International Journal of Gerontology xxx (2018) 1–5

Contents lists available at ScienceDirect

International Journal of Gerontology

journal homepage: www.ijge-online.com

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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ARTICLE INFO

Article history:
Received 15 June 2016
Received in revised form
17 December 2016
Accepted 26 May 2017
Available online xxx

Keywords:
ABI,
Aging,
Atherosclerosis,
CAVI,
Diabetes mellitus

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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https://doi.org/10.1016/j.ijge.2017.05.004

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