

Noninvasive optical methods to assess tissue perfusion in patients with peripheral arterial disease and diabetes mellitus: A scoping review and discussion

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ABSTRACT

Background: The global incidence of peripheral arterial disease (PAD) is 10.5 million individuals annually. There are 113 million people affected globally, which can result in limb loss. PAD is often part of a greater set of comorbidities, including diabetes mellitus (DM), chronic kidney disease, coronary artery disease and obesity. Diabetic foot ulceration is a debilitating complication of DM that occurs owing to a combination of neuropathy, PAD, and structural biomechanical changes. Poor tissue perfusion in the context of microangiopathy can result in impaired wound healing and eventual limb loss. The combination of diabetic foot ulceration and PAD can be burdensome socially, psychologically and economically, for patients and health systems. It is, therefore, imperative to be able to identify and continuously monitor high-risk patients to aid in the prevention, monitoring, and management of these conditions in a noninvasive, easily accessible and cost-effective manner. We sought to evaluate the current evidence relating to noninvasive optical tissue perfusion assessment modalities available and their use in patients with PAD and individuals with DM. We also aimed to collate how each assessment modality worked, and its advantages and disadvantages.

Methods: A systematic literature search was conducted of the Embase and Medline (via the Ovid interface), PubMed, and Google Scholar databases for articles relating to PAD in individuals with DM. Articles were reviewed by two independent reviewers. Findings were collated for each method of tissue perfusion.

Results: In the final review, 35 articles met criteria for inclusion. The modalities discussed included photoplethysmography, spatial frequency domain imaging, hyperspectral imaging, laser Doppler, laser speckle flowgraphy, near infrared spectroscopy, thermography, photoacoustic imaging, and indocyanine green.

Conclusions: Several modalities are available for the noninvasive monitoring of tissue perfusion in individuals with DM and PAD that show promise. Their clinical applicability is an area of ongoing research. (JVS-Vascular Insights 2024;2:100034.)

Keywords: Amputation; Diabetes mellitus; Limb loss; Macrovascular; Microvascular; PAD; Peripheral arterial disease; Tissue perfusion

Peripheral arterial disease (PAD) affects 113 million individuals globally, with 10.5 million new cases worldwide every year.¹ The spectrum of PAD includes intermittent

claudication, chronic limb threatening ischemia to tissue loss. PAD is often part of a greater set of comorbidities inclusive of coronary artery disease, diabetes mellitus (DM), chronic kidney disease, and obesity. PAD is accelerated in patients with DM, particularly affecting the crural vessels.² Often, there is evidence of underlying structural foot deformities, such as hallux valgus, hammer toes, claw toes, and Charcot neuroarthropathy. Minor repetitive foot injuries go unnoticed in patients with DM owing to underlying neuropathy and may result in diabetic foot ulceration (DFU); there may also be superimposed infection. In this context, with PAD the overall supply of blood into the lower extremities may be inadequate to allow healing to occur. The prevalence of DFU in diabetic patients is $\leq 10\%$ and the likelihood of its occurrence increases with age, the duration a patient has DM and poor glycemic control.³

DFU is a disabling complication that often results in amputation and limb loss if not managed effectively. DFU also accrues significant health care costs owing to

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the time and resources required to manage it, with a rate of recurrence of >50% within 3 years.⁴ It also has a significant psychological and economic impacts on the individuals affected. DFU continues to increase in incidence and prevalence; therefore, prevention, early detection, and organized management are essential. There is a noted increase in the research trends and overall research in the prevalence and management of DFU.⁵

With the presence of micro- and macrovascular disease in patients with DM, as well as vascular endothelial cell dysfunction, altered blood viscosity and wall tension in poor glycemic control, peripheral vascular disease is accelerated in patients with DM.⁶ Tissue perfusion monitoring may have usefulness in risk stratification, prioritization, early detection, guiding management, and monitoring DFU. The Society of for Vascular Surgery Wound, Ischemia and foot Infection classification system is often proposed in assessing the risk of amputation at 1 year; alternative specific methods of detecting tissue perfusion in a noninvasive and cost-effective manner may be helpful as part of this risk stratification.⁷ We sought to review the existing literature on current noninvasive optical methods and technologies to assess tissue perfusion in individuals with DM and PAD.

METHODS

We searched Medline and Embase (via the Ovid interface) databases, and Google Scholar. The medical subject heading terms and search syntax are attached in [Appendix 1](#). The results of these were added to the Rayyan Software for title and abstract screening independently by two reviewers. Included articles were then moved to Covidence Software where the full texts were reviewed. The opinion of a third reviewer was sought if there were any disagreements on whether an article was to be included or not.

The inclusion criteria were articles pertaining to noninvasive optical methods of detecting and measuring tissue perfusion in patients with PAD, critical limb ischemia, or chronic limb-threatening ischemia and DM, diabetic foot disease, or diabetic foot ulcers. Articles published between 1990 and 2022, in English, reporting studies pertaining to human participants over the age of 18 years. Article types included randomized controlled trials, case-control studies, cross-sectional, and cohort studies or reviews.

The exclusion criteria were articles published in languages other than English, studies where the participants were under the age of 18 years, animal model studies, posters, abstracts, commentaries, book chapters, case reports, editorials and expert opinions. We also excluded articles assessing transcutaneous oxygen measurements (TCOM), which has been extensively investigated in the past.

The studies included in the systematic review were graded using the Newcastle-Ottawa scale. The summary

ARTICLE HIGHLIGHTS

- **Type of Research:** A scoping review and discussion.
- **Key Findings:** The modalities available for non-invasive/minimally invasive tissue perfusion include photoplethysmography, spatial frequency domain imaging, hyperspectral imaging, laser doppler, laser speckle flowgraphy, near infra-red spectroscopy, thermography, photoacoustic imaging and indocyanine green.
- **Take Home Message:** A validated and cost effective method for consistent and reliable and non-invasive method of measuring tissue perfusion needs to be established.

marking for each study is included in [Appendix 2](#). We evaluated the technologies involved, current evidence relating to their use, applicability and the benefits they confer over traditional methods for PAD assessment including ankle-brachial pressure index (ABPI) and TCOM.

Data from the included studies was extracted by two reviewers on an Excel spreadsheet including the author, the year of publication, the number of patients, whether they had PAD or DFU, and if they underwent any intervention. We also recorded the method used for measurement of tissue perfusion, the comparator, if mentioned, and a summary of the findings and results, including any statistical analyses, if undertaken.

RESULTS

Initially, 775 articles were identified. Of these, 150 were duplicates and were removed. We screened 625 records and 160 were sought for retrieval. Of these articles, 13 were excluded because they discussed TCOM. We assessed 147 articles for eligibility. Three articles were identified from other websites and 20 via citation searching. Twelve of these were sought for retrieval and 10 were assessed for eligibility and included in the final review.

This process is summarized in the PRISMA flowchart in [Fig 1](#). We also identified a systematic review by Mennes et al⁸ from 2018 discussing novel optical techniques for imaging microcirculation in the diabetic foot.

The main noninvasive optical methods reported in the literature included photoplethysmography (PPG), spatial frequency domain imaging (SFDI), hyperspectral imaging (HSI), laser Doppler (LD), laser speckle flowgraphy (LSF), near infrared spectroscopy (NIRS), thermography, indocyanine green (ICG), and photoacoustic imaging (PAI). We found one study on SFDI, six studies on HSI, three on PPG, five on LD, four on LSF, four on NIRS, two on ICG, eight on infrared thermography, and one on PAI ([Figs 2 and 3](#)). We also found a systematic review discussing several of these modalities. The methods and current studies for each of these methods is summarized in [Table 1](#). Each modality is discussed in the Discussion;

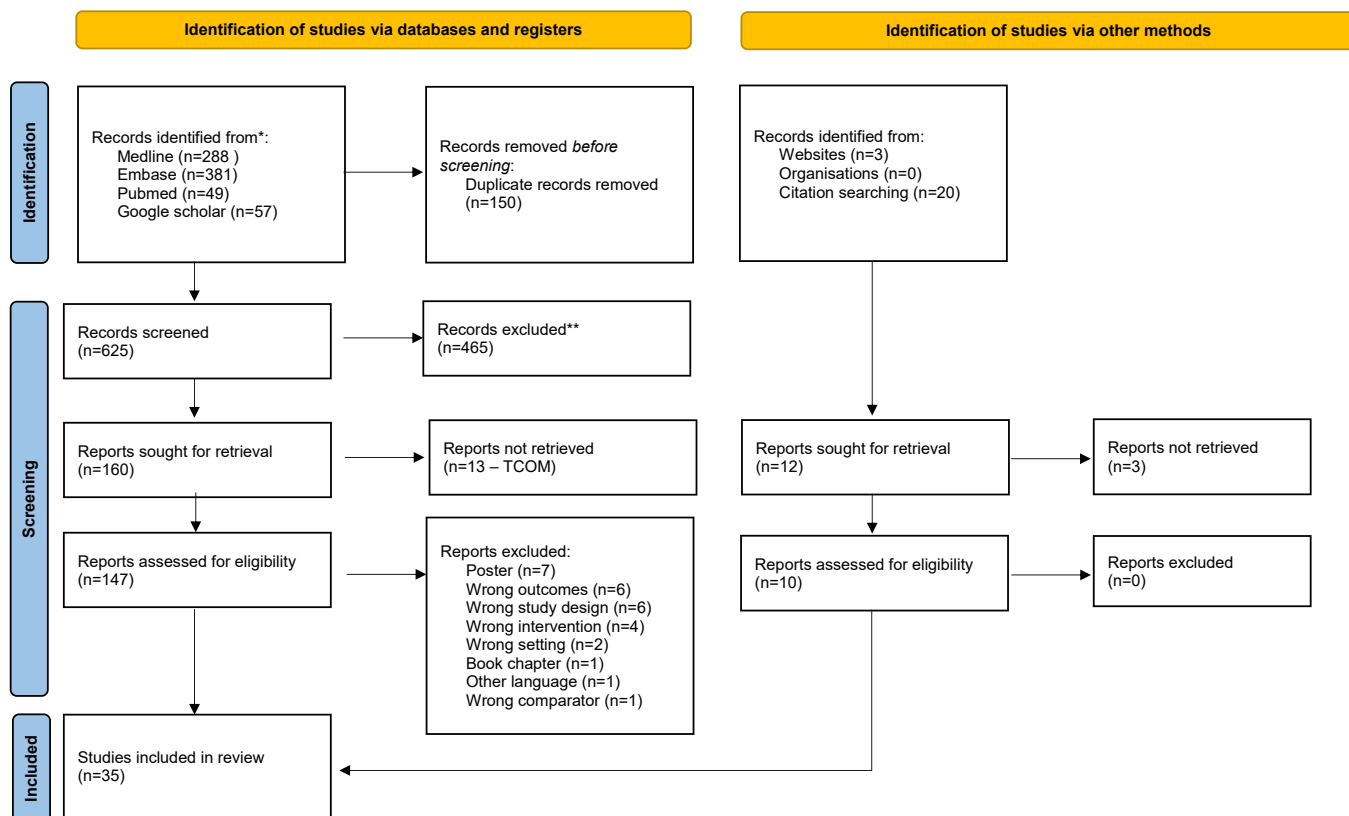


Fig 1. PRISMA flow diagram.

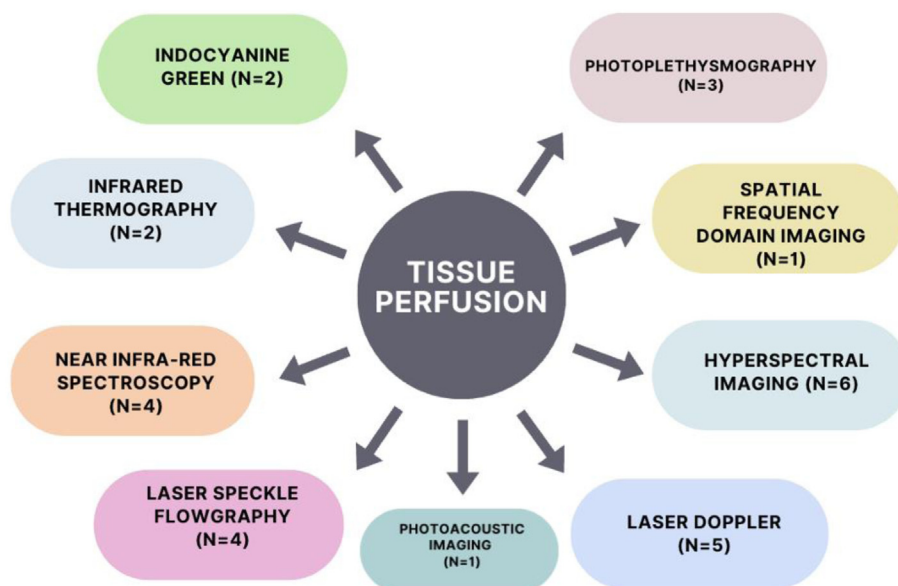


Fig 2. Nonoptical methods and the number of studies for each method.

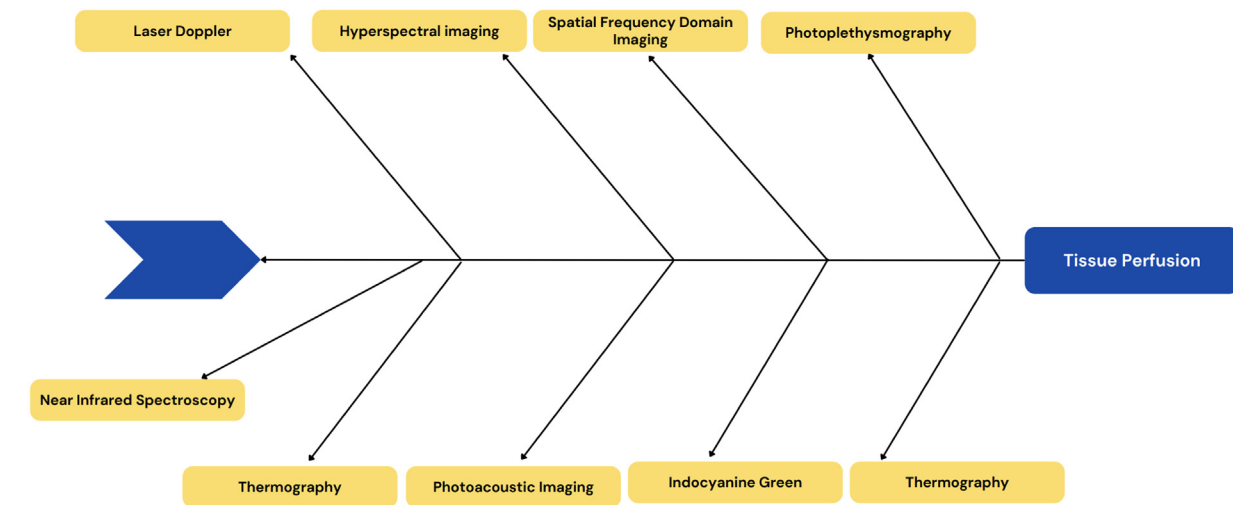


Fig 3. Fishbone diagram.

their advantages and disadvantages are summarized in Table II.

DISCUSSION

SFDI. SFDI is a noncontact optical method extension of NIRS, but it resolves the optical absorption and scattering parameters at different wavelengths.⁴² It separates and quantifies the multispectral absorption and optical scattering properties. It also accounts for the direct photon path and removes the varying reflectivity changes from contrast mechanisms. As such, it is capable of differentiating chromophore (the part of a molecule in each material that absorbs the wavelengths of visible light and, therefore, is responsible for its color such as melanin and hemoglobin) absorption vs tissue scattering from structural properties such as the presence and amount of collagen.⁴² This collagen is affected by the presence of advanced glycation end-products, which contribute to the inflammatory processes by directly impairing vascular function and contributing to disorganized fibrillar collagen arrangements, which can inadvertently lead to Charcot foot.⁴²⁻⁴⁴

An SFDI apparatus consists of a light source (which includes light emitting diodes at different wavelengths; $\lambda = 450-900$ nm), two detection cameras, one of which collects near infrared images of the spatially projected pattern along with a color camera and a spatial light modulator. Periodic spatially modulated illumination patterns of different frequencies are projected and the reflected images are captured with a camera. The image quality is measured using the modulation transfer function, which determines how much contrast is in the object being assessed and is maintained by the detector.

Height maps using the spatial varying phases are calculated to map the measurement of curved surfaces. Research has taken place in vascular occlusions in pedicled flaps and burns, but these have all been animal studies to date.^{42,45}

Weinkauff et al⁹ first discussed the use of SFDI in assessing tissue perfusion in the vascular assessment of feet in diabetic and nondiabetic patients. They utilize the data on absorption and how it can be used to provide functional chromophore concentrations of deoxyhemoglobin, oxyhemoglobin, tissue oxygen saturation (StO₂) and water at depths of 2 to 3 mm, as well as tissue hemoglobin in the dermal microcirculation and capillary beds of the papillary dermis which is more superficial (HbT1) and the hemoglobin concentration in the microcirculation of reticular dermis, which is the deeper blood supply (HbT2).⁹ The results are projected as a color coded map of tissue-coded chromophores for StO₂, HbT1, and HbT2. ABPIs in patients with DM may be flawed owing to vessel calcification. Weinkauff et al⁹ found that the median StO₂ was poorly correlated with ABPIs and TBIs. They found that the HbT1 was decreased in diabetic patients with compromised blood flow (monophasic Doppler waveforms) and normal blood flow (biphasic and triphasic Doppler waveforms).

They also found that the HbT2 and StO₂ were much higher in diabetic patients who had monophasic waveforms as compared with diabetic patients with biphasic and triphasic Doppler waveforms. This was hypothesized as being owing to shunting occurring as a result of vasomotor dysregulation. They also found that a high HbT2/HbT1 ratio was associated with diabetic patients regardless of their Doppler waveform.

Table I. Summary of findings

Author	Year	Number of patients	Patients	PAD severity/ intervention	Method measured	Comparator	Findings
Weinkauff et al ⁹	2019	47 (94 limbs)	Diabetics + nondiabetics	Nondiabetics - 25/31 patients ABPI<0.9 Diabetics - 8/16 ABPI<0.9	SFDI	ABPI	HbT1 values significantly lower in diabetic patients compared with nondiabetics in cases of diminished blood supply and normal blood supply ($P < .01$) HbT2 remains diminished in patients with bi or triphasic Doppler signals ($P = .03$)
Chin et al ¹⁰	2011	126 (252 limbs)	PAD + no PAD	No intervention	HSI	ABPI	Deoxyhemoglobin values for the plantar metatarsal, arch, and heel angiosomes significantly different in patients with and without PAD ($P < .005$). Significant correlation between deoxyhemoglobin values and ABI for the same three angiosomes ($P = .001$) in PAD patients
Greenman et al ¹¹	2005	108	Diabetic patients with and without neuropathy	No PAD	HSI	31P-MRI scan concentrations of inorganic phosphate and phosphocreatine and calculating the ratio of inorganic phosphate to phosphocreatine	Forearm oxyhemoglobin saturation at rest had the highest value in controls (mean, 42 ± 7), followed by the non-neuropathic (32 ± 8) and neuropathic (28 ± 8) groups ($P < .0001$). Foot oxyhemoglobin saturations were, at rest, higher in the control (38 ± 22) and non-neuropathic groups (37 ± 12) than in the neuropathic group (30 ± 12 ; $P = .027$).
Jeffcoate et al ¹²	2015	43	T1DM; T2DM	All ranges of PAD (ABPI range, 0.15 - 1.63)	HSI	Blood gas	Statistical correlation of baseline oxygenation determined by HSI and healing at 12 weeks ($P = .03$) This is also observed in those with clinical signs of infection but not observed at 24 weeks
Khaodhiar et al ¹³	2007	37	T1DM with ulcers, T1DM without ulcers, nondiabetics	No PAD	HSI	TCOM, LD	Statistically significant differences ($P < .0001$) in normal, T1DM and T1DM with ulcer groups in HT- oxy Differences in skin around ulcers that healed and those that did not ($P < .01$)

(Continued on next page)

Table I. Continued.

Author	Year	Number of patients	Patients	PAD severity/ intervention	Method measured	Comparator	Findings
Lopez-Moral et al ¹⁴	2022	21	Diabetics	Non-CLI patients	HSI	Transcutaneous oxygen pressure, ABPI, TBI	Higher TcpO ₂ found in ulcers that healed vs non healing ulcers ($P < .001$) TcpO ₂ sensitivity 91% specificity 100% - considered to be best predictor compared with HSI variables, ABPI and TBPI StO ₂ , NIR values higher in patients whose ulcer healed compared with nonhealers at 24 weeks whereas ABPI and TBPI showed no significant difference
Nuovong et al ¹⁵	2009	66	T1DM; T2DM	Mild PAD or better (ABPI > 0.78)	HSI	Transcutaneous oxygen pressure	Higher Ht oxy mapping result in feet with healed ulcer vs nonhealed feet ($P = .0013$) Healed ulcer group had higher StO ₂ ($P = .024$) and healing index ($P < .0001$)
Hoyer et al ¹⁶	2017	69	PAD patients	All ranges of PAD (Fontaine I-IV)	Plethysmography	Toe and ankle pressures	No difference in diagnostic classification of PAD in ankle and toe pressures derived from full or truncated displays of plethysmography Low interobserver variability for both plethysmography methods used
Ubbink et al ¹⁷	2004	70	Vascular laboratory; toe pressures in patients	All ranges of PAD	Plethysmography	LD	Heated LD yielded significantly higher TBP compared with plethysmography, whereas unheated LD did not differ from plethysmography Good intermeasurement agreeability between PPG and unheated LD to detect CLI ($\kappa = 0.77$). Findings similar between diabetics and nondiabetics
Widmer et al ¹⁸	2012	54	Vascular patients who had undergone EVT or had chronic limb-threatening ischemia	All ranges of PAD	Plethysmography	LD	TP readings differ significantly between LD, Nicolet Vasoguard and system apparatus. LD TP readings would be approximately 10 mm Hg higher than plethysmography measurement on average.
Caselli et al ¹⁹	2003	20 (10 with DM)	DM patients with peripheral neuropathy	Vasodilation induced by topical application of methyl nicotinate and comparison with acetylcholine and sodium nitroprusside	LD	None	Forearm and foot perfusion values with significant differences between DM patients and control patients between peak and baseline blood flow of the participants ($P = .001$)

Table I. Continued.

Author	Year	Number of patients	Patients	PAD severity/ intervention	Method measured	Comparator	Findings
Gschwandtner et al ²⁰	1999	25	DM patients with ischemic leg ulcers	Three areas defined in each ulcer - nongranulation tissue area, a granulation tissue area and adjacent skin area; no intervention	LD	None	Average flux (measured in arbitrary units) and number of capillaries/mm ₂ reported. Differences between granulation tissue area and nongranulation tissue area/skin area were statistically significant ($P < .001$)
Ishii et al ²¹	2019	128	End-stage renal failure patients on hemodialysis with PAD	PAD group - all stages of Fontaine classification	LD	SPP	SPP - significant differences between PAD and non-PAD groups on dorsum and plantar aspects of foot LD blood flow values - only significant difference between PAD and non-PAD groups on plantar aspect of feet ROC analysis of LD - plantar blood flow values adjusted for CRP, creatinine, and cholesterol showed a sensitivity of 0.88 and specificity of 0.78 at cut-off of 20 mL/min for PAD
Morimoto et al ²²	2014	22 (11 with DM)	DM patients with DFU	Neovascularization of LD conventional artificial dermis seeded with autologous fibroblasts cultured dermis and collagen/gelatine sponge applied after debridement		None	Perfusion units measured after application, at 1, 2 and 3 weeks after application + complete healing rates within 16 weeks compared. No significant differences in PUs seen between the two groups. Three weeks after application, the perfusion unit value in the cultured dermis group was significantly larger than those in the cultured dermis + collagen/gelatine sponge groups on day 0 ($P < .01$).
Newton et al ²³	2002	10 (5 with DM)	DM patients with peripheral neuropathy and DFU (7 ulcers); no PAD	Dermal replacement therapy	LD	None	Perfusion units measured immediately before and at 2, 5, and 8 weeks after application. Blood flow increased by an average of 72% in the base of 5/7 ulcers
Katsui et al ²⁴	2017	16	Symptomatic PAD patients	All ranges of PAD	LSF	Measured on the basis of cold induced vasodilatation using a thermal load test	No correlation between Tissue perfusion value at rest and conventional ABPI and TcpO ₂ On thermal loading those with perfusion value slope which plateaus had lower ABPI and TcpO ₂ than those whose perfusion value decreased after an initial rise - indicating the plateauing group had more severe ischemia TcpO ₂ was found to be most accurate method of determining severity of limb ischemia

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Table I. Continued.

Author	Year	Number of patients	Patients	PAD severity/ intervention	Method measured	Comparator	Findings
Katsui et al ²⁵	2018	63	PAD patients undergoing endovascular revascularization	All ranges of PAD	LSF	Measured on the basis of cold-induced vasodilatation using a thermal load test	Tissue perfusion value slope of plateau group improved following endovascular therapy
Kikuchi et al ²⁶	2019	31	PAD patients undergoing surgical revascularization	All ranges of PAD	LSF	SPP	Beat strength of skin perfusion significantly higher in non-PAD patients in all locations on plantar aspect of foot Beat strength of skin perfusion significantly increased immediately postoperatively and maximally by day 7 in all plantar locations compared with preoperatively and was correlated with SPP changes (all $P < .01$)
Mennes et al ²⁷	2021	61	Patients with DFUs	Offloading, wound dressings, antibiotics	Laser speckle contrast imaging of healed and nonhealed ulcers at 12 and 26 weeks-dorsum + plantar + ulcer aspect of foot	Noninvasive blood pressure measurements: arm, foot, and toe pressures	No significant difference ($P = .135-.989$) in the perfusion measurements using laser speckle contrast imaging and noninvasive blood pressure measurements between patients with healed or nonhealed foot ulcers at 12 or 26 weeks ($P = .135-.989$); 95% confidence interval
Kayama et al ²⁸	2021	89 patients for EVT - (34 with wounds)	Chronic limb-threatening ischemia (Fontaine IV); 17 with DM; patients with foot infections excluded	EVT with technical success	NIRS - dorsal foot	ABPI, SPP, and transcutaneous oxygen pressure	Wound healing was achieved in patients with a regional tissue oxygenation saturation $\geq 50\%$. In all wound healing cases, the SPP was ≥ 45 mm Hg, and the transcutaneous oxygen pressure was ≥ 40 mm Hg. ROC analysis of the SPP, the area under the curve was 0.846 (95% confidence interval, 0.683-1.000, $P < .01$) with an optimal cut-off value for predicting wound healing of 36.5 mm Hg (sensitivity of 89.5%; specificity 71.4%). ROC analysis of rSO_2 showed an area under the curve of 0.780 (95% confidence interval, 0.629-0.931, $P = .014$). Optimal cutoff value was 49.5 mm Hg (100% sensitivity and 64% specificity)

Table I. Continued.

Author	Year	Number of patients	Patients	PAD severity/ intervention	Method measured	Comparator	Findings
Lin et al ²⁹	2020	50	DFU patients with/without ulcers with PAD	3 groups: No PAD (group A), PAD without angioplasty (group B), PAD with angioplasty (group C)	NIRS - dorsal foot pre and post Buerger's exercises	None	Nonhealed patients in groups B + C had higher resting hemoglobin levels, higher tissue blood volume but lower tissue oxygen concentration. Nonhealed patients in group C showed paradoxically reduced hemoglobin and tissue blood volume after the Buerger's exercises.
Yata et al ³⁰	2019	72	PAD (Fontaine II-IV); no diabetic patients	None	NIRS - finger mounted oximeter to measure regional tissue oxygenation	ABPI, transcutaneous oxygen pressure, SPP	Relationships between the rSO ₂ values and the traditional diagnostic modalities (measurement of the ABI, TcpO ₂ , and SPP): rSO ₂ at the ankle and ABI ($P = .347$, $r = 0.084$), rSO ₂ and TcpO ₂ at the ankle ($P < .001$, $r = 0.465$), rSO ₂ and SPP at the ankle ($P < .001$, $r = 0.499$), rSO ₂ at the dorsal foot and ABI ($P = .002$, $r = 0.279$), rSO ₂ and TcpO ₂ at the dorsal foot ($P < .001$, $r = 0.492$) and rSO ₂ and SPP at the dorsal foot ($P < .001$, $r = 0.546$). TcpO ₂ and SPP in the F-III/IV group significantly lower than those in the F-IIa group. rSO ₂ in the Fontaine IIb and Fontaine III/IV groups was significantly lower than that in the Fontaine IIa group.
Yu et al ³¹	2010	11 (12 limbs)	Lower limb ischemia; no diabetic patients	Bypass graft (n = 7); percutaneous transluminal angioplasty (n = 4); aortofemoral bypass (n = 1)	NIRS measured at the calf	None	Elevations in calf muscle blood flow were observed after revascularization in patients with bypass graft whereas acute postrevascularization effects in muscle oxygenation were not evident.
Igari et al ³²	2013	21 (23 limbs)	PAD patients	Endovascular and surgical revascularization	ICGA	ABPI, TBI, tissue perfusion	Time from fluorescence onset to half maximum intensity. Region of interest number 3, which included the distal region of the first metatarsal bone, correlated more significantly with the traditional measurements than the other regions of interest.

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Table I. Continued.

Author	Year	Number of patients	Patients	PAD severity/ intervention	Method measured	Comparator	Findings
Nishizawa et al ³³	2016	62	PAD patients: dialysis (n = 20) vs no dialysis (n = 42)	Rutherford classification; no intervention	ICGA	ABPI, TBI	Time from fluorescence onset to half maximum intensity. Region of interest number 3, which included the distal region of the first metatarsal bone, correlated more significantly with the traditional measurements than the other regions of interest.
Armstrong et al ³⁴	1997	143	Diabetic patients with asymptomatic sensory neuropathy, with neuropathic foot ulcers, patients with neuropathic fractures (Charcot's arthropathy)	No intervention	Infrared thermography	None	Difference between the affected side with Charcot's arthropathy (mean difference 8.3; $P \leq .001$) and the contralateral side and those with neuropathic ulcers (mean difference 5.6; $P \leq .001$)
Chan et al ³⁵	1991	68 (35 with DM; 33 controls)	Diabetic patients with and without painful neuropathy	No intervention	Infrared thermography	None	Mean foot temperature in DM patients with painful polyneuropathy (mean $\pm$ SE $28.3 \pm 0.3^\circ\text{C}$) was significantly higher ($P < .001$) than in the control subjects ($25.9 \pm 0.5^\circ\text{C}$); the highest temperatures over the metatarsal areas and heel. Visual analogue scale pain score (mean, 5.3 ± 1.9 cm) did not correlate with mean foot temperature ($r = -0.14$, $P = .52$)
Chang et al ³⁵	2020	124	Critical limb ischemia (Rutherford 5 and 6)	Patients undergoing EVT	Infrared thermography	Temperature differences in patients whose wounds healed vs whose wounds did not	Mean pre- and post-EVT temperatures of the foot was significantly higher in the healing group than in the nonhealing group (30.78°C vs 29.42°C [$P = .015$]; and 32.34°C vs 30.96°C [$P = .004$], respectively). Multivariate analysis showed that DIFF2 (lowest temperature minus the mean post-EVT temperature of the 5 angiosome zones) stood out as an independent predictor for freedom from major amputation (hazard ratio, 0.51; $P = .045$). Receiver operating characteristic curve analysis showed a DIFF2 cut-off value of -1.30°C , which best predicted future risk of amputation

Table I. Continued.

Author	Year	Number of patients	Patients	PAD severity/ intervention	Method measured	Comparator	Findings
Huang et al ³⁶	2011	51	Patients at risk of lower limb PAD	PAD-associated questionnaires, including walking impairment, vascular quality of life, and 7-day physical activity recall questionnaires before a 6-minute walking test. No interventions	Infrared thermography	ABPI	Rest temperatures were similar in PAD and non-PAD patients; postexercise temperature dropped in the lower extremities with arterial stenosis, but maintained or elevated slightly in the extremities with patent arteries
Ilo et al ³⁷	2020	211 (118 DM; 93 controls)	Diabetic patients with PAD based on ABPI readings	No intervention	Infrared thermography	ABPI, toe pressure	Mean temperatures on the plantar side were significantly higher in the DM group than in the control group ($P < .001$). Mean temperatures on the plantar ($27.7 \pm 2.0^{\circ}\text{C}$) and dorsal sides ($29.9 \pm 1.7^{\circ}\text{C}$) among controls and in the DM group had a plantar temperature of ($28.7 \pm 2.5^{\circ}\text{C}$) ($P < .001$) and ($29.7 \pm 1.8^{\circ}\text{C}$) ($P =$ not significant) in the dorsal side) in the DM group. Side-to-side temperature comparison showed significant differences between feet ($P < .001$).
van Netten et al ³⁸	2013	15	Diabetic patients with no visible signs, local complications (callus/neuropathic ulcer), diffuse complications (Charcot foot, infected ulcers, critical ischemia)	No intervention	Infrared thermography	None	Mean temperatures similar in patients with local complications on the ipsilateral and contralateral side, but temperature at the region of interest was $>2^{\circ}\text{C}$ higher compared with the corresponding region in the contralateral foot and to the mean of the whole ipsilateral foot. In patients with diffuse complications, mean temperature differences of $>3^{\circ}\text{C}$ between ipsilateral and contralateral foot were found.
Staffa et al ³⁹	2017	41 (20 controls)	Patients undergoing percutaneous transluminal angioplasty	Fontaine classification I-III; percutaneous transluminal angioplasty	Infrared thermography	ABPI	Median temperature change in the treated limb was $+0.4^{\circ}\text{C}$, for nontreated limb was -0.5°C ($P = .11$; not statistically significant)
Zenunaj et al ⁴⁰	2021	40	Symptomatic PAD patients/critical limb ischemia	Patients undergoing EVT	Infrared thermography	ABPI	Mean difference of 1.7°C (range, 1.1 - 2.2°C ; $P < .001$) between the side treated and the contralateral limb. Positive correlation between ABI and temperature values of the limb for treatment before revascularization ($P = .025$; $r = 0.36$) and after revascularization ($P = .024$, $r = 0.31$)

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Table I. Continued.

Author	Year	Number of patients	Patients	PAD severity/ intervention	Method measured	Comparator	Findings
Placke et al ⁴¹	2023	169	Diabetic and nondiabetic patients	No intervention	PAI	None	Positive correlation between palmar PAI measurements and duration of DM ($P = .023$) after occlusion.
<i>ABPI</i> , Ankle-brachial pressure index; <i>CLI</i> , critical limb ischemia; <i>HSI</i> , hyperspectral imaging; <i>CRP</i> , C-reactive protein; <i>DFU</i> , diabetic foot ulceration; <i>DM</i> , diabetes mellitus; <i>EVT</i> , endovascular treatment; <i>ICG</i> , indocyanine green; <i>LD</i> , laser Doppler; <i>NIRS</i> , near infrared spectroscopy; <i>PAD</i> , peripheral arterial disease; <i>PAI</i> , photoacoustic imaging; <i>PPG</i> , photoplethysmography; <i>ROC</i> , receiving operating characteristic; <i>rSO₂</i> , regional oxygen tissue saturation; <i>SPP</i> , skin perfusion pressure; <i>StO₂</i> , tissue oxygen saturation; <i>T1DM</i> , type 1 diabetes mellitus; <i>T2DM</i> , type 2 diabetes mellitus; <i>TBI</i> , toe-brachial index; <i>TcpO₂</i> , transcutaneous oxygen tension.							

SFDI shows promise in extracting depth specific properties which are independent of factors such as skin pigmentation, as it not only looks at the epidermis but the papillary and reticular dermal layers. It allows wide field assessment and is relatively cost effective. However, further studies are needed with larger sample sizes to further evaluate the usefulness and applicability of this technology.

HSI. HSI helps to measure superficial tissue oxygenation by measuring the concentration of oxyhemoglobin and deoxyhemoglobin and is based on optical spectroscopy.⁸ It does this by measuring the differences in the refraction index between the stratum corneum and the surrounding air. The light transmitted through this space onto human skin is reflected. The light that enters the tissue and reemerges from the tissue toward the detector. The reflected light remains polarized; however, the light that reemerges from the tissue is depolarised.^{46,47} HSI involves the recording to two-dimensional images of biological tissue over a narrow spectral band at certain wavelengths called a hypercube, which can be analyzed to show the local concentration of various tissue chromophores.⁴⁷ Based on the measured spectral band and knowledge of light transport in the medium, an absorption spectrum of the tissue can be determined, and the spectra of many tissue chromophores are already known. This allows the chromophore content to be measured thus helping to characterize the tissue.⁸

Khaodhiar et al¹³ compared hyperspectral tissue oxygen measurements of the area around ulcers to provide an indication of oxygen delivery by measuring oxyhemoglobin, as well as an indication of oxygen extraction by providing a measurement of deoxyhemoglobin. It was hypothesized that wounded tissue undergoing healing has a greater oxygen demands and found increased levels of both in wounds that heal vs those that had lower levels of the two and did not eventually heal ($P < .001$).¹³ The authors were, thus, able to predict which wounds would heal and which wounds would fail to heal. In Nuovong's study,¹⁵ patients had similar ABPIs, but found that the HSI averages for oxyhemoglobin

and deoxyhemoglobin levels were lower in patients whose ulcers did not heal. They were further able to create a healing index based on the superficial tissue oxyhemoglobin and deoxyhemoglobin using HSI with a positive predictive value of 96%.¹⁵ Jeffcoate et al¹² also found a positive correlation between HSI measured oxygenation and healing, but a negative correlation between the HSI and blood gases. The HSI has also been used to quantify oxygen saturation of the hemoglobin, tissue hemoglobin index, the near-infrared perfusion index and tissue water index.¹⁴ They found that patients who had wound healing had higher transcutaneous oxygen pressures and higher oxygen saturation of hemoglobin. Their study found that HSI was effective in predicting the prognosis of healing when compared with noninvasive testing, but the transcutaneous oxygen pressure was still superior and more cost effective. Kleiss et al⁴⁸ found that the short-term test-retest reliability was good on a short-term basis, but lacked consistency over the long term. The HSI has been used for healthy patients, and it would be interesting to investigate how readings would differ in PAD and DFU patients.⁴⁸ Conversely, Greenman et al¹¹ included diabetic patients with and without neuropathy and found lower foot oxyhemoglobin saturations in neuropathic patients at rest, and this difference was found to be statistically significant. Chin et al¹⁰ examined the differences in the deoxyhemoglobin values for the plantar metatarsal, arch, and heel angiosomes in patients with PAD and found a positive correlation between the ABPI readings and the deoxyhemoglobin values. Overall, the HSI has been found to be a good short-term predictor and correlates well with other modalities. Furthermore, it allows a two-dimensional rendering of what is originally a three-dimensional structure. However, it is less cost effective when compared with other modalities.

PPG. PPG is an optical measurement method that detects blood volume changes in the microvasculature of tissue. PPG works using a red or near infrared wavelength light source and a photodetector to capture the varying light intensities reflective of changing perfusion over a

Table II. Summary of modalities, advantages and disadvantages

Modality	Wavelength	Measurement	Advantages	Disadvantages	Vascular
PPG	600-900 nm IR	Blood volume changes in the microvasculature	Low cost Simple Portable	Operator dependent Environment dependent Altered by patient physiology	Difference in PPG readings post endovascular treatment
SFDI	450-900 nm	Quantifies chromophores by separating effects of scattering and absorption measures oxygen	Large area assessment (wide field) Measure at various depths Noncontact Cost effective	<1 cm depth Relatively new technology	Lower HbTI in diabetic patients with compromised vasculature Statistically significant
HSI	200-2000 nm	Concentration of oxyhemoglobin and deoxyhemoglobin - optical spectroscopy	Good short-term predictor Correlates with other modalities 2D rendition	Less cost effective Not better than existing modalities	Ulcer healing prognosis DM patients with neuropathy
LD	390-750 nm	Reflection from moving particles in the microcirculation	Upper 1.5 mm layer High frequency response Can change probes to focus on an area	Not reliable over callus/necrotic tissue Difficult to calibrate	Detect changes in nongranulating tissue Measures perfusion after dermal replacement therapy Distal perfusion in patients with and without DM
LSF	785 nm	Tissue perfusion changes using correlations in speckle intensities	Real-time feedback Easily reproducible measures Correlates with skin perfusion pressures after revascularization Large field of view	Moderate sensitivity and specificity in diabetic ulcer groups Expensive Long acquisition time Does not measure chromophores	Wound healing after intervention
NIRS	650-950 nm IR	Tissue absorption of infrared light → Hb level	Greater depth 1-3 cm Useful if unable to tolerate blood pressure cuffs for ABPI	BMI can alter results	After endovascular intervention
IT	780 nm-1 mm	Temperature dissipated by skin over a given area	Easily accessible Cost effective Can be integrated into mobile phone devices Consistent data output	No specific studies looking at patients with diabetic foot disease Better than existing measurements	PAD patients After endovascular treatment

(Continued on next page)

Table II. Continued.

Modality	Wavelength	Measurement	Advantages	Disadvantages	Vascular
ICG	760-820 nm IR	Measures injected fluorophore	Correlates well with ABPI and toe- brachial pressure index	Contraindicated in patients with allergies to sodium iodide Controlled environment for accurate measurements Readings altered by presence of melanin in skin No parameters established to indicate positive outcomes	Wound healing in established regions of interest ie Lisfranc joint, Chopart and first metatarsal Postamputation wounds
PAI	5-1000 nanoseconds	Emission of photoacoustic ultrasound waves	Noninvasive Able to differentiate between artery and vein Possible predictive value for risk stratification	Not validated Further studies needed	Vasoconstriction and vasodilatation in hyperglycemic states

ABPI, Ankle-brachial pressure index; *BMI*, body mass index; *DM*, diabetes mellitus; *Hb*, hemoglobin; *HSI*, hyperspectral imaging; *ICG*, indocyanine green; *IR*, infrared; *IT*, infrared thermography; *LSF*, laser speckle flowgraphy; *NIRS*, near infrared spectroscopy; *PAD*, peripheral arterial disease; *PAI*, photoacoustic imaging; *PPG*, photoplethysmography; *SFDI*, spatial frequency domain imaging.

given area. The reflected signal is directly proportional to the presence of erythrocytes in the area. The PPG waveform has a pulsatile arterial physiological waveform attributed to cardiac related blood volume changes associated with each cardiac cycle, known as the alternating current component. This is superimposed onto a slow varying direct current component, which arises from the optical signals reflected or transmitted from the tissue and is influenced by thermoregulation, the sympathetic nervous system and respiration.^{17,49} PPG technology is often used in pulse oximeters and digital blood pressure measuring devices. It does, however, have its drawbacks because the results depend on factors such as probe-tissue interface pressure, movement artifact, posture, room temperature, and other underlying physiological patient factors, such as the baseline blood pressure, heart rate, and rhythm.^{16,49}

Ubbink¹⁷ found LD to be comparable with PPG, but with variations between the expected readings, which can be due to a number reasons including operator variability, difficulty in detecting the reappearance of a systolic signal, and the fact that the feet were not warmed before PPG measurements, which is difficult in patients with PAD. However, Widmer et al¹⁸ found that the mean difference between measurements was acceptable within a certain range and overall difference with repeating was <10 mm Hg across the different devices in patients who had undergone endovascular treatment.¹⁶

LD. An LD perfusion signal is obtained from the Doppler shift undergone by emitted infrared laser light (390-750 nm) after reflection from moving particles such as red blood cells in the microcirculation. It is useful for assessing the microcirculation in the upper 1.5 mm layer of the skin.¹⁷ The tissue perfusion is measured as an estimated average based on the speed and the blood concentration. It is worth noting that measurements may not be reliable where there is necrotic tissue or callus formation and would require debridement in the first instance.¹⁰ This method also uses a speckle pattern; however, it uses a fast detector or a high-speed camera in contrast with diffuse speckle contrast analysis, whereby the camera has a slower response time to capture the dynamic speckle.¹⁰ The study by Ishii et al²¹ compared skin perfusion with to LD signals in PAD patients on hemodialysis. The areas assessed included the plantar and dorsum of the foot. Further analysis also found that LD flow signals in the plantar aspects of those with DM and PAD was significantly lower than those without DM. Gschwandtner et al²⁰ found that ulcers with nongranulation tissue areas had lower LD area fluxes and low capillary density, whereas fluxes were higher in the granulating tissue areas. Significant differences in flux between baseline blood flow was also noted in patients with and without DM.^{19,22} Other studies that used LD for measuring perfusion after dermal replacement therapy also found LD as a useful indicator of neovascularization

and improved blood flow after their application.^{22,23} Furthermore, it has also been used in burn management to measure responses to iontophoresis of vasoactive substances, in patients with endothelium-related impairment in vasodilatation such as Raynaud's, and in systemic sclerosis.^{10,19}

Diffuse speckle contrast analysis/LSF. Speckle refers to the diffuse, granular patterns from reflections of coherent monochromatic light beams, such as a laser onto a complicated or rough structure. A speckle pattern is created by the mutual interference of a set of coherent wavefronts.⁵⁰ This optical method evaluates tissue perfusion changes using correlations in speckle intensities.⁵¹ It is similar to LD imaging in that the shift in frequency determines the particle velocity.²⁴ The advantage of this includes that it is easily reproducible and measures the microcirculation in and around the tissue of the ulcer directly with real-time feedback. It also has high inter- and intra-rater reliability.²⁷ Katsui et al²⁴ used laser speckle contrast imaging and tested relative cold induced vasodilatation after the application of a thermal load and found that abnormal relative cold-induced vasodilatation response denotes critical limb ischemia, but this could change to a normal response after revascularisation.^{24,25} This work builds on the concept of cold-induced vasodilatation, which usually consists of initial vasoconstriction leading to transient vasodilatation and then a phase of protracted vasoconstriction. By quantifying the change in blood flow in the latter third phase, they were able to predict patients with severe ischemic changes based on the perfusion patterns. They also found that there was a dynamic change noted following revascularization in their 2018 study as it led to changes in the perfusion patterns and peak perfusion values.²⁵ Kikuchi et al²⁶ reviewed this finding in patients undergoing surgical intervention and found that it offered advantages to wound healing prediction as it can measure pulsatile flow corresponding with the cardiac cycle delivered to distal peripheries, including an ulcer, through the assessment of the dynamic focal movement of the red blood cells. There was also correlation between LSF and skin perfusion pressures ($P < .01$).²⁶ However, there is little in terms of research looking at DFU and the use of laser speckle in these cases. Mennes et al²⁷ found no significant difference in the laser speckle readings between the healed and nonhealed ulcer groups, and receiver operating characteristic curves for laser speckle and noninvasive blood pressures showed poor to moderate sensitivity and specificity. However, the study excluded patients who went on to have revascularization or major amputation. LSF overall has moderate sensitivity in DF groups, is expensive and has long acquisition times,⁴¹ and requires further comparative studies.

NIRS. NIRS uses dual wavelengths between 650 and 950 nm, and the infrared light is absorbed by various molecules such as lipids, protein, glycogen, and carbohydrates. Each tissue biomolecule has a unique infrared absorption spectrum and therefore the tissue absorption is decreased as it passes through the layers. The light is able to reach the deeper layers of tissue (1-3 cm), measuring the tissue absorption and thereby calculating the hemoglobin concentration and oxygen saturation. The advantage this offers is that it is also able to take into account smaller vessels, such as the capillaries and venules.^{31,52} In recent years, NIRS has been combined with diffuse correlation spectroscopy flowmeter, which allows noninvasive and direct measurement of the relative changes to the blood flow.³¹ The use of this modality has previously been tested in evaluating the progression of diabetic nephropathy.⁵²

Yu et al³¹ noted the increase in the relative blood flow and the oxygenated hemoglobin levels after surgical bypass intervention and after percutaneous angioplasties, but transient decrease during balloon inflation. They did, however, note that NIRS is susceptible to giving inaccurate results based on the overall body mass index, which is an important factor to consider in the background of patient physiology and demographics. It is worth noting that it allows measurement of the relative oxygen saturation in those who may not otherwise be able to tolerate the blood pressure cuff used for ABPI in critical limb ischaemia.³⁰ Furthermore, most devices for NIRS are made to assess larger areas of the lower limb, which can also decrease accuracy for readings from the digits. Kayama et al²⁸ retrospectively reviewed wound healing in patients with PAD who underwent endovascular treatment. They then measured the relative oxygen saturations on their first postoperative day to suggest possible values to aim for in predicting ulcer healing, but this would require regular measurements because there are a plethora of factors involved in overall wound healing.²⁸ The accuracy of NIRS has yet to be determined in patients with DFUs. However, there is recent research by Lin et al²⁹ specifically studying the use of NIRS to predict wound healing in patients with DFUs using a wearable NIRS apparatus to calculate the tissue blood volume, oxyhemoglobin and deoxyhemoglobin saturations. They found that nonhealed in the PAD without angioplasty group and the PAD with angioplasty group had higher resting hemoglobin levels and higher overall tissue blood volumes, but had lower tissue oxygen concentrations. However, when these groups underwent Buerger's exercises, they paradoxically had lower hemoglobin and tissue blood volumes.

ICG. ICG is used as a near infrared fluorophore and is minimally invasive. It is initially injected and then detected at the region of interest using an infrared camera with a

light source emitting a wavelength of 760 to 820 nm with light-emitting diodes. It has previously been used in assessing liver function and flap perfusion.³² It cannot, however, be used in patients who are at risk of allergic reactions to sodium iodide. The infrared camera then captures the maximum intensity of the ICG fluorescence. It, however, depends on the amount of melanin present, the distance of the camera from the skin, and the presence and intensity of ambient lighting. ICG in lower limb assessment has looked at three areas or regions of interest—the Chopart Joint, the Lisfranc joint, and the distal region of the first metatarsal bone.^{32,33} Igari et al³² suggest that ICG can be used to predict wound healing, but this is based on specific areas in controlled settings (ie light and room temperature); the strongest correlation with ABPI and toe-brachial index was found in the Lisfranc Joint region. Nishizawa's study compares the transition of ICG in patients on dialysis and found there was a significant deterioration in the distal metatarsal bone areas.³³ Nakamura et al's region of interest in their study was the dorsum of the foot on the operative side and the contralateral side and the time to maximum ICG intensity and found perfusion in the contralateral limb decreased significantly, although the reason for this could not be fully explained.⁵³ Van der Hoven et al⁵⁴ studied post-amputation wounds, but further research is needed in establishing parameters, which would indicate the likelihood of wound healing. ICG, although generally safe and overall well-tolerated, is not without its risks and can cause allergic reactions and anaphylaxis. Furthermore, it also has certain contraindications, including liver disease, uremia, pregnancy, and patients with severe asthma.

Thermography. Infrared thermography measures the temperature dissipated by the skin over a given area of skin, which varies according to the tissue perfusion. Areas with good blood supply have increased flow and cellular metabolic rates than areas with low blood flow as is often the case in PAD. In recent years, this has become easily accessible and can be integrated using an attachment to readily available smartphone devices.⁵⁵ The infrared camera records the temperatures over specific areas supplied by blood vessels, that is, the angiosome concept, which refers to the three-dimensional volume of tissue vascularized by a single artery. Its merits include the ease of access, safe, and noncontact method, which can produce data efficiently; it also has lower costs, but research to date has primarily been undertaken in patients with PAD without much focus on diabetic foot ulcers. The costs of a thermography camera varies vastly costing anywhere between £350 for an ultra-basic handheld camera to >£50,000 for higher end cameras with better pixel thermal resolutions.

Zenunaj et al⁴⁰ noted in their study a median increase of 2°C in symptomatic PAD patients undergoing successful endovascular intervention ($P < .001$), as well as

correlation with the temperatures and ABPI. Chang et al³⁵ also noted higher foot temperatures in patients who underwent wound healing and further go on to outline independent risk factors for amputation, of which DM was not included, which further factor in the complexity of DFUs.⁵⁶ Staffa et al³⁹ found surface temperatures obtained by infrared thermography correlated with ABPI with both increasing after endovascular intervention, but fail to discuss regarding superiority to ABPI. This correlation is also confirmed by Huang et al,³⁶ who also noted a decrease in postexercise temperatures ($P < .001$) in patients with arterial disease. However, these studies do not consider the vessel calcification often seen in diabetic patients and therefore warrants further investigation.

PAI. PAI, also known as optoacoustic imaging, measures the emission of photoacoustic ultrasound waves which are optically induced. Short laser light pulses between 5 and 1000 nanoseconds, illuminate the tissue leading to a local thermoelastic effect, which then emits acoustic waves.⁸ Measuring the ultrasonic light pulses at varying wavelengths allows differentiation between oxyhemoglobin and deoxyhaemoglobin.⁸ This allows differentiation between arterial and venous flow. To date, its use has only been used in murine studies of the extremity to monitor vasoconstriction induced by acute hyperglycaemia.⁵⁷ The study found arteriolar constriction, but minimal changes to the venules.⁵⁷ Other studies using murine and swine models have also found decreased vessel diameter and reduced blood flow velocities in mice with induced DM.⁵⁸ A recent study by Placke et al⁴¹ found a positive correlation between the PAI palmer measurements and the duration of DM with statistical significance. Furthermore, they could also detect atypical PAI patterns in patients who were healthy, but were at risk of DM in future. This has scope for further development in future to assess how humans are also affected and the overall mass applicability of this method.

The current method of assessing tissue perfusion is transcutaneous oximetry (TcPO). TcPO is a noninvasive and well-validated method of assessing oxygenation around the wound and the microcirculation as hypoxia is a risk factor for poor wound healing.⁵⁹ It is, therefore, imperative to identify poor wound oxygenation and improve this where possible. This works by placing a polarographic oxygen electrode, which is approximately 43°C and leads to the vasodilatation of the underlying microcirculatory vessels and improving the oxygen diffusion toward the electrode to provide the partial oxygen pressure at that site.⁶⁰ It is not an infallible method and is susceptible to variability with position, edema, infection, scarring, sclerosis, ambient temperature, smoking, and caffeine consumption.⁶⁰ TcPO can be a good indicator of complications associated with poor wound healing

in lower limb amputations, but does not provide optimal threshold values and can be relative.⁶¹ New methods need to be accessible, cost effective, and easy to use.

There are multiple options for noninvasive optical methods available at present, each with their merits and disadvantages. Not all methods are reliable and some need to have controlled environments, such as room temperatures, activity, and equipment to allow replication of results and uniformity. However, with the rising popularity of cost-effective, noninvasive, and easy-to-use devices capable of measuring these with real time feedback, the options for wider applicability and mass use warrant further research into how patients can be offered proactive solutions for monitoring and management in the context of chronic illness and wound healing. The factor of the overall costs for each of these methods also has an impact. We attempted to collate the costs for each of these methods. HSI cameras cost approximately £14,000 as a very basic apparatus. PPG sensors cost between £12 and £280 without the machine apparatus to interpret and display monitor. LD apparatus can cost between £500 and £12,000. NIRS costs vary between £8000 and £62,000, depending on the whether it includes the spectrometer base, solids measurement cell, and the software. ICG contrast vials cost between £300 and £540 per 0.5-mL vial; however, this does not factor in the associated costs of the angiogram, which can vary vastly from region to region and the operator and staff costs involved, as well as the associated hospital costs. PAI equipment can cost between £259,000 and £780,000, but is still laboratory based.^{61,62} Thermography equipment is more readily available with lower costs of between £180 and £15,000. Other methods such as SFDI and diffuse speckle flowgraphy are still relatively laboratory based or not easily available; therefore, the exact costs are difficult to elucidate. Each methodology confers its own set of benefits including ease of use, reliability, costs, training, and the size and accessibility of equipment.

CONCLUSIONS

Current evidence shows promise in existing noninvasive optical methods, but further studies are needed to determine consistent reproducibility of results and reliability in the predicting wound healing, particularly in patients with DFU and PAD in various environments.

AUTHOR CONTRIBUTIONS

Conception and design: MA, AD, JS

Analysis and interpretation: MA, KP

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Writing the article: MA

Critical revision of the article: MA, KP, AD, JS

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DISCLOSURES

None.

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