The Utility of a Single-Application Human Decellularized Dermal Matrix

Here's a look at an up-and-coming treatment for DFUs.

BY WINDY COLE, DPM

The prevalence of diabetes is on the rise worldwide. Recent CDC reports show that 30.3 million Americans are living with diabetes. That equates to roughly one out of every 10 people in the U.S. alone having active diabetic disease.[1] As podiatrists and diabetic foot experts, we know the deleterious effects of diabetes on the tissues of the lower extremity. Among diabetes-related complications, the treatment and management of diabetic foot ulcers (DFUs) remains a major challenge for patients, caregivers, and healthcare systems alike.[2]

Advanced wound products that provide wound healing support through various mechanisms have proven to be effective adjunctive therapies and may improve DFU patient outcomes.

Multiple disrupted physiologic processes, including decreases in cellular signaling and growth factor responsiveness, lead to microvascular dysfunction and diminished peripheral blood flow that can contribute to the lack of healing in people with DFUs.[3] These chronic ulcers negatively impact patients' lives and contribute to rising healthcare costs.[2] Complications from DFUs are a leading cause of lower extremity amputations. It is estimated that up to 85% of all non-traumatic lower extremity amputations are a direct result of DFUs.[3]

Traditional treatments for DFU management include wound debridement, appropriate moisture managing dressings, off-loading of plantar surface wounds, glucose control, optimizing perfusion, and infection control if pathogens are encountered.[4] In one published meta-analysis, pooled data showed a healing rate of only 24% at 12 weeks in DFU patients receiving these standard of care therapies.[3]

Advanced wound products that provide wound healing support through various mechanisms have proven to be effective adjunctive therapies and may improve DFU patient outcomes. In recent years, Cellular and Tissue-Based Products (CTPs) have emerged as one of the most promising group of advanced wound care therapies for the management of DFUs.[4]

As a whole, this category of advanced therapies supports cellular functions essential for wound healing. The ideal CTP is non-toxic, has no antigenicity, is immunologically compatible, and does not transmit disease. Broadly. CTPs can be categorized as autologous grafts, scaffold grafts, living cell grafts, and amniotic tissue grafts. One distinct category of CTP is acellular dermal matrix allografts (ADMs).

To fully appreciate the utility of these CTP products, one must initially understand the wound healing process. Regardless of the method of tissue injury, the body's first response is that of hemostasis. Platelets are activated in response to damage to the endothelium and the coagulation cascade begins.[5]

The aggregation of platelets at the site of injury causes cytokines to be released, ultimately leading to vasoconstriction, clot formation and control of bleeding.[5]

Once hemostasis is achieved, the inflammatory phase begins. Polymorphonuclear cells migrate into wounded tissues to begin the clean-up process. Macrophages phagocytize bacteria, spent cells, and foreign debris.[6] Once the inflammatory phase has completed, the rebuilding stage known as proliferation follows.

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Clinical Innovations

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Fibroblasts enter the wound and begin to lay down collagen. This new collagen acts as a framework aiding in angiogenesis, tissue regeneration, and wound contracture.[6] Epithelial cells are concurrently working to rebuild the top layer of wounded tissue. This process occurs through cellular migration from the wound edge in a game of wound healing dubbed 'red rover'.[6] Once the ECM is laid down and epithelialization has completed, the final phase of wound healing, known as maturation or remodeling, begins. Scar tissue becomes more durable through collagen degradation and reformation.[7] Wound strength improves to approximately 80% of its pre-wound function.[7] This final phase of wound healing can go on for up to two years.[7]

Normal wound healing consists of multiple dynamic overlapping stages that rely on interactions between cells, signaling molecules, and a functional extracellular matrix (ECM). The ECM acts as the major structural component of the dermal tissue layer.[7] Collagen, fibronectin, proteoglycans, elastin, and hyaluronic acid make up the composition of the ECM.[7]

Unfortunately, not all wound healing follows these pre-planned steps in a timely fashion. Co-morbidities such as diabetes often lead to dysfunction of the ECM, thus resulting in wounds that are slow-to-heal. When wound healing is delayed, high levels of proteases can cause ECM degradation and lead to a disruption of the healing cascade.[7]

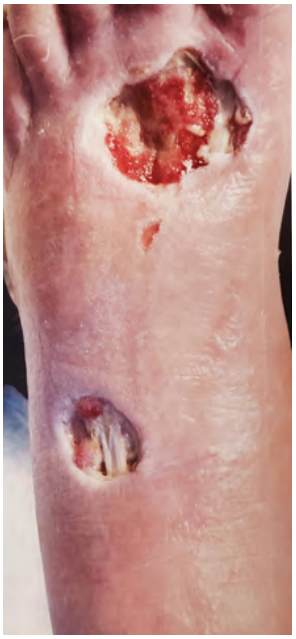

Figure 1: Post-op wound appearance with tendon exposed

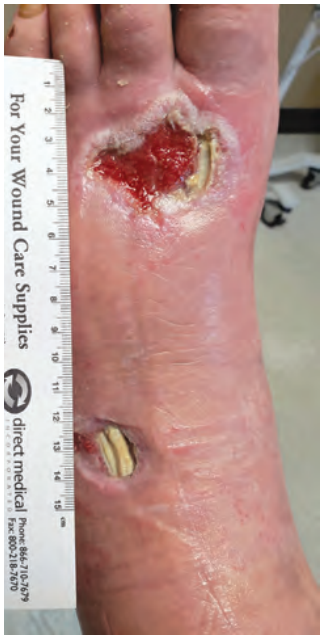

Figure 2: Wound appearance after NPWT

Acellular dermal matrices (ADMs) derived from human skin have been used in a variety of medical procedures, including wound healing, sports medicine applications, and soft-tissue reconstruction.

With advances in knowledge of the pathophysiology of wound healing, research has shown that supporting the ECM and correcting tissue disorganization is of paramount importance. Thus, wound care products that aim to stimulate and replace the ECM, such as acellular matrices, have gained utility in the space. These products are comprised of a three-dimensional native collagen matrix that provides a temporary scaffold supporting cellular migration and proliferation in an organized fashion, ultimately leading to tissue regeneration and wound healing.[8] Acellular matrices can be natural, synthetic, or composite, and can be derived from both humans or animals.[8]

Acellular Dermal Matrices

Acellular dermal matrices (ADMs) derived from human skin have been used in a variety of medical procedures, including wound healing, sports medicine applications, and soft-tissue reconstruction.[9,10] Human skin is a rich wound

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matrix. It can provide elastic structural and nutritional support to damaged tissues. ADMs are acquired by obtaining a full thickness section of donated human skin.[10]

These tissues are screened for all infectious diseases including HIV and hepatitis.[10] These CTPs are then run through company-dependent proprietary processes of decellularization, sterilization, and packaging.[10] ADM use has become increasingly popular to assist in wound closure in cases of significant tissue loss such as in cases of chronic DFUs.[11]

The remainder of this article will highlight two DFU cases using a unique ADM, DermGEN (DeCell Technologies, Halifax, Nova Scotia). DermGEN is an advanced regenerative tissue matrix derived from donated human skin and treated with a patented prECMTM process to remove all cellular immunogens and ensuring biocompatibility.[12]

The DermGEN matrix acts as a natural scaffold and encourages cellular chemotaxis to support tissue regeneration.

The product manufacturing occurs using the world's first-ever automated tissue processing system, allowing for the matrix to maintain the highest level of natural tissue structure and composition.[12] The final product is sterilized using a unique and validated liquid sterilization process that does not alter the tissue structure or change cellular response to the matrix.[12]

The DermGEN matrix acts as a natural scaffold and encourages cellular chemotaxis to support tissue regeneration.[13] DermGEN is the only advanced tissue product having a patented composition of matter.[12] These patented properties are known to be directly related to improved healing.[12] The matrix is stored at room temperature and is fully hydrated and ready to use to make DermGEN easy to integrate into office or wound care center workflows.[12]

Patients are monitored weekly for secondary bandage changes and wound monitoring. Perhaps one of the most advantageous features of DermGEN is that typically only one application is required to achieve complete wound healing.[13] Compiled data from a recent pilot study illustrated a significant cost savings over standard of care.[13]

Case Report 1

A 56-year-old, insulin-dependent diabetic man presented to the emergency department with a 2-week history of red, hot swollen left foot that appeared to worsen over the last 12 hours. He related no history of trauma to the area. On examination, it was noted that there were two areas of ulceration present on the dorsum of the foot with moderate amounts of necrotic tissue presented along with a foul odor and purulent drainage. Owing to the significant signs of infection noted upon the examination,

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coupled with the patient's uncontrolled diabetes, he was admitted into the hospital.

The patient was taken to surgery, and he underwent rigorous surgical debridement of all devitalized and necrotic tissue down to exposed tendon (Figure 1). Final culture results showed moderate Staphylococcus aureus and diphtheroid species present in soft tissue. No evidence of osteomyelitis was noted clinically or on MRI. His post-operative course included 4 weeks of intravenous antibiotic drug therapy consisting of 1 g of vancomycin daily and a rigorous regimen of wound care consisting of weekly serial debridement, wound vacuum therapy. The tissues were healthy and granular, but exposed tendons remained (Figure 2).

At this juncture, considering the improved health and character of the wound, but still having concern over the potential desiccation of the exposed tendons, DermGEN ADM was applied to both wounds. Prior to DermGEN application, debridement of all devitalized and nonviable tissue was performed. The 5x5 DermGEN graft was fenestrated and cut into two segments placing each over top of both wounds.

The ADM was covered with a meshed, one-sided wound contact layer to allow exudate to pass through to the secondary bandage layer while protecting the ADM and keeping it in contact with the wound tissue. A dry bulky secondary dressing was applied to the foot to keep the wounds protected. The patient was allowed to ambulate in a surgical shoe. He was seen in the wound care center for weekly bandage changes.

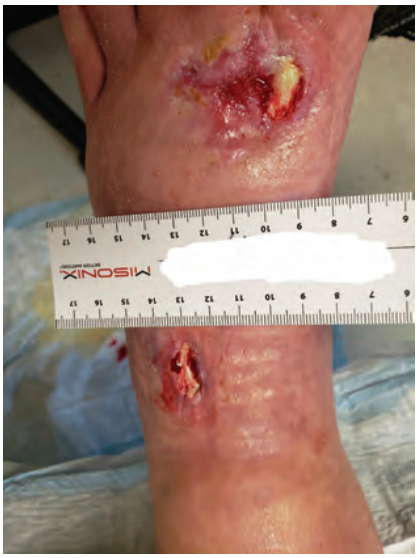

Figure 3: Wound progress 3 weeks after DermGEN application

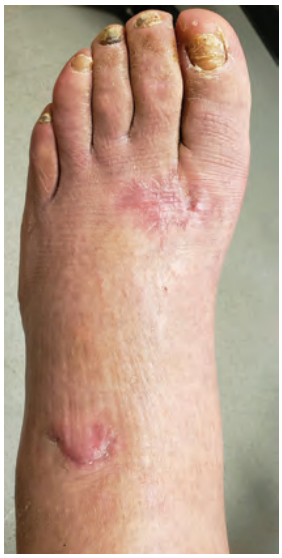

Figure 4: Wound is healed

The use of the DermGEN ADM material was able to successfully completely close two complicated DFU cases wound with only one application.

During these visits, only the secondary bandage was changed. The DermGEN graft and contact layer remained intact. Complete incorporation of the DermGEN material into the wound was noted when the bandage was removed three weeks after the initial application (Figure 3). With continued weekly wound care visits, the wound continued to decrease in diameter, with rapid closure noted six weeks after applying the DermGEN graft (Figure 4). There were no significant post-operative complications.

Case Report 2

This patient is a 67-year-old female with NIDDM who presented to the emergency department with a history of minor trauma resulting in an infection of the distal right hallux. She related that the process had been ongoing for 10 days with gradual worsening. The patient noted increased malodor and drainage for the preceding four days. She was newly diagnosed as having NIDDM diabetes mellitus. The patient had nothing significant in her past medical history except for diabetes.

On presentation, she complained of increased swelling and darkening of skin color to the right hallux for approx-

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imately 6 days followed by purulent drainage for the prior 4 days. She did not complain of any pain to the foot, but she did relate having fever and chills. Physical examination revealed an oral temperature of 100.5° F. She had a hallux malleolus deformity of the right great toe with an open ulceration at the distal aspect probing to bone (Figure 5).

There was slight purulent drainage and associated malodor with cellulitis of note to the level of the 1st MPJ. Protective sensation was absent by monofilament exam. Radiographic findings include degenerative disease of the 1st metatarsophalangeal joint and marrow edema affecting the distal phalanx of the great toe consistent with early osteomyelitis. No boney erosion was noted. The patient was admitted to the hospital and empirically placed on broad-spectrum antibiotic coverage with vancomycin and piperacillin/tazobactam.

Due to the severity of the infection, the patient was taken to the operating room for a debridement of non-viable soft tissue and bone biopsy. The patient was adamant that she did not want an amputation of the hallux. After all devitalized tissue was surgically excised from the toe, it was noted that the tip of the distal phalanx was exposed. There was active bleeding to all remaining tissues and no necrotic or devitalized tissue remained in the surgical site, yet there was a concern regarding further osteomyelitis and/or desiccation of tissues and bone should the wound be left uncovered.

At this time, it was decided to apply DermGEN to the remaining open wound in the OR. Similarly to the other case, the DermGEN graft was fenestrated and cut to fit the size of the wound. Because of the location of this ulcer, the DermGEN graft was secured in place with staples. It was then covered with a meshed, one-sided wound contact layer to allow exudate to pass through to the secondary bandage layer while protecting the ADM and keeping it in contact with the wound tissue.

A dry bulky secondary dressing was applied to the foot to keep the wounds protected. The patient was allowed to ambulate in a surgical shoe. She was discharged from the hospital 2 days later.

The patient was seen weekly at the wound care center post-operatively. Complete incorporation of the DermGEN graft occurred 2 weeks post-application. The wound was determined to be healed at 8 weeks post-operatively (Figure 6). The patient was transitioned into custom extra-depth diabetic shoes with plastizote inserts. There were no significant post-operative complications.

Discussion

Traditional, yet rigorous, wound care protocols often prove unsuccessful when treating DFUs with exposed deep tissue structures. The use of the DermGEN ADM material was able to successfully completely close two complicated DFUs with only one application. The rapid wound closure indicates that there may be value in using DermGEN earlier in complex or treatment-resistant cases, thus reducing the time and expense of traditional but often ineffective treatments for chronic wounds.

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The increasing pervasiveness of diabetes among Americans has had deleterious effects on the overall costs of healthcare, as well as on society and the economy. After adjusting for inflation, medical costs of diabetes in the United States increased by 26% from $188 billion in 2012 to $237.3 billion in 2017, due to the increased prevalence of diabetes and the increased cost per person with diabetes.[14]

Correspondingly, as podiatrists and wound care clinicians, we have patients presenting with serious sequelae due to diabetes such as non-healing wounds, infections, and lower extremity amputations in our clinics every day. The cost of treating a DFU is estimated to run $18,000 per case.[15] The economic burden of chronic non-healing ulcers has been estimated to be $28.1 to $31.7 billion annually.[16] When the cost of treating infections is included, the most expensive chronic wounds are surgical wounds ($11.7 to $13 billion) followed by diabetic foot ulcers ($6.2 to $6.9 billion).[16]

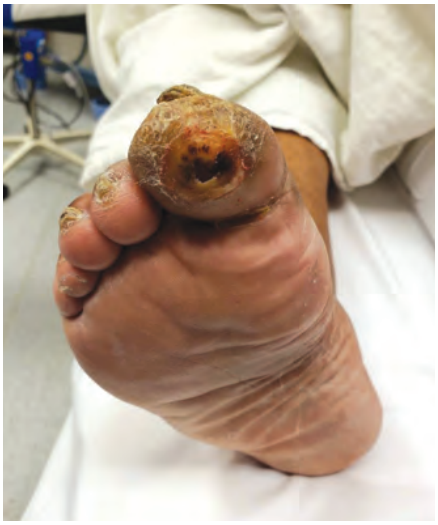

Figure 5: Initial wound appearance on intake

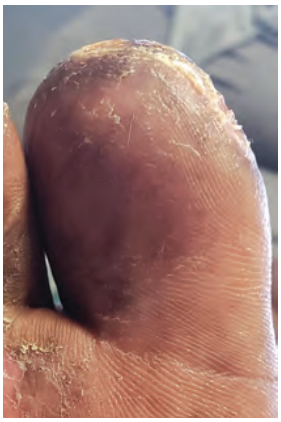

Figure 6: Wound is completely healed.

Clearly, the impact of the diabetes epidemic is wide-reaching and compounding, particularly as the numbers of the affected population grows. Increasing the number of effective DFU therapies available to this patient population would decrease chronic wound complications while increasing healing rates. The overall positive effects could be seen by positively influencing diabetic patients' overall quality of life.

Successful use of novel therapeutic modalities such as DermGEN into clinical algorithms for DFU management may fulfill an unmet need that is of increasing importance given the global diabetes epidemic. This two-patient case series contains the limitations necessarily present with such a small population; however, DermGEN was successful in healing these wounds that had been resistant to conventional treatment methods. Although not generalizable, this success provides support for future treatments using this new acellular dermal allograft, particularly in patients with chronic diabetic foot ulcers with exposed deep tissue structures. **PM**

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