Extracellular Wound Matrices: Small Intestinal Submucosa Wound Matrix for Chronic Wound Healing

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Abstract: Chronic wounds represent a state where healing has stagnated. Venous, diabetic, and pressure ulcers are typically difficult to heal and are at high risk of becoming chronic. In an attempt to restart the healing of chronic wounds, many biologically important molecules, such as collagen, hyaluronic acid, and growth factors have been used to treat these wounds with varying degrees of success. Until recently, the idea of replacing the failing extracellular matrix (ECM) with an intact and biologically complex substitute was unknown. Small Intestinal Submucosa Wound Matrix (SISWM) is both a biologically complex and intact ECM, and an effective therapy for treating chronic wounds. A “drop in” replacement for the ECM of difficult to heal or chronic wounds helps to stimulate tissue ingrowth, deposition of new matrix, and rapid epithelialization—potentially leading to improved quality of life for patients.

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The native dermis is normally able to direct wound healing following damage but in chronic wounds, the dermal extracellular matrix (ECM) and cells within it are diseased and unable to provide the correct signals needed to stimulate and coordinate healing.1,2 In deep, chronic diabetic foot ulcers, pressure ulcers, or venous leg ulcers, the dermal ECM may be completely absent and wounds may not efficiently epithelialize because the wound healing signals that are usually present in the dermis have been lost. Functional ECM is essential to wound healing. The healing process is stalled if functional ECM is absent in chronic wounds. In these particular situations, therapeutic strategies must include the use of exogenous factors to act as a surrogate for the native dermis if healing is expected to occur.

The Chronic Wound Problem

The extent of the chronic wound problem and its impact on quality of life and financial impact on the worldwide economy is immense. For example, in individuals...
65 years and older, venous leg ulcers affect approximately 1.69% of the population in the United States and cost approximately $9,600 to treat. In addition to the economic costs, most patients with chronic venous leg ulcers report pain (81%), itching (69%), and loss of sleep (67%) as a result of their wounds, as well as a significantly lower quality of life. Of the 13.8 million people in the United States diagnosed with diabetes, 6% may develop foot ulcers over a 3-year period with an estimated annual cost of approximately $6 billion. More than 50% of people with diabetes and a foot ulcer are expected to develop a wound infection, and up to 20% will require some degree of amputation during the course of their disease. Pressure ulcers afflict approximately 15% of patients in acute care facilities and up to 29% in long-term care facilities, burdening the healthcare system with more than $8.5 billion in annual costs. Pressure ulcers are often associated with fatal septic infections and are reported to cause thousands of deaths each year in the United States.

Observed together, these data indicate that chronic wounds are prevalent, costly, and have a significant negative impact on quality of life. Therefore, effective treatment strategies for chronic wounds could provide tremendous benefits to both patients and society as a whole. Unfortunately, complete healing rates for diabetic foot ulcers, venous leg ulcers, or pressure ulcers remain at approximately 25% to 50% following up to 20 weeks of treatment when standard wound care therapies and traditional synthetic dressings are used. These low rates suggest that standard of care is inadequate for many patients while highlighting the need for more aggressive management strategies in this population. Significant cost savings, decreased morbidity, and substantial increases in quality of life can be achieved with more rapid and complete ulcer healing.

Matrix Strategy for Healing

One aggressive management strategy that has been studied recently in randomized clinical trials is the application of an intact ECM material to the chronic wound bed. While other advanced strategies have concentrated on the delivery of individual matrix factors, such as collagen, hyaluronic acid, or growth factors, the application of an intact exogenous ECM that can supply many of the necessary factors in a single weekly treatment is a recent advance in effective care of chronic wounds. An intact, functional ECM is essential to achieving wound closure and restoring native tissue architecture. Materials that closely recapitulate the complex tissue structure and composition of the dermal ECM may fare better in stimulating the healing of chronic wounds than single, purified components.

An intact, biologically-derived ECM provides a complex of collagens, glycoproteins, glycosaminoglycans, growth factors and proteoglycans needed to direct all stages of
wound healing. Unlike single proteins or reconstituted collagen dressings, these structural proteins and associated bioactive molecules are dispersed in a unique and natural spatial distribution. This complex of structural collagens and matricellular proteins provides signals to direct the cells present in the wound to migrate into the open scaffold, synthesize new matrix, and encourage epithelialization, all while protecting the bioactive growth factors from rapid inactivation and degradation due to the proteolytic nature of chronic wound bed fluid.

These biologically-derived ECM materials can be obtained from a number of tissues. In addition to the dermis, the submucosa of the small intestine, urinary bladder, pericardium, basement membrane of the liver, decellularized Achilles tendon, artery, vein, ureter, and renal capsule can be isolated and used as sources of ECM materials. Of these tissues, the wound graft material derived from the small intestinal submucosa of pigs has been the most extensively characterized.25–33

**SIS Wound Matrix**

Small Intestinal Submucosa Wound Matrix (SISWM) consists of the tunica submucosa of the small intestine.26 The tunica submucosa is the layer of connective tissue arranged directly under the mucosa layer of the intestine and is 100–200 mm thick. In the living intestine, the submucosa supports the mucosal structures and is secreted and maintained by connective tissue fibroblasts. This tissue layer supports the growth and differentiation of the rapidly proliferating mucosal and glandular cells while maintaining a connective tissue structure that gives the intestine its integrity and strength.

As in the case of all clinical grade biomaterials derived from animals, SISWM must be purified to ensure its safety. SISWM is harvested from the mammalian small intestine by mechanically separating it from its outer muscular layers and internal mucosal layers.26 It is rinsed in highly purified water, treated with an aqueous solution of peracetic acid to ensure viral safety,27 and is then rinsed in sequential exchanges of water and buffers to yield a neutral pH. It is freeze-dried to stabilize the proteins within it and is later sterilized using ethylene oxide gas. When SISWM is implanted surgically or applied topically as a naturally occurring ECM graft, it stimulates angiogenesis, connective and epithelial tissue growth and differentiation, as well as deposition, organization, and maturation of ECM components that are functionally and histologically appropriate to the site where it has been applied.26,28,29 In chronic ulcers, the SISWM shifts the local wound environment from a chronic state, characterized by high and variable levels of pro-inflammatory cytokines and matrix metalloproteinases (MMPs), to a more acute state characterized by lower and more stable levels of these inflammatory proteins and proteolytic enzymes (J.P.H, unpublished observations, 2006).

Similar to skin, SISWM is comprised primarily of
fibrillar collagens and adhesive glycoproteins, which serve as a scaffold into which cells can migrate and multiply.\textsuperscript{26,30} The SISWM layers also contain potent regulatory factors, such as glycosaminoglycans, proteoglycans, and growth factors, which regulate cellular processes that maintain tissue homeostasis and respond to injury and infection. These components are retained in the SISWM matrix following processing and also retain their biological activity.\textsuperscript{30–33} Since SISWM contains many of the same components naturally seen in the dermis and is not reconstituted but supplied in its natural 3-dimensional state, it recapitulates the complex tissue structure and composition of the dermal ECM and provides bioactive wound healing factors that contribute to tissue restoration following extensive tissue loss or failed ulcer healing.

**Clinical Applications**

The SISWM material is easy to use, can be stored for up to 2 years at room temperature, and only needs to be applied to the wound once weekly. Two recently published, randomized, controlled, clinical trials have shown the effectiveness of SISWM (Oasis® Wound Matrix, Healthpoint Ltd, Fort Worth, Tex) in healing chronic diabetic foot ulcers\textsuperscript{18} and venous leg ulcers\textsuperscript{19,20} Niezgoda et al\textsuperscript{8} compared SISWM and becaplermin gel in a clinical trial of 73 patients with chronic diabetic foot ulcerations. The ulcers had to be present for more than 30 days, resistant to conventional therapy with debridement, offloading, and moist wound healing. SISWM was applied at the clinic on a once-weekly basis and becaplermin gel was applied daily as directed on the package insert for the 12-week trial period. All wounds in both groups were debrided as needed, secondary dressings were changed as needed, and patients were given a pressure-relief device. Healing was tracked over the course of 12 weeks. In the SISWM-treated group, 18/37 (49%) SISWM-treated patients had complete wound closure compared with 10/36 (28%) in the becaplermin gel-treated group. Although the sample size was not large enough to demonstrate that the incidence of healing in the SISWM group was statistically superior ($P = 0.055$), results showed treatment with SISWM to be at least as effective as becaplermin gel in leading to ulcer healing by 12 weeks. In addition, survival plot analysis showed that patients in the SISWM were twice as likely to heal at 7, 9, and 12 weeks than the becaplermin-treated group. Subgroup analysis further revealed that SISWM was more effective than becaplermin gel in healing plantar foot ulcers, some of the most difficult diabetic ulcers to heal (52% versus 14%; $P = 0.014$), and was also more effective in healing patients with type 2 diabetes (63% versus 29%; $P = 0.034$). These rates of improvement are significant in that it has been reported that even a modest (9%) increase in the healing rate by 20 weeks would lead to a cost savings of $189 per episode, based on an analysis of Medicare expenditures published in 2000.\textsuperscript{34} In this study, the average cost of the product needed to achieve closure in the SISWM group was $250 as
compared to $1,070 in the becaplermin gel group, yielding a
cost-per-patient savings of approximately $820.18

Mostow et al\textsuperscript{20} studied 120 patients suffering from
chronic (> 1 month) venous leg ulcers. SISWM plus
compression therapy was randomized against compression
therapy alone. Patients were enrolled into the study only if
their ulcers were nonhealing for at least 1 month and were
unresponsive to compression therapy during a 2-week
screening period. In this study, SISWM was applied on a
once-weekly basis for up to 12 weeks or until wound healing
occurred. All wounds in both groups were debrided as
needed and secondary dressings were changed at weekly
clinic visits. After 12 weeks of treatment, 34/62 (55\%) of
the wounds in the SISWM group were healed as compared
to 20/58 (34\%) in the standard care group ($P = 0.0196$). It
was concluded that SISWM, as an adjunct therapy,
significantly improved healing of venous leg ulcers over
compression therapy alone.

Even in these initial studies of difficult-to-treat
populations with chronic wounds, SISWM as an adjunctive
therapy led to complete wound healing in a significant
proportion of patients. Subgroup analysis also suggested
that certain patient populations may show higher than
average healing rates with SISWM, including those with
type 2 diabetes\textsuperscript{18} and those with venous leg ulcers debrided
at baseline.\textsuperscript{20} The latter finding suggests that the simple
step of debriding chronic venous leg ulcers prior to
application of an intact ECM material may increase the
likelihood of healing. This observation fits with the function
of an ECM material as a scaffold for the migration of the
body’s own viable cells, which the presence of necrotic
debris theoretically would be expected to hinder, along with
the need for functional, nonsenescent cells to respond to
biochemical signals initiated by the ECM replacement.

Summary

Diabetic foot ulcers, venous leg ulcers, and pressure
ulcers often fail to heal quickly and ultimately become
chronic as a result. These wounds are prevalent and costly,
and negatively impact the quality of life of many patients.\textsuperscript{3–
14} Standard of care is frequently insufficient to promote
healing of these wounds and many require aggressive,
active treatments to stimulate epithelialization.

Chronic wounds are characterized by high levels of
matrix-degrading enzymes,\textsuperscript{35} pro-inflammatory
cytokines,\textsuperscript{36} and senescent cells,\textsuperscript{2} which become
unresponsive to their surrounding environment and are
unable to effectively remodel their ECM. In these chronic
wounds, the body fails to generate a functional ECM. A
functional ECM is central to wound healing,\textsuperscript{37} and acts as a
scaffold for the migration of fibroblasts and other cells,
regulates cell-to-cell communication, and directs the
development of a biochemical environment that is conducive
to healing. The absence of an ECM impedes granulation
tissue deposition and epithelialization. Strategies to replace
the failing ECM may be beneficial in stimulating closure of chronic wounds.

SISWM is an active, intact, biologically-derived ECM that recapitulates the complex structure and composition of the dermal matrix. It contains the major components present in the dermal ECM during normal wound healing. It also contains bioactive growth factors, which remain bound to the matrix during its isolation and processing for clinical use. Preclinical studies have confirmed capillary ingrowth into the matrix, as well as the migration, attachment, and proliferation of cells. Clinically, SISWM has been found to significantly enhance the healing of chronic wounds compared with standard care alone and to work as well as becaplermin gel at a fraction of the cost in diabetic foot ulceration. As compared to other aggressive treatments available for chronic wounds, SISWM offers an effective combination of matrix and signals in a single weekly application while minimizing costs.

When treating high-risk wounds, aggressive, active interventions, such as SISWM are likely to be most beneficial if pursued early as part of a consistent treatment algorithm. Evidence indicates that the reduction in the area of the chronic wound during the first 4 weeks of treatment is a predictor of complete healing at 12 weeks for diabetic foot ulcers, and at 24 weeks for venous leg ulcers. Thus, for chronic wounds, a lack of response at 3–4 weeks to conventional therapy should prompt the re-evaluation of the patient and consideration of advanced therapies. Clinical evidence shows that sharp debridement can shift a chronic wound toward a more acute state and is associated with better outcomes if performed prior to ECM replacement with SISWM. Rapid wound closure minimizes the detrimental effects of these chronic ulcers on patients’ daily lives and in some cases avoid hospitalization, life-threatening complications, and amputations.

As a treatment that includes both matrix and signals in the form of growth factors, cell attachment factors, and matrix binding sites, SISWM provides the elements needed to address the ECM deficiencies that characterize chronic wounds. Its clinical efficacy, reasonable cost, and ease of storage and use suggest that SISWM may be advantageous as an early and potentially cost effective intervention for chronic wounds.

References


