CASE SERIES

Use of a Novel Purified Reconstituted Bilayer Matrix for Treatment of Chronic Diabetic Foot Ulcers: A Retrospective Case Series

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ABSTRACT

Background. With the lifetime risk of DFU being 34% and the rate of chronic wounds increasing, there is a need for advanced therapies offering rapid, reliable, and safe healing. **Materials and Methods.** A retrospective review was performed of 10 cases in which a novel PRBM was used for treatment of chronic DFUs. Patients who presented with DFUs refractory to topical wound care and offloading for longer than 4 weeks received weekly application of PRBM for up to 12 weeks along with a standard treatment regimen at a single outpatient center. At weekly visits, the wound was measured, inspected for signs of complications, cleaned, and debrided as necessary, followed by PRBM application until complete epithelialization or for 12 applications. The primary outcome was complete wound closure at 12 weeks. Secondary outcomes included time to closure, DFU percent area reduction, and material cost to closure. **Results.** Mean wound healing time was 6.1 weeks, with 90% of wounds closed at 12 weeks. Six wounds were healed at 6 weeks, 2 at 7 weeks, and 1 at 12 weeks. One wound did not close over the study period. Mean wound area reduction was 85% at 6 weeks and 94% at 12 weeks. Patients tolerated PRBM application with no reported pain or discomfort. No adverse events were reported. Mean PRBM cost to closure for healed wounds was $2624. **Conclusions.** Treatment of chronic DFUs with PRBM is safe and efficient to achieve complete healing.

Keywords: diabetic foot ulcers, wound healing, chronic wounds, wound care management

According to data from the International Diabetes Federation, there are 537 million adults living with diabetes worldwide, with 240 million of these cases undiagnosed.[1] The lifetime risk of a foot ulcer developing in a patient with diabetes is 34%,[2] and the most common diabetes-related complication leading to hospitalization and lower limb amputation is diabetic foot infection.[3] The economic burden of diabetic lower limb disease is substantial, comprising one-third of the annual direct costs for diabetes annually in the US.[4,5] And even with considerable effort and outlay for treatment of patients with diabetic foot disease, outcomes are often poor. In the US, diabetic limb complications are associated with significant clinical sequelae, including a 5-year mortality rate of 30.5%.[6] Holzer and colleagues conducted a retrospective analysis of the costs for lower extremity ulcers in patients with diabetes and concluded that, given the high costs associated with treating these ulcers, the development of better treatment strategies is warranted.[7] One such development for the treatment of chronic wounds is the use of a novel PRBM (Geistlich Derma-Gide; Geistlich AG).

PRBM is a second-generation, dual-sourced, porcine-derived bilayer matrix designed for the management of chronic wounds. In vitro analyses of the material describe its

Abbreviations: BMI, body mass index; CFR, Code of Federal Regulations; DFU, diabetic foot ulcer; MMP, metalloproteinase; PRBM, purified reconstituted bilayer matrix; SD, standard deviation.

Table 1. Summary of Patient Demographics

PATIENT NO.	SEX	AGE (Y)	WEIGHT (LB)	HEIGHT	BMI (KG/M²)
1	F	72	230	5'4"	40
2	M	58	240	6'5"	29
3	M	49	232	5'6"	37
4	M	38	220	5'8"	34
5	M	68	233	6'0"	32
6	F	31	204	5'9"	30
7	M	58	305	6'5"	36
8	M	59	252	6'5"	30
9	M	56	270	5'10"	39
10	M	59	247	6'5"	29
Mean (SD)	**N/A**	**55** (±13)	**243** (±28)	**6'0"** (±0.5)	**34** (±4)

Abbreviations: BMI, body mass index; F, female; M, male; N/A, not applicable.

matrix structure as an upper dense compact layer that mimics the upper dermis, including the skin's basement membrane, and allows keratinocyte migration as well as growth factor binding and preservation. The lower layer of the material is thicker and more porous in design, allowing for absorption of wound exudate. The matrix structure supports the modulation of matrix MMP activity, cell migration, attachment, and revascularization.[8]

PRBM has been used for the treatment of chronic wounds for 4 years in the US. An initial observational pilot study and subsequent prospective, randomized, controlled clinical trial by Armstrong et al recently reported promising outcomes associated with its application in 40 patients.[9,10] In the present study, the authors discuss their early experience with PRBM for treatment of chronic DFUs that have failed to heal with standard wound care treatment protocols.

MATERIALS AND METHODS

A retrospective case review of 10 consecutive patients with diabetes and a history of chronic DFUs treated with PRBM at a single outpatient center was performed. The research protocol was reviewed by Western IRB, which approved a request for waiver of authorization for use and disclosure of protected health information and determined the study to be exempt under 45 CFR §46.104(d)(4).

To be included, patients must have had nonhealing DFUs (Wagner grade 1 and 2) present for more than 4 weeks and refractory to standard of care topical wound dressing and appropriate offloading with a removable cast walker or total contact cast. Wounds treated with another graft dressing, negative pressure wound therapy, or hyperbaric oxygen therapy were excluded from this study. Baseline demographics—including age, height, weight, and comorbidities—were obtained from the medical records. Adequate circulation to the affected foot was determined by at least a biphasic Doppler of the dorsalis pedis and posterior tibial arteries.

Wounds were treated weekly with application of the PRBM as part of a routine wound care regimen for 12 weeks or until the wounds appeared completely epithelialized and were judged to be fully healed by the treating clinician.

At each weekly visit, standard practice included evaluation of the wound for biofilm infection and cleaning of the wound with sharp debridement as indicated until healthy, bleeding granulation tissue was apparent in the wound. If the wound was not completely epithelialized, an application of PRBM was performed per manufacturer's instructions for use. Following graft application, standard protocol included covering with Adaptic (3M Corporation, Saint Paul, MN) nonadhering dressing followed by gauze, soft roll, foam pad, wrap, and appropriate offloading utilizing a removable cast walker or total contact cast throughout the treatment course. Weekly assessments included measurement of the wound area and inspection of the site for signs of periwound changes, cellulitis, infection, and presence of PRBM. Any adverse events or complications were documented. Patients were asked to provide a subjective assessment of pain (none, low, moderate, or high) related to PRBM application.

The primary outcome measure was complete wound closure at 12 weeks. Probability of wound closure was evaluated through Kaplan-Meier analysis. Secondary outcome measures included time to wound closure, percent area reduction of the ulcer, and cost to closure defined as the direct cost of the PRBM material.

RESULTS

Ten patients with diabetes and chronic DFUs from a single suburban practice were treated from July 2019 to June 2020 and included in this study. Patient demographics are detailed in **Table 1**. Patients were nonsmokers, primarily male (80%), with a mean age of 55 years (range, 31-72 years; SD ±13) and mean BMI of 34 kg/m² (range, 29-40 kg/m²; SD ± 4). In addition to diabetes, patient histories included a range of comorbidities such as hypertension, hyperlipidemia, thyroid conditions, cancer, depression, and asthma.

Wound location and baseline wound characteristics are presented in **Table 2** and included DFUs present on the plantar foot in 5 patients (50%). Mean duration of wounds before treatment with PRBM was 12 weeks (range, 4-24 weeks; SD ± 8), and mean baseline wound area was 2.4 cm² (range, 0.8-7.0 cm²; SD ± 2.0). Wound depth ranged from 0.1 to 1.6 cm (mean, 0.5 cm; SD ± 0.5).

Ulcers were treated with weekly PRBM applications until wound closure was achieved or for a maximum of 12 applications. No patients required revascularization during treatment with

PRBM. Patients were monitored for signs of complications at each visit. Close inspection of wounds to identify evidence of infection or necrosis was performed before each application of PRBM. As described in in vitro evaluations,[8] clinical observations have found the porous nature of the PRBM extracellular matrix can allow for rapid absorption of wound exudate. The PRBM material filled and conformed to the curvature of the wound bed, which was particularly noticeable when placing the material in deeper wounds. **Figure 1** depicts application of the material and its conformance to the wound bed in a particularly deep central plantar wound.

All patients tolerated the application of PRBM and dressing changes with no reported pain, discomfort, or adverse reactions. Patients were instructed in proper use of appropriate offloading and were fit with either a removable cast walker (6 patients) or total contact cast (4 patients). Two of the 4 patients who received a total contact cast were changed to a removable cast walker midway through treatment due to discomfort. No adverse wound events or complications were observed at any time.

Complete closure was achieved in 9 of 10 wounds (90%) during the study period. Six wounds were healed at 6 weeks, two at 7 weeks, and one at 12 weeks. One wound did not close within 12 weeks. The mean time to closure was 6.1 weeks (SD ± 2.6). By week 2, the mean wound area reduction exceeded 60%. At 6 weeks, an overall mean 85% wound reduction was achieved and increased to 94% (SD ± 19%) at 12 weeks (**Figure 2**). Considering the direct cost of the PRBM material, the mean cost to closure for healed wounds was $2624 (SD ± $1569).

The single wound that failed to heal over the course of treatment involved a patient with type 2 diabetes, a BMI of 37 kg/m^2, and additional comorbidities that included stage 5 chronic kidney disease requiring dialysis. Furthermore, the patient appeared to be nonadherent with offloading, which may have contributed to the delayed nonhealing of the ulcer. Although the patient did return for weekly follow-up and dressing changes, the patient's total contact cast routinely appeared with excessive wear and was observed to be cracked at 1 visit. This patient also presented with the largest wound area in the case series, initially measuring 7.0 cm^2. While treatment failed to achieve complete closure over the course of the study, there was some improvement noted with a 41% reduction in wound area at 12 weeks.

The authors of the present study explored subsets of the cohort, further analyzing the outcomes in 2 groups of 5

Table 2. Baseline Wound Characteristics of DFUs Treated With PRBM

PATIENT NO.	WOUND DURATION (W)	BASELINE AREA (CM^2)	BASELINE DEPTH (CM)	WAGNER GRADE	LOCATION
1	20	0.8	0.2	1	Lateral, anterior, midfoot
2	4	1.4	0.2	1	Anterior forefoot
3	8	7.0	0.2	1	Posterior, plantar, forefoot
4	4	2.0	0.1	1	Plantar-lateral, forefoot
5	24	1.0	0.2	1	Plantar-medial, forefoot
6	12	1.1	0.9	1	Posterior, plantar, central, forefoot
7	24	1.9	0.5	1	Plantar, forefoot
8	4	2.2	1.6	2	Lateral, midfoot
9	12	1.5	0.4	1	Lateral, anterior, fifth digit
10	12	4.5	0.5	2	Lateral midfoot
Mean (SD)	**12** (±8)	**2.4** (±2.0)	**0.5** (±0.5)	N/A	N/A

Abbreviations: DFU, diabetic foot ulcer; N/A, not applicable; PRBM, purified reconstituted bilayer matrix.

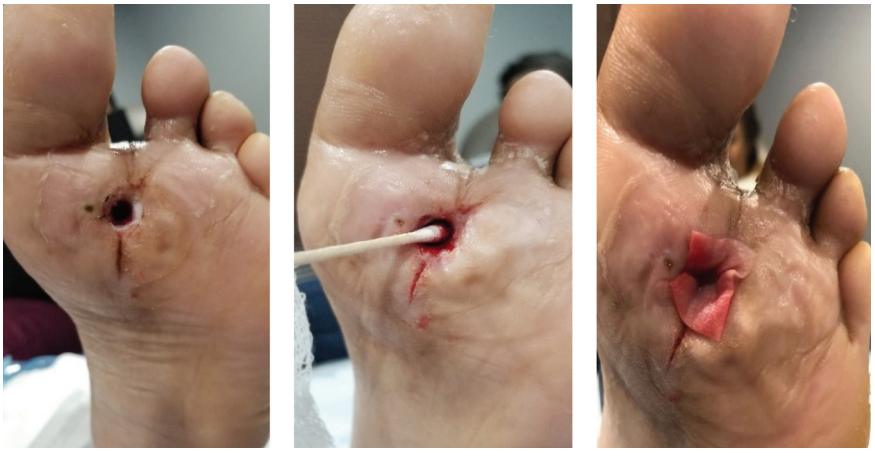

Figure 1. Central plantar wound with baseline depth of 0.9 cm treated with initial application of PRBM. The material conformed to the wound bed, absorbing exudate and filling the wound. Complete closure of this wound was achieved following 7 PRBM applications.
Abbreviation: PRBM, purified reconstituted bilayer matrix.

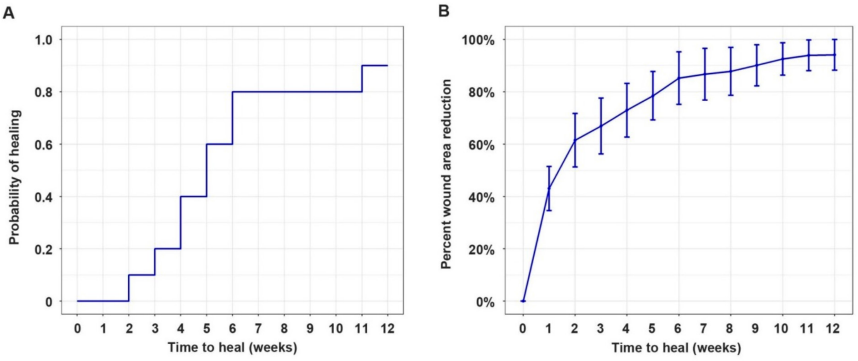

Figure 2. (A) Kaplan-Meier plot of time to heal; 60% of wounds healed within 6 weeks of treatment with PRBM, and 90% healed within 12 weeks. (B) Mean percent wound area reduction over the course of 12 weeks. Error bars represent SD.
Abbreviations: PRBM, purified reconstituted bilayer matrix; SD, standard deviation.

patients based on wound depth at baseline (**Table 3**). The "shallow" cohort included wounds with an initial depth of 0.1 to 0.2 cm (mean, 0.2 cm; SD ± 0.04), and the "deep" cohort included wounds with an initial depth of > 0.4 cm (mean, 0.8 cm; SD ± 1.3). All 5 wounds in the shallow subgroup were categorized as Wagner grade 1. The deep wound subset comprised 2 Wagner grade 2 and 3 Wagner grade 1 ulcers. Compared with shallow ulcers that healed in a mean of 4.8 weeks (SD ± 1.7), the deeper ulcers took somewhat longer to achieve complete closure, with a mean time to healing of 7.2 weeks (SD ± 2.8). Of note, the 1 nonhealing wound in this series occurred in the shallow subset. Complete closure was achieved in 100% of all wounds in the deep cohort at 12 weeks. **Figure 3** depicts a representative healing course for a patient with a deeper Wagner grade 1 chronic wound on the lateral anterior aspect of the fifth digit. After a previous history of failed response to standard therapies and offloading for 12 weeks, the wound was completely healed after 6 applications of PRBM.

DISCUSSION

Data from the US Wound Registry suggest that only 68% of DFUs heal with standard therapies,[11] leaving a significant share of patients with nonhealing wounds at risk for significant complications, including amputation. Numerous strategies have been explored to address the specific demands associated with successful chronic wound treatment in these challenging cases. One common approach to refractory DFU treatment is the application of advanced acellular biological materials to promote healing. Chronic DFUs are known to be difficult to resolve, and patients present with various comorbidities, lifestyle, and socioeconomic factors that must be considered. A comprehensive assessment of advanced skin substitutes by the Agency for Healthcare Research and Quality suggested a need for studies evaluating patients with more serious comorbidities, ie, a "real-world" patient population with more complex wounds.[12] Following reports by Armstrong et al of favorable clinical outcomes with PRBM, a novel advanced biological material,[9,10] the authors investigated the application of PRBM in a heterogeneous population of patients to gain insight into its performance under "real world" conditions. The subjects in this 10-patient cohort presented with a range of comorbidities usually associated with diabetes and known to negatively impact the healing of chronic DFUs.

In this series, 90% of PRBM-treated chronic foot ulcers were completely healed over the course of 12 weeks. This high rate of successful healing equaled the 90% healing rate in Armstrong's similarly sized pilot study[9] and was comparable to the results of the subsequent 40-patient randomized controlled trial in which 85% of chronic wounds treated with PRBM healed completely, a signifi-

Table 3. Baseline Chronic DFU Area and Depth With Associated Material Cost of Closure Reported for PRBM and Other Advanced Biologic Acellular Dressings

	CURRENT SERIES			PUBLISHED STUDIES					
	Patients 1-10	Patients 1-5	Patients 6-10	PRBM[9]	PRBM[10]	dHACA[13]	dHACM[14]	dHACA[15]	dHUC[16]
Mean wound area, cm^2 (SD)	2.4 (2.0)	2.4 (2.6)	2.3 (1.3)	3.3	2.5 (2.16)	2.1 (1.46)	2.6 (2.97)	2.4 (1.88)	2.6 (2.2)
Mean depth, cm (SD)	0.5 (0.5)	0.2 (0.0)	0.8 (0.5)	0.3	N/A (75% <0.2)	N/A	N/A	N/A	N/A
Mean cost to close (SD)	$2624 ($1569)	$1441 ($645)	$3571 ($1440)	$1203	$1731 ($1308)	$1771 ($1375)	$2798 ($4528)	$2200 ($2141)	$3251 ($2898)

Abbreviations: DFU, diabetic foot ulcer; dHACA, dehydrated human amnion and chorion allograft; dHACM, dehydrated human amnion/chorion membrane; dHUC, dehydrated human umbilical cord; N/A, not applicable; PRBM, purified reconstituted bilayer matrix.

cant improvement over the 30% healing reported following standard treatment.[10] Furthermore, the overall mean of 94% wound area reduction in the present case series was similar to the 96% to 99% mean wound area reduction reported in Armstrong's evaluations.[9,10] While complete healing required an average of 3.4 weeks longer in this study than initially reported by Armstrong et al in their 10-patient series, the present results were similar to the healing time reported in their larger trial.[9,10] The $2624 mean material cost to closure in the present series was higher than the $1203 to $1773 costs reported by Armstrong; however, it is well within the range of cost reported for other biological materials, including human tissues (eg, amniotic and umbilical) and other porcine-derived grafts, which have been found to range from $1771 to $3251.[9,10,13-16] The International Working Group on the Diabetic Foot analyzed large clinical DFU cohort studies and identified 8 factors most prominently associated with nonhealing wounds, amputation, and death.[17] While wound depth was one of the 8 prominent factors, most studies of DFU treatment only report wound characteristics of area, duration, and location. Wound depth is not commonly numerically reported, although the extent of wound involvement beyond superficial tissues is certainly considered as a component of routinely utilized observational classification systems.[17] Initial wound depth was measured and collected on each wound in the present study, and the impact of this variable was evaluated. Of note, the first 5 patients' wounds were noticeably shallower, with a mean depth of 0.2 cm. Wounds treated in the second group of 5 patients were deeper, ranging from 0.4 to 1.6 cm (mean, 0.8; SD ± 0.5) and included 2 Wagner class 2 ulcers. While unintentional, this distribution may have been a result of the authors' desire to explore the utility of PRBM in more challenging wounds after gaining familiarity with the product and observing early favorable outcomes. At study initiation, the average wound depth in these 10 cases was 0.5 cm, while the early Armstrong series reported the average wound depth at study initiation was 0.3 cm; in the Armstrong randomized controlled trial, 75% of patients treated with PRBM presented with an initial wound depth of <2 mm.[9,10] The higher costs and longer time to closure reported in the present series, compared with the Armstrong cohorts, may be attributed in part to these differences. When comparing the subset of shallower wounds in this series to the PRBM experience in the Armstrong trial, the secondary outcomes of time and material cost to complete closure closely align (**Table 3**[9,10,13-16]).

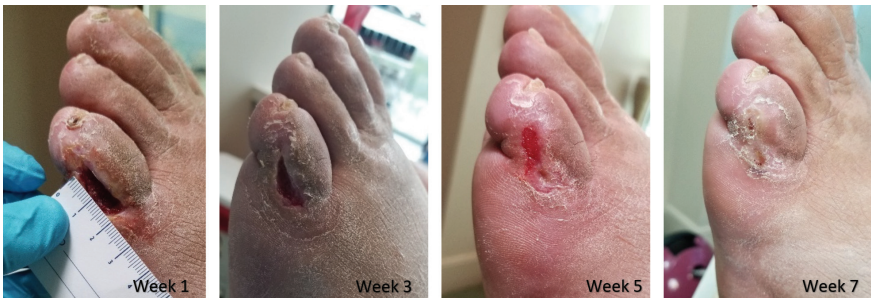

Figure 3. Patient 9; chronic Wagner grade 1 wound on the lateral anterior aspect of the fifth digit. With a history of 12 weeks' duration and failing standard therapies, the wound was completely healed after 6 applications of PRBM.
Abbreviation: PRBM, purified reconstituted bilayer matrix.

It is commonly acknowledged that offloading to redistribute pressure away from a DFU is of paramount importance in its treatment, and that no therapeutic options will succeed without sufficient pressure reduction on the wound.[18,19] It should be noted that the sole patient whose wound failed to heal over the course of the 12-week PRBM treatment in the present study was suspected to be nonadherent with therapy, particularly with regard to offloading.

The present study's findings concur with previously published prospective trials of various advanced biologic materials and recent meta-analyses of these studies, suggesting utilization of advanced wound matrices is beneficial, with fewer average days to complete healing and high wound closure rates of 70% to 97%.[13-16,20-22] The availability of several biologic materials demonstrating similar outcomes when used for treatment of chronic DFUs allows physicians to select products with preferred dimension and handling characteristics. As the bilayer PRBM is thicker and denser than frequently used human amniotic membrane therapies, it may offer a better alternative when treating deeper chronic wounds.

In summary, the clinical results observed while using PRBM for treatment of chronic DFUs in a heterogeneous population are promising and concur with previously reported outcomes.

LIMITATIONS

While retrospective reviews are the first step in the formulation of a hypothesis to answer a particular research question, the authors appreciate that a retrospective study design lacks the ability to account and control for potential patient selection biases. Furthermore, the data presented in this series originate from a relatively small number of patients and were collected from retrospective medical record reviews. Nonetheless, preliminary evidence is beneficial when considering whether PRBM is a potentially viable option to consider for the treatment of DFUs in a typical outpatient setting (ie, patients presenting with a wide spectrum of comorbidities). As with any small case series, the authors recognize all variables that are known to impact wound healing—such as glycemic control, nutrition, and medication—were not assessed in this study. Nevertheless, the data presented are supportive of further investigations, ide-

ally a prospective, randomized, controlled study focusing on the effectiveness of PRBM for treatment of chronic deep DFUs.

CONCLUSIONS

In this 10-patient study, 90% of DFUs refractory to standard of care were successfully healed with application of a novel PRBM. Closure was achieved in an average of 6.1 weeks with no adverse events. Outcomes were particularly encouraging in deeper wounds, which tend to be more difficult to close. Further clinical investigation—including a larger, prospective randomized trial—is recommended to evaluate the efficacy and economic value of PRBM for the healing of chronic DFUs as compared with standard of care protocols and other advanced wound dressings.

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