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Non-linear association between ankle-brachial pressure index and prevalence of silent cerebral infarction in Japanese patients with type 2 diabetes

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ABSTRACT

Objective: Patients with peripheral artery disease (PAD), defined as having low ankle-brachial pressure index (ABI), have increased risk for incident stroke compared with those without PAD. We aimed to reveal whether ABI abnormality, especially high ABI is associated with prevalent silent cerebral infarction (SCI) in type 2 diabetic patients.
Methods: We studied 538 Japanese type 2 diabetic patients, 227 women and 311 men, with a mean [±SD] age of 64 ± 11 years. All patients underwent cranial magnetic resonance imaging (MRI). Values of ABI were classified as low (<0.9), normal (0.9≤ and <1.3), and high (1.3≤). Logistic regression model was used to calculate odds ratio and 95% confidence interval (95% CI) for prevalent SCI.
Results: The mean ABI among the overall 538 patients was 1.09 ± 0.16. Low and high ABI values were found in 52 (9.7%) and 33 (6.1%) patients, respectively. SCI was detected in 297 (55.2%) patients. The prevalence in patients with low, normal, and high ABI values were 88.5%, 49.7%, and 78.8 (p < 0.001), respectively. In the multivariate logistic regression analysis, both patients with high and low ABI were significantly increased risk of prevalent SCI (odds ratio 4.53, 95% CI 1.67–12.34, p = 0.003 and odds ratio 3.50, 95% CI 1.50–10.29, p = 0.005), independently of other traditional cardiovascular risk factors, than those with normal ABI.
Conclusions: Both high and low ABI may be strongly associated with prevalent SCI in Japanese patients with type 2 diabetes.

1. Introduction

Ankle-brachial pressure index (ABI) is recognized as an easy, reliable, and noninvasive measurement of the presence and severity of peripheral artery disease (PAD) of lower extremities [1]. A low ABI has been reported to be associated with not only incident cardiovascular disease (CVD) in general population [2,3] and in patients with diabetes [4] but also recurrent stroke in patients with acute ischemic stroke or transient ischemic attack [5]. With regard to a high ABI, recent data from the Framingham Study [6] and Cardiovascular Health Study [7] indicated a significant association between a high ABI and incident CVD. Diabetic patients carry an increased risk of high ABI as well as low ABI due to the stiffened and even incompressible ankle arteries [8]. Therefore, it is clinically important to evaluate ABI abnormalities and estimate the risks of cardiovascular events in diabetic patients.

Silent cerebral infarction (SCI) is defined as a cerebral infarction that is detected by cranial magnetic resonance imaging (MRI), but has not been associated with clinical signs or symptoms corresponding to a stroke. SCI has also been reported to be associated with incident symptomatic stroke in general population [9]. Therefore, such infarcts should not be considered as benign even though patients with SCI have no symptom. With regard to the association between ABI and SCI, recent data from the Cardiovascular Health Study [10] revealed that a low ABI is significantly associated with incident SCI in general population. However, its predictive value in patients with diabetes who have increased risk of CVD including PAD, as compared with non-diabetic subjects, has received little attention. Furthermore, whether diabetic patients with a high ABI associate higher prevalence of SCI remains unknown. We, therefore, conducted this cross-sectional study to highlight the relationship of high and low ABI with prevalent SCI in Japanese patients with type 2 diabetes.

Abbreviations: ABI, ankle-brachial pressure index; ACR, albumin-to-creatinine ratio; CAD, coronary artery disease; CVD, cardiovascular disease; GFR, glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAD, peripheral artery disease; PWV, pulse wave velocity; SCI, silent cerebral infarction.

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2. Methods

2.1. Study population

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Tokyo Women's Medical University School of Medicine ethical committee. We studied Japanese type 2 diabetic patients consecutively visited at the Diabetes Center, Tokyo Women's Medical University Hospital, in Tokyo, Japan during the period between July 1, 2003 and April 30, 2008. Patients were eligible for the current study if patients were 20 years or older, had an estimated glomerular filtration rate (eGFR) $\geq$15 mL min^{-1} 1.73 m^{-2} and underwent an evaluation of SCI by cranial MRI and PAD by ABI. Patients undergoing renal replacement therapy, and those with infectious and malignant disease were excluded. Patients with a history of major amputation or percutaneous angioplasty of lower limbs were also excluded. Type 2 diabetes was diagnosed according to criteria from the World Health Organization [11].

Participants underwent routine medical history and physical examination as well as blood sampling. Information regarding smoking was obtained by using a standard questionnaire. Smoking habits were classified as current or not. Physical examination included blood pressure measurement and anthropometry; laboratory examinations included HbA1c, serum lipids, and creatinine, urinary albumin in the first morning urine specimen. Ophthalmoscopic examinations were performed by ophthalmologists in our center and diabetic retinopathy was evaluated by the international clinical diabetic retinopathy disease severity scale, proposed by the American Academy of Ophthalmology [12]. History of CVD was defined as stroke/transient ischemic attack and coronary artery disease (CAD). Clinical evidence of CAD was defined as the presence of any of the following conditions: angina pectoris which was diagnosed by clinical symptoms; coronary artery stenosis which was evaluated by coronary angiography; a history of myocardial infarction or previous coronary revascularization.

2.2. Measurements

Blood pressure was measured in the sitting position after at least 5 min rest, using an oscillometric Omron HEM-707 device (Omron Inc., Kyoto, Japan). ABI and Brachial-ankle PWV (baPWV) were measured automatically by using a FORM PWV/ABI device (Colin Co., Komaki, Japan) consisting of an automatic sphygmomanometer (BP-203RPE) with the subject in the supine position after a 5 min rest. Standard 12 cm blood pressure cuffs were applied to both ankles and arms to calculate ABI automatically [13]. ABI was calculated separately for each leg, the highest arm pressure was used to calculate ABI because of the strong association between PAD and subclavian artery stenosis [14]. Patients were classified into one of three ABI categories: "normal" when both legs had values of ABI greater than or equal to 0.9 and less than 1.3, "low" when at least one leg had a value of ABI less than 0.9, and "high" when at least one leg had a value of ABI equal to or greater than 1.3 and the other leg had a ABI more than 0.9. The lower ABI values of both legs were selected in patients with normal and low ABI and the higher ABI values of both legs were selected in those with high ABI in the present study. baPWV was conducted for screening of arterial stiffness in our hospital and there were no significant differences of age and gender between patients who had PWV measured and those not.

The presence of SCI was assessed by cranial MRI, as described previously [15,16]. In brief, SCI was defined as an area of low signal intensity measuring at least 3 mm on T1-weighted images which was also visible as a hyperintense lesion on T2-weighted images, without corresponding symptoms, in accordance with draft clinical guidelines of the Japanese Society for Detection of Asymptomatic Brain Disease [17]. In each case, SCI was diagnosed by consensus of two neuroradiologists at the Tokyo Women's Medical University Hospital.

In Japan, HbA1c has been measured by high-performance liquid chromatography (HPLC) by using a set of calibrators assigned by the Japan Diabetes Society (JDS, normal range: 4.3–5.8%). According to the correlational analysis, HbA1c values in Japan were estimated to be 0.4% lower than those measured by the National Glycohemoglobin Standardization Program (NGSP). To internationally standardize HbA1c values to NGSP units, 0.4% was added to the measured values and HbA1c values were expressed corresponding to NGSP units in this study [18].

Urinary albumin was measured using the latex agglutination method and was normalized by urinary creatinine and represented as albumin-to-creatinine ratio (ACR, mg/g). GFR was estimated by using the following modified three-variable equation for Japanese, as proposed by the Japanese Society for Nephrology: eGFR (mL min^{-1} 1.73 m^{-2}) = 194 × SCr ([μmol/L] divided by 88.4)$^{-1.094}$ × age (years)$^{-0.287}$ ([if female] × 0.739) [19].

High-density lipoprotein (HDL) cholesterol was determined enzymatically. Low-density lipoprotein (LDL) cholesterol was measured by a direct method or calculated using the Friedewald equation when serum triglycerides level was <4.48 mmol/L [20].

2.3. Statistical analyses

Data were expressed as percentage, arithmetic mean ± SD or geometric mean with 95% confidence interval (CI), as appropriate according to data distribution. Serum triglycerides and urinary ACR were logarithmically transformed due to skewed distributions. For statistical analyses, one-way analysis of variance (ANOVA) was used for between-group comparisons for continuous variables and the χ^2 test for categorical variables. Odds ratios and the 95% CI for predicting the prevalent SCI were estimated using multivariate logistic regression analyses with a stepwise selection procedure. Covariates incorporated in the model were; age, sex, duration of diabetes, presence of proliferative diabetic retinopathy, smoking status, systolic and diastolic blood pressures, body mass index, use of insulin, renin-angiotensin system inhibitors, antiplatelet agents and statins, HbA1c, triglycerides, HDL and LDL cholesterol levels, hemoglobin, uric acid, eGFR, urinary ACR. All statistical analyses were performed using the Statistical Analysis System (SAS Institute, Cary, USA) version 9.2. A p value <0.05 was considered significant.

3. Results

538 type 2 diabetic patients undergoing cranial MRI and ABI test at the Diabetes Center, Tokyo Women's Medical University hospital during the period between July 1, 2003 and April 30, 2008 were studied in the present study. There were 227 women and 311 men, and the mean (±SD) age was 64 ± 11 years (range: 32–89 years). The mean ABI among all 538 patients was 1.09 ± 0.16 (range: 0.39–1.90). Low and high ABI values were found in 52 (9.7%) and 33 (6.1%) patients, respectively. Clinical characteristic and laboratory data in patients with each ABI groups are listed in Table 1. There were significant differences of age, prevalence of CVD, diastolic blood pressure and pulse pressure among patients with the three ABI categories. Patients with high and low ABI were more likely to be treated with calcium channel blockers, diuretics and antiplatelet agents. They also had lower hemoglobin and estimated GFR and higher urinary ACR levels than those with normal ABI values. Medications and laboratory data are also shown in Table 1.

SCI was detected in 297 (55.2%) patients. As shown in Fig. 1, the prevalence in patients with low, normal, and high ABI values