The Use of Medical Hyperspectral Technology to Evaluate Microcirculatory Changes in Diabetic Foot Ulcers and to Predict Clinical Outcomes

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OBJECTIVE — Foot ulceration is a serious complication of diabetes, and new techniques that can predict wound healing may prove very helpful. We tested the ability of medical hyperspectral technology (HT), a novel diagnostic scanning technique that can quantify tissue oxy- and deoxyhemoglobin to predict diabetic foot ulcer healing.

RESEARCH DESIGN AND METHODS — Ten type 1 diabetic patients with 21 foot ulcer sites, 13 type 1 diabetic patients without ulcers, and 14 nondiabetic control subjects were seen up to 4 times over a 6-month period. HT measurements of oxyhemoglobin (HT-oxy) and deoxyhemoglobin (HT-deoxy) were performed at or near the ulcer area and on the upper and lower extremity distant from the ulcer. An HT healing index for each site was calculated from the HT-oxy and -deoxy values.

RESULTS — Hyperspectral tissue oxygenation measurements observed changes in tissue immediately surrounding the ulcer when comparing ulcers that heal and ulcers that do not heal ($P < 0.001$). The sensitivity, specificity, and positive and negative predictive values of the HT index for predicting healing were 93, 86, 93, and 86%, respectively, when evaluated on images taken at the first visit. Changes in HT-oxy among the three risk groups were noted for the metatarsal area of the foot ($P < 0.05$) and the palm ($P < 0.01$). Changes in HT-deoxy and the HT healing index were noted for the palm only ($P < 0.05$ and $P < 0.01$, respectively).

CONCLUSIONS — HT has the capability to identify microvascular abnormalities and tissue oxygenation in the diabetic foot and predict ulcer healing. HT can assist in the management of foot ulceration.

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K.T.S, S.V.P, J.E.F., and A.A.P. are all employees of HyperMed, Inc. S.V.P. and J.E.F. own stock in HyperMed, Inc., and R.L. is a paid consultant and owns stock in HyperMed, Inc.

Abbreviations: DFU, diabetic foot ulceration; HT, hyperspectral technology; HT-deoxy, HT measurements of deoxyhemoglobin; HT-oxy, HT measurements of oxyhemoglobin; TCOM, transcutaneous oxygenation monitor.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Diabetic foot ulceration (DFU) remains a serious problem, as 15% of all diabetic patients are expected to be affected with the complication during their lifespan (1). Infected and/or ischemic DFU accounts for ~25% of all hospital stays among diabetic patients, while foot ulceration precedes 85% of lower-extremity amputations (2). Currently, large multicenter studies (3–5) have reported that the healing rate of DFU over a 12- to 20-week period lies between 30 and 60%. Early identification of patients who will go on to fail to heal an ulcer can be of particular help, as it can allow the physician to make the right choice of treatment between a conservative and aggressive path. Pathways can be developed to streamline patient care and to apply new, expensive therapies only in patients who need them.

The evaluation of neuropathy, peripheral vascular disease, presence of infection, and the depth of the ulcer are standard procedures for the management of DFU (6). However, none of the above measurements can predict wound healing. The only method that has previously been shown to predict wound healing is the measurement of changes in the ulcer area over a 4-week period of intensive care (7). However, the positive predictive value of this technique is only 58%, while the negative predictive value is 91%. Additionally, using the measurement-of-change method requires sequential patient examinations and may delay the initiation of appropriate therapy. Therefore, new simple techniques that can provide immediate information with improved accuracy can be of great help in the effective management of DFU.

Medical hyperspectral technology (HT) provides a novel diagnostic tool that quantifies tissue oxygenation and presents it in an anatomically relevant map. HT has been shown to detect systemic and local microcirculatory changes associated with diabetes (8). We have used HT to evaluate oxygen delivery and oxygen extraction of cutaneous tissue based on

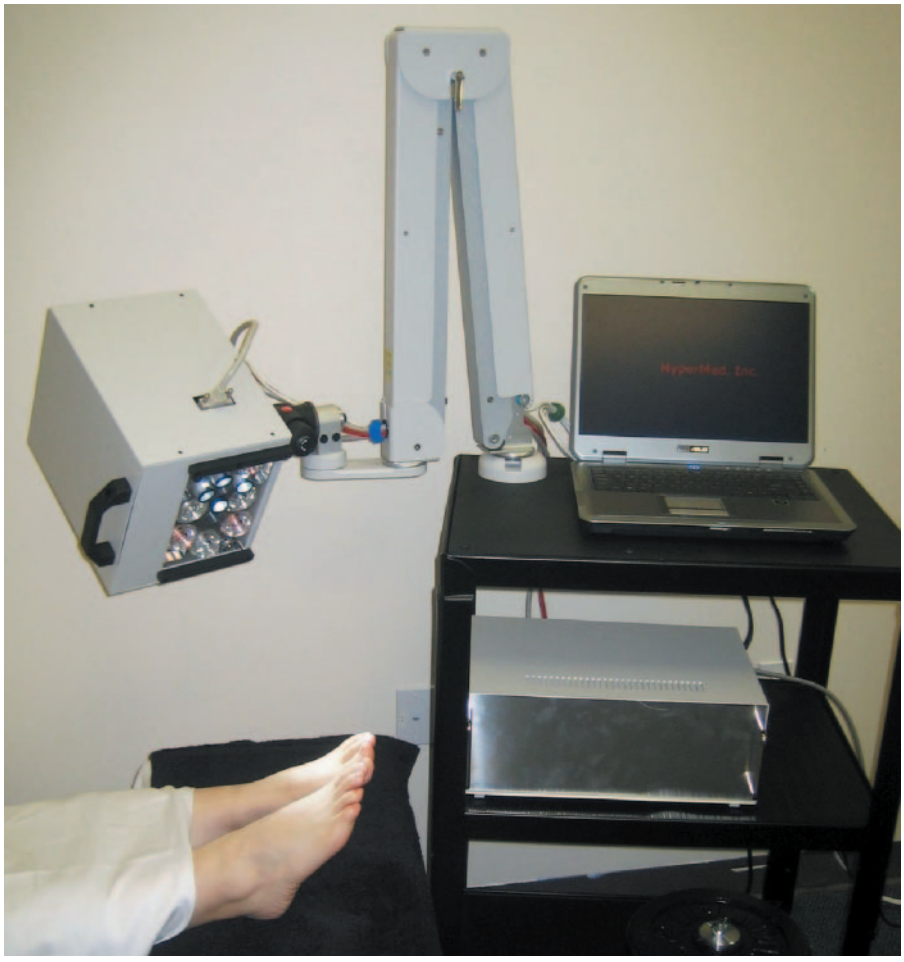

Figure 1—*CombiVu-R Hyperspectral Technology (HyperMed).*

pixel-by-pixel measurements of oxy (HT-oxy)- and deoxyhemoglobin (HT-deoxy) (7–9). In the present study, our main aim was to assess tissue oxygenation around DFUs and assess the ability of this technique to predict DFU healing and track the progress of foot ulcers over a relatively long period of 6 months. A secondary aim was to establish baseline differences between type 1 diabetic patients with ulcers and type 1 diabetic patients and nondiabetic subjects without ulcers.

RESEARCH DESIGN AND METHODS

The study included three groups: healthy nondiabetic subjects, type 1 diabetic patients with no ulcer, and type 1 diabetic patients with at least one foot ulcer at the beginning of the study. The diagnosis of type 1 diabetes was established according to the recommendations of the American Diabetes Association Expert Committee (10). Exclusion criteria included peripheral arterial occlusive disease that was severe enough to require surgical bypass operation, heart failure that resulted in lower-extremity edema, stroke or transient ischemic attack with residual nerve dysfunction, uncontrolled hypertension, end-stage renal disease, and any other serious chronic diseases that can affect wound healing, treatment with systemic glucocorticoids or antineoplastic medications, and pregnant or lactating women. The study protocol was approved by the Beth Israel Deaconess Medical Center Institutional Review Board. All participants gave written informed consent.

Procedures

The type 1 diabetic subjects were seen at baseline, 6 weeks, 3 months, and 6 months, while normal subjects were seen only at baseline and 6 months. Clinical evaluation included age, sex, weight, height, BMI, history of alcohol consumption, type and duration of diabetes, and presence of other micro- and macrovascular complications. The presence of diabetic peripheral neuropathy was defined according to the principles of the San Antonio Consensus criteria (11). For this, the Neuropathy Symptom Score and the Neuropathy Disability Score, the Vibration Perception Threshold using a biothesiometer (Biomedical Instruments, Newbury, OH), and the cutaneous pressure perception threshold using Semmes-Weinstein monofilaments were determined as previously described (12).

Ulcers were classified into two groups: ulcers that healed or ulcers that did not heal. Ulcers with complete reepithelialization and no exudates at the fourth visit (6 months) were considered healed. The healing status of ulcers from subjects who failed to return for the fourth visit was determined from a phone interview by a surgical physician placed at the end of the study. Due to the small size of this study, this criterion was chosen to minimize the loss of subjects due to a failure to complete the study. Patients received regular care by their physicians and were selected from a large number of practices treating type 1 diabetic patients. No criteria for wound size or duration were used to select patients. Physicians caring for the diabetic subjects were blinded to the data and measurements collected in the study.

Evaluation of HT-oxy and -deoxy

Data were collected with a HyperMed CombiVu-R System (HyperMed, Waltham, MA) as previously described (9). In brief, HT is a method of "scanning spectroscopy" based on local chemical composition (13). HT uses a spectral separator to vary the wavelength of light admitted to a digital detector to provide a spectrum for each pixel—a hyperspectral scan. Tissue spectra are compared with standard spectra for oxy- and deoxyhemoglobin and tissue oxyhemoglobin (HT-oxy) and tissue deoxyhemoglobin (HT-deoxy) determined for each pixel. HT-oxy and -deoxy units represent values for oxyhemoglobin and deoxyhemoglobin found in the tissue volume measured by HTcOM (hyperspectral technology cutaneous oxygenation monitoring). For this study, a 30-s tissue scan was obtained at a 12-inch focal distance and ratioed to a calibration scan obtained using a calibrator (Check Pad; HyperMed) The spatial resolution of the HT images was 60 μm. A picture of the HT system used in the study is provided in Fig. 1.

Subjects were studied in a standard reclining chair. HT scans were obtained from the plantar aspect of feet, the palm, and the area around the ulcer, if present.

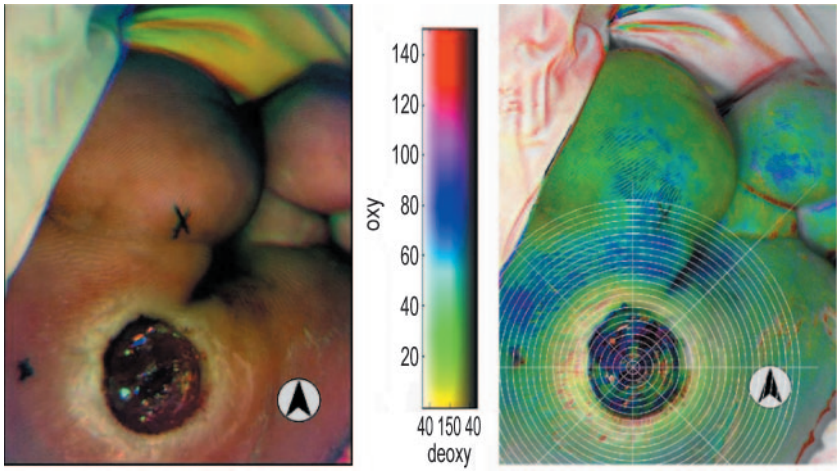

Figure 2—*Radial profile analysis. An example of a radial profile pattern centered on an ulcer in an HT scan; the corresponding true color image of the ulcer is shown. The color bar indicates HT-oxy values along the vertical color scale and HT-deoxy values along the shorter horizontal brightness scale. The color bar is used primarily to give the clinician a rapid way to assess tissue and to target areas from which to obtain quantitative measurements.*

Data were analyzed offline using spectral decomposition, two-dimensional scan processing, and scan registration techniques. Mean HT-oxy and -deoxy values were obtained from a 1-in diameter circle placed at the central region of the scans of the palm and soles. The images were taken from regions that are relatively flat, and the distance between the camera and tissue surface was also fixed to minimize variability in the measurements. Additionally, all foot ulcer scans were overlaid with a pattern of 25 concentric rings spaced by 1 mm and divided into eight (45[degree]) pie segments, thereby forming 200 sectors per ulcer region. The positioning of the pattern was determined in each case on the first subject visit and then replaced in a similar anatomic position in subsequent visits. The center of the concentric ring was placed at the center of the ulcer for ulcers <25 mm in any direction (Fig. 2). For one very large ulcer (>18 cm^2 at maximum), the center of the circular pattern was also placed at four equally spaced points along the quadrants of the ulcer border. This led to the analysis of 21 ulcer sites describing 17 ulcers.

HT-oxy and -deoxy values were obtained for each pixel in the scan. The ulcer margins were outlined from color images before HT analysis. Mean HT-oxy and -deoxy values were obtained from each of the sectors covering intact skin outside the ulcer. Hemoglobin oxygen saturation values were calculated from HT-oxy and -deoxy values as previously described (9). An HT healing index was also calculated to provide a single quantitative measurement to use in the prediction of ulcer healing. Mathematically, the HT healing index is a simple algorithm defined as the distance between the point defined by HT-oxy and -deoxy and a discriminant line that best separates healing and nonhealing ulcers. HT-oxy, -deoxy, and healing index are all reported in HT units. Colorized scans were created to demonstrate tissue oxygenation. HT-oxy levels are associated with different colors and HT-deoxy with different levels of brightness (intensity), as depicted on the color bar provided alongside each image.

Healing for the ulcers was determined at the fourth (6-month) visit, and ulcers were considered healed if the wound was completely reepithelialized. Healing for three ulcers was determined from a phone interview due to a missed fourth visit (two healed and one did not).

Laser Doppler blood flow measurements

Endothelium-dependent vasodilatation in the cutaneous microcirculation was measured by laser Doppler flowmetry. The measurement was performed on the dorsum of both feet and volar aspect of the forearm as previously described (14). Laser Doppler images at each site were obtained with a Laser Doppler Perfusion Imager (Lisca PIM 2.0; Lisca Development, Linkoping, Sweden).

Transcutaneous oxygenation monitor measurements

Transcutaneous oxygen pressures were measured on the dorsum of the left and right foot using a transcutaneous oxygen monitoring (TCOM) system (model PF5040; PeriMed). Oxygen partial pressures measured in millimeter of mercury (mmHg) were recorded from the sites 20 min after attaching the probes onto the skin, and equilibrium was established.

Statistical analysis

The statistical analysis was performed by a professional biostatistician (R.L.). All multivariate analyses were carried out using ANOVA and standard extensions of ANOVA such as mixed-effects ANOVA. In these analyses, the continuous outcomes were biometric indexes: HT-oxy, HT-deoxy, healing index, hemoglobin oxygen saturation, TCOM measurements, laser Doppler, ankle-brachial pressure index, Neuropathy Symptom Score, and Neuropathy Disability Score. The independent variable of primary interest was the level of risk: no diabetes, type 1 diabetes without ulcers, type 1 diabetes with ulcers, or a subset of these categories such as healing versus nonhealing ulcer. Covariates included body site and clinic visit. The compound variable subject*ulcer_segment was the random effect used in the mixed-effects models of HT measurements at each ulcer site. This conservative method accounted for the large number of repeated measures made at each ulcer site.

Analyses that report on pairwise differences used the standard *t* tests obtained after an ANOVA that set the SE equal to the root of the mean squared error. We distinguish between the raw unadjusted mean values and the ANOVA-balanced least-square means obtained after fitting an ANOVA model.

The discrimination analysis was obtained with linear discriminant analysis. The HT healing index is defined as the distance between each HT measurement point (HT-oxy and -deoxy) and the discriminant boundary that separates the healing ulcer sites from the nonhealing ulcer sites.

RESULTS — The study included 10 type 1 diabetic patients with foot ulceration, 13 type 1 diabetic patients without ulcers, and 14 nondiabetic control subjects. All groups were matched for age and sex. Details about the subjects' characteristics are given in Table 1. Based on the TCOM measurements and ankle-brachial pressure index baseline measurements, all patients with ulcers had typical neuropathic ulcers in the absence of peripheral arterial disease.

Table 1—*Demographics and clinical characteristics of participants*

	Type 1 diabetic subjects with DFU	Type 1 diabetic subjects without DFU	Control subjects
n	10	13	14
Age (years)	51 (38–64)	48 (24–68)	41 (23–70)
Sex (male/female)	6/4	8/5	6/8
BMI (kg/m^2)	29 ± 7	28 ± 4	28 ± 7
Diabetes duration (years)	31 ± 12	26 ± 13	—
Systolic blood pressure (arm, mmHg)*	133 ± 20	124 ± 16	113 ± 9
Diastolic blood pressure (arm, mmHg)	76 ± 8	76 ± 10	72 ± 7
Ankle-brachial pressure index	1.14 ± 0.19	1.14 ± 0.16	1.24 ± 0.14
TCOM (mmHg)	46 ± 16	54 ± 11	52 ± 18
Laser Doppler (AUs flux)	116 ± 18	112 ± 22	120 ± 50
Neuropathy Symptom Score*	5 ± 3	4 ± 3	1 ± 1
Neuropathy Disability Score†	15 ± 8	3 ± 3	0 ± 0
Vibration Perception Threshold (V)†	44 ± 10	18 ± 10	10 ± 7
Semmes-Weinstein filaments (marking number)†	6.2 ± 0.9	4.4 ± 0.8	3.6 ± 0.7

Data are means ± SD unless otherwise indicated. *Type 1 diabetic subjects with DFU vs. control subjects ($P < 0.05$). †DFU vs. type 1 diabetic subjects vs. control subjects ($P < 0.05$).

Comparison between healing and nonhealing ulcers and a symmetrical area of intact skin at the contralateral foot

For this analysis, we compared measurements from hyperspectral scans taken from intact tissue immediately surrounding the ulcer using a radial circle grid. The group estimates, which were based on all visits, were evaluated and are shown in Table 2.

There were 21 ulcer sites studied in 10 diabetic patients. Twelve ulcer sites were located on the plantar foot surface, six were located on the dorsal area of the foot, and three were located around the ankle. Initial ulcer size ranged from 0.1 to 6.5 cm^2. Initial size was not associated with nonhealing ulcers. Seven ulcer sites from three subjects failed to heal, and data from 27 visits were included for the analysis. Fourteen ulcer sites from nine subjects completely healed, and data from 39 visits were included in the analysis. Three sites (feet with healing ulcers, feet with nonhealing ulcers, and contralateral nonulcer feet) were treated as separate groups, in part because one subject had an ulcer on one foot that healed and an ulcer on the other foot that did not heal. As a result, the analysis was done at the foot level and not the subject level. All measured HT values were significantly different among all three groups ($P < 0.0001$). HT-oxy measurements were lowest in the skin area around the ulcers that did not heal when compared with those that did heal ($P < 0.01$) and with measurements from the contralateral limb ($P < 0.0001$). There were also differences noted between skin around ulcers that did heal and the contralateral limb ($P < 0.01$). The results of HT-deoxy measurements and the HT healing index were similar to the HT-oxy results; the same differences existed among all three groups, being lowest in the skin area around the ulcers that did not heal when compared with those that did heal and the intact skin of the contralateral limb. No differences were observed among any groups using measurements of the resting skin blood flow obtained by laser Doppler flowmetry or measurements of the skin oxygenation levels obtained by TCOM measurements.

Scans and numerical data from a subject with one ulcer on each foot, one of which healed and one of which extended and led to amputation, are provided in Fig. 3.

Identifying healing ulcers with hyperspectral tissue oxygenation measurements

The HT healing index was determined at 21 ulcer sites in tissue immediately surrounding the ulcer (Fig. 4). Ulcer sites that had healed at 6 months ($n = 14$) were

Table 2—*Assessment of tissue oxygenation and perfusion by multiple techniques in type 1 diabetic subjects*

	Subjects with nonhealing ulcers	Subjects with healed ulcers	Subjects with contralateral site without an ulcer	*P*
Measurement sites (*n*)	7	14	7	
Measurement site visits (*n*)	27	39	22	
HT-oxy (AUs)	38 ± 2	50 ± 3	62 ± 4	<0.0001
HT-deoxy (AUs)	26 ± 3	49 ± 2	71 ± 4	<0.0001
HT healing index (AUs)	−8.5 ± 2.9	16 ± 3	38 ± 5	<0.0001
TCOM (mmHg)	58 ± 4	53 ± 3	48 ± 3	0.2021
Laser Doppler (AUs units)	122 ± 10	112 ± 6	113 ± 7	0.6706
Ankle-brachial pressure index	1.2 ± 0.05	1.1 ± 0.03	1.2 ± 0.03	0.2132

Data are group estimates ± SEM unless otherwise indicated.

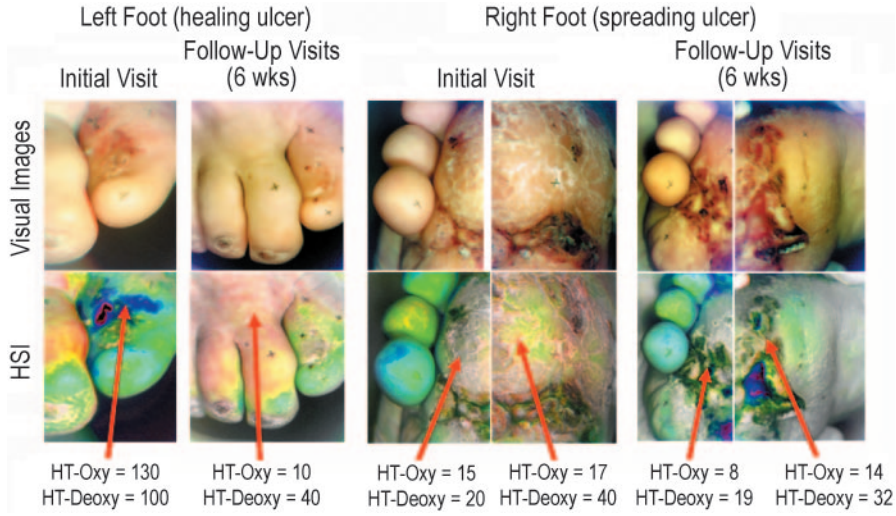

Figure 3—*This 52-year-old patient with a long-standing history of type 1 diabetes and recurrent ulcers bilaterally presented at his first study visit with an ulcer on each foot. Shown are two visits separated by 6 weeks. At his first visit, the patient had one ulcer on the big toe of the left foot and one ulcer on the 2nd metatarsophalangeal joint of the right foot. The elevated HT measurements on the right foot predicted that the ulcer would not heal. On return 6 weeks later, these predictions were seen to be correct, with areas that HT indicated would heal having healed, areas predicted not to heal having not healed, and areas indicated to be at risk becoming involved in ulcer spread. Of note, this patient's entire right foot deteriorated substantially between visits, not only with spreading of the ulcer but also a generalized decrease of both HT-oxy and -deoxy parameters. Note new sharp edges of the wound after debridement. This debridement may have contributed to the further deterioration of the right foot. This subject subsequently had a right below-the-knee amputation.*

compared with ulcer sites that did not heal ($n = 7$). HT healing index data collected at the first visit are reported in Fig. 4*A*. The HT healing index was determined to best separate healing from nonhealing ulcers. Sites having a positive HT healing index were predicted to heal, while sites with a negative HT healing index were predicted to not heal. The sensitivity, specificity, and positive and negative predictive values of the HT healing index to predict healing were 93% (95% CI 66–100), 86% (42–100), 93% (66–100), and 86% (42–100), respectively. In Fig. 4*B*, the same HT healing index was collected from ulcer sites at the first, second, and third visits. The sensitivity, specificity, and positive and negative predictive values for healing were 86% (70–95), 86% (64–97), 91% (76–98), and 78% (56–93) when evaluated on data from the first three visits. The reported positive and negative predictive values are reasonable approximations for this small population because the prevalence of ulcers that heal is close to 50% (15), which is the assumption made when using the equations to calculate these values. In all cases, healing was defined at the end of the 6-month study.

Comparison of HT measurements among the three groups of subjects

We measured HT-oxy and -deoxy and calculated the HT healing index at ulcer-free locations on the upper and lower extremities (mid-palm and metatarsal foot sole). Both of these tissue regions are covered by glabrous skin that is rich in arteriovenous anastomosis and allows extensive a-v shunting. Glabrous skin in general has higher levels of oxygenation and greater reactivity than skin from other parts of the body.

Changes in HT-oxy among the three risk groups were noted for the metatarsal area of the foot ($P < 0.05$) and the palm ($P < 0.01$). Differences among the three risk groups were also noted at the palm site for HT-deoxy ($P < 0.05$) and HT healing index ($P < 0.01$). Pairwise differences are presented in Fig. 5.

CONCLUSIONS

— In the present study, we have shown that tissue oxygenation measurements over a 6-month period using medical HT, a novel technique, can satisfactorily identify ulcers that progress to complete healing and ulcers that fail to heal. This was achieved by performing HT measurements in skin tissue immediately surrounding ulcers. Furthermore, differences were also observed in HT measurements from healthy, nonulcerated skin tissue at the contralateral limb and measurements at skin tissue surrounding healing or nonhealing ulcers.

Wounded tissue has a greater oxygen demand during the healing process, and this requires greater oxygen extraction and greater oxygen delivery. HT measurements of the area around a wound or ulcer provide an indication of oxygen delivery by providing a measurement of oxyhemoglobin (HT-oxy) and an indication of oxygen extraction by providing a measurement of deoxyhemoglobin (HT-deoxy). As expected, in the present study, there are increased levels of both HT-oxy and -deoxy in wounds that heal versus those that do not. Whether the primary culprit is macro- or microvascular disease, tissue with vasculature that is incapable of supplying sufficient blood and oxygen simply will not heal. In addition to the HT-oxy and -deoxy measurements, an HT healing index has been developed to incorporate information derived from these two measurements to provide a single number for easy clinical use. In general, if the HT healing index is >0, it is likely that a given wound or ulcer will heal. If the HT healing index is <0, it is likely that the ulcer will not heal.

As mentioned in the introduction, the best previously available technique to predict healing in DFU is the assessment of ulcer size reduction over a 4-week period (7). Of note, this technique is characterized by a strong negative predictive value, thereby identifying the ulcers that are not going to heal, but has only a moderate positive predictive value. In contrast, HT measurements were shown to have both high positive and negative predictive values. Importantly, these highly sensitive and highly specific HT values were based on data collected at a single visit. Thus, in our first analysis, the HT data collected at the first visit led to predictions of healing at 6 months. Furthermore, the technique held up, with similarly high predictive values, when the results of the first three visits were analyzed.

These findings may have important clinical implications, as they suggest that one HT measurement at the first visit of the patient or HT measurements every few months in slowly healing or nonhealing ulcers can assist the physician with diagnosis, choice of therapy, and therapeutic monitoring. At the initial visit, HT measurements may improve diagnosis

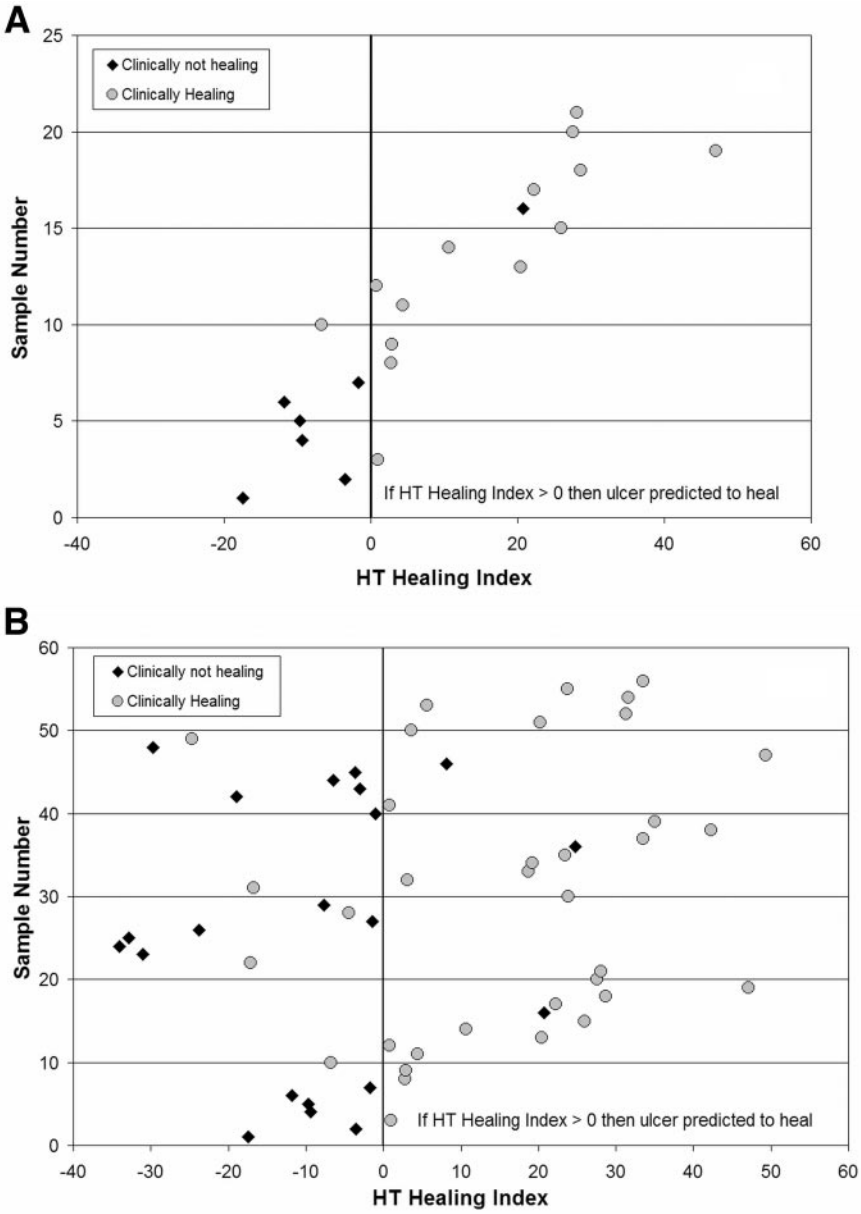

Figure 4—*HT healing index for healing and nonhealing ulcers as measured from tissue immediately surrounding the ulcer. Data for the first visit (*A*) and the first three visits (*B*) are shown. A positive index indicates that the ulcer should heal. From the first visit, the HT healing index correctly predicted 13 of 14 ulcer sites to heal that did heal and 6 of 7 ulcer sites not to heal that did not heal.*

and guide the physician toward earlier aggressive evaluation and therapy. Sequential HT measurements may then lead the physician to tailor and better individualize a patient's therapeutic regimen to follow a conservative or a more aggressive path. Throughout the treatment process, quantitative HT measurements may provide the physician with better information with which to decide whether intensive treatment with expensive new therapeutic modalities is required. HT may also provide a therapeutic monitoring tool to help the physician better evaluate the response to such treatment.

The intent of the present study was to perform an observational study that tracks the association between HT measurements and wound healing. It was not designed to test the efficacy of a particular treatment of the wound. Patients received regular care by their physicians and were selected from a large number of practices treating type 1 diabetic patients. No criteria for wound size or duration were used to select patients. Although these choices may introduce other confounding factors, these factors may affect the progress of wound healing but by no means affect the association between wound healing and HT measurements.

Previous studies in our unit have also shown that tissue oxygenation, assessed with HT at the forearm and the dorsum of the foot, is reduced in the skin of diabetic patients and that this impairment is accentuated in the presence of neuropathy at the foot level (8). In the present study, we compared differences in nonulcerated tissue in the lower and upper extremities. For our HT measurements, we examined the plantar metatarsal area of the foot and the palm that are covered by glabrous skin that is rich in arteriovenous anastomosis and has increased blood flow. We chose these areas because foot ulcers mainly occur in this type of skin and because previous studies (16,17) have indicated different mechanisms of vasodilation in this area when compared with hairy skin that has considerably less arteriovenous anastomosis. The observed results in glabrous skin areas were similar to HT results we previously observed at the dorsum of the foot and the forearm areas of hairy skin. Therefore, these results suggest that HT measurements are useful to identify differences in both glabrous and hairy skin. The fact that the differences were more pronounced at the palm, an area with high blood flow, further supports the fundamental principle that HT is measuring tissue oxy- and deoxyhemoglobin. The current data support previous findings that HT can demonstrate local, regional, and systemic changes associated with progression of diabetes.

Further to the above, we also believe that the small size of the three compared groups was the main reason for the lack of statistical significance in all of the comparisons among all three subject groups. However, it should be noted that the measurement of HT tissue oxygenation in these areas in the present study was mainly undertaken to obtain baseline measurements in glabrous areas of the two extremities and to show that these measurements are parallel to those observed in the hairy skin. We did not intend to replicate the results of a previous study in larger numbers of subjects (8). This is the main reason for the lack of statistical power to identify differences in every measured area among all three studied groups. Despite this, we believe that the observed results allow us to satisfactorily address our hypotheses. Clearly,

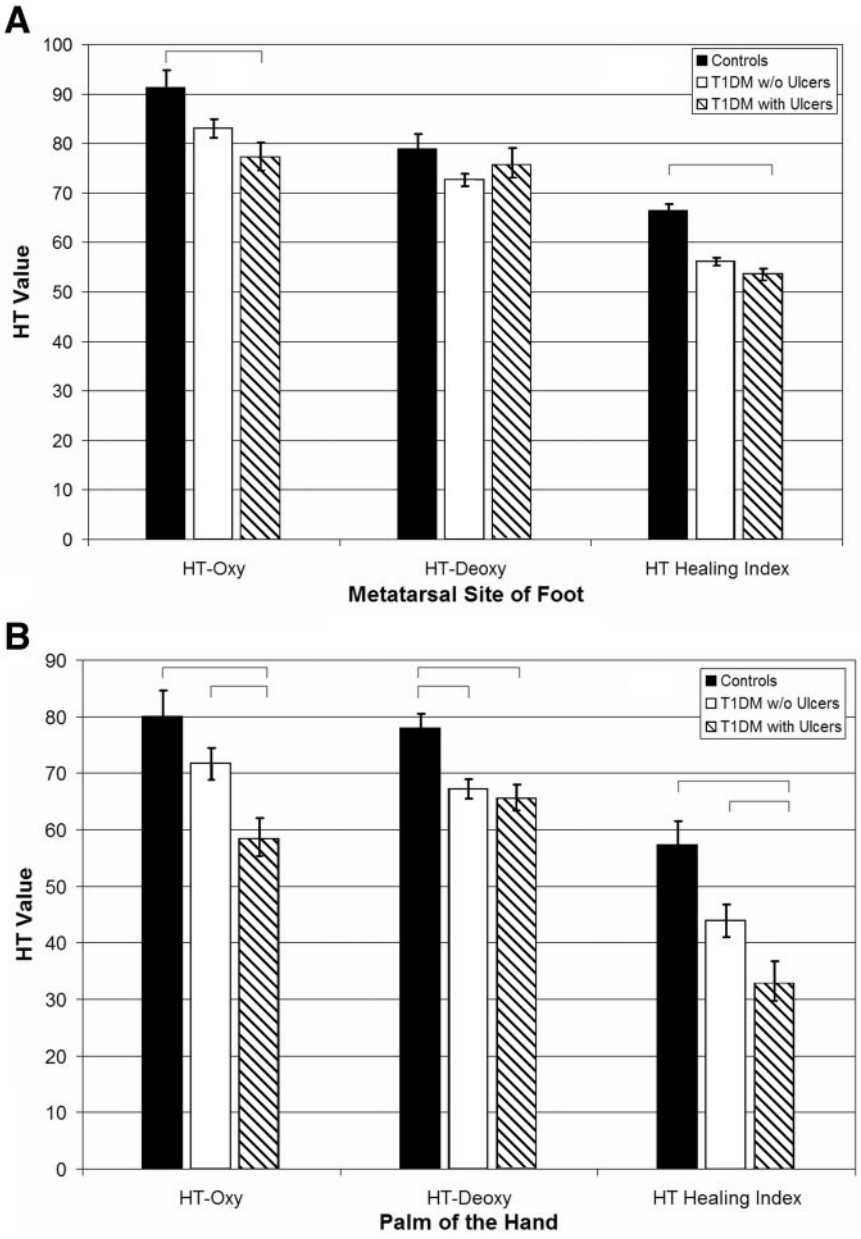

Figure 5—*HT-oxy and -deoxy and HT index values measured at the metatarsal area of the sole* (A) *and the palm of the hand* (B). *Values represent means ± SEM. Statistically significant pairwise differences* ($P = 0.05$) *are denoted by horizontal brackets.*

there were statistically significant differences in the upper-extremity measurements between subjects with ulcers and nondiabetic subjects and differences between subjects with ulcers and control subjects. The current data support previous findings that upper-extremity HT measurements are altered in diabetic subjects and further altered in subjects with more advanced disease as manifested by complications.

As we have seen before, upper-extremity HT measurements can be seen to be reflective of the systemic microvasculature, since the upper extremity is traditionally not differentially affected by diabetic microvascular or macrovascular disease to the extent of the lower extremities (14). Measurements at nonulcerated foot sole surfaces, in turn, provide regional information that can be considered indicative of the combination of both microvascular and macrovascular changes associated with atherosclerotic disease in large vessels exacerbated by diabetes. Most important, the HT technique can be used to investigate the area around an ulcer, which is subjected to a combination of local, regional, and systemic pathophysiology. The capability of a wound to heal is clearly influenced by all of these factors, and the anatomically relevant HT measurement at the wound site demonstrates the result of multiple factors on the wounded area.

The present study has its limitations. One limitation is that it included a relatively small number of subjects, and, when present, multiple ulcers from the same subjects or ulcer sites were entered in the analysis. The main reason for this is that this study was designed to provide proof-of-concept that HT can be used to predict DFU healing. The fact that we were able to obtain statistically relevant data from this relatively small sample size speaks to the power of the technique and its clinical relevance. Another factor to be considered is the limitation of the study exclusively to patients with type 1 diabetes. This decision was due to the fact that the work was supported by an NIH-NIDDK award that had been earmarked for research in type 1 diabetes. Because this work was supported by an NIH-NIDDK award, this study only included patients with type 1 diabetes.

However, given the current consensus that the pathogenesis, natural history, and healing rates of DFU are similar in both type 1 and 2 diabetes, we believe that the exclusive evaluation of type 1 diabetic patients does not affect the applicability of the results to the whole diabetic population with DFU (6). Further studies to provide data on larger numbers of patients and also to include patients with type 2 diabetes are underway.

In summary, in the present study we tested the ability of medical HT to predict DFU healing and track the progress of foot ulcers over a relatively long period of 6 months. Our results provide proof of concept that the technique can satisfactorily predict ulcer healing and has the capability to assist in the management of DFU. Use of HT to improve diagnosis can lead to implementation of early interventions and have important effects on clinical management of the diabetic foot.

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