

# Human Amniotic Membrane in the Treatment of Non-Healing Diabetic Foot Ulcers: A Prospective Randomized Controlled Trial

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## Abstract

Human amniotic membrane has been used as an allograft to treat cutaneous wounds for over a century, with medical literature including case series and randomized trials dating back as early as 1910.<sup>1-4</sup> Recently, improvements in preparation have led to the development of dehydrated human amniotic/chorionic membrane (dHACM), which is preserved to permit ease of use and storage while maintaining biological effectiveness. A central IRB approved prospective randomized controlled trial was conducted to compare efficacy of dHACM in the treatment of diabetic lower extremity ulcers versus standard of care (SOC) treatment. Twenty-five consecutive patients were enrolled from one site. Two outside wound care physicians reviewed and validated the clinical photos and date. All ulcers failed at least one month of conservative care prior to randomization. At 6 weeks 92% (12/13) of patients treated with dHACM were healed versus 8% (1/12) with SOC ( $p < 0.001$ ). At week 12 only one patient from the dHACM cohort had failed to heal and all remaining SOC patient's wounds remained open. Upon conclusion of the prospective trial, the SOC group of 11 patients failing to heal were offered bi-weekly treatment with dHACM. At that time their wounds had been present for a mean of 21 weeks and a wound size of 4.7cm<sup>2</sup>. A central IRB approved retrospective analysis of this group was performed and complete healing was achieved in 91% (10/11) by 12 weeks. These prospective and wrap around retrospective results are compelling and show that treating diabetic foot ulcers with serial debridement followed by application of dHACM is more effective than SOC and suggests that early effective treatment may decrease clinical operational costs and may prevent longer term medical complications.

## Introduction

Diabetes affects at least 6% of the population, or approximately 16 million people in the United States. Lower extremity ulcers are a serious complication for people with diabetes, developing in some 25% of individuals with the disease.<sup>5</sup> These ulcers are often difficult and expensive to treat, and lead to severe morbidities. Conservative treatments are based on clinical evaluation and judgment and may include sharp debridement, wet-to-moist dressings, application of enzymatic agent, and the application of standard dressings. Advanced therapies and biologic dressings are often initiated after conservative treatments have failed.

### Amniotic Membrane<sup>6</sup>

- Encapsulates the fetal compartments: composed of amnion and chorion layers
- Non-vascular tissue consisting of epithelium cells, basement membrane, a thick compact layer and fibroblast layer
- Fibrous layer contains cell anchoring collagen types: IV, V, and VII
- Biochemical properties help to reduce inflammation and enhance soft tissue healing
- Has antibacterial and pain reduction properties, are self-signaling and mediate tissue repair via the contained growth factors\*

### EpiFix<sup>®</sup> - A Dehydrated Human Amniotic /Chorionic Membrane Allograft

- A biologically active implant or graft for tissue regeneration application
- Amniotic membrane obtained from screened and tested donors to ensure safety
- Cleaned, dehydrated, and sterilized by the proprietary PURION<sup>®</sup> process which produces a safe tissue with a 5 year, room temperature, shelf life

## Study Design and Purpose

A retrospective crossover study of patients with Type 1 or Type 2 diabetes, having a diabetic foot ulcer (DFU) of at least 6 weeks duration that failed to heal with standard of care (SOC) was conducted. All patients had previously been enrolled in a prospective randomized trial comparing healing characteristics with SOC treatment alone vs. SOC with the addition of dHACM (EpiFix<sup>®</sup>, MiMedx, Kennesaw, GA) and had completed that study without healing of their DFU.

\* These properties are present in native amniotic membrane and may not reflect the properties of processed amniotic allografts.

## Methods

This retrospective study was conducted under an IRB approved protocol in Southwest Virginia. Patients read and signed an approved informed consent prior to any study involvement.

### Included

Patients with DFU previously randomized to SOC (n=11) who failed to heal upon completion of the clinical trial (dHACM vs. SOC).

### Study Outcomes

- Ulcer size reduction at 4 and 6 weeks
- Proportion of ulcers healed during the study period
- Mean time to healing

### Treatment

- Following surgical debridement of all necrotic tissue dHACM was applied to the wound.
- A non-adherent dressing was used to cover the dHACM, followed by a moisture-retentive dressing (hydrogel) and a compression dressing.
- All wounds were offloaded using a removable cast walker
- Dressing changes took place weekly during the office visit.
- If the ulcer had not completely epithelialized, an additional piece of dHACM was applied at week 2, week 4, week 6, week 8, and week 10.

### Data Analysis

- Each patient was used as their own control to compare wound size reduction between treatment periods (SOC only vs. SOC with dHACM).
- Paired t-test or Mann Whitney rank sum test were used to compare continuous variables between study intervals.
- The level of statistical significance was set at  $p < 0.05$ .

## Results

Table 1. Patient characteristics.

Variable	N=11
Male Gender	7 (63.6%)
Age (yr)	61.5 ± 10.5
BMI (kg/m <sup>2</sup> )	35.6 ± 6.9
Obese (>29.9 kg/m <sup>2</sup> )	8 (72.7%)
Smoker	2 (18.2%)
Caucasian race	10 (90.9%)
Wound size (cm <sup>2</sup> )	4.7 ± 5.0
Wound duration (weeks)	21.1 ± 12.4

Data presented as mean ± SD or percent as indicated. BMI = body mass index.

### References

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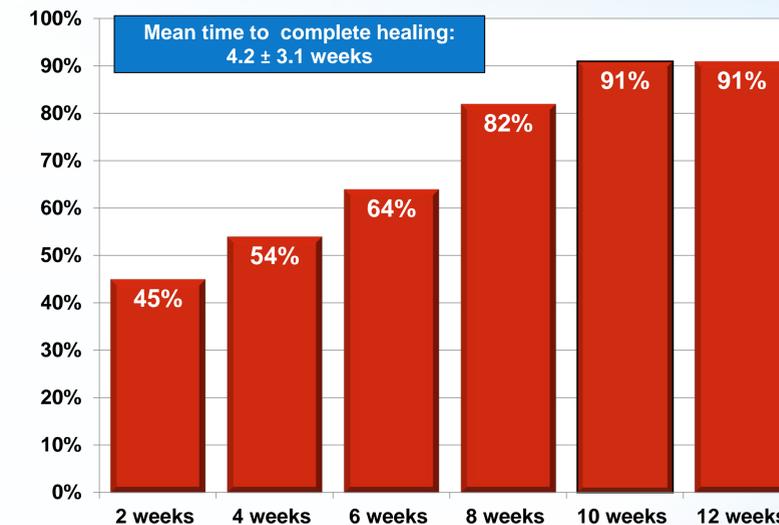
Table 2. Mean percent reduction in wound size vs. baseline during each treatment period.

Treatment week	SOC Period (RCT) (n=11)	After dHACM (n=11)	p-value
Week 1 (%)	21.4 ± 36.8	62.5 ± 29.9	0.013
Week 2 (%)	15.5 ± 52.3	76.2 ± 25.3	0.003
Week 3 (%)	13.3 ± 45.3	87.0 ± 15.9	<0.001
Week 4 (%)	26.8 ± 45.3	87.6 ± 16.0	<0.001
Week 5 (%)	6.7 ± 63.8	92.6 ± 12.6	<0.001
Week 6 (%)	-10.6 ± 65.8	93.9 ± 11.1	<0.001

Data presented as mean ± SD.

- In the initial study period while receiving SOC only, measurements of wound size were inconsistent week to week and by week 6 the overall mean wound size had increased over baseline. During the dHACM treatment period consistent reduction in wound size was noted week to week. (Figure 1)
- Wounds were reduced by > 50% in 81.8% patients (9/11) by week 2 (1 dHACM application).
- By week 4 (2 dHACM applications) all patients had achieved >50% reduction in wound size.
- Complete healing was achieved by 10/11 (91%) of patients once they received dHACM. (Figure 2)

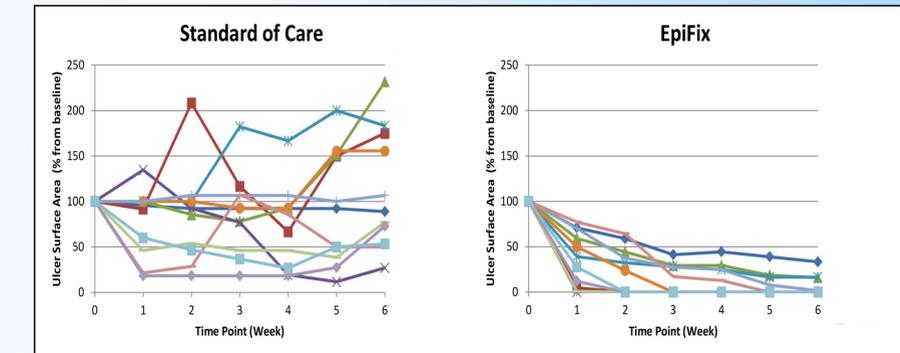
Figure 2. Percent of patients completely healed with dHACM after failing SOC.



Study sponsored by: MiMedx<sup>®</sup>, Kennesaw, GA  
EpiFix<sup>®</sup>, PURION<sup>®</sup> and MiMedx<sup>®</sup> are registered trademarks of MiMedx Group, Inc.

## Results

Figure 1. Rates of wound healing with SOC vs. dHACM (EpiFix<sup>®</sup>).



## Examples of Subjects Healed with dHACM

Case 1. Patient healed in 2 weeks (1 EpiFix<sup>®</sup> application)



Case 2. Healed in 9 weeks (5 EpiFix<sup>®</sup> applications)



## Conclusion

- In the present study of 11 patients with chronic diabetic foot ulcers that failed to heal with SOC, 11 (100%) showed >50% reduction in wound size within 4 weeks of starting treatment with dHACM and 10 (91%) had complete healing of their wound within 9 weeks of dHACM initiation.
- From the original 25 patients enrolled in the randomized trial, 23 (92%) were ultimately healed with dHACM.
- These results illustrate that the addition of dHACM to routine wound management can enhance wound healing in patients with diabetic foot ulcers.
- These findings should be confirmed and expanded with subsequent clinical trials.