**Abstract:** The extracellular matrix (ECM) of the dermis is a critical structural component required for normal wound healing. The ECM, along with its key signaling components, provides the support structure necessary for fibroblasts, immune cells, and keratinocytes. When ECM activity is dysfunctional, the normal wound healing process is compromised, leading to slow, irregular repair, which may result in the development of chronic wounds. To replace dysfunctional ECM, several strategies have been developed to promote the development of a proper ECM or to replace the ECM entirely. One such method is the use of small intestine submucosa (SIS) to replace the nonfunctional ECM. Small intestine submucosa closely mimics the normal ECM of the human dermis despite being of porcine derivation. Small intestine submucosa wound matrix is an example of an available ECM-based biomaterial that has demonstrated improvements in wound management in the clinical setting.

**Key words:** extracellular matrix, wound healing, small intestine submucosa

Human skin is the largest organ in the human body and acts as a barrier to infection. This barrier function depends on the presence of a properly working dermal extracellular matrix (ECM). The dermis is largely composed of fibroblasts that secrete and maintain ECM components, but also contains epidermal appendages, nerves, vasculature, and inflammatory cells. The ECM provides the epidermis structural support while also playing a key role in the strength, flexibility, and structural support of the dermis. The ECM itself is a complex scaffold of many structural and functional proteins, but is primarily composed of filamentous type I and III collagens and elastin. The lesser components of the ECM consist of glycoproteins, glycosaminoglycans, cytokines, and growth factors, all of which are required under normal and wound healing conditions. Collagen provides structural support to the skin and functions in signaling, while elastin lends elasticity. Fibronectin provides attachment sites for various cell types and helps to coordinate ECM remodeling. Heparin and hyaluro-
nan function in matrix hydration, bind growth factors, and act as signaling molecules during tissue repair and regeneration. Growth factors aid in matrix turnover by stimulating production of matrix components, angiogenesis, and cellular migration. Meanwhile, matrix metalloproteinases (MMPs) also function in matrix turnover by degrading the ECM to facilitate cell migration and ECM remodeling. Collectively, these components of the ECM serve to create a complex and dynamic scaffold that constantly interacts with itself and its surroundings to maintain homeostasis, while regulating the healing process. Restoring these dynamic interactions and returning to this homeostasis is required during injury or tissue loss.

**Coordination of wound healing process with ECM activity.** Wound healing normally proceeds in a 4-phase process of hemostasis, inflammation, proliferation, and remodeling. The remodeling phase can begin as early as day 8 but can last for months. These 4 phases and their physiological functions must occur in the appropriate sequence, timing, and duration for wound healing to occur properly in the minimal amount of time. In contrast to acute wounds, chronic wounds typically do not follow this organized process, but enter a state of pathologic inflammation or proliferation.

The most obvious feature of chronic wounds is the failure to reepithelialize, which is due to a failure of keratinocyte migration rather than proliferation. Failure of migration may occur due to the lack of a functional ECM, when fibronectin and collagen molecules needed for the cells to attach to the surface and migrate are deficient. The composition of the ECM must be accurate and precise for the epithelial cells to detach from the wound edge and to migrate across the ECM scaffold. The abnormal ECM delays reepithelialization, which is detrimental, as the likelihood of successful healing decreases the longer a wound remains open.

Additionally, chronic wounds frequently harbor other factors that may impede ECM function, such as high concentrations of ECM-degrading proteases, a misregulated rate of matrix repair and degradation, increased numbers of senescent fibroblasts, or altered cytokine expression and distribution. As a result, new ECM cannot be reorganized or becomes unresponsive to critical signals in the healing response and, ultimately, proper healing of the wound cannot take place.

As the ECM is essential for proper wound healing, strategies that correct ECM dysfunction may be beneficial in wound management.

**Biomaterials Used in Wound Healing**

Multiple therapies employing biomaterials for wound management have been developed. These bioengineered skin and soft tissue substitutes are derived from allogenic or xenographic tissue, synthetic materials, or a combination of both, and may be either acellular or cellular. One example of a commercially available biosynthetic wound dressing is Biobrane® (Smith & Nephew, London, UK), a biocomposite dressing composed of a silicon/nylon matrix in which porcine dermal collagen has been embedded. Acellular dermal matrix materials, which are derived from human tissue with all cellular components removed, include AlloDerm® (LifeCell Co, Branchburg, NJ), an acellular cadaveric dermis, and GraftJacket® (KCI, San Antonio, TX), an acellular human dermal-based regenerative tissue matrix.

Living cell therapies can be derived from human keratinocytes or fibroblasts, cultured epithelial autografts or xenographic sources. DermaGraft® (Shire Regenerative Medicine, San Diego, CA), a human fibroblast-derived dermal substitute, is one such model derived from cryopreserved human foreskin fibroblasts and collagen applied to a bioabsorbable mesh. Extracellular matrix-specific components for wound treatment involve both single ECM component materials, such as hyaluronan (eg, Jaloskin®, Anika Therapeutics Inc, Bedford, MA), and structurally intact ECM scaffolds, such as porcine-derived small intestine submucosa (SIS) biomaterial (eg, OASIS® Wound Matrix, OASIS® Ultra Tri-Layer Matrix [Healthpoint Biotherapeutics, Fort Worth, TX]).

These materials can help support the body’s own healing process by providing a pre-made ECM material.

**Small intestine submucosa biomaterial.** One current therapeutic strategy is small intestine submucosa
hydrates and lipids. The collagen network provides a protein (mostly collagen), and smaller amounts of carbohydrates and lipids. The SIS biomaterial forms a cross-linked 3-dimensional matrix, which is composed of 90% water, 10% protein (mostly collagen), and smaller amounts of carbohydrates and lipids. The collagen network provides a scaffold for tissue growth.

As a biomaterial, SIS possesses multiple properties that make it an ideal advanced therapeutic wound treatment option. The SIS biomaterial has low porosity value, which suggests it may be an effective barrier to wound bed dehydration. Small intestine submucosa also exhibits strength and flexibility similar to that of the tissue from which it is derived, even after long-term storage in lyophilized form. In vitro cell culture studies with SIS biomaterial as the substrate have shown SIS provides an environment that allows for proper fibroblast and keratinocyte cell attachment, proliferation, and migration, similar to wounded tissue.

The 2 commercially available SIS biomaterials are supplied as sterile single-use packages in multiple sizes, can be applied to a broad range of wound sizes, and do not require special handling or storage as needed for living products. The products can be fixed to the wound using common fixtures such as butterfly stitches, sutures, or staples, and any appropriate, nonadherent secondary dressing can be used. It is typically reapplied every 3-7 days until the wound has reepithelialized.

The difference in the thickness of these SIS preparations expands the range of wound types that can be managed with SIS biomaterial. The first formulation is composed of a single layer of ECM that is 100 microns thick, while the second formulation is a triple layer 300 microns thick. The greater thickness of the second formulation allows for improved ease of fixation on the wound, including the use of sutures and staples, and enhances its durability once it is incorporated within the wound environment. The triple layer formulation is 306% stronger and supports 616% more suture tension than the single-layer preparation. Both products are currently indicated for the management of partial and full-thickness wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds, drainage wounds, and surgical wounds. They are not indicated for patients with third degree burns and are contraindicated for patients with known porcine sensitivity. The commercially available SIS formulations have been evaluated for use in chronic wounds.

### Chronic leg ulcers

One of the first studies to test the efficacy of SIS wound matrix in the treatment of wounds in the clinical setting was a study by Mostow et al. The purpose of this prospective, randomized, investigator-blinded, controlled clinical trial was to compare the effectiveness of SIS wound matrix plus compression therapy vs compression alone. The current standard of care for chronic venous leg ulcers is to use compression bandages to control edema, reduce ambulatory venous pressure, and improve venous return. However, the 12-week healing rates from current methods of compressive care are 34% to 42%, with many ulcers recurring at a 12-month rate of 26% to 28%. Mostow and colleagues hypothesized that chronic full-thickness leg ulcers treated with SIS matrix would lead to better outcomes when compared to standard care alone. Eligible patients were randomized to receive either the control treatment (n = 58) or SIS plus control treatment (n = 62). All wounds were evaluated weekly and both treatment groups received standard care at each evaluation visit. For the SIS study group, the wound matrix was reapplied if deemed necessary by the clinician. Patients were then observed for up to 12 weeks and returned for a follow-up visit at 6 months. The primary outcome measure was the incidence of wound epithelialization with the absence of drainage at 12 weeks.
The standard care and SIS groups did not differ significantly in terms of patient demographics, complications observed, or baseline ulcer size and duration. However, covariate analysis indicated that patients in the SIS group maintained a consistent or greater proportion of activity in the presence of other comorbidities, such as vascular disease \((P = 0.0253)\), type II diabetes \((P = 0.0214)\), endocrine disease \((P = 0.0272)\), and hypertension \((P = 0.0204)\). After adjusting for baseline ulcer size, patients in the SIS group were almost 3 times more likely to have had their wound heal \((P = 0.0067; \text{odds ratio}, 2.996)\) than their counterparts in the standard care only group.

The wound matrix group maintained a consistent or greater proportion of wound closure than the standard-care group \((P = 0.0215)\). If baseline debridement was performed, patients in the SIS group \((19/30, 63\%)\) were 4 times more likely to have healed their wounds \((P = 0.0167; \text{odds ratio}, 4.10)\) than patients in the standard care only group \((8/27, 30\%)\).

Patients in the control group were given the option to cross over to SIS treatment if their wounds had not healed after the 12-week treatment period. Nineteen patients crossed over to the SIS group, and 5 \((26\%)\) had their wounds heal after receiving an average of 4 SIS wound matrix applications.

Fifty-four patients \((45\%)\) were seen at the 6-month follow-up visit \((\text{SIS}, n = 30; \text{standard-care}, n = 24)\) and 29 of their ulcers had healed after the 12-week study period. Twenty-six of these 29 ulcers remained healed at the 6-month follow-up: 100\% \((19/19)\) of the SIS group and 70\% \((7/10)\) of the standard care group. Of the 25 patients with ulcers that had not healed within the 12-week study period, 5 patients’ ulcers had healed by the 6-month follow-up or later: 9\% \((1/11)\) of the SIS wound matrix patients and 29\% \((4/14)\) of the standard care patients. Three of the 4 standard care patients whose wounds had healed at follow-up were part of the crossover group.

All of the SIS wound matrix patients who achieved wound closure within 12 weeks were ulcer-free at the 6-month follow up compared to 70\% of the standard-care group. This is a significant finding when considering that ulcer recurrence following standard care therapy has been estimated at 26\% to 28\%, and may actually occur as frequently as 66\%.58,59,62-64

Overall, the study authors concluded that SIS wound matrix was effective, easy to apply, and well-tolerated without the induction of clinically observable adverse immunologic reactions, and should be considered as a useful adjunct to the current standard of care for wound management. Although additional studies are warranted to make a definitive conclusion, the results presented here indicate SIS may help to reduce the likelihood of recurrent ulcers in patients with chronic leg ulcers.

**Diabetic ulcers.** Positive results also have been achieved using SIS biomaterial in the treatment of diabetic ulcers.52,53 A 2008 randomized, nonblinded study by Landsman et al52 compared patient outcomes following treatment with either an acellular, ECM-based SIS biomaterial, or a living skin equivalent (LSE) therapy such as a human fibroblast-derived dermal substitute. The authors hypothesized there would be no difference in the rate of wound closure or the percentage of patients achieving wound closure between these 2 types of therapies. Of the 40 potential subjects screened, 26 \((n = 13\) for each treatment arm) completed the study. After screening and phase-in, subjects were randomized to receive SIS matrix or dermal substitute. All wounds were debrided and thoroughly cleansed with sterile saline before the application of SIS or dermal substitute. Patients were evaluated once a week for the first 8 weeks, then every other week until wound closure occurred, or up to 12 weeks. The critical endpoint was wound closure without any evidence of drainage or bleeding.

The study authors found no significant differences between the SIS wound matrix and human fibroblast-derived dermal substitute treatment arms in terms of average baseline wound size \((P = 0.94)\), proportion of patients achieving wound closure, average time to wound closure, and probability of closure \((P = 0.37)\). Average baseline wound size was 1.85 cm$^2$ ± 1.85 cm$^2$ for the wound matrix group vs 1.88 cm$^2$ ± 1.39 cm$^2$ for the dermal substitute group \((P = 0.94)\). In this study, 76.9\% \((10/13)\) of patients in the SIS group and 84.6\% \((11/13)\) of patients in the dermal substitute group achieved wound closure. Average time to closure was 35.67 ± 41.47 days for the SIS group and 40.90 ± 32.32 days for the dermal substitute group \((P = 0.73)\). The Kaplan-Meier curves generated for both treatment groups were indistinguishable \((P = 0.37)\), indicating the probability of closure between the 2 groups was similar.

The authors concluded all wounds have specific deficiencies that need to be addressed by the clinician and that both SIS wound matrix and human fibroblast-derived dermal substitute expand the available tools that can be matched to a specific wound.

**Difficult-to-heal wounds of mixed arterial/venous etiology.** Evidence from other studies56,55 indicate...
SIS wound matrix also may be a useful and well-tolerated option for the treatment of mixed arterial/venous (A/V) or venous ulcers in addition to diabetic ulcers. This is important as healing rates for A/V ulcers range from 23% to 64% depending on the severity of arterial disease. These low healing rates indicate the current standard of care of sharp debridement and moist wound dressings is inadequate for this difficult-to-treat patient population, and that alternative strategies need to be considered.

**Mixed arterial/venous or venous ulcers.** A 2010 prospective, randomized clinical study by Romanelli et al. compared the efficacy and tolerability of SIS wound matrix vs petrolatum-impregnated gauze in the treatment of mixed A/V or venous ulcers. Eligible patients (n = 50) were randomized to receive either SIS wound matrix (n = 25) or a standard moist wound dressing of petrolatum-impregnated gauze (n = 25; completed, n = 23), and were evaluated twice a week for up to 8 weeks. Two patients in the control group discontinued due to their relocation to another city. Patients were evaluated for wound epithelialization, time to reapplication, and formation of granulation tissue.

After 8 weeks, the authors found that patients treated with SIS experienced significantly improved outcomes than those treated with petrolatum by all measures. Ulcers treated with SIS wound matrix healed in an average of 5.4 weeks compared to 8.3 weeks for patients in the control group (P = 0.02). In the SIS group, 80% (20/25) of patients’ wounds were closed at 8 weeks vs 65% (15/23) in the control group (P < 0.05). Among patients who had not achieved wound closure by 8 weeks, granulation tissue in the wound increased to 65% in the SIS group vs a decrease to 38% in the control group (P < 0.05). In addition, the wound matrix group also required fewer applications and experienced longer duration between applications compared to control (P < 0.05). Interestingly, a higher proportion of patients treated with SIS (80%) experienced healed ulcers than the 55% previously reported by Mostow et al. The authors concluded the better outcomes observed may be due to the fact that the average ulcer duration in this study was much shorter and the majority of patients may have been progressing from a slow-to-heal to a difficult-to-heal wound.

**Ulcers of mixed arterial/venous etiology.** Romanelli and colleagues investigated the efficacy of SIS wound matrix in the treatment of ulcers of mixed A/V etiology. The objective of this study was to compare the effectiveness of SIS and a hyaluronan therapy in treating mixed A/V ulcers. These authors sought to investigate if a single ECM component, such as hyaluronic acid (HA), could provide the same benefits seen with other ECM-based biomaterials. Patients in this study were randomized to receive either SIS wound matrix (n = 27; completed, n = 26) or HA dressing (n = 27; completed, n = 24), and were evaluated twice a week for 16 weeks. A total of 4 patients discontinued for reasons unrelated to ulcer healing. Three were lost to followup, and one left the study due to family issues.

The authors evaluated the percentage of patients with reepithelialized wounds, the time between product applications and patient pain, discomfort, and other adverse events. At the end of the study period, patients in the SIS wound matrix group experienced significantly better outcomes than those in the HA group by all measures for the treatment of mixed A/V ulcers. Wound closure was achieved in 82.6% (21/26) of the SIS group compared to 46.2% (11/24) in the HA treatment group (P < 0.001). The SIS-treated ulcers required fewer applications and longer duration between applications (P < 0.05). Patients in the SIS treatment arm also reported significantly greater comfort (P < 0.01) and less pain (P < 0.05) than patients in the HA dressing group.

**Discussion**

The ECM is an important component of the dermis that directs all phases of wound healing. Its structure as a complex scaffold of interacting proteins, proteoglycans, glycoproteins, and glycosaminoglycans provides the dermis with structural integrity, flexibility, sites of cellular attachment, and signaling. A delicate balance between the numerous components of the ECM is required to maintain and restore homeostasis, leading to successful healing. Unsurprisingly, a dysfunctional ECM is a major contributor to chronic wounds, where the dynamic interaction between ECM components is lost and the wound healing machinery is compromised.

It is important to understand how the ECM malfunctions in chronic wounds as these types of wounds present a difficult problem both for physicians to treat and for the wellbeing of patients. Chronic wounds are often impaired by vascular perfusion due to diabetes mellitus, venous hypertension, or chronic pressure secondary to sustained immobility. Common chronic wounds include venous leg ulcers, pressure ulcers, diabetic neuropathic foot ulcers, and leg ulcers of arterial insufficiency. It is estimated that in developed countries, 1% to 2% of the population will develop a chronic wound sometime in their lifetime.
KEYPOINTS

• The clinical efficacy of SIS in the management of many difficult-to-heal wounds has been demonstrated in multiple studies.
• Small intestine submucosa has demonstrated efficacy in the treatment of chronic venous and diabetic ulcers, and has been shown to improve the rate at which ulcers heal to 55% and 49% respectively, a significant improvement over standard care therapies.51,53
• With patients for whom standard treatment has been unsuccessful, incorporating adjunctive therapies, such as SIS, earlier into the treatment paradigm may improve outcomes in the long term.

Since chronic wounds typically fail to heal even after 3 months of standard care, advanced therapeutic intervention is required for healing to occur in these cases. Many strategies influence the role of ECM in wound healing, including promoting ECM synthesis, inhibiting ECM degradation, or replacing the defective ECM. Treatment with SIS wound matrix represents a clinical innovation for this therapeutic strategy.

The clinical efficacy of SIS in the management of many difficult-to-heal wounds has been demonstrated in multiple studies. Small intestine submucosa has demonstrated efficacy in the treatment of chronic venous and diabetic ulcers, and has been shown to improve the rate at which ulcers heal to 55% and 49% respectively, a significant improvement over standard care therapies. The SIS wound matrix also leads to better outcomes than standard care in wounds of mixed arterial/venous etiology. With patients for whom standard treatment has been unsuccessful, incorporating adjunctive therapies, such as SIS, earlier into the treatment paradigm may improve outcomes in the long term. Wound care treatment algorithms and practices should be reviewed and updated appropriately to reflect what has been learned from the current and emerging research.

Conclusion

Advanced therapeutic intervention is often required in the treatment of chronic wounds, which frequently have dysfunctional ECM. The SIS wound matrix represents a clinical innovation for therapeutic strategies that address ECM dysfunction.

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