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SUPPLEMENT ARTICLE

Effectiveness of bedside investigations to diagnose peripheral artery disease among people with diabetes mellitus: a systematic review

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Abstract

Non-invasive tests for the detection of peripheral artery disease (PAD) among individuals with diabetes mellitus are important to estimate the risk of amputation, ulceration, wound healing and the presence of cardiovascular disease, yet there are no consensus recommendations to support a particular diagnostic modality over another and to evaluate the performance of index non-invasive diagnostic tests against reference standard imaging techniques (magnetic resonance angiography, computed tomography angiography, digital subtraction angiography and colour duplex ultrasound) for the detection of PAD among patients with diabetes. Two reviewers independently screened potential studies for inclusion and extracted study data. Eligible studies evaluated an index test for PAD against a reference test. An assessment of methodological quality was performed using the quality assessment for diagnostic accuracy studies instrument. Of the 6629 studies identified, ten met the criteria for inclusion. In these studies, the patients had a median age of 60–74 years and a median duration of diabetes of 9–24 years. Two studies reported exclusively on patients with symptomatic (ulcerated/infected) feet, two on patients with asymptomatic (intact) feet only, and the remaining six on patients both with and without foot ulceration. Ankle brachial index (ABI) was the most widely assessed index test. Overall, the positive likelihood ratio and negative likelihood ratio (NLR) of an ABI threshold <0.9 ranged from 2 to 25 (median 8) and <0.1 to 0.7 (median 0.3), respectively. In patients with neuropathy, the NLR of the ABI was generally higher (two out of three studies), indicating poorer performance, and ranged between 0.3 and 0.5. A toe brachial index <0.75 was associated with a median positive likelihood ratio and NLRs of 3 and ≤ 0.1, respectively, and was less affected by neuropathy in one study. Also, in two separate studies, pulse oximetry used to measure the oxygen saturation of peripheral blood and Doppler wave form analyses had NLRs of 0.2 and <0.1. The reported performance of ABI for the diagnosis of PAD in patients with diabetes mellitus is variable and is adversely affected by the presence of neuropathy. Limited evidence suggests that toe brachial index, pulse oximetry and wave form analysis may be superior to ABI for diagnosing PAD in patients with neuropathy with and without foot ulcers. There were insufficient data to support the adoption

of one particular diagnostic modality over another and no comparisons existed with clinical examination. The quality of studies evaluating diagnostic techniques for the detection of PAD in individuals with diabetes is poor. Improved compliance with guidelines for methodological quality is needed in future studies.

Keywords peripheral artery disease; diagnosis; diabetes; investigations

Abbreviations ABI, Ankle brachial index; CDUS, Colour duplex angiography; CTA, Computed tomographic angiography; DSA, Digital subtraction angiography; NLR, Negative likelihood ratio; PAD, Peripheral artery disease; PLR, Positive likelihood ratio; PRT, Pulse reappearance time; QUADAS, Quality assessment for diagnostic accuracy studies; TBI, Toe brachial index; $TcPO_2$, Transcutaneous pressure of oxygen

Introduction

Diabetes is strongly associated with the presence of PAD; among individuals with diabetes in the US National Health and Nutrition Examination Survey, 11% had PAD as defined by ABI <0.9 in either leg, compared with 4% of individuals without diabetes [1]. Not only is PAD an independent risk factor for developing foot ulceration and limb loss, it is also associated with a higher risk of incident cardiovascular disease [2] and of overall mortality, irrespective of symptoms or the populations studied [3].

Data from the Eurodiale study of 1229 patients with diabetes presenting 14 secondary care institutions with a new foot ulcer showed that PAD was present in around 50% of patients with diabetic foot ulceration and in up to 71% of patients older than 70 years [4]. In these patients, PAD confers a greater risk of non-healing; when compared with patients without PAD, those with PAD had healing rates of 69% vs. 84% and major amputation rates of 8% vs. 2%, respectively [5]. Moreover, severe ischemia, defined by an ABI below 0.5, was associated with a poorer quality of life [6]. PAD is therefore clearly associated with poor outcomes in patients with diabetes. It is important for healthcare professionals to recognize it promptly, and accurately, and to risk stratify patients and take steps to minimize its deleterious effects.

The diagnosis of PAD is challenging in patients with diabetes for a number of reasons. Firstly, co-existing symmetrical distal polyneuropathy, present in a significant proportion of patients with diabetes and particularly those with foot ulceration, may mask symptoms of PAD such as intermittent claudication and ischemic rest pain. Patients may therefore present at a more advanced PAD stage than their non-diabetic counterparts [7]. Physical examination is of limited value [8] and does not provide reliable information to determine whether PAD is present nor does it reliably assess its severity. Oedema, neuropathy and infection, frequently co-existing in the presence of ulceration, make the clinical assessment for PAD difficult and may hamper the performance of diagnostic tests for PAD. Moreover, the greater prevalence of medial sclerosis (medial arterial calcification) among patients with diabetes can render pedal arteries incompressible on cuff inflation during external arterial pressure measurements such as with ABI or toe pressures [9]. There are few robust data on the usefulness of tests to diagnose or rule out PAD, including ABI, in diabetes and particularly in those with ulcerated feet. The aim of this systematic review was to evaluate the performance of index non-invasive diagnostic tests against reference standard imaging techniques for the detection of PAD among patients with diabetes.

Materials and methods

Data search

A systematic search of the literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidance [10]. The MEDLINE and Embase databases were searched for articles in English language pertaining to the diagnosis of PAD among patients with diabetes from 1980 to June 2014. The results of the search undertaken for a previous systematic review from the International Working Group on the Diabetic Foot on the effectiveness of revascularization for patients with a diabetic foot ulcer [11] were updated (search version 1, online Appendix A). In addition, a further search (search version 2, online Appendix B) was performed. The abstracts of identified studies were combined and evaluated for inclusion independently by two reviewers, with conflicts adjudicated by a third reviewer. At a later stage, full-text manuscripts of the selected studies were evaluated by two reviewers.

Criteria for inclusion/exclusion

Studies evaluating ulcerated and non-ulcerated patients were included to establish the potential effect of ulceration on the performance of diagnostic tests. Diagnostic tests were considered as any specific evaluation that sought to identify the presence of PAD. Serum markers that may be an expression of PAD were included.

Studies eligible for inclusion included those evaluating an index test for PAD against a reference test. Tests considered as an appropriate reference test included DSA, CTA, magnetic resonance angiography (MRA) and CDUS. Studies comparing two reference tests, defined by the criteria discussed earlier, were excluded. Also excluded were

studies involving purely patients with PAD; in studies lacking a non-diseased control group, calculation of sensitivity and/or specificity values was not possible. Only studies reporting separately on ≥10 patients with diabetes were considered, where studies reported on mixed cohorts of patients with and without diabetes; those with a proportion of patients with diabetes <80% were excluded. Studies that reported data in a fashion that did not permit the calculation of sensitivity and/or specificity values, and therefore likelihood ratios, were also excluded.

Data extraction and quality assessment

Data were extracted by one reviewer and independently verified by another reviewer. Methodological quality of included studies was assessed independently by the same two reviewers against parameters included in the QUADAS tool, a consensus quality assessment tool designed specifically for diagnostic accuracy studies [12]. Given the heterogeneity of populations studied in observational reports, the measures of test performance were reported separately where possible. For example, if a single study reported separate analyses on a cohort of patients with and without neuropathy, those separate groups are reflected in the evidence table. When not reported in the article, sensitivity and specificity were calculated from raw data, where available, as well as the PLR and the NLR.

The PLR and the NLR were the primary endpoints chosen for this systematic review. A PLR ≥10 and an NLR ≤0.1 were considered markers of good test performance [13,14]. Given the substantial heterogeneity in both the populations studied and the range of index/reference tests evaluated, a meta-analysis was not performed. The median and range of summary statistics, including estimates of test performance, are presented, stratified by index test and population studied.

Results

Search strategy and study selection

Out of the 6629 studies, a total of ten observational studies reporting data from 2585 patients with diabetes met the study criteria and were included in the qualitative data synthesis (Table 1) [15–24]. A flow diagram depicting the overall search results is shown in Figure 1.

Comorbidity and patient demographics

Overall, the mean or median age was reported as 60–76 years, and the proportion of men in each study varied between 47% and 88%; one study lacked data on sex [22]. Coronary artery disease was present in 9–29% of patients with a median of 20%; whereas 6–31% had experienced a stroke with a median of 16% (although definitions varied between studies, see footnote Table 1). The mean duration of diabetes ranged from 9 to 24 years (median 12 years) and was not stated in one study [23]. The presence of foot ulceration was reported only by a minority of studies ($n = 4$) [18,19,21,23], and no study categorized the severity of foot ulcers. The prevalence of neuropathy among cohorts of patients with diabetes ranged from 48% to 82% (median 72%) in three studies with available data [18,19,21].

Reference tests

A total of eight studies evaluated index tests for PAD against a CDUS reference measure [15,17–23]. Criteria for the diagnosis of PAD using CDUS included the following: an increase in peak systolic velocity ≥100% (or defined as >50% stenosis) in four studies [15,19,20,22], monophasic waveforms in two studies [17,23], peak tibial artery velocity ≤10 cm/s in one study [21] and a combination of significant velocity change and loss of reverse flow in a further study [18]. The remaining two studies used DSA as a reference test [16,24], both using a cutoff of >50% reduction in vessel diameter to diagnose PAD. No study reported the performance of a test using CTA or MRA as a reference measure of PAD. A variety of definitions were used to describe populations with PAD reflecting the problems associated with the nomenclature and classification of PAD in patients with diabetes. Terms used included lower limb ischemia, lower extremity artery disease, significant PAD and critical limb ischemia.

Index tests

Among the included studies, index tests evaluated included the biomarker serum cystatin C concentration, and non-invasive tests included audible Doppler waveform, ankle pressures, ABI, TBI, $TcPO_2$, PRT and pulse oximetry used to measure the oxygen saturation of peripheral blood. The ABI was the most common index test evaluated; eight studies evaluated its performance [17–24]. One study used lower and upper thresholds of a combination of <0.9 or >1.3 to define PAD [23], whereas the remaining seven studies used a cutoff <0.9 in isolation.

Data synthesis and analysis

Ankle brachial index. Most studies provided adequate data to derive sensitivity, specificity and therefore PLR and

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Table 1. Characteristics of included studies and measures of index test performance

Source	No. of DM patients	Proportion of men, %	Age, mean (SD) or (range), year	Population	Reference test*	Index test	Sensitivity, %	Specificity, %	PLR	NLR
Clairotte *et al.*, 2009 [19]	83	71	63 (11)	48% neuropathy; mixed ulcerated/intact	DUS	dABI <0.9	54	97	17	0.3
						oABI <0.9	29	96	8	0.5
Zhang *et al.*, 2009 [20]	92	78	63 (14)	Neuropathy/ulceration NS	DUS	ABI <0.9	95	86	7	0.1
Premalatha *et al.*, 2002 [22]	100	NS	60 (10)	100% foot infection; neuropathy NS	DUS	ABI <0.9	71	89	7	0.3
Parameswaran *et al.*, 2005 [17]	57	47	63 (41–84)	Neuropathy/ulceration NS	DUS	ABI <0.9	63	97	25	0.4
						Pulse oximetry	77	97	30	0.2
Lewis *et al.*, 2010 [23]	205	51	63 (13)	100% intact feet; neuropathy NS	DUS	ABI <0.9, OR >1.3	91	77	4	0.1
Williams *et al.*, 2005 [18]	NS	74	63–69	100% intact feet; 72% neuropathy	DUS	ABI <0.9 (PN−)	100	88	8	<0.1
						TBI <0.75 (PN−)	91	65	3	0.1
						Mono OR biphasic waveform (PN−)	100	92	13	<0.1
						ABI <0.9 (PN+)	53	95	11	0.5
						TBI <0.75 (PN+)	100	61	3	<0.1
						Mono OR biphasic waveform (PN+)	94	66	3	0.1
Aboyans *et al.*, 2008 [21]	158	88	68 (30–100)	94% ulcerated; 82% neuropathy	DUS	ABI ≤0.9	99	58	2	<0.1
Liu *et al.*, 2013 [15]	1609	57	60 (12)	Neuropathy/ulceration NS	DUS†	Cystatin C >1.2 mg/L	76	68	2	0.4
Ezio *et al.*, 2010 [16]	261	67	72 (9)	Neuropathy/ulceration NS	DSA	Ankle pressure <70 mmHg	67	NS		
						$TcPO_2$ <30 mmHg	82	NS		
Vogelberg *et al.*, 1988 [24]	20	65	61 (9)	47% gangrene; neuropathy NS	DSA	Pulse reappearance time	41	92	5	0.6
						ABI <0.9	36	93	5	0.7

dABI, doppler ankle brachial index; DM, diabetes mellitus; DSA, digital subtraction angiography; DUS, duplex ultrasound; NLR, negative likelihood ratio; NS, not stated; oABI, oscillometric ankle brachial index; PLR, positive likelihood ratio; PN+, with peripheral neuropathy; PN−, without peripheral neuropathy; SD, standard deviation; TBI, toe brachial index.
*Definition of peripheral artery disease using the same reference test varied; see Appendix Table 1 (Supporting information).
†In combination with ABI <0.9.

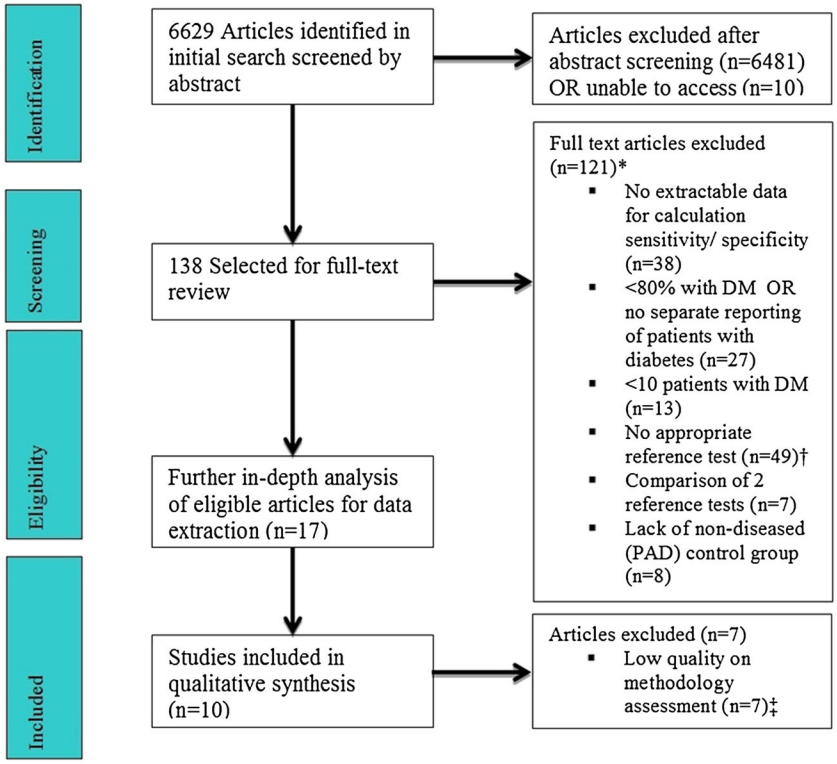

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram of articles included in the systematic review. *Sum of exclusions may not equal the total because of multiple reasons for exclusion. †Reference tests considered were digital subtraction angiography, magnetic resonance angiography, computed tomography angiography and colour duplex ultrasound. ‡SIGN methodology checklist 5: studies of diagnostic accuracy (based on QUADAS2). DM, diabetes mellitus; PAD, peripheral artery disease

NLR. One study failed to provide raw data to enable calculation of a specificity value and therefore PLR and NLR [16]. Given the variety of index and reference tests studied, results are presented in groups by index tests. Eight studies investigated the performance of ABI against a reference standard test involving CDUS, albeit using a variety of thresholds for the diagnosis of PAD with CDUS. Three studies used the same reference test and measure (increase in peak systolic velocity ≥100%), presenting data for the performance of ABI with a threshold <0.9. The reported sensitivities ranged from 29% to 95%, although when a single value from a study using an oscillometric ABI method was excluded and only ABI measurements using the Doppler method were considered, this range improved to 54–95%. Specificities reported in the same studies were more consistent, varying between 86% and 97%. When considering all studies reporting on the performance of ABI using a threshold <0.9, irrespective of the reference test, sensitivity and specificity ranged between 29% and 100% (median 63%) and 58% and 97% (median 93%), respectively. From these values, the PLR and the NLR were derived, ranging from 2 to 25 (median 8) and 0 to 0.7 (median 0.3), respectively. The study by Williams *et al.* compared the performance of ABI between patients with and without neuropathy, albeit in a relatively small number of patients ($n = 57$ and 32, respectively). The PLR in the group without neuropathy was 8 compared with 11 in the group with neuropathy, suggesting that neuropathy does not appear to have an adverse effect on PLR. In contrast, the NLR value for ABI measures was significantly poorer in the neuropathy group when compared with patients without neuropathy (0.5 vs. <0.1, respectively). These values were driven by a difference in the sensitivity of ABI <0.9 for the detection of PAD: 100% among patients without neuropathy and only 53% among those with neuropathy. One study combined an ABI threshold <0.9 with values >1.3 to account for the presence of incompressible vessels; however, no improvement was observed in comparison with the median overall PLR and NLR. When examining the differences between studies reporting on cohorts with intact feet and those with ≥90% of patients with active foot ulceration, no consistent improvement in the performance of an ABI threshold <0.9 was observed. Two studies evaluating ABI in patients with purely intact feet reported PLRs and NLRs ranging from 4 to 11 and <0.1 to 0.5, respectively, compared with 2 to 7 and <0.1 to 0.3, respectively, among studies in cohorts with ulcerated feet.

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Toe brachial index. A single study evaluated the performance of TBI, in separate groups of patients with and without peripheral neuropathy, using a threshold <0.75 for the diagnosis of PAD [18]. Using a reference standard of CDUS, the presence of neuropathy had little effect on the performance of the TBI with PLR of 3 and NLR ≤0.1 in both the groups with and without neuropathy. The technical success of TBI measurements was 100%, although patients with active foot disease were excluded from this study.

Pulse oximetry and transcutaneous pressure of oxygen. Pulse oximetry (oxygen saturation of peripheral blood) was evaluated in a single study and compared with another index test (ABI <0.9), using a CDUS measure of any monophasic waveform in the lower limb arteries as a reference standard for the diagnosis of PAD [17]. Pulse oximetry was used to measure SaO_2 of the hallux in a supine and elevated position. In comparison with ABI, data provided suggest that pulse oximetry is at least as useful as ABI; the PLR and NLR for pulse oximetry were 30 and 0.2, respectively, while an ABI threshold <0.9 produced equivalent values of 25 and 0.4. This example of a direct comparison between different diagnostic modalities, in the same population, is useful and was only seen in three of the included studies. A further study examined $TcPO_2$ measurements (partial pressure of oxygen on the skin surface) and compared the performance of $TcPO_2$ <30 mmHg with that of ankle systolic pressure <70 mmHg. An overall denominator of patients free of PAD was not provided, and therefore, no specificity or likelihood ratios could be calculated. The available data suggest that $TcPO_2$ may provide better sensitivity for the detection of PAD than ankle pressure (82% vs. 67%), although this is limited to a single study with moderate methodological quality [16].

Doppler waveform analysis. One study examined the diagnostic performance of the loss of an audible triphasic waveform, using CDUS as a reference standard (Table 1) [18]. The presence of monophasic or biphasic waveforms in the ankle vessels performed well with respect to the NLR (0.1 and <0.1 among patients with and without neuropathy, respectively), although PLR values were less consistent and varied depending on the presence of peripheral neuropathy (3 and 13 among patients with and without neuropathy, respectively).

Pulse reappearance time. One study evaluated whether PRT, after a 3-min compression of the thigh, could provide additional information on the presence or severity of PAD over and above an ABI threshold <0.9 (Table 1) [24]. Although no significant improvements in PLR and NLR were observed (5 vs. 5 and 0.6 vs. 0.7, respectively), the severity of PAD as measured by the degree of stenotic lesions identified on DSA was correlated with PRT but not ABI. A summary of all the data extracted is presented in the Evidence Table online (Table S2).

Discussion

Prompt recognition and expert assessment of PAD in patients with diabetes and either an intact, asymptomatic foot or an ulcerated foot allow measures to be taken to reduce the risk of amputation and cardiovascular events, while determining the need for revascularization to promote ulcer healing in symptomatic patients. PAD in patients with diabetes is associated with poorer lower extremity functioning (e.g. reduced walking speed), but only a minority of these patients report classical intermittent claudication [25]. Many medical history and physical examination findings for the detection of PAD are of limited use in diabetes, although diminished or absent peripheral pulses are associated with PAD (defined as a low ABI) [26]. Several pooled analyses have evaluated and compared diagnostic modalities for the detection of PAD in mixed cohorts of patients with and without diabetes [27,28]. Despite the distinctive anatomical features of PAD in diabetes and the challenges associated with its diagnosis, studies to support the use of a particular non-invasive method among patients with diabetes are lacking. As such, questions regarding the application and interpretation of various diagnostic tests remain largely unanswered among these patients. This systematic review examines the evidence to support the effectiveness of non-invasive bedside tests for the diagnosis of PAD. This is timely because not only is the number of people with diabetes increasing, the proportion of patients with diabetes and PAD with ulceration is also increasing [4].

The estimates of test performance are presented herein as likelihood ratios to provide the most meaningful comparator relating to the clinical decision-making process [29]. A PLR is the ratio of the probability that a particular test is positive in a person with a disease compared with the probability of this result in a person without the disease. In contrast, an NLR is the probability of a negative test in a disease-free individual compared with a person with the disease. A PLR above 10 and an NLR below 0.1 have been noted to provide convincing diagnostic evidence, whereas those between 5 and 10, and 0.1 and 0.2 give strong diagnostic evidence [13,14].

Among patients with an ulcerated foot, a low threshold for referral to a specialist foot team is warranted where clinically relevant PAD is suspected. In secondary care, establishing the extent of the perfusion deficit is the next step, allowing the identification of patients with a foot ulcer who may require revascularization to promote healing and prevent amputation. Lastly, once a revascularization

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procedure is considered in patients with a moderate to severe perfusion deficit, establishing the anatomical distribution of disease may be achieved using CDUS, CTA, MRA or DSA.

The performance of an initial non-invasive bedside test for PAD in the context of diabetes is best evaluated by the ability of a negative result to rule out PAD. That is, it should have a low NLR. Those patients with a positive test result will require additional investigations, including the reference tests used as a benchmark in this systematic review. Therefore, the accuracy of the non-invasive test to positively identify PAD is less important than the accuracy of a test in determining which patients do not have PAD, as the costs of missing significant PAD will likely outweigh the costs of a false positive classification of PAD by a candidate test. Those in whom the suspicion of PAD is low are less likely to be referred to secondary/specialist care for further investigations. A significant frequency of false negative tests in this respect would be alarming as patients at high risk of ulceration, or failure to heal, may not receive timely expert assessment, and an opportunity to save life or limb may be missed. For these reasons, the NLR is considered the most important measure of outcome in the present review.

In subjects without diabetes, measurement of the ABI is one of the cornerstones in diagnosing PAD, but its diagnostic performance varies according to the population studied, the cutoff threshold and the technique used to detect flow in the ankle arteries [30]. Values below 0.9 are commonly used to detect PAD compared with angiography. Two studies included in our review that reported on intact feet suggest that, compared with reference tests (CDUS), an ABI can be useful to refine the clinical diagnosis of PAD in subjects with diabetes. Lewis *et al.* provided an assessment of the performance of an ABI threshold <0.9 or >1.3, producing an NLR of 0.1, roughly corresponding to a reduction in probability of a patient having the disease of 45% [31]. In the study by Williams *et al.* that defined a threshold <0.9 in isolation, among patients without neuropathy and an intact foot, the derived NLR was <0.1. Of great interest was the comparator group in the Williams *et al.* study, which consisted of patients with intact feet and neuropathy. The presence of neuropathy is thought to reduce the reliability of ABIs by virtue of its association with medial sclerosis [32], which may render the vessel wall incompressible on cuff inflation [4,33]. A greater proportion of falsely high readings in the neuropathy group would reduce the sensitivity of an ABI threshold <0.9 for the detection of neuropathy. Indeed, the performance of an ABI threshold <0.9 among the neuropathy group was significantly poorer with an NLR of 0.5, corresponding with a 15% reduction in PAD post-test probability [31]. This trend is replicated in the study by Clairotte [19] that reported a neuropathy prevalence of around 50%. The NLRs for an ABI threshold <0.9 in this study were between 0.3 and 0.5, again indicating the adverse effect of neuropathy on the diagnostic performance of ABI. In contrast, Aboyans *et al.* reported an NLR <0.1 for an ABI threshold ≤ 0.9 in a cohort where 82% of patients had neuropathy [21]. No improvement was observed when comparing the performance of ABI <0.9 between intact and ulcerated feet although this comparison may be confounded by the differences in the prevalence of neuropathy between studies. Clearly, there are significant variations in the test performance of ABI for the reasons stated earlier. In summary, as most patients with a foot ulcer have neuropathy, PAD is less effectively ruled out when the ABI is within the normal range (0.9–1.1); on the other hand, when the ABI is <0.9, PAD is likely (with a PLR >5 in most studies).

Although an ABI measurement has become a standard procedure, there is a large variation in measurement techniques, the methods of calculation of the ABI value and the definition of threshold values, both in scientific reports and in clinical practice [34]. Different techniques for the measurement and calculation of ABI were not compared in this review, including the use of the peroneal artery, which is often spared at the expense of other crural vessels in diabetes. Such inter-observer differences might be one of the possible explanations for the variability in the test performance of the ABI presented herein. Recommendations for standardization of measurement, calculation and interpretation of the ABI were recently given by American Heart Association and will hopefully be implemented in future studies [30]. This lack of standardization also applies for the other techniques described in this review.

Toe pressure measurement and the calculation of TBI may allow more accurate measurement of perfusion in patients with diabetes and medial sclerosis, owing to the relative sparing of the digital arteries from calcification. In a proportion of patients, it is not possible to determine toe pressure, and this rate is dependent upon the presence of digital ulceration and minor amputation. Williams *et al.* evaluated the performance of this technique in groups with and without peripheral neuropathy, but with intact feet using a diagnostic threshold <0.75 [18]. The NLRs in both groups were ≤ 0.1, suggesting that TBIs can effectively rule out the presence of PAD irrespective of neuropathy status. Thus, the performance of the TBI threshold <0.75 among patients with neuropathy represents a marked improvement over that of the ABI. The PLR of TBI was 3 in each group, with and without neuropathy, indicating that a negative test result can be relied upon to a greater extent than a positive test result.

The diagnosis of PAD using pulse oximetry is an attractive proposition because it requires equipment that is relatively inexpensive and available in most healthcare environments. Parameswaran *et al.* assessed its efficacy as a screening tool and sought to determine whether it could be used to improve the performance of ABI in a

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cohort of patients with diabetes [17]. The accuracy of each test was similar, and pulse oximetry was associated with a superior NLR (0.2 vs. 0.4) and PLR (30 vs. 25) relative to an ABI threshold <0.9. Taken together, these data, albeit confined to a single study, are encouraging. A parallel combination of the tests had a higher sensitivity, but lower specificity for the detection of PAD. Only one study could be identified according to our inclusion criteria on $TcPO_2$ [16], but unfortunately, only sensitivity but not PLR's or NLR's could be calculated based on the reported data.

One study assessed the performance of qualitative waveform analysis with a threshold of monophasic or biphasic pulse wave, demonstrating superiority in a direct comparison with ABI (<0.9) and TBI (<0.75). The NLRs were ≤0.1 in patients with and without neuropathy, suggesting that a normal waveform can be used to render PAD less likely. On the other hand, the PLRs were 3 and 13, respectively, consistent with approximate increases in pre-test probability of 20% and >45% [31], again demonstrating the adverse effect of neuropathy on the performance of non-invasive tests.

The identification of patients with PAD using a biomarker seems appealing because of easy access to clinical laboratory testing, particularly as a screening tool in diabetes where clinical assessment of PAD is challenging. One study included in this review evaluated the performance of cystatin C, an endogenous marker of renal function that has shown an association with both PAD [35] and more broadly cardiovascular events among a population with PAD [36]. Despite a significant association with PAD, cystatin C performed poorly in the detection of PAD, with an NLR and a PLR of 0.4 and 2, respectively.

The quality of studies included in the present review was generally poor, and no study satisfied the majority of the QUADAS criteria for methodological quality for an overall 'high-quality' rating. Clinically relevant descriptions of the cohorts studied were not provided by the majority of studies, including specification of the proportion of patients with ulceration or neuropathy, thought to have a significant effect on the performance of diagnostic tests. A total of 38 studies were excluded owing to insufficient data to allow the construction of 2×2 contingency tables, from which sensitivity, specificity and likelihood ratio values are derived. As we did not contact the authors of these studies to provide missing data, selection of studies based on data presentation may have resulted in biassed estimates of diagnostic test performance. Further, we were unable to produce a valid meta-analysis including weighted averages of the summary statistics across studies because of the heterogeneity of populations, reference standards and index tests studied. Lastly, several studies failed to report on the technical success of the index test, and some made inappropriate exclusions, including the exclusion of patients with incompressible ABIs (≥1.3) while evaluating the performance of ABI.

Conclusions

The studies reported suggest that ABI (<0.9) is a useful test for the detection of PAD in asymptomatic patients without neuropathy, although its performance is variable among studies, suggesting either poor inter-observer reliability or confounding by factors that were not reported, such as the presence of neuropathy, ulceration or other unmeasured factors. The performance of ABI is adversely affected by the presence of peripheral neuropathy, whereas a TBI ≥0.75 or triphasic pedal pulse waveforms provide stronger evidence for the absence of PAD. Evidence of the performance of pulse oximetry was limited, although this simple technique shows promise in identifying patients with PAD. Overall, there was insufficient evidence to support a single bedside non-invasive diagnostic modality for the detection of PAD across a spectrum of patients with diabetes. A poor description of the cohorts studied limits the applicability of the findings to particular patient groups. There is an urgent need for standardized reporting of diagnostic studies, adhering to the guidance of QUADAS and STARD principles [37], to best establish which test(s) singly or in combination can best diagnose PAD and therefore assist in the prediction and management of diabetic lower extremity complications and cardiovascular risk.

Conflicts of interest

None declared.

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Supporting information

Table 2 (evidence table) and the search strategy can be downloaded as supplements from the publisher's website.