Use of AlloPatch® Pliable, a Human Acellular Dermal Matrix, as an Adjunctive Therapy for Chronic Non-Healing Diabetic Foot Ulcers

Case Studies and Clinical Review

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INTRODUCTION

Diabetes Mellitus continues to be a burden to many people in the United States and throughout the world. Nearly 285 million people internationally or close to 6.4% of the world's population is known to have diabetes, and it has been estimated that by the year 2030 this group will grow to 7.7% or 439 million people.[1,2] There are around 26 million individuals or roughly 8.3% of the population in the United States, who currently have diabetes mellitus.[3,4]

Peripheral neuropathy is one of the most debilitating lower extremity complications of diabetes and contributes to loss of pedal sensation, microvascular dysfunction, as well as increased risk of trauma to the soft tissue and bone leading to eventual plantar foot ulceration. Approximately 25% of diabetics will develop an ulcer. Studies show that these ulcerations precede 85% of all lower extremity amputations. With proper ulcer care, many of these amputations may be preventable.[2,5]

It is well known that wound healing involves three phases: inflammation, proliferation, and remodeling. Diabetic wounds tend to become stagnant in the first two phases due to failing fibroblast function, inflammation and bioburden.[6] The goal for wound healing should be to transform a chronic wound to an acute wound by creating an equilibrium between cell degradation and synthesis, eradication of fibrosis, and creation of new granulation with complete epithelialization. This is ultimately accomplished by recruiting growth factors and angiogenesis. [6-8] The final result is to accelerate the healing process in order to prevent terrible complications of life and limb threatening infections and amputations.[9]

The current guidelines published by The Wound Healing Society strongly recommend using advanced wound therapies when a diabetic ulceration does not decrease its dimensions by 40% or more after four weeks of standard of care dressings and local wound care.[10] The landmark study from Sheehan et al. has revealed that when a wound does not heal by 50% in four weeks, it has a less than 10% chance of healing by 12 weeks.[11]

Bioengineered Skin Substitutes (BSS) or Cellular and Tissue Based Products (CTPs) have been developed to expedite the wound healing process and transform long standing wounds into defined closure.[7] Also referred to as Bioengineered Alternative Tissue products (BATs), BSS and CTPs come in the form of allografts, autografts, and xenografts; are single layer dermal or epidermal; or bilayer with both epidermal and dermal composition.[7] These bioengineered tissues are classified into two different types, the first of which contains living cells such as fibroblasts and keratinocytes, as well as having matrix proteins,

and growth factors present (referred to in literature as "dermoinductive"). Examples of these include: Apligraf® and Dermagraft®. The second type of CTPs are tissues that serve as scaffolds that contain growth factors and cytokines; allow for vascular in-growth; and can stage the process of wound healing (referred to in literature as "dermoconductive"). Examples include: AlloPatch® Pliable, GraftJacket® RTM, and Oasis® Wound Matrix.[12]

A substantial body of knowledge has accumulated on human dermal matrices for wound healing. As early as the 1990's, human dermal matrices were illustrated as a viable option to accelerate the wound healing process.[13] Current literature on the efficacy of human dermal matrices are described in: plastic surgery[14-17], neurosurgery[18, 19], ophthalmology[20, 21], abdominal and hernia repair[22-24], and burn treatments[25-27]. These reports have led us to the current research interests in the difficult to heal chronic diabetic foot ulcers.

Human dermal matrices are well known to advance wound healing with their ability to minimize inflammation and scarring and achieve wound closure in short order. Winters et al. published a multi-center study of 100 patients using a human dermal matrix. Matrix development occurred in a mean of 1.5 weeks with an average of 5.1 weeks for 100% granulation tissue, and a significant 91% complete healing rate in 13.8 weeks.[28]

In another study, human dermis was also compared to sharp debridement alone over a 16 week period by Brigido and colleagues. Complete healing was noted in 12 of 14 patients for the human allograft dermal group vs. only 4 of 14 in the sharp debridement group advocating that human dermis fast tracks the wound healing process compared with standard care.[29]

Reyzelman et al performed a randomized controlled prospective multi-center trial that examined 47 patients who received Graftjacket® RTM versus 39 patients who received moist wound therapy with alginates, foams, hydrogels. The Graftjacket® RTM group had complete healing in 69.6% of patients over an average time of 5-7 weeks, vs. only 46.2% healing over 6-8 weeks in the control group.[30]

AlloPatch Pliable developed by the Musculoskeletal Transplant Foundation (MTF) is an acellular human dermal matrix that is aseptically processed and packaged for immediate use by the wound healing clinician. This unique matrix requires no rehydration or refrigeration, can be stored at ambient temperature, and is processed in multiple sizes needing only to be trimmed to fit the wound with a lavage with saline prior to application. In addition, the matrix is specially derived from a deep cut of the dermal tissue that may allow for better cellular integration in the wound.[31]

THE SCIENCE BEHIND THE MATRIX[32]

Histological analysis and scanning electron microscopy (SEM) of AlloPatch Pliable verify the uniformly open structure of the collagenous matrix throughout the graft, a feature that allows for better cell attachment and proliferation that may translate into better integration by the patient and faster healing.

Immunohistochemical (IHC) staining revealed the presence of various matrix proteins such as collagen I, III, IV, VI. Trace levels of elastin, fibronectin and laminin were detected ***(Figure 1)***. *In vitro* studies with natural human dermal fibroblasts (NHDFs) seeded on both sides of the scaffold demonstrate enhanced early attachment compared to tissues from more superficial dermal layers ***(Figure 2)*** and good proliferation over the first two weeks ***(Figure 3)*** that would lead to granulation and closing of a wound. SEM showcased cell attachment and infiltration within the open matrix structure and by day seven, a plethora of matrix covering the once open dermal structure can be visualized ***(Figure 4)***. Histology verified cell attachment and infiltration along with matrix deposition via collagen IV production over time ***(Figure 5)***.

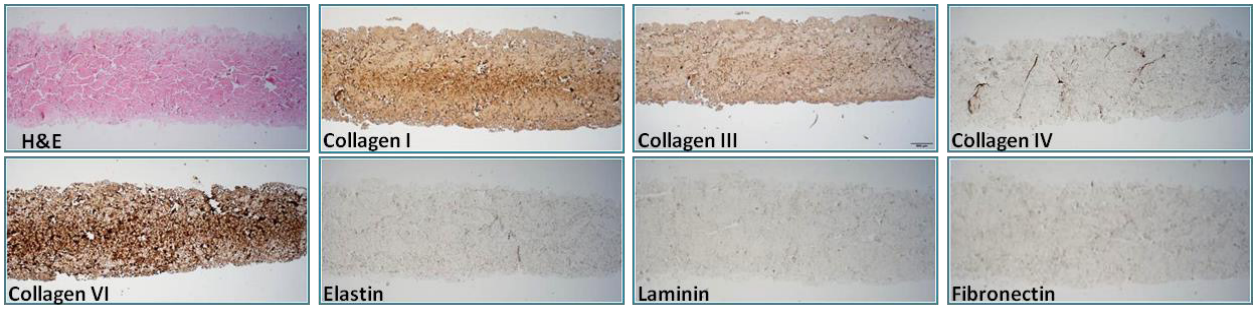

Figure 1: *Immunohistochemical staining of pre-hydrated human acellular dermis for matrix proteins revealed preservation of collagens I, III, IV, VI, with trace levels of elastin, laminin & fibronectin.*

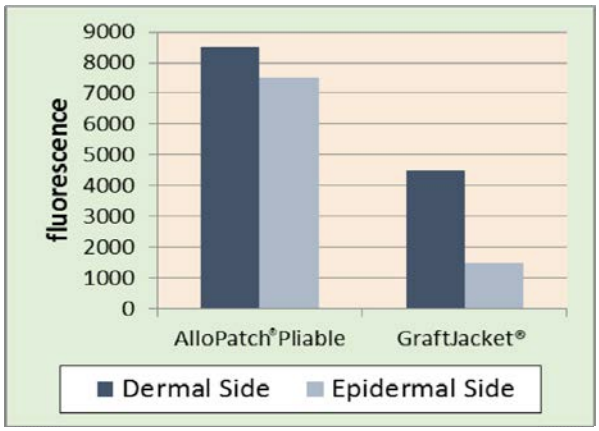

Figure 2: *AlloPatch Pliable promotes enhanced fibroblast attachment on both the epidermal-facing (5x) and the dermal-facing (2x) side compared to a more superficial layer of dermis.*

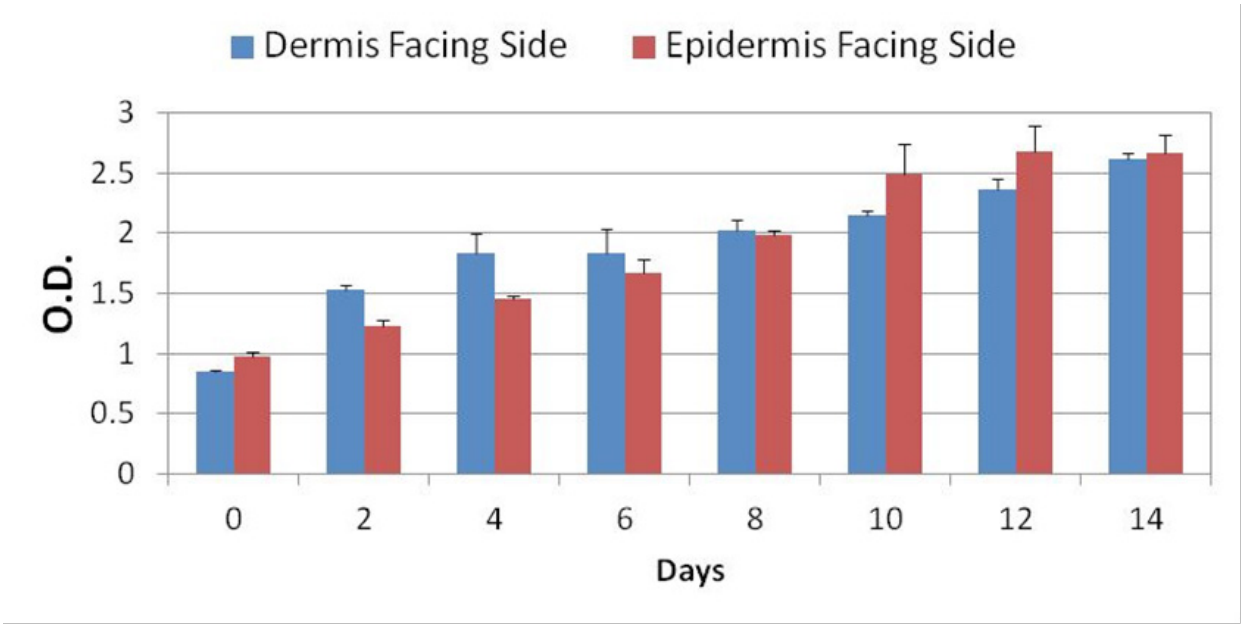

Figure 3: *NHDFs adhered and proliferated on the pre-hydrated human acellular dermis readily. Cell proliferation plateaued around 12-14 days and were similar on both sides of acellular dermis tissue.*

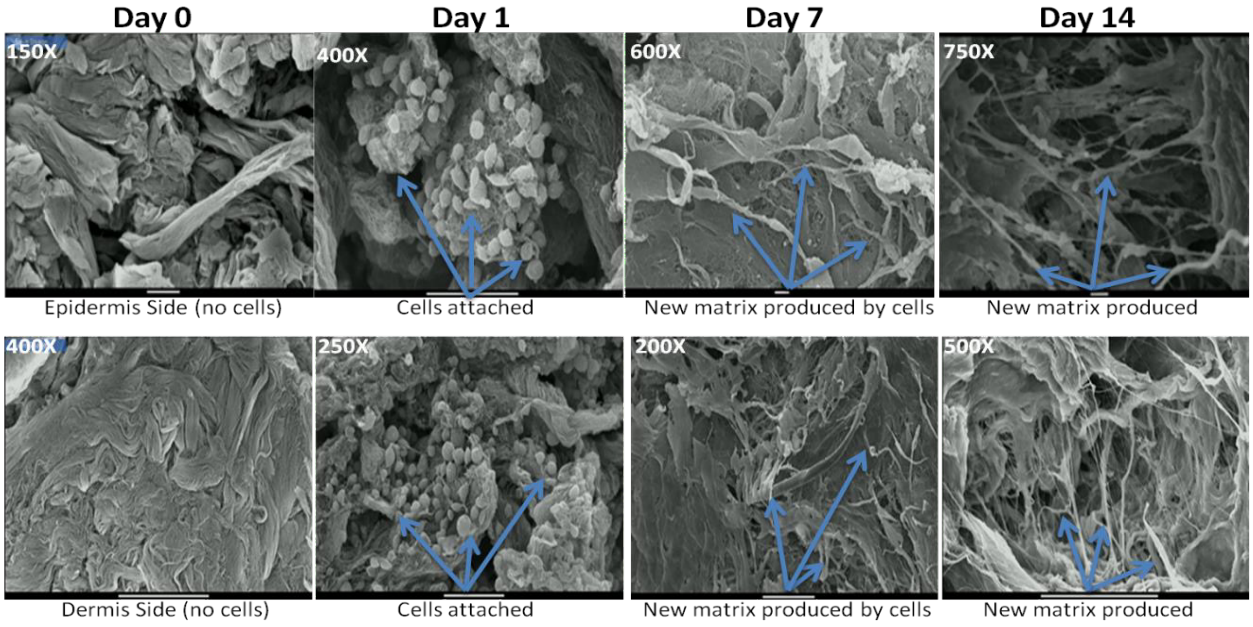

Figure 4: *SEM imaging demonstrates acellular dermal tissue readily supported cell attachment and proliferation. Extensive newly formed matrix can be seen by day 7 covering the porous structure of the scaffold.*

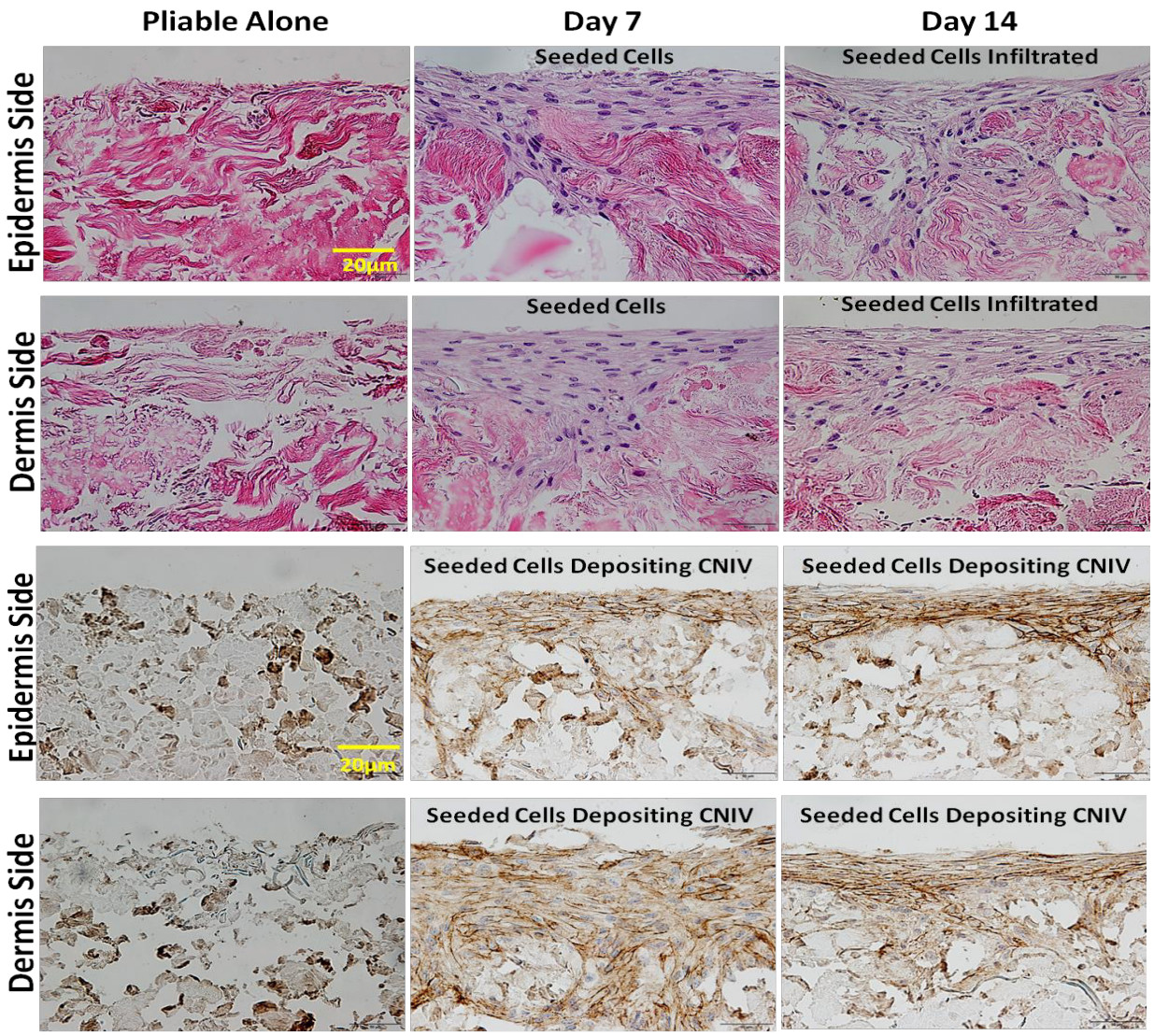

Figure 5: *Histology analysis of NHDFs cultured on human acellular dermis highlights cell attachment, proliferation and infiltration along with collagen IV matrix deposition (magnification 40X).*

CASE STUDIES

The following case studies highlight the healing properties of AlloPatch Pliable.

Case 1

A 44 year-old male with a past medical history of Type two diabetes mellitus with peripheral neuropathy, presented with a non-healing right foot ulceration that had been treated at a local hospital wound healing center without success for over a month. The patient has a history of recurring forefoot ulcers. He had been using gauze and antibiotic cream daily with an offloading shoe.

Past Medical History: Type two Diabetes Mellitus with Peripheral Neuropathy, Hypertension, Asthma, Hyperlipidemia, Herniated Discs, and Morbid Obesity.

A standard diabetic foot exam was performed, revealing Semmes Weinstein monofilament wire testing, 0/10 points confirming peripheral neuropathy. Pedal pulses were 2/4 and an arterial doppler exam was completed, which showed biphasic waveforms for both the dorsalis pedis and posterior tibial arteries. An initial HgA1c level was noted to be 9.3%, and serum creatinine was 0.9 mg/dl.

A two week screening period commenced, in which a standard of care alginate was used daily without much improvement seen in wound size. After week two, he received weekly AlloPatch Pliable treatments. The wound successfully healed with only two weeks of treatment using AlloPatch Pliable; final HgA1c was 9.9%; and the patient was progressed to diabetic shoes and insoles

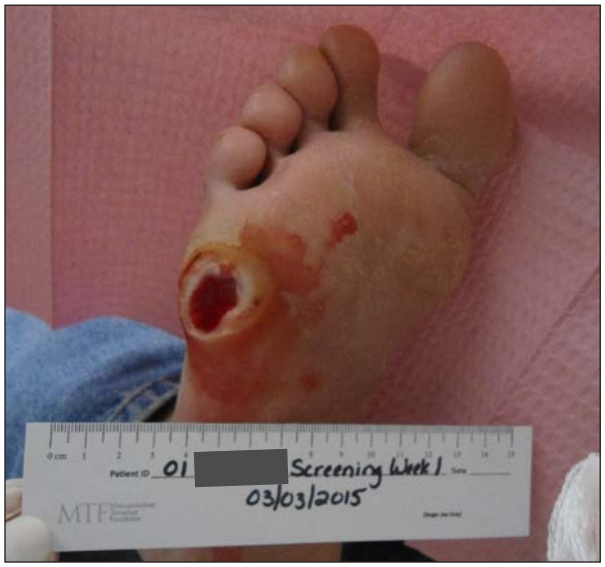

Figure 6a: *Screening Week 1 with standard of care alginate dressings. Ulcer History: 4 weeks. Length: 1.50cm, Width: 1.30cm, Depth: 0.10cm*

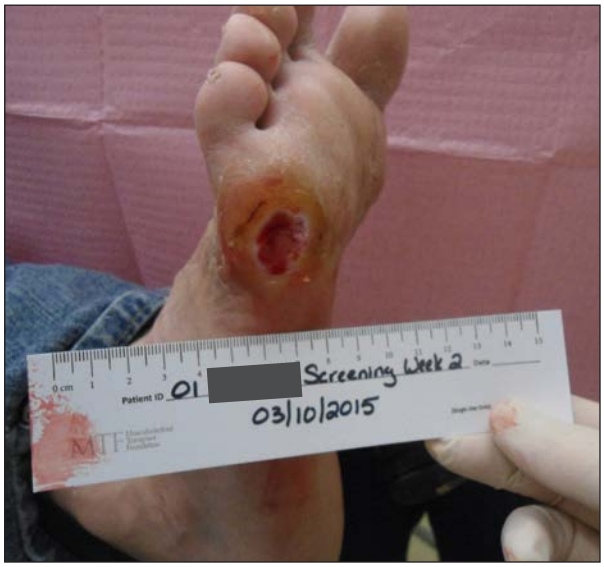

Figure 6b: *Screening Week 2 using standard of care treatment with alginate dressings. Length: 2.00cm, Width: 1.50cm, Depth: 0.10cm*

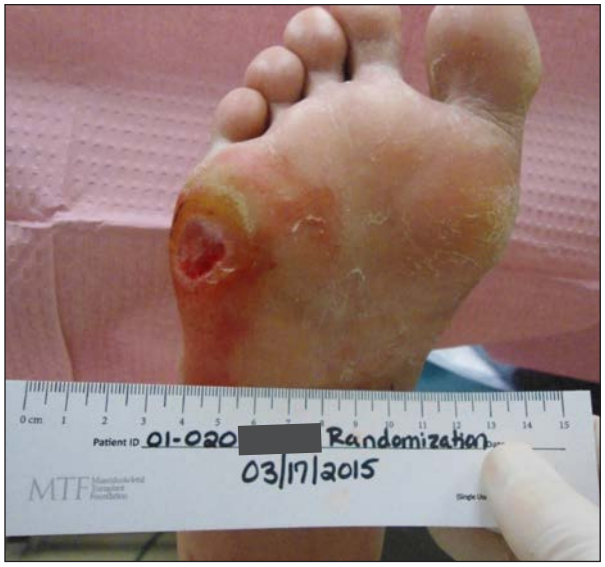

Figure 6c: *Randomization week. Patient randomized to receive AlloPatch treatment.*
Length: 2.00cm, Width: 1.70cm, Depth: 0.10cm

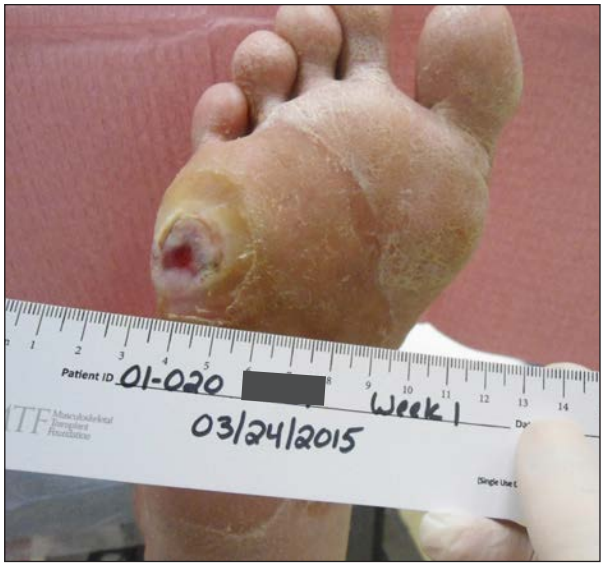

Figure 6d: *First visit after week 1 of AlloPatch Treatment.*
Length: 0.50cm, Width: 0.50cm, Depth: 0.10cm

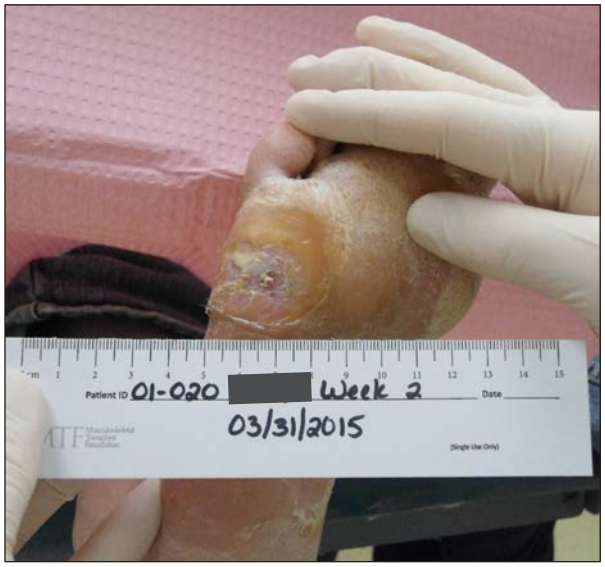

Figure 6e: *Week 2 – Diabetic Foot Ulcer has healed.*

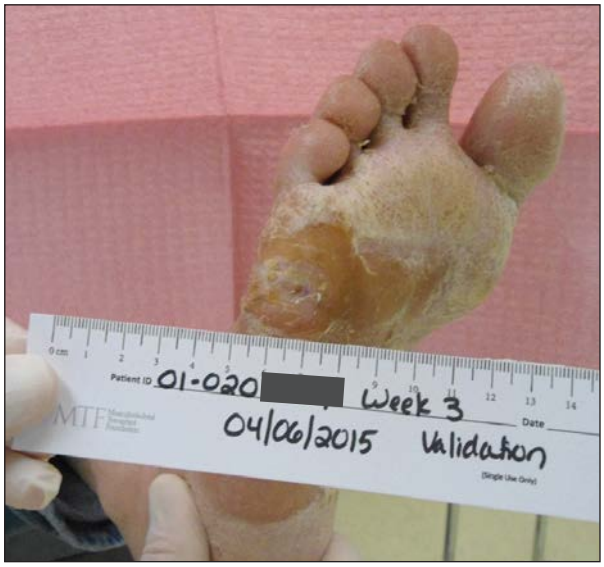

Figure 6f: *Validation visit, ulcer remains healed with epithelial tissue present.*

Case 2

A 72 year old male with past medical history of Type two diabetes mellitus with peripheral neuropathy presented with a non-healing left foot ulceration over his lateral column. The patient informed us that his ulceration had been there for over a month and had been very resistant to multiple forms of conservative care including alginates, antibiotic cream and offloading.

Past Medical History: Type two Diabetes Mellitus with Peripheral Neuropathy, Hypertension, High Cholesterol, Anxiety, Depression, Asthma, Atrial Fibrillation, and Kidney Stones, as well as a prior history of healed neuropathic fractures to his feet.

A standard diabetic foot exam was performed, revealing Semmes Weinstein monofilament wire testing 0/10 points confirming severe peripheral neuropathy. Pedal pulses were 2/4 and an arterial Doppler exam was completed which revealed biphasic waveforms for both the dorsalis pedis and posterior tibial arteries. A screening HgA1c level was found to be 7.4%, and serum creatinine was 1.3 mg/dL.

The patient went through a two week screening period and used a standard of care alginate dressing as well as offloading with a diabetic camboot without any significant improvement. After week two, he received one application of AlloPatch Pliable, size specific to minimize wastage. The wound remarkably healed after only one week of AlloPatch Pliable treatment. He was seen for validation a week after healing and remained healed with a HgA1c noted to be 8.2% at his final visit; and was progressed to diabetic shoes with insoles.

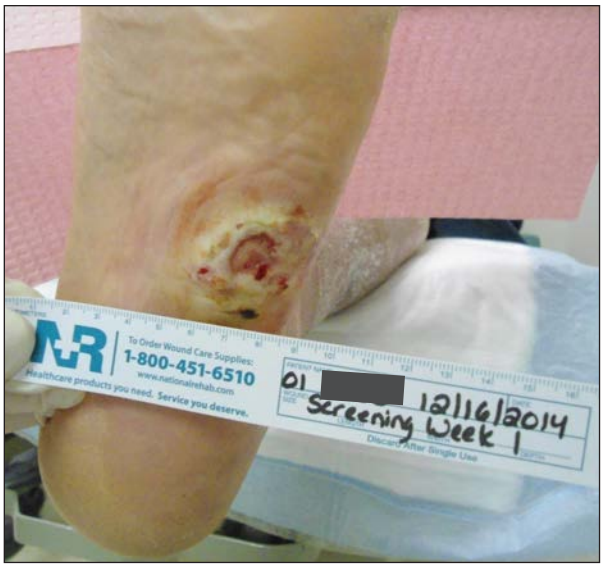

Figure 7a: *Initial screening visit.*
Ulcer history: 4 weeks
Length: 1.20cm, Width: 1.20cm, Depth: 0.10cm

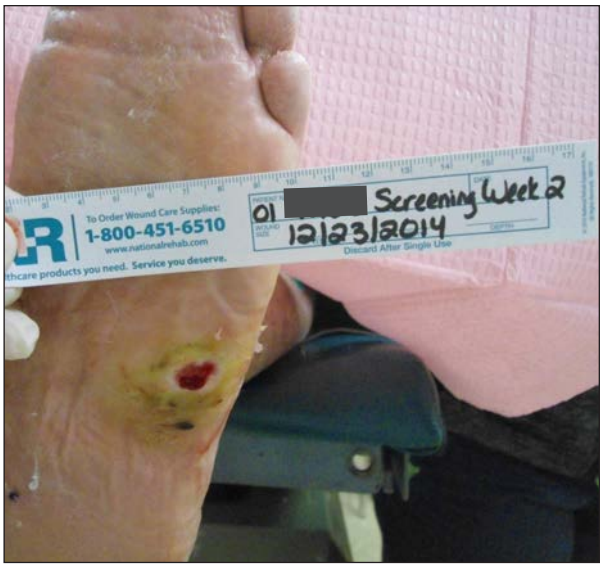

Figure 7b: *Screening period with standard of care with alginate dressings.*
Length: 1.10cm, Width: 1.20cm, Depth: 0.10cm

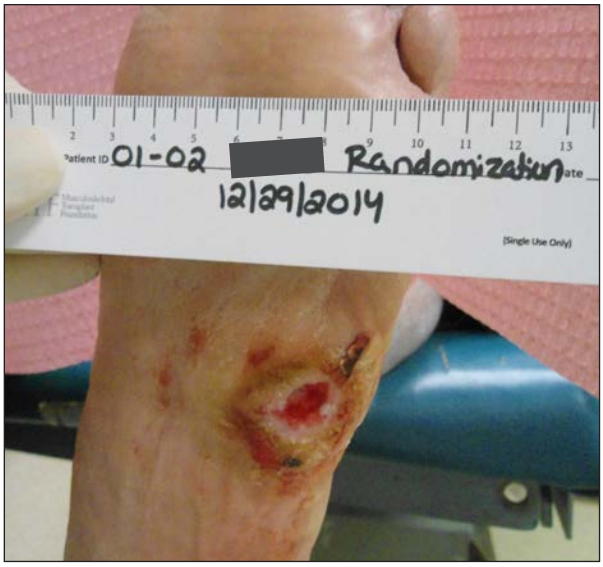

Figure 7c: *Randomization visit, received AlloPatch.*
Length: 1.20cm, Width: 1.20cm, Depth: 0.10cm

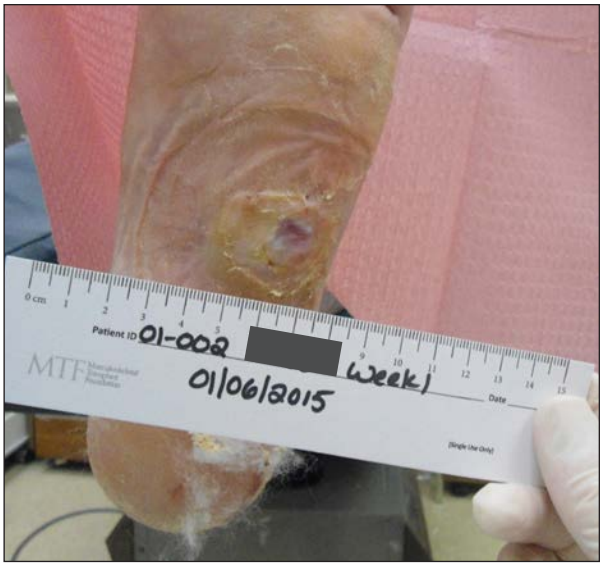

Figure 7d: *After only 1 week of treatment with AlloPatch the ulcer healed, with 100% epithelial tissue present.*

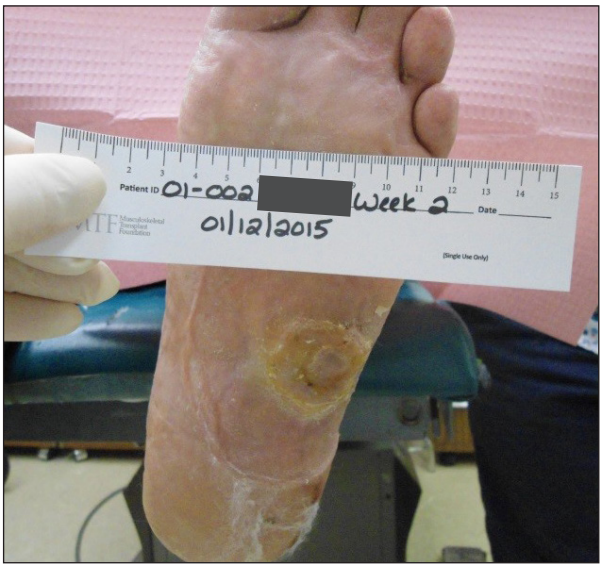

Figure 7e: *Validation Visit. Ulcer remains healed.*

Case 3

A 61 year-old morbidly obese male with past medical history of Type two diabetes mellitus with peripheral neuropathy presented with chronic, non-healing left hallux ulceration present for 36 weeks, resistant to a variety of conservative wound care modalities. He is a retired police officer and truck driver who has suffered from diabetic foot ulcers for many years. During his course of treatment he had received antibiotic creams, alginates as well as different offloading devices.

Past medical history: Type two Diabetes Mellitus with Peripheral Neuropathy; Cardiac Disease with previous Myocardial Infarction and placement of four Cardiac Stents, Depression, Hypertension, Hyperlipidemia, as well as previous Right Partial First Ray Amputation.

A standard diabetic foot exam was performed, revealing Semmes Weinstein monofilament wire testing, 0/10 points confirming severe peripheral neuropathy. Pulses were 2/4 and a Doppler exam was done which revealed biphasic waveforms for both the dorsalis pedis and posterior tibial arteries. An initial HgA1c level was found to be 11.4%, and serum creatinine was 1.0 mg/dl.

The patient underwent a two week screening period and used a standard of care alginate dressing and further offloading without improvement. After week two, he received weekly AlloPatch Pliable treatments. The wound successfully healed after five weekly applications. His final HgA1c was 10.2% on study exit and he was progressed to diabetic shoes with insoles.

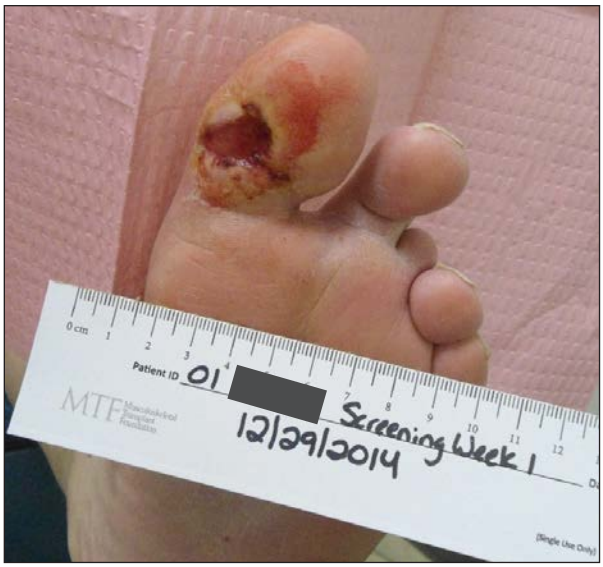

Figure 8a: *Initial screening visit.*
Ulcer History: 36 weeks.
Length: 1.50cm, Width: 1.50cm, Depth: 0.20cm

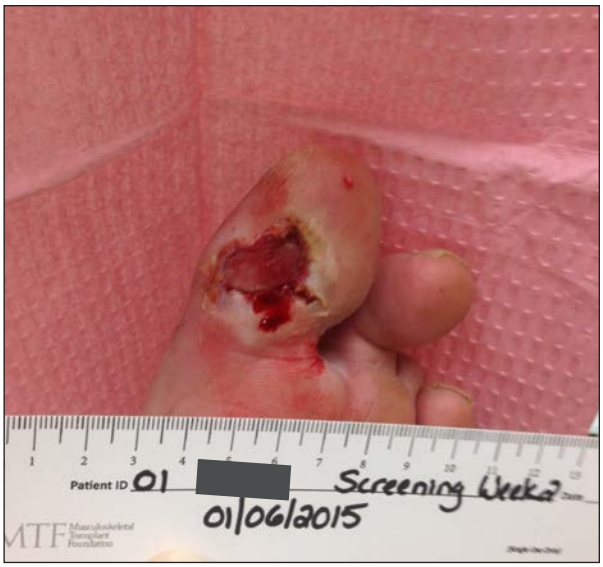

Figure 8b: *Screening Week 2. Still resistant to standard of care with alginate dressings.*
Length: 1.50cm, Width: 2.00cm, Depth: 0.20cm

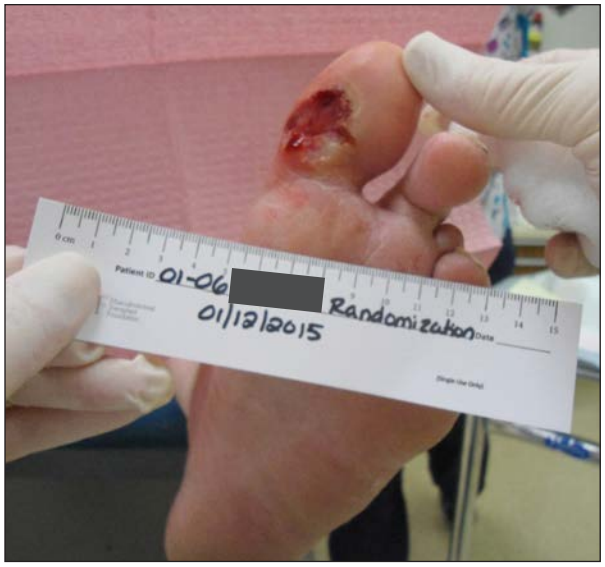

Figure 8c: *Randomization to receive AlloPatch.*
Length: 1.50cm, Width: 2.10cm, Depth: 0.10cm

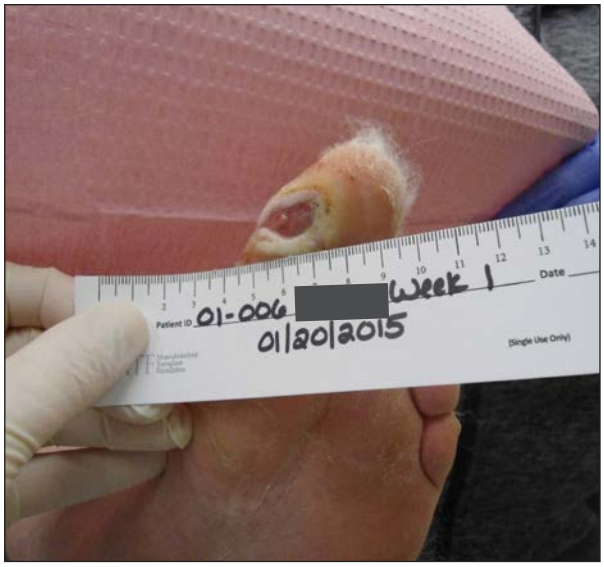

Figure 8d: *After 1 week of treatment with AlloPatch. Epithelial tissue has started to form.*
Length: 1.00cm, Width: 1.50cm, Depth: 0.10cm

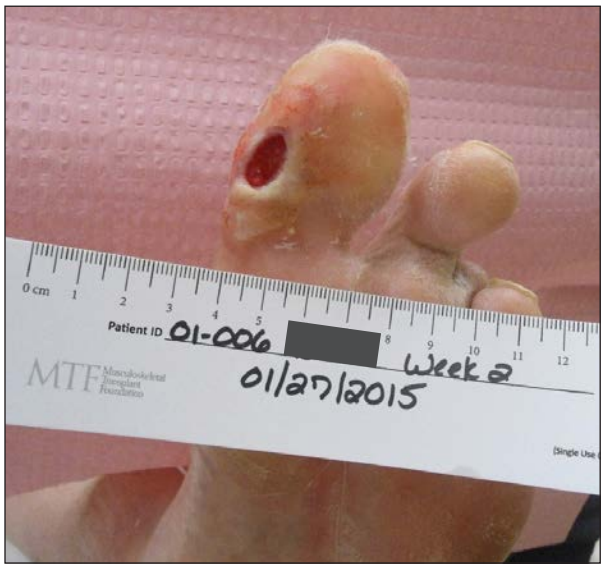

Figure 8e: *Week 2 – After 2 weeks of treatment with AlloPatch.*
Length: 1.00cm, Width: 0.70cm, Depth: 0.10cm

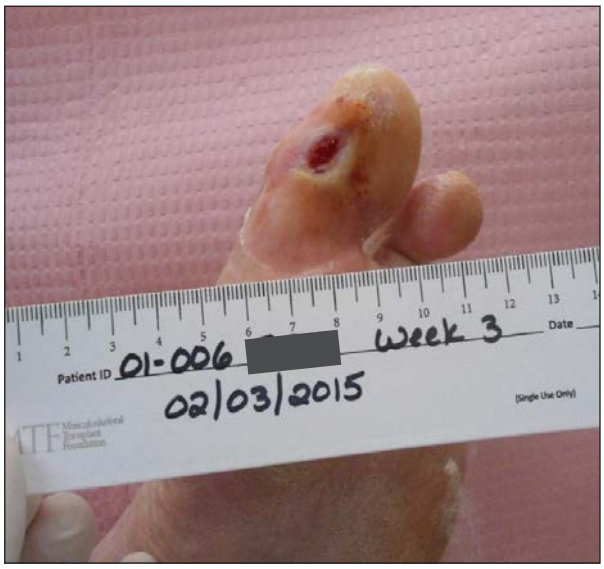

Figure 8f: *After 3 weeks of treatment with AlloPatch.*
Length: 0.60cm, Width: 0.40cm, Depth: 0.10cm

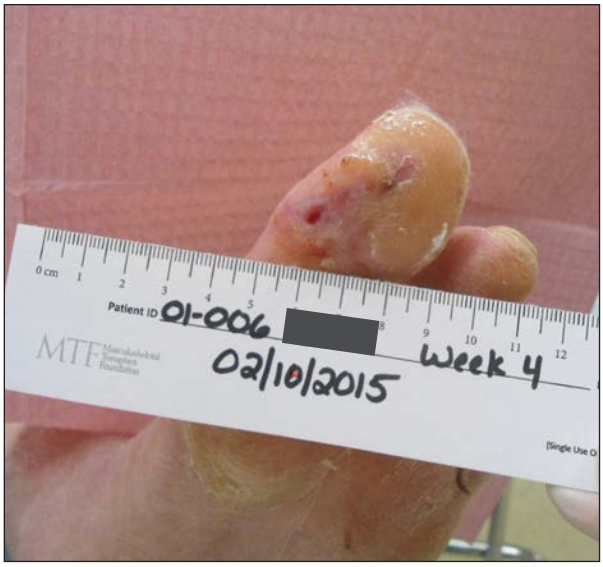

Figure 8g: *Week 4 of treatment with AlloPatch. Length: 0.20cm, Width: 0.20cm, Bcnrf: 0.10cm*

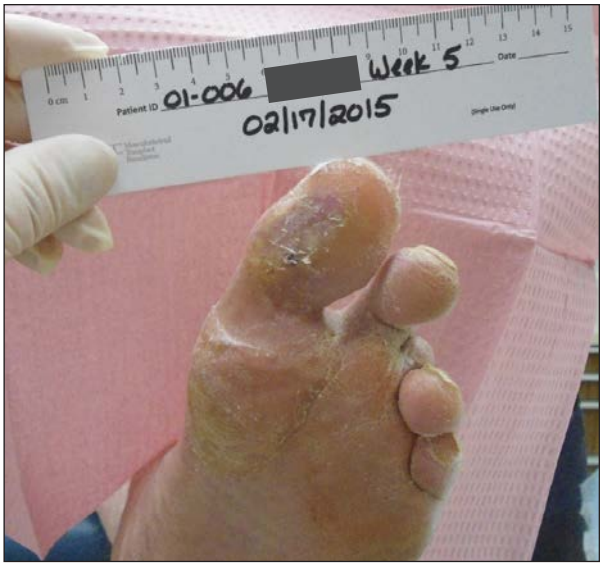

Figure 8h: *Ulcer has healed after 5 weeks of treatment with AlloPatch.*

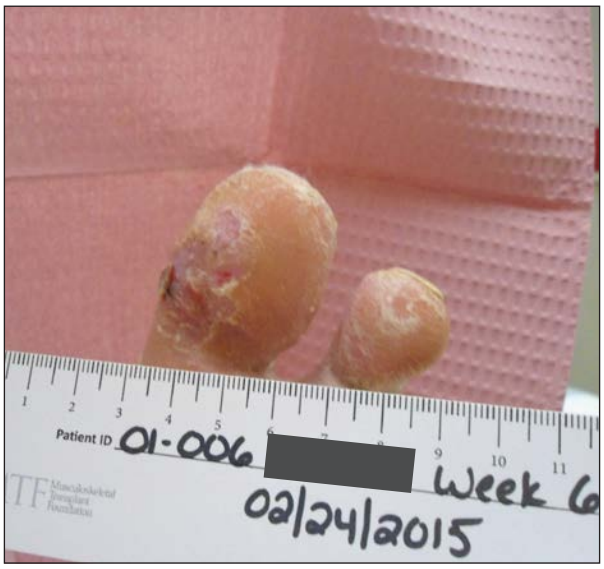

Figure 8i: *Validation visit. Ulcer remains healed with 100% epithelial tissue present.*

CONCLUSION

These three case studies using AlloPatch Pliable illustrate its effectiveness in healing diabetic lower extremity ulcers with limited applications of size-specific dermal grafts.

Both clinicians and insurers as well as our government are closely looking at wastage and cost to closure. The use of AlloPatch Pliable as a treatment option for diabetic foot ulcers with size specific grafts leads to minimal wastage and the lowest possible cost to closure as seen in this case series.

Elevated HgA1c levels do reduce healing rates and prolong overall healing.[33,34] However, the greatest interest in two out of three of these case studies with AlloPatch Pliable was an overall rise in the HgA1c, with patients still healing from these challenging wounds quickly.

Certainly the wound healing physician should consider a multitude of factors when choosing an advanced wound therapy. AlloPatch Pliable, with multiple sizes, a proprietary aseptic processing and a deeper cut of dermal tissue that allows for better incorporation and cell attachment, should be considered a first line choice for non-healing chronic diabetic foot wounds.

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