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Research Article

The Influence of Blood Flow on Skin Surface Temperature in the Lower-Limbs: A Research Article

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Abstract

Background: Peripheral arterial disease (PAD) tends to be associated with lower foot skin temperatures, however it is dubious whether there is enough evidence to support this claim. Skin temperature monitoring, and its ability to be an independent diagnostic modality for PAD, particularly in diabetes, has gained remarkable interest in recent years, but its ability to detect and diagnose PAD is not yet clear.

Methods: A systematic literature search was conducted in: Academic Search Ultimate, CINAHL, Cochrane Library, LISTA, and MEDLINE Complete until February 2022.

Results: A total of nine studies were eligible for review. For the purpose of this review, the inclusion studies were grouped according to the type of investigation analysed: those investigating lower-limb thermal patterns in various populations and those investigating comparisons between various outcome measures to assess blood flow to the feet, including skin temperature measurement. Findings suggest that higher foot skin temperatures were found in PAD patients with Diabetes Mellitus (DM). Foot skin temperature measurements also showed a clear correlation with blood flow to the feet, evaluated by ABI.

Conclusions: Variations in foot skin temperature play an important role in the diagnosis of PAD. Current evidence shows that the influence of blood flow on surface skin temperature is complex. The interpretation of thermography as a diagnostic modality for PAD and its severity needs to be considered within the context of the overall medical condition of the individual patient.

Keywords: Blood Flow; Skin Surface; Temperature; Lower-Limbs

Introduction

Lower extremity peripheral artery disease (PAD) is a manifestation of atherosclerosis whereby blood flow in the arteries is obstructed [1]. Major risk factors for PAD include smoking, renal failure, dyslipidemia, old age, and diabetes mellitus (DM) [2-4]. The risk of PAD increases dramatically when these risk factors coexist [5]. PAD is frequently associated with DM affecting 11% of individuals living with diabetes as opposed to 4% amongst patients without diabetes [6,7]. It is estimated that the majority of patients are undiagnosed and undertreated, constituting to a threat of limb amputation and cardiovascular disease [8,9].

Latest recommendations state that initial diagnosis of peripheral arterial disease (PAD) should include the use of ankle brachial pressure index (ABPI) where an ABPI < 0.9 is considered diagnostic

of PAD [10]. However, in approximately one-third of individuals living with diabetes arterial calcification may cause ABPI to be falsely elevated namely in patients with chronic kidney disease and smokers [7,10]. In such cases toe-brachial pressure (TP) is recommended and is diagnostic at 0.7 or lower [4]. The limitations of ABPI as a clinical tool have raised the need to investigate other diagnostic methods to assess PAD such as thermography, that involves detecting infrared radiation energy from the human body via an infrared thermal camera [12,13].

Infrared thermography (IRT) has several advantages such as being non-invasive, simple to use, inexpensive [14], fast [15], reliable [5] safe and non-contact [16-20]. Moreover, researchers stipulate that it has the potential to detect physiological changes from an alteration in the emitted skin temperature and distribution of skin temperature [16,21]. Since vascular integrity and function are the determining factors of cutaneous temperature, the application of thermography to detect compilations in the diabetic foot, namely peripheral vascular disease has been studied [22,23]. It has been reported that if one foot is significantly higher in temperature when compared to the contralateral foot, indicating asymmetry, pathology may be present [24]. On the contrary, in healthy feet temperature patterns are generally symmetrical [25]. Moreover, it has been stated that a temperature change of > 2.2^0C in one foot is indicative of a disease process [25,26].

While thermography seems to be a possible novel emerging technology to detect PAD, when both limbs are ischaemic, the difference in temperature between the two may not exist [13]. Therefore detection using the 'asymmetry' theory is challenging [12]. Additionally, there is an on-going debate on whether foot skin temperatures are lower in patients with PAD compared to those without [4,5,27], or unexpectedly higher with PAD in DM [12].

Vascular assessment of the lower limb require time, cost and technical skills and are presently performed far from sufficiently, since several patients being left undiagnosed through this method [28]. In this regard, thermography would potentially be a good tool since it less costly, less time consuming and does not require particular clinical skills. However, even though thermography has several great advantages, so far it is not accepted to clinically diagnose PAD. Further evidence is therefore required to investigate the potential use of infrared thermography as a useful surrogate for vascular screening assessments. This structured review focused on thermography in relation to diagnosis of PAD in the lower limbs. The aim of this systematic review is to evaluate the current evidence behind thermography as a diagnostic tool for PAD and whether it can be used to categorise levels of the disease.

Methods

Search strategy

This structured review was conducted according to the guidelines by the Preferred Reporting items for systematic reviews and Meta Analysis. The following databases were used for the literature search from 2005 up to February 2022: Academic Search Ultimate, CINAHL, Cochrane Library, LISTA and MEDLINE Complete. The search strategy included Medical Subject Headings (MeSH) keywords included: (blood flow OR vascular OR peripheral arterial disease OR perfusion OR blood supply) AND (infrared imaging OR continuous temperature monitoring OR temperature OR temperature monitoring OR thermography OR (thermography OR thermal camera) OR infrared imaging OR infrared thermography OR infrared temperature monitoring OR skin temperature OR skin temperature measurement) AND (Foot OR (lower extremity OR lower limb OR leg) OR lower extremity). The titles and abstracts were screened by two reviewers (T.M. and C.M). The full texts of the potential papers were then reviewed and assessed to be included in the final analysis if they met the eligibility criteria. Any disagreements were resolved by consultation with a third reviewer (S.M.). When full texts of potential inclusion articles were not found, the authors of these articles were contacted. Any other additional references found in the included articles were also considered (forward search) and included if eligible.

Inclusion and exclusion criteria

Restrictions were placed on language and publication date. Peer reviewed journals from 2005 to 2022 in English were selected and only human studies were included.

Articles that were not peer reviewed or focused on the following, were entirely excluded:

No inclusion of blood flow assessment to the feet, peripheral vascular/arterial disease or monitoring of skin foot temperature.

Solely focused on skin foot temperature and diabetic foot ulceration or diabetic peripheral neuropathy, without any focus on peripheral arterial supply to the feet

Focused only on therapy or treatment for peripheral arterial disease and did not include skin foot temperature monitoring

Exposed lower limbs to heat or cold or pressure

Outcomes

The primary outcome of interest was the correlation between thermographic temperature measurements in the feet and other valid diagnostic measures of PAD in the lower limb, including ABPI, TBPI and duplex angiography. This determined whether thermography could be used as a diagnostic tool in a clinical setting. A secondary outcome included categorization of PAD by thermography, the validation of thermography in different participant groups living with diabetes, namely patients with diabetic peripheral neuropathy without PAD, patients without diabetic peripheral neuropathy with PAD and patients with neuropathy and PAD.

Data extraction

Data were extracted by the primary reviewer and was reviewed for accuracy by the second reviewer. Key data from selected articles was extracted into structured data extraction sheets. The information extracted included descriptive data such as title, authors, year of publication, population characteristics, exclusion criteria and methods of assessment as well as outcome measures, and study results and conclusions. Any other relevant information identified was also included in the data extraction sheets.

Results

The PRISMA flow diagram (Figure 1) illustrates that the initial search identified 3,421 articles. After removing duplicates (n = 1,013), applying filters to the databases (n = 1,441) and, additional records were identified through hand searches in reference lists (backward search) (n = 2), the full-text articles assessed for eligibility were forty-two. Thirty-three articles were excluded nine articles remaining for synthesis.

The data collected was grouped according to the type of investigation analysed

Lower-limb thermal patterns in relation to measures of blood flow, including the effects of changes in blood flow on foot skin surface temperature [4,5,9,12,13,15,27,29,30],

Comparisons between various outcome measures assessing blood flow to the feet, including skin temperature measurement [4,5,9,15].

Both categories are explored in further detail in the subsequent sections.

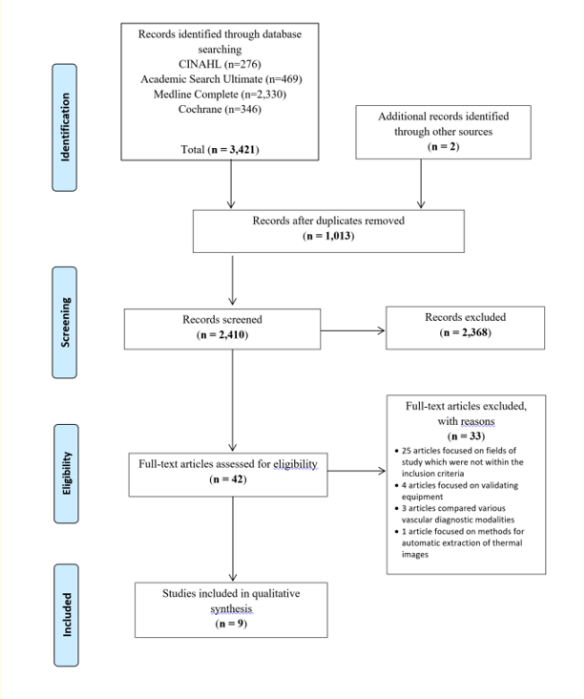

Figure 1: Flow Diagram: provides a representation of the full search strategy considered in this structured review.

Study characteristics

The sample size for the included studies ranged from 27 to 223 participants, with a mean age ranging from 59 to 74 years. Seven studies investigated populations living with diabetes [4,12,13,15,27,29,30], while the other two studies investigated participants with [5,9] and without PAD [5]. Since not all participants had diabetes (DM) [5,9], for the purpose of this review, the findings of the studies that included participants with diabetes and PAD are discussed separately to those having PAD without diabetes. In most of the included studies, participants acclimatized in a temperature-controlled room, which ranged between 20 to 26.5 °C.

Outcome measures

The studies included in this review used different devices to measure skin temperature data, to assess peripheral vascular status and to test for neuropathy (Table 1). An infrared camera was used in seven studies [4,12,13,15,27,29,30], while Huang., *et al*. [5] used a digital infrared thermal image system and Hayashi., *et al*. [9] used a non-contact thermometer. Table 1 include the various methods employed to assess peripheral neuropathy and peripheral vascular status across the studies.

Authors	Outcome Measures		
	Skin Temperature	Peripheral Neuropathy	Peripheral vascular status
Gatt., *et al.* [12]	Infrared camera FLIR SC7200	10g Semmes Weinstein monofilament	Ankle Brachial Pressure Index (ABPI) Spectral Doppler Waveform Analysis
Gatt., *et al.* [30]	Infrared camera FLIR SC7200	10g Semmes Weinstein monofilament	Ankle Brachial PressureIndex (ABPI) Spectral Doppler Waveform Analysis
Carabott., *et al.* [13]	FLIR SC630 uncooled bolometer camera	10g Semmes Weinstein monofilament	Ankle Brachial Pressure Index (ABPI) Spectral Doppler Waveform Analysis Toe Brachial Pressure Index (TBPI)
Ilo., *et al.* [4]	Infrared camera FLIR A325sc	No Information Given (NIG)	Ankle Brachial Index Bilateral brachial blood pressures Toe pressure (TP) Duplex Ultrasound Flow Measurement Magnetic Resonance Angiography (MRA) Digital Subtraction Angiography (DSA)
Chatchawan., *et al.* [15]	Ti10 Fluke Thermal Imaging Camera	Thai version of the Michigan Neuropathy Screening Instrument (MNSI) (cut off point was set for a score of ≥ 2.5)	Ankle Brachial Index using an automated oscillometry Omron VP-1000 Vascular Profiler

Huang., *et al.* [5]	Digital infrared thermal image system Spectrum 9000-MB series	Neuropathy not tested (NNT)	Nicolet VasoGuard ABI Segmental blood pressure measurement
Hayashi., *et al.* [9]	Non-contact thermometer ThermoFocus 01500A3	Neuropathy symptom score Neuropathy disability score	Form PWV/Ankle Brachial Index Limb arterial ultrasonography SSD-550 SV
Nagase., *et al.* [27]	IR thermography Thermotracer TH5108ME	NNT	Ankle Brachial Index (ABI) Toe brachial index (TBI) using form pulse-wave velocity/ABI (PWV/ABI) BP-203RPEII
Mori., *et al.* [29]	IR thermography Thermotracer TH5108ME	Semmes Weinstein mono-filament Vibratory sensation test Achilles tendon reflex	Ankle Brachial Index (ABI) Toe brachial index (TBI) using form pulse-wave velocity/ABI BP-203RPEII

Table 1: Outcome Measures utilized in the included studies.

Investigations on changes in blood flow and the effects on skin surface temperature

Comparisons of thermal patterns between different diabetic populations and healthy adults

The four studies [4,12,15,30] investigating thermal patterns in the feet in different diabetic populations have shown conflicting results. In a study by Ilo., *et al.* [4], patients with type 1 (T1) and type 2 (T2) DM with angiopathy were found to have the lowest mean temperature on the plantar and dorsal aspect, similar to healthy adults and to individuals with diabetes but without complications. This trend of thermal patterns was not observed in a study published by Gatt., *et al.* [12]. The authors reported higher mean resting forefoot skin temperatures in patients with T2DM with PAD (severe PAD: monophasic waveforms and ABPI < 0.6), when compared to DM individuals without neuropathy or PAD [12].

In the study by Gatt., *et al.* [30], thermal patterns in varying study populations living with diabetes were compared: non-complicated diabetes (presenting with DM but no significant medical comorbidities and/or complications), DM with PAD (severe PAD: ABPI < 0.6 and monophasic Doppler spectral waveforms at the ankles, but no neuropathy), DM neuropathy (presenting with positive 10-gram monofilament at any one of the ten tested sites and/or reduced vibration perception threshold measured with a tuning fork and an ABPI between 0.9 and 1.3) and DM neuroishaemia (presenting with an ABPI < 0.9 and neuropathy) with healthy adults. Gatt., *et al.* [30] followed the same study protocol of Gatt., *et al.* [12] and investigated the same ROI's which were the plantar aspect of all toes and forefoot, however the forefoot was further divided into the medial, central and lateral regions [30]. The authors reported no significant differences between healthy adults and individuals with diabetes without complications, or between participants living with diabetes and with PAD, neuropathy and neuroischaemia. When participants were further divided into two groups: "healthy group" (healthy adult and DM without complications) and "complications group" (DM with PAD, DM with neuropathy and DM with neuroischaemia), higher mean temperatures were found in the forefeet and toes in the "complications group". Whilst neuropathic feet have been previously reported as being warmer when compared to healthy feet, in the study by Gatt., *et al.* [30], both neuroischaemic and ischaemic feet were also found to exhibit the same trend.

Ilo., *et al.* [4] did not report this trend of findings in their study, as the mean temperatures significantly differed between subgroups of DM without complications and DM with angiopathy, neuropathy and neuroischaemia. In fact, mean temperatures were highest in DM with neuroischaemia followed by neuropathy when compared to healthy adults, however, this was not seen in the DM group with angiopathy when compared to healthy adults and non-complicated DM. Moreover, when investigating healthy adults alone (control group) versus the different study populations of individuals with diabetes (DM group: DM with ischeamia, DM with neuropathy and DM with neuroischaemia), the latter generally had warmer feet on the plantar aspect of the foot, with significantly higher temperatures ($p < 0.001$) [4]. A greater range in temperatures was also seen in the DM group (range of 21.5°C to 38.6°C) when compared to the control group (22.5°C to 34.3°C) [4].

In contrast to the findings presented by Ilo., *et al.* [4], Chatchawan., *et al.* [15], reported significantly lower foot skin temperatures ($p < 0.05$) (1.5 - 3°C) in the DM group with neuropathy (DPN) (a cutoff point score of ≥ 2.5 in the physical assessment section of the MNSI) when compared to the non-DPN group.

These temperature differences were considered to be clinically significant with a temperature difference greater than 2.2°C [25]. In contrast with other studies, Chatchawan., *et al.* [15] chose to investigate more areas of the plantar aspect of the foot by focusing on six specific areas: hallux, lesser toes, medial metatarsal head (MMH), lateral metatarsal head (LMH), midfoot and rearfoot. Thermal images were taken three times supine at rest within five minutes, however the participants did not acclimate prior to any investigations [15].

Whereas all the four shortlisted studies [4,12,15,30] explored thermal patterns in both feet between different study populations living with diabetes and healthy adults, Ilo., *et al.* [4] also investigated side-to-side skin temperature comparisons between feet in the group of individuals with diabetes and control group. The results revealed significant differences at all measurement sites ($p < 0.001$). Therefore, the mean side-to-side skin temperature differences between feet were greater in DM participants (range, 0.0°C-10.2°C) than healthy participants, and the temperatures were more constant between feet [4]. The healthy participants however, still showed a wide range in skin temperature (0.0°C-3.1°C) [4]. Moreover, within the DM group, the side-to-side difference between feet was highest in neuropathic (plantar side: 1.9°C ± 1.4°C; dorsal side: 1.6°C ± 1.7°C) and in neuroischemic feet (plantar side: 1.9°C ± 1.7°C; dorsal side: 1.5°C ± 1.3°C), and was lowest in participants with angiopathy (18%) (plantar side: 0.8°C ± 0.6°C; dorsal side: 0.9°C ± 0.8°C).

Comparisons of thermal patterns in PAD and non-PAD groups

Huang., *et al.* [5] and Hayashi., *et al.* [9], compared skin temperature measurements between PAD (ABI of ≤0.9) and non-PAD participants [5] and between PAD (ABI of ≤0.9) participants themselves [9]. In both studies the authors focused on participants who fulfilled pre-defined high risk criteria including adults under 50 years of age who live with diabetes and an atherosclerosis risk factor, such as smoking [9] and individuals over 70 years of age [5,9]. Therefore, not all participants had diabetes, rendering it difficult to compare these two studies with other studies where categories of individuals living with diabetes were investigated [4,12,30].

In the dynamic study by Huang., *et al.* [5], results of cutaneous temperature in PAD (n = 20) and non-PAD (n = 31) participants were recorded and imaged after a ten-minute acclimatization period in a supine position thrice supine at rest (before exercise), immediately after exercise (exercise-induced temperature change: post exercise minus pre exercise temperature) and one minute post-exercise [5]. All thermography images were taken at the shin and plantar aspect of the foot. At rest, similar temperatures were recorded between the PAD and non-PAD participants at the shins (32.6 ± 0.86, 32.6 ± 0.91 respectively) and soles (31.0 ± 1.75, 30.4 ± 2.37 respectively). During the six-minute walk test (6MWT), PAD participants walked shorter distances (218 ± 92 m vs 356 ± 102 m; $p < 0.001$), with 14 participants reported having claudication, while seven participants did not manage to complete the 6MWT. After the 6MWT (post-exercise), the cutaneous temperature decreased dramatically at the sole (from 31.0°C to 29.7°C; $p < 0.001$) in PAD participants (stenotic arteries) and increased slightly at the shin (from 32.6°C to 32.9°C; $p < 0.001$) in non-PAD participants (patent arteries) [5]. Moreover, the exercise induced temperature change at the sole was different in PAD vs non-PAD participants (-1.25°C vs -0.15°C; $p < 0.001$ respectively), meaning that the PAD group had the largest decrease in temperature at the sole, as in the non-PAD group the temperature was maintained at the sole [5]. At

post-exercise temperature recovery, the pattern did not differ between the two groups (PAD vs non-PAD) [5].

In another study, Hayashi., *et al.* [9] compared PAD participants, stratified according to severity of the symptoms. Participants acclimatised for thirty minutes before thermal images were taken, in a recumbent position with legs at heart level for at least five minutes. In this study, the authors recorded skin temperatures at the first and fifth metatarsal heads and the heel, thus representing the different angiosomal areas (medial plantar arterial angiosome, lateral plantar arterial angiosome, and lateral calcaneal branch area of peroneal artery, respectively). The limbs that were studied were split into four groups according to symptoms by the Fontaine Classification (229 limbs in Fontaine I which were asymptomatic, 81 limbs in Fontaine II with claudication, 24 limbs in Fontaine III with ischaemic rest pain, 11 limbs in Fontaine IV with ischaemic ulceration/necrosis) [9]. The foot skin temperatures were measured at the time of ABI measurement and limb ultrasonography. A total of 292 limbs had an ABI ≥ 0.91, 50 limbs had an ABI ≤0.90 and the ABI of 3 limbs were not performed due to calcification, whereas 85 limbs had stenosis or occlusion and 70 limbs had arterial calcification in the lower-limb arteries diagnosed by ultrasonography. Limbs with ABI ≤ 0.90 revealed lower skin foot temperatures than limbs with ABI ≥ 0.91 [9]. Likewise, limbs with stenotic/occluded lower-limb arteries had lower skin foot temperatures than limbs without [9]. By classification of Fontaine classes, the average ABI within each stage was 1.12 ± 0.10 in Fontaine I, 0.92 ± 0.20 in Fontaine II, 0.89 ± 0.24 in Fontaine III, and 1.09 ± 0.21 in Fontaine IV [9]. The ABI of Fontaine I was significantly higher than Fontaine II, III, and IV ($p < 0.0001$, $p < 0.0001$, $p < 0.005$, respectively) and there was no significant difference in ABI between Fontaine II, III, and IV [9]. The average lowest skin temperature of each group was 31.2°C ± 1.9°C in Fontaine I, 30.2°C ± 1.9°C, in Fontaine II, 28.3°C ± 2.6°C in Fontaine III, and 29.7°C ± 2.4°C in Fontaine IV. The skin temperature of Fontaine I was significantly higher than Fontaine II, III, IV ($p < 0.0001$, $p < 0.0001$, $p < 0.05$; respectively). Moreover, the skin temperature of Fontaine II was also significantly higher than for Fontaine III patients ($p < 0.0005$). However, the skin temperature of Fontaine IV was not lower than Fontaine III.

Comparisons of thermal patterns using angiosome-targeted thermography

Whilst some articles [12,26,30] extracted temperatures at specific points (ROIs) at the forefoot and toes, other articles utilized angiosome-targeted thermography [13,27,29]. The angiosome concept was introduced by Taylor and Palmer [31]. Angiosomes are areas in feet that are supplied by specific arteries [13]. There are six angiosomes of the foot and ankle that are supplied by three main arteries: the posterior tibial, anterior tibial and peroneal artery [4]. The plantar aspect of the foot is supplied by the posterior tibial artery [4], where Attinger., *et al*. [32] proposed four angiosomes in this area (the medial and lateral plantar artery angiosome, and the medial and lateral calcaneal artery branch of the peroneal artery angiosome [27]. The dorsal side is supplied by the anterior tibial artery and the peroneal artery supplies the lateral side of the calf and calcaneus (the calcaneal branch and anterior perforating branches) [4,31,32]. The surrounding angiosomes are known to be connected by 'choke vessels', which act as a safety valve, if the main source artery is not functioning as it should [31,32].

Carabott., *et al*. [13] investigated the thermal images of the plantar aspect of the feet and divided them into regions, namely the hallux, medial and lateral forefoot areas, corresponding to the angiosomes as per Kagaya., *et al*. [33]. The mean resting temperatures of all angiosomes were higher in the PAD group compared to the non-PAD group, after a 15-minute acclimatization period performed in a supine position [13]. Multiple images were captured when supine on the couch: first at baseline, after one-minute with the limbs elevated to a 20-degree angle during which images were taken at one-minute intervals for five minutes. Finally, more images were taken after one-minute with the legs lowered to a horizontal position [13]. The authors reported a significant difference in the mean initial temperature between these two groups, more specifically in the medial and lateral forefoot angiosomes ($p = 0.048$, $p = 0.049$, respectively), but not at the hallux ($p = 0.165$) [13]. When analysing the mean temperatures within the DM PAD groups, participants with mild PAD (biphasic waveforms, ABI between 0.6 and 0.9 and TBI between 0.5 and 0.7) reported higher mean temperatures when compared to DM participants with severe PAD (monophasic waveforms, ABI < 0.6 and TBI < 0.5).

Nagase., *et al*. [27] and Mori., *et al*. [29] on the other hand provide a detailed description of plantar thermographic patterns that may represent a screening option for daily foot care and surgical intervention. Both studies [27,29] explored the plantar aspect of the foot, and focused on the distal forepart, while Nagase., *et al*. [27] also included the heel. Nagase., *et al*. [27] compared a framework of conceptual classification with twenty different categories

of plantar thermographic patterns according to the foot angiosome concept between healthy participants and individuals living with diabetes without ulceration. Several investigators took part in the decision-making of allocations to the different categories. When images did not correspond to any the categories, they were classified as 'atypical'. In both studies [27,29] participants acclimatised in a supine position for fifteen minutes before thermal images were taken. To obtain the twenty different categories (I-a to V-d) the authors crossed the five distal patterns (type I-V) with the four heel patterns (type a-d) [27]. Mori., *et al*. [29] compared the thermographic patterns obtained in their previous research by Nagase., *et al.* [27], with the plantar forepart thermographic patterns found in their new and improved classification system, using an image-partitioning algorithm.

Both studies [27,29] presented wider variations in thermographic patterns between the DM group when compared to the control group. From the 258 feet of the 129 DM participants, 225 feet (87.2%) corresponded to eighteen out of the twenty categories [27], whereas in Mori., *et al.* [29] the system found six categories, therefore a new, different pattern, type 7 (Tiptoe low) was found for 198 feet. In the study by Mori., *et al*. [27] the system automatically also identified a new pattern that they named type 6 (forefoot low pattern - where the forefoot has lower temperatures than the other area) in the control group.

Both Nagase., *et al*. [27] and Mori., *et al*. [29] had the same two most frequent categories in both the diabetes and the control group. In the study by Mori., *et al.* [27], the most frequent category in the DM group was high temperatures in the whole plantar aspect (Type 2 -118 feet, 46%), followed by type 1 (butterfly pattern- 31 feet, 12%). In the control group, type 1 butterfly pattern was the most frequent, followed by type 2 (representing intact medial and lateral plantar artery angiosomes) [29]. In the study by Nagase., *et al.* [27], the feet ratio in the IIa category (intact Medial Plantar Artery and Lateral Plantar Artery in distal forepart and intact Medial calcaneal Artery and Lateral Calcaneal Artery in the heel) was significantly higher and the feet ratio in the Id category ('bilateral butterfly pattern' in the distal forepart and occluded Medial calcaneal Artery and Lateral Calcaneal Artery in the heel) was significantly lower in the diabetes group when compared to the control group.

Investigations comparing methods of blood flow assessments to determine peripheral circulatory status

The following studies [4,5,9,15] all compared various outcome measures, including skin temperature measurement to assess peripheral arterial circulation. The first researchers to explore the correlation between foot skin temperature and blood flow in patients with DPN and non-DPN, were Chatchawan., *et al*. [15]. The average ABI values for both right and left feet were 1.10 and 1.09 respectively, with corresponding average foot skin temperatures of 31.30 ^{0}C and 31.21^{0}C respectively. Moreover, the ABI values (of both feet) were lower in the DPN group when compared to the non-DPN group ($p < 0.05$) [15]. Likewise, the foot skin temperature values were lower in the DPN group when compared to the non-DPN group ($p < 0.05$) [15]. Therefore, a positive correlation was found between the foot skin temperatures and ABI values in both feet [15].

Other methods of assessment for PAD were employed to compare with IRT [4]. Mean skin temperatures (plantar and dorsal) were unexpectedly significantly higher in DM participants with abnormal Toe pressures (TP) (< 50 mmHg) when compared to the normal TP group (≥ 50 mmHg) ($p < 0.001$). DM participants were stratified by TP analysis using a cutoff value of 50mmHg, that were subdivided into two groups: normal/mild (TP ≥ 50 mmHg, n = 130 ft, 56%) or severe (TP < 50mmHg, n = 80 ft, 35%). Similarly, a higher foot skin temperature (30.2°C ± 1.9°C, dorsal side) in DM participants with an open anterior tibial artery together with stenosis or occlusion of the other crural arteries (dorsalis pedis angiosome) (n = 29), compared to participants without stenotic or occluded crural arteries (n = 39, 29.1°C ± 1.7°C, $p = 0.02$) [4]. Magnetic Resonance Angiography (MRA) or Digital Subtraction Angiography (DSA) was used to analyse angiosomes by collecting data on atherosclerotic lesions in the arteries of the lower limb (120 feet in the DM group) [4]. However, a higher plantar foot skin temperature (open plantar angiosomes: 28.3°C ± 2.1°C vs open crural arteries: 27.4°C ± 2.2°C, P = .11) was found in DM participants with an unrestricted posterior tibial artery (plantar angiosomes, n = 27) [4]. Therefore, IRT revealed differences between angiosome areas [4].

Furthermore, the dynamic study by Huang., *et al.* [5], compared exercise-induced temperature change (eTC) values with ABI. The eTC. changes at the sole were positively correlated with ABI (PAD severity; Spearman correlation coefficient = 0.48, $p < 0.001$, 95%

CI, 0.21-0.70). According to the receiver-operator characteristic (ROC) curve, the ideal cut-off point for identification of PAD diagnosis was 0.99°C for eTC., which showed 81.7% sensitivity and 65.0% specificity [5]. In support of a similar association reported in other research between ABI and skin temperatures, Hayashi., *et al.* [9], discovered that ABI showed significant positive correlation with foot skin temperatures in all three locations (first metatarsal head representing Medial Plantar Artery, fifth metatarsal head representing Lateral Plantar Artery and heel representing lateral calcaneal branch area of peroneal artery). Receiver operating characteristic (ROC) curves were repeatedly generated for ABI values and also skin temperature levels with ultrasound-verified stenosis/occlusion as criterion for PAD diagnosis. For optimal sensitivity and specificity of skin temperature level, the best cutoff value at all areas (first, fifth metatarsal head and heel areas) were 31.1°C, 31.0°C, and 31.4°C, with AUC (area under the ROC curve) of 0.645, 0.618, and 0.655, respectively [9]. The optimal cutoff value for the lowest skin temperature of the 3 angiosomal areas was 30.8°C with AUC of 0.644 and for ABI value it was 1.06 with AUC of 0.792 [9]. Diagnostic efficiency for lowest level of the three angiosomal areas showed sensitivity/specificity of 67%/62% using a cutoff of the lowest skin temperature < 30.8°C, while for the ABI it showed sensitivity/specificity of 41%/94%, using cutoff 0.90 [9]. From the 85 limbs with ultrasound-verified PAD, thirty-seven limbs (43.5%) had ABI of 0.9, while the other 48 limbs showed ABI of 0.91. However, fifty-seven (67.1%) of the 85 ultrasound-defined PAD limbs showed the lowest skin temperature of 30.8°C. Therefore, the use of the lowest skin temperature of 30.8°C detected a larger number of ultrasound-defined PAD limbs than the use of ABI 0.90.

Discussion

The veracity of DM foot temperatures

The general held view is that higher foot temperatures are associated with inflammation, infection, venous problems and diabetic peripheral neuropathy, whereas lower foot temperatures are associated with decreased perfusion to the lower limb in individuals living with diabetes [5,16,27]. In more recent studies [12,13,30], higher temperatures were recorded in patients with DM and PAD, similar to other complications of DM such as neuropathy and neuroischaemia. While in other studies, [4,5,23], a decrease in foot temperatures were found in patients with PAD when compared to those without PAD.

It is natural to assume that patients with certain comorbidities such as diabetes with complications, for instance PAD would have colder extremities than healthy adults, due to less blood reaching the peripheries. However, in the study by Gatt., *et al.* [30] it was found that the higher the foot temperatures of diabetes patients, the higher the probability that it is affected by PAD, neuroischaemia or neuropathy. Therefore, the results of these studies [12,13,30], revealed that in diabetes, a cooler foot temperature does not necessarily signify a less perfused limb when compared to the contralateral limb, and neither that a warm foot implies a well perfused limb [12]. Even though it is standard clinical practice to palpate the foot temperature differences in patients with diabetes, one must not immediately assume the possible evidence of ischaemia when a cooler limb is detected and vice versa. It has been suggested that clinicians should not rely on temperature assessment to assess perfusion in patients with diabetes, as this interpretation may be erroneous [12].

Though this novel data of higher temperatures in the feet of patients with diabetes and PAD is counterintuitive, a plausible explanation for this may be the disruption of normal thermoregulatory mechanisms in the feet [12,13,30], which may be affected by both neuropathy and PAD [30]. However, Sun., *et al.* [22] mention that little is known about the range of abnormal thermoregulation in DM patients, that present for screening and management. It is hypothesized that local ischaemia may lead to the alteration of sympathetically mediated noradrenergic vasoconstriction, which in turn leads to increased flow to the cutaneous vessels, rather than through the deeper nutritive vessels [4,12,12,30]. This then leads to higher heat emissivity [12,13,30], and therefore an increase in skin temperature is seen [12]. The skin in the soles, palms and lips is called glabrous skin, and is solely innervated by sympathetic noradrenergic vasoconstrictor nerves, while non-glabrous skin is also innervated by sympathetic vasodilator nerves [12]. Diabetes mellitus has been linked to various functional abnormalities of the microvasculature, including increased arteriovenous shunting [4]. Arteriovenous anastomoses (AVA) are thick walled, low resistance conduits that allow high flow rates directly from arterioles to venules [4,12,30], which are numerous in glabrous skin and are richly innervated by sympathetic vasoconstrictor nerves [4,12]. Depending on whether AVAs are open or closed, substantial changes occur in blood flow [33]. These changes in blood flow

have been reported to lead to capillary hypoperfusion, with the likelihood of wound healing impairment [34,35,36]. In diabetic patients with moderate PAD, this hypothesis may possibly explain the higher foot temperatures found [12]. Moreover, miniscule changes in skin blood flow can lead to big changes in heat dissipation [12]. In fact, an increase of only 8 ml/100 ml s/min in blood flow leads to double the amount of heat transfer to the environment [36]. On the other hand, it is suggested that in patients with critical ischaemia, the perfusion to the foot is so diminished that notwithstanding vasodilatation the foot may still be cooler [12]. This would elucidate the clinical dusky cool foot [12].

Other possible reasons for these counterintuitive results in these studies may be the small number of recruited participants [13] or the lack of screening for early subclinical small fibre autonomic neuropathy which perhaps may increase thermal emissivity in diabetic patients [12]. Only large fibre somatic nerve function was tested with the monofilament, however, no studies have assessed the impact of autonomic neuropathy on cutaneous temperature as measured by infrared thermography [12].

In the study by Ilo., *et al.* [4], patients with T1 and T2DM with angiopathy were found to have the lowest mean temperature compared to healthy adults and non-complicated DM patients, which is contrary to the results presented by Gatt., *et al.* [12] and Carabott., *et al.* [13]. However, the study by Ilo., *et al.* [4] entailed a heterogenous population, an extensive number of limitations and certain factors that are known to interfere with thermal patterns in the feet, such as active infection, were not excluded. Moreover, participants classified as 'healthy' adults had a number of previous complications such as vascular reconstruction for abdominal aneurysms and vascular injuries where one participant had undergone a previous minor amputation due to infection. Some DM participants had previously undergone major amputations, minor amputations due to atherosclerosis, infections or both [4]. The participants that had DM were older and had more comorbidities when compared to the 'healthy' participants [4]. Moreover, ABI could not be measured in one-fourth of the DM participants [4]. Therefore, these reasons may have influenced the findings, and thus may have contributed to why DM with PAD presented with lower foot temperatures [4].

Even though Ilo., *et al.* [4] did not agree with Gatt., *et al.* [12], and Carabott., *et al.* [13], they had similar trends to Gatt., *et al.* [30] with higher temperatures in participants with neuropathy and neuroischaemia. This was also seen in Bagavathiappan., *et al.* [23], where foot skin temperatures of DPN participants were higher than non-DPN participants. In contrast, Chatchawan., *et al.* [15] disagreed, however similar results to their study were seen in Lavery., *et al.* [25]. A possible reason as to why lower temperatures were found in participants with DPN, in studies like Chatchawan., *et al.* [15] and Lavery., *et al.* [27] is that vasodilation is usually impaired, which in turn leads to deficiencies in microcirculation [15]. The neuropathic foot is generally known to exhibit high foot skin temperatures that indicate increased cutaneous blood flow [38]. Although some literature clearly suggests this [12,13], they are not in agreement with other published studies [15,25]. Therefore, one must not assume that neuropathic feet are always warmer. Many authors [38,39,40,41] explain that neuropathy contributes to the increase and instability of temperatures at the plantar aspect of the foot. Furthermore, a chronic increase in foot skin temperature in participants with DPN may possibly be an increase in arteriovenous shunt flow [38,40]. Lavery., *et al.* [25] and Armstrong., *et al.* [24] mention that an acute increase in foot skin temperature may be a predisposing sign of pre-ulcer inflammation. However, in a more recent study [30], the authors stated that a rise in temperature does not necessarily imply impending ulceration, but simply the development of diabetic foot complications such as peripheral neuropathy, ischaemia or both. This is also further reported by Sun., *et al.* [22].

Temperature differences between contralateral feet are essential parameters when identifying unilateral disease [24]. It has been suggested that when a temperature difference between the two feet is higher than 2.2°C, it is an indication of pathology in individuals living with diabetes [25]. Therefore, mean side-to-side skin temperature differences between feet may be a useful tool when creating IRT software solutions for automatic recognition of skin temperature abnormalities. However, there still is a need for further investigations of the variation limits and tendencies in skin temperature mapping, and how this corresponds with patient's symptoms, conditions, and stages of disease [4].

The veracity of foot temperatures within PAD and non-PAD groups

Since lower extremity temperature largely depends on peripheral blood flow, thermography has been thought to be a useful tool in assessing vascular abnormalities [24]. However, the different

levels of stenosis in PAD participants did not result in different temperature gradients between the shin and the sole [5]. In this study, the PAD group were older and had a history of smoking, when compared to the non-PAD group and different participants had different clothing and shoes, which could have interfered with the results [5]. In contrast, Bagavathiappan., *et al.* [23] reported that temperature gradients are seen in the affected areas of patients with vascular abnormalities and ischemic gangrene, with the temperature being 0.7°C to 1°C higher than normal area due to slow blood circulation [23]. In their study, participants had both arterial and venous vascular diseases, therefore the rest temperature gradient needed to be investigated further in participants with pure arterial occlusion. For this reason studies focusing on temperature changes in the plantar aspect may be more reliable.

Hayashi., *et al.* [9] reported that as the severity of PAD increased, foot skin temperature increased. However, the authors stated that foot skin temperatures might have been affected by other factors such as the surrounding temperature, wet foot skin surface, marked oedema and the participants's posture, such as sitting or elevation of lower limbs [9]. They confirm that further investigations are required to investigate the effect of increasing stenosis and decreased perfusion (and vice versa) on skin temperature [9].

Angiosome-targeted thermography

Whereas, Carabott., *et al.* [13] compared DM PAD participants with non-complicated DM participants using the angiosome concept, Nagase., *et al.* [29] and Mori., *et al.* [29] compared plantar thermographic patterns by the angiosome-concept in healthy and DM participants without foot ulcers using a computer-based classification system. Detecting higher temperatures in certain areas might be useful in targeting angiosome-based revascularization to prevent ulceration [13]. Thermography allows for visualisation of a whole image of plantar temperature distribution, and was not fully appreciated in previous studies where only temperatures of several anatomical landmark points or areas were being measured [27]. A newly developed classification of the angiosome-concept system of plantar thermographic patterns by Nagase., *et al.* [27], was deemed too subjective and complicated for clinicians to use and it has not been fully elucidated to what extent the individual variations of these patterns demonstrate different trends between these two cohorts [29]. A novel classification system according to the angiosome-concept was proposed, where the authors objectively allocated plantar thermographic images by using an image-partitioning algorithm [30]. From this review it was observed that despite using different classification systems, DM participants exhibited wider variations in angiosome-targeted thermographic patterns compared to the control group with temperature elevation in neuropathic feet [13,27,29].

The correlation between ABI, TBI and thermography

Three studies [5,9,15] concluded that foot skin temperature correlates positively with blood flow evaluated by ABI, while Ilo., *et al.* [4] reported conflicting results when using TP and MRA or DSA to evaluate blood flow. Possible reasons could be: Firstly, whereas Chatchawan., *et al.* [15] compared ABI with skin temperatures in DPN and non-DPN participants, Ilo., *et al.* [4] measure neuropathy which may have influenced the results. Contrary to clinical expectation, higher temperatures were found in the severe PAD group, however as mentioned previously, a lower temperature must not lead to the assumption that the limb is less perfused and vice versa [12], indicating that current evidence is still unclear.

Some data of the angiosome analysis was missing due to missing toes or immeasurable TP (n = 26 ft, 11%) [4]. Moreover, thirty participants (54%) of the one-fourth diabetic participants who had immeasurable ABI's, had critical limb ischaemia (CLI). However, they managed to perform IRT on all of the participants that revealed tendencies which may be related to ABI and TP finding [4]. Chatchawan., *et al*. [15] explain that foot skin temperatures does reflect peripheral vascular status in individuals living with diabetes, signifying a positive correlation between the two. Reduced blood flow, which in turn leads to vasoconstriction of the blood vessels at the peripheries lead to a decrease in skin temperature [15]. Furthermore, it seems that according to which artery is patent or stenotic/occluded, the temperature varied without consistency [4]. This study presented with a number of limitations that need to be taken into consideration when analyzing and interpreting results [4].

Since temperatures were found to be higher or lower with no consistency in participants with DM with PAD, methods to evaluate blood flow such as ABI, TP and MRA or DSA seem to be a poor choice when used alone. Moreover, many PAD limbs remain undiagnosed with ABI method of assessment. Even though it is reported to have high specificity, it lacks in its sensitivity. Huang., *et al.*

[5] and Hayashi., *et al.* [9] investigated specificity and sensitivity of both skin temperature measurement and ABI, besides identifying whether there is a correlation between the two. Huang., *et al.* [5] reported that etc. were correlated with PAD severity (ABI) which is an indicator of PAD severity. A major limitation was that angiography was not utilized to confirm stenotic severity, level or collateral circulation [5], therefore, different stenotic patterns or collateral circulation that could have influenced the dynamic temperature changes, could not be determined [5]. Although all participants had an ABI ≤1.3, the authors could not rule out non-compressible vessels especially in participants with ESRD. Moreover, since a normal ABI presents in patients with isolated pedal arch stenosis, these could have been inappropriately classified in the non-PAD group [5]. The etc. ideal cut off point for PAD screening was of 0.99°C that was revealed by the ROC, which showed 81.7% sensitivity and 65.0% specificity. However, Huang., *et al.* [5] did not investigate the ideal cut off point of ABI to then compare sensitivity and specificity between the two outcome measures.

ABI 0.90 in the study by Hayashi., *et al.* [9] had a specificity of 94% as opposed to sensitivity of only 44% for PAD diagnosis. Whereas sensitivity/specificity of skin temperature measurement was 67%/62% using a cutoff of the lowest skin temperature < 30.8^{0}C. The results of Hayashi., *et al.* [9] are in agreement with recent studies that current PAD diagnostic criterion of ABI 0.90 takes advantage of a high specificity at the expense of sensitivity [43,44]. According to Hayashi., *et al.* [9], participants with less than 30.8°C in at least one of the three angiosome areas have more of a chance of having PAD. In eighty-five limbs with stenosis, only thirty-seven limbs (43.5%) showed ABI 0.90, as opposed to fifty seven limbs (67.1%) that showed the lowest skin temperature < 30.8C [9]. This can result in numerous amounts of underdiagnosed PAD participants, indicating the possibility of detecting more patients with PAD by using skin temperature measurement [9]. Skin temperature measurement is simple, easy, in-expensive and a better method for PAD screening, however, exact diagnostic specificity does not surpass the ABI [9], instead it can be used as an alternative to ABI as it is unaffected by arterial calcification. On the contrary, if the skin temperature is not low in these patients with PAD associated symptoms, it is possible that a decrease in skin temperature may not be detected, due to diabetic foot infection [9]. It is therefore best to combine ABI with skin temperature measurement to detect PAD [9].

Conclusion

By detecting skin temperature changes in the lower-limbs, infrared thermography (IRT) offers another easy, non-invasive, indirect method to assess peripheral arterial circulation that may be used as an adjunctive tool. As it stands, even though thermography has several advantages, it has not yet proven to be the main protagonist when it comes to diagnosis of PAD. Arguably, ABI is still the most reliable modality to diagnose and evaluate PAD for the time being, but simultaneously, ABI and thermography are useful to diagnose 'the whole picture'. We look forward to the potential role thermography may have in the evaluation and screening of PAD, that may eventually be adopted at a primary care level for early detection of PAD and limb salvage. From the several studies reviewed in this paper, unexpected higher temperatures seem to be present in the feet of DM patients with PAD, therefore the general assumption that lower skin foot temperatures are usually found in the presence of PAD, should be reconsidered. Various studies have utilized thermography to measure skin foot temperatures at rest, however there is a gap in literature when it comes to dynamic thermal data acquisition that has yet to be explored in more detail. Continuous temperature monitoring seems to be the way forward, however further studies are warranted in this area.

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