Percent Change in Wound Area of Diabetic Foot Ulcers Over a 4-Week Period Is a Robust Predictor of Complete Healing in a 12-Week Prospective Trial

PETER SHEEHAN, MD[1]
PETER JONES, MSC[2]
ANTONELLA CASELLI, MD[3]
JOHN M. GIURINI, DPM[3]
ARISTIDIS VEVES, MD[3]

OBJECTIVE — To assess the ability of the 4-week healing rate to predict complete healing over a 12-week period in a large prospective multicenter trial of diabetic patients with foot ulceration.

RESEARCH DESIGN AND METHODS — We examined the change in ulcer area over a 4-week period as a predictor of wound healing within 12 weeks in patients who were seen weekly in a prospective, randomized controlled trial.

RESULTS — Wound area measurements at baseline and after 4 weeks were performed in 203 patients. The midpoint between the percentage area reduction from baseline at 4 weeks in patients healed versus those not healed at 12 weeks was found to be 53%. Subjects with a reduction in ulcer area greater than the 4-week median had a 12-week healing rate of 58%, whereas those with reduction in ulcer area less than the 4-week median had a healing rate of only 9% ($P < 0.01$). The absolute change in ulcer area at 4 weeks was significantly greater in healers versus nonhealers (1.5 vs. 0.8 cm^2, $P < 0.02$). The percent change in wound area at 4 weeks in those who healed was 82% (95% CI 70–94), whereas in those who failed to heal, the percent change in wound area was 25% (15–35; $P < 0.001$).

CONCLUSIONS — The percent change in foot ulcer area after 4 weeks of observation is a robust predictor of healing at 12 weeks. This simple tool may serve as a pivotal clinical decision point in the care of diabetic foot ulcers for early identification of patients who may not respond to standard care and may need additional treatment.

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Foot ulcers remain a costly and disabling clinical problem, often resulting in a prolonged course of treatment and amputation of the limb in patients with diabetes. Foot problems in patients with diabetes also represent a major public health challenge of growing proportions (1). A total of ~2.5% of patients with diabetes develop foot ulcers each year, whereas the most frequent cause of hospitalization of diabetic patients is existence of serious foot or lower-extremity problems (2). More than 15% of foot ulcers result in amputation of the foot or limb (3). Lower-extremity amputations now surpass 100,000 individuals annually in the U.S. (4). The resulting burden to society in terms of costly health care is substantial. A 1998 study identified the total cost of treatment of a lower-extremity ulcer as $4,595 per ulcer episode (5). The associated costs of care for a foot ulcer approach $28,000 over a 2-year period (3). Other recent reviews suggest that the total costs of treating a diabetic foot ulcer range from $10,000 to nearly $60,000 (6–8).

The treatment of diabetic ulcers is complex. The fundamentals of good clinical care include adequate off-loading, frequent debridement, moist wound care, treatment of infection, and revascularization of ischemic limbs (9). Even when properly managed, the wounds may not heal in a timely fashion. Foot ulcers that do not heal in an expedient amount of time are expected to be more likely to become complicated by intervening infection, hospitalization, and amputation and, thus, to be more costly because of the increased utilization of healthcare resources.

New advanced wound care topical dressings are emerging that may improve wound care (10). Moreover, in the past few years, newer treatment technologies have been introduced that have been shown to increase the probability of complete wound closure in difficult-to-heal foot ulcerations in patients with diabetes. These include recombinant platelet-derived growth factor BB, a human living skin equivalent and a human fibroblast–derived dermal substitute (11–13). Because of the expense of these products, they cannot be used universally in the treatment of diabetic foot ulcers but rather are used and reserved for difficult-to-heal wounds. Presently, however, there are no early predictive factors to guide clinicians to differentiate patients who will heal readily from those who will have a prolonged course of treatment.

From the [1]Diabetes Foot and Ankle Center, Hospital for Joint Diseases Orthopaedic Institute, New York University School of Medicine, New York, New York; [2]With Confidence Ltd., Surrey, U.K.; and the [3]Joslin-Beth Israel Deaconess Foot Center and Microcirculation Laboratory, Department of Surgery, Beth Israel-Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts.

Address correspondence and reprint requests to Aristidis Veves, MD, Joslin Beth Israel Deaconess Foot Center, One Deaconess Rd., Boston, MA 02215. E-mail: aveves@caregroup.harvard.edu.

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

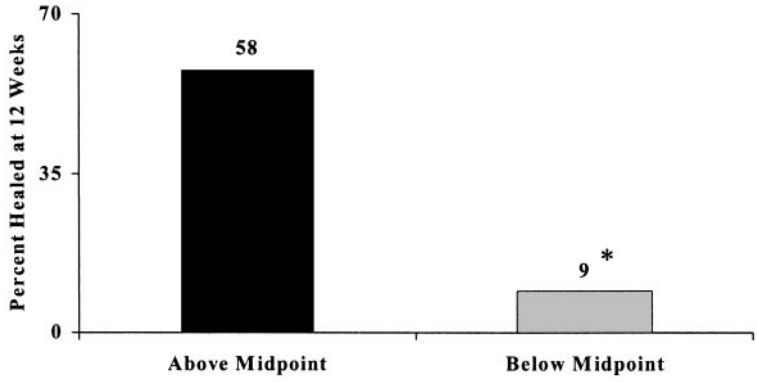

Figure 1—*Percentage of patients in whom ulcers healed during the 12-week period of the study. A total of 58% of the patients who had a reduction in the ulcer area above the midpoint between healing rates at 4 weeks (>53%) had healing of their ulcers (black column), compared with only 9% of the patients with an ulcer reduction area below the median (gray column,* $P < 0.001$*).*

Therapists can only rely on good clinical judgment and personal experience in deciding when to use more aggressive or more expensive technologies and interventions. Therefore, the establishment of predictors of complete wound healing would allow clinicians to have valuable clinical decision-making tools that assist in designing a treatment plan for patients with diabetic foot ulcers. Furthermore, validated predictors of healing could also serve as surrogate end points in the evaluation of new treatments and allow more efficient design of clinical trials.

The purpose of this study was to identify early factors predictive of complete wound healing in data derived from a large, prospective clinical trial of diabetic foot ulcers.

RESEARCH DESIGN AND METHODS

— The data of the present study are derived from a large, prospective multicenter trial that compared a collagen/oxidized regenerated cellulose dressing (Promogran; Ethicon, Somerville, NJ) with moistened gauze in management of diabetic foot ulcers. The methods and results of the study have been reported elsewhere (10). In brief, the trial was a multicenter study conducted in 11 U.S. sites; it was a prospective randomized, controlled trial that was open label with a parallel study design. The study duration was 12 weeks. Patients were eligible for enrollment in the study if they had diabetes and a foot ulcer of at least 30 days' duration (Wagner grade I–II) with an area of at least 1 cm^2 (greatest length × greatest width). All foot ulcers were uncomplicated by infection or ischemia.

The protocol was designed according to the fundamental treatment principles of the expert panel to the American Diabetes Association (ADA) Consensus Development Conference on Diabetic Foot Wound Care (14). This included frequent debridement, adequate off-loading, and moist dressings. The target wound's greatest length, width, and depth were measured at baseline. The ulcer size was calculated by multiplying the length and width. The ulcers were also photographed and measured with planimetry using an acetate tracing. Patients were randomized at the time of screening. Follow-up evaluations and ulcer assessments were completed on a weekly basis for complete healing during the 12-week period of the study. For the purpose of this study, complete wound healing was defined according to the criteria of the Wound Healing Society as 100% reepithelialization of the wound surface with the absence of drainage.

Statistical analysis

Data were entered and verification/validation programs were run on a Microsoft Access 97 database. Statistical analysis was performed using the SAS System Release 6.12 (SAS Institute, Cary, NC). The χ^2 test was used for comparison in the healing rate between the two groups.

RESULTS — A total of 276 patients from 11 centers were enrolled in the study and randomized to either moistened gauze or Promogran. A total of 138 patients (50%) were enrolled in each group, and all patients received study therapy according to their randomization. The comparison of the week 4 and week 12 results is limited to 203 patients, because data were insufficient for 73 subjects. Average age was 58 ± 11 years (mean ± SD), 74% were men, and average ulcer duration was 7.0 months (range 1–144). Average wound area was 2.8 cm^2 (range 0.2–42.4). There were no differences in any characteristics between patients who were included in this study and those who were not.

The midpoint between the percentage area reduction from baseline at 4 weeks in patients healed versus those not healed at 12 weeks was found to be 53%. In 20 participants, ulcers were healed before week 4. At 12 weeks, patients who

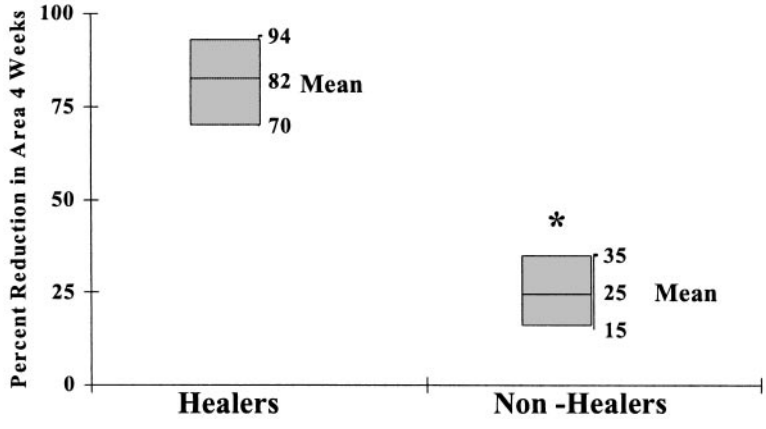

Figure 2— *Mean percent reduction in ulcer area during the first 4 weeks of the study in patients whose ulcers healed completed during the 12-week study period (healers) and those in whom ulcers failed to heal (nonhealers). The healers had a mean percent reduction in ulcer area of 82% (95% CI 70–94), which was significantly higher than that of the nonhealers, who had a reduction of 25% (15–35,* $P < 0.001$*).*

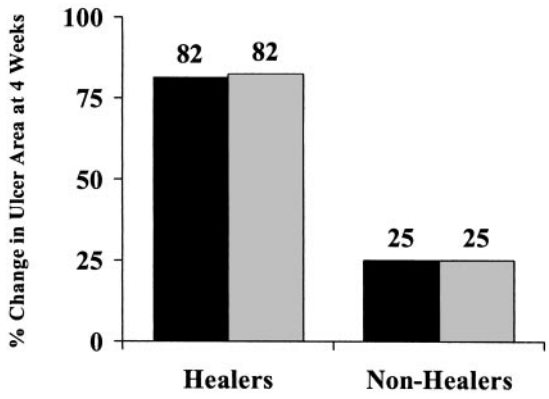

Figure 3—*Mean percent reduction in ulcer area during the first 4 weeks of the study in patients who were treated with Promogran, the investigational device (black columns), and those who received standard care with regular gauze moistened in normal saline (gray columns). In both groups of patients in whom ulcers healed during the 12-week study period (healers) and those who failed (nonhealers), the mean reduction was very similar, indicating no effect of the chosen treatment on the ability of the 4-week change in ulcer area to predict complete wound healing.*

had an ulcer area reduction greater than the median healed in 58% of cases, whereas those with reduction less than the median healed in only 9% of cases ($P < 0.001$, Fig. 1). The sensitivity of this cutoff point of 53% reduction in ulcer area during a 4-week period to predict complete wound healing over a 12-week period was 91%, the specificity was 58%, the positive predictive value was 58%, and the negative predictive value was 91%.

The mean absolute reduction in ulcer area at 4 weeks was 1.5 cm^2 in the healing group versus 0.8 cm^2 in the nonhealing group ($P < 0.02$). More striking, the mean percent reduction in ulcer area in the healers was 82 (95% CI 70–94) vs. 25 (95% CI 15–35, $P < 0.001$) in the control subjects (Fig. 2). The 4-week change in ulcer area in the healers and in the nonhealers was not affected by treatment, as the percent change observations were comparable between the Promogran-treated group and the gauze-treated group (Fig. 3). Therefore, the 4-week change in ulcer area, as a predictor of complete wound healing, was independent of the treatment each participant received.

CONCLUSIONS — In this study, the data were extracted from a prospective, controlled trial of diabetic foot ulcers that were not complicated by ischemia or infection, in which good clinical care was given, including off-loading, frequent sharp debridement, and moist wound dressings. Our data indicate that wound area changes, both absolute and relative, over a 4-week period can strongly predict complete wound healing over an extended 12-week period. Therefore, the absolute change in ulcer area at 4 weeks was significantly greater in healers versus nonhealers. The most striking finding of this study, however, is that the 4-week percent change in wound area was a strong predictor of complete healing. Therefore, using the 53% reduction in ulcer area as the cutoff point, very satisfactory sensitivity (91%) and negative predictive value (91%) were observed.

The importance of our findings is that the 4-week percent change in wound area can be used as an accessible and pivotal clinical decision point in the management of patients with diabetic foot ulcers, allowing a dichotomy of patients, distinguishing those in whom healing will be difficult from those who will heal readily with good standard care. Therefore, patients in whom ulcer size fails to reduce by half over the first 4 weeks of treatment are unlikely to achieve wound healing over a reasonable period. This can be extremely valuable in the costly and complicated management of foot ulcers in patients with diabetes and would allow early identification of patients who will require more aggressive or more expensive treatments.

Although many factors have been evaluated in the literature as early predictors of wound healing, none have been consistently identified. Wound duration has been the most commonly noted predictor (longer duration less likely to heal), followed by wound size and depth (15). Unfortunately, when used, the definitions are often arbitrary and are based on retrospective data. Recently, several studies involving wounds of differing etiologies have found that early changes in wound area may predict ultimate wound healing. Robson et al. (16) have emphasized early wound area changes and their relation to complete closure in the construction of area/time healing curves or wound healing trajectories. Van Rijswijk et al. (17) reported that the 2-week change in area of pressure ulcers is associated with complete wound healing. In addition, several authors (18–20) have found that healing of venous leg ulcers may be predicted by early healing rates. In their analysis of a large multicenter prospective trial of a bilayered skin equivalent in venous leg ulcers, Phillips et al. (21) found the percent wound area change at 3 weeks to be a good predictor of complete wound healing at 20 weeks but not as significant as wound duration.

It should be emphasized that venous ulcers have different pathophysiology than the diabetic foot ulcers, and therefore, data from these chronic wounds may have little significance in predicting diabetic foot ulceration. There are very few data available regarding diabetic ulcers, and the present study is one of the first to use a simple criterion, i.e., changes in ulcer area. A previous study, which was also based on a large prospective, randomized clinical trial, indicated that changes in healing rate can also predict complete wound healing (22). However, because evaluation of healing rate involves measurement of the wound perimeter, this method is not as easily performed and, therefore, not as clinically applicable as the measurement of wound area by the methods used in this study, i.e., measuring the length and width of the ulcer.

New treatments should be expected to promote complete wound healing by sustaining a normal healing rate over time, i.e., during the whole period that is required until the ulcer is healed, and not by accelerating the healing rate to supraphysiological levels. This is because the time required for cell division, proliferation, and formation of new tissue, such as blood vessels, is relatively fixed and cannot be easily manipulated. This is probably the main reason why the change in wound area was similar in the standard care and the Promogran-treated group in this study. Similar results have also been noticed in a previous large clinical trial (12,22) that showed a living skin equivalent to be more effective than standard care in promoting complete wound closure in diabetic foot ulcers. Therefore, the

efficacy of a new treatment should not be judged by the healing rate that is achieved during the study but, rather, by comparing the percentage of complete wound healing that is achieved in the active and control groups.

The present study has its limitations. The main limitation is that the tested population was participating in a clinical trial that selected patients with noninfected Wagner grade I–II ulcers, i.e., ulcers that did not penetrate to bone or tendon, and the results may not be generalizable to all patients with foot ulcers. However, it should be noted that most patients have such ulcers. Furthermore, even patients with infected ulcers convert to ulcers similar to those included in this study after the infection is cleared. Finally, most of the new therapeutic approaches have been tested on noninfected Wagner grade I–II ulcers. As discussed, these new approaches are considerably more expensive than the currently used standard care and should not be the first choice of treatment for all patients. Therefore, the results of this study will greatly help the physicians to correctly identify the patients earlier who will benefit most from receiving new expensive technology treatments while providing standard care to those who do not need anything more to heal their ulcers.

In conclusion, the results of the present study suggest that the percent change in foot ulcer area at 4 weeks' observation is a robust predictor of healing at 12 weeks. Therefore, this simple tool may serve as a pivotal clinical decision point in the care of diabetic foot ulcers for early identification of patients who may not respond to standard care and may need additional treatment.

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