Temperature as a Causative Factor in Diabetic Foot Ulcers

A Call to Revisit Ulceration Pathomechanics

Metin Yavuz, DEng*
Ali Ersen, PhD*
Jessica Hartos, PhD†
Lawrence A. Lavery, DPM‡
Dane K. Wukich, MD§
Gordon B. Hirschman, MEng||
David G. Armstrong, DPM, MD, PhD¶
Myla U. Quiben, PT, PhD, DPT#
Linda S. Adams, BS#

Background: Diabetic foot ulcers (DFUs) are a major burden to patients and to the health-care systems of many countries. To prevent or treat ulcers more effectively, predictive biomarkers are needed. We examined temperature as a biomarker and as a causative factor in ulcer development.

Methods: Thirty-seven individuals with diabetes were enrolled in this observational case-control study: nine with diabetic neuropathy and ulcer history (DFU), 14 with diabetic neuropathy (DN), and 14 nonneuropathic control participants (DC). Resting barefoot plantar temperatures were recorded using an infrared thermal camera. Mean temperatures were determined in four anatomical regions—hallux and medial, central, and lateral forefoot—and separate linear models with specified contrasts among the DFU, DN, and DC groups were set to reveal mean differences for each foot region while controlling for group characteristics.

Results: The mean temperature reading in each foot region was higher than 30.0°C in the DFU and DN groups and lower than 30.0°C in the DC group. Mean differences were greatest between the DFU and DC groups, ranging from 3.2°C in the medial forefoot to 4.9°C in the hallux.

Conclusions: Increased plantar temperatures in individuals with a history of ulcers may include acute temperature increases from plantar stresses, chronic inflammation from prolonged stresses, and impairment in temperature regulation from autonomic neuropathy. Diabetic foot temperatures, particularly in patients with previous ulcers, may easily reach hazard thresholds indicated by previous pressure ulcer studies. The results necessitate further exploration of temperature in the diabetic foot and how it may contribute to ulceration.
(J Am Podiatr Med Assoc 109(5): 345-350, 2019)

*Department of Physical Therapy, University of North Texas Health Science Center, Fort Worth, TX. Drs. Yavuz and Ersen are now with the Department of Healthcare Sciences, Prosthetics and Orthotics Program, University of Texas Southwestern Medical Center, Dallas, TX.

†Department of Physician Assistant, University of North Texas Health Science Center, Fort Worth, TX.

‡Department of Plastic Surgery, University of Texas Southwestern Medical Center, Dallas, TX.

§Department of Orthopaedic Surgery, University of Texas Southwestern Medical Center, Dallas, TX.

||Vivonics Inc and CranioSense, Bedford, MA.

¶Southwestern Academic Limb Salvage Alliance (SALSA) and Keck School of Medicine at the University of Southern California, Tucson, AZ.

#University of North Texas Health Science Center, Fort Worth, TX.

Corresponding author: Metin Yavuz, DEng, Department of Healthcare Sciences, Prosthetics and Orthotics Program, University of Texas Southwestern Medical Center, 5353 Harry Hines Blvd, Dallas, TX 75390. (E-mail: metin.yavuz@utsw.edu)

It has long been hypothesized that prolonged application of mechanical plantar stresses leads to the development of foot ulcers. Both increased plantar pressure and shear provoke an inflammatory response that results in increased pedal temperature and, ultimately, tissue necrosis.[1,2] Brand suggested that "the foot would heat up before breaking down."[3] Bergtholdt and Brand[1] also hypothesized that higher temperatures observed in the diabetic foot may be used to predict progressive soft-tissue damage produced by repetitive moderate stresses. The authors, however, focused on bilateral temperature asymmetries between the right and left feet, pointing out that regional differences may be indicators of an abnormality. They recommended using differences greater than 1°C to detect an abnormality and a possibility of ulcer development. Other researchers have also focused on bilateral temperature differences. A study by Armstrong et al[4] demonstrated that monitoring skin temperatures and limiting physical activity when abnormal temperatures are reached could prevent ulceration, and "abnormal temperature" was defined as a difference of more than 4°F (2.2°C) between bilateral plantar regions. Lavery et al[5] suggested that at-home patient self-monitoring with daily foot temperatures may be an effective adjunctive tool to prevent foot complications in individuals at high risk for lower-extremity ulceration and amputation.

A disadvantage of focusing only on bilateral asymmetries is that abnormally high temperatures at contralateral sites could occur without asymmetry. One may overlook abnormally high bilateral temperatures, leading to missed critical information. Similarly, cooler temperatures that present with bilateral asymmetry can trigger false-positives. Such scenarios may limit the clinical use of temperature as a prediction tool. In fact, a recent report by Frykberg et al[6] revealed that relying on bilateral asymmetries only may lead to a high rate of false-positives in predicting an ulcer.

Skin temperature has long been studied as a causative factor in the formation of pressure ulcers (ie, decubitus ulcers or pressure injury). In a swine model, Kokate et al[7] applied constant pressure of 13.3 kPa using discs that were maintained at different temperatures: 25°C, 35°C, 40°C, and 45°C. The results indicated that no tissue damage was observed at the 25°C sites but that substantial deep tissue damage and necrosis were observed at sites with temperatures of 35°C and higher. The degree of injury significantly correlated with elevated temperatures. Sae-Sia et al[8] confirmed previous computational models that demonstrated increased risk of ulceration due to increased tissue temperatures. Skin temperature in 17 patients was approximately 1.2°C higher ($P < .05$) in those who developed pressure ulcers than in those who did not.[8]

We hypothesize that elevated plantar stresses in patients with diabetes lead to increased tissue temperatures. Elevated temperatures, in turn, attenuate tissue's resistance against a biomechanical failure.[9] Diabetic feet are known to be warmer compared with healthy feet. Several investigators, including Sun et al[10] and Yavuz et al,[9] reported a significant increase in the mean foot temperatures of individuals with diabetic neuropathy (DN) compared with healthy individuals. Furthermore, a study has shown that plantar temperatures rise by approximately 5°C after walking for only a brief period.[11]

The purpose of this study was to quantify region-specific resting plantar temperatures in a cohort of participants with DN and diabetic foot ulcer (DFU) history and to compare nonnormalized results with two other cohorts: participants with DN and diabetic control participants without neuropathy (DC). We hypothesized that absolute nonnormalized plantar temperatures (true-measured) are higher in the DFU group than are temperatures in the DN and DC groups. Clinically, absolute plantar temperatures may not only provide a more reliable clinical tool in management of the diabetic foot but may also offer a research measure to better understand many physiologic and biomechanical factors contributing to the development of ulcers.

Methods

This observational case-control study included 37 people with diabetes: nine in the DFU group, 14 in the DN group, and 14 in the DC group. All of the study procedures were approved by the North Texas Regional Institutional Review Board (Fort Worth, Texas) and the Kent State University College of Podiatric Medicine Institutional Review Board (Independence, Ohio) before recruitment and testing, and informed consent was obtained from participants before testing. Recruitment occurred between January 1, 2011, and June 30, 2015, at two academic medical centers. Patients with confirmed diabetes were referred by physicians to the study. The DFU group consisted of individuals who were known to have a previous plantar ulcer. For the purposes of this study, the DFU group included only patients whose ulcers had remained healed for at least 30 days before enrollment. Participants without an ulcer history were categorized into either the

DN or DC group based on the presence or absence of peripheral neuropathy, respectively. Peripheral neuropathy was assessed with a biothesiometer (Bio-Medical Instrument Co, Newbury, Ohio) and a 5.07 Semmes-Weinstein monofilament according to the 2008 task force report of the American Diabetes Association.[12] A vibration perception threshold of 25 V was used in assessment of neuropathy. Ankle-brachial index (ABI) was calculated using blood pressure data obtained with a Summit Doppler LifeDop ABI unit (model L250ABI; Wallach Surgical Devices, Trumbull, Connecticut). Resting barefoot plantar temperatures were recorded after 10 min of acclimation at ambient room temperature using FLIR T650sc (FLIR Systems Inc, Wilsonville, Oregon) or Fluke TiR2 (Fluke Corp, Everett, Washington) infrared thermal cameras. The foot of each participant was masked by the same investigator into four regions on the thermographs: hallux, medial forefoot (first metatarsal head), central forefoot (second and third metatarsal heads), and lateral forefoot (fourth and fifth metatarsal heads).

The mean temperature in each region was determined, and separate linear models with specified contrasts among the DFU, DN, and DC groups were developed to reveal mean differences for each foot region while controlling for age, sex, body mass index, ABI, and duration of diabetes.

Results

Participant demographic characteristics are shown in Table 1. Significant differences among groups were found for age and sex ($P < .05$). As shown in Figure 1, mean temperature readings in all of the foot regions in the DFU and DN groups were higher than 30.0°C. Mean temperature readings in all of the foot regions were less than 30.0°C in the DC group.

Results of general linear regression models predicting temperature from group while controlling for age, sex, body mass index, ABI, and duration of diabetes indicate group differences in all of the temperature readings (Table 2). Comparing the DN and DC groups, the mean differences ranged from 3.1°C in the central forefoot to 4.5°C in the hallux. Compared with the DC group, the DFU group mean differences were even higher, ranging from 3.2°C in the medial forefoot to 4.9°C in the hallux. No significant differences were observed between the DFU and DN groups at any foot site.

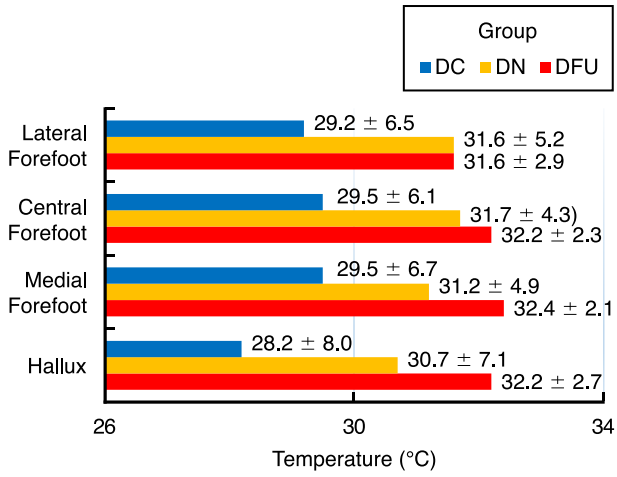

Figure 1. Unadjusted mean ± SD temperatures for the four masked regions of the foot: lateral, central, and medial forefoot and hallux. DC, diabetic nonneuropathy control group; DFU, diabetic neuropathy with diabetic foot ulcer history; DN, diabetic neuropathy.

Discussion

To our knowledge, this is the first study to report true-measured or absolute resting plantar temperatures (not bilateral asymmetries or normalized values) in a cohort of individuals with DN and ulcer history (DFU group) and compare results with individuals with and without DN.

Table 1. Characteristics of the 37 Study Participants

	DFU (n = 9)	DN (n = 14)	DC (n = 14)
Sex, F/M (No.)	2/7	2/12	9/5
Age (mean ±SD [years])	55 ± 15	65 ± 7	52 ± 13
Body mass index (mean ± SD)	33.5 ± 7.8	32.0 ± 5.1	28.9 ± 7.5
Duration of diabetes (mean ± SD [years])	13 ± 4	13 ± 11	14 ± 12
Type 1/2 diabetes (No.)	1/8	2/12	5/9
Vibration threshold (mean ± SD [V])	37.2 ± 14.1	35.8 ± 8.9	11.7 ± 4.8
Ankle-brachial index (mean ± SD)	1.18 ± 0.17	1.18 ± 0.16	1.23 ± 0.15

Abbreviations: DC, diabetic nonneuropathy control group; DFU, diabetic neuropathy with diabetic foot ulcer history; DN, diabetic neuropathy.

Table 2. Group Differences in Temperature Readings

Foot Region and Group[a]	Temperature (°C) Estimate	SE	*P* Value[b]
Hallux			
DN (versus DC)	4.50	1.87	.006
DFU (versus DC)	4.90	1.97	.004
Medial			
DN (versus DC)	3.21	1.40	.008
DFU (versus DC)	3.23	1.47	.012
Central			
DN (versus DC)	3.10	1.33	.007
DFU (versus DC)	3.35	1.40	.006
Lateral			
DN (versus DC)	3.28	1.47	.010
DFU (versus DC)	3.54	1.55	.009
Average temperature			
DN (versus DC)	3.52	1.45	.005
DFU (versus DC)	3.76	1.52	.005

Abbreviations: DC, diabetic nonneuropathy control group; DFU, diabetic neuropathy with foot ulcer history; DN, diabetic neuropathy.

[a]Results from general linear regression models predicting temperature from group while controlling for age, sex, body mass index, ankle-brachial index, and duration of diabetes.

[b]All of the comparisons are significant at $P < .05$.

A variety of factors, including inflammation, may contribute to higher resting plantar temperatures observed in patients with a history of ulceration. Autonomic neuropathy, which is experienced by many patients at an advanced stage of diabetes, may be another factor contributing to higher resting plantar temperatures. Temperature increases are likely with autonomic neuropathy because it impairs sweating, thus hampering regulation of body temperature.[9,13]

Yavuz et al[9] classified temperature increases seen in the foot as acute and chronic. Acute responses are observed immediately after load-bearing activity, such as walking or running, mostly due to kinetic friction initiated by shear forces.[11] Plantar shear stresses may also lead to tissue fatigue failure through exposure to forces that change directions (braking forces in the anterior direction and propulsive forces in the posterior direction) within the same stance phase.[14-17] A chronic thermal response results from prolonged exposure to these repetitive stresses and is usually characterized by inflammation.[9]

Regardless of contributing factors, acute and chronic temperature increases in the diabetic foot will unquestionably accelerate the tissue metabolic rate. For every degree Celsius rise in temperature, tissue metabolism increases by 6% to 13%.[18] In individuals with diabetes and impaired blood circulation, this increase in metabolic demands of the tissue may not be met. This disparity may lead to cell autolysis in diabetic tissue that is already strained due to mechanical factors.[9] In unloaded tissue, elevated temperatures can trigger a vasodilation effect and increase blood perfusion. However, a variety of studies have shown that this is not true in tissue that is under mechanical stress, which may occlude blood flow substantially depending on the magnitude of the stress.[19,20] Therefore, elevated temperatures in the weightbearing (ie, mechanically loaded) diabetic foot is thought to accelerate tissue breakdown. Although bilateral asymmetry, as suggested by Bergtholdt and Brand,[1] may in fact indicate an abnormality, if bilateral temperatures are equal or are over the hazard thresholds, these individuals would not be classified as being at risk for plantar ulceration.

Previous studies have identified specific risks for tissue ulceration.[7,9] Kokate et al[7] identified a plantar temperature of 35°C as the damage threshold when only a pressure of 13.3 kPa was applied. In comparison, the vertical stress experienced by the diabetic foot easily reaches ten times that, oftentimes in the proximity of 200 kPa in shod conditions and as high as 1,000 kPa in barefoot conditions. Moreover, patients with diabetic foot disease experience a substantial amount of shear stress,[13,14,17] a variable that was not applied in the animal model.[5] Therefore, we believe that the damaging effects of increased temperature may be more dramatic in the diabetic foot than what has been evidenced in animal tissue.

Although the resting temperatures in the diabetic foot are significantly higher, as demonstrated by the present study, Yavuz et al[11] revealed that walking for only a brief period resulted in an increase in plantar temperatures of 5.3°C. The study suggested that all of the foot regions in highly insulated diabetic footwear may easily reach the damage threshold of 35°C or greater during normal activity, particularly if the resting plantar temperatures are in the 30°C range. In fact, we revealed in this study that resting plantar temperatures at all of the foot regions were higher than 30.0°C in the DFU and DN groups. This increases the risk of plantar ulceration because temperatures may easily reach the 35°C damage threshold with walking for brief periods. In addition, all of the foot temperatures that we measured were resting barefoot temperatures. Considering that patients with diabetic neuropathy are typically instructed to use highly insulated shoes and socks to protect the feet, it is very likely that the

microclimate in the footwear may lead to higher resting temperatures. It is logical to infer that the temperature damage threshold of 35°C may easily be exceeded with minimal weightbearing activities inside the diabetic footwear, which is usually made of synthetic materials that insulate the foot. Although a study by Armstrong et al[21] indicated that absolute temperature as a one-time screening tool is not predictive of foot ulceration, we believe that continuous monitoring of absolute temperatures may be quite useful; as per Brand, the foot heats up before breaking down.[3]

There are limitations of this study that should be acknowledged. There were no controls in place, in an attempt to mitigate potential confounders such as physical activity. We acknowledge that we did not address physical activity before the study or during the day of the visit, except for the 10-min acclimation period. The three cohorts have a relatively small sample size and may have been underpowered to detect a significant difference in temperature between the DFU and DN groups. Also, the DFU group included only nine patients, which poses a limitation in multivariate statistics. In addition, the inclusion of patients from different study sites could introduce selection bias. Moreover, the use of different thermal cameras at two study sites might introduce additional variation in the results. Although we compare temperatures of the diabetic foot with the results of the study by Kokate et al,[7] we acknowledge that these authors studied only an animal model. However, the results of studies by Kokate et al[7] and others indicate that "the warmer the tissue the more fragile it is." We believe that it is essential to determine the level of damaging temperatures in the human foot. Finally, we recognize that the participant groups differed regarding age and sex.

Despite the limited sample size, this study suggests that elevated foot temperatures in patients with diabetes may be a causative factor in the foot ulceration process. Temperature and skin microclimate has long been associated with pressure ulcer (ie, decubitus ulcer) formation. In light of these findings, the clinical value of plantar temperature in identifying DFUs, and the role of elevated plantar temperature as a key causative ulceration factor, merit further prospective study. Of particular interest is whether plantar ulcers develop at sites experiencing both elevated temperatures and triaxial foot stresses. Detailed investigation of the relationship between shear stress and temperature may lead to better prediction and preventive tools. If it is shown that ulcers develop at sites that bear high true-measured temperatures, clinicians can take counter measures to prevent a developing ulcer, such as off-loading the high temperature regions.

Financial Disclosure: This research was possible due to support from NIH/NIDDK (R15DK082962). None of the funding or supportive agencies were involved in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Conflict of Interest: Yavuz Metin, DEng, Ali Ersen, PhD, Gordon B. Hirschman, MEng, and Linda S. Adams, BS are pursuing patents for temperature-regulating footwear.

References

1. Bergtholdt HT, Brand PW: Thermography: an aid in the management of insensitive feet and stumps. Arch Phys Med Rehabil **56:** 205, 1975.
2. Bergtholdt HT, Brand PW: Temperature assessment and plantar inflammation. Lepr Rev **47:** 211, 1976.
3. Boulton AJ: Diabetic foot: what can we learn from leprosy? Legacy of Dr Paul W. Brand. Diabetes Metab Res Rev **28** (suppl 1)**:** 3, 2012.
4. Armstrong DG, Holtz-Neiderer K, Wendel C, et al: Skin temperature monitoring reduces the risk for diabetic foot ulceration in high-risk patients. Am J Med **120:** 1042, 2007.
5. Lavery LA, Higgins KR, Lanctot DR, et al: Home monitoring of foot skin temperatures to prevent ulceration. Diabetes Care **27:** 2642, 2004.
6. Frykberg RG, Gordon IL, Reyzelman AM, et al: Feasibility and efficacy of a smart mat technology to predict development of diabetic plantar ulcers. Diabetes Care **40:** 973, 2017.
7. Kokate JY, Leland KJ, Held AM, et al: Temperature-modulated pressure ulcers: a porcine model. Arch Phys Med Rehabil **76:** 666, 1995.
8. Sae-Sia W, Wipke-Tevis DD, Williams DA: Elevated sacral skin temperature (T(s)): a risk factor for pressure ulcer development in hospitalized neurologically impaired Thai patients. Appl Nurs Res **18:** 29, 2005.
9. Yavuz M, Brem RW, Glaros AG, et al: Association between plantar temperatures and triaxial stresses in individuals with diabetes. Diabetes Care **38:** e178, 2015.
10. Sun PC, Lin HD, Jao SH, et al: Relationship of skin temperature to sympathetic dysfunction in diabetic at-risk feet. Diabetes Res Clin Pract **73:** 41, 2006.
11. Yavuz M, Brem RW, Davis BL, et al: Temperature as a predictive tool for plantar triaxial loading. J Biomech **47:** 3767, 2014.
12. Boulton AJ, Armstrong DG, Albert SF, et al: Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the

American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. Diabetes Care **31:** 1679, 2008.
13. Yavuz M, Ersen A, Hartos J, et al: Plantar shear stress in individuals with a history of diabetic foot ulcer: an emerging predictive marker for foot ulceration. Diabetes Care **40:** e14, 2017.
14. Yavuz M: American Society of Biomechanics Clinical Biomechanics Award 2012: plantar shear stress distributions in diabetic patients with and without neuropathy. Clin Biomech **29:** 223, 2014.
15. Yavuz M, Erdemir A, Botek G, et al: Peak plantar pressure and shear locations: relevance to diabetic patients. Diabetes Care **30:** 2643, 2007.
16. Yavuz M, Master H, Garrett A, et al: Peak plantar shear and pressure and foot ulcer locations: a call to revisit ulceration pathomechanics. Diabetes Care **38:** e184, 2015.
17. Yavuz M, Tajaddini A, Botek G, et al: Temporal characteristics of plantar shear distribution: relevance to diabetic patients. J Biomech **41:** 556, 2008.
18. Ruch R, Patton H: *Energy Metabolism*, 19th Ed, Saunders Press, Philadelphia, PA, 1965.
19. Lachenbruch C, Tzen YT, Brienza DM, et al: The relative contributions of interface pressure, shear stress, and temperature on tissue ischemia: a cross-sectional pilot study. Ostomy Wound Manage **59:** 25, 2013.
20. Patel S, Knapp CF, Donofrio JC, et al: Temperature effects on surface pressure-induced changes in rat skin perfusion: implications in pressure ulcer development. J Rehabil Res Dev **36:** 189, 1999.
21. Armstrong DG, Lavery LA, Wunderlich RP, et al: 2003 William J. Stickel Silver Award: skin temperatures as a one-time screening tool do not predict future diabetic foot complications. JAPMA **93:** 443, 2003.