A systematic review and meta-analysis of tests to predict wound healing in diabetic foot

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Background: **This systematic review summarized the evidence on noninvasive screening tests for the prediction of wound healing and the risk of amputation in diabetic foot ulcers.**
Methods: **We searched MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Scopus from database inception to October 2011. We pooled sensitivity, specificity, and diagnostic odds ratio (DOR) and compared test performance.**
Results: **Thirty-seven studies met the inclusion criteria. Eight tests were used to predict wound healing in this setting, including ankle-brachial index (ABI), ankle peak systolic velocity, transcutaneous oxygen measurement ($TcPo_2$), toe-brachial index, toe systolic blood pressure, microvascular oxygen saturation, skin perfusion pressure, and hyperspectral imaging. For the $TcPo_2$ test, the pooled DOR was 15.81 (95% confidence interval [CI], 3.36-74.45) for wound healing and 4.14 (95% CI, 2.98-5.76) for the risk of amputation. ABI was also predictive but to a lesser degree of the risk of amputations (DOR, 2.89; 95% CI, 1.65-5.05) but not of wound healing (DOR, 1.02; 95% CI, 0.40-2.64). It was not feasible to perform meta-analysis comparing the remaining tests. The overall quality of evidence was limited by the risk of bias and imprecision (wide CIs due to small sample size).**
Conclusions: **Several tests may predict wound healing in the setting of diabetic foot ulcer; however, most of the available evidence evaluates only $TcPo_2$ and ABI. The overall quality of the evidence is low, and further research is needed to provide higher quality comparative effectiveness evidence. (J Vasc Surg 2016;63:29S-36S.)**

In 2010, there were 25.8 million people in the United States with diabetes.[1] As a major cause of morbidity, 15% of these patients would develop diabetic foot ulcers (DFUs) resulting from diabetic neuropathy or peripheral arterial disease.[2] Inappropriately treated or untreated DFUs can lead to severe consequences, including lower extremity amputation and even death.

Predicting wound healing is an essential step in the management of DFUs. It is estimated that early detection and appropriate treatments may prevent up to 85% of amputations.[3] A range of noninvasive tests have been proposed in the literature to predict wound healing, including ankle-brachial index (ABI), toe-brachial index (TBI), transcutaneous oxygen measurement ($TcPo_2$), and toe systolic blood pressure (TBP).

Other tests have also been studied. Because in ischemic limbs blood moves at a much slower velocity in distal leg arteries (compared with nonischemic limbs), one other test is the ankle peak systolic velocity (APSV), which is estimated as the mean of the peak velocities measured across the distal tibial artery at the ankle level.[4] Hyperspectral imaging is a noninvasive diagnostic tool that quantifies tissue oxygenation and generates anatomically relevant maps of microcirculatory changes. The map is based on local molecular composition (as reflected by wavelength selection) of molecules such as oxyhemoglobin and deoxyhemoglobin.[5] Microvascular oxygen saturation (Sao_2) can be measured using a micro-lightguide spectrophotometer that sends light from a xenon lamp to the tissue, where it is scattered and then collected by surrounding fibers. Light signal is converted into an electrical signal, digitized, and analyzed in real time by comparing to pre-recorded spectra of fully deoxygenated and oxygenated hemoglobin spectra.[6] Skin perfusion pressure (SPP) can be measured by a laser Doppler scanner that is secured in a blood pressure cuff with a transparent window and records perfusion pressure during deflation.[7]

However, it is unclear which test has the best prognostic accuracy in detecting treatment outcomes.

Hereby, we conducted a systematic review and meta-analysis to summarize the evidence of available tests and to compare the performance of eight noninvasive tests in

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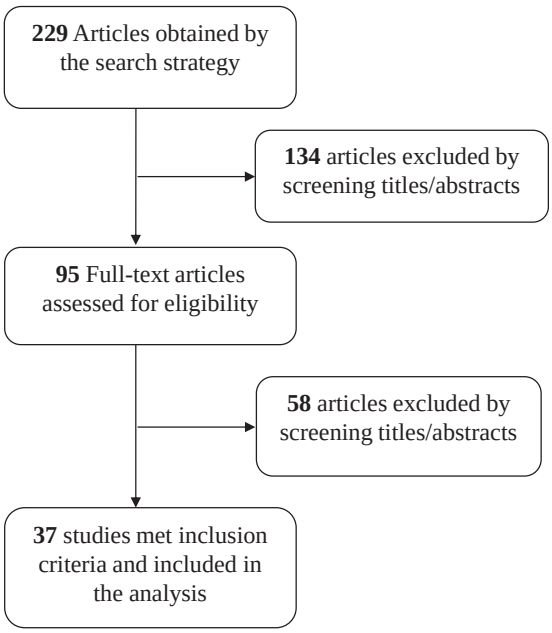

Fig 1. Study selection.

predicting wound healing of DFUs. To our knowledge, this is the first meta-analysis on this topic.

METHODS

The methodology and reporting of this systematic review are consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[8] The protocol of this systematic review was developed by the Society for Vascular Surgery Committee tasked to develop guidelines for the management of diabetic foot.

Study selection. To be eligible for this review, studies had to be clinical trials or observational studies that used one of these eight noninvasive tests: ABI, APSV, $TcPo_2$, TBI, TBP, microvascular Sao_2, SPP, and hyperspectral imaging. Studies had to report the incidence of subsequent healing of DFUs or the need for subsequent amputation. DFU patients, regardless of age, gender, ethnicity, and underlying symptoms, were included in analysis. Studies that reported only pretreatment test results were excluded, as were editorials, letters, errata, notes, and commentaries. Clinical reviews (systematic and nonsystematic reviews) and medical guidelines were used to identify relevant studies.

Literature search. We conducted a broad search of six electronic databases, including Ovid MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Scopus, from database inception to October 2011. The appropriate database search terms were developed for the concept of DFUs and for the concept of each noninvasive test. The search terms were broad without language or country restrictions. The detailed search strategy is available in the Appendix (online only).

Data abstraction. Two independent reviewers screened the study titles and abstracts using a predefined protocol. Full texts of the relevant studies were further assessed for inclusion by the same pair of reviewers. All discrepancies between the reviewers were resolved through consensus.

Two reviewers extracted study details independently, in duplicate, using a standardized pilot-tested form. The following data were abstracted: study design, patient characteristics (sex, age), sample size, diabetes type, baseline ulcer status, length of follow-up, tests, and outcomes. The outcomes of interest were the number of healed foot ulcers and the number of amputated limbs. The outcomes were extracted at the longest duration of complete follow-up. We extracted or calculated the number of healed vs nonhealed ulcers and amputated limbs vs nonamputated limbs and constructed contingency tables. Predefined thresholds were used (ABI, 0.8; $TcPo_2$, 30 mm Hg). When data reported were unclear, the authors of the included studies were contacted for clarification.

Risk of bias and methodologic quality assessment. Considering that the included studies were either nonrandomized or randomized for purposes other than the goal of this systematic review, we applied the Newcastle and Ottawa quality assessment tool and evaluated representativeness of study samples, exposure ascertainment, blinding of outcome assessors, and loss to follow-up.[9] The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methods.[10,11] Following this approach, randomized trials are considered to warrant high-quality evidence (ie, high certainty), and observational studies warrant low-quality evidence. Then the evidence grading can be increased (if a large effect is observed) or decreased if other factors are noted, such as studies being at increased risk of bias or imprecise (small with wide confidence intervals [CIs]).

Data synthesis. To evaluate the effectiveness of each test in predicting outcomes of interest, we calculated sensitivity and specificity for each test using bivariate binominal mixed models.[12,13] Developed by Reitsma et al and later refined by Chu and Cole, the bivariate binominal mixed model assumes independent exact binomial distributions of number of true positives and number of true negatives conditional on sensitivity and specificity for each study and constructs a bivariate normal model on the logit transforms of sensitivity and specificity between studies. This model accounts for within- and between-study variability and uses correlation between the studies to adjust an implicit threshold effect. The results, mean logit transforms of sensitivity and specificity, and related standard errors were back transformed and constructed 95% CI. We calculated the diagnostic odds ratio (DOR) based on the estimates of pooled sensitivity and specificity. DOR is a single global measure for diagnostic

Table I. Characteristics of the included studies

Study ID	*Study design*	*Pts*	*DM type*	*Age, years ± SD*	*Male, %*	*Duration of DM, years ± SD*	*Ulcer description (baseline)*	*Follow-up, months*
ABI								
Ballard,[18] 1995	Obs	55	Type 2: 40% Type 1: 60%	67 ± 13	62	—	Nonhealing ulcer: 91%	8
Castronuovo,[7] 1997	Obs	53	—	71 ± 10	62	—	—	—
Chen,[19] 2010	Obs	38	—	69 ± 9	42	13 ± 3	—	12
Edelman,[20] 1997	RCT	64	—	66 ± 6	1	15 ± 9	—	6
Faglia,[21] 1996	Obs	80	—	61 ± 9	70	—	Ulcer Wagner grade: II, 15%; III, 20%; IV, 65%	12
Faglia,[22] 1996	RCT	70	—	63 ± 10	69	18 ± 10	Ulcer Wagner grade: II, 13%; III, 25%; IV, 62%	2
Faglia,[23] 2002	Obs	221	—	70 ± 9	63	20 ± 6	Ulcer Wagner grade: I, 19%; II, 25%; III, 17%; IV, 38%; V, 1%	14
Hamalainen,[24] 1999	RCT	733	Type 2: 54% Type 1: 46%	47 ± 19	—	12 ± 9	—	84
Hanna,[25] 1997	Obs	29	—	62 ± 3	41	—	—	12
Huang,[26] 2005	RCT	28	Type 2: 71% Type 1: 29%	71 ± 6	64	12 ± 8	Texas wound classification: I C, 32%; I D, 32%; II C, 14%; II D, 14%; III C, 0%; III D, 7%	3
Johansen,[27] 2009	RCT	13	Type 2: 85% IDDM: 15%	64	77	18	—	6
Kalani,[28] 1999	Obs	50	—	61 ± 12	75	26 ± 14	—	12
Lee,[29] 1997	Obs	31	—	63 ± 10	50	—	—	—
Londahl,[30] 2011	RCT	75	Type 2: 71% Type 1: 29%	69 ± 10	—	—	Ulcer size (cm^2): 3.1 (1.2-6.4)	12
Nather,[31] 2008	Obs	202	Type 2: 95% Type 1: 5%	60	54	1-48	Gangrene: 32% Infection: 29% Ulcer: 28% Cellulitis: 6% Necrotizing fasciitis: 4% Charcot osteoarthropathy: 2%	—
Prochazka,[32] 2010	Obs	96	—	65 ± 9	81	—	—	4
Redlich,[33] 2011	Obs	28	Type 2	69 ± 8	82	20 ± 10	Critical limb ischemia and severe infrapopliteal peripheral vascular disease	12
Rigatelli,[34] 2011	Obs	220	—	79 ± 16	51	—	—	37
Winkley,[35] 2007	Obs	253	Type 2: 83% Type 1: 17%	62 ± 14	64	13.2	Duration of ulcer: 3.1 ± 3.6 months Ulcer size (cm^2): ≤1, 48.6%; >1, 51.4%	18
Xu,[36] 2011	Obs	37	Type 2: 73% Type 1: 35%	71 ± 9	65	18 ± 6	—	9
$TcPo_2$								
Ay,[37] 2004	Obs	50	—	58 ± 8	66	16 ± 3	—	1
Ballard,[18] 1995	Obs	55	Type 2: 40% Type 1: 60%	67 ± 13	62	—	Nonhealing ulcer: 91%	8
Caselli,[38] 2005	Obs	43	Type 2: 95% Type 1: 5%	73	58	20	Ulcer Wagner grade IV, 100%	11
Ezio,[39] 2010	Obs	261	—	73 ± 9	67	18 ± 12	Ulcer Wagner grade: 0, 6%; I, 30%; II, 10%; III, 7%; IV, 46%	—
Faglia,[21] 1996	Obs	80	—	61 ± 9	70	—	Ulcer Wagner grade: II, 15%; III, 20%; IV, 65%	12
Faglia,[22] 1996	RCT	70	—	63 ± 10	69	18 ± 10	Ulcer Wagner grade: II, 13%; III, 25%; IV, 62%	2
Faglia,[23] 2002	Obs	221	—	70 ± 9	63	20 ± 6	Ulcer Wagner grade: I, 19%; II, 25%; III, 17%; IV, 38%; V, 1%	14
Faglia,[40] 2005	Obs	993	—	70 ± 9	67	18 ± 11	Texas wound classification: 0 C, 12%; I C, 8%; I D,	26

(*Continued on next page*)

Table I. Continued.

Study ID	*Study design*	*Pts*	*DM type*	*Age, years ± SD*	*Male, %*	*Duration of DM, years ± SD*	*Ulcer description (baseline)*	*Follow-up, months*
							7%; II C, 6%; II D, 13%; III C, 3%; III D, 50%	
Faglia,[41] 2007	Obs	564	—	70 ± 10	65	17 ± 11	Ulcer Wagner grade: 0, 16%; I, 15%; II, 14%; III, 10%; IV, 46%	64
Ferraresi,[42] 2009	Obs	101	—	66 ± 9	84	15 ± 5	—	35
Hanna,[25] 1997	Obs	29	—	62 ± 3	41	—	—	12
Ichioka,[43] 2009	Obs	75	—	65	67	—	—	—
Jacqueminet,[44] 2005	Obs	32	Type 2: 84% Type 1: 16%	67 ± 10	85	22 ± 12	—	12
Kalani,[28] 1999	Obs	50	—	61 ± 12	75	26 ± 14	—	12
Khodabandehlou,[45] 2004	Obs	38	Type 2: 71% Type 1: 29%	68 ± 8	—	16 ± 11	—	12
Kim,[46] 2011	Obs	23	—	69 ± 7	74	20 ± 10	Ischemic diabetic ulcer	20
Londahl,[30] 2011	RCT	75	Type 2: 71% Type 1: 29%	69 ± 10	—	—	Ulcer size (cm^2): HBOT, 3.1 (1.2-6.4)	12
Nouvong,[5] 2009	Obs	66	Type 2: 57% Type 1: 43%	52 ± 9	88	13 ± 9	Ulcer size (cm^2): healed, 3.2 ± 3.9; nonhealed, 5.8 ± 6.2	6
Prochazka,[32] 2010	Obs	96	—	65 ± 9	81	—	—	4
Redlich,[33] 2011	Obs	28	Type 2	69 ± 8	82	20 ± 10	Critical limb ischemia and severe infrapopliteal peripheral vascular disease	12
Rigatelli,[34] 2011	Obs	220	—	79 ± 16	51	—	—	37
Uccioli,[47] 2010	Obs	510	Type 2: 93% Type 1: 7%	70 ± 1	64	20 ± 1		20
Wattel,[48] 1990	Obs	11	—	—	—	—	Chronic arterial insufficiency ulcers: 82%	12
Weng,[49] 2009	Obs	61	—	—	—	—	—	—
Zgonis,[50] 2005	Obs	35	Type 2: 97% Type 1: 3%	—	—	—	—	7
SPP								
Castronuovo,[7] 1997	Obs	53	—	71 ± 10	62	—	—	—
Prochazka,[32] 2010	Obs	96	—	65 ± 9	81	—	—	4
TBI								
Kalani,[28] 1999	Obs	50	—	61 ± 12	75	26 ± 14	—	12
Prochazka,[32] 2010	Obs	96	—	65 ± 9	81	—	—	4
TBP								
Kalani,[28] 1999	Obs	50	—	61 ± 12	75	26 ± 14	—	12
Prochazka,[32] 2010	Obs	96	—	65 ± 9	81	—	—	4
APSV								
Bishara,[4] 2009	Obs	62	—	63 ± 6	68	—	—	—
Microvascular Sao_2								
Rajbhandari,[6] 1999	Obs	14	Type 2: 86% Type 1: 14%	67 ± 10	93	14 ± 6	Duration of ulcers: 12 ± 10 weeks	9
Hyperspectral imaging								
Nouvong,[5] 2009	Obs	66	Type 2: 57% Type 1: 43%	52 ± 9	88	13 ± 9	Ulcer size (cm^2): 4.0	6

ABI, Ankle-brachial index; *APSV,* ankle peak systolic velocity; *DM,* diabetes mellitus; *HBOT,* hyperbaric oxygen therapy; *IDDM,* insulin-dependent diabetes mellitus; *Obs,* observational study; *Pts,* patients; *RCT,* randomized controlled trial; *Sao_2,* oxygen saturation; *SD,* standard deviation; *SPP,* skin perfusion pressure; *TBI,* toe-brachial index; *TBP,* toe blood pressure; *$TcPo_2$,* transcutaneous oxygen measurement; *Type 2,* non-insulin-dependent diabetes mellitus.

accuracy, used for general estimation of discriminative power of diagnostic procedures, and helps in comparing two or more diagnostic tests. DOR of a test is the ratio of the odds of positivity in subjects with disease relative to the odds in subjects without disease. We also pooled difference of test score across the included studies and constructed random-effects models using the DerSimonian and Laird method.[14] The effect size, standardized mean difference (SMD), was calculated using Hedges' adjusted g measure.[15] SMD is used when we compare tests that used different units. The results are standardized (ie, expressed in standard deviation units) to allow comparison between tests.

We assessed heterogeneity across individual studies using the I^2 statistic and Cochran Q test. Publication bias was assessed by the Begg adjusted rank correlation test.[16] All statistical analyses were conducted using Stata version 12 (StataCorp, College Station, Tex).

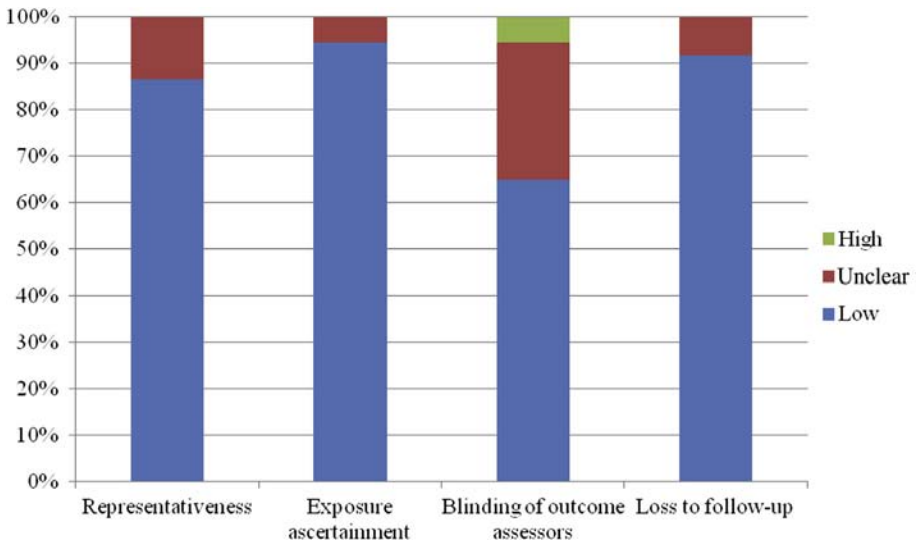

Fig 2. Risk of bias assessment of the included studies. *High risk*: studies do not meet quality criteria. *Unclear*: not enough information to judge study quality. *Low risk*: studies meet quality criteria.

Table II. Pooled sensitivity, specificity, and diagnostic odds ratio (*DOR*) of ankle-brachial index (*ABI*) and transcutaneous oxygen measurement ($TcPo_2$) tests

	ABI		$TcPo_2$	
Outcome	*Estimate*	*95% CI*	*Estimate*	*95% CI*
Complete ulcer healing				
Sensitivity	0.48	0.36-0.61	0.72	0.61-0.81
Specificity	0.52	0.42-0.63	0.86	0.68-0.95
DOR	1.02	0.40-2.65	15.81	3.36-74.45
Limb amputation				
Sensitivity	0.52	0.49-0.54	0.75	0.73-0.77
Specificity	0.73	0.63-0.81	0.58	0.52-0.64
DOR	2.89	1.65-5.05	4.14	2.98-5.76

CI, Confidence interval.

Sensitivity analysis. We constructed multivariate nested random-effects meta-regression models across all included studies to further compare prognostic accuracy of clinical tests.[17] To compare the regression coefficients between different tests in the model, we standardized the coefficients with one standard deviation. Thus, the standardized coefficients represent the standard deviation change of an outcome associated with one standard deviation increase of a test score. The higher value suggests the better discriminant test performance. The sensitivity analysis provided an alternative method to evaluate the findings.

RESULTS

Our searches identified 229 potential studies; 95 were retrieved for full-text screening, and 37 met our inclusion criteria and thus were included in this systematic review (Fig 1). Among them, 32 were observational studies and 5 were randomized controlled trials (RCTs). As the five RCTs were not initiated for evaluating diagnostic tests and were not prognostically balanced between test group and comparison group, we considered them observational studies in this review. The characteristics of the included studies are listed in Table I.

Risk of bias

Fig 2 reports the quality indicators of the included studies. The quality of the included studies was generally adequate. Blinding of outcome assessors was the quality indicator most absent; 13 of the 37 studies did not meet the criterion or did not provide sufficient information for evaluation. Because of the limited number of studies evaluating each test, it was inappropriate to conduct statistical tests to assess publication bias for almost all of the screening tests.[51] The only exception was the $TcPo_2$ test. We found no evidence of publication bias in the outcomes of interest using the Begg adjusted rank correlation test ($P > .05$). In summary, the risk of bias within the studies is medium.

Predictive ability of tests

Meta-analysis was possible on studies of ABI and $TcPo_2$. Because of the limited number of available studies on other tests, we were unable to pool prognostic accuracy of SPP, TBP, TBI, APSV, Sao_2, and hyperspectral imaging.

ABI. Twenty studies evaluated ABI values with a total of 2376 patients (range, 13-733). The patients were observed for an average of 15 months (range, 2-84). The pooled ABI values were significantly higher in the healed ulcer group than in the nonhealed group (SMD, 0.42; 95% CI, 0.05-0.79; $I^2 = 15.7\%$; heterogeneity, $P = .32$). The combined difference between the amputated limb group and the nonamputated group was also significant (SMD, −0.99; 95% CI, −1.44 to −0.54; $I^2 = 44.5\%$; heterogeneity, $P = .13$).

In terms of the ability of the test to predict healing, Table II summarizes the sensitivity, specificity, and DOR of ABI for predicting healed foot ulcers and limb amputations. In general, the prognostic accuracy of using the ABI for predicting healed foot ulcers was low, with the sensitivity of 0.48 (95% CI, 0.36-0.61) and the specificity of 0.52 (95% CI, 0.42-0.63). The overall DOR was 1.02 (95% CI, 0.40-2.64). In predicting limb amputations, the sensitivity was 0.52 (95% CI, 0.49-0.54) with the specificity of 0.73 (95% CI, 0.63-0.81). The DOR was 2.89 (1.65-5.05), suggesting a slightly better test performance for this outcome.

$TcPo_2$. Of the 37 included studies, 25 assessed $TcPo_2$; 3789 patients (range, 11-993) were included in these studies. The average follow-up length was 16 months (range, 1-64). There was a significant difference of $TcPo_2$ values between the healed group and the nonhealed group (SMD, 1.80; 95% CI, 1.06-2.54; $I^2 = 92.3\%$; heterogeneity, $P < .001$). The SMD was −2.26 (95% CI, −4.13 to −0.40) when the amputated-limb group was compared with the nonamputated group ($I^2 = 96.8\%$; heterogeneity, $P < .001$).

In terms of the ability of the test to predict healing (Table II), the results suggested high accuracy of the $TcPo_2$ test for predicting both ulcer healing and limb amputation. For ulcer healing, the combined sensitivity and specificity were 0.72 (95% CI, 0.61-0.81) and 0.86 (95% CI, 0.68-0.95), respectively. The DOR was 15.81 (95% CI, 3.36-74.45). For limb amputations, we found lower but still significantly better DOR with the combined estimate of 4.14 (95% CI, 2.98-5.76).

SPP. Two studies evaluated prognostic performance of the SPP test.[7,32] Castronuovo et al[7] studied a convenience sample of 53 critical limb ischemia patients, 75% of whom had diabetes. Using the threshold of 30 mm Hg, they estimated that the sensitivity for healed ulcers was 85% with the specificity of 73%. The overall area under the receiver operating characteristic curve was 0.79. Prochazka et al[32] compared SPP values between the healed group and the nonhealed group and found a significant difference (111.19 mm Hg vs 68.57 mm Hg, respectively).

TBP. We identified two studies reporting TBP measurements in patients with DFUs.[28,32] Kalani et al[28] estimated that the sensitivity and specificity for TBP were 15% and 97%, respectively, using a cutoff point of 30 mm Hg. The positive predictive value and the negative predictive value were 67% and 77%, respectively. Prochazka et al[32] also found a significant difference on TBP values between the healed group and the nonhealed group (25.63 mm Hg vs 12.43 mm Hg, respectively).

TBI. Two studies evaluated TBI.[28,32] Kalani et al[28] found no significant difference between the healed group and the nonhealed group in terms of TBI measurements. Conversely, Prochazka et al[32] reported that patients with healed wounds had higher TBI mean values at baseline than those who did not eventually heal.

Microvascular Sao_2. One study measured serial microvascular Sao_2 of 21 DFUs at the ulcer margin using a spectrophotometer. In healed ulcers, a significant reduction ($P < .05$) in Sao_2 occurred with healing (Sao_2 dropped from 58% at initial presentation to 45% just before healing). No such changes were noted on the control sites.[6] The study concluded that serial microvascular oxygen measurements may be used to identify at an early stage those ulcers that are unlikely to heal and may require surgical intervention.

APSV. Bishara et al[4] evaluated the performance of APSV. Using a sample of 100 limbs, the APSV value was significantly higher in the healed group than in the nonhealed group (53.0 cm/s vs 19.2 cm/s). The sensitivity, specificity, positive predictive value, and negative predictive value were 92.9%, 90.6%, 92.9%, and 90.6%, respectively. The authors concluded that APSV showed high accuracy in predicting the healing of DFUs.

Hyperspectral imaging. One study tested hyperspectral imaging of tissue oxyhemoglobin and deoxyhemoglobin in 73 DFUs.[5] Nouvong et al estimated that the sensitivity for healing was 80%, the specificity was 74%, and the positive predictive value was 90%.

Comparisons of tests

We were able to pool prognostic performance only for ABI and $TcPo_2$ because of the limited available evidence. As discussed before, $TcPo_2$ more reliably predicted wound healing and limb amputation than ABI. The sensitivity analysis showed $TcPo_2$ with larger standardized coefficients on healed ulcers ($b = 0.311$) and limb amputation ($b = 0.408$) than ABI ($b = 0.287$ and 0.334, respectively), also suggesting a better discriminatory performance of $TcPo_2$ than ABI.

DISCUSSION

Main findings. We conducted a systematic review and meta-analysis to evaluate several available tests to predict wound healing in the setting of DFU and compared the prognostic accuracy of the tests. Eight tests, reported by 37 studies, were included in this study: ABI, APSV, $TcPo_2$, TBI, TBP, microvascular Sao_2, SPP, and hyperspectral imaging.

We found that ABI had poor performance in predicting the healing of foot ulcers and modest performance in predicting limb amputations. $TcPo_2$ was a better test for predicting both outcomes.

With the limited number of the available studies, we were not able to quantitatively compare the prognostic accuracy of APSV, TBI, TBP, Sao_2, SPP, and hyperspectral imaging. Our results are consistent with findings in other studies. A case-controlled study by Reiber et al[52] showed transcutaneous oximetry to be the most associated with the risk of amputation in patients with DFU (compared with ankle-arm blood pressure index <0.45, absence of lower leg vibratory perception, and low levels of high-density lipoprotein subfraction 3).

Our results in the DFU setting are consistent with a systematic review that evaluated transcutaneous oximetry to predict complications of chronic wound healing. It concluded that a periwound level below a cutoff of

20 mm Hg or 30 mm Hg was an independent predictor of chronic wound healing complications (odds ratio, 3.21; 95% CI, 1.07-9.69; $I^2 = 77\%$).[8]

Strengths and limitations. The strengths of this systematic review include a comprehensive literature search, bias protection methods (reviewing and appraising evidence in duplicates), and both qualitative and quantitative summaries of the evidence. A sensitivity analysis was conducted to provide additional support for the findings.

There are several limitations to our findings. First, 32 of the 37 included studies were observational ones. The five RCTs were not designed for assessing test performance; thus, the test and comparison groups were not balanced. All 37 studies are subject to high risk of bias due to baseline imbalance and potential outcome confounding. Second, ecologic bias may affect our conclusions (ie, the performance of different tests was compared across different studies, not within the same study). Third, various and arbitrary choices of threshold may exaggerate test performance.

Thus, using the GRADE framework, the overall quality of this evidence (ie, confidence in the estimates) is low.[10,11]

Implications for practice and research. Although we identified some evidence suggesting that $TcPo_2$ has better prognostic accuracy than ABI in predicting wound healing of DFUs, each test has its own limitations in selected patients. ABI is not accurate when patients present with arterial wall calcification (medial calcinosis); TBI cannot be used to measure a toe when it is affected by ulcers or gangrene or has been amputated; SPP requires a cuff inflation to occlude capillary flow, which may be too painful for some patients and is not widely available. Such limitations along with cost, availability, and training factors need to be considered.

CONCLUSIONS

Several tests may predict wound healing in the DFU setting; however, most of the available evidence evaluates only $TcPo_2$ and ABI. The overall quality of the evidence is low, and further research is needed to provide higher quality comparative effectiveness evidence.

AUTHOR CONTRIBUTIONS

Conception and design: ZW, RH, BF, TE, AT, LP, JM, MM
Analysis and interpretation: ZW, MM
Data collection: ZW, RH, BF, TE, AT, LP, MM
Writing the article: ZW, LP, JM, MM
Critical revision of the article: ZW, RH, BF, TE, AT, LP, JM, MM
Final approval of the article: ZW, RH, BF, TE, AT, LP, JM, MM
Statistical analysis: ZW, MM
Obtained funding: MM
Overall responsibility: MM

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APPENDIX (online only).

Data sources and search strategies

A comprehensive search of several databases from each database's earliest inclusive dates to October 2011 (any language, any population) was conducted. The databases included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid Embase, Ovid Cochrane Database of Systematic Reviews, Ovid Cochrane Central Register of Controlled Trials, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principle investigator. Controlled vocabulary supplemented with keywords was used to search for the topic: tests for prediction of diabetic foot wound healing, limited to randomized and nonrandomized studies.

Actual search strategy

Ovid. Databases: Embase 1988 to 2011 Week 40, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to Present, EBM Reviews—Cochrane Central Register of Controlled Trials 4th Quarter 2011, EBM Reviews—Cochrane Database of Systematic Reviews 2005 to October 2011.

Search strategy:

#	*Searches*	*Results*
1	((diabetic or diabetes) adj3 (foot or feet)).mp.	14923
2	exp Diabetic Foot/	11805
3	1 or 2	14923
4	exp Ankle Brachial Index/	3560
5	((ankle or toe) adj brachial adj2 (index or indices or ratio)).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	7603
6	4 or 5	7603
7	exp transcutaneous oxygen monitoring/	1655
8	exp Blood Gas Monitoring, Transcutaneous/	3814
9	"transcutaneous partial pressure of oxygen".mp.	111
10	tcpo2.mp.	1665
11	hyperspectral imag*.mp.	635
12	skin perfusion pressure*.mp.	146
13	or/4-12	12855
14	3 and 13	417
15	exp controlled study/	3639965
16	exp evidence based medicine/	518676
17	evidence-based.mp.	175991
18	((control$ or randomized) adj2 (study or studies or trial or trials)).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	4669099
19	meta analysis/	87758
20	meta-analys$.mp.	139569
21	exp "systematic review"/	44105
22	systematic review$.mp.	98690
23	exp Guideline/ or exp Practice Guideline/	271941
24	guideline$.ti.	87215
25	or/15-24	5188997
26	exp case study/	1572995
27	exp Cohort Studies/	1330764
28	exp longitudinal study/	880349
29	exp retrospective study/	628418
30	exp prospective study/	532053
31	exp observational study/	23108
32	exp comparative study/	2198791
33	exp clinical trial/	1477518
34	exp evaluation/	1088304
35	exp twins/	39276
36	exp validation study/	28010
37	exp experimental study/ or exp field study/ or exp in vivo study/ or exp panel study/ or exp pilot study/ or exp prevention study/ or exp quasi experimental study/ or exp replication study/ or exp theoretical study/ or exp trend study/	6878167
38	((clinical or evaluation or twin or validation or experimental or field or "in vivo" or panel or pilot or prevention or replication or theoretical or trend or comparative or cohort or longitudinal or retrospective or prospective or population or concurrent or incidence or follow-up or observational) adj (study or studies or survey or surveys or analysis or analyses or trial or trials)).mp.	6826285
39	("case study" or "case series" or "clinical series" or "case studies").mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct]	154865

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Continued.

#	*Searches*	*Results*
40	or/26-39	12888282
41	14 and (25 or 40)	307
42	14	417
43	limit 42 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or twin study) [Limit not valid in Embase,CDSR; records were retained]	106
44	41 or 43	311
45	limit 44 to (book or book series or editorial or erratum or letter or note or addresses or autobiography or bibliography or biography or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	7
46	44 not 45	304
47	from 14 keep 404-417	14
48	46 or 47	305
49	remove duplicates from 48	221

Scopus.

1 TITLE-ABS-KEY((diabetes w/3 foot) or (diabetic w/3 foot) or (diabetes w/3 feet) or (diabetic w/3 feet))
2 TITLE-ABS-KEY((ankle w/1 brachial w/2 index) or (ankle w/1 brachial w/2 indicies) or (ankle w/1 brachial w/2 ratio) or (toe w/1 brachial w/2 index) or (toe w/1 brachial w/2 indicies) or (toe w/1 brachial w/2 ratio) or "transcutaneous partial pressure of oxygen" or ("transcutaneous oxygen" w/3 monitor*) or tcpo2 or "hyperspectral imag*" or "skin perfusion pressure*")
3 TITLE-ABS-KEY((evidence W/1 based) OR (meta W/1 analys*) OR (systematic* W/2 review*) OR guideline OR (control* W/2 stud*) OR (control* W/2 trial*) OR (randomized W/2 stud*) OR (randomized W/2 trial*))
4 TITLE-ABS-KEY("comparative study" OR "comparative survey" OR "comparative analysis" OR "cohort study" OR "cohort survey" OR "cohort analysis" OR "longitudinal study" OR "longitudinal survey" OR "longitudinal analysis" OR "retrospective study" OR "retrospective survey" or "retrospective analysis" OR "prospective study" OR "prospective survey" OR "prospective analysis" OR "population study" OR "population survey" OR "population analysis" OR "concurrent study" OR "concurrent survey" OR "concurrent analysis" or "incidence study" OR "incidence survey" OR "incidence analysis" OR "follow-up study" OR "follow-up survey" OR "follow-up analysis" or "observational study" OR "observational survey" OR "observational analysis" OR "case study" OR "case series" OR "clinical series" OR "case studies" or "clinical study" OR "clinical trial" or "evaluation study" OR "evaluation survey" OR "evaluation analysis" or "twin study" OR "twin survey" OR "twin analysis" or "validation study" OR "validation survey" OR "validation analysis" or "experimental study" OR "experimental analysis" or "field study" OR "field survey" OR "field analysis" or "in vivo study" OR "in vivo analysis" or "panel study" OR "panel survey" OR "panel analysis" or "pilot study" OR "pilot survey" OR "pilot analysis" or "prevention study" OR "prevention survey" OR "prevention analysis" or "replication study" OR "replication analysis" or "theoretical study" OR "theoretical analysis" or "trend study" OR "trend survey" OR "trend analysis")
5 1 and 2 and (3 or 4)
6 PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
7 5 and not 6
8 DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
9 7 and not 8