Ankle-brachial index, toe-brachial index, and cardiovascular mortality in persons with and without diabetes mellitus

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Background: **The prognostic utility of the ankle-brachial index (ABI) may be hampered in persons with diabetes due to peripheral arterial stiffening in the ankles. Stiffening of toe arteries occurs infrequently in diabetes. We aimed to determine the nature of the relationship of the toe-brachial index (TBI) and ABI with cardiovascular disease (CVD) mortality and to determine whether the associations are modified in individuals with diabetes.**

Methods: **Individuals with clinically suspected atherosclerotic peripheral arterial disease who underwent ABI and TBI measurements in a vascular laboratory were monitored longitudinally for CVD mortality.**

Results: **Among 469 participants (89% men), the mean age was 68 ± 9 years, and 36% had diabetes. The mean ABI was 0.83 ± 0.28 and the mean TBI was 0.60 ± 0.24. During median 7.0 years of follow-up, there were 158 CVD deaths. The association of the ABI categories with CVD deaths differed in diabetic vs nondiabetic participants ($P = .002$ for interaction). In contrast, the association of the TBI categories with CVD deaths was similar, irrespective of diabetes status ($P = .17$ for interaction). Among diabetic patients, a U-shaped relationship was observed between ABI categories and CVD death: those with low (<0.90) and high (>1.30) ABIs were both at higher risk than those with normal ABIs (range, 0.90-1.30). In nondiabetic patients, association of ABI categories with CVD death was linear, such that those with an ABI >1.30 were at the lowest risk, whereas those with an ABI <0.90 were at higher risk. In contrast, the association of TBI categories with CVD death was linear irrespective of diabetes status. High TBI categories consistently predicted low risk, whereas risk was higher with progressively lower TBI categories.**

Conclusions: **Among diabetic individuals with clinically suspected peripheral arterial disease, those with low and high ABIs are both at higher risk of CVD death. In contrast, a linear relationship was observed between TBI categories and CVD death irrespective of diabetes status. These findings suggest that stiffened ankle arteries may limit the predictive value of the ABI in individuals with diabetes, a limitation that may be overcome by measurement of the TBI. (J Vasc Surg 2014;60:390-5.)**

The ankle-brachial index (ABI), the principal diagnostic tool for peripheral arterial disease (PAD) screening, reflects the ratio of systolic blood pressure at the ankle relative to the arm.[1] However, its use is complicated in individuals with diabetes, who frequently have calcium deposition in the arterial media, a condition known as medial arterial calcification (MAC). The most common anatomic location for MAC is in the ankle arteries.[2] MAC contributes to arterial stiffening, which results in vessels that are more difficult to occlude in the ankle and artificially elevates the measured ankle systolic blood pressure. This leads to falsely elevated ABIs that may render the ABI less sensitive to the detection of flow-limiting atherosclerotic PAD in individuals with diabetes.

Although MAC is common in the ankle arteries,[2] the toe arteries are usually spared.[3] The toe-brachial index (TBI) uses similar principles to the ABI, but reflects the systolic pressures in the great toe to that in the arm. Because MAC commonly spares the toes, the TBI may be useful to detect atherosclerotic PAD in individuals with MAC. Given concerns that the ABI may miss PAD in individuals with diabetes, the American Diabetes Association[4] and the American Heart Association[5] have both recommended using TBI measurements to evaluate atherosclerotic PAD in individuals with incompressible ankle arteries or when the ABI is high (>1.30). Although low ABI measurements are known to predict cardiovascular disease (CVD) deaths in individuals with and without diabetes,[6] it is uncertain whether the associations of high ABI and CVD deaths differ by diabetes status and whether the TBI measurement may provide useful information about CVD risk when MAC is present.

Given that MAC and atherosclerotic PAD may coexist in individuals with diabetes, MAC may render the ABI less sensitive for detection of atherosclerotic PAD in individuals

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with diabetes and may therefore bias the relationship of ABI measurements with risk of CVD death toward the null. Because MAC is more common in diabetes, we hypothesized that low TBI measurements would be more strongly associated with CVD death than low ABI measurement and that such differences would be more evident in patients with diabetes.

METHODS

All individuals who participated in this study gave written informed consent. The study protocol and consent forms were approved by the University of California, San Diego Investigational Review Board.

Study participants. Between 1990 and 1994, patients who were seen in the previous 10 years for noninvasive lower extremity arterial testing at the San Diego Veterans Administration Medical Center or the University of California, San Diego Medical Center (UCSDMC) vascular laboratory were invited to participate in this study. Of the 2265 candidates, 481 had died, and among the remainder, 508 agreed to participate and returned for a repeat study evaluation. Among these, we excluded those with missing ABI measurements (n = 2 [0.4%]), TBI measurements (n = 9 [1.8%]), and CVD risk factor data (n = 28 [6%]), resulting in final analytic sample of 469 participants for this analysis.[7,8]

Vascular assessment. The ABI and TBI protocols have been described in detail previously.[7,8] Briefly, brachial, ankle, and toe pressures were measured bilaterally. Blood pressure cuffs were placed on the arms, ankles, and the bases of the big toes, and measurements were taken in a temperature-controlled environment, with the participant supine position, and after ten minutes of rest. Photoplethysmography was used to detect blood flow at the third finger for arm measurements and at the great toe for ABI and TBI measurements. The ABI and TBI were computed using the arm with the higher systolic pressure due to the strong correlation between PAD and subclavian stenosis.[9]

The reproducibility of the ABI and TBI has been evaluated in prior studies. For the ABI, the 95% confidence intervals for reproducibility are between 0.10 and 0.15.[10-12] Variability of the TBI is greater, reported anywhere from the same as the ABI[13] to about twice that of the ABI.[11] The higher variability of the TBI may be due to higher susceptibility of toe arteries to vasoreactivity.[14]

CVD mortality. All participants were monitored through December 31, 2001. Death was identified using the Social Security Death Index, and death certificates were obtained and coded by a certified nosologist using International Classification of Diseases (Ninth Edition) codes. When the cause of death was coded 401 to 437.9, excluding 412, participants were classified as having died of CVD.

Other measurements. Age, sex, ethnicity, and smoking history were self-reported. Participants were categorized as current, former, or never smokers. Diabetes was defined as a fasting plasma glucose ≥126 mg/dL, use of insulin, or use of oral hypoglycemic medications. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic pressure ≥90 mm Hg, or use of antihypertensive medications. Body mass index was calculated from values for weight (kg)/height (m^2). Dyslipidemia was categorized as use of lipid-lowering drugs or a ratio of total cholesterol to high-density cholesterol ratio of ≥5. Serum creatinine was measured by the Jaffe method and combined with age, sex, and ethnicity in the four-variable Modification and Diet in Renal Disease equation to estimate glomerular filtration rate (eGFR).[15]

Statistical analysis. We began by categorizing participants into four groups based on clinical ABI cut points of <0.60, 0.60 to 0.89, 0.90 to 1.30, and >1.30. We compared differences in demographics and traditional CVD risk factors across ABI categories using analysis of variance for continuous variables and the χ^2 test or Fisher exact test for categoric variables. Next, we categorized participants into four categories based on TBI scores of <0.40, 0.40 to 0.61, 0.62 to 1.08 and >1.08, such that the percentage of participants in each TBI category was similar to those in the corresponding ABI categories. We used Cox proportional hazards models to evaluate the associations of the ABI and TBI categories with time to CVD death. The ABI category of 0.90 to 1.30 and the TBI category of 0.62 to 1.08 served as the reference category.

The initial model was unadjusted. A final model was adjusted for demographics and traditional CVD risk factors, including age, sex, ethnicity, diabetes, smoking (current, former, never), systolic blood pressure, blood pressure medication use, total cholesterol, high-density lipoprotein cholesterol, cholesterol medication use, eGFR, and body mass index. Finally, we tested multiplicative interaction terms (ABI × diabetes and TBI × diabetes) in the fully adjusted models. When statistically significant interactions were detected, we evaluated the association of ABI and TBI categories in diabetic and nondiabetic participants separately. Analyses were conducted using STATA SE 11.0 software (StataCorp LP, College Station, Tex). $P < .05$ was considered statistically significant for all analyses, including interaction terms.

RESULTS

The 469 study participants had a mean age of 68 ± 9 years (range 39-100 years). A total of 417 (89%) were men, reflecting heavy sampling from the Veterans Affairs medical center, and 168 (36%) had diabetes. The mean ABI was 0.83 ± 0.28 and the mean TBI was 0.60 ± 0.24. Classic claudication systems were present in 139 individuals (30%), and 15 (3%) had at least one leg with an ABI <0.40, suggesting critical limb ischemia. CVD mortality risk did not differ significantly across these groups. Baseline characteristics by ABI categories are reported in Table I. Compared with participants with normal ABI (0.90-1.30), those in lower ABI categories were older, more likely to have diabetes, hypertension, worse kidney function, and lower TBI measurements.