Use of Human Fibroblast Derived Dermal Substitute (HFDDS) to Close a Complex Chronic Wound in the Presence of Peripheral Arterial Disease

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Abstract:
Chronic wounds often present a challenge to the wound care practitioner, especially in the presence of peripheral arterial disease. Complicating factors such as tendon exposure further increase the difficulty of effecting successful closure of such wounds. We herein report a case of a chronic lower extremity wound with exposure of the underlying anterior tibial tendon. Successful healing was achieved through the use of a human fibroblast derived dermal substitute (HFDDS) in concert with standard wound care and immobilization of the ankle. This case typifies our experience with advanced wound care products such as skin substitutes in the management of difficult to heal lower extremity wounds.

Key words: Chronic wounds, advanced wound therapies, dermal replacement therapy

INTRODUCTION

Chronic non-healing wounds present a challenging and demanding scenario to the podiatric physician. These wounds may precede severe complications such as infection, sepsis or even limb loss. There are many reasons that wounds remain chronic: vascular disease, metabolic disorders, nutritional deficiencies, psychosocial issues or any mixture of those mentioned. The main principles of chronic wound management include strict adherence to the principles of good wound care such as aggressive debridement of all non-viable tissue, adequate off-loading of pressure, prompt treatment of infection and moist dressings. Over the past decade, new adjuvants for wound healing have been developed that have become readily available to the practicing clinician. Such modalities include negative pressure devices, ultrasound, electrical stimulation, pulsed radio frequency energy, growth factors and various dermal or skin equivalents.

In this case report, we highlight the use of a human cell-derived wound care product for the treatment of a chronic wound in a patient with peripheral arterial disease.

CASE REPORT

A 60 year-old male presented to our outpatient podiatry clinic with an open wound on his right anterior shin that had been present for several weeks. The patient had suffered a crush-type injury over 20 years prior to his presentation that resulted in several episodes of closure and re-ulceration at this site.
This current ulcer had started after being in a hot tub for a few hours. The wound was treated initially with local wound care that included moist wet-to-dry dressings. His past medical history was significant for hypertension, peripheral arterial disease and tobacco use.

Physical examination revealed a full-thickness ulceration at the right anterior lower tibia with visual observation of the tibialis anterior tendon in the center of the wound (Figure 1).

The wound measured 3.5cm x 2.5cm and had a granular wound base with macerated wound edges. There was significant peri-wound erythema (cellulitis) as well as proximal tracking up the tibialis anterior tendon. There was no malodor or drainage appreciated, and there was no probing or tracking to bone. There was a significant amount of pain at the wound site. Additional examination findings included sluggish capillary refill to all of the digits as well as non-palpable pedal pulses. His protective sensation was intact to 10-gram monofilament testing. The initial crush injury had left him with a 1.2cm limb length discrepancy with the right leg shorter than the left. A white blood cell-labeled bone scan revealed only soft tissue infection along the anterior surface of the distal right tibia. Vascular studies revealed moderately severe peripheral atherosclerotic disease (PAD) of the bilateral lower extremities with an ankle/brachial index (ABI) of 0.64 and 0.44 on the left and right lower extremities, respectively.

Wound debridement was performed and daily wet-to-dry dressing changes were initiated, along with the daily use of a removable fixed ankle walker applied to the right lower extremity. Oral antibiotic therapy (cephalexin) was initiated in which the patient followed the medication regimen for a total of four weeks until the cellulitis resolved. At the first follow-up visit after wet-to-dry dressings were initiated the first application of the human dermal replacement product (Dermagraft®, Shire Regenerative Medicine, LaJolla, CA) was applied to a debrided wound bed that had a granular wound base. The tissue implant was covered with a silicone primary barrier dressing, polyurethane foam, and dry sterile dressings (Figure 2). The patient was then placed in a total contact cast (TCC) for one week. At that time we converted the TCC into a bivalve cast for ease of removal and reapplication (Figure 3). There were a total of nine weekly consecutive applications of HFDDS applied along with immobilization until closure was obtained at the wound site (Figure 4). The patient was followed up three weeks after the wound had closed and was discharged from our high-risk clinic. On follow-up, approximately 3 months later, the wound remained closed. This patient is currently under the treatment of vascular surgery with plans for revascularization to improve blood flow to the lower extremities.
Chronic wounds are thought to be arrested in a state of chronic inflammation, with an imbalance between protease activity and growth factor expression. The chronic wound environment has an excess of matrix metalloproteases (MMPs), diminished amounts of tissue inhibitors of MMPs (TIMPS), senescent and dysfunctional cells with reduced proliferative and synthetic activities, and deficiencies in growth factors and growth factor receptors. This environment suppresses fibroblast cell proliferation and motility as well as protein expression allowing the wound to remain in a chronic state. The theory of using healthy living dermal cells is to transform the wound back into an acute wound via appropriate expression of growth factors, matrix proteins and glycosaminoglycans.

Dermagraft® is a cryopreserved human fibroblast-derived dermal substitute that is composed of fibroblasts, extracellular matrix and a bio-absorbable scaffold. During the manufacturing process the fibroblasts proliferate and secrete human dermal collagen, matrix proteins, growth factors, and cytokines to create a three-dimensional human dermal substitute, which contain metabolically active, living cells (See Tables 1, 2 and 3). This dermal tissue construct is designed to replace the dermal layer of the skin and provide stimulus for the normal wound healing process.

### Table 1. Growth factors in the HFDDS (3)

<table>
<thead>
<tr>
<th>Growth factors</th>
<th>HFDDS</th>
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<tbody>
<tr>
<td>Fibroblast growth factor</td>
<td>FGF-1, 2, 7</td>
</tr>
<tr>
<td>Hepatocyte growth factor</td>
<td>HGF, HGF, SF</td>
</tr>
<tr>
<td>Insulin-like growth factor</td>
<td>IGF</td>
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<tr>
<td>Platelet-derived growth factor</td>
<td>PDGF-A, PDGF-B</td>
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<tr>
<td>Transforming growth factor</td>
<td>TGF-B1, TGF-B3</td>
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<td>Vascular endothelial cell growth factor</td>
<td>VEGF</td>
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A prospective randomized controlled single-blind study was carried out by Naughton and colleagues to assess the effectiveness of Dermagraft® versus standard wound therapy in the treatment of difficult to heal ulcers. The patients randomly selected for control treatment received conventional therapy to include debridement, saline-moistened gauze dressings and standardized off-loading. Patients selected randomly for the study treatment underwent conventional therapy along with the application of the tissue construct on day 0 and at weeks 1-7 for a total of 8 applications. The study demonstrated that the use of the dermal replacement product resulted in a statistically significant improvement in complete wound healing of plantar diabetic foot ulcers as compared to conventional treatment. Several other studies have confirmed the efficacy of this dermal substitute in healing chronic diabetic foot wounds as well as other various types of chronic wounds in the lower extremities.

The patient presented in this case suffered from moderately severe atherosclerotic disease of the lower extremities. PAD leads to limb ischemia that inhibits perfusion to skin areas that may be at risk of ulceration, in this case at the anterior right tibia, the site of previous injury. Wounds that remain open for long periods of time are at risk of developing infection, osteomyelitis or limb loss.

By using this advanced wound healing therapy in concert with standard wound bed preparation and immobilization, we were able to promote complete closure of this difficult wound without hospitalization or formal operative intervention.
CONCLUSION

Chronic wounds are a major contributor to morbidity and mortality leading to high medical costs, especially in those persons with diabetes mellitus. Standard chronic wound therapy has often proven to be inadequate in the healing of these types of wounds. High medical costs as well as the increasing risk of amputation and mortality in the presence of chronic wounds necessitates newer adjuvants to wound therapy. There have been major advances in the development of bio-engineered tissue products that can enhance the wound healing process.

Dermagraft® has been shown to significantly accelerate the healing process in several prospective randomized trials for the treatment of non-healing diabetic foot wounds4-7. Other wound care principles such as adequate off-loading, decreasing bacterial bio-burden and proper wound debridement must also be used in conjunction with bio-engineered tissue products. It was highlighted in this case report that dermal replacement therapy can be used as an adjuvant for chronic wound management in a patient with severe PAD. However, it is necessary that a comprehensive approach be used in the management of these patients. In this case, the involvement of vascular surgery and cessation of smoking were required. As clinicians it is our responsibility to be aware of the advanced therapeutic agents that are available to us and to recognize when it is appropriate to initiate such therapies.

References


