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Placental Membrane Provides Improved Healing Efficacy and Lower Cost Versus a Tissue-Engineered Human Skin in the Treatment of Diabetic Foot Ulcerations

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Background: Aseptically processed dehydrated human amnion and chorion allograft (dHACA) (AmnioBand) has shown great promise in the treatment of recalcitrant diabetic foot ulcers (DFUs) when compared with standard wound care but has not yet been compared to any other tissue forms used in treating DFUs. The hypothesis was to conduct a randomized controlled trial in which dHACA was compared to one of the earliest and most commonly accepted tissue-engineered skin substitutes (TESS) (Apligraf) in the treatment of nonhealing DFUs over a period of 12 weeks to assess the superiority of healing.

Methods: Following a 2-week screening period during which subjects with DFUs were treated with collagen alginate dressing, 60 subjects were randomized at 5 sites to receive either dHACA or TESS applied weekly, with weekly follow-up for up to 12 weeks.

Results: The mean time to heal within 6-week time period for the dHACA group was 24 days (95% CI, 18.9–29.2) versus 39 days (95% CI, 36.4–41.9) for the TESS group; the mean time to heal at 12 weeks was 32 days (95% CI, 22.3–41.0) for dHACA-treated wounds versus 63 days (95% CI, 54.1–72.6) for TESS-treated wounds. The proportion of wounds healed at study completion (12 weeks) was 90% (27/30) for the dHACA group versus 40% (12/30) for the TESS group. The mean product cost for the dHACA group was significantly lower than that for the TESS group [dHACA: $2,200 (median: $1,300); TESS: $7,900 (median: $6,500)]. The mean wastage (%) at 12 weeks was also significantly lower for the dHACA group than that for the TESS group (36% vs 95%).

Conclusions: It was concluded that aseptically processed dHACA heals diabetic foot wounds more reliably, statistically significantly faster than and at significantly lower cost than TESS. *(Plast Reconstr Surg Glob Open 2019;7:e2371; doi: 10.1097/GOX.0000000000002371; Published online 30 August 2019.)*

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Dehydrated human amnion and chorion allograft (AmnioBand; MTF Biologics, Edison, NJ) is aseptically processed amnion and chorion that is approved for use under the FDA HCT/P, 21 CFR 1271 regulations on homologous use of human tissue. Tissue-engineered skin substitute (Apligraf; Organogenesis, Canton, MA) is an FDA-approved engineered tissue skin substitute approved with PMA Number P950032 05/22/98 for use with standard diabetic foot ulcer care for the treatment of full-thickness neuropathic diabetic foot ulcer of greater than 3 weeks in duration, which have not adequately responded to conventional ulcer therapy.

This trial was registered on Clinical Trials.Gov (ClinicalTrials.gov Identifier: NCT02870816). This trial was approved by the Western Institutional Review Board, Pullup, WA (WIRB Protocol Number: 20161439-MTF-DFU-ABAG-01).

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INTRODUCTION

Diabetic foot ulcers (DFUs) are a serious complication of long-standing diabetes with a cost to the Medicare program in the United States of up to 18.7 billion dollars in healthcare-related treatments.[1] The cost to the patient clinically is also significant with each incident, leading to an overall lower quality of life.[2] Most importantly, the appearance of the first DFU substantially increases the risk of further ulcerations, lower extremity amputation, and mortality.[3–6] Although good basic wound care (debridement, infection management, offloading, proper dressing, and lower extremity revascularization when appropriate)[7–10] will heal many chronic DFUs, a high proportion become intractable, requiring additional advanced therapeutics to progress the wound out of the chronic inflammatory phase of healing and into a normal cascade of wound repair with epithelialization.

The transition from the inflammatory to proliferative phase of healing requires order and balance in terms of the dozens of cellular cytokines and growth factors that stimulate angiogenesis and generate an extracellular matrix, which serves as the framework for granulation and epithelialization.[11] To encourage this process, tissue-cultured grafts, xenografts, and allografts are often used to supply the missing biochemical moieties and cellular architecture. One of the earliest examples is Apligraf (Organogenesis, Canton, MA), a tissue culture-derived human skin equivalent, hereon referred to as tissue-engineered skin substitute (TESS) that has been used for nearly 20 years and is one of the most commonly accepted tissues for the treatment of DFUs.[12] Another group of products was developed from human amniotic tissue, including dehydrated human amnion and chorion allograft (dHACA; AmnioBand; MTF Biologics, Edison, NJ) (**see Supplemental Digital Content, http://links.lww.com/PRSGO/B229**), which is an aseptically processed amnion and chorion that provides an extracellular matrix abundant in growth factors and cytokines, and is approved for use under section 361 of the Public Health and Safety Act and Title 21 of the Code of Federal Regulations, Part 1271 (21 CFR 1271) regulations on homologous use of human tissue.[13]

The primary objective of this study, as well as experimental hypothesis, was to compare time to heal in patients with nonhealing DFUs after 6 weeks of weekly application of dHACA or TESS as an adjunct therapy to standard of care (SOC). Additional secondary objectives included comparison of the 2 groups in regard proportion of wounds healed within 12 weeks, time to healing over 12 weeks, and percentage area reduction (PAR) over 12 weeks and comparison of cost to closure and percentage wastage of the grafts.

Disclosure: *Site investigators and the principal investigator were financially compensated for their time involved in conducting this clinical trial using research funds. Each investigator filled out a conflict of interest form with the IRB. Although Western IRB does not consider receiving research funds to conduct a clinical trial as a conflict of interest, no individual with an actual conflict as defined by the Western IRB was permitted to consent or participate in the management of any patient in this trial. Dr. Glat is the medical director and owner of Dr. Glat PC and receives research funds from MTF to conduct this clinical trial. Dr. Orgill is a consultant for MTF and receives research funding through grants to Brigham and Women's Hospital. Dr. Galiano is a consultant for MTF and receives research funding through grants to Northwestern University School of Medicine. Dr. Serena is the CEO and medical director of Serena Group and receives research funds for clinical trial from MTF. L.A. DiDomenico is the medical director of LEIRT and receives research funds from MTF to conduct this clinical trial. Dr. Kaufman is a consultant for MTF and receives funds for speaking engagements. Dr. Carter receives funds as a consultant from MTF. A.M. Jacobs is a Medical Director and owner of Alan M Jacobs and Associates, PLC, and receives research funds from MTF to conduct this clinical trial. C.M. Zelen is the medical director and CEO of the Professional Education and Research Institute and receives funds from MTF to conduct this clinical trial. Dr. Armstrong has no financial interest to declare in relation to the content of this article.*

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METHODS

Patients with at least 1 chronic Wagner grade 1 DFU, which had not responded to SOC for at least 4 weeks and could not be present for over 52 weeks in the same location, were randomized 1:1 to either dHACA + SOC or TESS + SOC. The study was conducted at 5 outpatient wound care centers in the United States. The study protocol and patient consent form were reviewed and approved by the Western Institutional Review Board protocol number 20161439 on June 30, 2016. Written consent was obtained from all participants before any study-related procedure.

The study was preregistered at ClinicalTrials.gov NCT02870816, and confidentiality was maintained with all patient records in accordance with HIPAA requirements. The trial was conducted between August 31, 2016, and June 14, 2018.

Patient Screening, Eligibility, and Randomization

After signing consent forms, patients were screened in regard to the inclusion and exclusion criteria (Table 1), receiving a physical examination with medical history documentation if these were met. Blood was drawn for serum creatinine and glycosylated hemoglobin analysis. After index wound selection (the largest wound when multiple DFUs were present in a single eligible patient), assessment of infection was conducted according to guidelines[14] followed by cleansing and debridement. Wound surface area was calculated by acetate tracing, and digital photography was conducted at a distance of 30 cm with a graded centimeter ruler present and a legible label directly adjacent to the ulcer.

The 2-week screening period between the first screening visit and randomization visit used SOC to treat the index ulcer, defined as debridement carried out with a 15 blade

or curette as needed, offloading with a removable diabetic CAM walker (DARCO International, Huntington, WV) or an instant total contact cast only in the instance that the patient could not be fitted with a standard offloading boot. A collagen alginate, Fibracol (Acelity, San Antonio, TX), and a 3-layer dressing were applied daily. As long as the percent area reduction of the index ulcer was less than or equal to 20% improved during screening and all other inclusion and exclusion criteria were met, the patient was randomized.

Randomization was based on a block size of 10 constructed with 5 sheets of paper having TESS assignment and 5 sheets of paper having dHACA assignment, placing each sheet of paper in an envelope and sealing it (thus satisfying allocation concealment), shuffling the envelopes, and labeling them 1–10. This was carried out by the study coordinator and observed by the principal investigator and study staff. The process was repeated 5 times, and the envelopes distributed to the individual sites.

TESS

Sheets of TESS (Apligraf), 44 cm^2 in area with only one size available per patient application, were utilized. An outline of the wound was drawn onto the graft employing the acetate drawing used to measure wound area. The sheet was trimmed with a 15-blade scalpel and fenestrated and placed over the wound site, dermis side down, taking care to ensure that the graft was consistently covering and adhering to the entire wound surface making sure to place the graft following the manufacturer's recommended application procedure. After photographing the graft to document size and portion not used and discarded (wastage), it was covered with a nonadherent dressing (Adaptic Touch; Acelity), followed by steri-strips to anchor the graft in place, and topped with a moisture-retentive dressing (hydrogel bolster) and a padded 3-layer dressing Dynaflex (Acelity) or equivalent.

dHACA

dHACA (AmnioBand) was utilized by investigators in a variety of size-specific grafts, from 1.0-cm diameter disks to 4×6 cm^2 sizes to minimize wastage. The application process for the graft was similar to that for TESS except that size appropriate grafts were available for dHACA and therefore the smallest size that would fit the wound was used when the amnion-chorion graft was applied.

Treatments

Postrandomization, patients were seen weekly until the index wound closed or for 12 weeks. At each visit, blood glucose levels were measured using an Accu-Chek test; patients with poor metabolic control were referred to their primary care physician or endocrinologist to ensure good diabetes management. Index wounds were cleansed with sterile normal saline solution and debrided if required, and wound area was measured before wound photography. If guidelines suggested that infection was present, anaerobic and aerobic cultures were obtained from wound swabs and appropriate systemic antibiotic treatment instituted and maintained until the infection was clinically resolved. If the infection precluded graft application or caused problems with scheduled visits due to unresponsiveness to antibiotics over a period of 2 weeks, the patient was withdrawn from the trial and considered a treatment failure. The schedule for all graft applications was weekly during the study period until complete epithelialization occurred, the patient was withdrawn, or the study was completed.

Six weeks after randomization, PAR was calculated for the index wound. If the DFU failed to reduce in area by

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Male or female age 18 y or older • Type 1 or type 2 diabetes mellitus (ADA diagnostic criteria) • Index wound diabetic in origin and present anatomically on the foot as defined by beginning below the malleoli of the ankle • Index wound is ≥1 and <25 cm^2 • Index wound present for a minimum of 4 wk duration and a maximum of 1 y • Serum creatinine <3.0 mg/dL • HbA1c <12% within past 90 d unless under the care of a diabetologist • Adequate circulation to the affected extremity, as evidenced by one of the following within the past 90 d: dorsum TCOM or SPP ≥30 mm Hg; or ABI with results of ≥0.7 and ≤1.2 in conjunction with Doppler arterial waveforms, which are triphasic or biphasic at the ankle of affected leg • Patient is willing to provide informed consent and is willing to participate in all procedures and follow-up evaluations necessary to complete the study	•Wounds of greater severity than Wagner I •Other wounds within 2 cm of the index wound •Patients participating in another clinical trial • Patients with a history of radiation therapy at the index wound site • Patients with known or suspected local skin malignancy to the index wound • Active infection at index wound site (at randomization) • Patients who have received investigational drug(s), therapeutic device(s), or any kind of tissue-engineered product within the previous 30 d • Patients likely to receive negative pressure wound therapy or hyperbaric oxygen therapy • Patients taking immunosuppressants in the past 2 wk or likely to take such medications • Patients who have had cytotoxic therapy within 14 d or are likely to have such treatment • Osteomyelitis or bone infection of the affected foot as assessed by x-ray • Subjects with a known history of poor adherence to medical treatment • Patients who are pregnant or breast feeding • Patients with wounds healing greater than 20% during the screening period • Inadequate offloading during screening period

HbA1c, glycosylated hemoglobin; SPP, skin perfusion pressure; TCOM, transcutaneous oxygen measurement; ADA, American Diabetes Association; ABI, Ankle Brachial Index.

50% or more,[15] the patient was withdrawn from the study and considered a failure of treatment and allowed to seek other wound care modalities.

Healing Validation

Healed wounds were defined as complete (100%) epithelialization without drainage and need for dressing, as determined by the site investigator. Any wound that healed was subject to confirmation of wound closure 2 weeks later after initial wound closure (healing validation). Decisions involving wound closure and whether the patient exited the trial or continued in the study were approved by the study principal investigator and were based on photographic review and protocol rules. Healing validation was conducted by an independent body of reviewers. This adjudication panel blinded to patient study group assignments also reviewed decisions made by site investigators regarding patient enrollment, healing, and study continuation. The adjudication team included plastics surgeons, a vascular surgeon, a general surgeon, and a podiatrist.

Study Outcomes

The primary endpoint of the study compared time to heal at 6 weeks between the 2 treatment groups. Secondary endpoints subject to formal statistical testing included proportion of wounds healed at 6 and 12 weeks, time to heal within 12 weeks, graft cost, graft wastage, and safety analysis.

Sample Size Calculations and Statistical Analysis

Sample sizes of 30 in each group were calculated to achieve at least 80% of power (83% actual) to detect a hazard ratio of 2.0 when the proportion of unhealed wounds in the TESS group was 0.5. Dropout rates of 12% for each group were assumed over 12 weeks. The test statistics used was the logrank test. The significance level achieved by this design was 0.05.

Intent-to-treat (ITT) and safety populations consisted of randomized patients who received at least 1 treatment. All analysis used the ITT population. Right-censored variable data were imputed with the last observed value through 12 weeks based on the last observation carried forward principle. Study variables were summarized as mean and SD for continuous variables and additionally medians when data were non-normal. Categorical variables were presented as counts and proportions or percentages. Although CONSORT guidelines[16] do not recommend statistical testing between treatment groups at baseline, this was carried out to examine randomization success.

A χ^2 test was performed to test statistical differences between groups regarding proportion of wounds healed at 12 weeks. Kaplan–Meier analysis was carried out to determine time to heal within 6 or 12 weeks between the treatment groups. A Cox regression (time to heal within 6 weeks) was also conducted to adjust for available covariates that might have affected wound healing. Covariates were entered into 1 block with stepwise elimination of nonsignificant covariates; model fit was assessed using –2log likelihood and by checking that stepwise addition of covariates produced the same result. The proportional hazards assumption was tested by adding covariate–time interactions in the refined model to assess if these were statistically significant. Log linearity of covariates was examined by omitting 1 covariate, computing the Martingale residuals, and plotting them against the omitted covariate. Mean graft costs were calculated for every wound based on the smallest graft that would fit the wound site. When discs of dHACA were used, the calculation assumed a circular graft was applied. Graft costs for each wound were then calculated by summing the costs of the dHACA and TESS applications from all visits using the current published fee schedule for each graft and rounding mean figures to the nearest $100. Percentage graft wastage (percentage of the graft area that was discarded) was calculated by determining the difference between the graft and wound area and expressing it as a percentage of the graft area. Comparisons between treated groups used the Kolmogorov–Smirnoff test. PAR for the index wound at 6 weeks was calculated as $[(A_I - A_{XW})/A_I] \times 100$, where A_I is the area of the index wound at randomization and A_{XW} is the area at 6 weeks.

To adjust for the family-wise error rate, *P* values were reported using the Hochberg step-up procedure. Adjusted 2-sided *P* values <0.05 were considered significant. PASW 25 (IBM, Chicago, IL) was used to perform the statistical testing.

RESULTS

Seventy-two subjects were screened, of whom 60 subjects met the eligibility criteria and were randomized to dHACA + SOC (n = 30) or TESS + SOC (n = 30) (Fig. 1). Two subjects treated with TESS exited at weeks 3 and 4 due to serious adverse events (SAEs) (foot infections progressing to osteomyelitis), which by protocol were considered a treatment failure. One subject whose wound was treated with TESS initially healed at week 6 but was observed to be re-opened at week 8 at the wound-healing validation visit; therefore, this subject was exited from the study as a treatment failure per protocol. Ten subjects treated with TESS and 1 subject treated with dHACA were exited from the study at 6 weeks as treatment failures for not meeting the PAR rule. The groups were well matched regarding patient and wound-related parameters without any statistically significant differences (Table 2).

Time to heal (within 6 weeks) for the dHACA group was 24 days (95% CI, 18.9–29.2) compared with 39 days (95% CI, 36.4–41.9) for the TESS group ($P = 8.0 \times 10^{-6}$). Initial area (week 0) was categorized as follows: 1–1.2, 1.2–1.7, 1.71–3.8, and >3.8 cm^2. Only area category and treatment were retained in the Cox regression model. Although the model met the proportional hazards assumption, there was some nonlinearity for both categorical initial area and treatment covariates in relation to log hazard function. The results (Table 3 and Fig. 2) showed that, compared with the TESS-treated reference group, the dHACA-treated group had a hazard ratio of 5.8 ($P = 1.3 \times 10^{-4}$).

The proportion of wounds closed at 6 weeks for the dHACA group was 77% (23/30) compared with 23% for the TESS group (7/30). By 12 weeks, percentages had increased for both treatment groups with 90% (27/30)

of DFUs healed in the dHACA group compared with 40% (12/30) of DFUs healed in the TESS group (Fig. 3; $P = 4.9 \times 10^{-5}$). At 12 weeks, the mean time to heal was 32 days for the dHACA group (95% CI, 22.3–41.0) compared with 63 days for the TESS group (95% CI, 54.1–72.6) ($P = 3.2 \times 10^{-5}$).

At 12 weeks, the mean PAR was 98% for the dHACA group (SD: 10.27; median: 100) compared with 44% for the TESS group (SD: 90.64; median: 91).

At 12 weeks, the mean number of grafts used per wound including all dHACA-treated wounds was 4.4 (SD: 3.71; median: 2.5). However, if we look at healed wounds, the mean number of graft applications for dHACA-treated DFUs wounds was 3.7 (SD: 3.05; median: 2).

Mean number of graft applications for the TESS group at 12 weeks were 7.5 (SD: 3.52; median: 6) for all wounds and for those that healed the mean number of grafts was 6.1 (SD: 2.63; median: 5.5).

Mean product cost for the dHACA group was significantly lower compared with the TESS group for both the total cohort and those wounds that healed. Looking at healed wounds at 12 weeks, the mean cost to closure for dHACA was $2,200 (SD: $2,141.00; median: $1,300 per healed wound), whereas the mean cost for TESS was $7,900 (SD: 3,270.54; median: $6,500 per healed wound).

Examining the entire cohort at 12 weeks, the total cost of treatment per dHACA patient was $2,900 (SD: $2,975.88; median: $1,600), whereas TESS had a much higher mean cost of $9,700 (SD: 4,635; median: $7,800) ($P = 2.1 \times 10^{-6}$).

Mean wastage (%) at 12 weeks was significantly lower for the group treated with dHACA (36%; SD: 15.03; median: 38%) compared with the group treated with TESS (95%; SD: 6.26; median: 98) ($P < 10^{-6}$).

Adverse events (AEs) are common in diabetic foot trial due to the comorbidities seen in these patient populations. Five AEs occurred in the dHACA group, of which 3 were SAEs. The 3 SAEs were severe foot infections and were considered serious due to required hospitalization for each of these patients; the other 2 AEs were a local soft tissue foot infections and a urinary tract infection. In the TESS group, there were 7 AEs, of which 4 were SAEs (also all severe foot infections that required hospitalization); the other AEs comprised a local soft tissue foot infection, a pulmonary infection, and leg cellulitis. On a per patient basis, there were no statistically significant differences between groups ($P = 0.52$). No AEs were found to be graft related.

DISCUSSION

The results of this comparative trial clearly demonstrate that when dHACA is combined with SOC, even after controlling for other important confounding variables, the resultant therapy is statistically superior to that of TESS added to SOC. Moreover, the results have a high degree of certain-

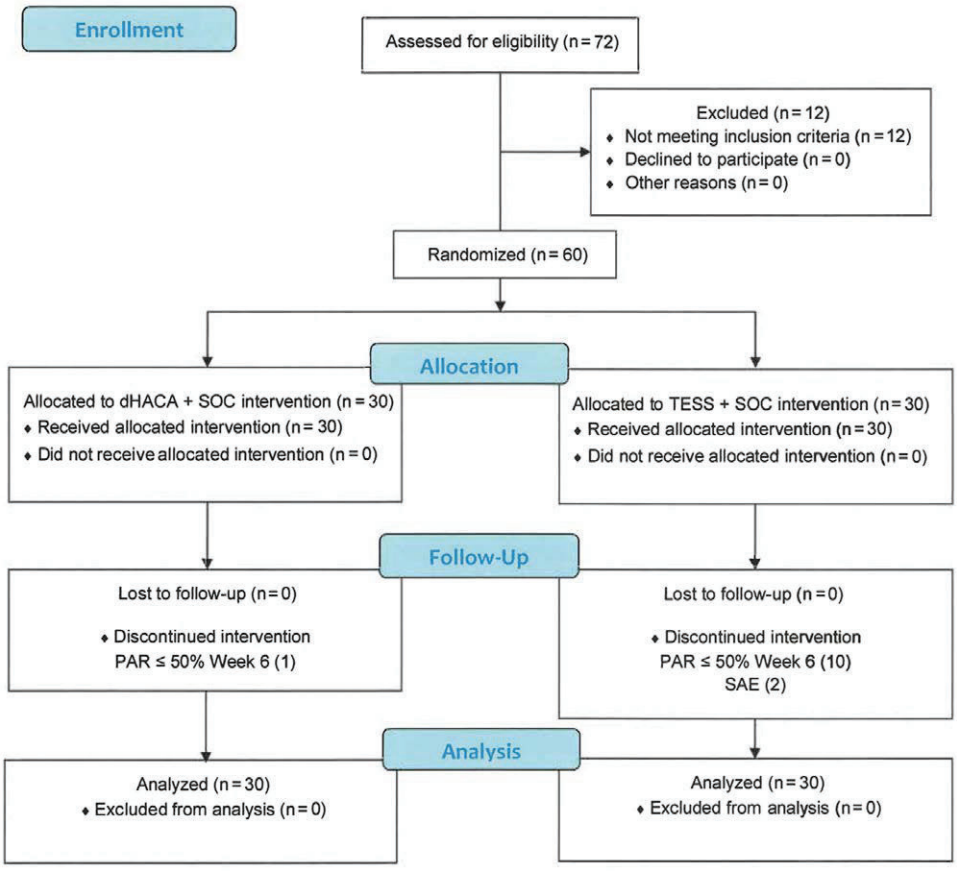

Fig. 1. Flow chart of trial participants.

Table 2. Wound- and Patient-related Variables Between Groups at Randomization Compared to Assess Success of Randomization

Variable	dHACA	TESS	*P*
Age (y)	62 (13.20)	62 (15.28)	0.80
Race			
Caucasian	28 (93)	27 (90)	1.0
African American	2 (7)	3 (10)	
Sex			
Male	16 (53)	23 (77)	0.058
Female	14 (47)	7 (23)	
BMI	32 (5.81)	33 (6.46)	0.49
Smoker	5 (17)	5 (17)	1.0
Multiple wounds	7 (23)	5 (17)	0.52
HbA1c*	7.5 (1.58); median: 7.4	7.9 (2.15); median: 7.2	0.80
Creatinine	1.2 (0.50)	1.0 (0.41)	0.13
Wound area (cm^2)	2.4 (1.88); median: 1.4	3.1 (2.29); median: 2.1	0.13
Wound age (wk)	12.3 (14.25); median: 7.5	14.5 (14.70); median: 8.0	0.95
Wound plantar surface	26 (87)	23 (77)	0.32
Wound location			
Toe	10 (33)	5 (16)	0.41
Forefoot	16 (53)	21 (70)	0.18
Midfoot	1 (3)	2 (7)	
Heel/ankle/hindfoot	3 (11)	2 (7)	

*Average of HbA1c values (beginning and end of study).
HbA1c, glycosylated hemoglobin.
Continuous variables are reported as mean and SD, and categorical variables are reported as number (n) and percentage (%).

ty, meaning that the healed wound percentages would have to change drastically for the *P* value to be nonsignificant, which is highly unlikely as the healing rates for dHACA in this study are comparable to previous RCTs looking at this unique dehydrated amnion and chorion graft.[14,17]

When reviewing the TESS group, although the percentage of healing was slightly lower at 12 weeks than previously reported by Veves et al,[12] the time to heal within 12 weeks was very similar in both studies. In addition, allowing all patients to continue to 12 weeks without excluding those with PAR less than 50% at 6 week would have likely permitted up to 5 more patients to heal in the TESS group making the percentage healed almost identical to prior studies,[12] illustrating that TESS is still a reasonable treatment for DFUs. However, the addition of these patients would unlikely change the statistical significance of this trial.

Furthermore, given our results of the current trial, and the fact that the proportion of wounds healed in a slightly larger RCT involving dHACA (85%)[17] was similar to this

Table 3. Cox Regression Results, Time to Heal Within 6 Weeks

				95% CI	
Variable	*B*	*P*	HR	Lower	Upper
Area (cm^2)*					
1.21–1.7	–0.71	0.099	0.49	0.21	1.14
1.71–3.8	–0.72	0.154	0.49	0.18	1.31
>3.8	–3.29	0.002	0.037	0.005	2.87
Treatment§	1.75	1.3×10^{-4}	5.76	2.35	14.12

*Reference group: 1–1.2 cm^2.
§Reference group: TESS.
HR, hazard ratio.

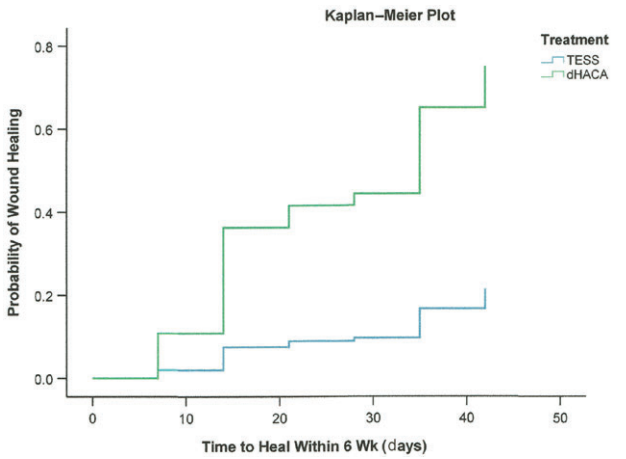

Fig. 2. Adjusted primary endpoint results: time to heal within 6 weeks for dHACA and TESS after controlling for initial wound area (Cox regression).

study (consistency of efficacy), it suggests that dHACA trials might meet the moderate category in terms of quality of evidence using the GRADE system and perhaps even the high category.[18]

When examining the wound-healing trajectories, it was observed that, over the first 2 weeks, 50% of the dHACA-treated wounds healed compared with only 7% of the TESS-treated wounds; after 4 weeks, the wound-healing trajectories were similar (Fig. 4). All of these results suggest that dHACA not only is highly efficacious but also heals diabetic wounds at a very fast pace. We believe that this may be due to the unique properties of this aseptically processed human amnion and chorion allograft. These types of placental grafts are rich in extracellular matrix proteins, growth factors, and cytokines and as such can induce angiogenesis and dermal fibroblast proliferation, which can lead to accelerated healing.[19–22] Additional published literature further illustrates these high healing rates of placental grafts versus other tissue-cultured skin products.[23,24] Furthermore, multiple studies have been performed that examine acellular dermal templates and, in these studies, the healing rates of the dermal matrices, at 70% and 80% healing over 12 weeks, are lower than the healing rates found with dHACA, again illustrating the unique nature, construct, and clinical effectiveness of this specific amnion and chorion graft.[25,26] The following clinical cases will illustrate the comparative healing appreciated in the dHACA cohort versus the TESS group (Fig. 4).

Cost and wastage are also the significant drivers in surgeon selection of their graft for application on a DFU. dHACA has consistently shown to be one of the most cost-effective choices for the wound-healing surgeon. In this trial, when comparing all wounds or simply healed wounds, dHACA was nearly a third of the cost of TESS. Furthermore, when evaluating wastage, little dHACA was wasted (36%) versus TESS, where over 95% was left unutilized. This is an important endpoint that was also evaluated in a previously published trial, which

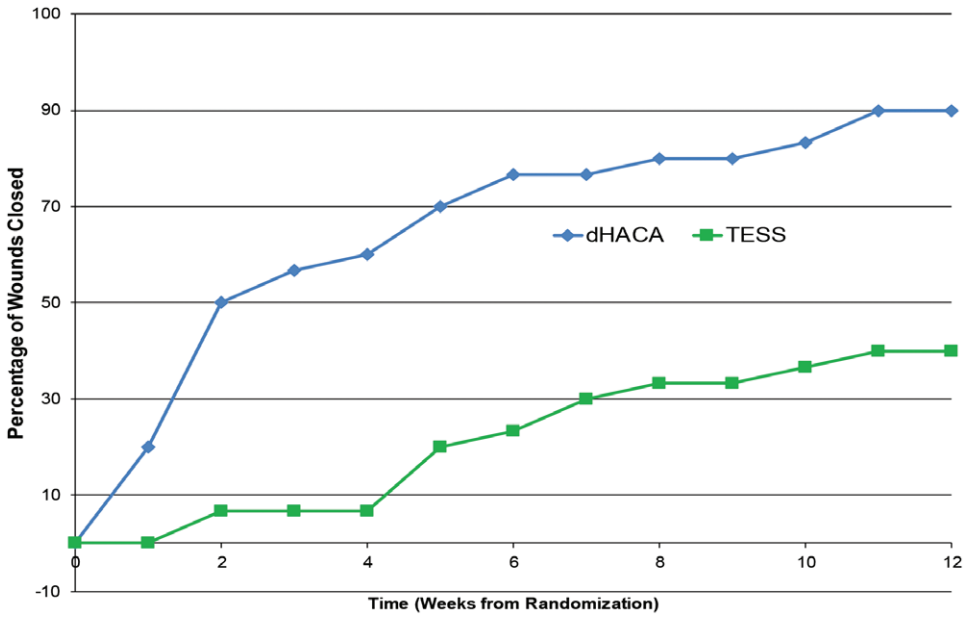

Fig. 3. Percentage of wounds healed weekly up to 12 weeks by treatment group.

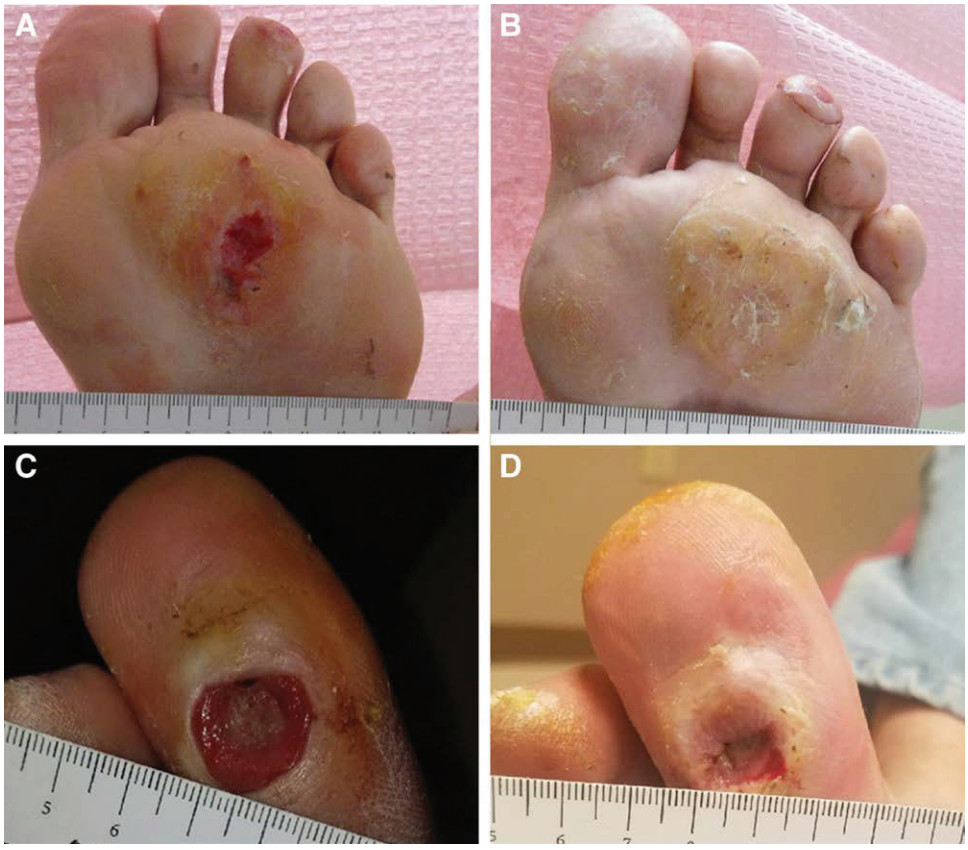

Fig. 4. A and B, A patient's treatment with dHACA. C and D, A patient's treatment with TESS.

also illustrated a significantly high wastage in the TESS group.[24] An important aspect of this wastage in the TESS group is the fact that the graft is only available in one size (44 cm^2), which contributes to the wastage significantly, and the graft can only be used on 1 patient due to sterile precautions and TESS instructions for use. These results are statistically significant as both public and private health insurers (payers) move toward a value-based payment methodology for the delivery of health care in our country.

Strengths of this study included satisfactory allocation concealment, ITT analysis, sufficient statistical power for the primary endpoint, appropriate adjustment for multiple statistical testing, and reporting according to CONSORT guidelines. Study limitations include lack of principal investigator blinding, which is not possible due to visual dissimilarity of the tissues. Also, measuring the time to application was not performed. In addition, the recalcitrant nature of the wound in the location that the graft was applied was not looked at. Finally, withdrawing patients at 6 weeks rather than continuing through 12 weeks of treatment if their wounds were not sufficiently responding to treatment to ensure patient safety and permit other treatment pathways could be considered a limitation as well.[15] Future studies may consider looking at even more treatment algorithms that will further help enhance wound-healing technique in our diabetic patients.

In conclusion, dHACA + SOC treatment was shown to be superior to TESS + SOC in terms of healing efficacy endpoints, graft cost, and graft wastage over a period of 6 and 12 weeks of treatment. Given the fact that TESS is one of the earliest and most commonly accepted engineered skin substitutes, this study demonstrates that dHACA brings even greater value to our patients.

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