Smith+Nephew

A closer look at the use of placental membranes for wound closure

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Charles B. Parks, DPM, is one of the treating physicians at Zuckerberg San Francisco General Hospital and Trauma Center (SFGH)/University of California, San Fancisco (UCSF) in the Department of Orthopedics and specializes in treating lower extremity wounds in patients at high risk of amputation, in patients requiring forefoot reconstruction, and in sports medicine. Dr. Parks completed his three-year surgical residency in podiatric surgery at the Veterans Hospital in San Francisco (VASF) where he worked at many different surgery centers and hospitals in the Bay Area, including VASF, UCSF, and SFGH. In 2016, he joined the UCSF faculty as an Assistant Clinical Professor where he has continued his research and teaching while also holding an Assistant Clinical Professor role at the California School of Podiatric Medicine. In 2018, he was named Chief of Podiatric Surgery at Zuckerberg San Francisco General Hospital. Dr. Parks is a member of numerous professional associations and is double board certified by the American College of Foot and Ankle Surgeons and the American Board of Podiatric Medicine.

Introduction

Chronic wounds, sometimes referred to as stalled wounds, are characterized by a failure to reduce in size by 40% in 30 days. In 2019, there were 8.2 million people in the United States with chronic wounds.[1] Annually, about 1.5 million Americans experience a diabetic foot ulcer and 1 million a venous leg ulcer.[2]

Such wounds can greatly benefit from the application of placental tissues, such as GRAFIX PL◊ and GRAFIX◊ Membranes and STRAVIX PL◊ and STRAVIX◊ Tissue by Smith+Nephew. GRAFIX PL, GRAFIX Membranes, STRAVIX PL, and STRAVIX Tissue all contain native living cells, growth factors, and an extracellular matrix. These products also promote re-epithelization and speed wound closure, even for the most complex of chronic wounds.

Chronic wounds in the United States: Prevalence, risk factors, and best practices

Lower extremity wounds tend to have poor outcomes: for patients with diabetic foot ulcers, there is a 40% recurrence rate within one year.[3] This is particularly troubling because some 85% of all lower limb amputations are preceded by a diabetic foot ulceration.[4-6] For patients with venous leg ulcers, there is a 70% recurrence rate within three months, and 66% of such wounds fail to heal with standard of care in 12 weeks.[7-11] Ultimately, each day a chronic wound remains open, the risk that the patient will develop an infection, be hospitalized, or undergo an amputation increases.

Chronic wounds negatively impact most patients who have them. In fact, 68% of people with chronic leg wounds reported that their life was negatively affected by the wound.[12] Negative effects of chronic wounds on patients include reduced quality of life, as well as reduced worker productivity that can lead to financial burden. Risk factors for developing chronic wounds include obesity, diabetes, smoking, hypertension, and immune deficiency.[13-18]

For chronic wounds to heal, the wound bed must be cared for according to the TIME principles. **T** stands for tissue; **I**, infection and/or inflammation; **M**, moisture imbalance; and **E**, edge of wound.[19-23]

According to the TIME principles, wounds have the best chance at healing when:

- Non-viable tissue is debrided.
- Infection or inflammation is managed through antimicrobial agents or further debridement.
- Moisture balance is maintained.
- An intact epithelium is re-established, restoring skin function.

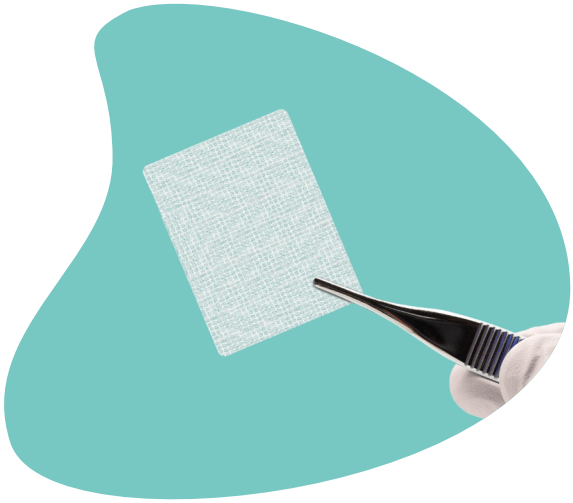
Re-establishing an intact epithelium (or re-epithelization) can be facilitated in chronic wounds by using placental tissues as a wound cover, wrap, or barrier.

Why use placental tissues in the treatment of chronic wounds?

Fresh placental tissues contain native living cells, such as epithelial cells, fibroblasts and mesenchymal stem cells, a collagen-rich extracellular matrix, growth factors, and other mediators.

Since the early twentieth century, placental tissues have been used as a biological dressing to care for wounds, treat burns, and reconstruct ocular surfaces. Although the thinner placental membranes (which consist of amnion and chorion) are utilized most often, there is an increasing interest in using umbilical cord tissue for surgical applications, particularly limb salvage cases, because it is thicker and more durable than placental membranes.

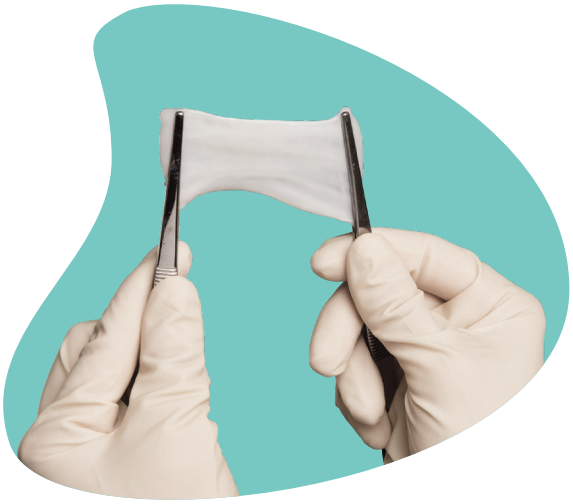
Donors of placental tissues are screened for most diseases.



GRAFIX PL◊ Lyopreserved Placental Membrane

Preserving placental tissues

Before the placental tissue can be used in a clinical setting, it must be preserved to make a shelf-stable commercial product. Most placental tissue products undergo traditional tissue lyophilization, which can kill native living cells, remove growth factors, and alter the structure of the extracellular matrix.[24]



STRAVIX◊ Cryopreserved Umbilical Tissue

Fortunately, there have been advances in preservation techniques in recent years. Prestige Lyotechnology◊, for example, preserves the extracellular matrix, growth factors, and native living cells. This technology produces a product that can be stored at room temperature, thus eliminating the need for ultralow-temperature storage.

Prestige Lyotechnology, a type of lyopreservation, is the preservation method for GRAFIX PL◊ Membrane and STRAVIX PL◊ Tissue. Cryopreservation is the preservation method for GRAFIX◊ Membrane and STRAVIX◊ Tissue, both of which must be stored in a freezer until use. Both the cryopreservation and lyopreservation processes retain the placental tissue extracellular matrix, growth factors and other mediators, and native living cells.

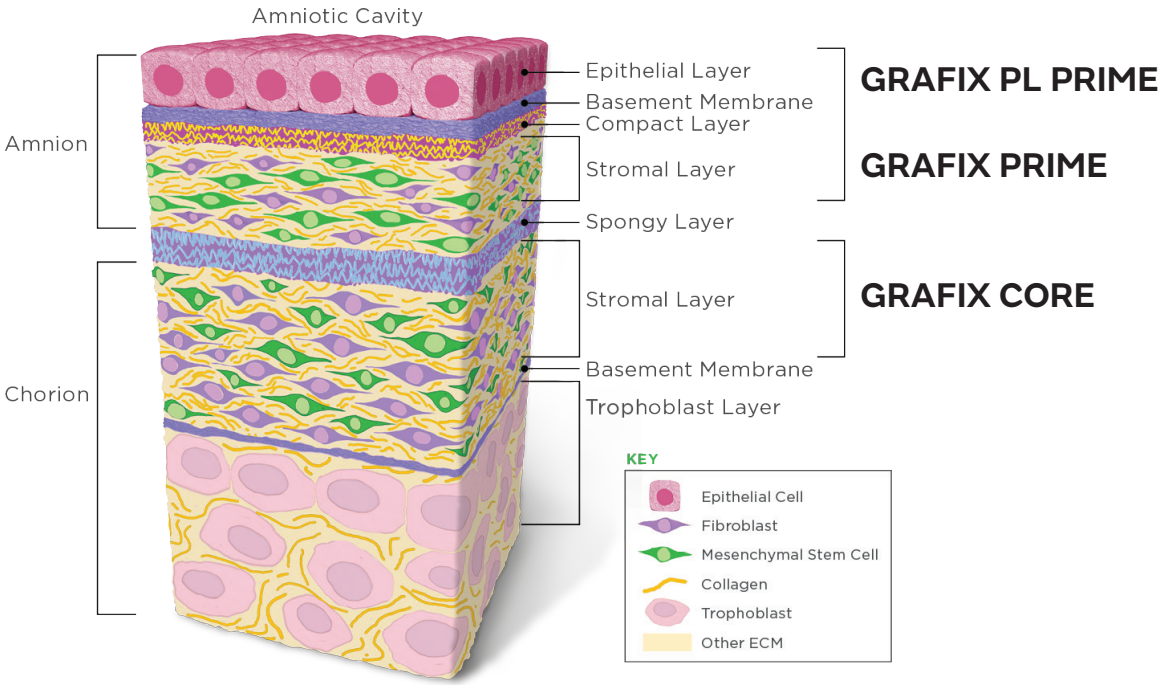
Why use GRAFIX PL◊ and GRAFIX◊ Membranes to treat chronic wounds?

GRAFIX PL and GRAFIX Membranes are human placental membranes composed of an extracellular matrix, growth factors, and native living cells. They were developed as wound covers for a wide variety of acute and chronic wounds in head-to-toe locations. They naturally conform to complex anatomic locations and may be used over exposed bone, tendon, joint capsule, muscle, and hardware. Each lot is tested to ensure that native living cells are present across at least 70% of the membrane.

GRAFIX PL PRIME◊ and GRAFIX PRIME◊ Membranes are derived from amnion. They contain an epithelial layer with epithelial cells, as well as a stromal layer with fibroblasts and mesenchymal stem cells. GRAFIX CORE◊ Membrane is derived from chorion. It contains a stromal layer with fibroblasts and mesenchymal stem cells, is trophoblast free, and contains no epithelial cells. The three products differ only slightly in terms of their tensile strength and handling properties, but they are structurally and functionally equivalent in terms of efficacy and outcomes.

Both GRAFIX PL PRIME and GRAFIX PRIME Membranes come in different sizes, ranging from 1.5 cm x 2 cm to 5 cm x 5 cm. Both are also offered in 16 mm discs. GRAFIX CORE Membrane is available in 3 cm x 4 cm and 5 cm x 5 cm sizes. A variety of sizes allows for minimal waste and decreased costs to the health care system. GRAFIX PL PRIME Membrane is packaged between two mesh sheets that can be easily peeled apart to release the membrane, whereas GRAFIX PRIME and GRAFIX CORE Membranes are supplied on a plastic applicator.

Cross-section of placental membranes



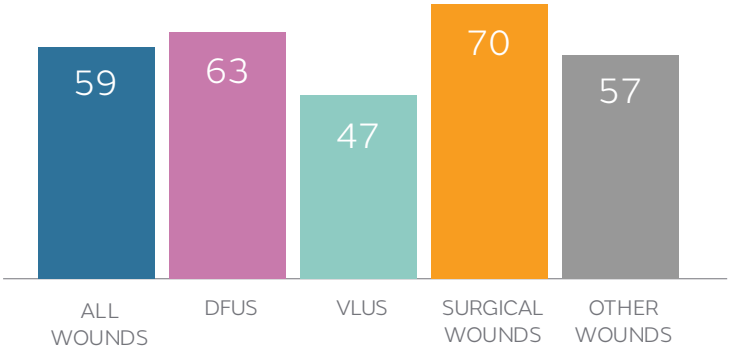
What is the evidence for using GRAFIX PL◊ and GRAFIX◊ Membranes?

Robust evidence supports the effectiveness of GRAFIX PL and GRAFIX Membranes. In 2019, Ananian et al. published a retrospective, open-label, multicenter study of GRAFIX PL Membrane in the management of chronic wounds that had not responded to standard of care.[25] There were 78 patients in the study, with 98 wounds, and most of the patients had more than two comorbidities. The wounds included venous leg ulcers, diabetic foot ulcers, and surgical wounds, among other wound types, with an average wound area of 13.3 cm^2. The mean wound duration before treatment with GRAFIX PL Membrane was just under nine months. The authors showed that the application of GRAFIX PL Membrane caused 59% of non-healing wounds to achieve complete closure. It took median 63 days for wounds treated with GRAFIX PL Membrane to achieve closure, with median six graft applications.

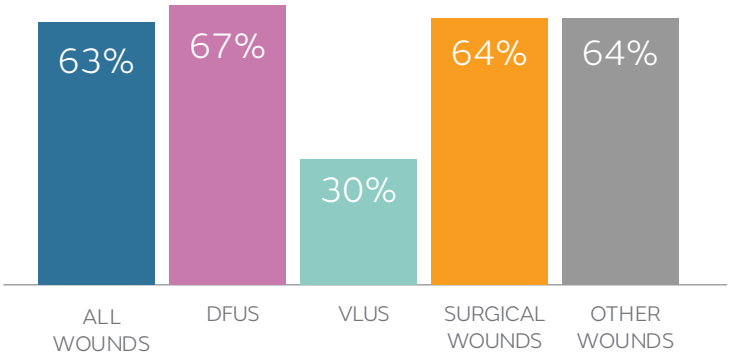
Patient Demographics and Baseline Wound Characteristics	
Patients	78
Wounds	98
Age (mean)	62.7 years
Patients with ≥ 2 comorbidities	65%
Wound area (mean)	**12.7 cm^2**
Wound duration prior to treatment (mean)	**8.9 months**
Wound >12 months duration	20.4%

Most of the clinical studies conducted to analyze the impact of GRAFIX PL and GRAFIX Membranes on chronic wounds have tended to focus on diabetic foot and venous leg ulcers. For that reason, the recent publication of a study in *Wounds* is particularly welcome: it shows that non-diabetic and non-venous chronic wounds of the upper and lower extremities also respond well to GRAFIX Membranes.[27] Johnson et al. performed a study involving 92 patients with 104 such wounds.[27] The wounds were 12.7 cm^2 in size, with a wound duration before treatment of 3.9 months. According to these authors, 83.7% of the wounds—burns, pressure injuries, surgical and traumatic wounds, and necrotizing fasciitis, among others—completed closure within median 41 days, with a median of three grafts per wound.

Proportion of Patients Who Achieved Closure[25]

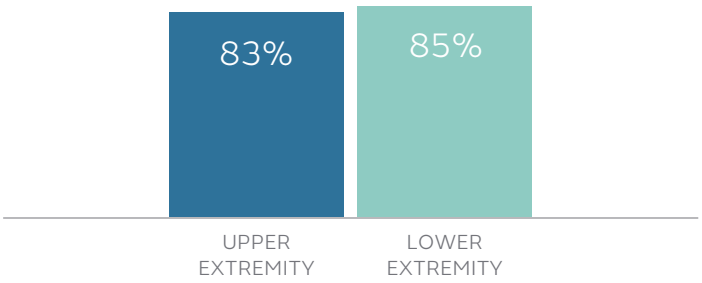


Median Days to Closure[25-26]

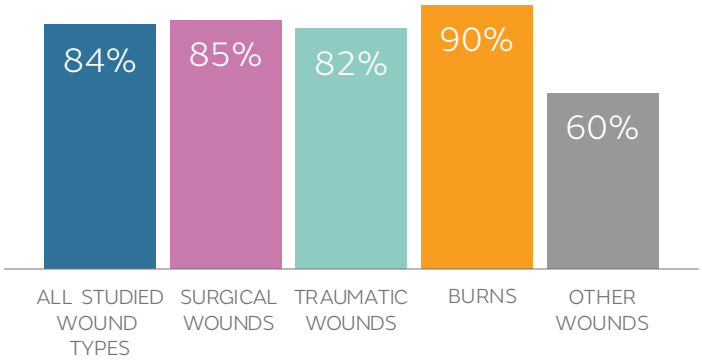


There are many large clinical trials and studies that analyze the efficacy of GRAFIX PL and GRAFIX Membranes.[25, 27-33] Altogether, according to these studies, the closure rates for wounds treated with the membranes range from 53% for the most complicated refractory venous leg ulcers to up to 83% for non-diabetic and non-venous chronic wounds.

Wound Closure by Location[27]



Wound Closure by Wound Type[27]



Why use STRAVIX◊ Tissue in the treatment of chronic wounds?

Like GRAFIX PL and GRAFIX Membranes, STRAVIX Tissue is preserved to maintain the extracellular matrix, growth factors, and native living cells. It is conforming, adapting to injured tissue. STRAVIX Tissue is well suited for surgical soft tissue repair in the operating room such as limb salvage, and it is commonly used across many surgical specialties, with usage including wraps over tendon repair sites.

STRAVIX Tissue is composed of the umbilical amnion and Wharton's jelly of human umbilical cord (which contains hyaluronic acid). To prevent an immune response in the patient receiving STRAVIX Tissue, the blood vessels in the umbilical cord are removed. Because the placement of the blood vessels within the umbilical cord varies from donor to donor, the appearance and thickness of the final product may vary. It is available in three sizes (2 cm x 2 cm, 2 cm x 4 cm, and 3 cm x 6 cm) and can be sewn or stapled together to make larger pieces or trimmed to make it smaller.

Patient Demographics and Baseline Wound Characteristics	
Patients	10
Age	59.8 years
BMI (mean)	28.6 kg/m^2
NPWT Used	9/10 patients
Wound size	**45.9 cm^2**

What's the difference between GRAFIX PL and GRAFIX Membranes and STRAVIX Tissue? The primary difference is that STRAVIX Tissue is more durable. It is also thicker, ranging from 1 mm to 3 mm in thickness, and has greater tensile strength than GRAFIX PL and GRAFIX Membranes.

What is the evidence for using STRAVIX◊ Tissue?

In 2018, Dr. McGinness investigated the use of STRAVIX Tissue to manage large, open soft tissue defects with gas gangrene.[34] The 10 patients chosen for the study had recently undergone surgery that resulted in a large, open defect with exposed structures, with wounds averaging 45.9 cm^2 in size.

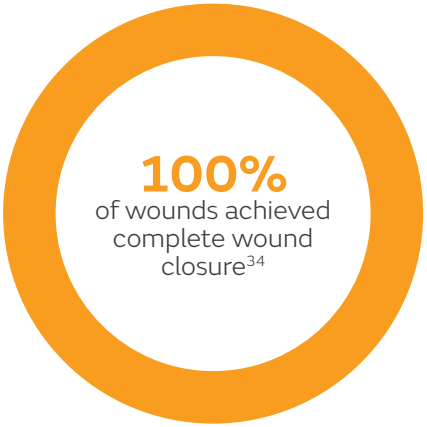
All patients in the study had a history of diabetes, and many had coronary heart disease, congestive heart failure, hypertension, and other comorbidities. Because the patients had inadequate surrounding soft tissue or skin, surgical wound closure was not possible. The patients were not candidates for autologous skin grafts or flaps.

Before treatment with STRAVIX Tissue, the patients received aggressive debridement to remove infected, necrotic, and devascularized tissue. After irrigation by motorized pulse lavage, STRAVIX Tissue was fenestrated or sutured into the wound bed. The patients were administered intravenous antibiotics during their hospital stay, and nine of 10 of these patients received negative pressure wound therapy (NPWT) after surgery. It is important to note that there was no debridement performed after surgery.

Each patient achieved complete wound closure with one application of STRAVIX Tissue in 13.4 weeks on average. Remarkably, the mean length of these patients' hospitalization was only nine days. This is particularly significant compared to a large database review of over 11,000 patients with gas gangrene of the lower extremity that found the average length of hosptial stay to be 31.1 days.[35]

In 2020, Mullins et al. investigated the use of STRAVIX Tissue in the management of complex wounds with exposed bone, tendon, hardware, or other underlying structures.[36] The study was designed to be a quick pilot study to gather preliminary prospective data on a single application of STRAVIX Tissue. Ten patients with 12 wounds were treated over a four-week period. Wounds included venous leg ulcers, diabetic foot ulcers, pressure injuries, traumatic wounds, and one surgical wound. The average wound size was 16.5 cm^2, and the mean wound duration before treatment was 10 months. Eighty percent of the wounds achieved full granulation in four weeks or less. The time to complete granulation was about 17.5 days. In addition, 30% of the wounds achieved complete closure in four weeks or less.

These data show good progression to wound closure in a short period of time. If the patients had been followed for longer, it is anticipated that more patients would have achieved complete wound closure, which occurred in the study by McGinness et al. discussed earlier.[34] Moreover, the data in this study support the use of STRAVIX Tissue as a cover until the wound is fully granulated, after which the wound could be ready for a skin graft or flap at the physician's preference.

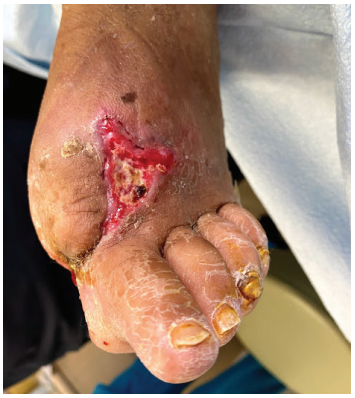


Case studies

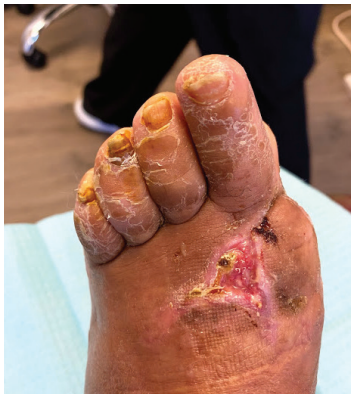
Case study no. 1: Treatment of a chronic wound with GRAFIX PL◊ Membrane

A 48-year-old woman presented with a 9 cm^2 chronic dorsal foot wound with a mixed fibrogranular wound base. The patient had a history of foot infection and previously underwent a partial first-ray resection. She had uncontrolled type 2 diabetes with glycosylated hemoglobin (HbA1C) of 13.5. She was also obese and had hypertension.

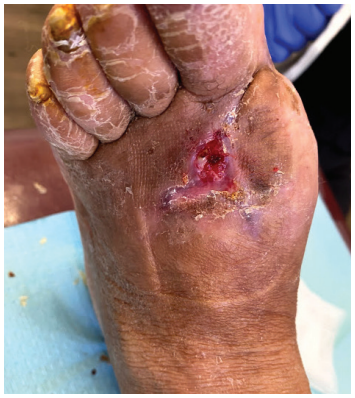
The wound was first irrigated, and all non-viable soft tissue was debrided. Then, after thorough excisional debridement, a GRAFIX PL Membrane was applied over the wound. After two applications of GRAFIX PL Membrane with serial debridement, the wound base was granular, and the wound was smaller. In total, there were six weekly applications of the GRAFIX PL Membrane. At six weeks, there was complete wound closure.



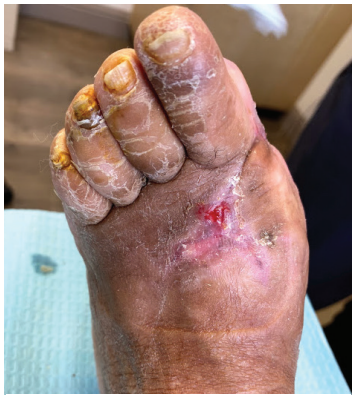
1. Initial Presentation



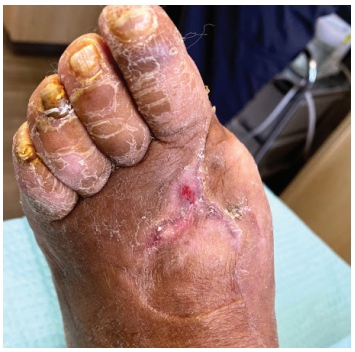
2. Application #2



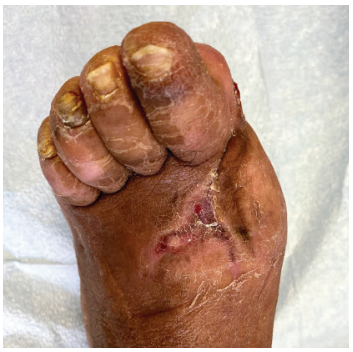
3. Application #3



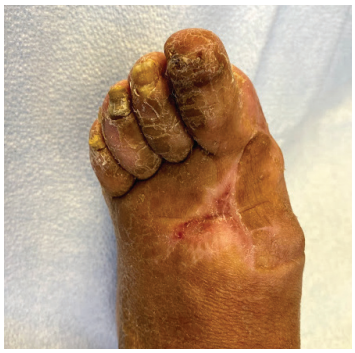
4. Application #4



5. Application #6



6. One week later



8. Closure achieved

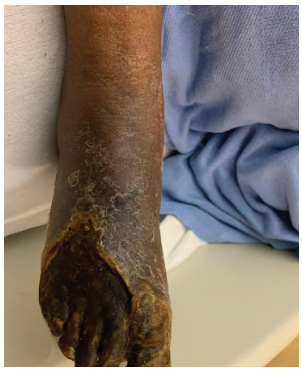
Case study no. 2: Treatment of an amputation site with GRAFIX◊ Membrane and STRAVIX◊ Tissue

A 59-year-old man presented with forefoot gangrene with a surgical defect. He had type 2 diabetes, peripheral vascular disease, and end-stage renal disease requiring daily hemodialysis. Before amputation of the forefoot, he underwent an angioplasty to revascularize the leg.

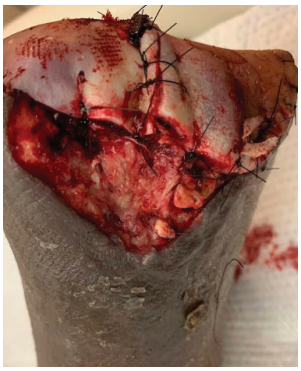
After amputation, there was a 32 cm^2 dorsal foot wound, which was covered with STRAVIX Tissue. NPWT was applied for one week. At four weeks, the graft was still incorporating, as the wound continued to shrink in size.

At six weeks, the wound was fully granular with a little bit of the plantar fat pad exposed. The initial thought was to take the patient back to the operating room to debride the fat pad and perhaps regraft the wound. However, by the time of the surgery, most of the fat pad was granulized over. For that reason, minimal debridement was performed, and the fat pad was tacked in place. Then, GRAFIX PRIME◊ Membrane was placed over the wound.

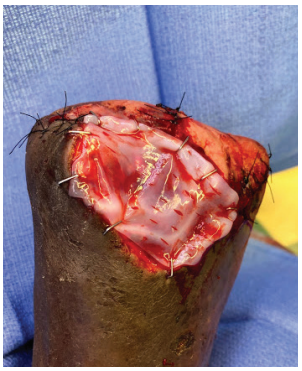
Ten weeks after the STRAVIX Tissue application and one week after the GRAFIX PRIME Membrane application, the grafts were fully incorporated. The wound continued to decrease in size, and, at week 18, there was complete wound closure. In total, there was one STRAVIX Tissue application and one GRAFIX PRIME Membrane application.



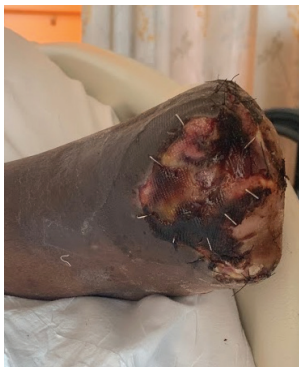
1.Amputation site



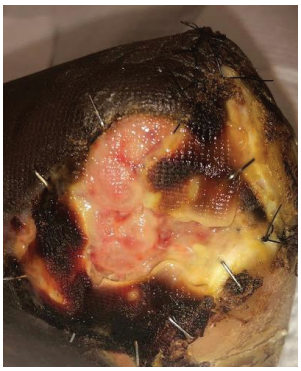
2.Initial Amputation



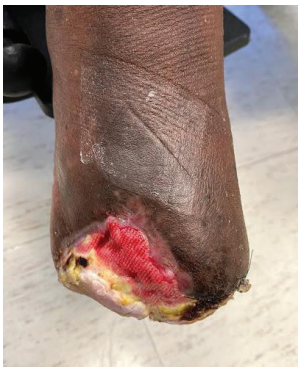
3. Application of STRAVIX◊ Tissue



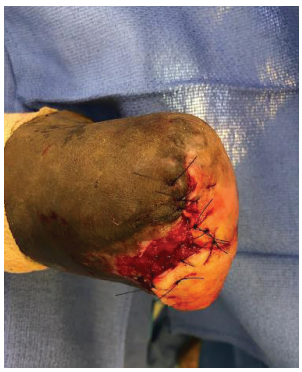
4. 12 days after STRAVIX Tissue application



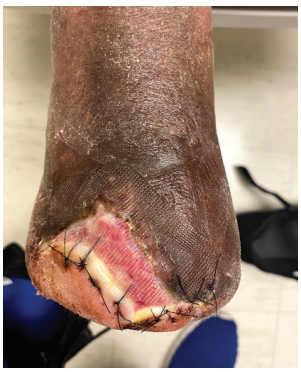
5. 4 weeks after STRAVIX◊ Tissue placement



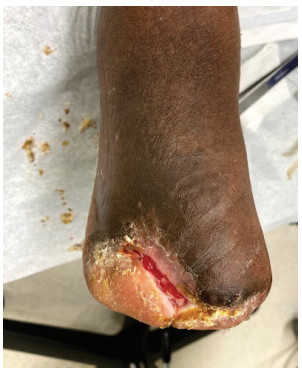
6. 6 week follow up



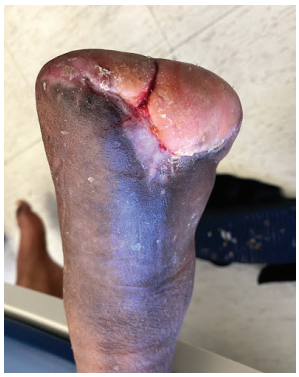
7. OR debridement with GRAFIX PRIME◊ membrane placement at 9 weeks



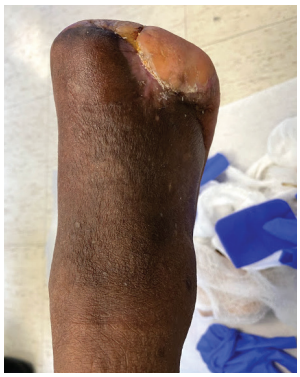
8. 10 weeks post GRAFIX PRIME Membrane



9. 12 weeks post GRAFIX PRIME Membrane



10. 14 weeks post GRAFIX PRIME Membrane



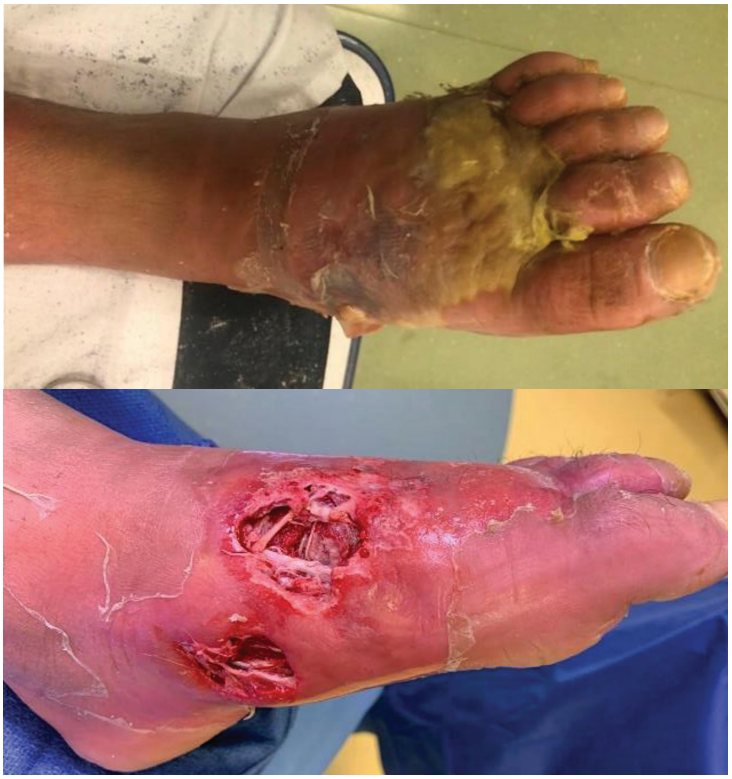
11. Closure at 18 weeks

Case study no. 3: Treatment of a postoperative infected wound with STRAVIX◊ Tissue

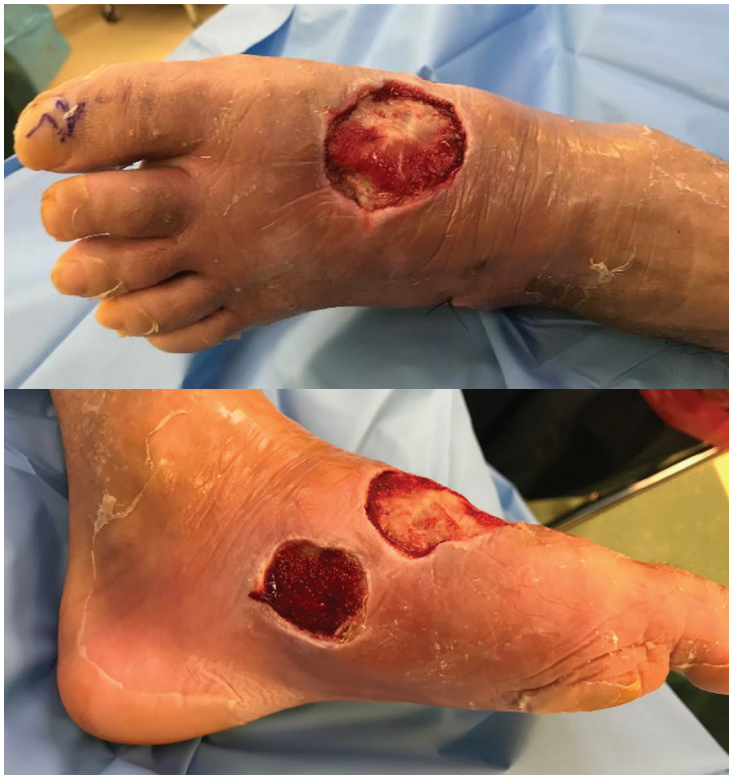
A 48-year-old man presented with a Lisfranc fracture that was treated with open reduction and internal fixation surgery. The patient was HIV positive and had progressive macular hypomelanosis. He also had bipolar disorder and polysubstance dependence.

After surgery, the patient did not attend post-surgery follow-up appointments. When the patient eventually returned for treatment, he presented with a deep-space infection that went down to the hardware and joints. He underwent irrigation and debridement to remove the non-viable tissue and hardware. He also received six weeks of intravenous antibiotics (nafcillin) to resolve the infection.

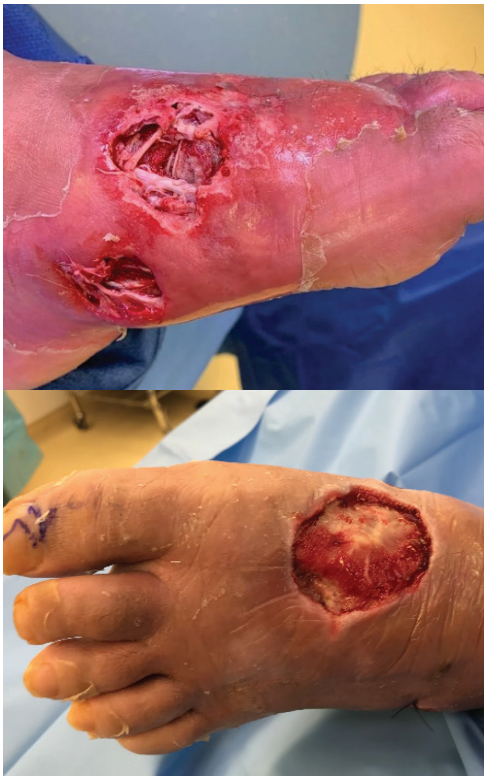
He ultimately had two wounds on his foot—one dorsal and the other medial—that went down to the joint and joint capsule. One application of STRAVIX Tissue was applied with a non-adherent dressing, and NPWT was applied for one week. At one month, the wounds were smaller. More importantly, the wounds were completely granular and filled in. At four months, both wounds were fully closed.



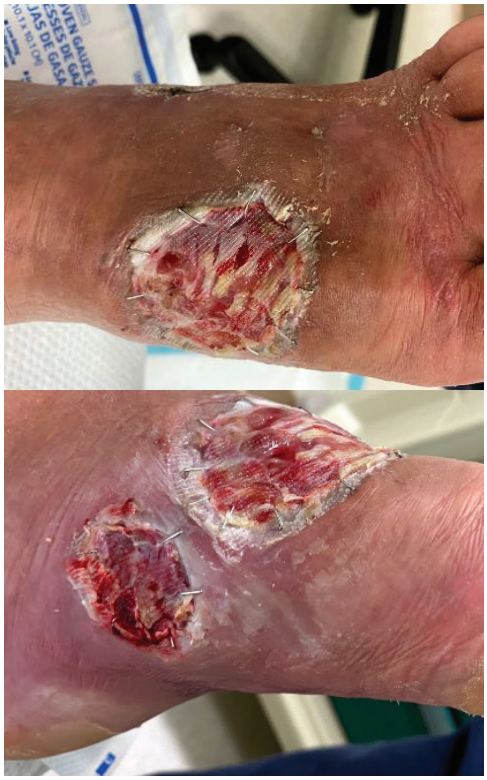
1. Preoperative



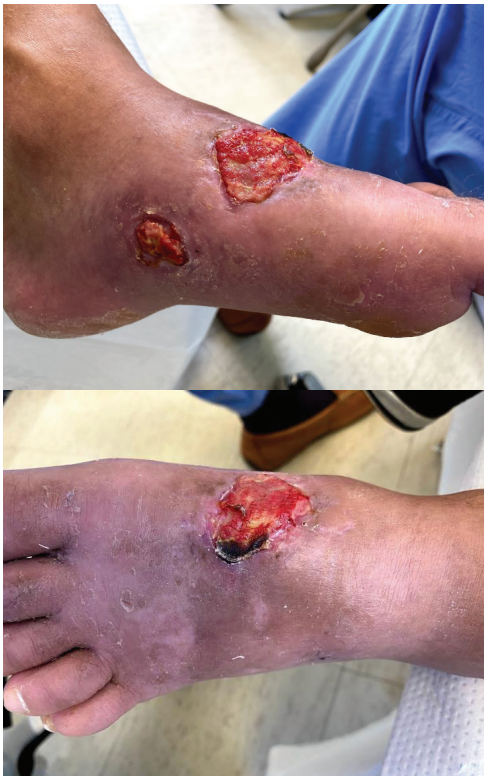
2. Procedure



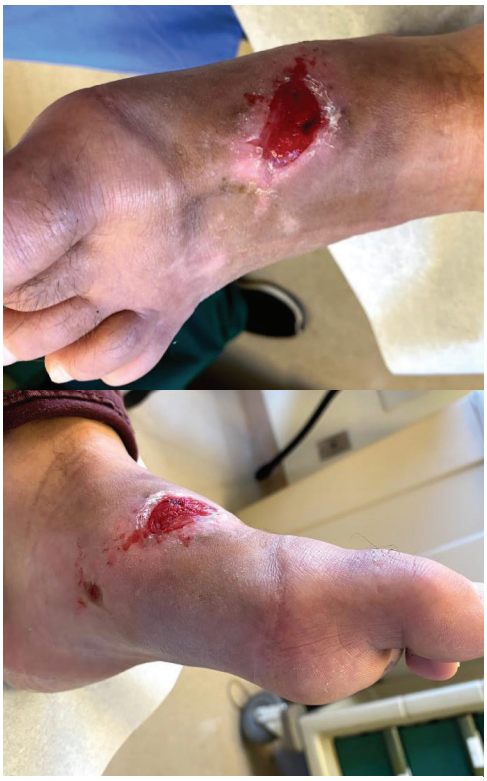
Initial presentation
STRAVIX® Tissue application



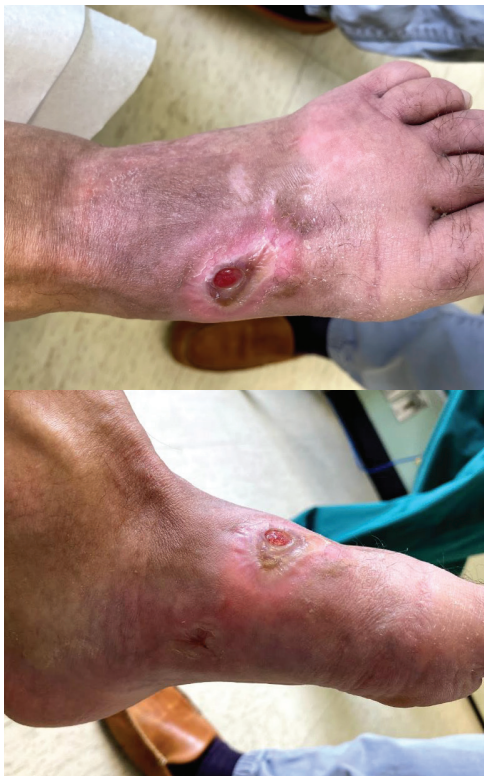
1 week after application



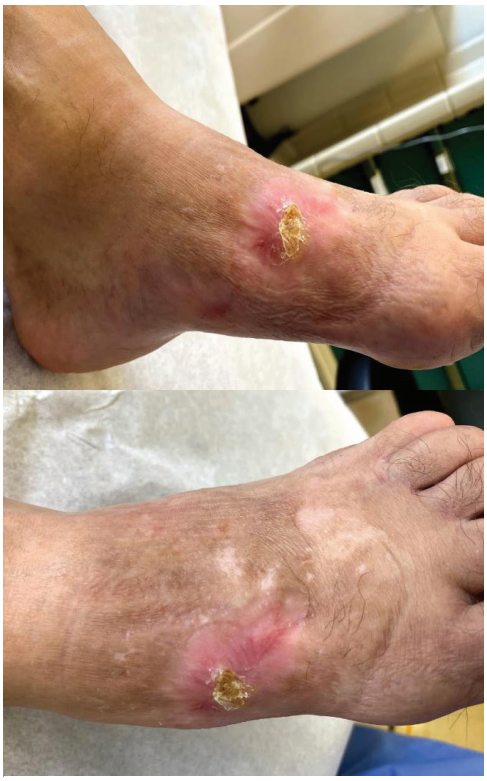
One-month status post-STRAVIX®
Tissue application



Two months status post-STRAVIX® Tissue
application



Three months status
post-STRAVIX® Tissue application



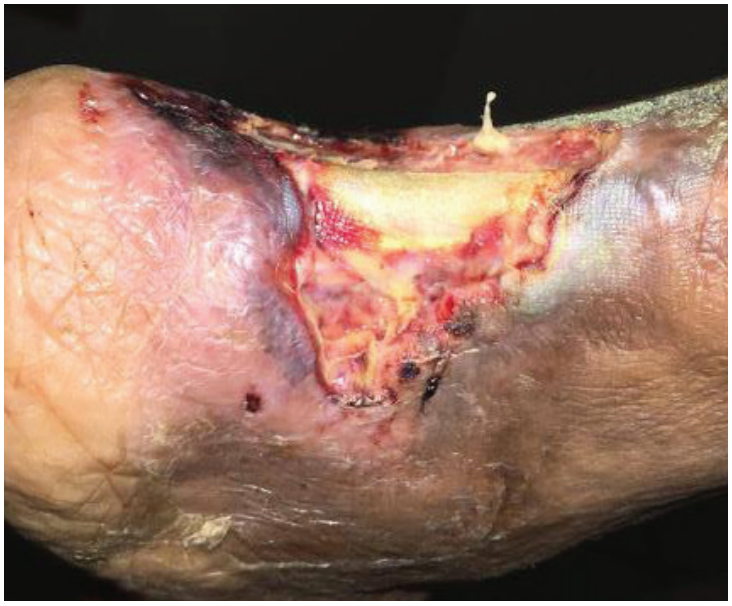
Four months -
Closure of both wounds

Case study no. 4: Treatment of a posterior ankle wound with an exposed Achilles tendon with STRAVIX◊ Tissue

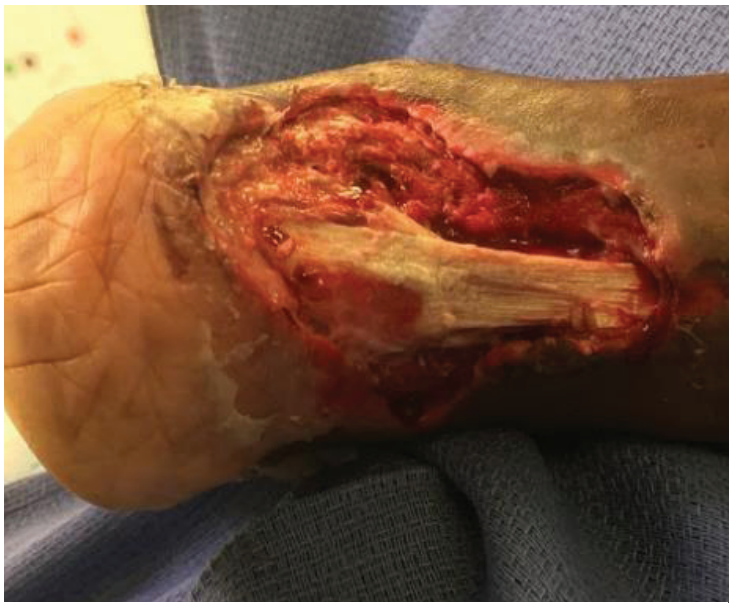
A 59-year-old woman presented with a full-thickness posterior ankle ulcer with exposed Achilles tendon. The patient had type 2 diabetes, chronic limb-threatening ischemia, calciphylaxis, hypertension, and end-stage renal disease that required hemodialysis three times a week. The ankle ulcer was caused by pressure and calciphylaxis, and the soft tissue was affected with methicillin-resistant *Staphylococcus aureus* (MRSA).

After two sharp debridements were performed, the wound left the Achilles tendon exposed. The wound was covered in two pieces of STRAVIX Tissue that were stapled together, over which a non-adherent dressing was placed. STRAVIX Tissue was chosen because of the size and depth of the ulcer and because the patient had complex comorbidities known to affect wound healing negatively. After STRAVIX Tissue was applied, the patient underwent NPWT for one week. In addition, the patient underwent an angiographic procedure with interventional popliteal angioplasty for near-total occlusion of her left tibial-peroneal trunk. She also received two weeks of post-hemodialysis antibiotics (vancomycin).

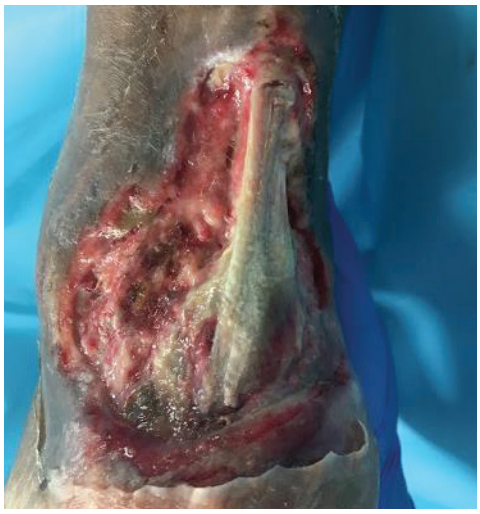
After six weeks, the wound was smaller and granular, with some creeping granulation over the Achilles tendon. The wound continued to grow smaller, and, at 15 weeks, complete wound closure occurred. One year later, the wound was still closed, and she had good range of motion of the ankle joint.



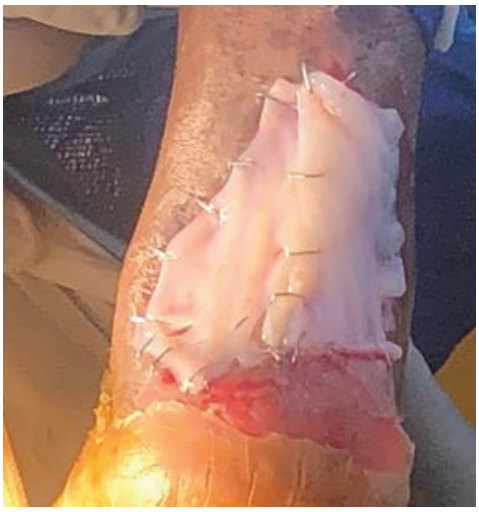
1. Initial presentation



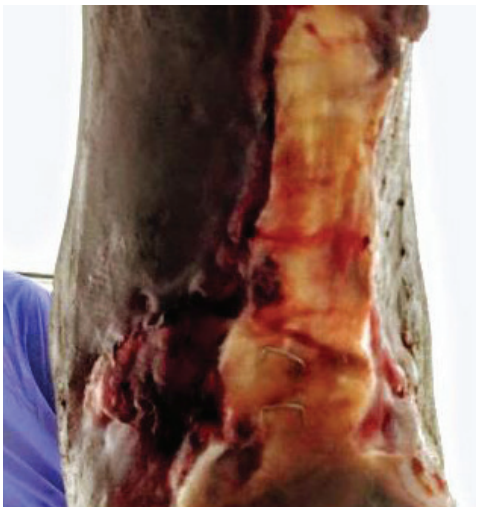
2. Follow up: s/p 2nd sharp debridement with 5 days of NPWT



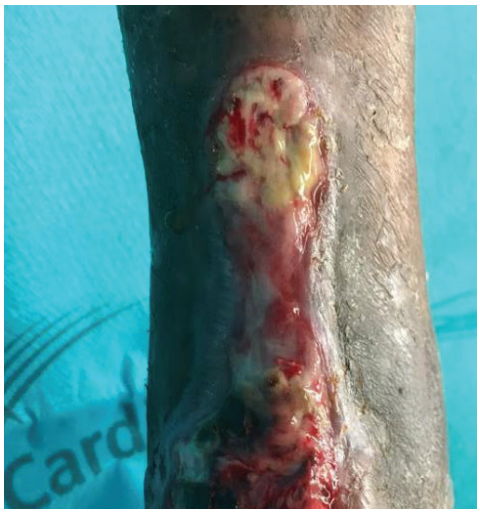
3. Pre-application



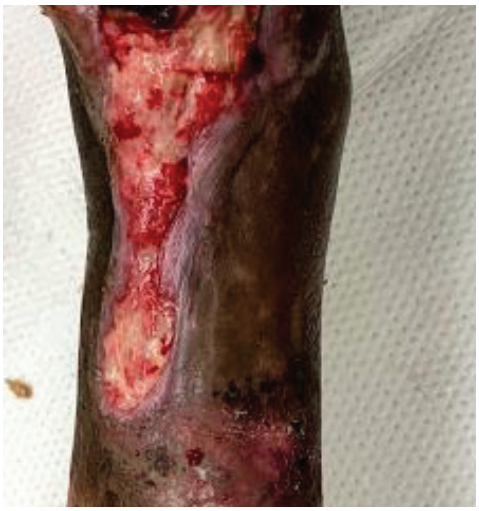
4. Application of STRAVIX® Tissue
8 cm x 4 cm x 0.7 cm



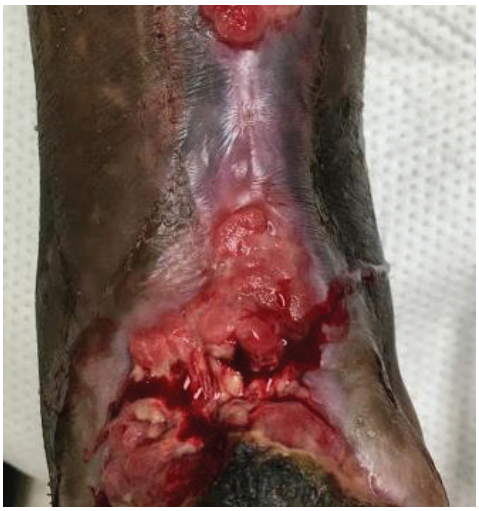
5. 6 weeks after application



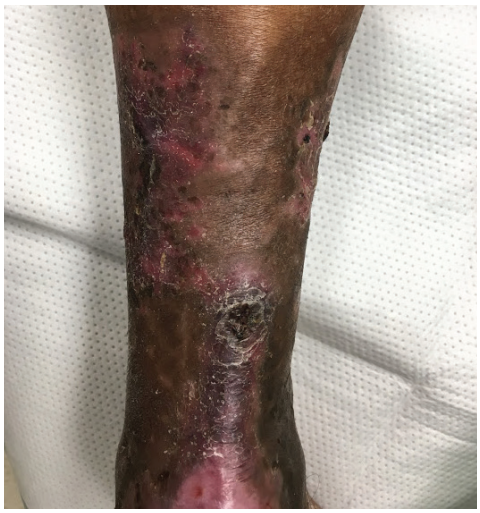
6. 7.5 weeks
6.2 cm x 2.1 cm x 0.2 cm



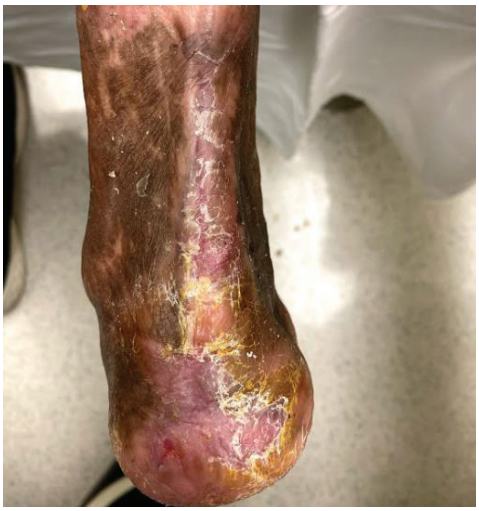
7. 8.5 weeks
5.5 cm x 2.1 cm x 0.2 cm



8. 9.5 weeks
Proximal: 1.5 cm x 1.5 cm x 0.1 cm
Distal: 2 cm x 2.2 cm x 0.1 cm



9. Closed at 15 weeks

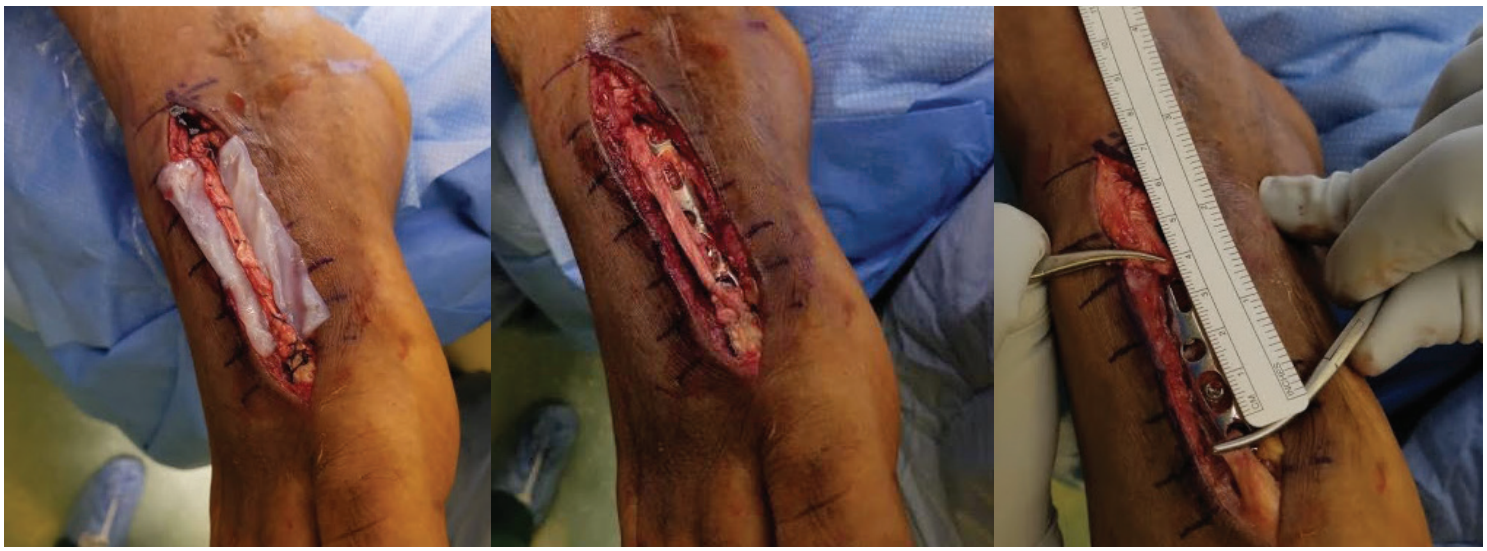


10. Remains closed at 1 year

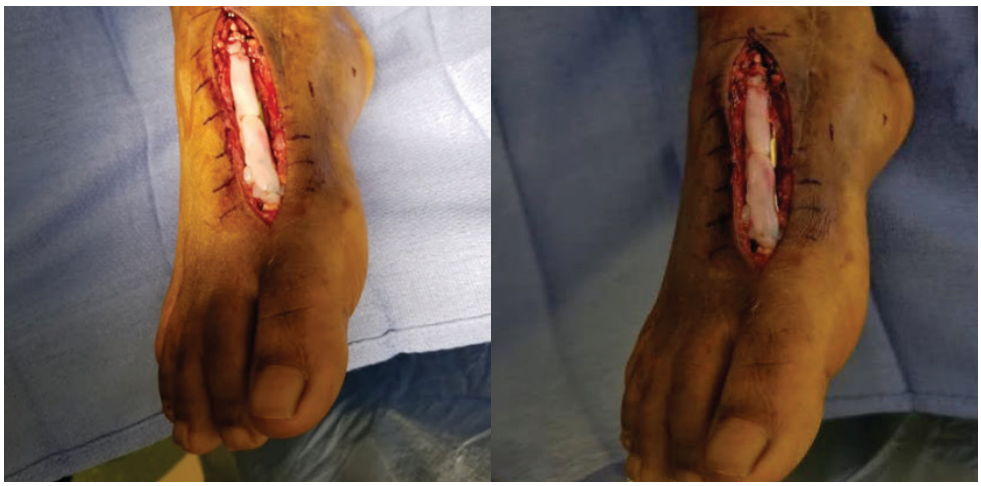
Case study no. 5: Treatment of an extensor hallucis longus rupture repair with STRAVIX◊ Tissue

A 42-year-old man presented with degeneration of the talonavicular joint after talonavicular fusion surgery with a dorsal spanning plate. Unfortunately, the plate ruptured his extensor hallucis longus tendon. By the time he was taken to the operating room, which was only one week after the rupture, there was a 4 cm gap from end to end.

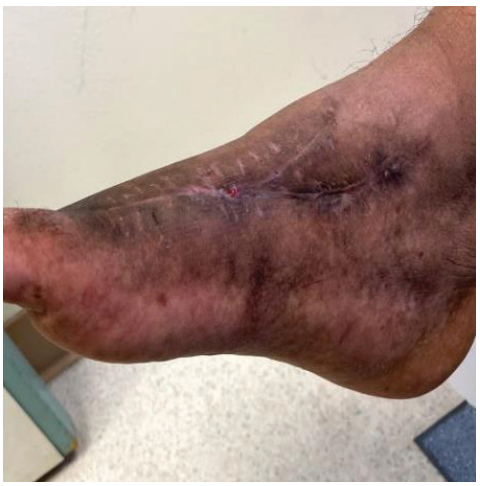
After the extensor hallucis longus tendon repair, the repair and the tendon itself were wrapped in STRAVIX Tissue and sutured in place. The patient was kept non–weight bearing in a short leg cast for six weeks. At six weeks, he was transferred to a controlled ankle motion (CAM) boot. Full closure of the wound occurred eight weeks after surgery.



1. EHL Rupture Repair



2. Intra-op



5. Eight weeks post-op

Conclusion

A growing body of research shows that chronic wounds that are challenging to treat may respond well to placental tissues. There is a variety of skin substitute products available on the market, but, unfortunately, the quality of most of these products is greatly reduced during the preservation process.

Thanks to the advanced preservation methods pioneered by Smith+Nephew, GRAFIX PL◊ and GRAFIX◊ Membranes and STRAVIX◊ Tissue retain all components of fresh placental tissue, including native living cells, as well as growth factors and an intact extracellular matrix. Studies have proven that the Smith+Nephew suite of placental tissues hastens wound closure, thus improving patients' health and quality of life.

Studies have demonstrated that placental tissues such as those used in GRAFIX PL, GRAFIX Membranes, STRAVIX PL, and STRAVIX Tissue hasten wound closure.[27,31] Achieving wound closure can help patients get back to their normal daily routines, improving quality of life.

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