A novel approach for the treatment of diabetic foot ulcers using a multimodal wound matrix: a clinical study

Objective: Innovation in wound healing, particularly regarding diabetic foot ulcers (DFUs), is needed to reverse the number of diabetes-related amputations. This study evaluated a novel approach and performance of a multimodal wound matrix in converting stalled DFUs into a healing trajectory.
Method: Patients with either type 1 or 2 diabetes and with foot ulcers (Wagner grade 1 and 2), were screened to determine eligibility for treatment. Ulcers improving >30% in area during a two-week screening phase were not eligible for the study treatment phase. The study was an open-label trial conducted in three phases: screening, treatment and healing confirmation. Patients enrolled in the study received a treatment protocol that included application of a wound matrix to the ulcer and offloading.
Results: A total of 19 patients (15 males, four females) with a median age of 60 years, and a median ulcer duration of 36 weeks took part in the study. Patients showed an average four-week percentage area reduction (PAR) of 62%, a 12-week PAR of 94%, and a 12-week healing rate of 57% (8/14).
Conclusion: Results of this study support the viability and potential of a novel approach to treating DFUs that includes use of a multimodal wound matrix.
Declaration of interest: SB, Chief Scientific Officer, and DB, Chief Medical Officer, are employees of Omeza, LLC, US. The remaining authors have no conflicts of interest to declare.

CAMPS refractory wounds • cellular, acellular and matrix-like products • customised wound healing • diabetic foot ulcer • DFU • multimodal wound matrix • wound • wound care • wound dressing • wound healing

As the prevalence of diabetes continues to increase in the US and globally, so does its associated complications, including limb and life-threatening diabetic foot ulcers (DFUs).[1] Individuals with diabetes have a 19–34% lifetime risk of developing a DFU—one of the most serious complications associated with the disease.[2] Despite an ever-increasing understanding of the pathophysiology pertaining to the development and course of DFUs, current standard treatment for their management includes: surgical debridement; dressings to control exudate and to provide a moist environment; vascular assessment; infection control; glycaemic control; and offloading.[3] Although guidelines and other algorithms exist for the treatment of DFUs, adoption of such recommendations is inconsistent among wound care practitioners.[4]

Technological advancements designed to promote greater efficiency in DFU healing have not produced residual results that positively impact diabetes-related lower extremity amputation rates.[5–7]After a 20-year decline in lower-extremity amputations, the US may now be experiencing a reversal in the progress—from 2009–2019, the number of diabetes-related hospitalisations due to amputation doubled.[8] Innovation in wound healing, particularly in relation to DFUs, is one part of a larger strategy needed to reverse these trends, and positively impact both individuals and global healthcare systems. Adjunctive wound healing therapies used in the treatment of DFUs include cellular, acellular, and matrix-like products (CAMPs) that support tissue repair or regeneration through various mechanisms of action.[9] These products are generally used to manage wounds that have failed to respond to conservative treatment, and after the patient's risk factors and comorbidities have been addressed.[9] A retrospective Medicare database analysis showed that first administration of advanced wound healing therapy was delayed until approximately 80 days after diagnosis of a lower extremity diabetic ulcer, and that reapplication of the product did not occur regularly.[10] A delay in time to administer effective treatment for DFUs ultimately increases healthcare costs and has a negative impact on patients' morbidity and mortality.[11,12]

In this paper, we present the results of a study that examined the treatment of DFUs with a therapy that has been developed as a multimodal wound matrix (MWM) (OCM, Omeza, LLC, US).[13] This drug/device includes peptides, omega fatty acids, and anabolic metabolites in a matrix that supports comprehensive synthesis of new tissue and regeneration of the wound.[13] The central concept in the design of this technology originated from a physiological understanding of how the healing cascade becomes stalled in wounds, with a focus on stimulating the body to transform the wound

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microenvironment through the inflammatory, proliferative and regenerative phases into a healing state.[13]

This study was designed to evaluate the performance of the wound matrix in converting stalled ulcers into a healing trajectory. Moving a hard-to-heal ulcer from the inflammatory phase to the proliferative phase increases the potential for eventual healing. It has been shown that a >50 percentage area reduction (PAR) in DFUs after four weeks of treatment is a predictor of healing.[14,15] The present study was designed to assess the PARs of DFUs managed with the wound matrix application and offloading after four weeks of treatment, and to evaluate the performance of the matrix in a 12-week period.

Methods

Patients, study design and treatment

This study was an open-label trial conducted in three phases: screening, treatment and healing confirmation. The study was conducted from September 2022 to December 2023.

Patients were enrolled from the Promedica Health Care System at the Toledo Wound Care Center, Toledo, US, and the Defiance Clinical Wound Center, Defiance, US. Patients were enrolled at the clinical site and pre-screened.

After provision of informed consent, screening, including a physical examination, occurred to determine patient eligibility, diabetes status, medical history, vital signs, body mass index (BMI), pregnancy status, duration and measurement of the target ulcer.

Adult (≥21 years) patients with a diagnosis of type 1 or 2 diabetes and with a DFU (Wagner grade 1 or 2) were eligible for enrolment. Patients whose ulcers were caused by a condition other than diabetes were not eligible to participate in the study. Study DFUs could not be infected, and could not have been treated with tissue engineered material or other scaffold materials within 30 days before start of study. Patients with an unlimited BMI or who were active smokers, were currently undergoing dialysis, or had active cancer or suspicion of malignancy in the study DFU were also excluded.

Screening phase

The screening phase (1–14 days) was designed to determine whether patients' DFUs were eligible to proceed to the treatment phase. At screening visit 1, target DFUs were identified, cleaned, debrided as necessary, dressed and offloaded. If a ≥30% decrease in DFU size over the previous 14 days with standard treatment was observed, the DFUs were not eligible for inclusion in the study treatment phase.

Treatment phase

The treatment phase included 12 weekly visits. During this time the patients' DFUs were assessed, and treated with a preparation solution applied to the periwound area. This was followed by application of the wound matrix to the DFU, and a skin protectant applied to the periulcer area. Adherence to offloading was addressed at each visit, as best as could be determined. Non-adherence to offloading resulted in the patient being withdrawn from the study. Debridement of the study DFU at each treatment visit was left to the judgement of the provider treating the patient.

Healing confirmation

DFU closure confirmation occurred at any time during the study. If the study DFU was 100% re-epithelialised, as determined by the principal investigator, it was considered closed.

DFU evaluation

Photographic ulcer evaluation, measurements and ulcer progress in study patients were captured by Tissue Analytics (Net Health, US), a US Food and Drug Administration Class 1 artificial intelligence-powered digital planimetry and imaging application. The study was closed by agreement of the sponsor and study principal investigator after completion of wound matrix treatment for the final patient.

Ethical approval and patient consent

The study was approved by the ProMedica Institutional Review Board/Independent Ethics Committee (Approval #22-142) and was conducted in accordance with the principles consistent with the Declaration of Helsinki, Good Clinical Practice, applicable regulatory requirements, and the Belmont Principles of respect for persons, beneficence and justice.

All patients provided written informed consent prior to enrolment, which included consent to publish photographs of their DFUs. Photographs have been examined to eliminate patient identification.

Study outcomes

The primary objectives of this study were to evaluate the safety profile of the wound matrix, and to evaluate the impact of treatment and offloading on chronicity of DFU healing after four weeks of wound matrix treatment.

Secondary objectives were to evaluate the healing of DFUs over four weeks of wound matrix treatment, and the time to maximum or complete ulcer closure.

Primary endpoints were change in PAR at four weeks compared with baseline measurements and incidence of DFU closure at four weeks and by 12 weeks.

Statistical analysis

All analyses of data from this study were descriptive (without p-value generation) as the study was not powered for inferential analyses and no formal hypothesis testing was performed.

Results

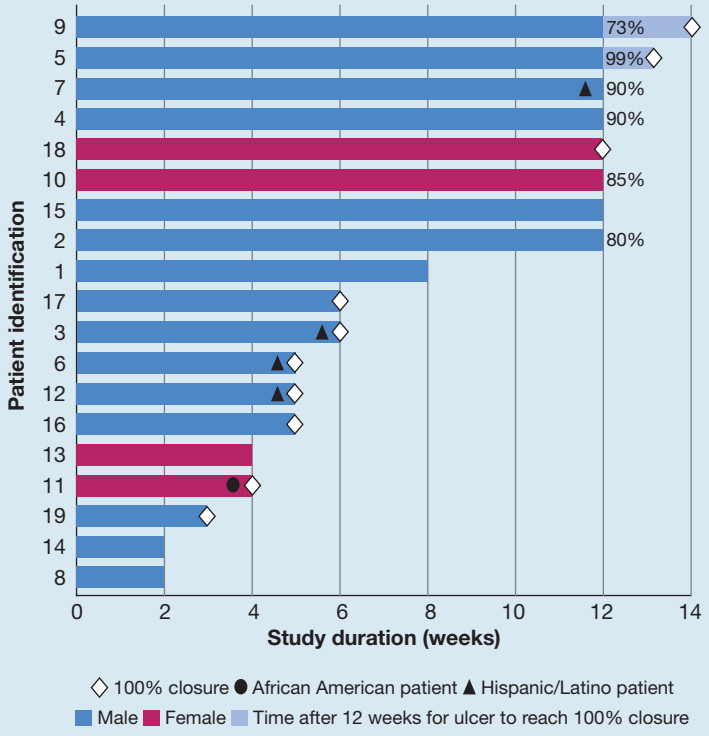
The study included 19 patients (15 males, four females) (Fig 1) with a median age of 60 years (range: 44–85 years) (Table 1). Median DFU duration prior to treatment was 36 weeks (range: 4–72 weeks) (n=17), with five DFUs present for >1 year without closure (Fig 2).

A total of five patients included in the analysis did not complete the study (Fig 2): four patients were withdrawn by the investigator for non-adherence to offloading, and one patient died from their comorbidities.

Median DFU size was 1.7cm^2 (mean: 5.05cm^2; range: 0.37–25.0cm^2) at treatment visit (TV)1 (Table 1). At TV5, the median DFU size reduced to 0.63cm^2 (n=16; mean: 1.45cm^2; range: 1–10.06cm^2) (Table 1).

The average four-week PAR was 62%, with three patients experiencing 100% closure of their DFUs (Fig 2). At TV12, median DFU size was 0.0cm^2 (mean: 0.38cm^2; range: 0–2.59cm^2) (Table 1). The average 12-week PAR was 94%, with five additional patients experiencing 100% closure of their DFUs. In total, eight patients experienced 100% closure of their DFUs by week 12. No DFUs increased in size over the 12 weeks of the study (Fig 2).

Fig 1. Plot with ulcer outcomes and treatment duration. Start time denotes treatment visit 1



Among patients with both 4- and 12-week PAR measurements (n=14), all DFUs treated with the wound matrix improved from treatment week 4 to treatment week 12 (Fig 2). For one patient, their DFU healed at 13 weeks (12-week PAR of 99%). Another patient's DFU continued to close with two further treatments through week 14 (PAR of DFU at 12 weeks was 73%) (Fig 1). At the time of the 12-week timepoint, the DFUs of six patients had not healed and presented with PARs of 73%, 80%, 85%, 90%, 90% and 99% (Fig 1).

Of the 14 patients who completed the study, eight experienced complete closure of their DFUs and six experienced PARs of 73–99%. Among these, three experienced complete healing of their DFUs after four applications of wound matrix and offloading.

Of the five patients in the study who had DFUs of ≥1 year's duration, three patients' DFUs completely healed by week 12 (the remaining two DFUs had 12-week PARs of 73% and 85%).

The dressings and treatments used on the DFUs prior to treatment in this study with the wound matrix included alginate with dry dressing, gentian violet, collagen, manuka honey and Dakin's solution (0.125%).

Fig 3 provides some examples of use of the MWM in patients with DFUs.

Safety

There was one serious adverse event in the study where the patient was admitted for an acute kidney injury and later died from comorbidities. The event was not related to the product or the study. No other safety events were reported in the study.

Discussion

This clinical trial evaluated DFUs managed with a wound matrix and offloading. The trial results were encouraging, with an overall PAR of 62% at week 4, which increased to a PAR of 94% by week 12.

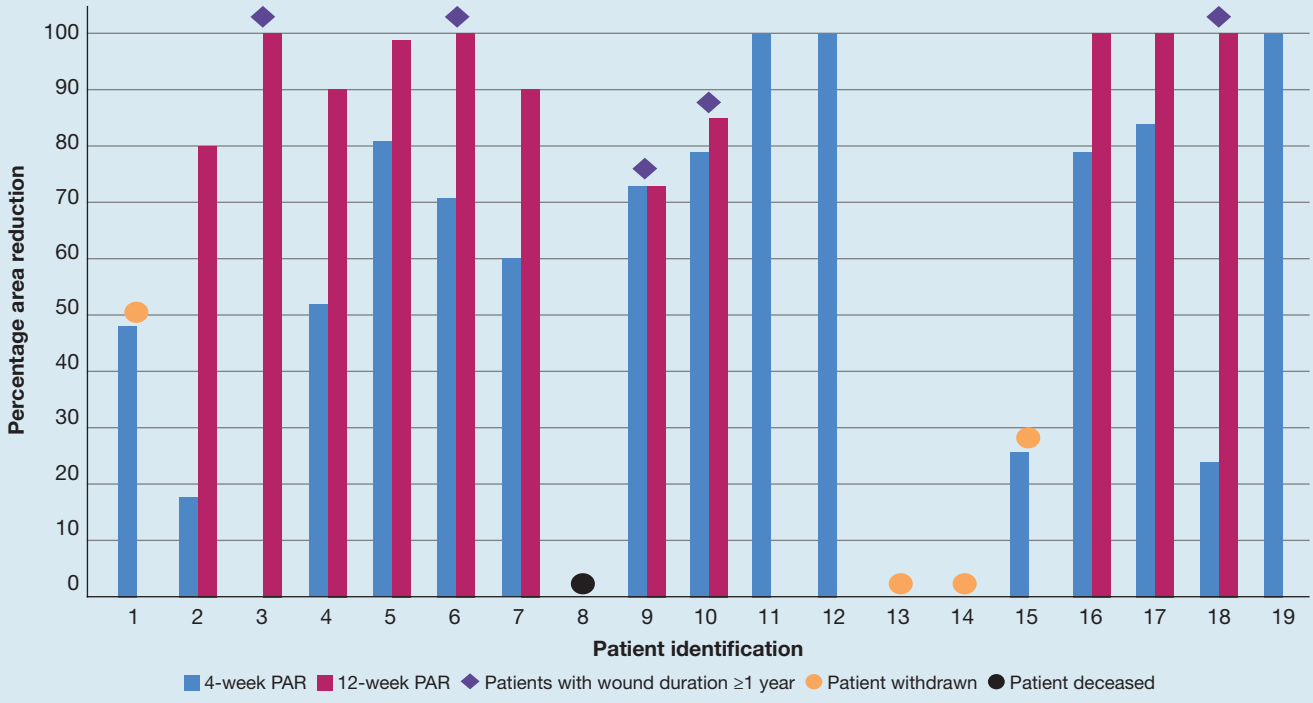
The complex challenges that make each DFU unique demands skills from the wound practitioner in identifying the best tools to move the DFU to healing and to optimise healing rates. By treating these DFUs with a multimodal approach, such as that delivered by the wound matrix in this study, the aim is to push stalled DFUs towards healing and to reduce the need for multiple tools required to optimise healing rates, but which can, potentially, take longer.

Table 1. Characteristics of patients and diabetic foot ulcers (DFU) treated with the wound matrix

Wound matrix	Patient age, years	DFU duration, weeks	DFU size, cm^2	TV5 DFU size, cm^2	TV12 DFU size, cm^2
Range	44–85	4–72	0.37–25.0	1.0–10.1	0–2.59
Median	60	36	1.7	0.63	0.0
Mean	59.75	32.50	5.05	1.43	0.38

TV5—treatment visit 5; TV12—treatment visit 12

Fig 2. Plot showing percentage area reduction (PAR) of patient ulcers at four weeks and at 12 weeks



The 12-week healing rate of DFUs managed with standard treatment in 26 clinical trials and reported in the US Wound Registry was 37.9%.[7] Results of a randomised controlled trial (RCT) that compared bioengineered skin substitute and standard treatment in patients with DFUs (n=208) without restriction on DFU duration showed 12-week healing rates of 56% and 38%, respectively.[16] Similarly, 12-week healing rates for a fish skin graft product and standard treatment were 56.9% and 31.4%, respectively, in a RCT of DFUs (n=102).[17] Mean 12-week PAR of DFUs managed with the fish skin graft product was 86.3%.[17]

Although the sample size of the current study was small (n=19), results for DFUs of any duration (including five wounds of ≥1 year) managed with the wound matrix are encouraging, with a 12-week healing rate of 57% (8/14), and a 12-week PAR of 94%.

Limitations

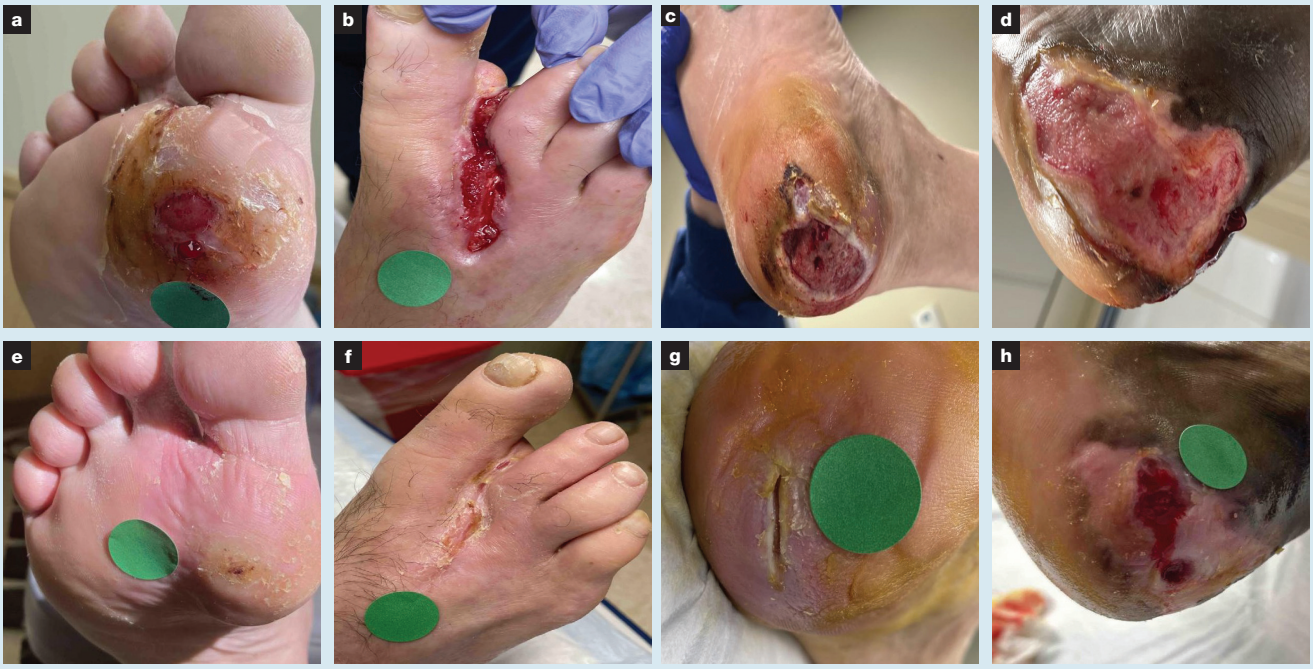
As noted, this was an open-label trial with a population of 19 patients with limited diversity. Results from clinical studies that enrol a more diverse population of patients from multiple sites are needed to validate the growing body of evidence supporting use of the wound matrix therapy in the management of DFUs. The small number did not allow statistical analysis of the efficacy outcomes. Further clinical trials and studies to increase the size and number of patients treated with the wound matrix are needed, as well as RCTs comparing the matrix to other treatments.

Table 2. Offloading types for each patient

Patient ID	Offloading	Max PAR
1	TCC	48
2	TCC	80
3	Offloading surgical boot	100
4	Surgical shoe with peg	85
5	TCC/soft cast	99
6	Diabetic show with insert	100
7	NWB with waffle boot	90
8	Deceased	n/a
9	Podus brace	73
10	Surgical shoe with peg	85
11	NWB/wheelchair bound	100
12	Surgical shoe with peg	100
13	Surgical offloading shoe	n/a
14	Surgical offloading shoe	n/a
15	Surgical shoe with peg	26
16	Orthotic shoe	92
17	Orthotic shoe	100
18	Surgical shoe with peg	100
19	Orthotic shoe with insert	100

ID—identification; Max PAR—maximum percentage area reduction; NWB—non-weightbearing; TCC—total contact casting

Fig 3. Case 1: Treatment visit (TV) 1: A 76-year-old male patient presented with a six-week-old diabetic foot ulcer (DFU) **(a)**. TV4: DFU closed after three treatments **(e)**. **Case 2**: TV1: Ulcer post-debridement in a 65-year-old male patient with a nine-week-old ulcer. Ray amputation of right foot, second metatarsal **(b)**. TV6: DFU closed after five treatments **(f)**. **Case 3**: TV1: A 53-year-old male patient with a three-month-old ulcer measuring 11.55cm^2 post-debridement **(c)**. TV12: percentage area reduction (PAR) of ulcer was 99% **(g)**. **Case 4**: TV1: A 65-year-old male patient with a 36-week-old ulcer measuring 25cm^2 **(d)**. PAR of 90% at TV12 **(h)**



Conclusion

In conclusion, results of this clinical trial are encouraging and indicate the potential for this multimodal wound matrix to serve as an important therapeutic modality for more expeditious management of DFUs, especially when considering the benefit to this patient population who is at significant risk for lower extremity amputation. Patients who have experienced the frustration of prolonged wound duration, including previously failed advanced therapies, may benefit extensively from this unique wound matrix. JWC

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Reflective questions

- What is a multimodal approach to wound healing?
- How does the wound matrix mentioned in the article differ from other cellular, acellular and matrix-like products or skin substitutes?
- How does the wound matrix cited in the article 'customise' wound healing?