing normal distributions. Means of each variable were compared between men and women by using Student's t-test or the Mann-Whitney *U* test. Categorical variables were compared using the chi-squared test. In multivariate analysis, the mean levels of each variable were compared by using analysis of covariance (ANCOVA) followed by Student's t-test after Bonferroni correction. In linear regression analysis, Pearson's correlation coefficients, Spearman's rank correlation coefficient, and standardized regression coefficients were calculated. Since % decrease in ABI after exercise did not show a normal distribution and its log transformation was impossible due to inclusion of the value of zero, the multivariate linear regression analysis for % decrease in ABI after exercise could not be performed. Probability (p) values less than 0.05 were defined as significant.

3. Results

3.1. Comparison of the characteristics of male and female subjects

Table 1 shows the characteristics of subjects. Mean ages of men and women were comparable. The percentage of smokers was significantly higher in men than in women. The percentage of current drinkers was significantly higher in men than in women, and the percentage of subjects showing proteinuria was slightly but not significantly higher in men than in women. Systolic and diastolic blood pressure levels and the percentage of subjects with hypertension were not significantly different in men and women. HDL cholesterol was significantly higher in women than in men, while LDL cholesterol and ratio of LDL cholesterol to HDL cholesterol were not significantly different in men and women. Fasted blood glucose and hemoglobin A1c were significantly higher in men than in women. CAVI and the percentage of subjects showing high CAVI were significantly higher in men than in women. ABI was significantly lower in women than in men, and the percentage of subjects showing low ABI tended to be higher in women than in

Table 1
Characteristics of subjects.

	Men	Women
Number	113	53
Age (years)	68.7 ± 9.4	68.7 ± 8.9
Smokers (%)	29.2	3.8**
Alcohol drinkers (%)	47.8	28.3*
Proteinuria (%)	24.8	16.8
Body mass index	24.8 ± 4.1	25.9 ± 5.0
Systolic blood pressure (mmHg)	138.5 ± 19.3	144.2 ± 20.5
Diastolic blood pressure (mmHg)	85.4 ± 11.1	83.5 ± 10.5
Hypertension (%)	80.5	92.5
HDL cholesterol (mg/dl)	52.5 ± 18.4	63.8 ± 23.0**
LDL cholesterol (mg/dl)	106.1 ± 29.3	114.7 ± 35.6
LDL cholesterol-to-HDL cholesterol ratio	2.28 ± 0.99	2.01 ± 1.00
Fasted blood glucose (mg/dl)	140.5 ± 48.7	116.9 ± 21.0**
Hemoglobin A1c (%)	7.27 ± 1.20	6.80 ± 1.00*
C-reactive protein (mg/dl)	0.1 (< 0.1, 0.22)	0.1 (< 0.1, 0.18)
CAVI	9.72 ± 1.51	8.90 ± 1.20**
High CAVI (%)	43.4	18.9**
ABI	1.08 ± 0.15	1.03 ± 0.16*
Low ABI (%)	8.0	13.2
Decrease in ABI after exercise (%)	3.42 (−0.94, 7.29)	3.88 (−0.84, 8.86)

Numbers, means with standard deviations and percentages of the variables are shown. Medians with 25 and 75 percentile values in the parentheses are given for C-reactive protein and decrease in ABI after exercise. Asterisks denote significant differences from men. *, $p < 0.05$; **, $p < 0.01$.

men, although the difference was not significant. Decrease in ABI after exercise was not significantly different in men and women.

3.2. Correlations between each pair of the indicators of atherosclerotic progression in men and women

There were no significant correlations between each pair among CAVI, ABI and decrease in ABI after exercise in men and women (Pearson's correlation coefficient: between CAVI and ABI, 0.092 [$p = 0.331$] in men and −0.062 [$p = 0.661$] in women; Spearman's rank correlation coefficient: between CAVI and decrease in ABI after exercise, 0.011 [$p = 0.910$] in men and −0.019 [$p = 0.893$] in women; between ABI and decrease in ABI after exercise, −0.011 [$p = 0.909$] in men and 0.059 [$p = 0.677$] in women).

3.3. Correlations between age and each indicator of atherosclerotic progression in men and women

Table 2 shows results of univariate and multivariate analyses for the relationships of age and three indicators of atherosclerotic progression. Multivariate linear regression analysis for the relationships of age with CAVI and ABI was performed using various variables including smoking, BMI, mean arterial pressure, hemoglobin A1c, ratio of LDL cholesterol to HDL cholesterol and CRP. As shown in Table 2, in men, CAVI showed significant positive correlations with age and mean arterial pressure and a significant inverse correlation with BMI, while ABI showed no significant correlation with any of the explanatory variables tested. In women, CAVI showed a significant positive correlation with age but not with other explanatory variables tested, and ABI showed a significant inverse correlation with age but not with other explanatory variables tested. Scatter plots for the relationships are shown in Fig. 1. Both in men and women, decrease in ABI after exercise showed no significant correlation with age.

In order to remove the effect of confounding by smoking, relationships of age with ABI, decrease of ABI after exercise and CAVI were investigated in male nonsmokers (n = 80). In male nonsmokers, a significant correlation of age was found with % decrease of ABI after exercise but not with ABI, while there was a relatively strong correlation between age and CAVI in male nonsmokers

Table 2
Correlations between age and each of the indicators and risk factors for atherosclerosis in men and women.

	CAVI	ABI	Decrease in ABI after exercise
Men			
Univariate analysis			
Age	0.497**	−0.167	0.129
Multivariate analysis			
Age	0.412**	−0.118	n.d.
Smoking	−0.017	−0.141	n.d.
BMI	−0.190*	0.173	n.d.
MAP	0.310**	0.128	n.d.
Hemoglobin A1c	0.016	−0.137	n.d.
LDL-C/HDL-C	−0.036	−0.010	n.d.
CRP	0.126	−0.123	n.d.
Women			
Univariate analysis			
Age	0.480**	−0.280*	0.020
Multivariate analysis			
Age	0.389**	−0.368*	n.d.
Smoking	−0.226	−0.291	n.d.
BMI	−0;189	−0.040	n.d.
MAP	0.326*	−0.148	n.d.
Hemoglobin A1c	−0.057	0.058	n.d.
LDL-C/HDL-C	0.041	−0.172	n.d.
CRP	−0.157	−0.055	n.d.

Shown are Pearson's correlation coefficients or Spearman's rank correlation coefficients in univariate analysis and standardized regression coefficients in multivariate analysis. Since %decrease in ABI after exercise did not show a normal distribution, Spearman's correlation coefficient was used for this variable. Pearson's correlation coefficients were used for CAVI and ABI. In multivariate analysis, smoking, BMI, mean arterial pressure (MAP), hemoglobin A1c, LDL cholesterol-to-HDL cholesterol ratio (LDL-C/HDL-C) and CRP were used as other explanatory variables. *, $p < 0.05$; **, $p < 0.01$. n.d., not determined.

(Pearson's correlation coefficient: 0.460 [with CAVI, $p < 0.01$]; −0.172 [with ABI, $p = 0.127$]; Spearman's rank correlation coefficient, 0.232 [with decrease of ABI after exercise, $p < 0.05$]).

3.4. Comparison of each indicator of atherosclerotic progression in men and women

CAVI and ABI were compared between men and women. In the multivariate analysis, age, smoking, BMI, hypertension, HbA1c and

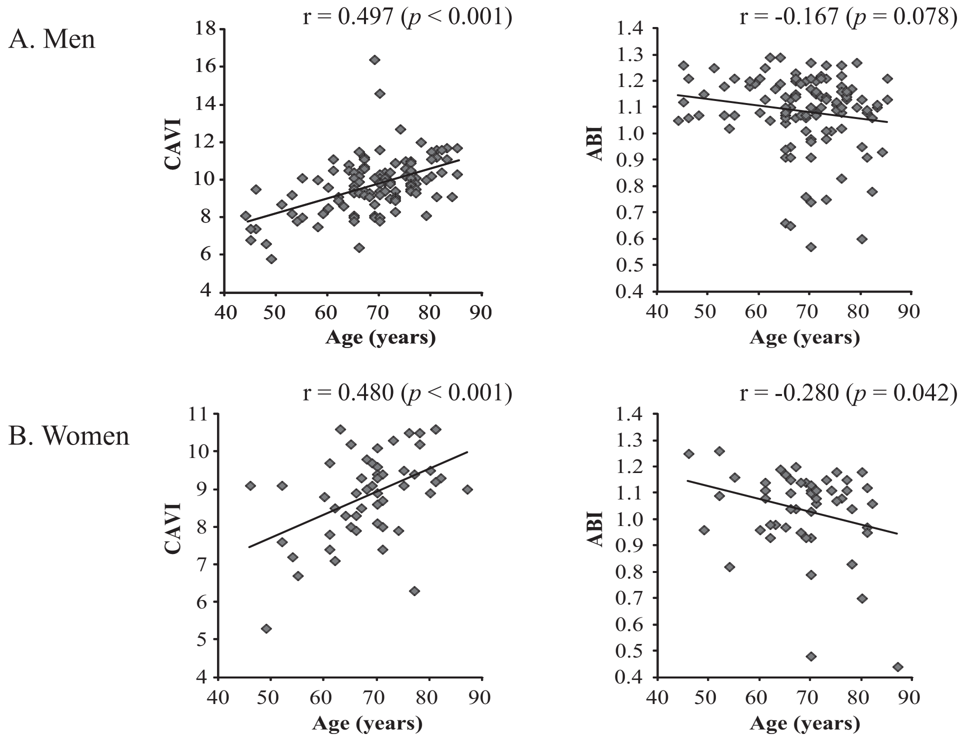

Fig. 1. Scatter plots of the relationships of age with CAVI and ABI in men (**A**) and women (**B**). Regression line, Pearson's correlation coefficient and its statistical significance for each relationship are shown in the figure.

LDL cholesterol-to-HDL cholesterol ratio were used as other explanatory variables. Adjusted means of CAVI and ABI as well as their crude means were significantly higher ($p < 0.01$) in men than in women (Fig. 2).

4. Discussion

Both in men and women with diabetes, age was shown to be associated with CAVI, a blood pressure-independent indicator of arterial stiffness,[12] which is closely related to atherosclerosis.[10] The association between age and CAVI was independent of other major risk factors of atherosclerosis including smoking, obesity, blood pressure, dyslipidemia, glycemic status and CRP. This finding is reasonable since arterial stiffness as well as atherosclerosis is accelerated by aging.[16] ABI was also inversely correlated with age both in uni- and multivariate analyses in women. Thus, the correlation between age and ABI is thought to reflect progression of leg arterial atherosclerosis with an increase of age in women. However, in men, age was not associated with ABI and exercise-induced decrease in ABI in the present study. These findings suggest that ABI does not reflect atherosclerotic progression in male patients with diabetes. Moreover, ABI and its decrease by exercise were not significantly correlated with CAVI both in male and female patients with diabetes. Therefore, ABI is not a reliable indicator for atherosclerotic progression in lower limb arteries of diabetic patients. CAVI showed a significant inverse correlation with BMI in men. One

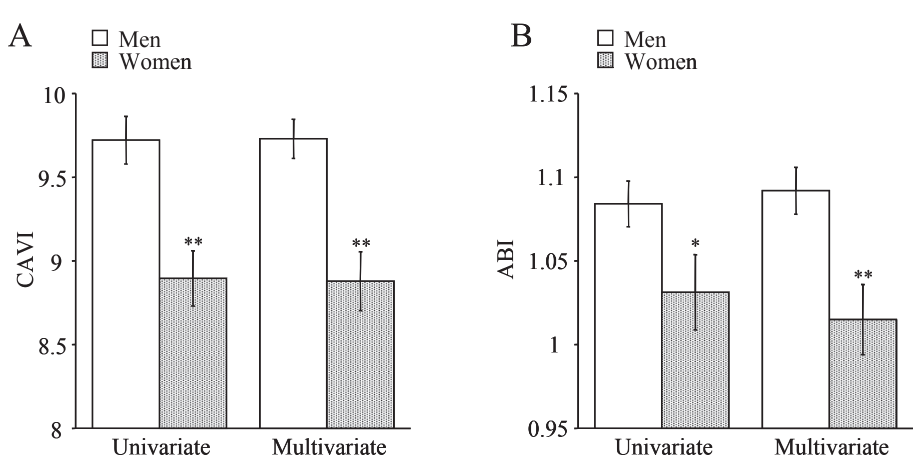

Fig. 2. Comparison of mean CAVI and ABI between men and women in univariate (**A**) and multivariate (**B**) analyses. In the multivariate analysis, age, smoking, BMI, hypertension, hemoglobin A1c and LDL cholesterol-to-HDL cholesterol ratio were used as other explanatory variables. Means and their standard errors of CAVI and ABI are shown. Asterisks denote significant differences from men (*, $p < 0.05$; **, $p < 0.01$).

possible explanation for this association is that BMI decreases with progression of diabetes stage in elderly men, which is associated with arterial stiffness.[11]

In the analysis for overall male and female subjects, a significant correlation was found between age and ABI in women but not in men. Thus, there seems to be a gender-related difference in the relationship between age and ABI. It is reasonable that there was a positive correlation between age and CAVI both in men and women since atherosclerosis progresses with an increase of age, and CAVI is a marker of arterial stiffness that strongly reflects atherosclerosis. On the other hand, ABI was significantly correlated with age in women but not in men. A possible reason for no association between age and ABI in men is complicated calcification in arteries of patients with diabetes, which results in higher ABI.[8] Moreover, a possible reason for the gender-related difference in the relationship between age and ABI is less arterial calcification in women than in men, resulting in a significant correlation between age and ABI in women but not in men, although this possibility needs to be examined in the future.

A significant correlation between age and decrease in ABI after exercise was found in male nonsmokers, while no significant correlation was observed between age and decrease in ABI after exercise in overall male subjects. Thus, smoking is thought to confound the relationship between age and % decrease of ABI after exercise in men. This is reasonable because smoking is a major risk factor for PAD and the percentage of smoker declines at elderly ages. The reason for no significant correlation between age and ABI in male smokers might be due to lower sensitivity of ABI than exercise-induced decrease of ABI to detect leg ischemia in patients with diabetes.

The percentages of subjects with hypertension and level of systolic blood pressure were slightly but not significantly higher in women than in men. ABI was significantly lower in women than in men and, the prevalence of PAD (ABI < 0.9) was slightly but not significantly higher in women than in men. These results agree with the findings of previous studies that an adverse cardiometabolic risk profile, including abdominal obesity, hypertension, dyslipidemia and metabolic syndrome, was shown to be more prevalent in women with diabetes than in men with diabetes.[3–5] Although the exact reason for the gender-related difference in the cardiovascular risk profile in patients with diabetes remains unknown, there are two possible reasons as follows. One is attenuation of estrogen-related protective mechanisms in women with type 2 diabetes, which is likely to be due to a decrease in ovarian aromatase activity.[17] Control of systolic blood pressure and LDL cholesterol after cardiovascular events was reportedly poorer in women with diabetes than in men with diabetes.[18] Thus, the other possible reason for the gender-related difference in the cardiovascular risk profile in diabetes patients is poorer control and treatment of cardiovascular disease risk factors in female patients with diabetes than in male patients.

5. Conclusion

CAVI was associated with age in male and female diabetes patients, and ABI was associated with age in female patients but not in male patients. In female patients, CAVI was associated with age more strongly than was ABI. There was no association between CAVI and ABI in male and female patients. Therefore, ABI may not be a reliable indicator for atherosclerotic progression in patients with diabetes. The population size of the subjects was small in the present study, and further studies using larger populations of patients with diabetes are needed to confirm the findings of the present study.

Conflicts of interest

The authors declared no conflict of interest.

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