The predictive capacity of toe blood pressure and the toe brachial index for foot wound healing and amputation: A systematic review and meta-analysis

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ABSTRACT

Foot wounds are a growing international concern, as the incidence of risk factors such as diabetes, obesity, vascular disease and advancing age rises. This systematic review and meta-analysis was performed to determine the prognostic capabilities of toe blood pressure and the toe brachial index for predicting chronic foot wound healing or progression to amputation. MEDLINE, CINAHL, EMBASE, PubMed Central and the reference lists of retrieved studies were systematically searched in June 2014. Two authors independently reviewed selected studies reporting original research. Methodological quality was assessed using STROBE and CASP appraisal tools. Ten studies were reviewed; six investigated wound healing and four investigated amputation as the outcome. Study quality was inconsistent; most failed to report aspects of their methodology and used different equipment or techniques. Meta-analysis indicated a cut-off toe blood pressure of 30 mmHg was associated with a relative risk of 3.25 (95% CI: 1.96, 5.41) for non-healing, however, significant heterogeneity was found. Additionally, serial assessments or grading of toe blood pressure values may improve accuracy and utility. Toe blood pressure and related indices may be useful in predicting the outcome of chronic foot wounds; however, further high-quality research is required before clinical utility is confirmed.

Keywords: Toe brachial index, toe blood pressure, peripheral arterial disease, wound healing, ischaemic ulcers.

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INTRODUCTION

Foot wounds represent a significant and growing international concern. In Australia, foot wounds are estimated to affect 2.1% of people with diabetes and are the main precipitating factor for the requirement for non-traumatic amputation, resulting in 4.1 amputation hospitalisations per 1000 people with diabetes[1,2]. The prevalence of risk factors for foot wounds within the community including diabetes, obesity, vascular disease and advancing age is rising and suggests the incidence of wounds, particularly of a chronic nature where healing is delayed and there is increased risk of amputation, will continue to increase[3]. This is expected to result in escalating personal and social burden and substantial increases in financial cost to health care systems in coming years[4,5].

Non-invasive lower limb vascular assessment is an essential aspect of determining those at risk of foot wounds and wound healing capacity. Toe systolic blood pressure (TSBP) and the toe brachial index (TBI), calculated as the TSBP divided by the brachial pressure, have been suggested as non-invasive methods of assessing risk of wound development and wound healing capacity in the foot[6]. These techniques provide quantification of the skin perfusion in the foot and are sensitive to the presence of macro- and micro-vascular disease affecting the lower limb either as co-morbidities or occurring in isolation. Measures of distal skin blood flow are proposed to be more accurate indicators of the likelihood of healing or ulceration than

Table 1: Search terms and strategy

1.	toe blood pressure
2.	toe pressure
3.	hallux blood pressure
4.	toe brachial index
5.	1 OR 2 OR 3 OR 4
6.	predict*
7.	prognos*
8.	6 OR 7
9.	amputation*
10.	ulcer*
11.	wound*
12.	gangrene
13.	9 OR 10 OR 11 or 12
14.	5 AND 8 AND 13
15.	5 AND 13
16.	5 AND 8

other non-invasive vascular assessments that focus on large artery assessment in the lower leg such as palpation of pulses or an ankle brachial index (ABI)[7]. Presently there is significant evidence that TSBP and the TBI can be reliability and validly used as indicators of overall reductions in peripheral blood flow of any cause[8-12]. Additionally, there is evidence to suggest these measures may be associated with healing potential and, consequently, risk of amputation[7,13].

Although TSBP and the TBI have potential utility as a means of identifying those at risk of foot wounds and assessing healing capacity, there is little consensus in the literature on relevant cut-off values. TSBP values between 30 and 70 mmHg have been associated with non-healing wounds; however, these values are not strongly supported by the literature[14]. This ambiguity may prevent clinical utilisation of digital pressure measurements for detecting reduced blood flow to the foot and determining tissue viability, including the likelihood of healing or risk of amputation. A review of the research investigating the predictive value of, and any relationships between, TSBP or TBI and outcomes including amputation and healing is therefore warranted.

The purpose of this systematic review and meta-analysis is to evaluate cohort studies investigating the prognostic capacity of TSBP and the TBI for foot wound healing or need for amputation, in people with poor peripheral blood flow or a foot wound referred to a vascular or high-risk foot clinic. This will serve to inform clinical practice and guide the direction of future research.

METHODS

Search strategy

A search of the databases MEDLINE (1946 – Nov 2013), CINAHL (1983 – Nov 2013), EMBASE (1947 – Nov 2013), and PubMed Central (1950 – Nov 2013) was undertaken in June 2014. An example of the search terms and strategy used in each database is presented in Table 1. Reference lists of all retrieved papers were manually searched for additional studies.

Inclusion and exclusion criteria

Original research that investigated any associations between TSBP or the TBI, and wound healing or risk of amputation was included for review. Studies reporting relationships between TSBP or the TBI and healing following surgical interventions (including amputation) or other treatment therapies, or those comparing measurement techniques or devices were excluded. There were no language or publication restrictions.

Study selection and data extraction

One reviewer conducted the electronic searches (JS). The titles and abstracts were then assessed by two reviewers independently for inclusion (JS and VC). A standardised data extraction form was used to collect participant characteristics, measurement equipment and technique, outcome data and overall conclusions from each study. Outcome measures used in this review were healing and amputation. Information was extracted independently by two researchers (JS and VC) and in cases where studies provided insufficient detail attempts were made to contact authors for clarification.

Meta-analysis

Relative risks (RR) for each study were calculated on the basis of the risk of non-healing at TSBP of less than 30 mmHg divided by the risk of non-healing when TSBP was greater than 30 mmHg. This value is the most consistently used value in the literature[12,14]. In some cases, these were already presented in the studies but, for the rest, proportions or risk ratios were computed from the literature from the number of participants who had no healing compared to those who did. A random effects meta-analysis was performed on the log RR of each study and I^2 statistic was used to estimate heterogeneity. A Funnel plot was used to assess publication bias and Egger's and Begg's corresponding tests were employed to detect asymmetry.

Quality assessment

Each study was assessed for quality using a modified Critical Appraisal Skills Program (CASP) for Cohort Studies checklist and for reporting adequacy using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement[15,16]. Where reviewers disagreed, specific criteria were discussed with an independent researcher (Angela Searle — AS) until consensus was reached. If consensus could not be reached on an item on the checklist then this was reported as unable to determine (UTD).

RESULTS

Forty-two studies were identified from database searches and a further five from hand searching reference lists. Of the total 47 abstracts, 19 studies were retrieved in full text, with nine studies subsequently rejected based on exclusion criteria[17-26]. Of the nine excluded studies, three examined the relationship between pre-amputation toe blood pressure and amputation healing[22-24], two assessed the sensitivity of TSBP measurement for diagnosing PAD or critical limb ischaemia[17,18], one evaluated limb salvage rates in people undergoing amputations[20], one investigated associations between toe blood pressure and the presence of foot ulcerations but not in relation to healing or amputation as outcomes[19], one included participants with a specific vascular condition[26] and one reported the results of an intervention[25]. Ten studies fulfilled the criteria and were included for review[6,7,13,27-33]. Six included TSBP and/or TBI in relation to the healing of chronic wounds[6,7,27,28,30,31] and four studies assessed TSBP and risk of lower limb amputation[13,29,32,33]. The process of study selection is detailed in Figure 1.

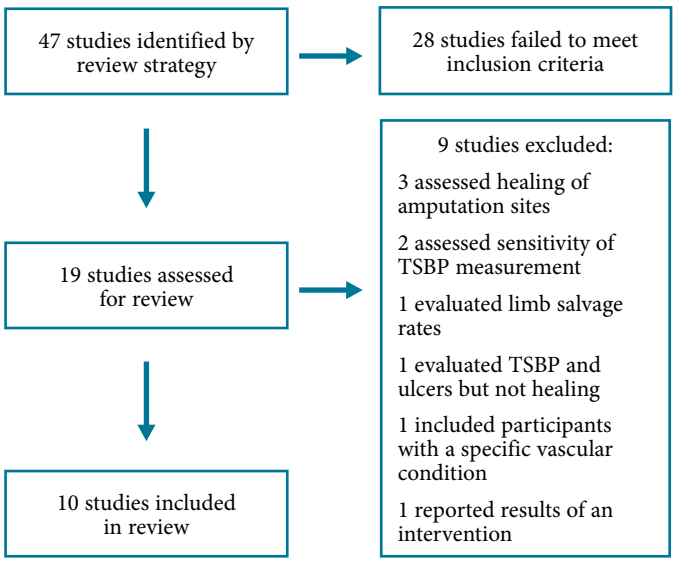

Figure 1: Overview of the review process

Characteristics and overview of included studies

Six studies[6,7,27,28,30,31], including 667 participants with an age range of 28[30] to 90[31] years, investigated the relationship between TSBP and/or TBI, and the healing of lower limb wounds (Table 2). Four studies[13,29,32,33], including 431 participants aged between 40[32] and 101[13] years, assessed TSBP and/or TBI, and risk of lower limb amputation (Table 3). One study was retrospective[32] while all the others were prospective in design[6,7,13,27-31]. The proportion of participants with diabetes ranged from 26%[29] to 100%[7,27,28,30,31] of study populations. Participants were recruited from vascular or high-risk foot clinics in all 10 studies for assessment and management of critically ischaemic limbs and/or treatment of foot wounds. Wounds were present for an average of one month[6] to 4.3 months[29] (range 0.5 to 13 months) at the time of enrolment and duration of follow-up ranged from three months[32] to eight years[33]. When reported, wound management strategies involved appropriate wound dressings[6,7,27,28] and, if necessary, plantar pressure reduction (footwear modification or insoles)[6,7,27,28], antibiotic treatment[6,7,27,28], improving metabolic control[7,27,28], and surgical debridement[6,27,28]. Healing was defined in one study as intact skin for three months[30] and in two others as intact skin for at least six months or at time of death[27,28]. Major amputation was defined as below knee or above knee[13,32] and minor amputation as digital amputation[13]. TSBP was measured using strain-gauge[6,27-29,31,32], pneumatic occluding cuff with photoplethysmography (PPG)[13] and occluding cuff with laser Doppler fluxmetry[7]. When included, brachial pressures were measured using mercury sphygmomanometer with occluding cuff and Doppler[13,27], and Riva-Rocchi technique with mercury sphygmomanometer[29]. Results were presented as mean and median TSBP and TBI values associated with healing or amputation, ranges of values associated with rates of healing or amputation, and positive predictive value (PPV) and negative predictive value (NPV) of blood pressure values for likelihood of amputation.

Quality assessment

Methodological appraisal using a modified CASP checklist is provided in Table S2 and highlighted failure to identify important confounding factors and account for these in design and/or analysis in four studies[7,29,31,32]. All studies addressed a clearly focused issue,

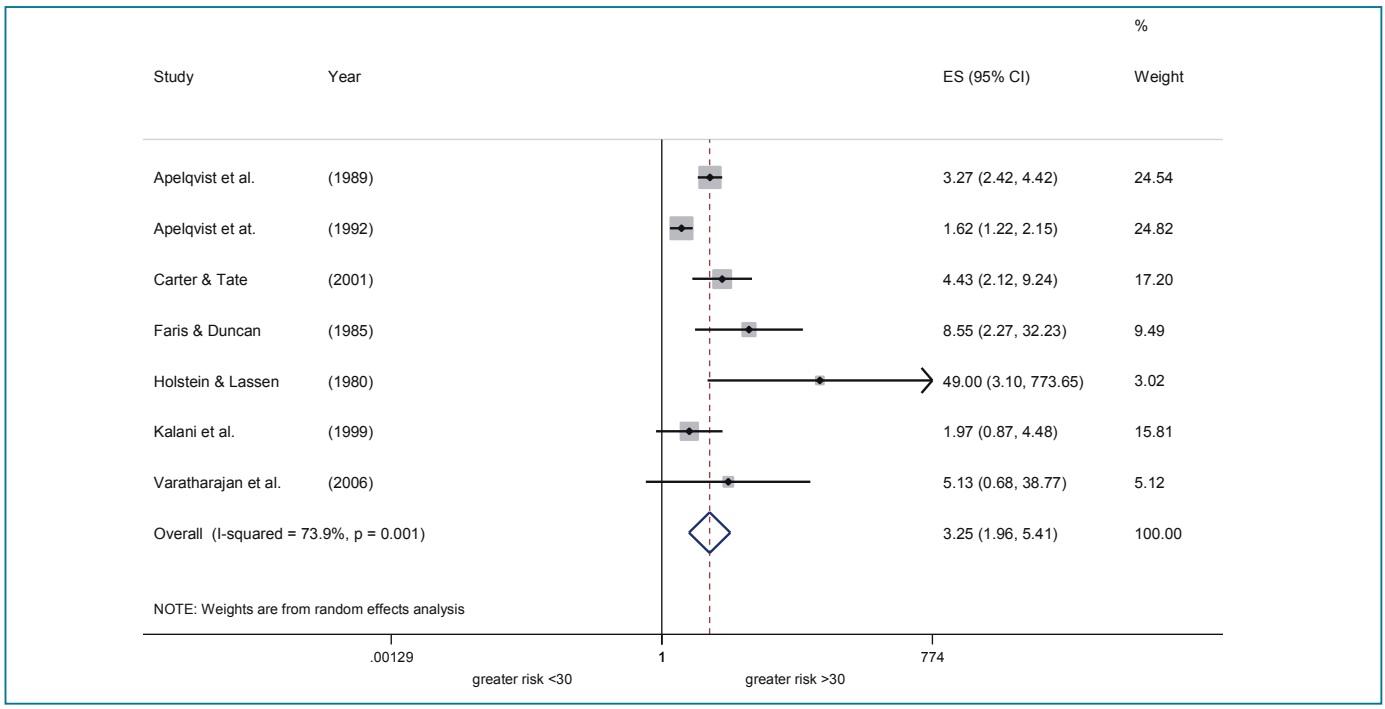

Figure 2: Forrest plot of the risk ratio (RR). The summary RR = 3.25 (95% CI: 1.96, 5.41).

utilised acceptable recruitment methods and followed participants for adequate time periods. Results of the STROBE checklist are presented in Table S1 and indicated reporting was incomplete in all studies. Key findings were failures to report limitations in study design[6,7,27-31,33], participant eligibility (including sources and methods of participant selection)[7,13,27,29,31], and methods used to determine study size[13,17,18,29-33,35] and address potential bias[6,13,28-33]. Outcome measures were generally well defined, with most studies listing criteria used to evaluate healing. One study published protocols and results separately and did report numerical results, reporting only that they did not find a significant relationship between TSBP and healing[30].

Toe blood pressure and TBI in relation to wound healing

The results of the six studies investigating the relationship between TSBP or the TBI, and wound healing were variable; however, a generally strong relationship between lower values and poorer outcomes was reported in all but one study. Using a single initial measurement, Holstein and Lassen reported 96% of wounds healed when TSBP was greater than 30 mmHg and similarly Kalani *et al.*[7] and Faris and Duncan[31] reported mean pressures required for complete healing were 75 ± 31 mmHg[7] and 78 ± 37 mmHg[31], respectively. Greater variation in pressures associated with healing were reported by Apelqvist *et al.*[27], who found pressures of more than 106 mmHg were required to achieve wound healing in 95% of cases and pressures in the range of 31 to 45 mmHg resulted in just 51% of cases healing. Apelqvist *et al.*[27] also reported 23% of participants achieved healing when TSBP was less than 15 mmHg and Londahl *et al.*[30] reported no significant relationship between healing capacity and TSBP; however, vascular procedures were performed in both studies. Higher TBI values were also associated with wound healing. In two studies wound healing occurred at a mean TBI of 0.55 ± 0.3[27] and 0.6 ± 0.2[7], while failure to heal was associated with a TBI of less than 0.2 ± 0.18[28] and 0.4 ± 0.2[7].

Toe blood pressure and TBI in relation to risk of amputation

The association between TSBP or the TBI and the likelihood of lower limb amputation generally indicated a higher risk when pressures were lower. A TSBP of ≤30 mmHg resulted in an odds ratio of 4.2 (95% CI 2.09-8.46) for risk of amputation and TSBP of ≤20 mmHg gave an odds ratio of 3.24 (95% CI 1.94-5.41)[33]. A TBI cut-off value of ≤0.10 was associated with a RR of 2.77 (95% CI 1.73–4.41) for amputation[33]. A TSBP of ≤30 mmHg was demonstrated to have a PPV of 0.28 and NPV of 0.87 for requirement for amputation[32]. A TBI of <0.07 was associated with an 82% risk of amputation, a TBI of 0.08–0.13 with 38% and a TBI of 0.14–0.25 with a 27% risk of amputation[29]. Varatharajan *et al.*[13] compared single to serial assessments in relation to amputation outcomes. When measurements from a single assessment were used, major amputation was associated with a TSBP of 10.4 mmHg, yet, minor amputation was associated with a higher TSBP (20.3 mmHg) than no amputation (13.1 mmHg)[13]. However, when two or more serial assessments were made, the relationship between higher values and better outcomes resumed. This was the case for TBI also.

Relationship between TSBP, wound healing and risk of amputation

Seven studies were included in the meta-analysis to establish a critical or cut-off TSBP value below which healing of foot wounds is unlikely[6,7,13,27,28,31,33]. Five studies assessed the predictive value of TSBP for wound healing in diabetic patients, while the remaining two studies examined the predictive value of TSBP for risk of amputation. Both types of studies were combined into one meta-analysis where the emphasis was reversed from healing to non-healing which was

Table 2: Characteristics of studies investigating outcome of wound healing in relation to TSBP and the TBI values

Study	Sample size	Participant characteristics	Recruitment criteria	Measurement techniques	Relationship between TSBP and healing	Relationship between TBI and healing
Apelqvist *et al.*[27]	281	Age:	Active foot wound	Toe: Strain-gauge technique	Healing rate per TSBP range: 0-15 = 23%	Not reported
		60±17years healed		Brachial: Mercury sphygmomanometer and Doppler	16-30 = 38%	
		69±13years non-healed			31-45 = 51%	
		74±13years deceased			46-60 = 77%	
		Males: 49%			61-75 = 77%	
		Diabetes: 100%			76-90 = 81%	
					91-105 = 77%	
					106-120 = 95%	
					121+ = 98%	
Apelqvist *et al.*[28]	208	Males: 50%	Active foot wound	Toe: Strain-gauge technique	Healing rate per TSBP range:	Not reported
		Diabetes: 100%	TSBP ≤45mmHg		≤45 = 38%	
					31-45 = 56%	
					38% healed primarily	
					40% heal after amputation	
					21% deceased before healing	
					Healing more common if TSBP >30mmHg	
Faris & Duncan[31]	29	Age: Median 72 years (38-86 years)	Active foot wound or gangrene	Toe: Mercury in silastic strain-gauge	Mean TSBP associated with healing: 78+-37mmHg	Not reported
		Males: 51%			Mean TSBP associated with non-healing: 21+-19mmHg	
		Diabetes: 100%			Healing in 1 participant with TSBP <40mmHg	
Holstein & Lassen[6]	62	Age: Mean 69.2 DM; 68 non-DM	Active foot wound	Toe: Strain-gauge technique	Healing rate per TSBP range:	Not reported
	(66 limbs*)	(41-90 years)			*1st Appointment:*	
		Males: 62%	Arterial insufficiency		<20 = 29%	
		Diabetes: 51%			20-29 = 50%	
					>30 = 91%	
					Final Appointment:	
					<20 = 9%	

Table 2: Continued

Study	Sample size	Participant characteristics	Recruitment criteria	Measurement techniques	Relationship between TSBP and healing	Relationship between TBI and healing
					20-39 = 64%	
					>30 = 100%	
					<20mmHg healing rare	
					>30mmHg ischaemia did not a prohibit healing	
Kalani *et al.*[7]	50	Age: Mean 61±12 years	Active foot wound	Toe: Laser Doppler fluxmetry and occluding cuff	Using TSBP cut-off values to predict healing:	Impaired healing:
		Males: 74%			*<30 and ≥30mmHg*	Mean TBI 0.4+-0.2
		Diabetes: 100%			Sensitivity = 15%	Improved healing:
					Specificity = 97%	Mean TBI: 0.5+-0.2
					PPV = 67%	Healed with skin intact:
					NPV = 77%	Mean TBI: 0.6+-0.2
					<40 and ≥40mmHg	
					Sensitivity = 46%	
					Specificity = 84%	
					PPV = 50%	
					Impaired healing:	
					Mean TSBP 57mmHg+-31	
					Improved healing:	
					Mean TSBP: 71+-29mmHg	
					Healed:	
					Mean TSBP: 75+-31mmHg	
Londahl *et al.*[30,37]	37	Age: Mean 68 years (28-86 years)	Active foot wound	Not reported	Average TSBP associated with healing:	Not reported
		Males: 84%			55mmHg (range 15 – 160)	
		Diabetes: 100%				

TSBP: toe systolic blood pressure; TBI: toe brachial index; PPV: positive predictive value; NPV: negative predictive value;
*Study analysed limbs separately.

assumed to be synonymous with foot amputation. The predictive value of the cut-off value of 30 mmHg, a suggested criterion for severe ischaemia (severe ischaemia group), was examined relative to values >30 mmHg (control group)[14]. Although all studies had a higher risk of non-healing/amputation for the severe ischaemia group (RR >1), for two studies the results were not significant[7,13].

The meta-analysis showed a statistically significantly higher risk of amputation or non-healing for those with severe ischaemia (TSBP <30 mmHg) relative to the control (TSBP >30 mmHg). In particular, on the original scale the RR was 3.25 (CI 95%: 1.99, 5.41), which suggests that the true risk of amputation or non-healing is anywhere from 1.97 to 5.41 times higher for the severe ischaemia group compared to the control.

Although all studies were in favour of increased risk of non-healing or amputation with a pressure of <30 mmHg, there was a significant amount of heterogeneity between the studies. In particular, the variance arose from true differences in RR between the studies. Some asymmetry was present in the funnel plot; however, Egger's (z=0.00, p=0.881) and

Table 3: Characteristics of studies investigating the likelihood of amputation in relation to TSBP and TBI values

Study	Sample size	Sample characteristics	Recruitment criteria	Measurement technique/s	Relationship between TSBP and risk of amputation	Relationship between TBI and risk of amputation
Carter *et al.*[33]	238	Age:	Active foot wound or gangrene	Toe: PPG	Relative risk & 95% CI of major amputation associated with TSBP:	Not reported
	(266 limbs*)	Males: mean 72±10 years				
		Females: mean 74±9 years	Arterial disease		*Arterial disease*	
		Males: 58%			-TSBP≤ 30mmHg = 4.20 (2.09-8.46)	
		Diabetes: 56%			≤ 20mmHg = 3.24 (1.94-5.41)	
					Severe disease (64/181)	
					≤20mmHg = 1.96 (1.04-3.69)	
Matzke *et al.*[32]	110	Age: mean 75 years	Critical ischaemia	Toe:	Using TSBP cut-off values to predict amputation: *<10mmHg:*	Not reported
	(145 limbs*)	(Range 40-96 years)	TSBP ≤30mmHg	Strain-gauge plethysmography	Sensitivity = 0.14	
		Males: 46%			Specificity = 0.93	
		Diabetes: 51%			PPV = 0.40	
					NPV = 0.76	
					Accuracy = 0.72	
					<20mmHg:	
					Sensitivity = 0.50	
					Specificity = 0.77	
					PPV = 0.42	
					NPV = 0.82	
					Accuracy =0.70	
					≤30mmHg:	
					Sensitivity = 0.93	
					Specificity = 0.16	
					PPV = 0.28	
					NPV = 0.87	
					Accuracy = 0.36	
Paaske *et al.*[29]	43	Age: Mean 68 years	Severe ischaemia	**Toe:** Strain-gauge	Not reported	Amputation rate per TBI range:
		(Range 52-82 years)		Brachial: Strain-gauge mercury sphygmomanometer		TBI 0-0.07
		Males: 60%				Amputation rate 82%
		Diabetes: 26%				TBI 0.08-0.13

Table 3: Continued

Study	Sample size	Sample characteristics	Recruitment criteria	Measurement technique/s	Relationship between TSBP and risk of amputation	Relationship between TBI and risk of amputation
						Amputation rate 38%
						TBI 0.14-0.25
						Amputation rate 27%
Varatharajan *et al.*[13]	40	Age: Mean 75.6 years	TSBP <40mmHg	Toe: PPG and pneumatic occluding cuff	Average TSBP values for each outcome:	Average TBI for each outcome:
	(56 limbs*)	(Range 55-101 years)		Brachial:	Single initial value:	Single initial value:
		Males: 63%		Cuff and Doppler	Major Amp = 10.4	Major amp = 0.06
		Diabetes: 53%			No major amp* = 13.7	No Major Amp* = 0.09
					Minor amp = 20.3	Minor Amp = 0.14
					No Amputation* = 13.1	No amputation* = 0.09
					Serial follow-up:	Serial follow-up:
					Major Amp = 13	Major Amp = 0.08
					No major Amp* = 23.6	No major amp* = 0.15
					Minor Amp = 20.3	Minor amp = 0.14
					No Amp*** = 23.9	No amputation*** = 0.18

TSBP: Toe systolic blood pressure; TBI: toe brachial index; PPV: positive predictive value; NPV: negative predictive value;
PPG: Photoplethysmography; * Studies analysed limbs separately; **No major amputation consisted of minor or no amputations;
*** No amputation consisted of arterial reconstructive surgery, angioplasty or no intervention.

Begg's (t=0.52, p=0.625) corresponding tests were not significant, indicating no apparent presence of publication bias (Figure 3).

DISCUSSION

This systematic review and meta-analysis assessed the relationship between the TBI and TSBP, with wound healing and risk of amputation in the foot. The review included 10 cohort studies and 1098 participants and supports a relationship between TSBP and the TBI, with wound healing and risk of amputation, suggesting that lower values are associated with a greater risk of adverse outcomes. By using a meta-analysis of the combined data of studies investigating the relationship between TSBP and healing or amputation we were further able to demonstrate that a TSBP of less than 30 mmHg is associated with a relative risk of 3.25 for non-healing or amputation. This finding supports current recommendations of 30 mmHg as a cut-off for severe ischaemia and non-healing, and suggests this may be an important indicator of potential inability to heal.

TSBP and the TBI offer several advantages over large artery screening including the ability to detect altered skin blood flow resulting from microvascular disease or autonomic neuropathy, a condition which may produce functional ischaemia and impair wound healing yet remain undetected using other vascular screening methods[34]. Our systematic review supports the role of TSBP and the TBI in identifying people at risk of non-healing wounds due to reduced tissue perfusion. The six studies investigating the relationship between TSBP or the TBI and wound healing generally demonstrated lower pressures were associated with poor or reduced healing; however, there was some variability in this relationship. This may be in part due to the specific methodologies of blood pressure measurement employed by the included studies. Accurate measurement of very low pressures, like those associated with non-healing, is compromised by some methods of blood pressure measurement[35]. Evidence of highly variable measurements

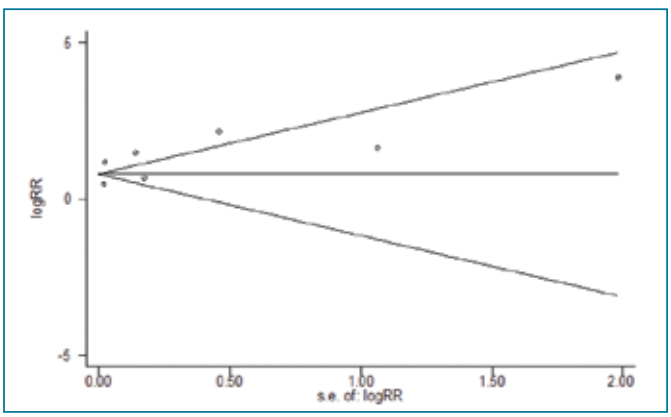

Figure 3: Begg's funnel plot with pseudo 95% confidence limits

particularly in relation to the TBI associated with healing suggests both measurement accuracy and reliability may limit the clinical utility of this measurement for predicting healing and amputation outcomes. The wide range of TSBP and TBI values found to be associated with healing and amputation is consistent with the varied methods of blood pressure measurement and study protocols employed.

Lower TSBP and TBI values were also generally associated with an increased risk of amputation and with increased amputation severity; however, the magnitude of this association varied among studies. This may result from the difference in foot health status of participants in the studies as only Carter *et al.*[33] included participants with an active wound or gangrene, while the remaining three studies recruited participants with arterial disease only. The use of multiple or serial measurements resulted in a more consistent association between decreasing TSBP and TBI values and increasing amputation level. Similarly, the accuracy of the ABI has also been shown to be increased when the average of multiple values is used and suggests the use of multiple or serial TSBP and the TBI measurements may increase accuracy and clinical utility[36].

This study is the first to bring together the available literature on the predictive capability of TSBP and the TBI and demonstrates low values are consistently associated with non-healing and increased risk of amputation. The cut-off value of 30 mmHg may be a useful clinical indicator of the outcome of lower limb wounds, and may be even more accurate with the use of serial assessment. As not all participants with TSBP values below the cut-off failed to heal or required amputation, it is also possible a more detailed grading system of TSBP or TBI values, similar to that available for the ABI, may prove more useful. A classification system would allow stratification of risk of amputation and help guide treatment and represents a potential area for future research.

LIMITATIONS

Although this review was designed to be comprehensive with a robust search strategy, it is possible that not all studies were identified. The strength of evidence in this review is limited by the lack of high-quality research and substantial heterogeneity, and as such only generalised indications of the association between TSBP or the TBI, and healing potential and risk of amputation can be interpreted from existing studies. Additionally we included a study in the meta-analysis that investigated amputation as the outcome assuming amputation was synonymous with non-healing wounds. By doing so, the risk of non-healing at TSBP less than 30 mmHg may have been overestimated. Lastly, the substantial heterogeneity among studies included in the meta-analysis may limit the ability of the Begg's funnel plot to detect publication bias.

CONCLUSION

The limited evidence available supports an association between TSBP and the TBI with wound healing and risk of amputation. A cut-off value of 30 mmHg was found to be associated with a 3.25 times greater risk of non-healing or amputation. Further benefit would likely be gained with the use of multiple assessments and the development of a grading system for TSBP and TBI values.

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COMPETING INTERESTS

None declared.

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SUPPORTING INFORMATION

S1: Results of STROBE checklist

	Apelqvist *et al.*	Apelqvist *et al.*	Carter *et al.*	Farris *et al.*	Holstein *et al.*	Kalani *et al.*	Londahl *et al.*	Matzke *et al.*	Paaske *et al.*	Varatharajan *et al.*
Title and abstract 1 (a) Indicate the study's design with a commonly used term in the title or abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Background/rationale 2 Explain the scientific background and rationale for the investigation being reported	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Objectives 3 State specific objectives, including any prespecified hypotheses	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Study design 4 Present key elements of study design early in the paper	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	No
Setting 5 Describe the setting, locations and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Participants 6 (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	No	Yes	Yes	No	Yes	No	Yes	Yes	No	No
Variables 7 Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes
Data sources/measurement 8* For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bias 9 Describe any efforts to address potential sources of bias	Yes	No	No	No	No	Yes	No	No	No	Yes
Study size 10 Explain how the study size was arrived at	No	No	No	No	No	No	No	No	No	Yes
Quantitative variables 11 Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes

S1: Results of STROBE checklist (continued)

	Apelqvist *et al.*	Apelqvist *et al.*	Carter *et al.*	Farris *et al.*	Holstein *et al.*	Kalani *et al.*	Londahl *et al.*	Matzke *et al.*	Paaske *et al.*	Varatharajan *et al.*
Statistical methods 12 (a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	Yes	No	Yes	No	No	Yes	Yes	Yes	No	Yes
Participants 13* (a) Report numbers of individuals at each stage of study — e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes
Descriptive data 14* (a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (e.g. average and total amount)	No	Yes	Yes	No	No	Yes	Yes	No	No	Yes
Outcome data 15* Report numbers of outcome events or summary measures over time	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Main results 16 (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorised (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful period	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Other analyses 17 Report other analyses done — e.g. analyses of subgroups and interactions, and sensitivity analyses	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes

S1: Results of STROBE checklist (continued)

	Apelqvist *et al.*	Apelqvist *et al.*	Carter *et al.*	Farris *et al.*	Holstein *et al.*	Kalani *et al.*	Londahl *et al.*	Matzke *et al.*	Paaske *et al.*	Varatharajan *et al.*
Key results 18 Summarise key results with reference to study objectives	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Limitations 19 Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	No	No	No	No	No	No	No	Yes	No	Yes
Interpretation 20 Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Generalisability 21 Discuss the generalisability (external validity) of the study results	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Funding 22 Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No

* Give information separately for exposed and unexposed groups.

S2: Results of modified CASP for cohort studies appraisal

		Apelqvist *et al.*	Apelqvist *et al.*	Faris & Duncan	Holstein & Lassen	Kalani *et al.*	Londahl *et al.*	Carter *et al.*	Matzke *et al.*	Paaske *et al.*	Varatharajan *et al.*
1	Did the study address a clearly focused issue?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Was the cohort recruited in an acceptable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Did they accurately measure/classify wounds or vascular state at inclusion?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
4	Was the outcome accurately measured to minimise bias?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
5 (a)	Have the authors identified all important confounding factors?	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes
5 (b)	Have they taken into account the confounding factors in the design and/or analysis?	No	Yes	No	Yes	No	Yes	Yes	No	No	Yes
6 (a)	Was the follow-up of subjects complete enough?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6 (b)	Was the follow-up of subjects long enough?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
9	Do you believe the results?	Yes	Yes	Yes	Yes	Yes	UTD	Yes	Yes	UTD	Yes
10	Can the results be applied to the local population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11	Do the results of this study fit with other available evidence?	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes

UTD; Unable to determine.