CASE STUDY

Successful Limb Salvage Combining Revascularization Surgery with an Advanced Acellular Dermal Matrix (ADM) in Treating Multiple Non-Healing Diabetic Foot Ulcers

By Asem Saleh, MSc MD RPVI FRCSC; Idevania Costa, RN NSWOC PhD; Paul F. Gratzer, MASc PhD PEng

Introduction

The number of people with diabetes is increasing each year and is projected to reach 439 million by 2030, approximately 10% of the world's adult population.[1] Up to 25% are expected to have non-healing foot ulcers, with the success rate for wound closure with standard of care ranging from 35 to 50% and taking an average 8–9.5 weeks.[2,3] It is known that 85% of lower extremity amputations are preceded by a diabetic foot ulcer (DFU),[1,2] with a limb being amputated somewhere in the world every 20 seconds.[3] In Canada, the annual cost for treating non-healing DFUs is $500 million.[4] In addition to the economic burden of non-healing DFUs leading to amputation, few diseases have a higher mortality rate, reaching 30–50% after two years.[5] Over 65% of DFUs have an ischemic component, making vascular surgery an essential procedure for limb preservation.[6] Even with revascularization and best standard wound care practices, however, significant challenges remain in healing DFUs and avoiding amputations. This report features a case study of a patient with diabetes with multiple non-healing necrotic lesions on both feet. Despite aggressive standard treatments and surgeries, the wounds remained open. After amputation of the left foot was necessary, a new approach using a combination of revascularization and an advanced acellular dermal matrix (ADM) (developed by the 3rd author) was successfully used to preserve the right foot.

Presentation

Mr. W is a 75-year-old male with diabetes. He is insulin-dependent (over 10 years), uses an insulin pump, is an ex-smoker (quit 10 years ago) and has hypothyroidism. His A1c levels indicate his sugars are well controlled. He has a history of peripheral neuropathy and loss of protective sensation. He was first seen in February 2020 due to a 3-month history of multiple necrotic lesions on both his feet.

His right foot had ulcers located at the 1st digit medial side (3 cm x 4 cm), lateral side of the foot at the base of 5th toe (3 cm x 3 cm), and a heel ulceration (2.5 cm x 3 cm), all of which displayed dry gangrene. He also had a 3rd digit amputation five

years ago that was healed. His left foot had ulcers on the 1st digit toe (2 cm x 2 cm), and two on the 4th digit toe (both 1 cm x 1 cm). He also had a 3rd digit amputation seven years ago, which was healed.

A CT (computer-aided tomography) angiogram of both feet revealed extensive vascular disease, with vessels at the lower third and below ankle chronically occluded. Initially, a bypass to the posterior tibial artery was performed on the left foot but failed after six weeks due to occlusion. A posterior pedal loop reconstruction was then performed endovascularly. The foot then developed a severe infection while on a one-week trip with his family. Unfortunately, the left foot was subsequently amputated due to the severe infection.

The right foot had an initial vascular reconstruction using a posterior pedal loop. Wounds were healing but then stopped, and surgery was performed to reopen the pedal loop. Mr. W was then sent for hyperbaric oxygen therapy (HBOT), along with aggressive serial debridement and very compliant offloading. Very slow healing and periods of regression occurred over the next eight months. Vessel re-occlusion and reopening operations occurred a total of four times. His blood vessels were very calcified and re-occluded quickly. Amputation of the leg was discussed with Mr. W, but he wanted to fight to heal. Given that the wounds on his foot seemed under control at this point and that his left foot was amputated already, aggressive standard wound care was continued. Unfortunately, even with this approach, the wounds persisted, along with recurrent superficial infections.

Interventional ADM Product

The product utilized in this case study is an advanced human acellular dermal matrix (ADM) material (DermGEN™) that is the first to have been developed and manufactured entirely in Canada (Figure 1). The product is created from donated human skin that has been supplied by an American Association of Tissue Banks (AATB)-accredited tissue bank in Canada. The donated skin is processed using an innovative method of decellularization whereby the donor cells that cause rejection are removed while the remaining non-living protein

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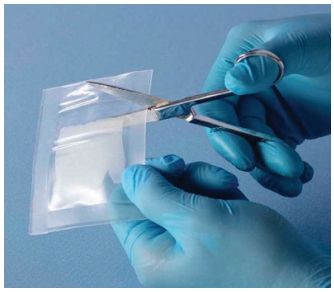
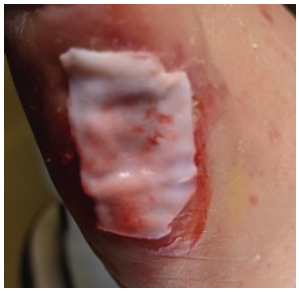
Dr. Ide Costa is an advanced clinical nurse with expertise in the management of complex wounds. She was educated in both Brazil and Canada as a registered nurse, wound care specialist and researcher and has over 24 years of combined experience in clinical practice, teaching and research. Currently, she is an assistant professor in the School of Nursing and adjunct professor in the Faculty of Health Science at Lakehead University in Ontario. She practises wound care at her own clinic in Thunder Bay. She has been the recipient of multiple national and international awards in recognition of her outstanding work as a wound care nurse and researcher in Canada and Brazil. She is an advocate for improving timely access to wound care specialists for vulnerable populations and for empowering patients and families to take control of their own health.

Dr. Paul Gratzer is a licensed Professional Engineer (PEng) and an Associate Professor in the School of Biomedical Engineering at Dalhousie University in Halifax, NS, with cross-appointments in the Departments of Surgery and Process Engineering and Applied Science. He holds degrees in Chemical Engineering, Biomaterials Science and Biomedical Engineering. His research has been focused on soft tissue regeneration and decellularization technology for over 25 years. He is a co-founder and the inventor of the patented decellularization technology used by DeCell Technologies Inc. He is active as an author and on journal editorial boards, is a reviewer for many prominent biomedical journals, participates as an expert on many research funding agency committees and has been a technical advisor with Canadian Blood Services for Tissue Banking.

Figure 1: Example of the Canadian acellular dermal matrix (ADM) DermGEN™ and its application on a wound





"scaffold," the extracellular matrix (ECM), which makes up most of the physical structure of the skin, is left intact. By removing the immune-reaction-causing cells and retaining the ECM, the ADM retains properties and characteristics of skin (proteins, growth factors and cytokines) that attract and stimulate cells within a wound to migrate into the ADM and begin the process of regenerating new tissue. In particular, for hard-to-heal wounds like DFUs, the ADM also acts as a "reset button" for inflammation, breaking the inflammatory cycle and destructive cell behaviour and pushing cells into regenerative and tissue-building activity. In short, this Canadian ADM is a scaffold that the patient's cells recognize as the framework of skin that is incomplete and needs to be remodelled and replaced by repopulating it with appropriate cells and new ECM from the patient—thereby accelerating the healing of hard-to-heal wounds.

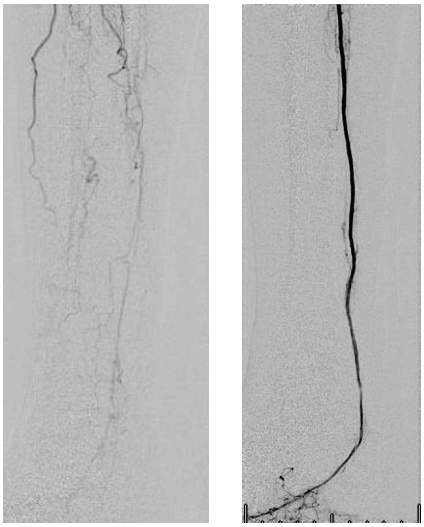
The ADM product is unique on the Canadian market and is the only advanced regenerative matrix technology approved by both Health Canada and the FDA. In comparison to other advanced wound care products available internationally, it is stable at room temperature, ready to use off the shelf, easy to apply, sterile and has been shown in a clinical study[10] and in an increasing number of clinical cases to be highly effective in healing difficult and complex wounds in most cases with only one application.[11] Further, the production of this ADM uses a first-ever automated closed system that ensures quality, consistency and safety of the product. Unlike other tissue-based products that use radiation to ensure sterility, this Canadian ADM uses a validated first-ever liquid sterilization process that does not alter or degrade the product's properties.

A recent Ontario Health Technology Assessment Committee (OHTAC) report has reviewed and recommended ADM products for the treatment of DFUs based on their health treatment economics and efficacy.[12]

Clinical Intervention with ADM

After the ADM product was supplied to our clinic (1st author), a final repair of the artery was conducted. The outcomes of that procedure are shown in the angiograms in Figure 2 and blood pressure measurements in Table 1. The ADM was placed onto each of the three wounds, with each wound prepared by debridement to provide a bleeding wound bed (a requirement to help the ADM incorporate into the wound). A piece of ADM was applied to each wound by cutting a 5 cm x 5 cm piece to approximately 2–3 mm past the margins of the ulcer, with the dermal side in contact with the wound bed. No other prep-

Figure 2: Angiogram of leg before and after revascularization procedure



Before After

Table 1: Blood pressures and indices after revascularization procedure

Artery	Pressure (mm Hg)	Index Value	Index
Brachial	157		
Dorsalis Pedis	75	0.43	
Posterior Tibial	185	1.06	ABI
Great Toe	38	0.22	TBI

aration of the ADM was required prior to use (e.g., thawing or rehydration) as it was supplied in a sterile and hydrated form and stored at room temperature. A non-adherent dressing with moisture-controlling foam with border was used as a secondary dressing to cover the graft. No sutures or staples were needed to fix the ADM onto the wound bed. After applying the ADM graft, the patient was taught how to offload the foot and was seen weekly for follow-up and secondary wound dressing changes.

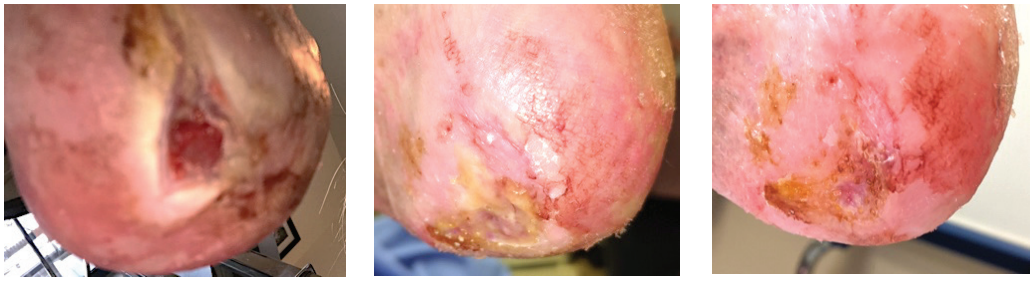
Outcomes

One week following the ADM application, all three foot ulcers had good uptake and integration of the ADM graft into the wound bed (Figures 3, 4, 5). The heel ulcer closed after 10 days post-treatment (Figure 3), and the lateral ulcer closed after three weeks post-treatment (Figure 4). The medial ulcer slowly healed and then presented with a necrotic central area three weeks post-treatment. The medial ulcer required debridement of the necrotic area, and a second ADM graft was applied. The ulcer closed four weeks later (Figure 5).

Discussion

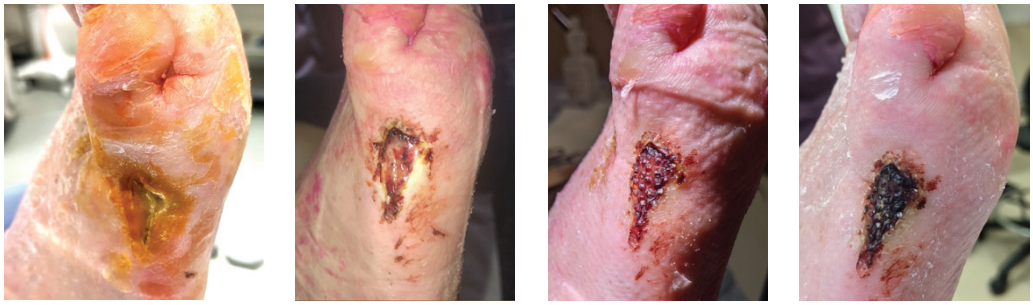
While the focus of most research into wound healing treatments has been on moisture and bacterial control, new approaches that target the instability

Figure 3: Progression of healing of the heel wound from treatment day with the ADM to closure



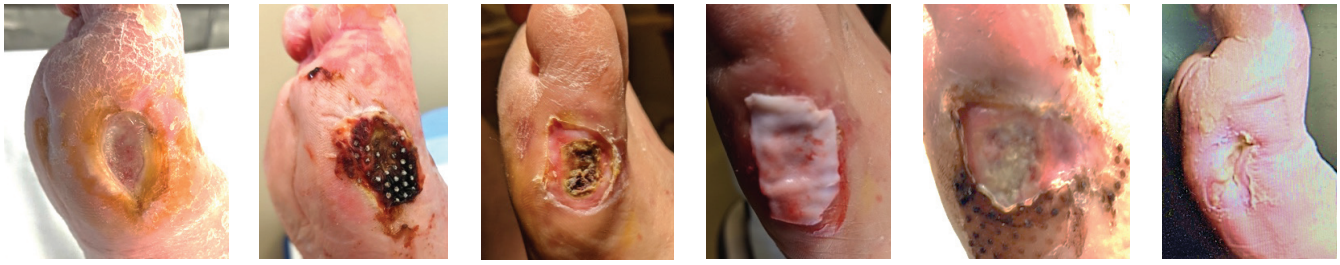
Treatment day | 1 week | 2 weeks

Figure 4: Progression of healing of the lateral foot wound from treatment day with the ADM to closure



Treatment day | 1 week | 2 weeks | 3 weeks

Figure 5: Progression of healing of the lateral foot wound from treatment day with the ADM to closure. Note that at week 3, a necrotic centre was present in the wound. Debridement of the necrotic tissue was conducted and a second piece of ADM was placed onto the wound. The wound then went on to close four weeks later



Treatment day | 1 week | 3 weeks | 4 weeks | 28 weeks

of the extracellular matrix (ECM) in a wound is timely and much needed—particularly for hard-to-heal wounds such as DFUs. Innovative technologies that provide ECM interactions halt the chronic inflammatory cycle and stimulate cells that allow for tissue regeneration and wound healing—and have the potential to accelerate healing.[7,8] In the clinical practice guidelines (CPG) published by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and Society for Vascular Medicine, adjuvant therapies were recommended when DFUs failed to demonstrate improvement of >50% wound area reduction after a minimum of four weeks of standard wound therapy.[9] In this CPG, under item four entitled Wound Care for DFUs, recommendation 9 states "We suggest consideration of the use of extracellular matrix products employing acellular human dermis or porcine small intestinal submucosal tissue as an adjunctive therapy for DFUs when recalcitrant to standard therapy."[9]

This case study illustrates that providing adequate blood flow to a lower extremity in combination with offloading, debridement and HBOT may not be enough to promote complete healing and save a limb. Patients can suffer through multiple attempts over months and even years to achieve wound healing. The multiple attempts can delay healing and may lead to infection with a devastating outcome: amputation as a final resort.

Demonstrated in a pilot study,[10] and now here, is a new product and solution to accelerate the healing of hard-to-heal wounds that traditionally have challenged clinicians and raised fear of amputation among patients. This first-ever Canadian ADM played an important role in saving Mr. W's remaining foot and has the potential to save many others. As a vascular surgeon (1st author) and an advanced wound care nurse (2nd author) dealing with a variety of challenging, hard-to-heal wounds, we believe the use of this new ADM graft to treat non-healing ulcers may help provide the missing elements required to promote successful DFU healing and avoid amputations. ■

Disclosure

Dr. Paul F. Gratzer is the inventor of the technology, Co-Founder and Chief Scientific Officer (CSO) for DeCell Technologies Inc. Dr. Asem Saleh and Dr. Idevania Costa have no conflicts of interest and have not received payment to write this paper.

Acknowledgments

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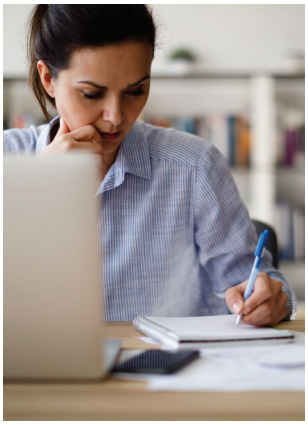

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