Accepted Manuscript

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PII: S0010-4825(17)30356-6

DOI: 10.1016/j.compbiomed.2017.10.030

Reference: CBM 2823

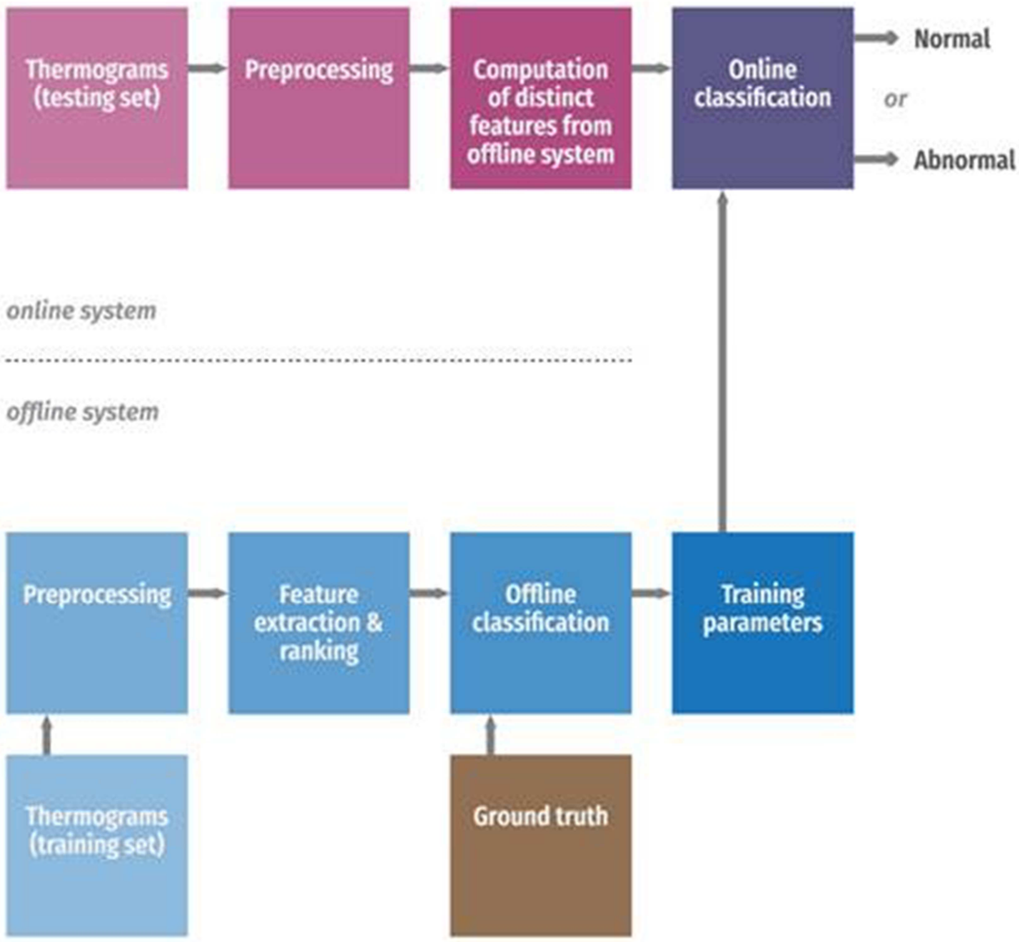
To appear in: *Computers in Biology and Medicine*

Received Date: 8 August 2017

Revised Date: 24 October 2017

Accepted Date: 25 October 2017

Please cite this article as: M. Adam, E.Y.K. Ng, J.H. Tan, M.L. Heng, J.W.K. Tong, U.R. Acharya, Computer aided diagnosis of diabetic foot using infrared thermography: A review, *Computers in Biology and Medicine* (2017), doi: 10.1016/j.compbiomed.2017.10.030.


Thermograms (testing set)
Preprocessing
Computation of distinct features from offline system
Online classification
Normal
or
Abnormal
online system
offline system
Preprocessing
Feature extraction & ranking
Offline classification
Training parameters
Thermograms (training set)
Ground truth

Computer Aided Diagnosis of Diabetic Foot Using Infrared Thermography: A Review

Muhammad Adam[1*], Eddie Y K Ng[2], Jen Hong Tan [1], Marabelle L. Heng[5], Jasper W.K. Tong[6], U Rajendra Acharya[1,3,4]

[1]Department of Electronics and Computer Engineering, Ngee Ann Polytechnic, Singapore.
[2]School of Mechanical and Aerospace Engineering, Nanyang Technological University, Singapore.
[3]Department of Biomedical Engineering, School of Science and Technology, SIM University, Singapore.
[4]Department of Biomedical Engineering, Faculty of Engineering, University of Malaya, Malaysia.
[5]Podiatry Department, Singapore General Hospital.
[6]Allied Health Office, KK Women's and Children Hospital.

*Corresponding Author
Postal Address: [1]Department of Electronics and Computer Engineering, Ngee Ann Polytechnic, Singapore 599489
Telephone: +65-64607887; Email Address: muhdadam@hotmail.com

ABSTRACT

Diabetes mellitus (DM) is a chronic metabolic disorder that requires regular medical care to prevent severe complications. The elevated blood glucose level affects the eyes, blood vessels, nerves, heart, and kidneys after the onset. The affected blood vessels (usually due to atherosclerosis) may lead to insufficient blood circulation particularly in the lower extremities and nerve damage (neuropathy), which can result in serious foot complications. Hence, an early detection and treatment can prevent foot complications such as ulcerations and amputations. Clinicians often assess the diabetic foot for sensory deficits with clinical tools, and the resulting foot severity is often manually evaluated. In recent years, various infrared thermography-based computer aided diagnosis (CAD) systems for diabetic foot have been proposed. Infrared thermography is a fast, nonintrusive and non-contact method that allows the visualization of foot plantar temperature distribution. In this paper, the diabetic foot, its pathophysiology, conventional assessments methods, infrared

thermography and the different infrared thermography-based CAD analysis methods are reviewed.

Keywords: foot, diabetes, neuropathy, atherosclerosis, plantar, infrared image

1. Introduction

Diabetes mellitus (DM) is a serious endocrine disorder characterized by chronic high blood glucose (hyperglycemia) caused by deficiency in the secretion of insulin, or ineffective use of insulin by the body (1). In general, insulin is produced by beta cells of the pancreas to maintain normal blood glucose level in the body. The characteristic symptoms of DM are weight loss, blurred vision, dehydration and frequent urination. Prolonged uncontrolled DM may lead to specific complications such as nephropathy leading to kidney failure, retinopathy resulting in blindness, and neuropathy with increased risk of ulceration, Charcot foot development and amputation (1). These complications may affect the quality of life, cause disability and even early death.

According to the World Health Organization (WHO), an estimated 3.7 million deaths were reported in 2012 due to high blood glucose levels (2). In this, 1.5 million deaths were directly caused by diabetes and remaining 2.2 million deaths were due to heart diseases, renal disease and tuberculosis in relation to high blood glucose. Further, majority of these deaths (43%) happen prior to the age of 70, which are considered as premature and accounting for 1.6 million global deaths (2). In any case, diabetic foot ulcers (DFUs) are among the most common foot complication that critically affect about 15% of the diabetic population (3). Moreover, diabetic patients are 12% to 25% more likely to develop foot ulcers in their lifetime (4, 5) with nearly 85% of the lower limb amputations due to non-healing and infected foot ulcers (6). The risk factors leading to the development of foot ulcers are primarily neuropathy and arterial disease in the lower limb (7). It is approximated that 50% of the diabetes patients with foot ulcer will have neuropathy, nearly 20% of them will have lack of arterial blood perfusion as illustrated in Figure 1, and almost 80% of them will have both conditions (8, 9).

The diabetic foot wounds are many times develop in patient who at least have two risk factors simultaneously, with peripheral neuropathy as the major one (10). Nearly 66% of the diabetic patients are at risk of developing peripheral neuropathy (11). Because of this neuropathy, the foot sensation is impaired and may leads to foot deformity which causes gait abnormalities (10). For diabetic patients with neuropathy, foot ulcerations may develop due to a minor wound. This minor wound can be caused by bruise, blister, improper footwear or even barefoot walking. Equally important, the foot may also experience unnatural biomechanical loading as result of insensitive and deformed foot, and limited joint movement. This yields large pressure on certain regions which in turn results in the formation of callus (dense skin) (10). Generally, the further increase in loading results in bleeding into the skin and ultimately ulcerations. Consequently, the wound healing process on the insensitive foot will be impaired if patients continue to walk.

Typically, diabetic patients will have their feet screen at least once annually to determine patients with at risk foot and to search for signs of peripheral arterial disease or peripheral neuropathy. Minimally, the examination and inspection of the feet comprised of foot and medical history examination and, neuropathy assessment (10). The foot and medical history examinations includes health conditions of the vascular, skin, bone and joint, and the previous history of ulceration or amputation (10). For neuropathy assessment, the following methods are being conducted: enquiring on pain or tingling symptoms in the lower extremities; pressure perception using Semmes-Weinstein monofilaments; vibration perception using 128 Hz tuning fork; discrimination using pin prick on dorsum of foot superficial; tactile sensation using cotton wool or by lightly touching the toes tips with index fingers; and assessing the Achilles tendon reflexes (10).

The advancement in infrared (IR) camera technology, in terms of resolution and response time, has transformed the field of measuring temperature and is now being extensively used for medical purposes (12). The IR techniques allow rapid capturing of large number of pixels, or picture elements (13). The individual pixels at the respective points denote the temperature. Collectively, these pixels create an image illustrating the surface temperature distribution. Essentially, temperature changes are linked to certain diseases detected by viewing the temperature distribution on the body using IR thermography. The IR thermography has been employed in various medical studies, namely vascular disorders (14-17), rheumatoid arthritis (18), breast cancer (19-23), muscular pain (24, 25) and dry eye (26, 27). Also, infrared thermography has been widely used for diabetes detection such as to analyze body temperature variations (28) and metabolic parameters (29), estimate blood glucose (30), detect temperature variations in hypoglycemia (31), and compare infrared thermography with biochemical assay methods (32). Also, IR thermography is used in many diabetic foot studies as tabulated in Table 1, 2,3, and 4. These diabetic foot studies are based on the temperature distribution of the plantar foot that rely on blood perfusion. In conditions, when blood circulation is significantly reduced (ischemic), especially at the peripheral limbs, the temperature pattern will change (33).

In this review, the aim is to highlight the potential of infrared thermography in the medical field as a temperature measurement method. The IR thermogram based CAD system for diabetic foot and provide an overview on the various proposed diabetic foot studies using different analysis methods on the foot plantar thermograms. These analysis methods are categorized into four types of analysis: separate lower limb, asymmetric temperature, temperature distribution and, independent thermal and physical stress.

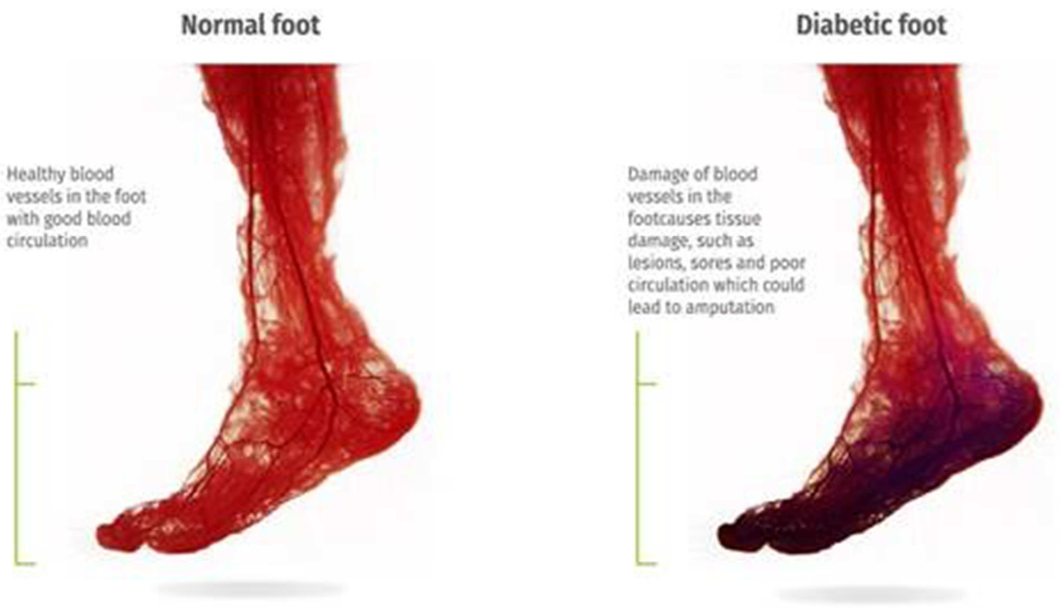


Figure 1: Illustrations of blood circulation in normal and diabetic foot.

2. Infrared thermography

The human beings are homeotherms with the capability to sustain inner body temperature regardless of the variations in the surrounding temperature by altering heat loss and heat production rates (34-36). Indeed, this is achieved by the thermoregulatory mechanism of the human body, namely behavioral adjustments to the surrounding temperature and autonomic nervous responses. The autonomic nervous responses include the cutaneous vasomotor and sweating responses for heat loss (34). Therefore, any unusual changes to the body temperature can be an indication of a disease.

The first use of thermobiological diagnostic began around 480 BC, discovered in the writings of Hippocrates (37). Basically, color changes of the mud placed on the abdomen of a patient is studied while drying. The regions, where the mud is observed to have dried first are considered to indicate underlying pathology in that body part.

Many physical achievements have elucidated the reasons for this phenomena throughout history. The discovery and acquisition of thermal radiation from the human body by William Herschel in the early 1800s was a huge stepping stone (38). Based on the physical laws, any object which includes the human body, with a temperature higher than absolute zero (-273 K) emit the electromagnetic radiation, called infrared radiation (39). In addition, the human skin has an emissivity within the wavelength range of 2-20 μm and an average peak of 9-10 μm.

Despite this knowledge, it was in 1934 that Hardy et al. (40) explained the physiological characteristics of infrared emitted from the body surface. They further found that the skin thermal properties and physiological activities are affected by numerous factors. This is because the skin helps to regulate the core body temperature. Nonetheless, the presence of disease will cause these factors to change. Thus, infrared measurement can be utilized for diagnostic reasons. With this fundamental knowledge, infrared thermography was introduced to the medical sciences as a potential imaging modality (41). The infrared thermography was first present to the modern medicine by Lawson in 1956, later discovered the relationship between breast carcinoma and increasing skin temperature

(42). The potential and feasibility of infrared (IR) thermography are explored as an instrument for breast lesions study (43). The IR thermography measures the temperature distribution using IR radiation emitted from the body surface, that creates an image known as thermogram. The acquired 2D thermogram is a distinct representation of temperature distribution by capturing the reflected IR radiation from the body in the presence of external IR energy origins (44). The IR thermography is a non-contact, non-invasive and fast approach of measuring temperature. Further, IR thermography offers the real time visualization of temperature distribution on the body surface without affecting the surface temperature (44).

A black body is defined as one that absorbs all the energy reaching it but does not reflect anything back (45). Based on the Planck's law, the spectral intensity ***I*** of thermal radiation at temperature ***T*** and at all wavelengths $\boldsymbol{\lambda}$ from black body in relation to wavelength is defined as:

$$I_{\lambda^b}\ (\lambda, T) = \frac{2\pi h c^2}{\lambda^5 (e^{\frac{hc}{\lambda k T}} - 1)}\quad W\, cm^{-2} \mu m^{-1} \tag{1}$$

where ***h*** is the Planck constant (6.626 x 10^{-34} $J\ s$), ***k*** is the Boltzmann constant (1.381 x 10^{-23} $J\ K^{-1}$), ***c*** is the speed of light in vacuum (2.998 x 10^{8} $m\ s^{-1}$), $\boldsymbol{\lambda}$ is the wavelength (m) and ***T*** is the absolute temperature (K).

The spectral emissivity power of black body as a diffuse emitter is given by:

$$E_{\lambda^b}\ (\lambda, T) = I_{\lambda^b}\ (\lambda, T) = \frac{A_1}{\lambda^5 (e^{\frac{A_2}{\lambda T}} - 1)} \tag{2}$$

where $A_1 = 2\pi hc^2 = 3.742 \times 10^8\ W \mu m^4/m^2$ and $A_2 = hc/k = 1.439 \times 10^4\ \mu m\ K$.

The integration of Planck function with respect to all the frequencies results in attaining the Stefan-Boltzmann's law relating to the overall emissivity of black body (46):

$$E_b = \int_0^\infty \frac{A_1}{\lambda^5 (e^{\frac{A_2}{\lambda T}} - 1)}\ d\lambda = \sigma T^4 \tag{3}$$

where σ is the Stefan-Boltzmann constant (5.67 x 10^{-8} $W/m^2\ K^4$).

For a black body, the overall energy emitted per unit area is directly proportional to the fourth power of its absolute temperature. The radiation emitted by most real objects are often partial to that emitted by black body of the same wavelength and temperature. The emissivity is defined as ratio of radiation emitted by real object E_λ to the radiation emitted by black body $E_{b,\lambda}$ at same temperature (T) (46):

$$\varepsilon(T) = \frac{E_\lambda(T)}{E_{b,\lambda}(T)} \tag{4}$$

From Eq. (4), the Stefan-Boltzmann's law can be rewritten for real object in relation to emissivity as:

$$E = \varepsilon\sigma T^4 \tag{5}$$

As shown in Eq. (5), the energy radiated by real object is proportional to the surface temperature, which is then captured by the infrared detectors. Nevertheless, the detected energy relies on the surface emissivity coefficient. This coefficient ranges from 0 (non-emitting) to 1 (fully emitting) depending on the material (47). In this case, the human skin has an emissivity coefficient of about 0.98±0.01 at normal angles (13). This is a crucial factor as it allows the true plantar foot temperature to be determined. Hence, infrared imaging method is highly effective in studying the skin temperature distribution (48).

3. Computer Aided Diagnosis (CAD) system

The computer aided diagnosis (CAD) system assists in providing the accurate diagnosis for clinicians. The assessment of medical images by human are prone to errors due to negligence, fatigue and sensory overwhelm by huge amount of information (49). Moreover, the limitations due to human visual perception, and optical illusions may affect the diagnosis accuracy (50). Besides, few healthcare institutions may not have sufficient clinicians for the diagnosis task. Therefore, the development of CAD system is necessary to overcome these drawbacks. Recent studies have proposed image processing algorithms with enhanced detection accuracy based on automated segmentation, image improvement and restoration and, feature extraction and classification approaches (21, 51-53).

The general layout of typical CAD system is shown in Figure 2. In general, the block diagram is separated into online and offline systems. For an offline system, the images are first preprocessed and subsequently the features are extracted using different feature extraction methods. The extracted features are then analyzed using statistical techniques to determine the highly significant features for the subsequent classification process. In the online system, the same distinct features are obtained and then classified to get the unknown class.

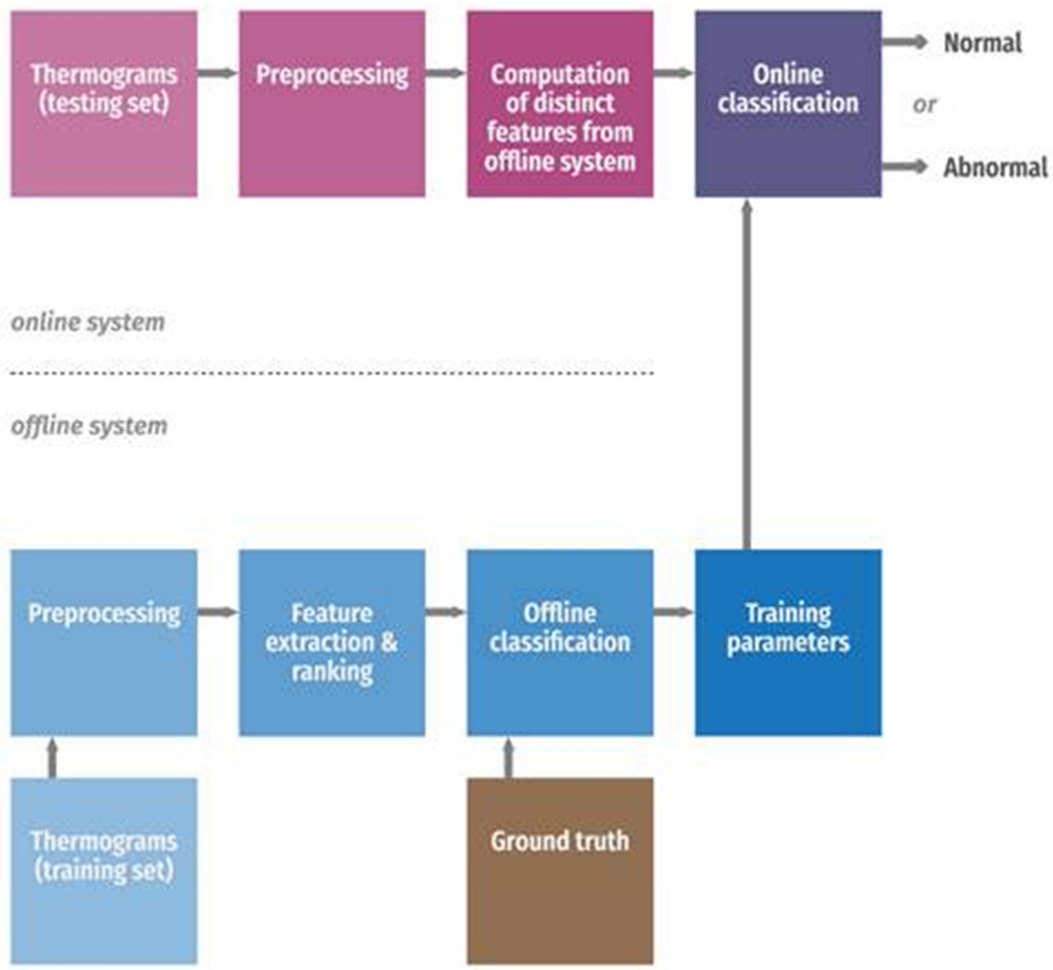
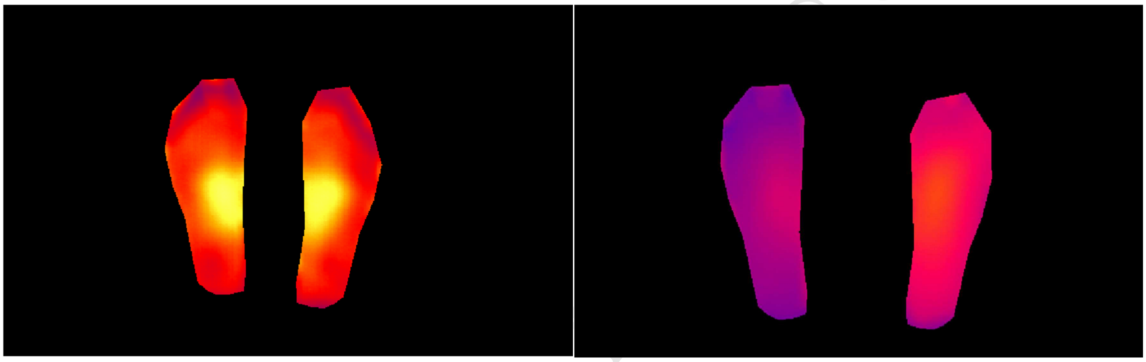


Figure 2: Block diagram of CAD system based on foot plantar thermogram.

4. Infrared thermography (temperature) analysis

IR thermography is widely used in many studies to detect the diabetic foot problems based on the temperature distribution of plantar foot. The examples of segmented feet thermograms (°C) of normal and diabetes patient without neuropathy are shown in Figure 3(a)-(b) respectively. The diabetic foot study using IR thermography is categorized into four types. They are separate lower limb temperature, asymmetric temperature, temperature distribution and, independent thermal and physical stress analysis. The individual analysis is briefly described below.



(a) (b)

Figure 3(a) - (b): The cropped feet thermograms (°C) of (a) normal and (b) diabetes patient without neuropathy.

4.1. Separate lower limb temperature analysis

The summary of studies performing temperature analysis on the lower limb separately using IR thermography is presented in Table 1. Ammer et al. (54) studied the statistical relationship between the hotspots on the plantar and development of callus, toe nail onychomycosis and foot deformities. However, there is no relationship between the skin changes and areas of elevated skin temperature. The thermal imaging not useful in detecting skin changes normally present in the diabetic foot. Melnizky et al. (55) analyzed the development of thermal gradient inversion among the type 2 diabetic patients and then correlated the temperature gradient with blood glucose level, foot deformation, limited range of motion and nerve conductivity measurements. Their study confirmed that almost half of the diabetic patients have inverted temperature gradient on the leg but could not clearly explain the phenomenon. Nishide et al (56) employed ultrasonography and thermography to determine the latent inflammation around the foot callus and studied the correlation between inflammation observed in callus and, with or without diabetes. The proposed methods may be useful to detect early ulcerations in diabetic patients with callouses. Bharara et al. (57) presented a quantitative thermography method using thermal index on a single case report of diabetic foot ulcer assessment and correlated with the standard wound measurement method. Nevertheless, the index analysis requires more patients. Bagavathiappan et al. (58) explored the relationship between type 2 diabetic patients with neuropathy and foot temperature using IR thermography. Their study revealed that IR thermography may be applicable as an additional screening device to evaluate high risk diabetic feet.

Table 1: Separate lower limb temperature analysis using IR thermography.

Reference (Year)	**Methodology**	**Findings**
Ammer et al, 2001. (54)	• Physical examination of feet • Neurological assessment • Thermal imaging • Single Measure Intraclass Correlation • Mann-Whitney U-test	• No relationship between skin changes and increased skin temperature
Melnizky et al, 2002. (55)	• Physical examination of feet • Nerve conduction test • Thermal imaging • SPSS 10.0 for statistical analysis	• A pathological temperature gradient was detected on the right limb of 36 diabetes patients (mean pathological gradient: -0.27±0.68K vs -1.84±0.81K) whereas 39 patients on the left limb (-0.77±1.15K vs -1.49±1.21K) • No correlation between temperature measurements and nerve conduction
Sun et al, 2005. (59)	• Electromyography for sympathetic skin response (SSR) test • Thermal imaging • Compute average temperature of six sub regions on each healthy sole • Analyze sole temperature normalization relative to forehead temperature of diabetes patients • SPSS for statistical analysis	• Highest temperature (29.3±0.9^{o}C) in the arc areas and lowest for the toes (26.2±1.2^{o}C). • Diabetes patients without sympathetic skin response (SSR) had higher mean plantar temperature (27.6±1.8^{o}C) compared to those with SSR (26.8±2.2^{o}C) • Equilibrium temperature is

		achieved at mean plantar temperature (27.8±1.0°C) after 15 *minutes*
Sun et al, 2006. (60)	• Seattle Wound Classification system • Thermal imaging • Electromyography for sympathetic skin response (SSR) test • Neurological assessment • SPSS for statistical analysis	• At risk diabetes patients with pre-ulcerative skin and without SSR had highest mean foot temperature (30.2±1.3°C) compared to diabetes patients without SSR (27.9±1.7°C), diabetes patients with SSR (27.1±2.0°C), and normal subjects (26.8±1.8°C)
Sun et al, 2008. (61)	• Seattle Wound Classification system • Thermal imaging • Electromyography for sympathetic skin response (SSR) test • Neurological assessment • Nerve conduction test • SPSS for statistical analysis	• At-risk class is 13.4 times more likely to develop plantar ulcerations than the diabetes patients with and without SSR during the 4-year period
Nishide et al, 2009. (56)	• Ankle Brachial Index (ABI) • Toe Brachial Index (TBI) • Achilles tendon reflex and vibratory perception • Semmes-Weinstein monofilament test • Thermography • Ultrasonography • Fisher's exact probability test • Mann-Whitney U-test • SPSS for statistical analysis	• Ultrasonography and thermography detect inflammation symptoms in 10% of the calli in diabetes class whereas no inflammation detected in the normal class.
Bharara et al, 2010. (57)	• Thermal imaging • Thermal index • Image J Software	• Thermal index/ wound inflammatory index moved from negative to positive ($p<0.05$) prior to reaching zero
Bagavathiappan et al, 2010. (58)	• Anthropometric measurements • Glycated hemoglobin (HbA1c) • Neuropathy assessment • Vascular sufficiency assessment • Thermal imaging • SPSS for statistical analysis	• Diabetes neuropathy patients recorded highest foot temperature (32 – 35°C) than non-neuropathy diabetes patients (27 – 30°C) • Higher mean foot temperature (MFT) for Diabetes neuropathy patients • No relationship between MFT and glycated hemoglobin

4.2. Asymmetric temperature analysis

The studies on asymmetric analysis of diabetic foot thermograms are summarized in Table 2. Kaabouch et al in (62-65) proposed an asymmetric analysis method for the detection of inflammation and predicting foot ulcerations risk using IR thermography. All the proposed methods can detect the inflammation and ulcers accurately. Kaabouch et al. (66) proposed an asymmetry analysis-based scalable scanning technique which provided a valid comparison of both feet, particularly of different sizes and shapes. The implemented scalable scanning method yielded fewer false abnormal regions and, the genetic algorithms effectively cropped the feet from background and eliminated most of the noise. Liu et al. (67) studied the effectiveness of proposed dermal thermography as a screening instrument for the early detection of ulcers. The segmentation of the feet from the background remains challenging because the foot, especially the toes have lower temperature compared to other body parts. Peregrina-Barreto et al. (68) proposed a technique that provides quantitative details with regard to the temperature difference and distribution, and the divided four regions (angiosomes) on the plantar. The proposed method can provide a reliable complimentary information to assist the clinicians in early identification of foot ulcers risk. van Netten et al. (69) studied various cut-off values of skin temperatures for the identification and treatment of diabetic foot problems. The proposed method yielded low specificity, which may result in over diagnosis. Nevertheless, the *mean* temperature difference between the left and right foot may be a good marker to determine the need for treatment. Liu et al. (70) initiated an asymmetric analysis technique that include the color image segmentation and non-rigid landmark based registration B-splines of the right and left foot. The proposed method can significantly detect diabetic foot ulcers with high accuracy including all the Charcot foot.

Table 2: Asymmetric temperature analysis using IR thermography.

Reference (Year)	Methodology	Findings
Harding et al, 1998. (71)	• Infrared imaging • Radiography	• Out of the 26 diabetes patients with positive thermograms, 21 of whom are confirmed with osteomyelitis by radiological evidence • Positive thermogram is described as at least 0.5°C rise in temperature of the affected foot skin with respect to the contralateral foot sole
Kaabouch et al, 2009. (62)	• Infrared imaging • Segmentation • Geometric transformation • Asymmetry analysis	• Able to detect and determine inflammation and ulcers accurately and rapidly
Kaabouch et al, 2009. (63)	• Infrared imaging • Automatic thresholding • Geometric transformation • Asymmetry analysis • Features extraction	• Genetic algorithm yields superior thresholding results • Low and high order statistics effectively enhance the asymmetry analysis in detecting foot abnormalities
Kaabouch et al, 2010. (65)	• Infrared imaging • Segmentation • Geometric transformation • Asymmetry analysis	• Genetic algorithm produces superior thresholding results
Kaabouch et al, 2011. (64)	• Infrared imaging • Segmentation • Geometric transformation • Asymmetry analysis and abnormality identification • Features extraction	• Genetic algorithm produces superior thresholding results • Low and high order statistics effectively enhance the asymmetry analysis in detecting foot abnormalities
Kaabouch et al, 2011. (66)	• Infrared imaging • Genetic algorithms • Asymmetry analysis-based scalable scanning	• Genetic algorithms effectively crop the feet from background and eliminate most noise • Scalable scanning method yield fewer false abnormal regions
Liu et al, 2013. (67)	• Infrared imaging • Foot segmentation • Feet registration • Abnormal detection	• Active contours without edges method acquire reasonable result • Automated detection of pre-symptoms ulceration by computing temperature difference of the feet • 2.2°C as the clinical relevant difference
Peregrina-Barreto et al,	• Infrared imaging • Color characterization	• The temperature estimate difference between corresponding angiosomes can

2013. (72)	• Foot angiosomes and color classification	be used to screen for abnormality
van Netten et al, 2013. (73)	• Infrared imaging • Mean temperature of whole foot and regions of interest	• Mean temperature of contralateral and ipsilateral foot is the same in patients with localized problems • Temperature at ROI was more than 2°C compared to the similar area in contralateral foot and to the mean of the entire ipsilateral foot • Mean temperature differences between the contralateral and ipsilateral foot was more than 3°C in patients with diffuse problems
Peregrina-Barreto et al, 2014. (68)	• Infrared imaging • Color characterization • Temperature estimated difference • Hot spots detection	• HSE capable of detecting abnormal small areas in the early phase that were not detected by ETD estimator
van Netten et al, 2014. (69)	• Infrared imaging • Clinical foot assessments • Kruskal-Wallis test • Receiver operating characteristic (ROC) curve and area using SPSS	• Optimal cut-off value for skin temperature in identifying diabetes foot problems was difference of 2.2°C between contralateral spots, with 76% sensitivity and 40% specificity • Optimal cut-off values for skin temperature to decide the urgency for treatment was difference of 3.5°C between left and right foot mean temperature, with 89% sensitivity and 78% specificity
Vilcahuaman et al, 2014. (74)	• Infrared imaging • Image processing	• In the clinical study, 10% of the diabetes patients had signs of significant hyperthermia on the foot plantar with temperature difference of more than 2.2°C
Vilcahuaman et al, 2015. (75)	• Infrared imaging • Image processing	• High risk group had significantly higher temperature (32±2°C) than medium risk group (31±2°C) • In the study, 9 out of 82 diabetes patients had significant hyperthermia
Liu et al, 2015. (70)	• Infrared imaging • Foot segmentation • Registration optimization • Asymmetric analysis	• The study yielded an accuracy of 95% with 35 out of the 37 diabetic foot ulcers identified • All three Charcot feet are successfully detected.

4.3. Temperature distribution analysis

Many studies have observed similar skin temperature distribution on the feet of healthy individuals compared to varying temperature distribution in diabetic patients. In 1991, Chan et al. (76) described the temperature distribution on the feet of healthy individuals as symmetric butterfly pattern in which the highest temperature is at the arch and lowest at the toes.

The summary of studies on temperature distribution analysis is shown in Table 3. Nagase et al. (77) and Bharara et al. (78) proposed a characterization method of plantar thermography patterns based on plantar angiosomes concept. The disadvantages in their studies may be bias of variations in the control group due to smaller number of participants. The unmatched gender and age in the control group may lead to confounding factors during data interpretation. Besides, the proposed manual classification method of 20 categories may be complicated for clinical purposes. Oe et al. (79) studied the thermography data of patients with osteomyelitis and the diabetic foot. The limitations are that the morphology analysis of thermography patterns are subjective and possibly affected by the surrounding environment, expertise of the researcher and patients' information biasness. Furthermore, the diagnosis of osteomyelitis is based on MRI without performing biopsy of the tissues or bone. Thus, the pathophysiology condition that underlie the ankle pattern cannot be fully understood. Mori et al. (80) proposed a system that characterized plantar thermal patterns with image segmentation technique based on mode seeking technique. The drawbacks are that variables biasness may be present in the control group because of smaller number of participants. Again, the unmatched gender and age in the control group may lead to difficulties in data interpretation. Moreover, the proposed method only focused on the forefoot region of the thermographic patterns. Hernandez-Contreras et al. (81) proposed a characterization technique to distinguish the thermal patterns of normal and diabetic patients. The proposed technique analyzed the regions of high temperature, localization and distribution. The analysis using pattern spectrum yielded reasonable results. Nonetheless, the technique is unable to offer details relating to the position of these regions. Again, Hernandez-Contreras et al. (82) proposed a characterization technique to distinguish the thermal patterns of normal and diabetic patients. The technique comprised of plantar area and hotspot segmentations, characterization and pattern classification, which yielded an average classification rate of 94.33% with the extracted features.

Table 3: Temperature distribution analysis.

Reference (Year)	Methodology	Findings
Branemark et al, 1967. (83)	• Infrared imaging • Clinical assessment	• Abnormal emission patterns from hand and feet of all diabetes patients • Reduced emission on the metatarsal and toes areas
Nagase et al, 2011. (77)	• Infrared imaging • Conceptual classification comprising of 20 categories of plantar thermography patterns	**Normal** • 48 feet (or 75%) are characterized to the seven categories and the remaining 16 feet characterized as atypical • The Id category (butterfly pattern) is mostly identified with 30 feet (or 46.9%) **Diabetes** • 225 (or 87.2%) diabetes feet are characterized to 18 categories and the remaining 33 feet (or 12.8%) as atypical • The IIa category (medial and lateral plantar arteries undamaged) is mostly identified with 101 feet (or 39.1%)
Oe et al, 2013. (79)	• MRI scans • Infrared imaging • Ankle-brachial index (ABI) • Toe-brachial index (TBI) • Nerve conduction velocity • SPSS for statistical analysis	• Ankle pattern is mostly common in patients with osteomyelitis • Sensitivity = 60% • Specificity = 100% • PPV = 100% • NPV = 71.4%
Mori et al, 2013. (80)	• Ankle-brachial index (ABI) • Toe-brachial index (TBI) • Achilles tendon reflex • Semmes-Weinstein monofilament test • Vibratory sensation test • Infrared imaging • Image partitioning algorithm • T test or chi square test	**Normal** • 47 feet are characterized to the four categories and the remaining 17 feet characterized as anomalous • The type 1 (butterfly pattern) (44%) is mostly identified **Diabetes** • 198 diabetes feet are characterized to six categories and the remaining 60

		feet as atypical • The type 2 (46%) is mostly identified
Bharara et al, 2014. (78)	• Clinical assessment • Semmes Weinstein monofilament • Vibratory perception threshold • Infrared imaging	**Normal** • Subjects are mostly represented by Id category (Butterfly Pattern) during measurements with 47.2% at rest, 13.8% at post stress and 27.8% at recovery **Diabetes** • Subjects are mostly represented by IIa category (medial and lateral plantar arteries undamaged) during measurements with 50% at rest, 50% at post stress and 28.57% at recovery
Hernandez-Contreras et al, 2015. (81)	• Infrared imaging • Grayscale characterization • Arch segmentation based on histogram distribution • Mathematical morphology	**Normal** • Butterfly pattern is presented in the subjects and pattern spectrum is same as oval • Mean percentage of pixels for control group is highest in quadrant 4 with 88.05% **Diabetes** • Pattern spectrum is irregular due to the dissimilar pattern • Mean percentage of pixels is 28.87% for diabetes group in quadrant 3.
Hernandez-Contreras et al, 2015. (82)	• Infrared imaging • Grayscale characterization • Foot segmentation • Temperature pattern • Mathematical morphology • Pattern spectrum • Multilayer perceptron • K-fold cross validation	• Proposed technique achieved average classification rate of 94.33%

4.4. Independent thermal and physical stress analysis

The goal of independent thermal and physical stress analysis is to study the reaction of body thermoregulation system under applied thermal and/or physical stress. The stress may include soaking the body part into cold or hot water, or mechanical stress like running or walking.

The summary of studies based on independent thermal and physical stress analysis prior to thermogram acquisition is presented in Table 4. Fushimi et al. (84) studied the vasoreactions of peripheral arteries by subjecting the hands of normal and diabetic subjects to cold stimuli and then record the temperature changes in the toes using IR thermography. The pattern for abnormal temperature changes is classified into 3 types, namely increasing, decreasing and flat. The atherosclerosis of peripheral arteries is highly related to the abnormal vasoreaction of toe arteries following the application of cold stimulus on both hands. The advantage of this study is that cold stimulated IR thermography helps to assess the peripheral atherosclerosis condition. Fujiwara et al. (85) evaluated the blood flow in the skin of diabetic patients using IR thermography before and after soaking the lower limb into cold water. The study confirmed that lower skin temperature recovery rate in diabetic patients is attributed to peripheral arterial sclerosis, abnormal blood coagulation fibrinolysis and sympathetic nerve dysfunction. Hosaki et al. (86) proposed a novel and nonintrusive diagnosis method for peripheral circulation in diabetic patients. The study found that the results for peripheral circulation in these patients obtained using laser-Doppler blood flowmetry and thermography are correlated. The study showed that these methods can determine diabetic patients with poor peripheral perfusion. Balbinot et al. (87) assessed the specificity and sensitivity of plantar thermography in diagnosing diabetes patients with polyneuropathy by utilizing heart rate variability (HRV) as a reference. Evidently, the plantar thermography is applicable in diagnosing diabetic neuropathy early, especially the autonomic and small fibers that are related to sub clinical condition. Nonetheless, this is a cross sectional study that includes sensitive test. Barriga et al. (88) proposed a CAD system for pre-clinical stages of peripheral neuropathy based on thermogram analysis. The study confirmed that cold stimuli and IR thermography can successfully identify patients with microvascular abnormities. Najafi et al. (89) studied the dynamic fluctuation in plantar temperature with respect to the pre-defined steps taken by the diabetic and peripheral neuropathic patients with and without Charcot neuroarthropathy. There are several disadvantages in this study. The development stage of Charcot foot is not controlled in this study whereby few patients may be in the coalescence phase. Moreover, the offloading foot wear is not standardized and hence, unable to sufficiently perform stratified analysis by stage and type of offloading foot wear. Lastly, due to the technology drawbacks, a short hold-up is needed to analyze the plantar temperature after each gait. Balbinot et al. (90) compared the plantar temperatures and analyzed the plantar re-warming index repeatability after cold stress on two separate days and groups (diabetes and normal). The proposed study observed good repeatability between two days presented by the re-warming index after the cold stimuli. However, the drawback is that, small sample size is used as it is a pilot study and neurophysiological study is not done to assess the existence of diabetic peripheral neuropathy. Further, the clinical assessment performed has not identified diabetic patients with neuropathy. Yavuz et al. (91) studied the statistical correlation between the plantar stresses and increase in foot plantar temperature after exercise using IR thermography. The disadvantages are that small number of participants without diabetic patients are involved. Also, there are more female subjects in this study and the size of the customized pressure shear instrument restrict the shear measurements of the whole foot. Agurto et al. (92) proposed a technique for the classification of diabetic peripheral neuropathy patients using IR thermography and independent component analysis (ICA). The limitations of this study are that few initial frames are not considered for the analysis and some areas, particularly the toes, present artifacts which require stabilizing the toes to avoid significant movements.

Table 4: Independent thermal and physical stress analysis.

Reference (Year)	**Methodology**	**Findings**
Fushimi et al, 1996. (84)	• ECG • Ankle pressure index • Infrared imaging • Ultrasonic imaging	**Normal** • All subjects had normal pattern **Diabetes** • 43 had normal, 19 increasing and 26 decreasing and 24 flat patterns
Fujiwara et al, 2000. (85)	• Infrared imaging • Ankle-brachial index • Doppler meter • Motor nerve conduction velocity • Sensory nerve conduction velocity • ECG • Schellong's test • Photo-dispersion method • ANOVA with Neuman-Keuls multiple comparison test	• Smaller skin temperature drop in diabetes patients compared to normal subjects after immersing into cold water • Diabetes patients had lower skin temperature recovery rate due to causal factors such as peripheral arterial sclerosis, abnormal blood coagulation fibrinolysis and sympathetic nerve dysfunction
Hosaki et al, 2002. (86)	• Infrared imaging • Laser Doppler blood flowmeter	• Recovery ratios for the 27 diabetes patients were in the range of 0-93.5%

	• Hot loading at 36 °C • Cold loading at 20 °C • Compute recovery ratio	and the average was 34% • Blood flow and recovery ratio were correlated (r = 0.634, p<0.0001) • Ratio of blood flow after cold loading over the blood flow after hot loading was in the range of 38.1% - 122% and average of 80.6%. • This ratio and recovery ratio is correlated (r = 0.502, p<0.0001)
Balbinot et al, 2012. (87)	• Clinical assessments • Heart rate variability • Infrared imaging • Electromyography • Statistical analysis	**Diabetes** • Interdigital anisothermal method performed better than thermal recovery index with 46.2% specificity and 81.3% sensitivity **Prediabetes** • All three tests achieved 25% specificity and 80% sensitivity equally
Barriga et al, 2012. (88)	• Infrared imaging • Motion tracking of thermal features • Exponential curve fitting	• Diabetes neuropathy patient recorded recovery rate of 2% at the two toes and approximately 0.4% at the heel • Normal subject recorded high recovery of 4% at the medial arch as compared to less than 1.5% in the diabetes neuropathy patient
Najafi et al, 2012. (89)	• Two pre-defined paths of 50 and 150 steps • Infrared imaging • Image processing • Student t test • ANOVA	• In Charcot neuroarthropathy group, the decreased in temperature for non-affected foot is 1.9 folds more than the affected foot • Plantar temperature for both foot in Charcot neuroarthropathy group significantly increased beyond 50 steps and remain higher on the affected foot at 200 steps
Balbinot et al, 2013. (90)	• Clinical assessments • Infrared imaging • Data analysis • Statistical analysis	• Significant difference in the average temperatures of normal subjects between the two days before and after cold stress test compared to no difference in the average temperatures for diabetes patients • Rewarming index of both groups did not differ between the two days
Yavuz et al, 2014. (91)	• Walking on pressure shear plate • Treadmill walking • Infrared imaging • Peak shear stress and peak resultant stress • Statistical analysis	• Significant correlation between temperature rises and peak shear stress (r =0.78) • Increased in plantar temperature can predict the site of peak resultant stress and peak shear stress in 39% and 23% of the subjects
Agurto et al, 2015. (92)	• Cold stimulus • Infrared imaging • Independent component	• Components 2, 6 and 8 significantly differentiate the normal and diabetes peripheral neuropathy patients

analysis (ICA)	• Higher recovery rate in normal subjects for component 6 • Diabetes peripheral neuropathy patients have lower temperature recovery rate in most parts of the foot plantar

5. DISCUSSION

An early detection of diabetic foot problems and the subsequent medical treatment can prevent the occurrence of foot ulcerations and lower limb amputation. Undeniably, the complications of the diabetic foot are costly and it reduces the quality of life in most of the patients. In this case, neuropathic foot ulcers are the leading cause of morbidity and prolonged hospitalizations (93).

The conventional clinical techniques are not able to identify changes in the integrity of the skin until occurrence of ulcerations (64). Moreover, the seriousness of neuropathy may be diagnosed with electrophysiological analysis and quantitative examinations using sensory modalities. However, these assessments are unable to specifically determine the cause of neuropathy, either due to diabetes or other reasons (94). Nonetheless, not all classification/scoring systems available are robustly verified within and among the healthcare centers (95). It is notably less assuring that a particular system is robust, meaningful and possible for populations in other countries. This is crucial because the etiological factors may vary among countries. For instance, arterial disease is particularly common in United States and Europe as compared to developing countries. Furthermore, bacterial infection may have significant impact in countries where the antibiotics availability is less. Hence, external verification is essential when the results of the system are taken into consideration as management plan (95). In the case of bone infection management, surgical intervention by bone amputation or debridement is needed based on protocols. A system in one center may give a high score for bone visibility as poor predictor of healing without surgery. However, this may not be applicable elsewhere where bone infection may be first treated with antibiotics.

The peripheral neuropathy and vascular disease are the main risk factors of the diabetic foot. These risk factors generate superficial temperature fluctuations that can be detected using temperature measurement methods (96). Many studies have indicated the temperature fluctuations on the plantar foot areas due to diabetic foot complications (76, 97-102). The IR thermometry (97, 98, 100, 101), liquid crystal thermography (LCT) (76, 99, 102, 103) and IR thermography (14, 59, 77, 104, 105) have been used to measure the plantar temperature. The IR thermometry is a temperature monitoring method that measures the temperature at various points on the feet (100). Nevertheless, it becomes difficult to measure the temperature at many points on the foot. Next, the LCT method produces a color reaction relative to the temperature of the skin surface, which touches the thermochromic liquid crystals. Despite being cheap and providing visualization of plantar thermal distribution, LCT is a contact method which produces slow responses and thus, may not be useful for certain applications (12).

Lastly, the infrared thermography is a fast, nonintrusive and non-contact method that allows the visualization of plantar temperature distribution. Further, it is passive whereby no harmful radiation passes through the body but only capturing of the body heat radiation (12). Infrared thermography is a non-contact method and has the advantage over the other assessment tools such as the monofilament and vibration sensation tests. It limits the unnecessary contact and pressure that may affect the temperature readings and mitigate the spread of infection through the apparatus (77). Moreover, IR thermography permits the measurement of temperature distribution of the whole foot regardless of the shapes or surfaces, particularly the medial arch which is a non-contact surface of the foot. Finally, IR thermography can be administered (picture taken) by a non-clinician and passed on to clinician for assessment and correlating clinically. For this purpose, the applications of IR thermography have significantly increased over the years especially in the study of diabetic foot related complications (33).

The infrared thermography is used to observe the morphology of the skin temperature pattern, which is influenced by blood perfusion. In conditions where blood circulation at the peripheral limbs are reduced (ischemic), there will be a change in the temperature patterns

(33). The various analysis methods performed with diabetic foot problems are presented in Table 1, 2, 3 and 4. Table 1 presents a separate lower limb temperature analysis representing the range of temperatures for the respective study groups. However, this analysis is not able to determine the specific risk regions associated to diabetic foot complications. In contrast, the temperature distribution analysis in Table 3 does not compare the plantar temperature between feet but instead, studied each foot independently. Despite studies showing same plantar temperature distribution in normal subjects, there has been no representative pattern for this group thus far. In addition, the plantar temperature distribution in diabetic patients are irregular in patterns. Hence, classification of the temperature distribution may be difficult. The independent thermal and physical stress analysis in Table 4 analyzed the plantar temperature reaction to the applied external stimulus. The temperature is evaluated by analyzing separately before and after the application of external stress. Nevertheless, the external stress that consist of walking or immersing the limb into cold or hot water for a period may result in subjects feeling uncomfortable and inconvenient.

Comparatively, asymmetric temperature analysis is the most commonly used method in analyzing the foot plantar thermograms. Several studies in Table 2 have achieved satisfactory results in detecting diabetic foot risk regions. The asymmetric temperature analysis performed temperature comparison between one foot and the contralateral foot. The foot plantar temperature distribution of healthy individuals is contralateral symmetric whereas asymmetric temperature distributions on the foot plantar indicate abnormality (35). Evidently, Gatt et al. (106) observed that the healthy skin temperature of similar areas in contralateral limbs is generally symmetrical in terms of pattern and magnitude using IR thermography. Hence, pre-established thermal pattern atlas is not required for healthy individuals, which are normally used as a control group. The diagnosis process involved the application of image processing and feature extraction techniques that extract details from the temperature pattern differences among the feet. Nevertheless, the application of feature extraction and machine learning algorithms are inconsistent among the studies. In fact, no classification techniques were implemented for classification performance evaluation. In addition, asymmetric temperature analysis may not be able to identify the risk regions if the same complications are present on both feet.

The association between diabetic foot and heat pattern on the plantar foot is subtle and often nonlinear (49). Therefore, the development of computer aided system is essential in helping to interpret the plantar thermograms. The knowledge discovery and data mining algorithms may provide improvement to the thermogram based CAD system in various main areas. First, screening clinicians may experience possible visual overloading. With thermogram based CAD system, diagnosis workload can be reduced and more attention can be given on complicated cases. Thus, enhancing the level of medical care. Second is the inter observer variability. Thermogram diagnosis based on human can be subjective and the qualities may vary extensively. Thus, objective technique based on mathematics and computer science can help in objectifying the diagnosis and decrease the inter observer variability. The last part is the quality of diagnosis. To a large extent, the progress of thermogram diagnosis based on human depends on training level and experience of the screening clinicians. Meanwhile, the progress of CAD system is based on the software and hardware in which computing machinery is increasingly becoming more potent. Moreover, the software domain progresses by integrating and from developing better image processing algorithms. Hence, CAD system may be able to outperform the clinicians based on cost, accuracy and speed.

6. CONCLUSION

Diabetes mellitus is a long term metabolic disorder affecting various parts of the human body. The high blood glucose level causes reduction in the blood perfusion, which may often result in diabetic foot complications. The diabetic foot is the most critical and expensive complication causing disability and impairing the quality of life. The burden of diabetic foot diseases is expected to rise in future due to the growing number of diabetic patients. Thus, an early detection of diabetic foot complication is important for effective medical treatments. In this paper, conventional foot assessment methods, infrared thermography and, CAD system analysis for the diabetic foot using infrared thermography are discussed. Indeed, the IR thermography application has been growing over the years particularly in the field of medicine due to its advantages over other methods. Various techniques for thermal image analysis are presented in this paper. Among them, asymmetric temperature analysis is commonly used technique as it is simple to implement and yielded satisfactory results in previous studies. Also, new algorithms need to be developed to overcome the drawbacks of this analysis. The continuous advances in the image processing and data mining algorithms may help to overcome the existing limitations. This may help in the early detection of diabetic foot complications, and hence, assist the clinicians to intervene early. The accuracy of the CAD system can be improved further using better nonlinear features and deep learning techniques. The developed CAD system can be introduced in clinics and healthcare institutions to assess the severity of diabetic foot complications.

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Highlights

- Pathogenesis and burden of diabetic foot is reviewed
- Automated diagnosis methods of diabetic foot are studied
- Various infrared thermography methods are discussed
- Asymmetric temperature analysis has yielded better results

Conflict of Interest Statement

Muhammad Adam Bin Abdul Rahim
Department of Electronics and Computer Engineering, Ngee Ann Polytechnic, Singapore.
Singapore 599489
Email: muhdadam@hotmail.com
Home: https://scholar.google.com.sg/citations?user=zXBM-D4AAAAJ&hl=en&oi=ao

Journal Manager
Computers in Biology and Medicine

Sub: Submission of revised manuscript for the Computers in Biology and Medicine

Dear Sir,

We are submitting the manuscript entitled *"Computer Aided Diagnosis of Diabetic Foot Using Infrared Thermography: A review"* to the Computers in Biology and Medicine journal for possible publication. **There is no conflict of interest in this work**.

Best Regards,
Muhammad Adam Bin Abdul Rahim