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With a Hepatic-derived Wound Matrix

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ABSTRACT

Introduction. Difficult-to-heal diabetic foot ulcers (DFUs) increase the likelihood of significant pathology and increased health care costs. **Objective.** This study evaluates the ability of a novel hepatic-derived wound matrix (HD-WM) to treat hard-to-heal DFUs. **Materials and Methods.** In total, 53 patients were enrolled and 38 completed per protocol. Patients had ulcers that had been present for at least 90 days and were non-responsive to at least 2 applications of an advanced biologic wound care product. Patients were treated with standard of care and offloading for a 2-week run-in phase. If they satisfied criteria, they were enrolled in the trial and treated with the HD-WM, and then seen weekly for assessment and additional treatment as needed. Patients continued weekly visits until the wound healed or went 12-weeks posttreatment without healing. **Results.** Mean starting wound size was 3.5 cm² and mean wound duration was 41.1 weeks. Median previous treatment applications of an advanced biologic were 3.0. Complete closure of the wound occurred in 22 of the 38 patients (57.9%) within the 12-week study period, while 16 of 38 (42.1%) of the wounds had failed to completely heal. The mean time to wound closure was 8.1 weeks; these patients received a median of 1 application of the HD-WM under investigation. Closure of the wound by 50% or greater at week 4 was highly predictive of complete wound closure by 12 weeks. Except for bodily pain (36-Item Short Form Health Survey), which significantly improved in patients whose wounds healed, quality of life measures did not show changes. **Conclusions.** The HD-WM under evaluation did well at closing difficult-to-heal wounds with minimal applications. These results are consistent with a previous study on this HD-WM.

KEY WORDS

hepatic wound matrix, diabetic foot ulcer, difficult-to-heal ulcer, biological matrix

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Wounds Epub 2020 June 21

Current data suggest that there are more than 400 million people worldwide suffering from diabetes, including more than 30 million in the United States.^{1,2} Patients with diabetes have lifetime incidence of up to 25% for developing a diabetic foot ulcer (DFU) and at any given time 4% to 10% will have a DFU.³ Standard treatment, debridement, offloading, daily dressing changes, and infection control^{4,5} may only heal up to 24% of these ulcers after 12 weeks of treatment,⁶ suggesting standard treatment is generally insufficient. Diabetic foot ulcers are associated with a host of medical, psychological, and social issues, making their successful treatment that much more important. Substantial medical problems include greater likelihood

of infection, lower extremity amputation, and increases in mortality rate.^{7,8} Patients who have a lower extremity amputation have a 50% 5-year survival rate.⁹ Not surprisingly, these patients also report lower satisfaction with life.

Diabetic foot ulcers that have not shown substantial healing after 4 weeks of treatment are often considered nonhealing, with some using data to argue that a wound that fails to close by at least 50% after 4 weeks will not likely heal within 12 weeks.^{6,10} The criterion of 50% closure has not only been put forward as a predictor of timely wound healing but also has been used as a surrogate endpoint for successful wound treatment.¹¹ When wounds do not show substantial healing after 4 weeks, it is recommended to move to

treatment with advanced care. The urgency is to close the wound and avoid complications and health care costs as previously described. A number of advanced acellular and cellular wound matrices have been developed to treat DFUs that are considered nonhealing after no substantial improvement is observed after 4 weeks of standard care¹²; however, no currently available advanced wound treatment grafts are perfusion decellularized and hepatic derived.

The hepatic-derived wound matrix (HD-WM; MIRODERM; Miromatrix) is a novel, non-crosslinked, acellular wound graft that is produced by perfusion decellularization of a whole porcine liver. This process removes cellular material, leaving a highly vascularized collagen

Table 1. Inclusion and exclusion criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
<ul style="list-style-type: none"> • ≥ 18 years old at the time of treatment • Type 1 or 2 diabetes • DFU had to be $\geq 1\text{cm}^2$ and $\leq 12\text{cm}^2$ at enrollment • Full thickness (Wagner Grade I or II) and distal to the malleolus • No exposed capsule, tendon, or bone; tunneling; undermining; or sinus tracts • Ulcer present for ≥ 90 days • Minimum of 2 applications of an advanced biologic • Adequate vascular perfusion of at least 1 of the following: <ol style="list-style-type: none"> 1. ABI ≥ 0.8 2. $\text{TcPO}_2 \geq 30\text{mmHg}$ 3. Toe pressure $\geq 50\text{mmHg}$ • No biologic or topical growth factor within 4 weeks of enrollment (effectively, 6 weeks prior to treatment) 	<ul style="list-style-type: none"> • Pregnant or planning to become pregnant during the study • Have had a Chopart's amputation or more proximal amputation • History of bone cancer of the affected limb • Undergoing dialysis • Active osteomyelitis or be receiving treatment for osteomyelitis • Diagnosed with unstable Charcot foot on the affected side • $\text{HbA}_{1c} \geq 12\%$ within the past 90 days • Have another ulcer within 2cm of the study ulcer • Immunocompromised or at risk of immunosuppression as determined by the treating investigator • Have a known collagen vascular disease or connective tissue disease • Received treatment of the study ulcer with a skin substitute product or topical growth factor within the past 4 weeks • Participating in another medical research study • Sensitive to porcine material

DFU: diabetic foot ulcer; ABI: ankle-brachial index; TcPO_2 : transcutaneous oxygen pressure; HbA_{1c} : hemoglobin A_{1c}

**Figure 1.** Hepatic-derived wound matrix product.

matrix and an epithelial basement membrane. When a matrix of this type is reseeded with functional cells to produce whole organs, the cells migrate so that there is physiological appropriate organization of the cells. This suggests the decellularized matrix retains some potentially beneficial proteins, eg, anabolic

proteins.¹³ The utility of this HD-WM was originally demonstrated by Fridman and Engelhardt¹⁴ in a pilot study of patients with difficult-to-heal DFUs. The authors followed patients who had a DFU open more than 3 months and at least 1 previous treatment attempt with an advanced biologic. Fifty percent of the study patients' wounds were closed within the 12-week period, with a fourth wound showing good healing and more than 90% smaller at 12 weeks.¹⁴ These data also suggested that initial treatment response was predictive of the 12-week closure.

This multicenter study was conducted to replicate and expand on Fridman and Engelhardt.¹⁴ The study prospectively assessed hard-to-heal DFUs in a larger, more geographically diverse population. It was hypothesized that the results obtained here would be consistent with the pilot study. This scientific replication would lend confidence to complete a more definitive randomized controlled trial. The primary endpoint of this study is the proportion of wounds that healed at or prior to 12 weeks, and the authors expect it to be similar to that observed in the previous pilot study. The data also will allow for an analysis of the

predictive ability of the 50% healed by 4 weeks criterion.

MATERIALS AND METHODS

Study design and administration

The study was a single-arm, multicenter, prospective follow-up. The protocol was approved centrally by the Western Institutional Review Board (Protocol No. 20170878).

Study population

Nine centers enrolled 53 patients. The patients had to be 18 years old or older at the time of treatment and have type 1 or 2 diabetes. The DFU had to be equal to or greater than 1 cm² and less than or equal to 12 cm² at enrollment. In addition, the ulcer must have been present for at least 90 days, have had a minimum of 2 applications of an advanced biologic, and be full thickness and distal to the malleolus. The ulcer could not have exposed capsule, tendon, or bone; tunneling; undermining; or sinus tracts. Adequate vascular perfusion was demonstrated by having at least 1 of the following: an ankle-brachial index ≥ 0.8 , a transcutaneous oxygen pressure of ≥ 30 mm Hg, or a toe pressure of ≥ 50 mm Hg. Patients could not have had another biologic or topical growth factor

within 4 weeks of enrollment (effectively no other biologic or topical growth factor for 6 weeks prior to treatment). Main exclusion criteria included undergoing dialysis, active osteomyelitis, and another ulcer within 2 cm of the study ulcer. **Table 1** provides the inclusion/exclusion criteria. Study conduct included 3 distinct stages: screening/consent, enrollment/treatment, and confirmation of closure.

Study device

This study examined MIRODERM Biological Wound Matrix (Miromatrix Medical Inc), a novel hepatic-derived wound matrix (**Figure 1**).

Screening/consent

Patients who appeared likely to be eligible were recruited by investigators from their existing patient population. Patients were consented and formally screened with respect to inclusion and exclusion criteria. If a patient did not meet all criteria, they were not considered enrolled and had no further study activity. Patients who met eligibility criteria continued to participate in study activities. At screening patients' medical history, comorbidities and wound characteristics were documented. The patients were given the 36-Item Short Form Health Survey (SF-S6) to assess quality of life. They were instructed on proper nutrition and given a copy of the *Cleveland Clinic Nutritional Guidelines to Improve Wound Healing*. Patients were fitted for, instructed on the use of, and received either a DH Offloading Walker or a DH Offloading Post-Op Shoe with a customizable peg insert (Össur) that was to be worn throughout the run-in phase. The ulcer was sharply debrided to healthy bleeding tissue, photographed, and traced using the E-Z Graph Wound Assessment System (E-Z Graph). The ulcer was dressed using standard of care (SOC), which consisted of applying hydrogel as needed, applying a layer of 4 in x 4 in gauze, and wrapping with conformable stretch gauze. Patients were instructed to change the dressing daily until the treatment visit and were provided dressing supplies. Then, patients were instructed to return in 2 weeks for

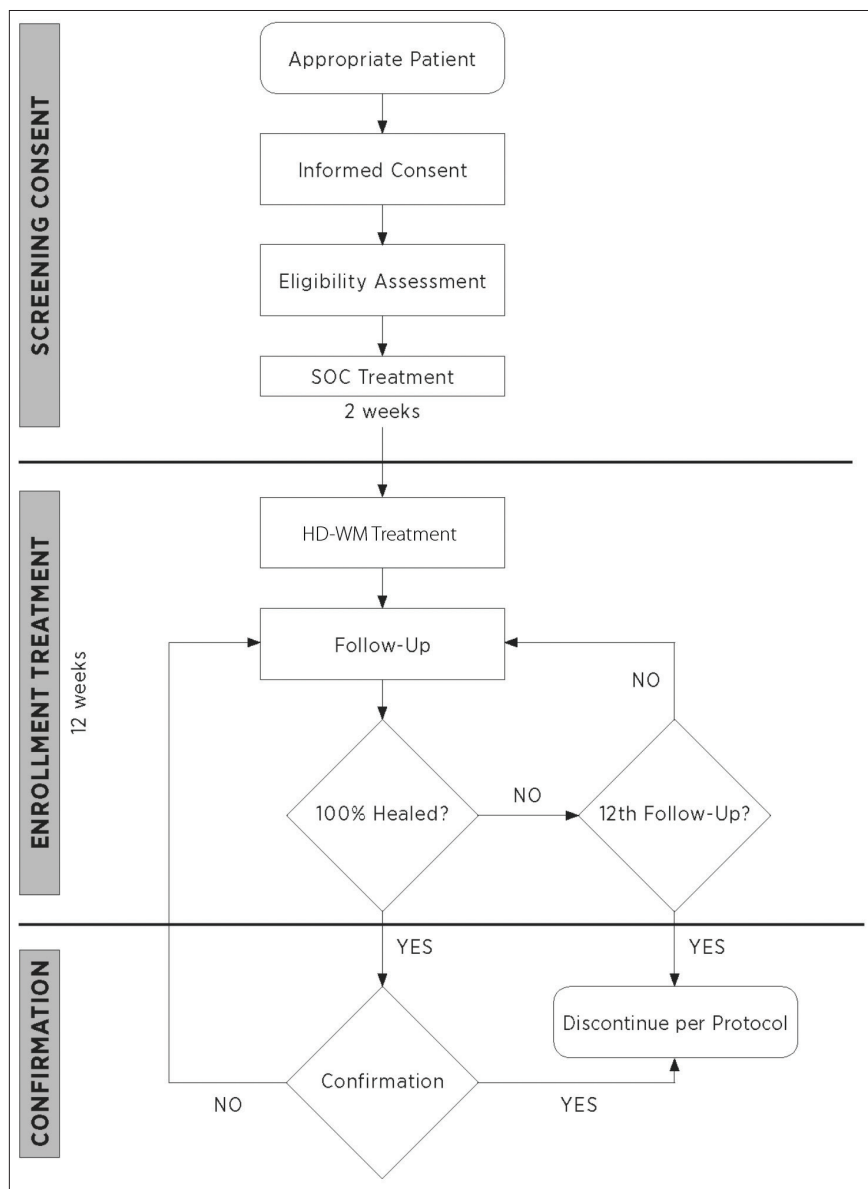


Figure 2. Patient study treatment flow.

SOC: standard of care; HD-WM: hepatic-derived wound matrix

consideration for enrollment. At the treating physician's discretion, the patient could be seen 1 week after initial assessment, but this visit was not considered a study visit and no study information was collected or documented.

Treatment/enrollment

After a 2-week run-in phase, patients presented to the clinic for treatment. The ulcer was cleaned, debrided as necessary, photographed, and traced. If the ulcer had improved during this period

by greater than 30% from offloading and SOC alone, the patient was excluded from the trial. This ensured that only hard-to-heal wounds that had not improved with SOC and offloading alone were enrolled in the study. The HD-WM was placed on the DFU. Care was taken to bolster the HD-WM to ensure maximum direct contact with the ulcer surface and to leave at least a few millimeters of graft overhanging the ulcer. The HD-WM was secured using Steri-Strips (3M), staples, or sutures per the treating physician's

Table 2. Patient characteristics for entire cohort and stratified by patients whose DFUs were healed or not healed

	ALL PATIENTS (N=38)	HEALED	NOT HEALED	P VALUE
Age (y±SD)	61.7±9.2	61.5±8.8	62.1±10.0	.851
Male (% , n)	73.7 (28)	72.7 (16)	73.7 (17)	1.000
Race (% , n)				
Asian	2.6 (1)	4.5 (1)	0.0 (0)	.674
African American	13.2 (5)	9.1 (2)	18.8 (3)	
Hispanic	21.1 (8)	22.7 (5)	18.8 (3)	
Pacific Islander	5.3 (2)	9.1 (2)	0.0 (0)	
Caucasian	55.3 (21)	54.5 (12)	56.3 (9)	
Not answered	2.6 (1)	0.0 (0)	6.3 (1)	
BMI (kg/m ² ±SD)	31.2±6.3	32.7±7.0	29.1±4.6	.081
HbA_{1c} (%±SD)	7.8±1.5	7.8±1.4	7.7±1.7	.801
ABI (ratio±SD)	1.02±0.2	0.98±0.2	1.06±0.3	.302
Tobacco use (% , n)				
None	89.5 (34)	90.9 (20)	87.5 (14)	.750
<1 pack/d	7.9 (3)	9.1 (2)	6.3 (1)	
>1 pack/d	2.6 (1)	0.0 (0)	6.3 (1)	
Alcohol use (% , n)				
None	73.7 (28)	81.8 (18)	62.5 (10)	.429
Occasional (<1x/mos)	13.2 (5)	9.1 (2)	18.8 (3)	
Monthly	7.9 (3)	4.5 (1)	12.5 (2)	
Weekly	2.6 (1)	0.0 (0)	6.3 (1)	
Daily	2.6 (1)	4.5 (1)	0.0 (0)	

DFU: diabetic foot ulcer; y: year; SD: standard deviation; BMI: body mass index; HbA_{1c}: hemoglobin A_{1c}; ABI: ankle-brachial index; d: day; mos: month

preference. The ulcer was dressed using an absorbent, nonadherent top layer (XTRASORB Super Absorbent Dressing; Integra LifeSciences Corporation) and then covered and secured with roll gauze. Patients were instructed to return to the clinic weekly for follow-up. The importance of continued offloading was stressed, and the patient was instructed to wear their study-related offloading boot/shoe for all weightbearing for the duration of the trial. During follow-up visits, and if the DFU was still present, the ulcer was examined, cleaned as needed, photographed, and traced. The ulcer was dressed as previously described, and patients continued with weekly follow-up.

If the DFU had healed, defined as 100% epithelialization, no exudate, and no need for further dressing, the patient moved to the confirmation phase as described in the following subsection. At follow-up visits, the HD-WM was reapplied if (1) it was no longer visible on the ulcer, and (2) the ulcer had appeared to stall. Patients continued weekly follow-up treatment until either 12 weeks of follow-up were completed or until the DFU healed. In the former case, patients received the typical care and also completed a SF-36. They then were discontinued from the study. If a patient's ulcer healed during the follow-up period, they were seen 1 week later for a confirmation visit.

Confirmation visit

The ulcer area was examined, and if closed, the patient completed an SF-36 and was discontinued from the study. If the ulcer remained open, the visit was treated as if it was the next scheduled follow-up visit and continued in the treatment phase until 12 weeks were completed or the ulcer healed again. A diagrammatic representation of the patient's study progression is presented in **Figure 2**.

Outcome assessments

The primary endpoint of this study was the proportion of ulcer healed at or prior to 12 weeks. Ulcers that healed during follow-up (ie, before the last week 12 follow-up visit) but were not healed at confirmation are not reported in the final analysis. Secondary endpoints included time to heal (as appropriate) and percent wound closure over time. Wound measurements were obtained using a graph wound assessment system, which has been shown to be valid and reliable.¹⁵ Ulcer tracings were independently measured by 2 observers using a planimetric tracing software (ImageJ 1.51w; National Institutes of Health) The SF-36 was used to assess general health at screening and when the patient was discontinued from the study after confirmation or at the week 12 follow-up visit.

Statistical analysis

Continuous variables are summarized by mean, median, standard deviation, and range as appropriate. Quantal variables are summarized in frequency counts and percentages as appropriate. Differences in patient variables between patients whose DFUs healed and patients whose DFUs did not heal were tested using Student's *t* test or Fisher's exact test as appropriate. Differences over time in outcome variables (eg, SF-36) were tested using a paired *t* test. In all cases, statistical significance was assumed when *P* < .05.

To assess interrater reliability (IRR) for this trial, a subset of data was gathered, and all raters measured 10 randomly selected images twice, at least 1 week between

measurements. The IRR was assessed using the Shrout and Fleiss¹⁶ intraclass correlation coefficient (ICC[3,1]) with a 2-way mixed effects, consistency, single rater/measurement model to assess the degree that raters were consistent in their ulcer size measurements across patients. The resulting ICC was in the excellent range with an ICC > 0.98 indicating that raters had a high degree of agreement and suggesting that ulcer area was rated similarly across raters. The high ICC suggests that a minimal amount of measurement error was introduced by the raters, and that wound size data were suitable for analyses.

RESULTS

From July 2017 through June 2018, 53 patients were screened, consented, and enrolled into this study. Patients were recruited from the treating physicians' practice. Of the 53 patients who were enrolled, 15 were discontinued from the study prematurely. Of these, 9 developed an infection or osteomyelitis at the index ulcer, a condition under which use of the test device must be discontinued. Of the

remaining 6 patients discontinued, 4 were lost to follow-up and 2 withdrew consent for non-study-related reasons.

Patient demographics and characteristics are presented in **Table 2** for the entire cohort and for those with DFUs that healed or did not heal. There were no significant differences between the ulcers healed and ulcers not-healed groups on any

subject characteristic. All patients except 1 had type 2 diabetes. Comparing the medical history of patients whose ulcers healed with patients whose ulcers did not heal, there were significantly more patients whose ulcers healed that reported a history of peripheral arterial disease (36.4% vs. 0.0%; $P = .012$) and myocardial infarction (27.3% vs. 0.0%; $P = .030$).

Table 3. Ulcer characteristics and treatments

	ALL PATIENTS (N=38)	HEALED	NOT HEALED	P VALUE
Ulcer size screen (mean cm ² ; SD)	3.5±3.5	2.6±3.2	4.7±3.2	.067
Ulcer size treatment (mean cm ² ; SD)	3.5±3.8	2.2±2.3	5.3±4.8	.010
Ulcer age (mean weeks; SD)	41.1±27.2	39.3±25.9	43.7±29.5	.628
Prior treatments (median; range)	2.0 (2–13)	2.0 (2–6)	2.5 (2–13)	.174
Ulcer location (%; n)				
Toes	7.9 (3)	4.5 (1)	12.5 (2)	.341
Forefoot	36.8 (14)	45.5 (10)	25.0 (4)	
Midfoot	36.8 (14)	27.3 (6)	50.0 (8)	
Heel	18.4 (7)	22.7 (5)	12.5 (2)	
SD: standard deviation				

Table 4. Details of previous treatments

ADVANCED WOUND PRODUCT	PTS RECEIVING AT LEAST 1 APP	% OF PTS RECEIVING AT LEAST 1 APP	TOTAL NO. OF APP	MEAN APP/PTS
EpiFix ^a	12	31.6	30	2.5
REGANEX ^b (PDGF)	7	18.4	8	1.1
Cytal Wound Matrix ^c	5	13.2	9	1.8
EpiCord ^a	5	13.2	5	1
Bilayer Wound Matrix ^d	3	7.9	5	1.7
Kerecis Omega3 ^e	3	7.9	6	2
Omnigraft Dermal Matrix ^d	3	7.9	5	1.7
PriMatrix Dermal Scaffold ^d	3	7.9	4	1.3
Other ^f (≤2 pts receiving)	9	23.7	29	3.2

Pts: patients; App: application; No.: number; PDGF: platelet-derived growth factor

^a MiMedx

^b Smith+Nephew

^c ACell

^d Integra LifeSciences Corporation

^e Kerecis

^f AmnioExcel (Integra LifeSciences Corporation), Apligraf (Organogenesis Inc.), CELLUTOME Epidermal Harvesting System (3M + KCI), Dermagraft (Organogenesis, Inc.), MicroMatrix (ACell), skin autograft, unspecified collagen matrix

Ulcer characteristics can be found in **Table 3**. At treatment, mean ulcer size for patients with an ulcer that was not healed was significantly bigger than those that healed. There were no differences in mean ulcer size at screening and treatment for either group or the entire cohort (healed, $P = .12$; not healed, $P = .38$; entire cohort, $P = .99$). Mean ulcer age for patients whose ulcer was healed was 39.3 weeks and 43.7 weeks for those whose ulcer did not heal. This difference was not significant ($P = .63$). Similarly, the mean number of previous advanced biologic attempts for patients whose ulcers were healed or not healed was 3.8 and 2.8, respectively. This difference was not significant.

The median number of previous applications was 2.0 for both the entire cohort and also for those whose ulcers healed; patients whose ulcers did not heal received a median of 2.5 applications of the HD-WM (**Table 3**). Ulcers had been previously

treated with a total of 101 applications of some advanced wound care product. In total, there were 14 wound care products used as previous treatments, with 7 of those being applied to ulcers on 2 patients or less. The most common previous treatment was EpiFix (MiMedx) with a total of 30 applications distributed among 12 (32%) patients. Previous treatment details can be found in **Table 4**.

Complete ulcer closure within 12 weeks occurred in 22 of the 38 (57.9%) patients who completed the study, as assessed by the treating physician, according to the criteria outlined previously. In contrast, the ulcers on 16 of 38 patients (42.1%) failed to close by week 12 of the trial. One patient's ulcer healed at week 12, as assessed by the defined study criteria, had a new ulcer in the same area at the confirmation visit. Another patient's ulcer was healed at 6 weeks but open at the confirmation visit (week 7); this patient continued treatment per protocol but the patient's ulcer did not close by week 12. Of the 16 patients whose ulcers did not close by week 12, 7 (58.3%) ulcers had closed 85% or greater by week 12. The median number of HD-WM applications for the entire cohort was 2.0, while those patients with an ulcer that healed had a median of 1.0 application and those patients with an ulcer that did not heal had received a median of 3.5 applications.

Regarding the 50% closure by posttreatment week 4 criterion, 23 patients' ulcers had reduced in area by greater than 50% (69.7%) and 10 patients' (30.3%) ulcer area reduced less than 50% (**Table 5**). For patients whose ulcers were at least 50% smaller at week 4, 65.2% of the ulcers (15/23) were completely healed within the 12-week follow-up period. In contrast, in 10 patients with ulcers that were not at least 50% healed by week 4, only 20% (2/10) of the ulcers were healed in the same timeframe. Examination of the 2 patients whose ulcers healed in 12 weeks but were not reduced in area by greater than 50% at week 4 had reductions of 41.7% and 47.3% at week 4. The patients who had a 50% reduction in ulcer size by 4 weeks had a statistically greater proportion of ulcers healed at 12 weeks ($P = .026$). Five patients were excluded from this analysis, including 4 whose ulcer was closed at 4 weeks, and 1 who did not have a 4-week wound tracing.

For patients whose ulcer healed within the study period, mean time to wound closure was 8.1 weeks (range, 2–12 weeks). The mean time the ulcer was open for these patients was 40.9 weeks. The effective mean weekly healing rate was 16.0%, 5.5%, and 11.6% for patients whose ulcers healed, did not heal, and the entire cohort, respectively. The difference in mean percent healing rates between patients whose ulcers healed and did not heal was significant ($P < .001$). The mean absolute weekly reduction in ulcer size was 0.32 cm², 0.28 cm², and 0.30 cm² for the healed, not healed, and entire cohort groups, respectively. There were no significant differences in absolute healing rates. Mean ulcer size for both ulcers that healed and those that did not over time are presented in **Figure 3**. There were no adverse events reported that were attributable to the HD-WM.

Several examples of the progress of a healed ulcer are shown in **Figure 4**. Top frames show a 70-year-old male, with a DFU measuring 1.8 cm². The patient had a body mass index (BMI) of 29.0 and was a non-smoker. The DFU had been open for 90 weeks and had been previously treated with both 3 applications of EpiFix

Table 5. Healing rates at 4 weeks and 12 weeks

		100% AT 12 WEEKS	
		No	Yes
50% 4 weeks	No	8	2
	Yes	8	15

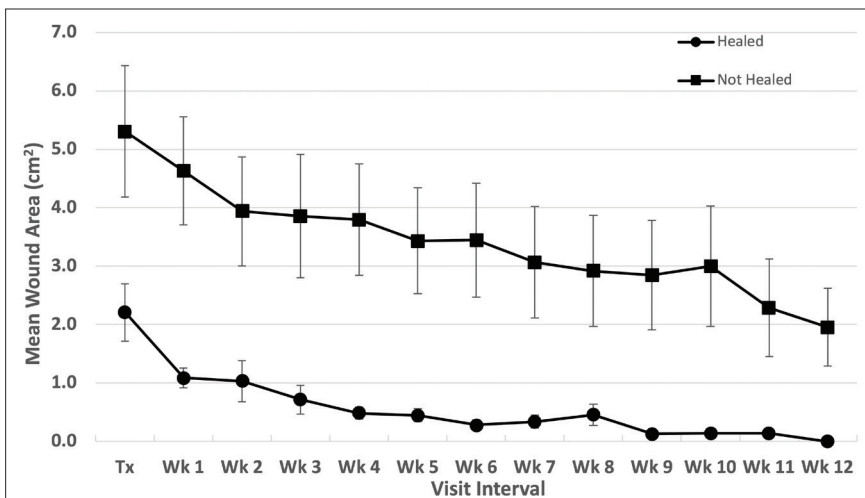


Figure 3. Mean wound area as a function of visit interval for ulcers that healed and ulcers that did not heal. Error bars indicate 1 standard error of the mean. Tx: treatment; wk: week

(MiMedx) and 1 treatment regimen of REGRANEX (Smith+Nephew). The ulcer healed in 8 weeks and was closed on confirmation. Bottom frames show a 69-year-old female, with a DFU measuring 6.6 cm². The patient had a BMI of 23.4 and was a non-smoker. The ulcer had been open for 34 weeks and had been previously treated with 2 applications of Omnigraft Dermal Regeneration Matrix (Integra LifeSciences Corporation) and 1 of CELLUTOME Epidermal Harvesting System (3M + KCI). The ulcer healed in 6 weeks and was closed on confirmation.

A Kaplan-Meier analysis is presented in **Figure 5** showing the proportion of healed ulcers at treatment and at each posttreatment visit interval with grey shading showing 95% confidence intervals. This analysis reveals a 57.0% healed rate at 12 weeks and a 71.4% study end healed rate.

At time of enrollment, the mean SF-36 physical component summary score was 35.8 and 39.5 for patients whose ulcers healed and did not heal, respectively. At the confirmation visit (for patients whose ulcer healed) the mean score improved to 37.2, and at the 12-week posttreatment visit (for patients whose ulcers did not heal) the mean score declined to 38.4. Neither changes between groups nor over time were significantly different. The mean SF-36 mental component summary score was 48.5 and 51.2 for patients whose ulcers healed and did not heal, respectively. At the second assessment with patients whose ulcer healed (confirmation visit), the score was 48.8, and for patients whose ulcer did not heal (12-week visit), the score was 50.5. Again, neither changes between groups nor over time were significantly different. Similarly, the 8 component scores—Physical Function, Role Physical, Bodily Pain, General Health, Vitality, Social Function, Role Emotion, and Mental Health—generally did not show any significant differences between group or over time. The 1 exception was Bodily Pain, in this case patients whose ulcer healed showed an 8.4-point improvement in their Bodily Pain score, while those patients whose ulcer did not heal had a decline of 1.3. The patients that had ulcers which healed showed a

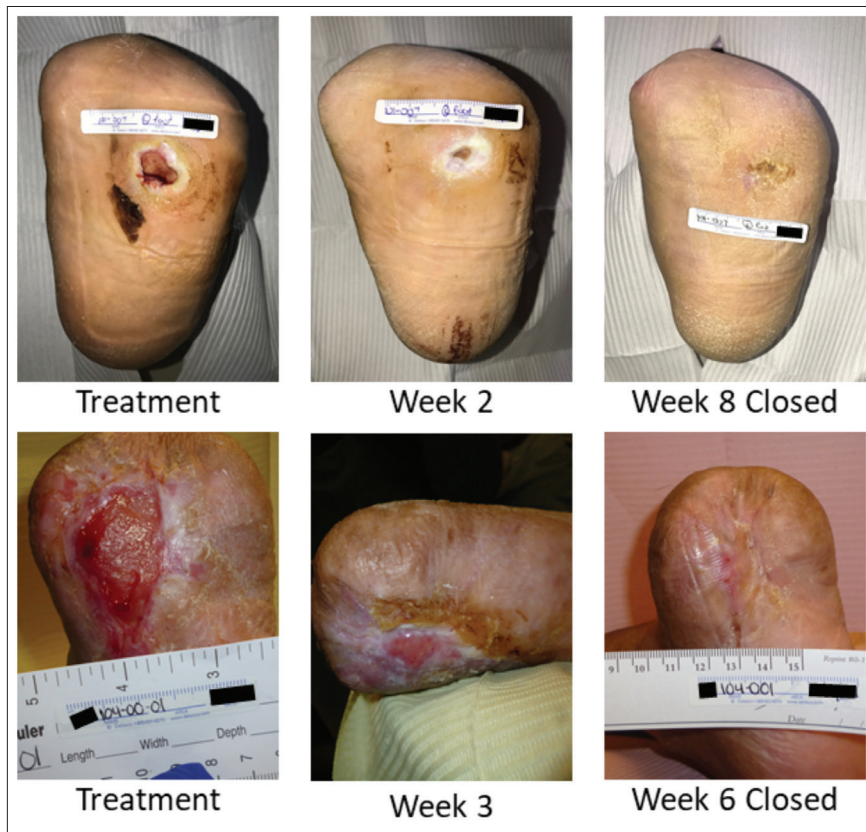


Figure 4. Wound healing progress for 2 patients.

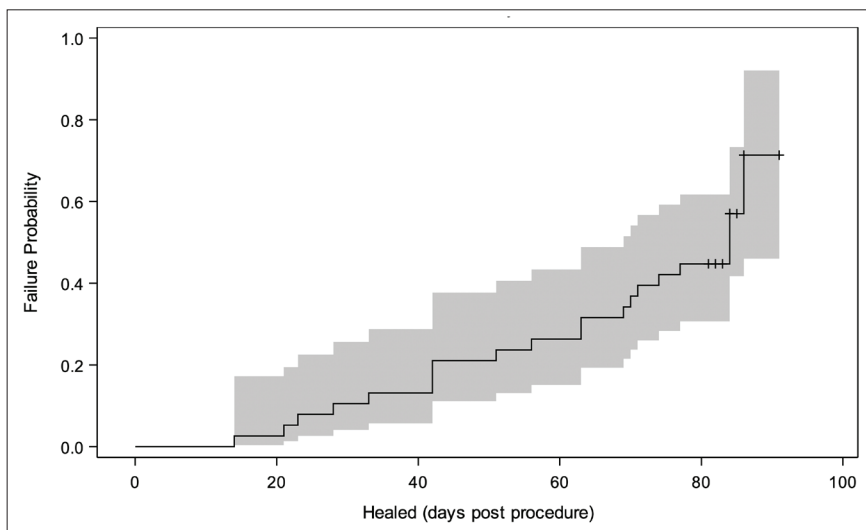


Figure 5. Kaplan-Meier curving showing probability of healing as a function of time posttreatment.

statistically significant improvement post HD-WM treatment ($P = .01$) and had a statistically greater improvement compared with patients with DFUs that were not healed ($P = .02$).

DISCUSSION

People with diabetes have a 25% lifetime risk of developing a DFU.³ In turn, DFUs are associated with a plethora of increasingly nefarious conditions, including

declining quality of life, infection, lower extremity amputation, and increased mortality.¹⁷⁻²¹ Standard of care, on average, heals 24% of DFUs within 12 weeks, and 31% in 20 weeks.⁶ The present study yielded a 58% closure rate in chronic, difficult-to-heal DFUs within 12 weeks, over twice that seen in standard DFUs and SOC.

There are few studies evaluating chronic DFUs. A DFU may be considered chronic if they are refractory to SOC for 3 weeks.²² A challenge in comparing healing rates across studies includes differences in the how “chronic” or “difficult-to-heal” is defined, the time of the final assessment, and other procedural details. For example, Cazzell et al²³ reported a 12-week healing rate of 65% for chronic DFUs where chronic was defined as having been open and receiving SOC for 30 days. The Cazzell et al²³ “chronic” was not consistent with and less rigorous than the current study using 90 days and a minimum of 2 previous biologic applications. Similarly, Wang et al²⁴ examined shockwave treatment in the treatment of chronic DFUs and found a 31% healed rate in the shockwave treatment group, but this was measured at 6 weeks. Thus, though the 58% healed rate in this study is clearly superior to SOC, clear comparisons to other “chronic” DFU studies remains elusive.

A post-hoc analysis of these data revealed the mean wound size at treatment was significantly larger in the patients that had ulcers which did not heal compared with those that did. The mean absolute effective healing rate was not different between these groups (0.32 cm²/week vs. 0.28 cm²/week). Further, in the patients whose ulcers did not heal, 7 of 16 (58.3%) had ulcers that reduced greater than 85%, showing substantial positive impact. Thus, it may be that the wounds that failed to close were not “non-responders” but had a wound size that was not conducive to healing in the time allowed. Taken together, this suggests that had the observation time been extended for a few weeks, the overall healed rate may have been even higher. Increasing healing rates over time is consistent with other studies of chronic

wounds.²³ This is also consistent with the results of the Kaplan-Meier analysis of the data presented herein, which suggest a 71.4% healed rate at 13 weeks posttreatment.

Sheehan et al¹⁰ have proposed a robust predictor of DFU healing within 12 weeks is a reduction in size of 50% or more within 4 weeks of treatment. The data obtained here are consistent with this proposal. These data show that 65.2% of patients with ulcers that healed by 50% or more by week 4 went on to heal, contrasted with only 20% of patients with ulcers that did not heal by 50% at week 4 going on to completely heal by the end of the 12-week observation period. Four patients who were not included in the statistics, because they were healed at 4 weeks, would theoretically meet these criteria; if these had been included, the healed by 12 weeks rate would be 70.4%. Continued analysis of this type, regardless of treatment, is beneficial on illuminating objective criteria that may guide treatment options.

Quality of life measures typically show differences between patients with diabetes with and without DFUs²⁰ and increases in quality life in patients whose DFU healed.¹⁷ The current study used the SF-36 to assess quality of life at the time of initial assessment and either after the ulcer healed, or at the 12-week posttreatment visit when the ulcer was not healed. Generally, there were no statistical improvements in the component summary scores (Physical and Mental) or the sub-scales. The 1 exception was Bodily Pain, which was statistically improved. The general lack of impact on quality of life is likely a combination of a small sample size in a population who suffer from multiple pathologies. A larger sample would help elucidate this issue.

The percent of patients with difficult-to-heal ulcers that went on to close within 12 weeks was 57.9%. This is generally better than many biologics, as reported in the literature. For example, Wieman et al²⁵ demonstrated a 50% healed rate with the use of recombinant human platelet-derived growth factor. Other closure rates obtained following treatment with advanced biologics include Apligraf (Organogene-

sis, Inc) of 56% at 12-weeks.²⁶ Marston²⁷ reported a 12-week closure rate of 30% following treatment with Dermagraft (Organogenesis, Inc). Other controlled clinical trials examining Integra Dermal Regeneration Template (Integra LifeSciences Corporation),¹² DermACELL (Stryker), and GRAFTJACKET Regenerative Tissue Matrix (Wright Medical Group)²⁸ revealed 12-week healing rates of 51%, 68%, and 48%, respectively. The HD-WM used in this study yielded wound healing rates above or competitive with these other treatment methods. Importantly, the current study examined DFU healing in patients who had wounds documented to be recalcitrant to other advanced treatment options. It is likely that looking at all patients who initially present with a DFU would result in a greater healing rate.

LIMITATIONS

This study expanded on and is consistent with data acquired by Fridman and Engelhardt.¹⁴ This study was limited by its modest sample size, which may, to some extent, have been affected by withdrawals due to infection or osteomyelitis. Although unfortunate with respect to the number of patients completing the study per protocol, the rates were not inconsistent with this patient population (eg, Marston²⁷). These data would be further bolstered with the completion of a randomized controlled trial.

CONCLUSIONS

In this clinical trial, 59% of patients with difficult-to-heal DFUs who were treated with the HD-WM had healed within the 12-week study period. These wounds had been open for a mean of more than 40 weeks and had previously failed at least 2 applications of 1 or more advanced treatment modalities. Further, these data are consistent with previous work that suggests that when this HD-WM is applied its efficacy can be apparent within 4 weeks, helping the treating physician guide the treatment plan. The results indicate this HD-WM shows a robust potential to manage wounds and is an appropriate technology to treat difficult-to-heal DFUs. **▲**

ACKNOWLEDGMENTS

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Disclosure: The authors disclose no conflicts of interest. The study product was provided by Miromatrix Medical Inc.

REFERENCES

- Centers for Disease Control and Prevention (CDC). National diabetes statistics report: estimates of diabetes and its burden in the United States. US Department of Health and Human Services, 2017.
- NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet*. 2016;387(10027):1513–1530. doi:10.1016/S0140-6736(16)00618-8
- Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. *JAMA*. 2005;293(2):217–228. doi:10.1001/jama.293.2.217
- International best practice guidelines: wound management in diabetic foot ulcers. *Wounds Int*. May 10, 2013. www.woundsinternational.com/resources/details/best-practice-guidelines-wound-management-diabetic-foot-ulcers
- Doupis J, Veves A. Classification, diagnosis, and treatment of diabetic foot ulcers. *Wounds*. 2008;20(5):117–126.
- Margolis DJ, Kantor J, Berlin JA. Healing of diabetic neuropathic foot ulcers receiving standard treatment: a meta-analysis. *Diabetes Care*. 1999;22(5):692–695. doi:10.2337/diacare.22.5.692
- Lavery LA, Armstrong DG, Wunderlich RP, Mohler MJ, Wendel CS, Lipsky BA. Risk factors for foot infection in individuals with diabetes. *Diabetes Care*. 2006;29(6):1288–1293. doi:10.2337/dco5-2425
- Brownrigg JRW, Davey J, Holt PJ, et al. The association of ulceration of the foot with cardiovascular and all cause mortality in patients with diabetes: a meta-analysis. *Diabetologia*. 2012;55(11):2906–2912. doi:10.1007/s00125-012-2673-3
- Sen CK, Gordillo GM, Roy S, et al. Human skin wounds: a major snowballing threat to public health and economy. *Wound Repair Regen*. 2009;17(6):763–771. doi:10.1111/j.1524-475X.2009.00543.x
- Sheehan P, Jones P, Caselli A, Giurini JM, Veves JM. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of healing in a 12-week prospective trial. *Diabetes Care*. 2003;26(6):1879–1882. doi:10.2337/diacare.26.6.1879
- Avarahami R, Rosenblum J, Gazes M, Rosenblum S, Litman L. The effect of combined ultrasound and electric field stimulation on wound healing in chronic ulcerations. *Wounds*. 2015;27(7):199–208.
- Driver VR, Lavery LA, Reyzelman AM, et al. A clinical trial of Integra template for diabetic foot ulcer treatment. *Wound Repair Regen*. 2015;23(6):891–900. doi:10.1111/wrr.12357
- Baptista PM, Siddiqui MM, Lozier G, Rodriguez SR, Atala A, Soker S. The use of whole organ decellularization for the generation of a vascularized liver organoid. *Hepatology*. 2010;53(2):604–617. doi:10.1002/hep.24067
- Fridman R, Engelhardt J. A pilot study to evaluate the effects of perfusion-decellularized porcine hepatic-derived wound matrix on difficult-to-heal diabetic foot ulcers. *Wounds*. 2017;29(10):317–323.
- Thawer HA, Houghton PE, Woodbury MG, Keast D, Campbell K. A comparison of computer-assisted and manual wound size measurement. *Ostomy Wound Manage*. 2002;48(10):46–53. doi:10.1901/jaba.2012.45-797
- Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull*. 1979;86(2):420–428. doi:10.1037/0033-2909.86.2.420
- Armstrong DG, Lavery LA, Wrobel JS, Vileikyte L. Quality of life in healing diabetic wounds: does the end justify the means? *J Foot Ankle Surg*. 2008;47(4):278–282. doi:10.1053/j.jfas.2008.02.015
- Brownrigg JR, Hinchliffe RJ, Apelqvist J, et al. Performance of prognostic markers in the prediction of wound healing or amputation among patients with diabetic foot ulcers in diabetes: a systematic review. *Diabetes Met Res Rev*. 2016;32(Suppl 1):128–135. doi:10.1002/dmrr.2704
- Faglia E, Favales F, Morabito A. New ulceration, new amputation, and survival rates in diabetic subjects hospitalized for foot ulceration from 1990–1993: a 6.5-year follow-up. *Diabetes Care*. 2001;24(1):78–83. doi:10.2337/diacare.24.1.78
- Meijer JWG, Trip J, Jaegers SMH, et al. Quality of life in patients with diabetic foot ulcers. *Disabil Rehabil*. 2001;23(8):336–340. doi:10.1080/09638280010005585
- Ndosi M, Wright-Hughes A, Brown S, et al. Prognosis of the infected diabetic foot ulcer: a 12-month prospective observational study. *Diabet Med*. 2018;35(1):78–88. doi:10.1111/dme.13537
- Shultz GS, Sibbald RG, Falanga V, et al. Wound bed preparation: a systematic approach to wound management. *Wound Repair Regen*. 2003;11(Suppl 1):1–28. doi:10.1046/j.1524-475X.11.s2.1.x
- Cazzell S, Vayser D, Pham H, et al. A randomized clinical trial of a human acellular dermal matrix demonstrated superior healing rates for chronic diabetic foot ulcers over conventional care and an active acellular dermal matrix comparator. *Wound Repair Regen*. 2017;25(3):483–497. doi:10.1111/wrr.12551
- Wang CJ, Kuo YR, Wu RW, et al. Extracorporeal shockwave treatment for chronic diabetic foot ulcers. *J Surgical Res*. 2009;152(1):96–103. doi:10.1016/j.jss.2008.01.026
- Wieman TJ, Smiell JM, Su Y. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers: a phase III randomized placebo-controlled double-blind study. *Diabetes Care*. 1998;21(5):822–827. doi:10.2337/diacare.21.5.822
- Veves A, Falanga V, Armstrong DG, Sabolinski ML; Apligraf Diabetic Foot Ulcer Study Group. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers. *Diabetes Care*. 2001;24(2):290–295. doi:10.2337/diacare.24.2.290
- Marston WA. Dermagraft, a bioengineered human dermal equivalent for the treatment of chronic nonhealing diabetic foot ulcer. *Expert Rev Med Devices*. 2004;1(1):21–31. doi:10.1586/17434440.1.1.21
- Walters J, Cazzell S, Pham H, Vayser D, Reyzelman A. Healing rates in a multicenter assessment of a sterile, room temperature, acellular dermal matrix versus conventional care wound management and as active comparator in the treatment of full-thickness diabetic foot ulcers. *Eplasty*. 2016;16:e10.

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SM-00160 Rev. A 06/20