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# Complete wound closure following a single topical application of a novel autologous homologous skin construct: first evaluation in an open-label, single-arm feasibility study in diabetic foot ulcers

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## Abstract

Diabetic foot ulcers (DFUs) are a growing burden on patients and health care systems that often require multiple treatments of both conventional and advanced modalities to achieve complete wound closure. A novel autologous homologous skin construct (AHSC) has been developed to treat cutaneous defects with a single topical application, by leveraging the endogenous repair capabilities of the patient's healthy skin. The AHSC's ability to close DFUs with a single treatment was evaluated in an open-label, single-arm feasibility study. Eleven patients with DFUs extending up to tendon, bone, or capsule received a single topical application of AHSC. Closure was documented weekly with high-resolution digital photography and wound planimetry. All 11 DFUs demonstrated successful graft take. Ten DFUs closed within 8 weeks. The median time-to-complete closure was 25 days. The mean percent area reduction for all 11 wounds at 4 weeks was 83%. There were no adverse events related to the AHSC treatment site. This pilot study demonstrated AHSC may be a viable single application topical intervention for DFUs and warrants investigation in larger, controlled studies.

**KEYWORDS**

autologous homologous skin construct, diabetic foot ulcer, novel therapy, wound healing

## 1 | INTRODUCTION

Diabetic foot ulcers (DFUs) affect 1.5 million Americans with a lifetime risk of a diabetic patient developing an ulcer of 19% to 34%.[1] Nearly 85% of diabetic related amputations are preceded by an ulcer.[2] The percent of all DFUs closed with standard of care treatment (SOC) can be as high as 59.3% after 12 weeks with recalcitrant ulcers healing at an even lower rate.[3] A wide array of advanced wound care therapies has been developed in an attempt to improve these treatment outcomes.[4,5] These include biological skin substitutes such as placental membranes, acellular tissue matrices, and cultured biosynthetic dressings.[4-6] Several randomised studies, a meta-analysis, and a Cochrane review comparing biological skin substitutes to SOC suggest they improve wound closure.[4,7] However, most products require multiple applications to achieve closure, with a single application potentially costing over a thousand dollars (Table 1). Repeat applications and refractoriness to the standard care contribute to the significant expense in treating lower extremity wounds, which is estimated to cost the US health care system $58 billion dollars.[1] Treatments such as split-thickness skin grafting (STSG) do contribute new healthy tissue to the wound bed but have shown failure rates of approximately 30% when used for DFUs.[8-12] This is attributed to the compromised ability of the chronic wound bed to support and incorporate the graft, bacterial contamination, and patient comorbidities such as diabetes and vascular insufficiency.[10,13] Additionally, skin grafting requires a surgical procedure in the operating room, whereas the majority of DFUs are treated in the outpatient setting.

A novel autologous homologous skin construct (AHSC) has shown promise in treating complex and refractory wounds.[14-16] Manufactured from a small harvest of full-thickness, healthy skin, it retains the endogenous regenerative populations responsible for native wound healing.[14-17] To date, it has been used to treat patients without any reported adverse reactions. AHSC is not expanded ex vivo, but rather it is expeditiously returned in a syringe to the provider within 14 days of harvest. The product is easily administered topically over a properly debrided wound bed and covered using standard of care dressings, making it convenient to use in the outpatient setting (Figure 1). Manufacturing optimises the AHSC for austere wound beds such as chronic wounds allowing for the delivery and engraftment of healthy autologous tissue. The AHSC forms small skin islands that expand and coalesce and initiate wound closure from multiple foci of epithelialisation rather than only from the original wound margin.[14,15] A single-arm, open-label feasibility study was performed to assess the ability of AHSC to provide a safe autologous treatment that achieves complete closure of DFUs although only a single application, in contrast to other advanced wound modalities that require multiple applications.

**Key Messages**

- a novel autologous homologous skin construct (AHSC) leverages the endogenous repair capabilities of the patient's healthy skin has been developed to treat cutaneous defects with a single topical application
- diabetic foot ulcers receiving (AHSC) closed with a single application in the outpatient setting
- treated wounds closed within 8 weeks. The median time to closure was 25 days. There were no treatment related adverse events

## 2 | RESEARCH DESIGN AND METHODS

### 2.1 | Study design and population

This single-armopen-label feasibility study was conducted from November 6, 2018 through May 14, 2019. The

**TABLE 1** Number of applications of biological skin substitutes that have been evaluated in more than one randomised controlled trial within the last 10 years[4]

| Product | Mean no. of reported applications | Range of reported no. of applications | References |
|---|---|---|---|
| ADM | 2.5 | 1.1 to 4.7 | 22-26 |
| Amnion | 4.5 | 2.5 to 7 | 27-35 |
| CBD | 3.7 | 1.5 to 6 | 21,25-27,36,37 |
| DRT | 1 | 1 to 15 | 38,39 |

Abbreviations: ADM, acellular dermal matrix; Amnion, placental membranes; CBD, cultured biosynthetic dressings; DRT, dermal regenerative template.


**FIGURE 1** Diagram of events during the harvest and application of autologous homologous skin construct (AHSC). A 2 × 1 cm piece of healthy tissue was harvested from the proximal calf of each patient in the office. This was shipped overnight to an FDA-registeredbio-manufacturing facility, where it was processed into AHSC. It was returned to the provider the following day. The AHSC was deployed on the debrided wound bed on the third day in the clinic. FDA, U.S. Food and Drug Administration

**TABLE 2** Patient inclusion/exclusion criteria

| |
|---|
| Inclusion criteria |
| Diabetic foot ulcer that could extend to the ligament, tendon, joint capsule, or deep fascia, provided that it was at or below the aspect of the medial malleolus |
| Index ulcer had been present for at least 4 wk and did not achieve a healing rate > 30% prior to AHSC treatment |
| Index ulcer had been offloaded for ≥14 d prior to AHSC treatment |
| Index ulcer had a clean granular base, was free of necrotic debris, and appeared to healthy, vascularised tissue at time of AHSC placement |
| Affected foot had adequate circulation as documented by a dorsal transcutaneous oxygen measurement or a skin perfusion pressure measurement of ≥30 mmHg, or an ankle brachial index of ≥0.7 and ≤ 1.2, or arterial Doppler with a minimum of biphasic flow within 3 mo of treatment |
| Provider deemed the patient stable for treatment |
| Patient provided written informed consent |
| Exclusion criteria |
| Active osteomyelitis, cellulitis, soft tissue infection, or active Charcot's arthropathy of the affected foot involving or near the index ulcer site, or on the same limb as the index ulcer |
| Index ulcer was suspicious of cancer |
| History of radiation at the index ulcer site |
| History of >2 wk treatment with immune suppressants (including systemic corticosteroids), cytotoxic chemotherapy, or application of topical steroids to the index ulcer surface within 1 mo prior to AHSC placement |
| In the opinion of the provider, the patient had evidence of unstable HIV, hepatitis B, or hepatitis C |

Abbreviations: AHSC, autologous homologous skin construct.

objective of this pilot study was to treat 11 adult patients with a Wagner 1 or 2 DFU to evaluate both safety by capturing all adverse events (AE) and the ability of a single application of AHSC in the office setting to close DFUs. Table 2 details complete inclusion and exclusion criteria. Patients provided their written informed consent. The primary safety endpoints were the occurrence of AE, which were defined as any untoward event that happened to the patient beginning with the harvest procedure, and graft-related complications. The secondary safety endpoint was patient-reported pain during the harvest procedure, application procedure, and follow-up visits, based on a visual analogue scale (VAS) of 0 through 10. The primary efficacy endpoint was the rate of closure at 12 weeks following AHSC treatment. Secondary efficacy endpoints included graft take rate at 12 weeks and

**TABLE 3** Patient and wound characteristics

| Patient no. | Age (y) | Race | Sex | BMI | Comorbidities | Duration of ulcer (wk) | Off-loading system | Ulcer location | Wagner class | Initial wound area ($cm^2$) | Prior amputation of study foot | Time to heal (d) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 59 | W | M | 42 | Hypertension, hyperlipidemia, BFN, hypothyroidism, anaemia, depression, anxiety, BPH, myasthenia gravis | 4 | Cam boot | Left, plantar, lateral, midfoot | 1 | 1.0 | None | 18 |
| 2 | 55 | AA | M | 29 | Hypertension, hyperlipidemia, BFN, anaemia, CKD, diabetic retinopathy | 8 | Cam boot | Left, plantar, lateral, midfoot | 2 | 1.3 | None | 33 |
| 3 | 82 | W | M | 28 | Hypertension, BFN, gout, arthritis, bunion, hammertoes, glaucoma | 5 | Cam boot | Left, plantar, medial, forefoot | 2 | 1.7 | None | 25 |
| 4 | 55 | W | M | 26 | Hypertension, hyperlipidemia, BFN, GERD | 5 | Cam boot | Right, plantar, medial, forefoot | 2 | 2.7 | Hallux | 46 |
| 5 | 78 | W | F | 28 | Hypertension, hyperlipidemia, BFN, hypothyroidism, depression, GERD, venous leg ulcer, bunion, hammertoes | 10 | Cam boot | Left, plantar, medial, hallux, first digit toe | 1 | 1.4 | None | 21 |
| 6 | 53 | W | F | 38 | Hypertension, hyperlipidemia, BFN, hypothyroidism, anxiety, arthritis | 4 | Cam boot | Left, plantar, lateral, heel | 2 | 5.1 | None | 21[a] |
| 7 | 48 | W | F | 25 | Hyperlipidemia, BFN, CKD, GERD, heart attack, CHF | 14 | Cam boot | Right, plantar, medial, heel | 1 | 21.7 | None | 56 |
| 8 | 87 | W | F | 31 | Hyperlipidemia, BFN, hypothyroidism, GERD, CHF, Addisons Disease, glaucoma | 4 | Diabetic shoes | Right, plantar, lateral midfoot | 1 | 1.3 | None | 11 |
| 9 | 75 | W | F | 35 | Hypertension, hyperlipidemia, BFN | 5 | Cam boot | Right, plantar, lateral midfoot | 1 | 1.0 | None | 11 |

(Continues)

**TABLE 3** (Continued)

| Patient no. | Age (y) | Race | Sex | BMI | Comorbidities | Duration of ulcer (wk) | Off-loading system | Ulcer location | Wagner class | Initial wound area ($cm^2$) | Prior amputation of study foot | Time to heal (d) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 10 | 63 | W | F | 26 | BFN, hypothyroidism, anaemia depression, anxiety, CKD, GERD, hyperkalemia, asthma | 8 | Cam boot | Left, plantar, medial, heel | 2 | 2.0 | None | 18 |
| 11 | 72 | W | F | 21 | Hyperlipidemia, BFN, heart attack, glaucoma | 26 | Cam boot | Right, plantar, medial, hallux, first digit toe | 1 | 3.4 | None | 46 |

Abbreviations: AA, African-American; BMI, Body Mass Index; BFN, bilateral foot neuropathy; BPH, benign prostatic hyperplasia; CHF, congestive heart failure; CKD, chronic kidney disease; F, female; GERD, gastroesophageal reflux disease; W, White.

[a]Patient was withdrawn on day 21 due to infection; ulcer was unhealed.

harvest site closure rate at 12 weeks. The product cost of AHSC treatment per DFU was analysed. This study was conducted according to the principles expressed in the Declaration of Helsinki. The study was conducted under the guidance of Western Institutional Review Board (Puyallup, Washington) who approved the clinical study. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines were followed in reporting this series.

## 2.2 | AHSC preparation, application, and follow-up

Harvests were performed at initial patient visit. Before the harvest procedure, the subject's clinical and wound history were recorded. A 1 × 2 cm full-thickness harvest of healthy skin was taken from the proximal calf of the affected limb of each patient using sterile technique and local anaesthesia. Harvest sites were sutured closed. The harvest was mailed overnight to a Food and Drug Administration–registered biomedical manufacturing facility (PolarityTE, Salt Lake City, Utah), where the AHSC (SkinTE, PolarityTE) was created from the tissue. The AHSC was returned to the provider within 48 hours of tissue harvest, per provider discretion, and was applied to the wound bed 3 days after the harvesting procedure.

For the application procedure, the wound was cleaned and sharply debrided. The AHSC was topically spread evenly across the wound bed and covered with a silicone dressing, then covered by an absorbent foam dressing (DermaFoam, DermaRite, North Bergen, New Jersey), followed by a 3-layer compression bolster (DYNA-FLEX, Acelity, 3M Corporation, Minnesota). Dressings were changed weekly, and wounds were offloaded with a diabetic offloading boot. The silicone dressing was replaced by a nonadherent contact layer (Adaptic Touch, KCI, 3M Corporation) at the third dressing change, and covered by the aforementioned 3-layer compression bolster. Standard of care wound management was maintained until wound closure.

Patients had weekly follow-up visits and dressing changes until closure was confirmed for up to 12 weeks. A DFU was deemed closed if it remained completely epithelialised without drainage 2 weeks after it was first determined to be closed by the treating provider, and closure was confirmed by consensus of three blinded plastic surgeons through review of high-resolution digital photography. At each visit, the provider assessed graft take (yes/no), assessed the wound for infection, recorded patient-reported pain using a VAS, and wound measurements were recorded by a wound imaging system (Insight, eKare Inc, Fairfax, Virginia).

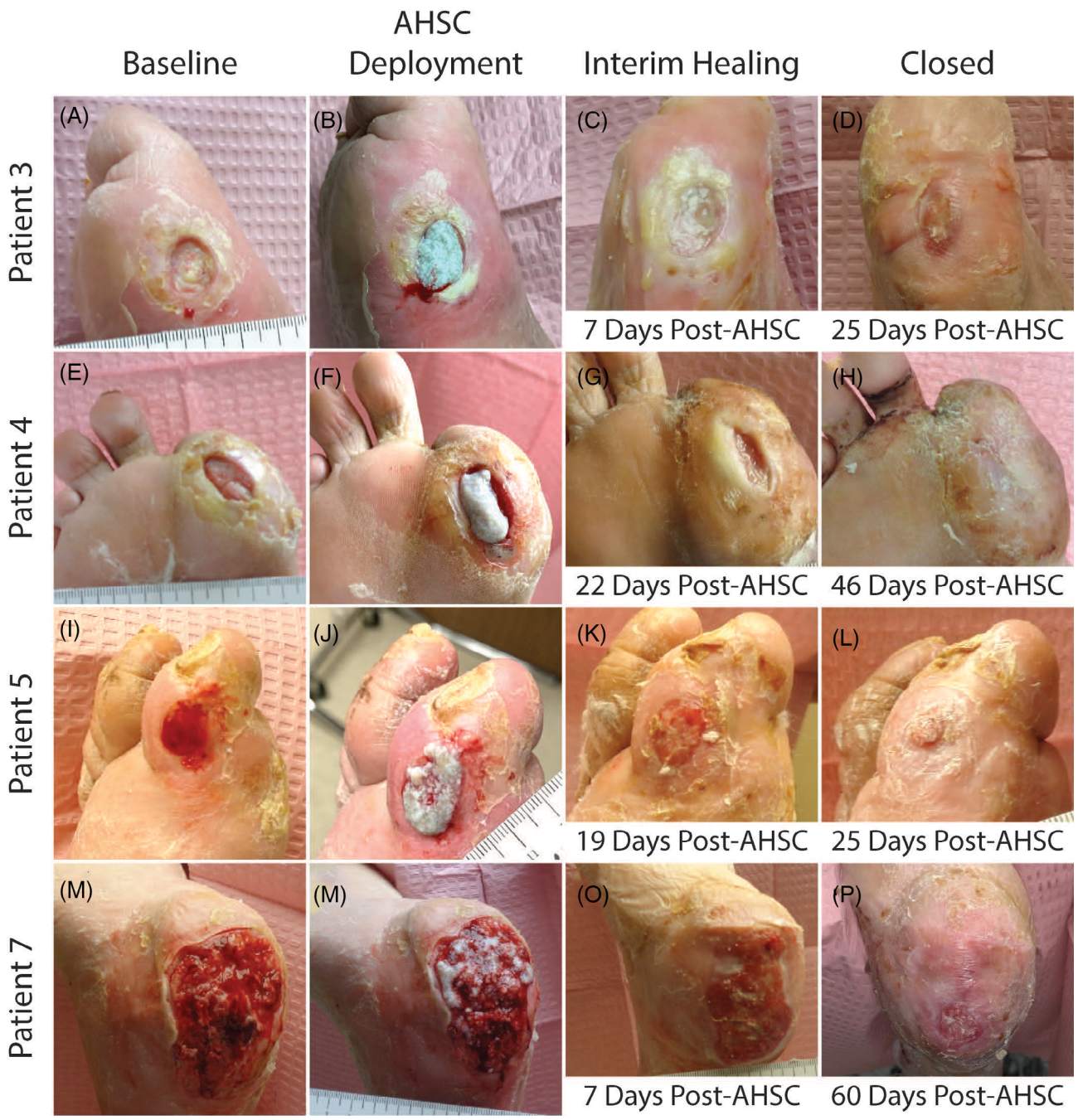


**FIGURE 2** Representative images of Patient No. 3, an 82-year-old man with diabetes, hypertension, neuropathy, gout, arthritis, and glaucoma, who presented with a 2 $cm^2$ diabetic foot ulcer (DFU) on the left, plantar, medial, forefoot; Patient No. 4, a 56-year-old man with diabetes, hypertension, hyperlipidemia, gastroesophageal reflux disease, and neuropathy and a previous amputation of the hallux, who presented with a 3 $cm^2$ DFU on the right, plantar, medial, forefoot; Patient No. 5, a 78-year-old woman with diabetes, hypertension, hyperlipidemia, gastroesophageal reflux disease, neuropathy, hypothyroidism, depression, and venous leg ulcer, who presented with a 1 $cm^2$ DFU on the first digit toe of the left foot; and Patient No. 7, a 48-year-old woman with diabetes, hyperlipidemia, gastroesophageal reflux disease, neuropathy, chronic kidney disease, and heart disease, who presented with a 22 $cm^2$ DFU on the right, plantar, medial, heel

## 2.3 | Data collection and analysis

Data were stored in an Excel database. A statistician (Strategic Solutions, Inc, Cody, Wyoming) performed statistical analysis. Descriptive statistics were used to analyse patient and wound characteristics and pain data. Percent in wound area reduction (PAR) was analysed for all wounds at 4 weeks. Time-to-close was analysed for all wounds with Kaplan–Meier analysis.

AHSC was provided by the manufacturer; however, the cost of AHSC graft utilisation was calculated using

the manufacturer's pricing. Constructs with an area of ≤5 $cm^2$ cost $950, >5 $cm^2$ but ≤10 $cm^2$ cost $1600, and > 10 $cm^2$ but ≤40 $cm^2$ cost $3400.

## 3 | RESULTS

Eleven patients (7 female, 4 male) with a mean age of 67 years (SD: 13 years), Type 2 diabetes, and a combined six Wagner 1 and five Wagner 2 DFUs were consecutively screened and enrolled into the study (Table 3). The patients had on average six comorbidities (SD: 2, Table 3). The mean initial wound area was 4 $cm^2$(SD: 6 $cm^2$, range 1-22 $cm^2$, Table 3). The mean pre-AHSC treatment duration was 8 weeks (SD: 7 weeks) with weekly debridement and alginate dressings for at least 4 weeks prior to enrollment.

All 11 DFUs had graft take at 1 week after a single topical AHSC application. Ten of 11 DFUs (91%) completely closed within 8 weeks of AHSC application. The mean time to closure for all 11 wounds was 30 days (SE: 5; 95% confidence interval [CI[: 20-39); the median time to close was 25 days (SE: 5; 95% CI: 14-36, Figures 2 and 3). At 4 weeks, the mean percent area reduction (PAR) for all 11 wounds was 83% (SD: 31%; range −2% to 100%). Digital photography documented small skin islands visible after AHSC application that expanded and coalesced with time (Figure 2). All harvest sites successfully closed with one requiring a second closure.

There were no AHSC treatment site-related AEs or SAEs. Two AEs were reported (18%), including 1 serious AE (SAE). One AE occurred when the harvest site of patient No. 4 opened the night of primary closure. It was sutured closed in the emergency room and remained closed with no further complications. The SAE occurred in patient No. 6, who was withdrawn from the study at week 4 after a secondary wound developed on the ankle at a Charcot

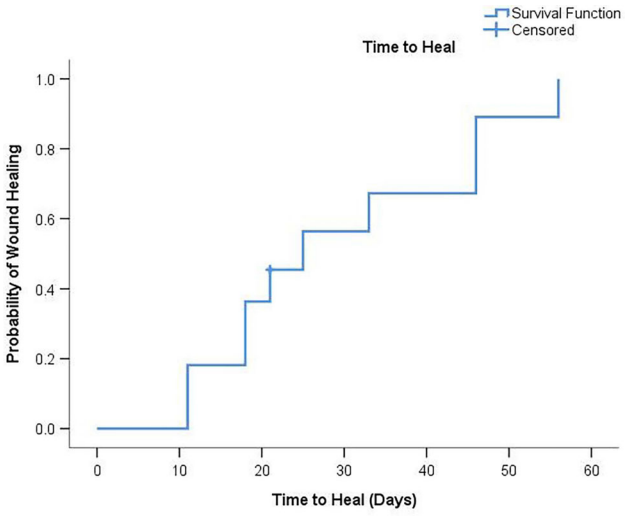


**FIGURE 3** Kaplan–Meier graph of the time to closure

**TABLE 4** Summary of patient-reported pain during course of study, based on visual analogue scale (VAS) of 0 through 10

| Study visit | No. of patients reporting pain (%) | Mean VAS (SD) | Range |
|---|---|---|---|
| Harvest | 11 (100%) | 2 (2) | 0 to 5 |
| Application | 11 (100%) | 3 (2) | 0 to 5 |
| Week 1 | 11 (100%) | 2 (2) | 0 to 5 |
| Week 2 | 10 (92%) | 2 (2) | 0 to 6 |
| Week 3 | 11 (100%) | 1 (2) | 0 to 4 |
| Week 4 | 7 (64%) | 1 (2) | 0 to 5 |
| Week 5 | 6 (54%) | 1 (2) | 0 to 4 |
| Week 6 | 5 (45%) | 1 (2) | 0 to 4 |
| Week 7 | 4 (36%) | 1 (2) | 0 to 4 |
| Week 8 | 2 (18%) | 2 (3) | 0 to 4 |
| Healing confirmation | 10 (92%) | 1 (1) | 0 to 4 |

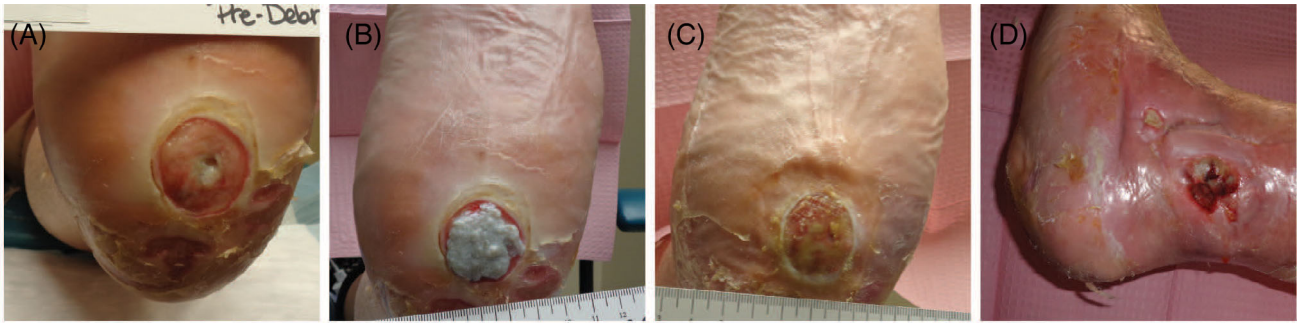


**FIGURE 4** Images of Patient No. 6, a 53-year-old woman who was treated for a 5 $cm^2$ left plantar lateral heel diabetic foot ulcer (DFU) and was withdrawn from the study following an infection of the study foot of indwelling hardware from a prior Charcot foot reconstruction procedure. A, Pretreatment wound; B, ASHC applied; C, interim closure 13-days following treatment; D, development of infected left lateral wound related to prior Charcot foot reconstruction requiring surgical intervention

fusion site and became infected, requiring surgery (Figure 4).

Summaries of patient-reported pain, which was minimal throughout the study, including during the harvest and application procedure are illustrated in Table 4. All patients reported some level of pain at the beginning of the study prior to treatment; by week 8, only 2 patients (18%) reported some pain.

All patients required only 1 AHSC application for complete closure. The calculated mean cost of graft utilisation in this study with AHSC was $1230 (SD: $750; median: $950).

## 4 | DISCUSSION

DFUs are a growing burden for both patients and health care systems, and they are often refractory to standard of care management. Biological skin substitutes have demonstrated success in closing DFUs.[4,7] However, they require multiple applications, which results in increased product costs, and they rely on the impaired tissues and cells within the chronic wound environment to enact wound closure. Skin grafting supplies healthy tissue to the wound bed, but STSGs have increased failure rates in DFUs, require a surgeon and operating room with attendant costs, and are largely not amenable to office-based management of DFUs. The goal of this study was to evaluate the ability of a novel AHSC treatment to close DFUs with only a single application performed in a busy office-based wound care practice. Ten (91%) of 11 DFUs closed within 8 weeks following a single application of the AHSC with a median time to closure of 25 days and a percent area reduction at 4 weeks of 83%. This is in contrast to the closure rate that is achieved with standard of care, which can be as high at 59% and even less in recalcitrant hard to heal wounds.[3]

The historical difficulty in treating DFUs is inherent to the disease. DFUs are a manifestation of the prolonged systemic exposure to diabetes, which results in the body's inability to repair itself and the development of life-threatening ulcers from injuries that a healthy integumentary system could resolve. The aetiology of chronic wounds is multifactorial. Reduced levels of active growth factors, an imbalance of proteinases, and decreased proliferation of cells in and around the wound bed are attributed with wound persistence.[18] Biological skin substitutes including placental membranes, acellular matrices, and cultured biosynthetic dressings are believed to favourably alter the chronic wound environment facilitating cellular proliferation and closure.[4-6] Studies demonstrate several applications are required and may not always be sufficient because of the compromised underlying tissue in the chronic wound (Table 1). Repeat applications result in increased product and overall treatment expenditures given the higher costs of these advanced therapies. STSGs supply healthy autologous tissue to the wound bed that can engraft and facilitate wound closure. However, they have significantly greater failure rates in chronic wounds, and are not amenable to office-based care, and incur operating room and other surgery-related costs.[8-12]

The AHSC for this study was created from an approximately 1.5 $cm^2$ healthy piece of skin harvested in the outpatient setting from the proximal calf with minimal morbidity to the patient (Table 3). The resulting AHSC was sufficient to treat wounds ranging from 1 to 22 $cm^2$. The AHSC processing optimises the tissue for engraftment and retains all of the endogenous regenerative cellular populations associated with wound healing that reside within hair follicles, glands, and the interfollicular epidermis. This optimisation achieves a high surface area to volume ratio, which facilitates the sustenance from plasmatic imbibition of the primed AHSC cellular populations in austere chronic wound environments during the first 48 hours before inosculation and vascularisation occurs.[19,20] This enables these "fresh" healthy tissues to close DFUs in a relatively short time period with a single application, which has significant implications for overall treatment success and expenditures.

The calculated mean and median AHSC utilisation costs were $1230 and $950, respectively. This study was not designed to compare product costs. However, it is interesting to note that AHSC product costs are substantially less than those previously reported for advanced skin substitutes such as Dermagraft and Apligraf (Organogensis, Canton, MA), which have reported DFU-treatment product costs of $14 424 and $5364–8918 per DFU, respectively.[20,21]

Importantly, the AHSC-regenerated skin qualitatively mimicked native, healthy skin (Figure 2), a finding that was previously reported in a study that demonstrated equivocal sensation of AHSC-regenerated skin compared with native skin, regenerated hair follicles equivalent in cellular and structural architecture to native follicles, and minimal scarring after 6 months.[19]Long-termfollow-up is required to see if the use of the AHSC created from healthy tissue with all the elements important for native skin repair will result in more durable DFU closure and increased patient quality of life.

In our small study, there were no AEs of AHSC-treated sites and only minimal harvest and treatment site discomfort. This study is limited by a small sample size, its single-arm and open-label design, and lack of an expansive number of site. On the basis of these promising results, a large RCT was developed to evaluate the effect of the AHSC on DFUs (NCT03881254).

In conclusion, this study demonstrated that a single topical treatment of the AHSC applied in an office-based wound care practice can close DFUs with a favourable overall

success rate and time to closure. Larger, controlled studies designed from this study will further assess these findings.

## ACKNOWLEDGEMENT

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## CONFLICT OF INTEREST

The Professional Education and Research Institute, for which Medical Director Charles Zelen DPM, received research support from PolarityTE to administer this study.

The Surgery Department for the University of Southern California has received research funds from PERI provided by PolarityTE for D.G.A. to serve as principal investigator and assist in completion of this study and is assisting in the completion of the DFU RCT. D.P.O. is a consultant for PERI and has received funds from PERI to assist in completion of this study and in the completion of the DFU RCT. P.M.G., PC for which P.M.G. is the Medical Director and owner has received research funds from PERI provided by PolarityTE to assist in completion of this study and is assisting in the completion of the DFU RCT. R.G. is a consultant for PERI and has received research funds from PERI provided by PolarityTE to assist in completion of this study and is assisting in the completion of the DFU RCT. M.C. is a consultant for PERI and has received funds from PERI to assist in completion of this study and perform the statistical analysis. The Professional Education and Research Institute (PERI), for which C.M.Z. is medical director and CEO has received research funds from PolarityTE to conduct this study and is assisting in the completion of the DFU RCT. LLC for which W.W.L. is the Medical Director and owner has received research funds from PERI provided by PolarityTE to assist in completion of this study, serve as medical monitor and is assisting in the completion of the DFU RCT.

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## REFERENCES

1. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. *N Engl J Med*. 2017;376(24):2367-2375. https://doi.org/10.1056/nejmra1615439.
2. Pendsey S. *Diabetic Foot: A Clinical Atlas*. London, UK: Martin Dunitz; 2004 Distributed in the USA by Fulfilment Center, Taylor & Francis.
3. Ince P, Game FL, Jeffcoate WJ. Rate of healing of neuropathic ulcers of the foot in diabetes and its relationship to ulcer duration and ulcer area. *Diabetes Care*. 2007;30(3):660-663.
4. Gordon AJ, Alfonso AR, Nicholson J, Chiu ES. Evidence for healing diabetic foot ulcers with biologic skin substitutes: a systematic review and meta-analysis. *Ann Plast Surg*. 2019;83(4S suppl 1):S31-S44.
5. Halim AS, Khoo TL, Shah SJ. Biologic and synthetic skin substitutes: an overview. *Indian J Plastic Surg*. 2010;43:S23-S28. http://www.ncbi.nlm.nih.gov/pubmed/21321652. Accessed February 9, 2020.
6. Davison-Kotler E, Sharma V, Kang NV, García-Gareta E. A universal classification system of skin substitutes inspired by factorial design. *Tissue Eng Part B Rev*. 2018;24:279-288. https://doi.org/10.1089/ten.teb.2017.0477.
7. Santema TB, Poyck PPC, Ubbink DT. Skin grafting and tissue replacement for treating foot ulcers in people with diabetes. *Cochrane Database Syst Rev*. 2016;11-17. https://doi.org/10.1002/14651858.CD011255.pub2.
8. Ramanujam CL, Han D, Fowler S, Kilpadi K, Zgonis T. Impact of diabetes and comorbidities on split-thickness skin grafts for foot wounds. *J Am Podiatr Med Assoc*. 2013;103(3):223-232.
9. Donegan RJ, Schmidt BM, Blume PA. An overview of factors maximizing successful split-thickness skin grafting in diabetic wounds. *Diabet Foot Ankle*. 2014;5(1):24769. https://www.tandfonline.com/doi/full/10.3402/dfa.v5.24769 Accessed January 19, 2019.
10. Ramanujam CL, Stapleton JJ, Kilpadi KL, Rodriguez RH, Jeffries LC, Zgonis T. Split-thickness skin grafts for closure of diabetic foot and ankle wounds: a retrospective review of 83 patients. *Foot Ankle Spec*. 2010;3(5):231-240. https://doi.org/10.1177/1938640010375114.
11. Thourani VH, Ingram WL, Feliciano DV. Factors affecting success of split-thickness skin grafts in the modern burn unit. *J Trauma*. 2003;54(3):562-568.
12. Reddy S, El-Haddawi F, Fancourt M, et al. The incidence and risk factors for lower limb skin graft failure. *Dermatol Res Pract*. 2014;2014:582080. https://doi.org/10.1155/2014/582080.
13. Donegan RJ, Schmidt BM, Blume PA. An overview of factors maximizing successful split-thickness skin grafting in diabetic wound. *Diabet Foot Ankle*. 2014;5:1-3.
14. Granick MS, Baetz NW, Labroo P, Milner S, Li WW, Sopko NA. In vivo expansion and regeneration of full-thickness functional skin with an autologous homologous skin construct: clinical proof of concept for chronic wound healing. *Int Wound J*. 2019;16:1-6.
15. Patterson CW, Stark M, Sharma S, Mundinger GS. Regeneration and expansion of autologous full-thickness skin through a self-propagating autologous skin graft technology. *Clin Case Rep*. 2019;7(12):2449-2455. http://www.ncbi.nlm.nih.gov/pubmed/31893078. Accessed January 4, 2020. https://doi.org/10.1002/ccr3.2533.
16. Isbester K, Wee C, Boas S, Sopko N, Kumar A. Regeneration of autologous, functional, full thickness skin with minimal donor site contribution using autologous homologous skin construct. *Plast Surg Case Stud*. 2019:2-3.
17. Snippert HJ, Haegebarth A, Kasper M, et al. Lgr6 Marks stem cells in the hair follicle that generate all cell lineages of the skin. *Science (80-)*. 2010;327(5971):1385-1389. http://www.ncbi.nlm.nih.gov/pubmed/20223988. Accessed November 1, 2018. https://doi.org/10.1126/science.1184733.
18. Harding KG, Morris HL, Patel GK. Science, medicine and the future: healing chronic wounds. *BMJ*. 2002;324(7330):160-163. http://www.ncbi.nlm.nih.gov/pubmed/11799036. Accessed December 14, 2018. https://doi.org/10.1136/bmj.324.7330.160.
19. Martinson M, Martinson N. A comparative analysis of skin substitutes used in the management of diabetic foot ulcers. *J Wound Care*. 2016;25(suppl 10):S8-S17. https://doi.org/10.12968/jowc.2016.25.sup10.s8.

20. Januszyk M, Rennert R, Sorkin M, et al. Evaluating the effect of cell culture on gene expression in primary tissue samples using microfluidic-based single cell transcriptional analysis. *Microarrays*. 2015;4(4):540-550. https://doi.org/10.3390/microarrays4040540.
21. Zelen CM, Serena TE, Gould L, et al. Treatment of chronic diabetic lower extremity ulcers with advanced therapies: a prospective, randomised, controlled, multi-Centre comparative study examining clinical efficacy and cost. *Int Wound J*. 2015;13(2):272-282. https://doi.org/10.1111/iwj.12566.
22. Zelen CM, Orgill DP, Serena TE, et al. An aseptically processed, acellular, reticular, allogenic human dermis improves healing in diabetic foot ulcers: a prospective, randomised, controlled, multicentre follow-up trial. *Int Wound J*. 2018;15(5):731-739. http://www.ncbi.nlm.nih.gov/pubmed/29682897. Accessed February 25, 2020. https://doi.org/10.1111/iwj.12920.
23. Zelen CM, Orgill DP, Serena T, et al. A prospective, randomised, controlled, multicentre clinical trial examining healing rates, safety and cost to closure of an acellular reticular allogenic human dermis versus standard of care in the treatment of chronic diabetic foot ulcers. *Int Wound J*. 2017;14(2):307-315. http://www.ncbi.nlm.nih.gov/pubmed/27073000. Accessed February 25, 2020. https://doi.org/10.1111/iwj.12600.
24. Cazzell SM, Lange DL, Dickerson JE, Slade HB. The management of diabetic foot ulcers with porcine small intestine Submucosa tri-layer matrix: a randomized controlled trial. *Adv Wound Care*. 2015;4(12):711-718.
25. Didomenico L, Landsman AR, Emch KJ, Landsman A. A prospective comparison of diabetic foot ulcers treated with either a cryopreserved skin allograft or a bioengineered skin substitute. *Wounds*. 2011;23(7):184-189.
26. Sanders L, Landsman AS, Landsman A, et al. A prospective, multicenter, randomized, controlled clinical trial comparing a bioengineered skin substitute to a human skin allograft. *Ostomy Wound Manage*. 2014;60:26-38.
27. Ananian CE, Dhillon YS, Van Gils CC, et al. A multicenter, randomized, single-blind trial comparing the efficacy of viable cryopreserved placental membrane to human fibroblast-derived dermal substitute for the treatment of chronic diabetic foot ulcers. *Wound Repair Regen*. 2018;26(3):274-283. http://www.ncbi.nlm.nih.gov/pubmed/30098272. Accessed February 25, 2020.
28. DiDomenico LA, Orgill DP, Galiano RD, et al. Use of an aseptically processed, dehydrated human amnion and chorion membrane improves likelihood and rate of healing in chronic diabetic foot ulcers: a prospective, randomised, multi-centre clinical trial in 80 patients. *Int Wound J*. 2018;15(6):950-957. http://www.ncbi.nlm.nih.gov/pubmed/30019528. Accessed February 25, 2020.
29. DiDomenico LA, Orgill DP, Galiano RD, et al. Aseptically processed placental membrane improves healing of diabetic foot ulcerations: prospective, randomized clinical trial. *Plast Reconstr Surg Glob Open*. 2016;4(10):2-8. https://doi.org/10.1097/GOX.0000000000001095.
30. Lavery LA, Fulmer J, Shebetka KA, et al. The efficacy and safety of Grafix® for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. *Int Wound J*. 2014;11(5):554-560. http://www.ncbi.nlm.nih.gov/pubmed/25048468. Accessed February 25, 2020.
31. Lavery L, Fulmer J, Shebetka KA, et al. Open-label extension phase of a chronic diabetic foot ulcer multicenter, controlled, randomized clinical trial using cryopreserved placental membrane. *Wounds*. 2018;30(9):275-278.
32. Snyder RJ, Shimozaki K, Tallis A, et al. A prospective, randomized, multicenter, controlled evaluation of the use of dehydrated amniotic membrane allograft compared to standard of Care for the Closure of chronic diabetic foot ulcer. *Wounds*. 2016;28(3):70-77.
33. Tettelbach W, Cazzell S, Reyzelman AM, Sigal F, Caporusso JM, Agnew PS. A confirmatory study on the efficacy of dehydrated human amnion/chorion membrane dHACM allograft in the management of diabetic foot ulcers: a prospective, multicentre, randomised, controlled study of 110 patients from 14 wound clinics. *Int Wound J*. 2019;16(1):19-29. http://www.ncbi.nlm.nih.gov/pubmed/30136445. Accessed February 25, 2020.
34. Tettelbach W, Cazzell S, Sigal F, et al. A multicentre prospective randomised controlled comparative parallel study of dehydrated human umbilical cord (EpiCord) allograft for the treatment of diabetic foot ulcers. *Int Wound J*. 2019;16(1):122-130. http://www.ncbi.nlm.nih.gov/pubmed/30246926. Accessed February 25, 2020.
35. Zelen CM, Serena TE, Denoziere G, Fetterolf DE. A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. *Int Wound J*. 2013;10(5):502-507.
36. Steinberg JS, Edmonds M, Hurley DP, King WN. Confirmatory data from EU study supports Apligraf for the treatment of neuropathic diabetic foot ulcers. *J Am Podiatr Med Assoc*. 2010;100(1):73-77. http://www.ncbi.nlm.nih.gov/pubmed/20093548. Accessed February 25, 2020.
37. You HJ, Han SK, Lee JW, Chang H. Treatment of diabetic foot ulcers using cultured allogeneic keratinocytes—a pilot study. *Wound Repair Regen*. 2012;20(4):491-499. http://www.ncbi.nlm.nih.gov/pubmed/22672334. Accessed February 25, 2020.
38. Campitiello F, Mancone M, Della Corte A, Guerniero R, Canonico S. To evaluate the efficacy of an acellular Flowable matrix in comparison with a wet dressing for the treatment of patients with diabetic foot ulcers: a randomized clinical trial. *Updates Surg*. 2017;69(4):523-529. http://www.ncbi.nlm.nih.gov/pubmed/28497218. Accessed February 25, 2020.
39. 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. http://www.ncbi.nlm.nih.gov/pubmed/26297933. Accessed February 25, 2020.


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