**Risk Factors of Peripheral Arterial Disease and Relationship Between Low Ankle–Brachial Index and Mortality From All-Cause and Cardiovascular Disease in Chinese Patients With Type 2 Diabetes**

Jue Li, MD; Yingyi Luo, MD; Yawei Xu, MD; Jingang Yang, MD; Liqiang Zheng, MD; Buaijiaer Hasimu, MD; Jinming, Yu, MD; Dayi Hu, MD

**Background**  The aim of the present study was to evaluate the risk factors for peripheral arterial disease and the relationship between the ankle–brachial index (ABI) and mortality from all-cause and cardiovascular disease (CVD) in Chinese patients with type 2 diabetes mellitus (DM).

**Methods and Results**  ABI was identified at baseline by measuring systolic pressure in the bilateral brachial and tibial arteries. Mortality surveillance was completed from November 2004 to January 2006. Among 1,647 participants with type 2 DM at baseline, 531 (32.2%) were in the low-ABI group. Older age, female gender, higher serum level of total cholesterol, longer duration of DM and a history of smoking were associated with low ABI. During the 13-month follow-up, there were 132 deaths, of which 47 were from CVD. Low ABI was associated with mortality from all-cause and CVD, the adjusted relative risk of which was 1.851 (95% confidence interval 1.280–2.676) and 3.211 (1.703–6.053), respectively, in Cox regression models. The survival rate was significantly lower in the low-ABI group than in the normal-ABI group.

**Conclusion**  Low ABI was independently associated with a high risk of all-cause and CVD mortality in Chinese patients with type 2 DM. ABI should be promoted as an ideal tool for predicting mortality in diabetic patients.  

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**Key Words:** Ankle–brachial index; Peripheral arterial disease; Mortality; Type 2 diabetes

Peripheral arterial disease (PAD) is a clinical manifestation of the atherosclerotic process, which is associated with cardiovascular disease (CVD) and increased CVD risk. Noninvasive testing reveals that up to 20% of elderly individuals have PAD and because only a small percentage of these individuals are asymptomatic, the condition is poorly recognized in primary care practice. Several cohort studies have shown that a low ankle–brachial index (ABI) is a risk factor of fatal and nonfatal coronary heart disease (CHD) and all-cause mortality among people with and without existing clinical coronary artery disease, and among people with existing peripheral vascular disease. Low ABI is also associated with the incidence of stroke in the elderly.

Diabetes mellitus (DM), a major chronic disease, is able to accelerate atherosclerosis and numerous studies have identified it as a key risk factor for PAD. Several cohort and randomly selected studies have revealed that CVD event rates in patients with PAD and DM are higher than in their nondiabetic counterparts. The adjusted risk of death for PAD patients with DM is 2-fold higher than in patients without DM. A recent prospective study reported that in diabetic patients with low ABI (<0.9), CVD and all-cause mortalities were 31.7 and 70.5 per 1000 person-years, respectively.

Except for 1 study that reported 16.7% PAD prevalence in Chinese patients with type 2 DM, this issue has not been researched extensively. Thus, the purposes of this study were to evaluate the risk factors of PAD and to elucidate the relationship between ABI and mortality from all-cause and CVD in diabetic Chinese patients.

**Methods**

**Study Subjects**

Subjects were recruited from the endocrinology or cardiology in-patient clinic at 8 university hospitals in Beijing and Shanghai from July to November 2004. Participants were diagnosed as diabetic if they had a fasting plasma glucose (FPG) ≥7mmol/L, reported use of hypoglycemic medication, or had DM at the baseline examination. The inclusion criteria were age older than or equal to 35 years, and FPG ≥7mmol/L or 2hPG ≥11.1, or reported having DM at the baseline examination. The exclusion criteria were severe heart failure or renal failure and patients with an ABI >1.4. There were 1,706 participants in the DM cohort, 59 of whom had missing follow-up data. Therefore, the study sample comprised 1,647 valid participants (815 men, 832 women; mean age 67.8±10.6 years) who were followed up from November 2004 to January 2006.

This study was approved by the ethics committee of Tongji University and informed consent was given by the participants.
More recently, the American College of Cardiology and the American Heart Association (ACC/AHA) guidelines have recommended ABI ≤ 0.90 as the criterion to define PAD, 23,24 but most of the recent studies have used an ABI cut-off point ranging from <0.90 to <0.80 to define PAD. 29 Carter considered that an ABI of <0.90 had 95% sensitivity and was specific for angiographically documented PAD. 27 This cut-off point has been also accepted by The Strong Heart Studies (SHS) in which the upper limit of normal ABI did not exceed 1.40. 28

Table 1 Comparison of Baseline Characteristics According-ABI in Patients With Type 2 DM

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Baseline characteristic</th>
<th>OR (95%CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td>1.071 (1.056–1.087)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.984 (0.948–1.021)</td>
<td>0.068 (0.504–0.938)</td>
<td></td>
</tr>
<tr>
<td>HBP</td>
<td>1.118 (0.813–1.537)</td>
<td>1.006 (0.999–1.013)</td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>0.999 (0.986–1.012)</td>
<td>1.149 (0.878–1.503)</td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td></td>
<td>1.125 (1.032–1.258)</td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>1.026 (0.922–1.141)</td>
<td>0.905 (0.715–1.146)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.670 (0.447–1.005)</td>
<td>0.670 (0.447–1.005)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.017 (1.000–1.035)</td>
<td>1.786 (1.297–2.458)</td>
<td></td>
</tr>
<tr>
<td>Ever smoked</td>
<td></td>
<td>0.687 (0.504–0.938)</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean and percent of continuous and categorical variables, respectively. See text for abbreviations.

Identification of Death From All-Causes and CVD

Death was confirmed from hospital records or by contact with participants and their families. Cause of death was investigated using medical records and interviews. All materials were reviewed independently by a physician of the ABI Cohort Study to confirm the cause of death.

Statistical Analysis

Data were analyzed using the software program SPSS13.0 (Chicago, IL, USA). Continuous variables are expressed as the mean±SD, and categorical variables as a percentage. Independent-samples t-test and the chi-square test were used to compare continuous and categorical differences, respectively. A p-value <0.05 was considered statistically significant. Crude deaths from all-cause and CVD were examined by ABI stratification. The relationship between ABI and deaths from all-causes and CVD were adjusted for potential confounders, including age, gender, HBP and smoking experience, and duration of DM, using a Cox regression model.

Results

There were 1,647 participants with type 2 DM whose baseline ABI was available. Of these, 531 (32.2%) were in the low-ABI group and the remainder was in the normal-ABI group. According to our criterion described earlier, the prevalence of PAD was 32.2%. During the 13-month follow-up, there were 132 deaths, and 47 of these were from CVD.

Baseline Characteristics of the ABI Groups

As shown in Table 1, participants with low ABI were older, had a lower BMI, higher SBP, more hypertension, longer duration of DM, and had a history of smoking compared with those with a normal ABI at baseline.

Independent Risk Factors for Low ABI

Logistic regression analysis was used to evaluate the independent significance of associated factors. Table 2 shows the adjusted odds ratios (OR) and 95% confidence interval (CI) for low-ABI participants. We found that older age, female gender, higher serum level of TC, longer duration of DM, and a history of smoking were associated with low density lipoprotein-cholesterol (LDL-C) and FPG were analyzed.
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ABI in patients with type 2 DM.

All-Cause and CVD Mortality Rates in the ABI Groups

All-cause mortality rates in the low- and normal-ABI groups were 12.4% and 5.9%, respectively, and for CVD were 5.5% and 1.6%, respectively. All-cause and CVD mortality rates were significantly higher in the low-ABI group than in the normal-ABI group. The crude OR of the low-ABI group was 2.258 (95% CI 1.578–3.231) for all-cause mortality, and 3.524 (95% CI 1.939–6.405) for CVD mortality. When the low- and normal-ABI groups were examined in relation to mortality in the Cox regression models adjusted for multiple CVD risk factors, low ABI was associated with adjusted all-cause and CVD mortality risks of 1.851 (95% CI 1.280–2.676) and 3.211 (95% CI 1.703–6.053), respectively.

Survival Analysis of the ABI Groups

Figs 1A,B shows the survival distributions of the 2 ABI groups for all-cause and CVD mortality. The information shows a survival trend even though our follow-up time was short. Kaplan-Meier analysis yielded the survival data, and for both all-cause and CVD mortality, the survival rate for the low-ABI group was significantly less than for the normal-ABI group (p<0.001).

All-Cause and CVD Mortality in Different ABI Groups

If ABI was subdivided into ≤0.4, 0.41–0.90, 0.91–0.99 and 1.00–1.40, all-cause mortality was 25.5%, 11.0%, 5.3%, 6.1%, respectively (p<0.001) (Fig 2). However, there was no statistical difference between the 0.91–0.99 group and the 1.00–1.40 group, both of which were considered as normal ABI. CVD mortality was 15.7%, 4.4%, 2.7%, 1.3% with a significant difference from each other (p<0.001).
Mortality Risk According to Different ABI

Figs 3A,B shows the adjusted relative risk (RR) of the different ABI groups. ABI groups were examined in relation to mortality in Cox regression models that adjusted for age, sex, history of HBP, duration of DM and smoking. The mortality risk from all-cause and CVD increased with decreased ABI.

Discussion

A previous study demonstrated that PAD prevalence in Chinese DM patients was 16.7%, and that the major independent risk factors were age, sex, BMI, history of HBP and smoking. In the present study, PAD prevalence was 32.2%, almost 2-fold higher, and the difference in these reported prevalences is likely to be caused by the different sample sizes and diagnostic criteria used in the studies. The prevalence of atherosclerosis in type 2 DM is significantly higher because the excessive metabolism of lipid and glucose damages vascular endothelial cells, resulting in large vessel disease.

In the present study the patients with a low ABI were older by univariate analysis, and the adjusted OR was 1.071 (95% CI 1.056–1.087) by logistic regression analysis. Consistent with the results of the previous study, female gender was a risk factor for low ABI. We found that patients with low ABI had a lower BMI, but BMI was not an independent risk for low ABI after logistic regression analysis. Therefore, we attributed it to the older age of the low-ABI group. This finding was inconsistent with studies conducted in Taiwan with patients with type 2 DM. In our study, patients with low ABI also had higher SBP, but diastolic blood pressure (DBP) was not significantly different between the low-ABI and normal-ABI groups by univariate analysis. Pulse pressure (PP) increases with age because blood vessels progressively lose their elasticity. In the present study, PP increased in the low-ABI group they were older than the subjects in the normal ABI group. However, HBP history, and the SBP and DBP levels were not independent risks for low ABI after logistic regression analysis. Interestingly, a history of smoking was an independent risk with an adjusted OR of 1.786 (95% CI 1.297–2.458). The relationship between dyslipidemia and low ABI is still unclear. Although the serum levels of TC, TG, HDL-C and LDL-C were not significantly different between the 2 groups, a higher serum level of TC was an independent risk for low ABI with an adjusted OR of 1.256 (95% CI 1.032–1.528). It is therefore very important to improve lipidemia when treating Chinese patients with DM. Duration of DM is another risk factor for PAD with an adjusted OR of 1.017 (95% CI 1.000–1.035), so patients who have been diabetic for longer have a greater risk for PAD. Because the FPG level is affected by many factors, we did not include it in this model.

All-cause and CVD mortality rates were 12.4% and 5.5%, respectively, in the low-ABI group, twice as high as for those with normal ABI. Compared with the normal ABI group, the adjusted RR after 13-month follow-up was 1.851 (95% CI 1.280–2.676) for all-cause death and 3.221 (95% CI 1.703–6.053) for CVD death in Chinese patients with type 2 DM. This is comparable with previous reports that individuals with low ABI are at increased risk of death relative to individuals with normal ABI. Our results are close to those from the SHS study, in which RR's of all-cause and CVD mortality after 10-year follow-up were 1.69 and 2.52, respectively. In the Edinburgh Artery study, RRs of all-cause and CVD mortality after 5-year follow-up were 1.58 and 1.85, respectively, for persons aged 55–74 years old with ABI <0.90. CVD mortality was higher in the present study than in the Edinburgh Artery study, possibly because diabetic patients with low ABI are more susceptible to CVD death. Other possibilities include different ethnic groups and different duration of follow-up. However, an ABI ≤0.90 was independently associated with a high risk of all-cause and CVD mortality.

When participants were further divided into 4 subgroups, all-cause and CVD mortality still differed among them. The lowest ABI (≤0.4) group had the highest all-cause and CVD mortality rates, and mortality declined with increasing ABI. In comparison to the highest ABI group (1.00–1.40), the adjusted RRs of all-cause and CVD mortality increased at the lower end of the ABI distribution. The respective adjusted risk of all-cause mortality in the ≤0.4 group and 0.41–0.90 group was 3.997 and 1.605 times that of the 1.00–1.40 group. The adjusted risk of CVD mortality in the ≤0.4 group and 0.41–0.90 group was 12.855 and 3.279 times that of the 1.00–1.40 group. This demonstrated that low ABI was independently associated with increased risks of all-cause and CVD mortality in Chinese patients with type 2 DM. In other words, a patient with a lower ABI has a higher risk of all-cause and CVD mortality. The adjusted risk of all-cause and CVD mortality for the 0.91–0.99 group, defined as the equivocal ABI level by PAD guidelines was not significantly different from that of the 1.00–1.40 group in this study.

In conclusion, our study analyzed the risk factors for PAD and the relationship between low ABI and all-cause and CVD mortality in Chinese patients with type 2 DM. Older age, female gender, higher serum level of TC, longer duration of DM, and a history of smoking were independent risk factors for low ABI. After 1-year follow-up, low ABI was independently associated with an increased risk of all-cause and CVD mortality. Both all-cause and CVD mortality rates of survival were significantly lower in the low-ABI group than in the normal-ABI group. Our findings further support that ABI is an ideal tool for predicting mortality in diabetic patients. Regular PAD screening and then intensive management of vascular risk factors should be encouraged in clinical practise.

Acknowledgments

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References

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