

Coming events cast their shadows before: detecting inflammation in the acute diabetic foot and the foot in remission

Manish Bharara¹

Jeffrey Schoess²

David G. Armstrong^{1*}

¹*Southern Arizona Limb Salvage Alliance (SALSA), College of Medicine, University of Arizona, Tucson, AZ, USA*

²*Eden Medical Inc., Howard Lake, MN, USA*

*Correspondence to: David G. Armstrong, Southern Arizona Limb Salvage Alliance (SALSA), College of Medicine, 1501, N Campbell Ave, Room 4318, University of Arizona, Tucson, AZ 85724, USA.
E-mail: Armstrong@usa.net

Summary

The incidence of diabetic foot complications, most notably wounds, is increasing worldwide. Most people who present for care of a foot wound will become infected. Globally, this results in one major amputation every 30 seconds with over 2500 limbs lost per day. Presently, clinicians assess circulation, neuropathy and plantar pressures to identify the risk of foot ulceration. Several studies have suggested prevention of foot ulcers by identifying individuals at high risk and treating for lower extremity complications. Our group has proposed several diagnostics as well as prevention strategies, especially thermography and thermometry for management of patients with diabetic foot complications. These strategies employ non-invasive assessment of inflammation for acute as well as chronic care for the foot, with the intent to prevent ulceration/re-ulceration and subsequent traumatic amputations. The authors' review some important clinical studies and ongoing research in this area, with the long-term goal to further the role of thermography and thermometry in clinical care for the diabetic foot. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords diabetic foot; infection; prevention; thermography; ulceration; inflammation

Introduction

Diabetic foot

The incidence of diabetic foot complications, most notably wounds, is increasing worldwide. More than half of the people who present for care of a foot wound will become infected [1]. Globally, this results in one major amputation every 30 seconds with over 2500 limbs lost per day [2]. Studies have demonstrated that the 5-year mortality rate in patients with diabetes following a major amputation is significant and even greater than many major forms of cancer [3]. With five year mortality rates for wounds, vascular disease and subsequent diabetes-related amputations conservatively in the range of 50-70%, these have frequently been compared to the mortality rates of aggressive forms of cancer. Our group and others have continued this comparison, in suggesting that healing should be equated with 'remission' and diabetic foot care delivery similar to interdisciplinary cancer centre care [3,4]. Regardless of these comparisons, though, the incidence of diabetic foot disease is growing worldwide leading to the increased socio-economic burden on health care systems of both developed and developing nations [5–8].

Received: 7 September 2011

Revised: 3 October 2011

Accepted: 13 October 2011

Current status of care

Presently, clinicians assess circulation, neuropathy and plantar pressures to identify the risk of foot ulceration [9]. Several studies have suggested prevention of foot ulcers by identifying individuals at high risk and treating for lower extremity complications [10–12]. Our group has proposed several prevention strategies for disease management to improve clinical outcomes for patients suffering from diabetic foot complications [2,13]. There are many clinical parameters available to the physician that are used to assess the severity of a diabetic foot infection and other risk factors; however, most are largely subjective with very few reliable practical clinical markers available to assist the clinician. The key common factor that appears to be present both in dysfunctional healing and in predicting breakdown may be inflammation.

Thermographic evaluation of the diabetic foot: acute and chronic assessments

Non-invasive assessment for inflammation might be best divided into care of acute diabetic foot conditions [wound healing, Charcot neuro-osteoarthropathy (CN)] and preventative care for the foot in remission (prevention of severe ulceration/re-ulceration). We will divide our discussion into those topics.

Acute inflammation detection

Wound-healing assessment

It is important that any proposed methodology for analysing a thermal image be standardized to create uniformity in the process for measuring and collection of data. In the use of infrared (IR) thermography, the anatomical surfaces of the foot are examined to identify potential hot or cold spots where inflammation or circulatory loss may be occurring. One can then supplement the examination with visible imagery or a composite (visual superimposed on thermal) image to determine the size, shape and curvature of the wound, which can help answer the question of how large or extensive the wound may be.

This approach, however, only provides the clinician a general qualitative process for the analysis of the thermal images of wounds, and there remains a need for an objective parameter or alternatively an index based on thermal profile of the wound site. This is most important when tracking the progress of wound healing over time.

Peripheral neuropathy and underlying inflammation impairs the wound healing. These effects may be quantified by using thermal imaging. The underlying cellular mechanisms for wound healing are complex, and responses are severely affected by the presence of

diabetes that modulates in the metabolic activity. Wound healing in a diabetic patient presents a challenging problem for clinicians for a number of reasons. In a healthy patient, wound healing progresses through three distinct stages: the inflammatory stage, which begins at the time the wound occurs and is signalled by the adherence of platelets to exposed collagen, which aggregate with fibrin to form a clot. Polymorphonuclear leukocytes then arrive and assist in combating infection. In the proliferative phase, new capillaries form, and fibroblasts activate to synthesize collagen and proteoglycans. Lastly, the maturation stage occurs in which collagen tissue is remodeled.

Figure 1 illustrates the contextual framework for the application of thermography (or thermometry) in an assessment of diabetes-related lower extremity complications. Although the aforementioned mechanisms are hard to quantify by a single test or modality, the assessment of thermal patterns provides a unique way to measure the effect of cellular or metabolic activity of healing. The progression of wound healing can be determined by calculating the thermal index (TI) of the wound on the basis of the thermal profile obtained by IR thermometry. This processed image can be used to calculate an index described as follows.

$$TI = (\Delta T * a)/A,$$

where ΔT is the temperature difference between the ulcer and mean foot temperature, a is the area of the isotherm (highest to lowest temperature) in the ulcer area, and A is the area of the wound bed. Area is calculated in terms of the pixels for this analysis. The choice of the highest and lowest isotherms must be made at the beginning of the analysis and followed consistently. Currently, these features are manually obtained from the thermal image.

Figure 2 provides a typical thermal image and a visual image for the plantar foot ulcer. Figure 3 provides schematic for the wound inflammatory index calculation. The image is from a 78-year-old test subject recorded on 11 November 2009. The average foot temperature of 85.4 F was obtained by recording the temperature at six anatomical sites (metatarsal head (MTH) nos. 1–5 and hallux). The active wound bed was measured to be 22 387 pixels, while the area of the lowest temperature had a pixel count of 2753. The lowest temperature was 78.4 F. The resultant TI was calculated to be 0.862. Another set of thermographic measurements was performed 21 days later on 01 December 2009. The analysis indicated an increase in average foot temperature up to 88.0 F (increase of 2.7 F), a larger wound area of 33 856 pixels and a TI of 0.443, indicating progress towards wound healing.

Bharara *et al.* [14] reported the wound inflammatory index for a patient with plantar foot wound, followed serially until healing. We found that the TI/wound inflammatory index may indicate a shift from negative to positive ($p < 0.05$), before it reaches zero at healing. The changes in thermal patterns or thermal morphology indicate a flare response at the wound periphery, which triggers at around

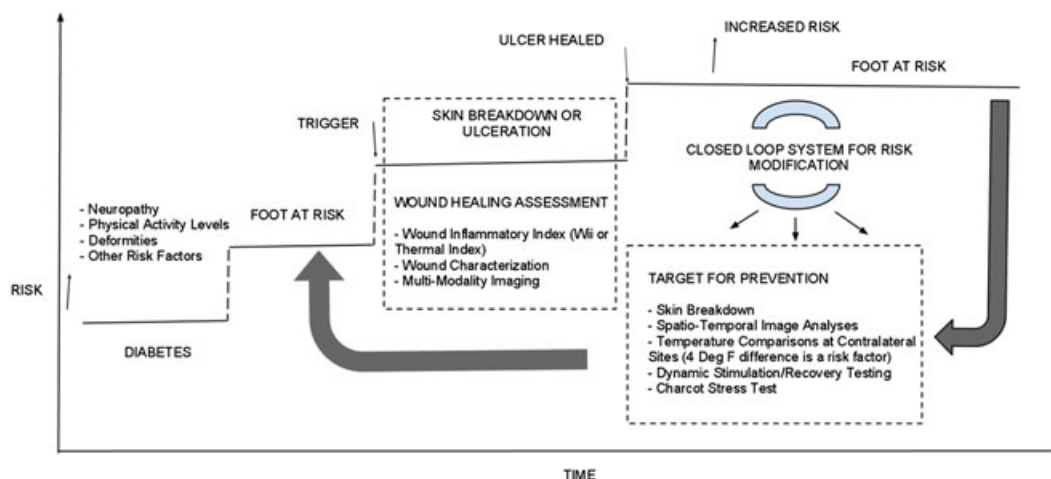


Figure 1. Contextual framework for thermography and thermometry in management of diabetic foot complications

day 14, and this acute inflammation around the wound begins to subside leading to healing. The wound inflammation index correlated with the standard wound size measures at weekly patient visits [14].

Assessment of CN

Najafi *et al.* [15], in a recent investigation, provided evidence about the poor metabolic regulation following controlled walking test for patients with acute CN [15]. They reported that at 50 steps, patients with CN had a significantly higher temperature drop compared with those with no CN. Additionally, at 200 steps, the temperature for patients with CN significantly increased unilaterally, while those with no CN had a non-significant difference between the two feet. This is the first study evaluating the stress and recovery response in patients with CN. Such strategies need further evaluation to study the variability in thermal response to controlled walking with the intent to develop interventions that address trauma (and increased temperatures) during activities of daily living, such as walking.

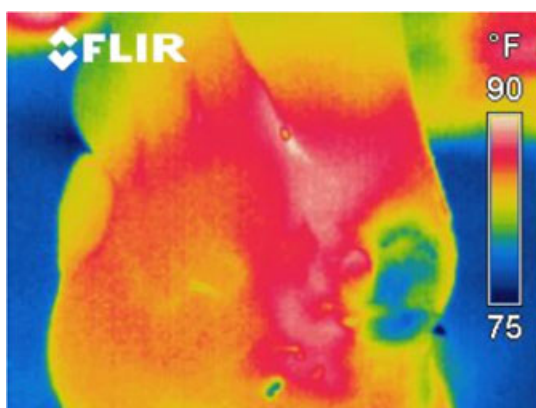


Figure 2. Typical thermal image (A) and visual image (B) of a wound (Courtesy of Eden Medical, Inc.)

Chronic assessment

Inflammation: target for prevention in care of the foot in 'remission'

It is often the pressure–activity imbalance, where repetitive stress on the plantar tissue in concert with the underlying neuropathy and biomechanical abnormalities, that leads to an ulcer (or frank skin breakdown) [16–19]. Inflammation is one of the earliest signs of impending foot ulceration in a diabetic patient. While many of the characteristic signs of inflammation (i.e. pain, redness, swelling and loss of function) are difficult to assess objectively, warmth can be measured objectively through thermal imaging. In the neuropathic extremity, pain and loss of function may be absent because of degenerated nerve fibres. However, the signs of redness, swelling and excessive heat are robust diagnostic indicators of pathology change leading to wound-related ulceration. Local skin warmth has been found to be a relatively consistent surrogate marker for inflammation [20]. Thermography may be one of the more promising emerging modalities for the evaluation of diabetic foot wounds [11,21–23].

Thermal changes under the plantar aspect of the foot may be the result of vascular compromise, diabetic neuropathy, skeletal changes (repetitive stress-induced inflammation), infection or a combination of these factors. IR thermography is a real-time temperature measurement technique, which produces a coloured visualization of thermal energy emitted by the measurement site at temperature above absolute zero. The technological advances in IR cameras in speed and spatial resolution now make it possible to quantitatively assess thermal patterns [11]. Although IR thermography has poor specificity, it can be used in conjunction with other modalities to help predict current and future outcomes for diabetic neuropathic wounds.

Progressive degeneration of sensory nerve pathways is thought to affect thermoreceptors and mechanoreceptors equally. However, clinical evidence suggests a bias towards evaluation of mechanoreceptors. Thermal imaging is a valuable adjunct to the physical examination of the foot. Table 1

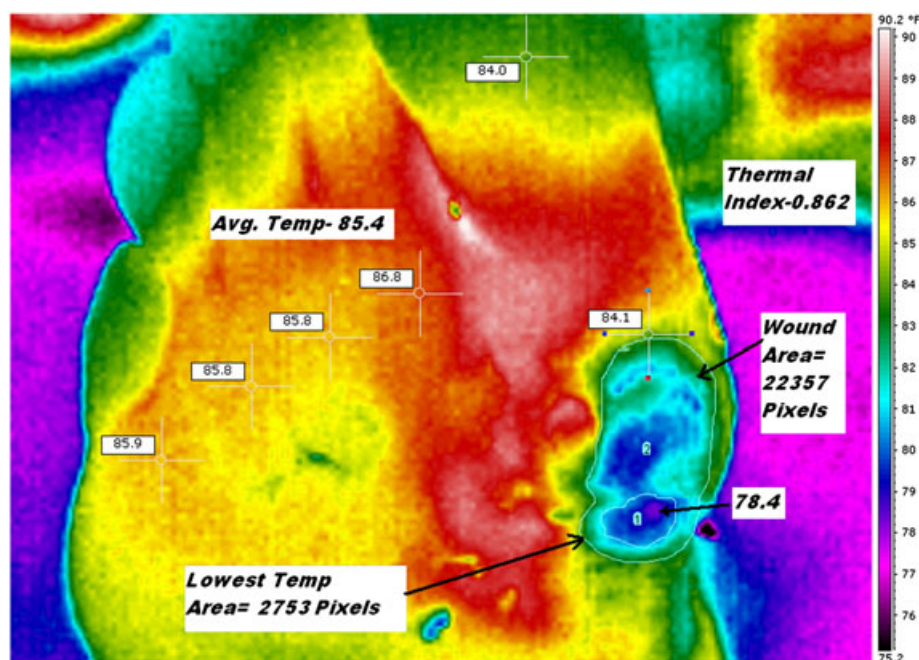


Figure 3. Illustration of wound inflammatory index calculation (Courtesy of Eden Medical, Inc.)

lists key studies from the published literature by specific applications in diabetes lower extremity complications.

The current evidence on the use of thermography (and thermometry) could be divided into seven main areas, which are real-time dynamic thermometry, longitudinal foot temperature analysis, infection outcome analysis, preventing ulcer recurrence, response to external stimuli, spatio-temporal image analysis and wound analysis. Specific studies addressing each area are referenced in Table 1. However, it must be emphasized that the largest clinical evidence supporting thermometry exists in the area of preventing recurring ulcers. Lavery and Armstrong have

shown the efficacy of using handheld dermal thermometers in reducing rates of recurring ulcers by four to ten times, in three independent clinical trials [24–26]. Table 2 lists the three randomized clinical trials and their findings.

Although the prevention strategy is effective, there is a need for a clinical thermography system that can predict wound healing as well as aid clinicians in adapting their therapies per wound-healing response. Recent advances in technology have now afforded cost-effective means to realize such prediction algorithms [14,27,28]. In this article, we review the recent advances in thermal assessment technology and its specific applications for diabetic foot care.

Table 1. Summary of key studies published in this area, stratified by specific applications in diabetic foot complications

Study No.	Year	Type	Description
1	2003–2007	Ambulatory temperature analysis	Dynamic (real time) plantar temperature analysis for polyneuropathy evaluation [30–32]
2	2009–2010	Foot temperature analysis	Foot temperatures in patients with type 2 diabetes with and without neuropathy [33,34]
3	2007	Infection outcome evaluation	Assessment of thermal imaging's ability to predict outcomes in diabetic foot infections [20]
4	2009	Prevention	Liquid crystal thermography for preventing diabetic foot wounds [22,35]
5	2004–2007	Prevention	Three randomized clinical trials evaluating home monitoring of foot temperatures – 4 °F difference between contralateral foot sites predicts recurring ulcers [24–26]
6	2008	Response to external stimuli	Cold immersion/warm immersion recovery response in diabetic neuropathic patients [36,37]
7	1996	Response to external stimuli	Cutaneous reactive hyperemia analysis in porcine model [38]
8	2011	Spatio-temporal image analysis	Thermographic pattern analysis for circulatory analyses in the diabetic feet based on the angiosomes concept [39]
9	2009	Spatio-temporal image analysis	Thermal imaging for screening at-risk patients and identifying latent callous, circulatory disorders and diabetic neuropathy [29,40,41]
10	2002	Wound analysis	Wound as well as thermal recovery tendency analysis for diabetic patients [27]
11	2010	Wound analysis	Wound healing trajectory analysis for diabetic foot wounds using wound inflammatory index [14]
12	2005	Wound analysis	Wound characterization and metabolic correlation with thermal as well as hyperspectral imaging [28]

Table 2. Summary of the three randomized clinical trials demonstrating the effectiveness of handheld dermal thermometers

Study	Study design	Duration of study (months)	Ulceration control group (%)	Ulceration thermometry group (%)
Diabetes Care (2004)	RCT (85)	6	20	2
Diabetes Care (2007)	RCT (172)	12	29.3 and 30.4	8.5
American Medical Association (2007)	RCT (255)	15	12.2	4.7

RCT, randomized clinical trial.

Discussion

The pathophysiology behind a diabetic foot ulceration and subsequent complication is well understood. The clinician will generally obtain a thorough medical history and assess the orthopaedic, vascular, dermatological and neurological statuses of a patient to identify risks associated with foot ulceration. More recently, technological advances have provided efficient modalities that can advance the management of patients with diabetic foot disease through early diagnosis, surgical management and future prevention for these patients. Thermometry is a prime example of such technological advances and has shown clinically that assessments of plantar foot temperatures are not only useful in the prevention of recurring ulcers but also may be indicative of subclinical neuropathy and assess the wound healing trajectory [14].

The advantages of the IR technique over other modalities available include its noninvasive nature, the safety of the examination and ease and speed of use. This type of system provides a complimentary assessment alongside routine sensory-testing modalities, aimed to objectively address the risk factors and/or response to therapy. Although several limitations of the proposed technique exist such as patient positioning, camera positioning, image registration (overlay of the visual image on the thermal image) and automation of the analysis, these all can be addressed in an elaborate feasibility study with extended efforts in developing the analytical tools and processes to minimize computational errors for the wound area.

From a clinical standpoint, with the combination of this technique with other modalities currently available, we can help develop a pervasive health care regime that will provide economical and standardized treatment that will result in decreased outpatient visits, unnecessary hospitalizations and traumatic complications such as amputation [28,29]. One important benefit of the imaging modalities is the real-time education and empowerment of patients, as visual feedback on health status may help motivate patients to monitor their pathological state and maximize adherence to therapy.

References

1. Lavery LA, Armstrong DG, Wunderlich RP, Tredwell J, Boulton AJ. Diabetic foot syndrome: evaluating the prevalence and incidence of foot pathology in Mexican Americans and non-Hispanic whites from a diabetes disease management cohort. *Diabetes Care* 2003; **26**(5): 1435–1438.
2. Bharara M, Mills JL, Suresh K, Rilo HL, Armstrong DG. Diabetes and landmine-related amputations: a call to arms to save limbs. *Int Wound J* 2009; **6**(1): 2–3.
3. Armstrong DG, Wrobel J, Robbins JM. Guest editorial: are diabetes-related wounds and amputations worse than cancer? *Int Wound J* 2007; **4**(4): 286–287.
4. Armstrong DG, Mills JL. Toward a change in syntax in diabetic foot care:

Conclusion

There is a growing body of evidence emerging from our group's work in this area to build a knowledge base in thermal measurements. This may assist the primary care team's ability to successfully use diabetic ulcer prevention strategies. A brief summary of some important clinical studies and ongoing research is presented earlier. The long-term goal of this research is to further the role of thermometry and thermography in clinical care for the diabetic foot, especially by empowering the primary care team to identify high-risk patients and preventing traumatic consequences of this disease through objective parameters. Review of key work published in this area, suggests that thermal imaging provides a useful tool for preventing wounds and assessing wound healing.

The wound inflammatory index or TI and Charcot stress test may provide a scoring range for the assessment of wounds and acute CN, respectively, by considering physiological as well as morphological changes to the skin's surface. This additionally helps achieve a comprehensive understanding of the significance of small temperature changes in the wounds and its association with wound chronicity. The use of thermal techniques has largely remained a research tool; however, the availability of quantitative tools may help clinical integration and routine assessments. Further works should be aimed at studying as well as documenting thermal findings in lower extremity wounds in well-designed clinical trials.

Conflict of interest

M Bharara and DG Armstrong are on the Scientific Advisory Board for Medavinci, The Netherlands.

J Schoess is the president and the chief executive officer of the Eden Medical Inc., which is the prime recipient of the National Institutes of Health Grant (#1R43DK083782) for developing an infrared thermal scanning system for the lower extremity assessment, especially foot ulcers.

- prevention equals remission. *J Amer Pod Med Assoc* 2011 in press.
5. Gordoia A, Scuffham P, Shearer A, Oglesby A, Tobian J. The healthcare costs of diabetic peripheral neuropathy in the US. *Diabetes Care* 2003; **26**: 1790–1795.
 6. Abbott CA, Garrow AP, Carrington AL, et al. Foot ulcer risk is lower in South-Asian and African-Caribbean compared with European diabetic patients in the U.K.: the north-west diabetes foot care study. *Diabetes Care* 2005; **28**(8): 1869–1875.
 7. Singh N, Armstrong D, Lipsky B. Preventing foot ulcers in patients with diabetes. *J Am Med Assoc* 2005; **293**: 217–228.
 8. Reiber GE, Lipsky BA, Gibbons GW. The burden of diabetic foot ulcers. *Am J Surg* 1998; **176**(2A Suppl): 5S–10S.
 9. Service NH. Type 2 Diabetes: Prevention and Management of Foot Problems. National Institutes of Health and Clinical Excellence: London, 2004.
 10. Boulton A, Connor H, Cavanagh PR (eds). *The Foot in Diabetes*. John Wiley & Sons, 1998.
 11. Bharara M, Cobb J, Claremont DJ. Thermography and thermometry in the assessment of diabetic neuropathic foot: a case for furthering the role of thermal techniques. *Int J Low Extrem Wounds* 2006; **5**(4): 250–260.
 12. Reiber G. Diabetic foot care: financial implications and practical guidelines. *Diabetes Care* 1992; **15**(Supplement 1): 29–31.
 13. Boulton AJ, Armstrong DG. Whither progress in the diabetic foot – clinical and research? *Int J Low Extrem Wounds* 2004; **3**(4): 182–183.
 14. Bharara M, Schoess J, Nouvong A, Armstrong D. Wound inflammatory index: a “proof of concept” study to assess wound healing trajectory. *J Diabetes Sci Technol* 2010; **4**(4): 773–779.
 15. Najafi B, Wu S, Crews RT, Wrobel J. Dynamic plantar temperature may provide a sensitive and reliable measure to predict foot ulcers. In *Charcot Neuroarthropathy Patients*. American Diabetes Association: Orlando, Florida, 2010.
 16. Armstrong DG, Abu Rumman PL, Nixon BP, Boulton AJM. Continuous activity monitoring in persons at high risk for diabetes-related lower extremity amputation. *J Am Podiatr Med Assoc* 2001; **91**: 451–455.
 17. Armstrong DG, Boulton AJM. Activity monitors: should we begin dosing activity as we dose a drug? *J Amer Podiatr Med Assn* 2001; **91**: 152–153.
 18. Armstrong DG, Lavery LA, Holtz-Neiderer K, et al. Variability in activity may precede diabetic foot ulceration. *Diabetes Care* 2004; **27**(8): 1980–1984.
 19. Bus SA, Valk GD, van Deursen RW, et al. Specific guidelines on footwear and off-loading. *Diabetes Metab Res Rev* 2008; **24**(Suppl 1): S192–193.
 20. Armstrong DG, Lipsky BA, Polis AB, Abramson MA. Does dermal thermometry predict clinical outcome in diabetic foot infection? Analysis of data from the SIDESTEP* trial. *Int Wound J* 2006; **3**(4): 302–307.
 21. Bharara M. Liquid crystal thermography in neuropathic assessment of the diabetic foot. PhD Thesis, Bournemouth, UK: Academic Biomedical Engineering Research Group, School of Design, Engineering & Computing, Bournemouth University, 2007.
 22. Roback K, Johansson M, Starkhammar A. Feasibility of a thermographic method for early detection of foot disorders in diabetes. *Diabetes Technol Ther* 2009; **11**(10): 663–667.
 23. Ring F. Thermal imaging today and its relevance to diabetes. *J Diabetes Sci Technol* 2010; **4**(4): 857–862.
 24. Armstrong DG, Holtz-Neiderer K, Wendel C, Mohler MJ, Kimbriel HR, Lavery LA. Skin temperature monitoring reduces the risk for diabetic foot ulceration in high-risk patients. *Am J Med* 2007; **120**(12): 1042–1046.
 25. Lavery LA, Higgins KR, Lanctot DR, et al. Preventing diabetic foot ulcer recurrence in high-risk patients: use of temperature monitoring as a self-assessment tool. *Diabetes Care* 2007; **30**(1): 14–20.
 26. Lavery LA, Higgins KR, Lanctot DR, et al. Home monitoring of foot skin temperatures to prevent ulceration. *Diabetes Care* 2004; **27**(11): 2642–2647.
 27. Cheng K-S, Yang J-S, Wang M-S, Pan S-C. The application of thermal image analysis to diabetic foot diagnosis. *J Med Biol Eng* 2002; **22**(2): 75–82.
 28. Chen M, Kerechanin C, Greenspan D, et al. Development of a thermal & hyperspectral imaging system for wound characterization & metabolic correlation. *Johns Hopkins Apl Technical Digest* 2005; **26**(1): 67–74.
 29. Nishide K, Nagase T, Oba M, et al. Ultrasonographic and thermographic screening for latent inflammation in diabetic foot callus. *Diabetes Res Clin Pract* 2009; **85**(3): 304–309.
 30. Kang PB, Hoffman SN, Krimitsos E, Rutkove SB. Ambulatory foot temperature measurement: a new technique in polyneuropathy evaluation. *Muscle Nerve* 2003; **27**(6): 737–742.
 31. Rutkove SB, Chapman KM, Acosta JA, Larrabee JE. Foot temperature in diabetic polyneuropathy: innocent bystander or unrecognized accomplice? *Diabet Med* 2005; **22**(3): 231–238.
 32. Rutkove SB, Veves A, Mitsa T, et al. Impaired distal thermoregulation in diabetes and diabetic polyneuropathy. *Diabetes Care* 2009; **32**(4): 671–676.
 33. Papanas N, Papatheodorou K, Papazoglou D, Kotsiou S, Maltezos E. Association between foot temperature and sudomotor dysfunction in type 2 diabetes. *J Diabetes Sci Technol* 2010; **4**(4): 803–807.
 34. Papanas N, Papatheodorou K, Papazoglou D, Monastiriotes C, Maltezos E. Foot temperature in type 2 diabetic patients with or without peripheral neuropathy. *Exp Clin Endocrinol Diabetes* 2009; **117**(1): 44–47.
 35. Frykberg R, Tallis A, Tierney E. Diabetic foot self examination with the Tempstat™ as an integral component of a comprehensive prevention program. *J Diabetic Foot Complications* 2009; **1**(1): 13–18.
 36. Bharara M, Viswanathan V, Cobb JE. Cold immersion recovery responses in the diabetic foot with neuropathy. *Int Wound J* 2008; **5**(4): 562–569.
 37. Bharara M, Viswanathan V, Cobb JE. Warm immersion recovery test in assessment of diabetic neuropathy – a proof of concept study. *Int Wound J* 2008; **5**(4): 570–576.
 38. Hansen GL, Sparrow EM, Kommamuri N, Iaizzo PA. Assessing wound severity with color and infrared imaging of reactive hyperemia. *Wound Repair Regen* 1996; **4**(3): 386–392.
 39. Nagase T, Sanada H, Takehara K, et al. Variations of plantar thermographic patterns in normal controls and non-ulcer diabetic patients: novel classification using angiosome concept. *J Plast Reconstr Aesthet Surg* 2011; **64**(7): 860–865.
 40. Bagavathiappan S, Philip J, Jayakumar T, et al. Correlation between plantar foot temperature and diabetic neuropathy: a case study by using an infrared thermal imaging technique. *J Diabetes Sci Technol* 2010; **4**(6): 1386–1392.
 41. Bagavathiappan S, Saravanan T, Philip J, et al. Infrared thermal imaging for detection of peripheral vascular disorders. *J Med Phys* 2009; **34**(1): 43–47.