

An Evaluation of the Efficacy of Methods Used in Screening for Lower-Limb Arterial Disease in Diabetes

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OBJECTIVE — Foot-related disease is the most common cause for hospital admission among the diabetic population. Lower-limb peripheral arterial occlusive disease (PAOD) is a major risk factor in diabetic foot disease. Screening for PAOD commonly includes foot pulses and the ankle-brachial pressure index (ABPI) and/or the toe-brachial pressure index (TBI), but concerns persist regarding their accuracy. We evaluated the efficacy of several commonly used screening methods in different subject populations.

RESEARCH DESIGN AND METHODS — We studied 130 limbs in 68 individuals with no critical ischemia over 8 months. Limbs were grouped on the basis of the presence or absence of diabetes, clinically detectable peripheral neuropathy, and PAOD identified on color duplex imaging. Comparative analyses of foot pulses, the ABPI, the TBI, and distal Doppler waveform analysis were performed.

RESULTS — Foot pulses, the TBI, and qualitative waveform analyses were highly sensitive screening methods in individuals with and without diabetes. However, detectable peripheral neuropathy was associated with a reduced sensitivity and poor specificity of foot pulses, a reduction in sensitivity of the ABPI (71 to 38%), and a reduction in specificity of the TBI (81 to 61%) and qualitative waveform analysis (96 to 66%). Quantitative analysis failed to detect disease with severely damped and low-intensity signals.

CONCLUSIONS — Screening tools that are effective in screening for lower-limb PAOD in the nondiabetic population are less efficacious in diabetes, particularly in the presence of detectable peripheral neuropathy. Qualitative waveform analysis and the TBI were demonstrated to be more effective screening methods than the ABPI and foot pulses particularly in high-risk limbs with detectable peripheral neuropathy.

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Foot-related disease is the most common cause for hospital admission among the diabetic population and is recognized as the most common cause of nontraumatic lower-limb amputation

in the western world. People with diabetes are >20 times more likely to undergo an amputation than the rest of the population (1). The main risk factors for the development of diabetic foot disease are

peripheral neuropathy and peripheral arterial occlusive disease (PAOD). The detection of significant arterial disease is vital to the prevention and treatment of foot disease. The unreliable nature of the symptoms and signs of lower-limb arterial insufficiency in diabetes means that noninvasive tests are essential to achieve effective screening (2,3). The European Working Group on Critical Leg Ischaemia recommends an additional, noninvasive vascular assessment for patients with diabetes and foot ulceration (4).

Screening techniques commonly used in assessing lower-limb perfusion are the palpation of foot pulses and calculation of the ankle-brachial pressure index (ABPI) and/or the toe-brachial pressure index (TBI). There is continued debate regarding the influence of peripheral neuropathy and arterial calcification on the reliability of vascular screening in diabetes. Arterial wall calcification causes increased rigidity, making palpation of foot pulses potentially more difficult and artificially elevating the ankle systolic blood pressure and ABPI measurement (5). The detection of pulsatile flow using Doppler analysis may, however, still be possible. The International Consensus on the Diabetic Foot (ICDF) guidelines suggested that an ABPI of 1.15 be the upper limit above which measurements are deemed unreliable (6). The TBI is then an alternative test, but the influence of arterial calcification and neuropathy on toe pressures is uncertain (7–11).

Color duplex imaging (CDI), incorporating Doppler waveform analysis, has been demonstrated to accurately grade the severity of arterial stenotic disease. However, the accuracy of waveform analysis alone in assessing the severity of lower-limb arterial disease is uncertain (12,13).

We aimed to evaluate the efficacy of foot pulses, the ABPI, the TBI, and Doppler waveform analysis in screening for lower-limb arterial disease in diabetes, by comparison with the gold standard noninvasive assessment, CDI. Stringent inclusion and exclusion criteria, particularly

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Abbreviations: ABPI, ankle-brachial pressure index; CDI, color duplex imaging; ICDF, International Consensus on the Diabetic Foot; PAOD, peripheral arterial occlusive disease; PPG, photoplethysmography; TBI, toe-brachial pressure index.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—Group distributions and characteristics

Group no.	Groups (abbreviation)	No. of limbs
1	Controls with arterial disease (V)	14
2	Diabetes (D)	25
3	Diabetes with neuropathy (DN)	41
4	Controls (C)	27
5	Diabetes with arterial disease (DV)	7
6	Diabetes with neuropathy and arterial disease (DNV)	16
Total		130

for individuals with arterial disease, would reduce the number of subjects eligible for participation. Therefore, based on pragmatic factors related to feasibility of recruitment, study duration, and participant burden, it was estimated that analysis of 120 limbs would be required to facilitate valid comparisons of the efficacy of the modalities in individuals with and without arterial disease. The study was approved by the local ethics committee, and all subjects gave written informed consent.

RESEARCH DESIGN AND METHODS

No individuals had active foot disease, rest pain, or signs suggestive of lower-limb critical ischemia. Individuals without diabetes with and without arterial disease were used as control subjects. Patients with types 1 and 2 diabetes were confirmed as having diabetes in their medical records. Subjects were grouped according to the presence or absence of diabetes, peripheral neuropathy, and peripheral vascular disease on CDI. Neuropathy was tested using a 10-g monofilament, 128-Hz tuning fork, and proprioception at the first metatarsophalangeal joint, using ICDF guidelines. Loss of sensation of any modality was indicative of peripheral neuropathy.

The study was performed over a period of 8 months. All tests were performed at one visit. All individuals had capillary blood glucose measurements and arterial CDI performed at the end of each visit.

Exclusion criteria included smoking, other causes of peripheral neuropathy, history of reconstructive vascular surgery, other causes of peripheral vascular disease, skin changes associated with venous disease, pyrexia, and significant cardiorespiratory and/or renal disease. All patients (with two exceptions of serum creatinine ~ 0.3 mmol/l) had serum creatinine < 0.2 mmol/l and hemoglobin values ≤ 11 g/dl.

Room temperature was maintained at 24–25°C. Individuals were rested reclining at $\sim 20^\circ$ to the horizontal and acclimatized for 20 min. Foot skin temperatures were measured until a steady state was achieved.

Both foot pulses were palpated by at least two examiners and classified as present or absent. Absence of one or both foot pulses was used as an indicator of arterial disease. Toe pressures were measured by the photoplethysmography (PPG) method, employing an infrared sensor placed on the hallux (Dopplex Assist; Huntleigh Healthcare, Cardiff, U.K.). Both brachial pressures were measured using index finger PPG and a hand-held Doppler unit (Huntleigh Healthcare); the higher value was used in calculating the ABPI and TBI. Toe pressures were taken at 3- and 5-min intervals, and a mean was calculated. Ankle pressures were then measured using PPG and the hand-held Doppler unit to avoid the potential influence on subsequent toe pressure measurement. ABPI values < 0.9 and TBI values < 0.75 were used as indicators of significant PAOD. Both qualitative and quantitative Doppler waveform analysis was performed on the dorsalis pedis and posterior tibial arteries using the Dopplex Assist, with an 8-MHz Doppler probe. Qualitative waveform analysis was performed by visual interpretation of continuously displayed waveforms. The on-screen loss of reverse flow (loss of triphasic signal) was used as an indicator of significant arterial disease. Quantitative waveform analyses were performed simultaneously by the Dopplex Assist. Three indexes (pulsatility index, resistance index [Pourcelot], and spectral broadening index) were recorded for each artery.

CDI was performed at the end of each session using a Toshiba SSH-140A ultrasound system (Toshiba Medical Systems,

Crawley, U.K.) with two probes, a 5-MHz linear array probe (PLF-503NT), and a 3.75-MHz curvilinear probe (PVF-375MT). All individuals were scanned from the common femoral artery to the distal third of the tibial and peroneal arteries. Arterial disease on CDI was deemed significant when occlusions, single or multiple stenoses, or diffuse stenotic disease in the femoropopliteal segments, individually or collectively, caused significant velocity change and flow disturbance locally and resulted in loss of reverse flow distally. Occlusions of below-knee arteries were also recorded. Quality control was assured by acquiring a second CDI scan of 10 individuals with and without arterial disease within 1 month of the original scan. The repeat scan was performed by medical physicists at the local teaching hospital. Statistical analysis was performed using SPSS version 10 software (Chicago, IL).

RESULTS— A total of 130 limbs from 68 volunteer subjects were studied (Table 1). All subjects in the diabetic groups were Caucasian and predominantly male (74%). Type 2 diabetes accounted for 85% of the total number of subjects with diabetes and was evenly distributed through all groups except group 5. The male-to-female ratio and the preponderance of individuals with type 2 diabetes reflect the patient population attending our outpatient clinics. The groups were matched for age, with means ranging from 63 to 69 years and BMI (mixed ANOVA with post hoc analysis assuming nonhomogenous variance, $F_{5,74} = 0.783$, $P = 0.565$ and $F_{5,74} = 2.04$, $P = 0.083$, respectively). All groups with diabetes had mean BMI > 25 kg/m²; the group with neuropathy had BMI > 30 kg/m². Duration of diabetes was similar for all groups ($F_{3,52} = 2.08$, $P = 0.115$), with means ranging from 11 to 24 years. When formally tested, individuals recruited for the study frequently had detectable peripheral neuropathy, and this factor is reflected in the relatively high numbers of limbs in the neuropathy groups.

Repeat CDI demonstrated complete agreement on the presence or absence of significant arterial disease. The strong association between detectable peripheral neuropathy and arterial disease meant that group 5 (arterial disease but no neuropathy) was relatively small and contained the limbs of individuals with type 2

Table 2—Validation table: all groups

	Analysis (%)											
	Control				Diabetes, no neuropathy				Diabetic neuropathy			
	Pulse	ABPI	TBI	Wave	Pulse	ABPI	TBI	Wave	Pulse	ABPI	TBI	Wave
Sensitivity	93	83	100	86	87	100	91	100	81	53	100	94
Specificity	70	100	81	96	53	88	65	92	56	95	61	66
Positive predictive value	62	100	72	92	39	70	42	78	42	80	48	52
Accuracy	78	95	87	93	62	91	72	94	63	84	71	74

diabetes only. Analysis of data from this group required cautious interpretation.

Foot pulses

The absence of one or more pulses was common in groups without arterial disease on CDI, making this test prone to a high false-positive rate and poor specificity. Both foot pulses were palpable in some individuals with significant arterial disease. In the groups with arterial disease, the absence of one or more pulses in the control group was a more sensitive test than in the groups with diabetes, in which almost 20% of limbs had both pulses present (Table 2).

ABPI

There was a strong positive correlation between Doppler and PPG ankle pressure measurements ($n = 125, r = 0.954, P < 0.001$). The hand-held Doppler unit consistently gave marginally higher readings.

Control groups. In agreement with CDI findings, all limbs without arterial disease had ABPI values >0.9 . With Doppler, 4 of 14 limbs with arterial disease had values >0.9 (29% false-negative rate). With PPG, only 2 limbs had values >0.9 (14% false-negative rate).

Diabetic groups. Several ABPI values >1.3 were demonstrated in individuals with and without arterial disease (Fig. 1).

Three limbs with no arterial disease had values <0.9 .

With Doppler, 12 of 23 limbs with significant arterial disease had ABPI values >0.9 (53% false-negative rate). Using PPG reduced the false-negative rate to 32%. Mean ABPI values for limbs with no arterial disease but detectable peripheral neuropathy were higher than those for limbs with no neuropathy (1.21 vs. 1.06, $t = -2.39$, degrees of freedom [df] = 64, $P = 0.02$).

With PPG, all 7 ABPI values >0.9 identified in the groups with diabetes and arterial disease were associated with detectable peripheral neuropathy (Table 2).

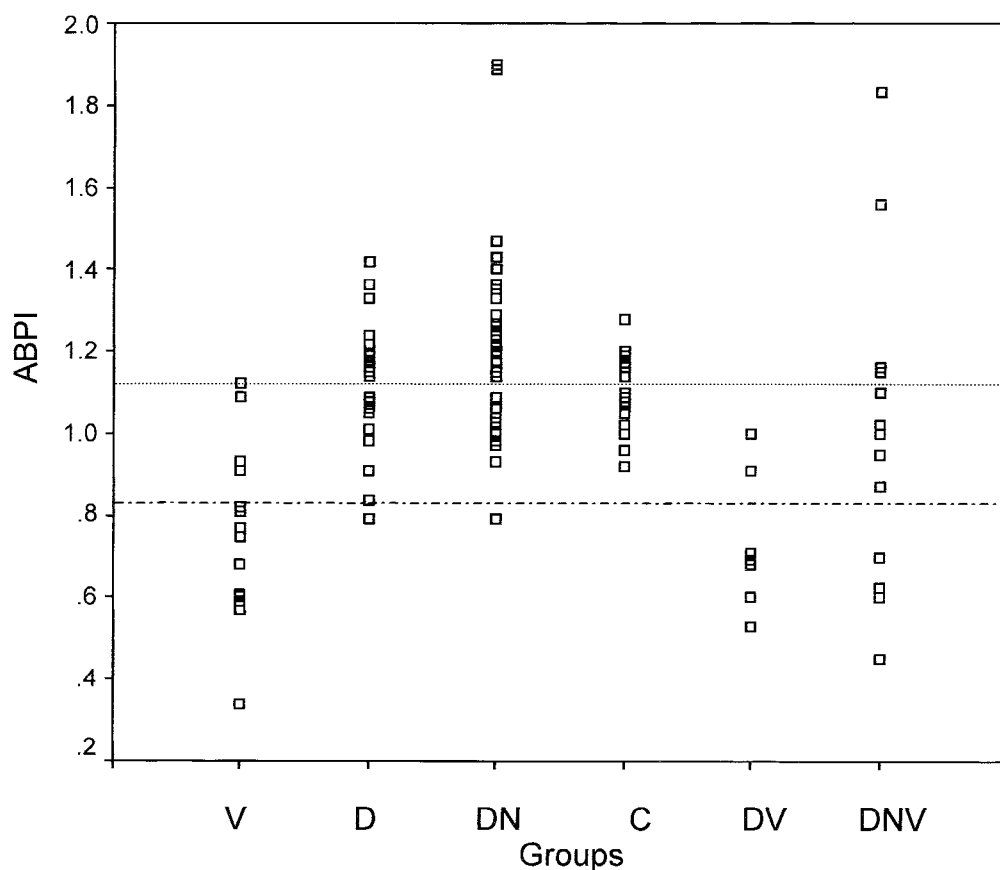


Figure 1—ABPI using PPG, all limbs. Horizontal lines represent ABPI values of 1.15 and 0.9. V, control subjects with arterial disease; D, diabetes; DN, diabetes with neuropathy; C, control subjects; DV, diabetes with arterial disease; DNV, diabetes with neuropathy and arterial disease.

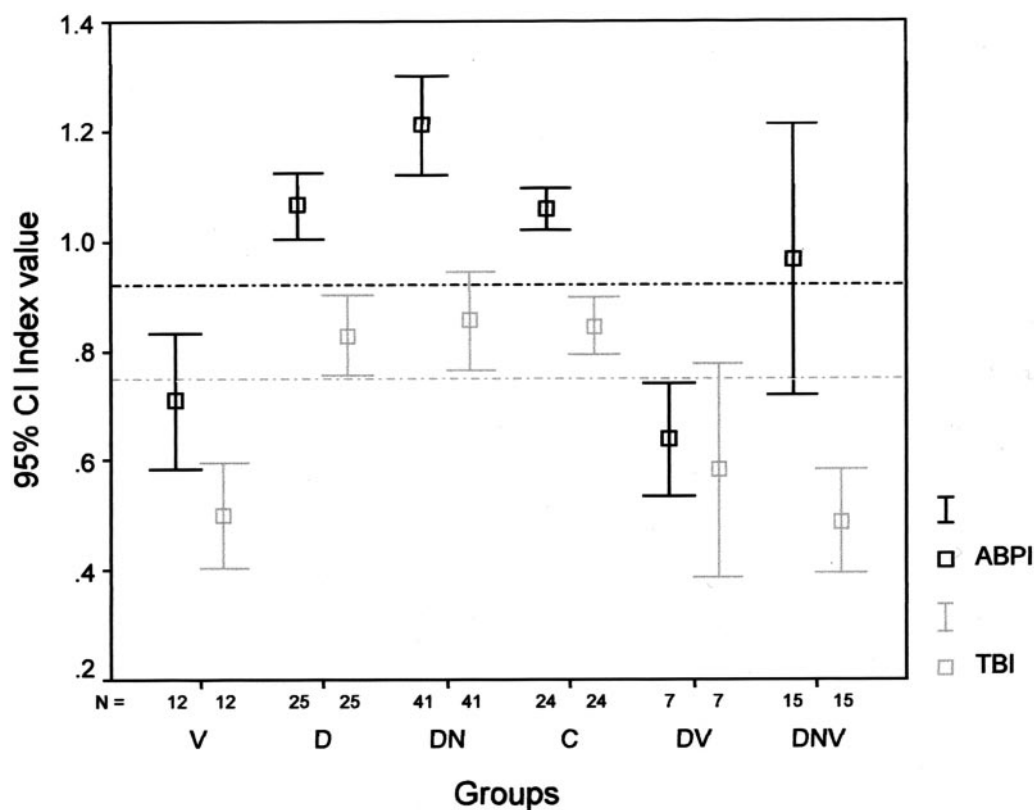


Figure 2—ABPI versus TBI, all groups. Horizontal lines represent an ABPI value of 0.9 and a TBI value of 0.75. V, control subjects with arterial disease; D, diabetes; DN, diabetes with neuropathy; C, control subjects; DV, diabetes with arterial disease; DNV, diabetes with neuropathy and arterial disease.

ICDF guidelines for ABPI measurement, limiting the upper range to 1.15, would still have resulted in a false-negative rate of 6 of 16 (38%) with Doppler and 5 of 15 (33%) with PPG in the group with peripheral neuropathy and arterial disease.

TBI

Comparatively lower toe pressures were reflected in TBI values that were universally lower than ABPI values across all groups ($t = 10.7$, $df = 123$, $P < 0.001$). The TBI did reflect the presence of arterial disease in all groups ($F_{5,121} = 13.56$, $P < 0.001$) (Fig. 2).

Control groups. The TBI identified all 13 limbs with arterial disease, but 5 of 21 with no arterial disease had values < 0.75 .

Diabetic groups. In the groups with arterial disease, there were 15 limbs with neuropathy vs. 7 without. Mean TBI values were 0.49 and 0.58, respectively ($t = 1.32$, $df = 20$, $P = 0.27$). In the absence of arterial disease, of the 41 limbs with neuropathy and 25 without, mean TBI values were 0.85 and 0.82, respectively ($t = -0.438$, $df = 64$, $P = 0.628$). These results demonstrated that peripheral neuropathy did not influence TBI values in this study.

Of the 22 limbs with arterial disease, 2 had TBI values > 0.75 (10% false-negative rate). Of the 66 limbs with no arterial disease, 23 demonstrated TBI values < 0.75 (35% false-positive rate).

Continuous waveform analysis

Qualitative analysis. In the control groups, 2 of 14 limbs with arterial disease had triphasic profiles in both foot vessels, (15% false-negative rate). One of the two limbs had a monophasic signal in one tibial vessel on CDI and no proximal disease. Of 27 limbs with no arterial disease, 1 had an absent flow in a single vessel (4% false positive rate).

In the diabetic groups, of those limbs with no detectable peripheral neuropathy or arterial disease ($n = 25$ limbs), 2 limbs had absent flow in a single vessel. Where flow was detected, all signals were triphasic (8% false-positive rate). However, in those limbs with no arterial disease but detectable peripheral neuropathy ($n = 41$ limbs), 12 limbs had at least one waveform with loss of reverse flow and 2 had undetectable flows (34% false-positive rate).

In the presence of arterial disease, the false-negative rate was 0% when any ves-

sel waveform anomaly was regarded as indicative of the presence of arterial disease in the absence of neuropathy ($n = 7$). When neuropathy was present ($n = 16$), one limb had two triphasic signals but had diffuse atherosclerotic disease on CDI (false-negative rate of 6%).

Quantitative waveform analysis. The resistance index was the more accurate indicator of arterial disease than the pulsatility or spectral broadening indexes. However, the major limitation of this modality in this study was its inability to produce accurate analyses in the presence of low amplitude and/or low-intensity signals, often allocating normal index values to qualitatively abnormal waveforms. This was most evident in the group with diabetes and arterial disease, for which 14 of 46 analyses (30%) were erroneous.

CONCLUSIONS — In the clinical assessment of lower limbs for arterial disease, palpation of foot pulses is mandatory. However, the test is subjective and is influenced by many factors (14). In our assessment, the absence of one or both foot pulses was found to be a sensitive test in individuals without diabetes. In subjects with diabetes, its sensi-

tivity was reduced, detecting four of five limbs with arterial disease in the presence of detectable peripheral neuropathy. However, the frequent absence of one or both foot pulses in subjects with no arterial disease resulted in a notable loss of specificity and overall accuracy.

The ABPI accurately reflected underlying arterial disease in the limbs of individuals without diabetes and those with diabetes but no detectable peripheral neuropathy. However, a mean ABPI >0.9 in the group with arterial disease and detectable peripheral neuropathy reflected a considerable loss of sensitivity, probably due to the presence of arterial calcification. The ABPI demonstrated the highest specificity and positive predictor value of all the tests across all groups (Table 2), with low values being highly indicative of arterial disease. However, its inability to detect arterial disease in the presence of detectable peripheral neuropathy resulted in false-negative results in one-third of limbs. The ABPI was less sensitive than palpation of foot pulses in screening for arterial disease in diabetes in the presence of detectable peripheral neuropathy.

The TBI did not improve on the screening results offered by pulses and the ABPI in limbs without neuropathy, but was superior to the ABPI in limbs with neuropathy, with a normal TBI effectively excluding the presence of significant arterial disease. The sensitivity of the TBI was maintained through all the diabetic groups. Its specificity was reduced, however, in the presence of peripheral neuropathy, resulting in reduced accuracy (Table 2). The TBI was demonstrated to be an effective screening tool in diabetes, both in limbs with and without detectable peripheral neuropathy and appears therefore to be less influenced by arterial calcification than the ABPI.

Qualitative waveform analysis in diabetes was as sensitive and specific as pulses and the ABPI in limbs without detectable neuropathy. The modality was as sensitive as the TBI in the presence of detectable peripheral neuropathy, with a marginally better specificity. The presence of a triphasic waveform with reverse flow in both foot arteries was demonstrated to effectively exclude significant arterial disease in $>90\%$ of limbs with neuropathy. Monophasic or biphasic flow (with loss of reverse flow) in either foot artery was highly suggestive of hemodynamically significant arterial disease.

Quantitative waveform analysis in this study was a very poor screening modality. The high frequency of erroneous results demonstrated on our equipment excludes it as a screening tool.

Further analysis of the 14 limbs that had no arterial disease on CDI but loss of reverse flow in one foot artery on qualitative waveform analysis demonstrated that all but one of these results occurred in the presence of detectable peripheral neuropathy. These limbs also had reduced TBI values ($r = 0.409$, $P = 0.008$) and absent foot pulses ($r = 0.495$, $P < 0.001$), suggesting that CDI may have been less sensitive than waveform analysis and the TBI in detecting significant arterial disease in these individuals.

Qualitative waveform analysis was the most effective screening tool of all the methods tested in this study. In the absence of neuropathy its performance was as good as those of the ABPI and pulses, but in neuropathic limbs it was clearly superior to pulses and the ABPI with comparable sensitivity and marginally better specificity than the TBI. Our findings indicate that in the assessment of lower-limb perfusion in diabetes, the combination of pulse palpation and noninvasive assessment using the TBI or, ideally, qualitative waveform analysis provides effective screening for significant arterial disease. In practice, waveform analysis is a relatively quick test to perform and does not require application of tourniquets. However, further work is required to evaluate the feasibility of undertaking this form of vascular assessment in clinical practice.

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