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Hide and Seek: Does the Toe-brachial Index Allow for Earlier Recognition of Peripheral Arterial Disease in Diabetic Patients?

R.M. Stoekenbroek [a,*], D.T. Ubbink [a], J.A. Reekers [b], M.J.W. Koelemay [a]

[a] Department of Surgery, Academic Medical Center, P.O. Box 22660, 1100 DD Amsterdam, The Netherlands
[b] Department of Radiology, Academic Medical Center, Amsterdam, The Netherlands

WHAT THIS PAPER ADDS

Arterial stiffness in diabetics may render the ankle-brachial index (ABI) unreliable, even below the guideline recommended threshold for a falsely elevated ABI of $>$ 1.4. Consequently, the use of the toe-brachial index (TBI) is advocated in the initial vascular examination of diabetics. However, there is no evidence that the TBI yields additional information compared with the ABI in diabetic patients if the ABI is not obviously elevated.

Objective/Background: Arterial calcification may render the ankle-brachial index (ABI) unreliable in diabetic patients. Although guidelines recommend the toe-brachial index (TBI) for patients with falsely elevated ABI arbitrarily defined as an ABI $>$ 1.4, arterial calcification is also common among diabetic patients with an ABI $\leq$ 1.4. This could result in a "falsely normalized" ABI and under-diagnosis of peripheral arterial disease (PAD). We investigated whether diabetes invalidates the ABI as opposed to the TBI, and if the TBI may therefore be more suitable for detecting PAD in diabetic patients.

Methods: The difference between ABI and TBI was compared between diabetic and non-diabetic patients with an ABI $\leq$ 1.4 referred to the vascular laboratory. A Bland–Altman plot was constructed to assess whether ABI–TBI differences were dependent on the magnitude of the measurements. Subgroup analyses were performed for patients with a normal ABI, and for patients with critical ischemia.

Results: The population comprised 161 diabetic (252 limbs) and 160 non-diabetic (253 limbs) patients (mean age 67). Median ABIs (0.79 vs. 0.80) were similar, while median TBI was 0.07 higher in diabetics ($p = 0.024$). The ABI–TBI difference in diabetics and non-diabetics was similar (0.32 vs. 0.35; $p = .084$), and was also similar for patients with a normal ABI. Moreover, ABI–TBI differences in diabetic- and non-diabetic patients overlapped, irrespective of the magnitude of the measurements. Diabetes was not associated with larger differences between ankle and toe pressures (mean difference −0.9 mmHg, 95% confidence interval −15 to 13 mmHg) among patients with critical ischemia.

Conclusion: No evidence was found that the TBI may overcome the potentially invalidated ABI in diabetic patients with an ABI $\leq$ 1.4. ABI and TBI are strongly associated, and this relationship is not influenced by diabetes. Therefore, the TBI does not allow for earlier detection of ischemia in diabetes.

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INTRODUCTION

Background

Lower extremity peripheral arterial disease (PAD) ranges in severity from asymptomatic to critical limb ischemia with tissue loss. Early detection of PAD is crucial, not only to provide symptomatic patients with adequate therapy, but also to guide the intensity of secondary prevention for these patients, who are at high risk of subsequent cardiovascular (CV) morbidity and mortality.[1,2] PAD is particularly common among patients with diabetes, who have more severe disease and worse outcomes than those without diabetes.[2,3] The ankle-brachial index (ABI) is widely recommended in the initial assessment of lower extremity perfusion, based on a substantial body of evidence linking low ABI to imaging-confirmed PAD, and increased CV morbidity and mortality.[4] However, the sensitivity of the ABI may be lower in diabetic patients, presumably as a result of the high prevalence of medial arterial calcification (MAC) and the resulting arterial stiffening.[5–9] Clinical guidelines recognize that the ABI may be unreliable in diabetic patients and recommend alternative tests, such as the toe-brachial index (TBI) for patients suspected of having a falsely elevated ABI. The threshold for a falsely elevated ABI is

* Corresponding author.
E-mail address: r.m.stoekenbroek@amc.uva.nl (R.M. Stoekenbroek).
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often arbitrarily set at 1.3—1.4. However, MAC is also frequently observed in the ankle arteries of patients with an ABI below this threshold, and imaging-confirmed arterial stenosis is common among diabetic patients with an ABI within the normal reference range.[8,10—14] Based on the assumption that the toe arteries are less susceptible to MAC, it is frequently suggested that assessment of the TBI in addition to the ABI may enable earlier detection of PAD in the initial vascular examination of diabetic patients, even when the ABI is not obviously falsely elevated.[8,10—14]

Objectives

The aim of the study was to investigate if the ABI underestimates the severity of ischaemia in diabetic patients, even below the recommended threshold for falsely elevated pressures of 1.4, and whether it is useful to include assessment of the TBI in the initial vascular examination of diabetic patients. The difference between the ABI and the TBI was therefore compared between diabetic and non-diabetic patients, for whom the ABI has been validated, in a population with suspected PAD referred to the vascular laboratory.

METHODS

Design

A retrospective cross-sectional study was performed to compare the differences between the ABI and TBI among diabetic and non-diabetic patients referred to the vascular laboratory of the Academic Medical Center (AMC), Amsterdam, the Netherlands, for a non-invasive vascular examination of the lower extremities. The current article was written in accordance with the STROBE statement for cross-sectional studies, which is a checklist to ensure accurate and complete conduct and reporting of observational studies.[15] Ethical approval from the local institutional review board is not necessary for retrospective chart reviews.

Patient selection. The vascular laboratory of the AMC serves as the primary diagnostic unit for non-invasive vascular examination for all in- and outpatients at the tertiary hospital. A sample of consecutive patients referred for non-invasive vascular examination was taken from the 10,464 measurements performed between 1993 and 2005. Patients were included if ankle, toe, and brachial blood pressures were simultaneously obtained during a single visit, irrespective of other characteristics, to assure that the sample reflected the population referred to the vascular laboratory. Patients with acute limb ischemia were excluded, as were patients with unknown diabetes status, an ABI $>$ 1.4, or measurement results deemed unreliable by the vascular technician owing to the inability to comply with the measurement protocol. Patients were identified using unique identifying numbers, and only the first measurement was included.

As this was an exploratory study, the sample size required to detect a clinically relevant difference in ABI—TBI between diabetic and non-diabetic patients could only be estimated tentatively. A study by Brooks et al. reported an ABI—TBI difference for diabetic patients of 0.37, with an SD of 0.15.[16] Including 222 measurements in the diabetic and in the non-diabetic group provides 80% power to detect a 10% difference in the mean ABI—TBI between diabetic and non-diabetic patients at a two-sided significance level of 0.05. A margin of 15% was taken to improve the statistical power, and data on 505 measurements were included.

Measurements. Experienced vascular technicians from the vascular laboratory at the AMC carried out all measurements. Great toe blood pressures were obtained using a photoplethysmograph (Nicolet VasoGuard; VIASYS Healthcare, Madison, WI, USA). Ankle systolic blood pressures (SBPs) in both the posterior tibial and the dorsalis pedis arteries were obtained using a Doppler device (Nicolet VasoGuard; VIASYS Healthcare). Prior to 2005, ankle SBPs were measured using an 8-MHz Doppler probe (Stöpler; PV Lab, Electronic Diagnostic Instruments, Burbank, CA, USA) and a 12-cm cuff just proximal to the ankle, and toe SBPs were measured by photoplethysmography (Stöpler; PV Lab) and a digital cuff with a width depending on the diameter of the toe (1.9 or 2.5 cm). The ABI and TBI were calculated by dividing the highest systolic ankle or toe blood pressure by the highest of both systolic brachial artery blood pressures. For the ABI, values between 0.91 and 1.4 were considered within the normal range.

All measurement results and baseline characteristics were documented on examination and subsequently validated by checking the medical charts. A patient was considered to have diabetes or hypertension if this was documented in the patient chart, or if the patient was prescribed antidiabetic or antihypertensive drugs, respectively. Smoking was defined as smoking within the last 5 years, or a history of $>$ 15 pack years. End stage renal disease, defined as dialysis dependence or history of kidney transplantation, and clinical disease stage (i.e., asymptomatic, intermittent claudication, rest pain, or tissue loss), were considered potential effect modifiers. Age at examination was considered a potential confounder as it is a known predictor of arterial calcification and may be influenced by the presence of diabetes.[17]

Statistical methods

Continuous values were expressed as means and SD, or medians and interquartile ranges, where appropriate. Baseline characteristics of diabetic and non-diabetic patients were displayed as differences with 95% confidence intervals (CIs) and analyzed statistically using chi-square tests or two-sampled Student *t* tests/Mann—Whitney *U* tests, depending on the normality of the data.

Limbs were used as the unit of analysis. The ABI—TBI difference was compared between diabetic and non-diabetic patients using a Student *t* test. A Bland—Altman plot was constructed to assess whether the difference between the ABI and TBI was dependent on the magnitude of the pressure values for diabetic and non-diabetic patients. Lines for the 95% limits of agreement were constructed