Prevalence of Peripheral Arterial Disease and Risk Factors for the Low and High Ankle-Brachial Index in Chinese Patients with Type 2 Diabetes

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The aim of this study was to evaluate the prevalence of peripheral arterial disease (PAD) in Chinese type 2 diabetic patients, and to compare the different risk factors for the low and high ankle-brachial index (ABI). A total of 2040 patients (1001 men and 1039 women) aged 67.0 ± 10.7 years were recruited from 8 university hospitals. PAD was diagnosed by ABI < 0.9 on either leg. Thirty-four possible risk factors were analyzed. Univariate analyses were used to compare the different risk factors between three ABI groups (ABI < 0.9, ABI 0.9–1.3 and ABI > 1.3), and logistic regression analyses were used to identify the independent risk factors. The overall prevalence of PAD was 16.7%. Older age, female gender, history of coronary heart disease (CHD), cerebral infarction (CI), PAD, claudication, longer diabetes mellitus (DM) duration, high blood pressure (HBP), smoking, using diuretics and having a high level of uric acid (UA) were independently associated with low ABI (ABI < 0.9), and male gender and high body mass index (BMI) were associated with high ABI (ABI > 1.3).

Key words ——— prevalence, peripheral arterial disease, risk factor, ankle-brachial index, type 2 diabetes

INTRODUCTION

peripheral arterial disease (PAD) is caused by atherosclerotic occlusion of the arteries to the legs, and increases the risk of cardiovascular (CVD) events.[1,2] Several cohort and randomly selected studies have revealed that CVD event rates in patients with PAD and diabetes mellitus (DM) are higher than those of their nondiabetic counterparts.[3–5] The increased mortality associated with PAD progression was significant only in individuals with DM (alone or with PAD). The adjusted risk of death for patients with PAD and DM was 2.2 times that for PAD alone.[6] PAD in DM also adversely affects quality of life, contributing to long-term disability and functional impairment that is often severe.[4,7] Due to the poor cardiovascular and functional outcomes associated with unrecognized PAD, the American Diabetes Association (ADA) consensus panel recommends screening for PAD in all diabetic patients older than 50 years, and is considering screening diabetic patients younger than 50 years if they have other risk factors (*e.g.* smoking, hypertension, hyperlipidemia, or duration of diabetes > 10 years).[4]

Using similar diagnostic techniques and criteria, the prevalence of PAD in diabetic patients seems to differ depending on the country and district, such as 3.6% in southern Sardinia,[8] 10.0% in Taiwan,[9] 11.8% in India,[10] 20.0% in U.S.A.[11] and 61.4% in Saudi Arabia.[12] The major risk factors for PAD in patients with type 2 diabetes were older age, lower body mass index (BMI), higher systolic blood pressure (SBP), duration of DM, pulse pressure, C-reactive protein, lipoprotein (a) and uric acid (UA) levels.[9,13–16]

The results of previous studies evaluating the risk factors for PAD in patients with type 2 diabetes have been reported. However, there have been few examinations about the presence of medial arterial calcification in diabetic patients. A recent prospective study using ankle-brachial index (ABI) showed that CVD deaths occurred in diabetic patients at a rate of 31.7 per 1000 person-years (PY) in the low-ABI (ABI < 0.9) group and 23.3 per 1000 PY in the high-ABI (ABI > 1.4) group. In the low-ABI group, all-cause mortality was 70.5 per 1000 PY and was 75.7 per 1000 PY in the high-ABI group.[17]

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The purpose of this study was to evaluate the prevalence and risk factors of PAD in Chinese patients with type 2 diabetes, and to compare the differences in these risk factors for low and high ABI.

MATERIALS AND METHODS

Subjects —— Subjects were recruited from the Endocrinology or Cardiology in-patient clinic at 8 university hospitals from July to November 2004 in Beijing and Shanghai. A total of 2040 type 2 diabetic patients (1001 men and 1039 women) participated, and the mean patient age was 67.0 ± 10.7 years. The patients were treated with either oral antidiabetic drugs or insulin at the time of recruitment. They had no history of diabetic ketoacidosis at the onset of DM, nor did they receive insulin treatment within 1 year of diagnosis. The study was approved by the ethics committee and informed consent was obtained from the subjects.

Diagnosis of PAD —— The diagnosis of PAD was based on an ABI < 0.9 on either side of the lower extremities as described in the ADA consensus recommendations. Doppler ultrasound (Nicolet Vascular, Elite100R, U.S.A.) was used to measure the systolic pressures on bilateral brachial, position tibial, and dorsal pedal arteries in a supine position after a 5-min rest. The occluding cuffs (55 × 12.5 cm) were applied just above the malleoli to measure ankle pressure. The Doppler probe was used at a frequency of 5 MHz. Right and left ABI were calculated by the higher pressure on the dorsal or posterior tibial arteries on the right and left sides, respectively, and by the higher brachial pressure on either side.

Risk Factors —— A questionnaire was developed to assess the general characteristics, diagnosis, medical history and relation factors, medical treatment and biochemical examination.

Possible risk factors included age, sex, BMI, history of coronary heart disease (CHD), percutaneous coronary angioplasty (PTCA), coronary artery bypass graft (CABG), CI, PAD, claudication, kidney trouble, history and duration of DM, high blood pressure (HBP), hyperlipidemia, smoking, and patients receiving drugs during the hospitalization period [including statins, fibrates, angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), anti-platelet, beta adrenergic blockade, Ca-channel antagonist, diuretics, oral antidiabetic drugs or insulin, nitrates, and digitalis], and biochemical analysis [including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), blood urea nitrogen (BUN), creatinine (CRE), UA, fasting plasma glucose (FPG)].

Statistical Analyses —— The data were analyzed using the software program SAS6.12. Continuous variables were expressed as the mean ± S.D., and categorical variables as percentage. Analysis of variance (ANOVA) (F-test), and the chi-square test were used to compare continuous and categorical differences, respectively, between three ABI groups in univariate analyses. A p-value of < 0.05 was considered statistically significant. Rewritten was used to identify the independent risk factors, and the odds ratios (OR) and their 95% confidence interval (CI) in three ABI groups of significant independent variables were estimated from logistic regression.

RESULTS

Prevalence of PAD

Among the 2040 participants, 340 were diagnosed with PAD. The overall prevalence of PAD was 16.7% and there was a gender difference, 15.1% men and 18.2% women ($p < 0.01$). Age was significantly associated with PAD in patients with type 2 diabetes. The age-specific prevalence of PAD for patients aged < 50, 50–69, ≥ 70 years was 2.92, 4.88, and 5.38%, respectively ($p < 0.05$). The prevalence of PAD was closely associated with the duration of DM. In DM durations of < 5, 5–14 and ≥ 15 years, the prevalence of PAD was 2.83, 5.63, and 10.2% ($p < 0.01$). The PAD prevalence was 24.2 and 15.3% for patients with and without CHD history, respectively ($p < 0.01$), and 23.2 and 13.2% for patients with and without CI history, respectively ($p < 0.01$). The prevalence of PAD was also found to be associated with using diuretics and serum UA levels. The respective prevalence for those not receiving or receiving diuretics was 13.7 and 24.8%, respectively ($p < 0.01$), and the serum UA value in patients with PAD were significantly higher compared with those without PAD. The differences in PAD prevalence in other factors were not statistically significant.

Comparison of Risk Factors in Three ABI Groups

Table 1 compares the possible risk factors in diabetic patients for three ABI groups. In univariate analyses by ANOVA (F-test) and chi-square test, 19 risk factors were significantly different. The mean age, percent history of CHD, CI, PAD, claudication,

Table 1. Comparison of Three ABI Groups on Risk Factor in Patients with Type 2 Diabetes

Risk Factor[a)]	ABI			
	< 0.9 (n = 340)	0.9–1.3 (n = 1526)	> 1.3 (n = 174)	total (n = 2040)
Age, mean (S.D.), Y	73 ± 7.92*,**	66 ± 10.8	66 ± 10.7	67 ± 10.7
Men, n (%)	151 (44.4)**	742 (48.6)	108 (62.1)†	1001 (49.1)
BMI, mean (S.D.), kg/m^2	24.2 ± 3.6**	24.4 ± 3.5	25.6 ± 4.7†	24.5 ± 3.7
CHD history, n (%)	78 (22.9)*,**	220 (14.4)	24 (13.8)	322 (15.8)
CI history, n (%)	162 (47.6)*,**	480 (31.5)	56 (32.2)	698 (34.2)
PAD history, n (%)	37 (10.9)*,**	61 (4.0)	4 (2.3)	102 (5.0)
Claudication history, n (%)	77 (22.6)*,**	135 (8.8)	15 (8.6)	227 (11.1)
DM duration, mean (S.D.), Y	8.6 ± 8.0*,**	6.7 ± 6.9	5.4 ± 5.5†	6.9 ± 7.0
HBP duration, mean (S.D.), Y	14.0 ± 13.9*,**	10.0 ± 11.6	9.4 ± 10.9	11.0 ± 12.0
PP, mean (S.D.), mmHg	63.8 ± 21.1*,**	59.7 ± 17.3	59.2 ± 17.2	60.4 ± 18.0
Smokers duration, mean (S.D.), Y	15.0 ± 20.3*,**	10.0 ± 16.0	12.0 ± 15.2	11.0 ± 16.8
Using Diuretic, n (%)	136 (40.0)*,**	371 (24.3)	41 (23.6)	548 (26.9)
Using ACEI, n (%)	194 (57.1)*	700 (45.9)	95 (54.6)†	989 (48.5)
Using Anti-platelet, n (%)	235 (69.1)*	967 (63.4)	127 (73.0)†	1329 (65.1)
Using nitrate, n (%)	201 (59.1)*	708 (46.4)	94 (54.0)	1003 (49.2)
Using digitalis, n (%)	47 (13.8)*,**	100 (6.6)	13 (7.5)	160 (7.8)
UA, mean (S.D.), mmol/l	342 ± 128*,**	308 ± 113	316 ± 108	315 ± 116
BUN, mean (S.D.), mmol/l	9.86 ± 20.5*,**	7.11 ± 7.76	6.81 ± 4.41	7.55 ± 12.4
CRE, mean (S.D.), mmol/l	108 ± 67.1*	95.2 ± 77.2	108 ± 102†	98.5 ± 78.2

Date are % or means ± S.D. *a*) BMI, Indicates body mass index; CHD, Coronary heart disease; CI, Cerebral infraction; PAD, Peripheral arterial disease; DM, Diabetes mellitus; HBP, High blood pressure; PP, Pulse pressure; ACEI, Angiotension converting enzyme inhibitor; UA, Uric acid. BUN, Blood urea nitrogen, CRE, Creatinine. ANOVA (F-test) for continuous variables. Chi Square Test for Categorical variables. p-Value derived from F-tests for means and X^2 tests for proprtions. *$p < 0.05$ ABI < 0.9 *vs.* ABI 0.9-1.3. **$p < 0.05$ ABI < 0.9 *vs.* ABI > 1.3. †$p < 0.05$ ABI 0.9-1.3 *vs.* ABI > 1.3.

HBP duration, smoking duration, percent using diuretics, nitrates or digitalis, levels of pulse pressure (PP), UA, or BUN in the ABI < 0.9 group were higher than in the ABI 0.9–1.3 and ABI > 1.3 groups. The male percent and mean BMI in the ABI > 1.3 group were higher than in the ABI < 0.9 and ABI 0.9–1.3 groups. The percent of ACEI and anti-platelet, and CRE levels in the ABI 0.9–1.3 group were lower than in the ABI < 0.9 and ABI > 1.3 groups. The DM duration was significantly different between three ABI groups.

Independent Risk Factors in Low and High ABI

To evaluate the independent significance of each associated factor studied, logistic regression analysis was used. Older age, female gender, history of CHD, CI, PAD, claudication, and longer DM, HBP or smoking, using diuretics and a higher serum level of UA were independently associated with low ABI (ABI < 0.9), and male gender and higher BMI were independently associated with high ABI (ABI > 1.3) in the type 2 diabetes (Table 2).

The serum level of UA was also found to be associated with diuretics. The UA value in patients taking diuretics was higher than patients without diuretics in the ABI < 0.9 and ABI 0.9–1.3 groups (Fig. 1).

DISCUSSION

In this study, the 16.7% prevalence of PAD in diabetics was higher than the 10.0% in Taiwan[9)] and 11.8% in India,[10)] and it was also lower compared with the 20.0% in U.S.A.,[11)] and 61.4% in Saudi Arabia.[12)] Different methods of recruitment, different sample sizes, and different distributions of risk factors can result in variations in the reported overall prevalence; it is also possible that the development of PAD in diabetic patients can vary in different ethnic groups.

Aging has been shown as an important risk factor for low ABI.[9,18)] In this study, low ABI patients with type 2 diabetes were older by univariate analysis and OR (CI) was 1.058 (1.042–1.074) by logistic regression analysis.

Table 2. ORs and Their 95% CI for Low and High ABI Groups in Patients with Type 2 Diabetes

Risk Factors[a)]	Change of Risk Factor	Low ABI		High ABI	
		OR (95%CI)	*p*	OR (95%CI)	*p*
Age	Per 1-year increase	1.058 (1.042, 1.074)	< 0.0001	1.004 (0.989, 1.020)	0.5805
Men	Yes *vs.* No	0.788 (0.678, 0.917)	0.002	1.325 (1.101, 1.594)	0.0028
BMI	Per 1kg/m2 increase	0.974 (0.939, 1.011)	0.1645	1.084 (1.039, 1.130)	0.0002
CHD history	Yes *vs.* No	1.216 (1.036, 1.427)	0.0166	0.924 (0.745, 1.191)	0.6146
CI history	Yes *vs.* No	1.254 (1.102, 1.428)	0.0006	1.021 (0.852, 1.223)	0.8193
PAD history	Yes *vs.* No	1.513 (1.128, 1.937)	0.001	0.794 (0.468, 1.348)	0.3927
Claudication history	Yes *vs.* No	1.484 (1.246, 1.769)	< 0.0001	1.027 (0.762, 1.383)	0.8598
DM duration	Per 1-year increase	1.026 (1.010, 1.044)	0.0019	0.975 (0.949, 1.002)	0.0651
HBP duration	Per 1-year increase	1.013 (1.003, 1.023)	0.01	0.992 (0.977, 1.007)	0.2791
Smokers duration	Per 1-year increase	1.020 (1.012, 1.028)	< 0.0001	0.997 (0.986, 1.008)	0.5885
Using diuretic	Yes *vs.* No	1.280 (1.117, 1.467)	0.0004	0.980 (0.804, 1.195)	0.8364
UA	Per 1 mmol/l increase	1.238 (1.071, 1.431)	0.0039	0.893 (0.720, 1.107)	0.3026

n = 2040. *a*) BMI, Indicates body mass index; CHD, Coronary heart disease; CI, Cerebral infarction; PAD, Peripheral arterial disease; DM, Diabetes mellitus; HBP, High blood pressure; UA, Uric acid.

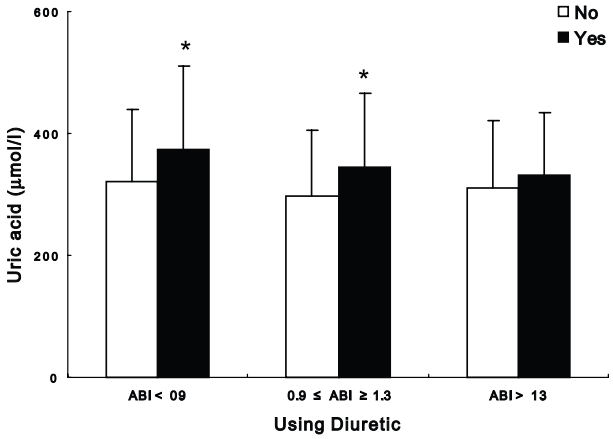

Fig. 1. Effect of Using Diuretic on the Serum Uric Acid Levels in Three ABI Groups in Type 2 Diabetic Patients
*$p < 0.05$.

In this study, gender has been shown as a risk factor for low ABI and high ABI in patients with type 2 diabetes. That was inconsistent from the results of previous studies.[9,14,16)] Male gender was a risk factor (OR 1.325, CI 1.101–1.594) in high ABI, and was found to have an inverse association with low ABI (OR 0.788, CI 0.678–0.917).

The results of previous studies showed that in Taiwanese type 2 diabetic patients, low ABI was actually associated with lower BMI.[9)] However, the results of this study showed that BMI was not significantly different between low ABI and normal ABI, but that was a risk factor for high ABI in univariate and logistic regression analyses (OR 1.084, CI 1.039–1.130).

Most patients with diabetes, including those with atherosclerotic disease, demonstrate endothelial function and vascular regulation abnormalities. They increase with the duration of DM and worsening blood glucose control.[19)] In this study, a history of CHD, CI, PAD or claudication was associated with low ABI, and DM duration and HBP duration were two important risk factors for low ABI in diabetic patients, and OR (CI) were 1.026 (1.010–1.044) and 1.013 (1.003–1.023), respectively.

Smoking has been shown to be a risk factor for PAD in the general population in many studies.[20–22)] However, in several studies, it was not found to be a risk factor.[9,16)] The results of this study showed that the duration of smoking was an independent risk factor for low ABI (OR 1.020, CI 1.012–1.028).

Diuretics have been shown to reduce morbidity and mortality in hypertension,[23)] but in high doses, they can worsen insulin resistance and atherogenic dyslipidemia.[24)] In this study, diuretics were a risk factor for low ABI and OR (CI) was 1.280 (1.117–1.467). In this study, elevated UA levels were a significant and independent risk factor for low ABI in patients with type 2 diabetes. This finding is consistent with that of the Taiwanese study.[16)] The mechanisms by which UA may be associated with atherosclerotic disease remain to be investigated. This study also found that the serum level of UA was associated with diuretics in low ABI and normal ABI groups. Increased UA levels have been known to be a side effect of diuretic. The use of diuretics may be associated with plasma viscosity.[25)] However the serum level of UA was not associated with diuretics

in high ABI group. It requires further investigation.

In univariate analyses in this study, the use of ACEI, anti-platelets, nitrates or digitalis, and the levels of PP, BUN or CRE were significantly different between three ABI groups (Table 1). However, they were not found to be independent risk factors of low and high ABI in the logistic regression.

In this study, 10 of 12 independent risk factors were associated with low ABI in patients with type 2 diabetes (Table 2). This result supports that low ABI was significantly increased CVD events rates and mortality more than high ABI.[17] This study also showed that male gender and high BMI were independent risk factors in high ABI. In a cohort study, diabetic men had a higher risk of death than women[26]; however, in another cohort study, there were no discernible differences between the hazard ratios in men and women.[27] A higher BMI is known to be associated with an increased risk of all-cause and CVD mortality in the general population[28]; however, in other cohort studies there was no strong relationship between BMI and mortality in type 2 diabetes.[29] In high ABI, there was no clear relationship between men, BMI and all-cause mortality.

In conclusion, the prevalence of PAD and risk factors for low and high ABI in Chinese patients with type 2 diabetes were analyzed. The overall prevalence was 16.7%, higher than reported in India and Taiwan, and lower than in the U.K. and U.S.A. The major independent risk factors were age, sex, BMI, history of CHD, CI, PAD, claudication, duration of DM, HBP or smoking, using diuretics and the serum level of UA for low and high ABI, and the serum level of UA was associated with the use of diuretics in Chinese patients with type 2 diabetes.

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