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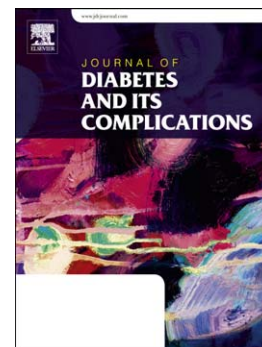
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Non-invasive vascular assessment in the foot with Diabetes: sensitivity and specificity of the ankle brachial index, toe brachial index and continuous wave Doppler in detecting peripheral arterial disease

ORIGINAL ARTICLE

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Abstract

Background & Aims– Non-invasive lower limb vascular assessment in people at risk of peripheral arterial disease (PAD) including those with diabetes is crucial. There is evidence that standard assessment techniques such as the ankle-brachial index (ABI) may be less effective in people with diabetes. However there is limited evidence for other frequently used tests including continuous wave Doppler (CWD), and the toe-brachial index (TBI). The aim of this study was to determine the sensitivity and specificity of CWD, ABI and TBI in a population with, and without diabetes.

Methods – Participants with and without diabetes who met current guidelines for vascular screening were recruited and CWD waveforms, an ABI and a TBI were obtained from the right lower limb. Diagnostic accuracy was determined using colour duplex ultrasound (CFDU).

Results – 117 participants were recruited, seventy-two with diabetes and forty-five without diabetes. CWD had the highest sensitivity in people with diabetes (74%) and without (84%). CWD also had the highest specificity in people with diabetes (74%) and without (84%) compared to both TBI and ABI. In participants with diabetes, the ABI was a poor test ROC: 0.58($p=0.27$).

Conclusions – CWD waveform is more likely to detect significant PAD compared to ABI and TBI in people with and without diabetes.

Keywords: continuous wave Doppler, ankle-brachial index, toe-brachial index, sensitivity, specificity, peripheral arterial disease

1. Introduction

Non-invasive lower limb vascular assessment is essential for detecting peripheral arterial disease (PAD). Early detection and on-going monitoring of PAD through routine screening facilitates effective management of the condition and, can ultimately prevent foot complications such as wounds, gangrene and amputation[1]. As PAD commonly occurs with systemic atherosclerosis [2], timely diagnosis is also necessary to ensure cardiovascular risk factors are managed to avoid more serious complications such as heart attack and stroke.

People with diabetes are at a four-fold increased risk of developing PAD. In this cohort the condition also progresses more quickly, is more severe than in the general population, tends to affect distal rather than proximal arteries and is more likely to result in ischaemic ulceration and amputation [3-5]. Due to the heightened risk of foot complications associated with diabetes-related PAD, accurate non-invasive vascular assessments of the lower limb are essential in this population.

Both the ankle-brachial index (the ratio of ankle arterial pressure to that in the brachial artery) and toe-brachial index (the ratio of toe arterial pressure to that in the brachial artery) are non-invasive vascular assessment techniques used to quantitatively evaluate arterial status of the lower limb[6, 7]. Although the ankle-brachial index (ABI) is used more widely, it has been demonstrated to have significant limitations in the presence of diabetes-related PAD including inability to detect distally located PAD and poor accuracy in the presence of medial arterial calcification, a condition associated with diabetes resulting in incompressible lower leg arteries [8].

As the toe-brachial index (TBI) measurement is taken more distally in the lower limb there is a greater likelihood of detecting arterial pressure changes caused by stenosis located below the knee as occur in the presence of diabetes[9]. The digital arteries are also less likely to be affected by MAC [10-12], and these factors potentially make the TBI a more sensitive test for

PAD than the ABI across diabetes cohorts. However, there are varying levels of diagnostic accuracy of the TBI in the limited current literature. Although there is some evidence that the TBI has superior sensitivity in the presence of diabetic neuropathy, in groups with diabetes alone, the TBI has shown lower sensitivity and specificity compared to ABI. In control populations, the TBI has demonstrated lower levels of specificity compared to ABI, but higher sensitivity [13]. However as these findings varied significantly between small groups (n=7 to n=41) and the study eligibility criteria were tightly controlled- most significantly excluding people with a smoking history or significant cardiovascular disease which are known to be associated with PAD, there is a need for more investigation in larger samples which reflect patients that clinicians encounter in clinical practice.

Continuous wave Doppler ultrasound (CWD) is frequently used alongside pressure measurement in non-invasive lower limb vascular assessment to assist in diagnosis of PAD, monitor disease progression and estimate severity [4]. CWD is a low cost screening tool that is accessible and quick to use. However, diagnostic accuracy of CWD for detecting PAD is not well known in people with diabetes, with a single small study demonstrating that CWD has high sensitivity and specificity for diabetes-related PAD than the ABI or TBI[13]. As interpretation of the CWD waveform relies upon the skill of the operator, and is considered more subjective than pressure measurements, further larger scale investigation of the utility of the assessment in a diabetes-cohort is required.

The aim of this study was to determine individual sensitivity and specificity of the ABI, TBI and CWD for detecting significant PAD in people with and without diabetes to further inform clinical use of non-invasive lower limb vascular assessments.

2. Materials and Methods

This was a prospective, single centre, cross sectional case-control study to determine the diagnostic accuracy of three non-invasive lower limb vascular assessment techniques in people with and without diabetes. This study was undertaken at Vascular Health Care, a private

vascular clinic in Lake Macquarie, New South Wales, Australia. Ethical approval was obtained from the University of Newcastle Human Research Ethics Committee. All participants provided written informed consent prior to participation.

Over a period of twenty-eight months (August 2011- December 2013) a volunteer convenience sample was recruited via flyer advertising from a private vascular clinic and a community health service in Newcastle. The following inclusion criteria were set in accordance with current guidelines for lower extremity vascular screening [6, 7]: participants aged over 65 years; or aged over 50 years with a history of diabetes; or aged over 50 years currently smoking; or with exertional leg pain or non-healing wounds. Exclusion criteria were: known allergy to coupling gel, presence of a wound preventing Doppler probe or ankle cuff placement or previous bilateral mastectomy preventing bilateral brachial blood pressure examination.

All participants attended a single testing session at the vascular clinic with one of three ultrasonographers (RK, RR, and AC). During the testing session CWD waveforms, ankle pressures and the hallux toe pressure were taken from the right side. Brachial pressures were performed bilaterally. Colour duplex ultrasound (CFDU) was performed on the right side from the distal aorta to the foot and used as the reference standard. CFDU was chosen as it has been demonstrated to be a valid imaging technique in non-invasive vascular diagnostic testing [14, 15]. The right limb only was used to reduce the incidence of type 1 error [16]. Following the initial testing session medical history was obtained from the general practitioners of individual participants. A subset of 10 participants randomly selected returned within one week of the initial testing session. At the second testing session all vascular tests were repeated by a different clinician blinded to the results of the initial test to establish inter-tester reliability.

Sonographers were trained in performing a basic neurological assessment by an experienced Podiatrist. The neurological assessment was performed by testing for protective sensation with the 10 gram Semmes-Weinstein monofilament at 10 points on the plantar surface of both feet. The 128Hz tuning fork was applied at the apex of the hallux bilaterally to assess vibration

perception [17]. Participants were classified as insensate if they failed either examination – more than four sites were undetected for the test of protective sensation or there was absent vibration perception.

CFDU was performed with either a Phillips CX-50 or GE Logiq-I. Pressures and CW Doppler tracings of pedal arteries were taken using the Parks Vascular Mini Lab 1050c, 8.2 Mhz continuous wave Doppler, Parks standard 10 cm inflatable cuff, and ERKA switch blood pressure gauge. Size of cuff used was in accordance with current guidelines for cuff size [6]. Room temperature was monitored with a thermometer and was maintained between 23°C and 25°C [18]. Participants were asked to avoid alcohol, smoking, exercise and caffeine one hour prior to the testing session to avoid influencing pressure measurement [19]. Participants were placed in a supine position and rested for at least 10 minutes prior to pressure measurements being taken. Bilateral brachial systolic pressures were obtained in all participants using a Parkes continuous wave Doppler and hand-held sphygmomanometer. Ankle systolic pressures of the right leg only were taken by placing the brachial pressure cuff around the lower leg, proximal to the medial and lateral malleoli. Both dorsalis pedis and posterior tibial artery pressures were recorded, with the higher of the two being used in calculation of the ABI. A single toe systolic pressure was obtained by placing a PPG probe directly on the distal pulp of the right great toe affixed with adhesive tape. Once a clear signal was obtained, a toe cuff was placed immediately proximal to the PPG probe. In the event of the great toe being too large for the toe cuff, the second toe was used. The cuff was then inflated to 20 mmHg above the last visual PPG signal. The cuff was then slowly deflated - the pressure reading was recorded when a consistent waveform returned. The TBI was calculated by dividing the toe pressure by the highest brachial pressure. CFDU was performed following pressure measurements, from the abdominal aorta to the distal ankle on the right side as the reference standard.

For calculations relating to diagnostic accuracy, PAD was defined as one or more arteries with $\geq 50\%$ stenosis indicating the presence of significant PAD [20-22]. Sensitivity, specificity,

positive and negative predictive values and ratios of the ABI for the presence of PAD were calculated using the standard cut-off score for an abnormal ABI of ≤ 0.90 or greater than 1.4, consistent with current screening guidelines[6, 7]. TBI normal values were considered ≥ 0.70 . CWD waveforms were analysed by a single researcher who assessed each waveform, blinded to the results of CFDU and pressure measurement. Loss of multi-phasic pattern (ie bi-phasic or tri-phasic) demonstrated by low resistance, slow systolic acceleration and no diastolic flow reversal were considered positive for PAD[23]. Standard deviations ([SD]) were derived for all means. 95% confidence intervals were calculated for sensitivities, specificities and positive and negative predictive values and ratios. Calculations of diagnostic accuracy were performed using Microsoft Excel. Receiver Operating Characteristic (ROC) analysis was performed for ABI and TBI and was calculated using SPSS version 22 statistical software.

Inter-tester reliability of CFDU scanning was calculated using the presence or absence of PAD as a dichotomous variable and an unweighted Cohen's Kappa (K) statistic. Inter-tester reliability of the neurological examination was also calculated using the presence or absence of sensorimotor neuropathy as a dichotomous variable and an unweighted Cohen's Kappa (K) statistic. Intra-class correlation coefficients (ICC) with 95% confidence intervals (CI) were calculated to determine level of agreement between test and retest for the ABI. All ICC values for inter-tester reliability were interpreted according to cut-offs suggested by Fleiss [24]. Interpretation of the Cohen's K statistic was performed using the method proposed by Landis and Koch [25] and interpretation of positive and negative predictive values was using the guide proposed by Geyman et al [26]. To compare the groups with and without diabetes, independent samples t-tests will be performed for age, ABI and TBI. Fisher's exact test compared history of smoking and severity of PAD, and pearson's chi-square compared gender, known history of cardiovascular disease and neurological status. P values were calculated for all comparative data. All reliability and comparative analyses were conducted using SPSS version 22 statistical software.

3. Results

A total of 117 participants were recruited. Participants were categorised into the diabetes (n=72) or no diabetes group (n=45) post-hoc. The no diabetes group served as the control group. Comparison of the two groups, with and without diabetes showed that overall there were no significant differences in gender ($p=0.56$), neurological status ($p=1.00$), age ($p=0.20$), severity of PAD ($p=0.75$), known cardiovascular disease ($p=0.90$) and smoking history ($p=0.37$) (Table 1). Inter-tester reliability of the CFDU scans between the three ultra-sonographers was high (K 0.78, $p<0.01$) [25]. ICCs demonstrated good test-retest reliability of the toe pressures (ICC: 0.80, 95% CI: 0.39-0.95), moderate reliability of brachial pressures (ICC: 0.66, 95% CI: 0.09-0.90), and ankle pressures (ICC 0.62, 95% CI: 0.03-0.89).

Means for ABI and TBI were comparable in both groups. Mean ABI was 1.16 in the diabetes group, and 1.08 in the group without diabetes, both within normal range and not significantly different between groups ($p=0.97$). The mean was TBI 0.70 in the diabetes group which was also within normal range however was slightly below normal for the group without diabetes but not significantly different between groups (0.67, $p=0.50$).

Sensitivity and specificity results of the three methods of assessment (CWD, ABI and TBI) for the presence of significant PAD in people with and without diabetes are shown in table 2, along with positive and negative predictive values. Overall CWD had the higher sensitivity, specificity, positive and negative predictive values for detecting significant PAD in both groups. The TBI was more sensitive than the ABI in both groups but had notably better sensitivity in the group of people without diabetes (83.33%) compared to the group with diabetes (63.63%). The sensitivity of the ABI was low in both groups but specificity was high and similar for both groups (approximately 92%). Likelihood ratios revealed important [26] positive likelihood ratios for the ABI and CWD in people with (ABI 6.17, CWD 10.39) and without diabetes (ABI 6.39, CWD 22.74) (Table 2). Negative likelihood ratios were important for CWD in people

without diabetes (0.16). The TBI had somewhat important positive likelihood ratios in people with (3.21) and without diabetes (3.55).

ROC analysis in the group without diabetes indicated similar clinical efficacy for both the ABI (ROC area: 0.81, $p=0.0001$) and TBI (ROC area: 0.81, $p=0.0001$) (Figure 1). In the group with diabetes, the TBI had greater clinical efficacy (ROC area: 0.75 $p=0.0001$) than the ABI (ROC area: 0.58, $p=0.27$) (Figure 2).

4. Discussion

To the best of our knowledge, this is the largest prospective diagnostic accuracy study examining the most commonly used non-invasive vascular assessment methods in diabetes. This study is unique in that the sample is substantial, and the participants are reflective of those encountered in clinical practice.

The specificity of the ABI was high in participants with (92.68%) and without diabetes (92.59%) and important positive likelihood ratios were also present in those with (6.17) and without diabetes (6.39) which was consistent with previous studies involving similar populations [13, 27, 28]. The sensitivity of the ABI was poor in both groups, with (45.16%), and without diabetes (47.37%). This was slightly lower than previous studies [27, 28] however this may have occurred as a result of the characteristic of the population we recruited. The participants in our study were older (mean age 72 and 74 years for participants with and without diabetes respectively), and there was also a large proportion of people with distally distributed PAD (36% in both groups). Our sample included a larger number of individual participants than previous studies [13] and represented a community-based population requiring non-invasive vascular screening including people with smoking history, significant cardiovascular disease and any form of neuropathy. This suggests these findings are reflective of the utility of this test in clinical practice. Based on our results the ABI was unlikely to yield false positive results in those with and without diabetes, however, it was highly likely to

produce false negatives, which has significant clinical implications, particularly as PAD is frequently asymptomatic[29].

The sensitivity of the TBI for detecting PAD was lower in people with diabetes (63%) than those without diabetes (83%). Although sensitivity of the TBI for PAD in the diabetes cohort was lower than reported in a previous research [13], our findings of superior sensitivity with a TBI than an ABI in this population is consistent with existing evidence. The specificity of the TBI in detecting PAD was higher in the group with diabetes (82%), than without (74%). ROC analysis demonstrated that overall the TBI was a superior test in the group with diabetes (ROC area: 0.75) compared to ABI which had limited diagnostic utility (ROC area 0.58). Both ABI and TBI demonstrated equal diagnostic utility in the group with no diabetes (both ROC area: 0.81).

The most sensitive test in both groups was CWD, which was more sensitive (74.19%) for the presence of PAD in people with diabetes than both the TBI (63.64%) and ABI (45.16%).

Important positive likelihood ratios in both participants with (10.39) and without diabetes (22.74) also indicated good test performance. These results are fairly consistent with a previous study [13] which showed CWD to have high sensitivity in populations with diabetes. We also defined PAD as a single lesion of >50% stenosis or more as diagnosed by CFDU, which has also been used in a previous study [13]. However, this cut-off for defining PAD may lead to increased sensitivity of CWD, as a minor stenosis proximally may be sufficient to alter the distal CWD, but not cause a significant drop in pressure at rest. Therefore peripheral pressure measurements may not be able to detect minor degrees of PAD.

4.1 Potential Limitations

The findings of this study should be considered in light of some potential limitations. This study used CFDU as the reference standard, and whilst this method is used extensively clinically, and considered an accurate method of non-invasive testing, it is operator dependant. We conducted an intra-tester reliability study, which whilst yielded good results, was limited to ten due to financial restraints. However, this was similar to previous studies utilising CFDU as a reference

standard[13]. Diagnosis of PAD by CFDU below the knee is known to be problematic. However, the participants in this study with distally located stenoses demonstrated more severe PAD, with almost all participants with distal PAD having complete occlusions in vessels below the knee. This makes the likelihood of a false positive unlikely. The post-hoc categorisation of the two groups may limit the generalizability of the results, however, statistical analysis revealed there were no significant differences between the groups so this is not likely. Although signs and symptoms that may indicate PAD were collected by the vascular sonographers at the time of scanning rigorous investigation and classification of these using the widely accepted Rutherford-Becker classification system was not performed. Therefore from our data it was not possible to determine the relationship between symptom severity and the ABI, TBI and CWD in this cohort, limiting the clinical utility of our results

The prospective nature and sample population of this study did not allow for more accurate and more invasive methods of vascular assessment as the reference standard. People with any form of neuropathy were included in this study population. A previous study has shown that diabetic neuropathy affected sensitivity of the ABI. However due to the small number of neuropathic participants recruited for our present study (only 15 out of the 117 participants) a separate sub analysis was not conducted on this group. It is possible that this may have affected our results as although incidence of peripheral neuropathy was evenly distributed between the groups, currently it is only diabetic peripheral neuropathy that is known to sensitivity of the ABI, and there is no data for peripheral neuropathy of other causes. This warrants investigation in a larger cohort.

5. Conclusion

All non-invasive testing was less sensitive in the group with diabetes, which draws attention to the difficulties of performing accurate vascular assessment in this population. Perhaps most striking was the low sensitivity of the ABI in both groups, suggesting this may not be the most appropriate vascular test even in the absence of diabetes, particularly where PAD is suspected.

The results of this study suggest that relying on an individual test such as an ABI or TBI for vascular screening is likely to be problematic.

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Tables

Table 1: Participant Characteristics

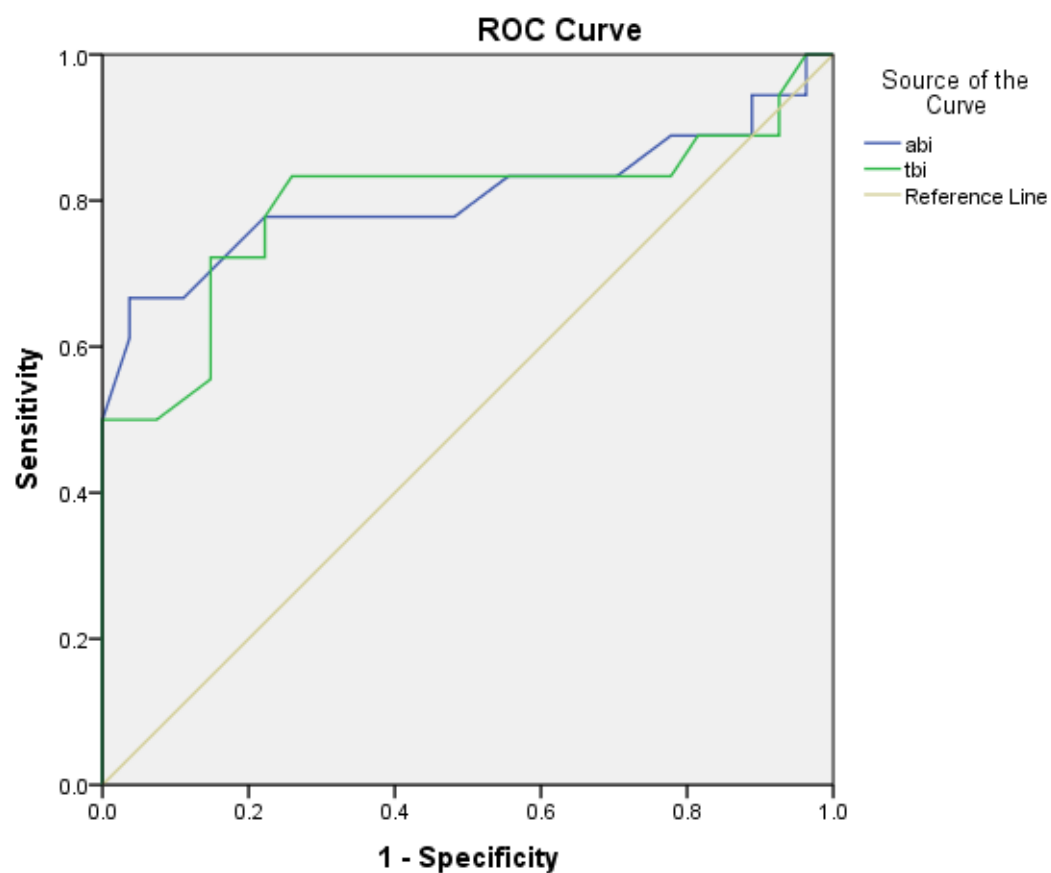
	DM Group	No DM group	Comparison
Total Participants N	73	46	
Males n (%)	48 (65)	27 (58)	0.338 ^B (p=0.56)
Females n (%)	25 (34)	19 (41)	
Age Range (Years)	53 -86	65 - 91	1.28 ^D (p=0.20)
Mean Age (years)	72.47	74.21	
Neuropathy n (%)	9 (12)	6 (13)	0.000 ^B (p=1.00)
History of smoking (%)	43 (58)	21 (46)	2.112 ^C (p=0.37)
Currently smoking (%)	2 (02)	3 (6)	
Known CVD (%)	23 (31)	15 (32)	0.01 ^B (p=0.90)
Mean ABI (^A)	1.16 (0.24)	1.08 (0.22)	1.67 (p=0.09)
Mean TBI (^A)	.70 (0.23)	0.67 (0.24)	0.67 (p=0.51)
Incompressible ankle pressure n (%)	8 (10)	2 (4)	
Distal PAD n (%)	27 (36)	17 (36)	
Proximal PAD n (%)	10 (13)	4 (8)	
PAD n (%)	36 (49)	19 (41)	
>50% stenosis n (%)	4 (5)	1 (2)	1.382 ^C (p=0.75)
>75% stenosis n (%)	4 (5)	1 (2)	
Occlusion n (%)	24 (33)	17 (37)	

^A=standard deviation, PAD= Peripheral arterial disease, DM= Diabetes Mellitus CVD= Cardiovascular disease ^BPearson's chi-square ^CFishers exact test ^DIndependent samples t test

Table 2: Validation table: All groups

	Participants with Diabetes			Participants without Diabetes		
	<i>Ankle Brachial Index</i>	<i>Continuous Wave Doppler</i>	<i>Toe-Brachial index</i>	<i>Ankle Brachial Index</i>	<i>Continuous Wave Doppler</i>	<i>Toe-Brachial index</i>
<i>Sensitivity (95% CI)</i>	45.16 (27.33 to 63.96)	74.19 (55.38 to 88.11)	63.64 (45.13 to 79.58)	47.37 (24.49 to 71.10)	84.21 (60.40 to 96.43)	83.33 (58.56 to 96.23)
<i>Specificity (95% CI)</i>	92.68 (80.05 to 98.38)	92.86 (80.49 to 98.42)	82.05 (66.46 to 92.43)	92.59 (75.67 to 98.88)	96.3 (80.97 to 99.38)	74.07 (53.71 to 88.84)
<i>Positive likelihood ratio (95% CI)</i>	6.17** (1.94 to 19.62)	10.39** (3.42 to 31.52)	3.55* (1.73 to 7.28)	6.39** (1.55 to 26.33)	22.74** (3.29 to 157.15)	3.21* (1.64 to 6.28)
<i>Negative likelihood ratio (95% CI)</i>	0.59 (0.43 to 0.82)	0.28 (0.15 to 0.51)	0.44 (0.28 to 0.71)	0.57 (0.37 to 0.88)	0.16** (0.06 to 0.46)	0.22 (0.08 to 0.65)
<i>Positive predictive value (95% CI)</i>	82.35 (56.55 to 95.99)	88.46 (69.82 to 97.42)	75.00 (55.12 to 89.26)	81.82 (48.24 to 97.18)	94.12 (71.24 to 99.02)	68.18 (45.13 to 86.08)
<i>Negative predictive value (95% CI)</i>	69.09 (55.19 to 80.85)	82.98 (69.18 to 92.33)	72.73 (57.21 to 85.03)	71.43 (53.69 to 85.34)	89.66 (72.62 to 97.69)	86.96 (66.38 to 97.07)

**Important likelihood ratio, *relatively important likelihood ratio



Diagonal segments are produced by ties.

Figure 1 ROC analysis of TBI and ABI for detecting PAD in people without diabetes

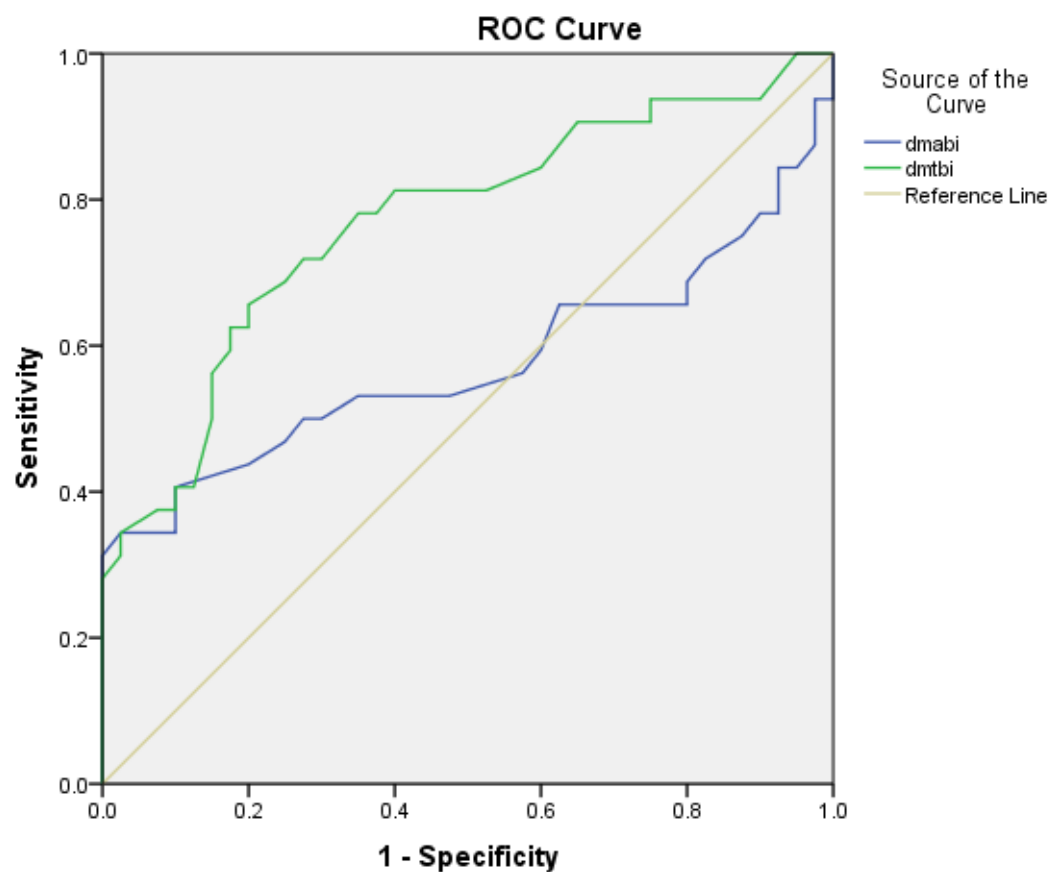


Figure 2: ROC analysis of ABI and TBI in detecting PAD in people with diabetes

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