



State-of-the-Art Wound Healing: Skin Substitutes for Chronic Wounds

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The care of chronic wounds represents an important and evolving area of dermatology. With a rising prevalence of chronic wounds bearing notable effects on patient morbidity including amputations, appropriate and effective intervention to treat these debilitating wounds can make a significant clinical impact. In recent years, several advanced bioactive wound dressings have been developed to specifically treat chronic nonhealing wounds. These wound dressings encompass a wide range of products containing synthetic matrix scaffolds, animal-derived matrices, and human tissue. With several of these wound dressings, randomized controlled trials (RCTs) have demonstrated improvement in wound healing; furthermore, cost-effectiveness studies have suggested that these products may reduce the overall cost of treating a chronic wound. Familiarity with these products and their appropriate use may be helpful to dermatologists treating chronic wounds.

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The care of chronic wounds is a challenging topic and a growing area for clinical and research interest within dermatology. A review of wound care was presented in a *Cutis*® resident corner column last year.¹ When routine wound care does

not achieve adequate healing for chronic wounds, it may be necessary to pursue other approaches. It has been estimated that chronic ulcers occur in up to 1.3% of the US adult population, mostly in the lower extremities.^{2,3} With the vast majority of amputations directly resulting from nonhealing ulcers in the legs,⁴ appropriate and effective intervention can have a substantial clinical impact. In recent years, numerous advanced wound dressings have been developed specifically to treat chronic nonhealing wounds. Because dermatologists will treat these patients, it is important for us to become familiar with these skin substitutes, which may become a more integral part of our armamentarium in caring for chronic wounds.

Wound healing normally progresses through distinct phases, with the ultimate goal of reestablishing barrier function and the structures normally found in intact skin. Several mechanisms exist whereby wound healing does not progress, often due to underlying factors such as arteriovenous insufficiency, diabetes mellitus, nutritional deficiency, infection, or physical factors (ie, pressure ulcers). Some of these underlying conditions are straightforward to treat; for example, in the case of infection, antibiotics and active wound dressings containing silver, betaine, polyhexamethylene biguanide, or other antimicrobial substances can help promote wound healing. However, many of the other pathways to chronic wound physiology are much more difficult to manage, with the underlying factor often being insufficient delivery of oxygen and nutrients to the wound.⁵ It is well known from the literature on burn wounds that a large nonhealing wound has direct effects on the body's metabolism, increasing the cardiac index and total body oxygen consumption to levels comparable with other conditions (eg, hyperthyroidism).⁶ As a result, keratinocytes at the wound edge are no longer able to

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successfully migrate centripetally to heal the wound and instead proliferate in place, forming a thick hyperkeratotic layer that serves as the hallmark of a chronic wound edge.⁷ Synthetic skin substitutes have been used to treat chronic wounds, not only forming a dressing to cover the ulcerated wound base but also actively participating in the wound healing process with the addition of growth factors or cytokines that may directly stimulate angiogenesis or reepithelialization. In the early 1980s, the field of bioactive wound dressings started with cultured skin cells, which were then applied to the wounds or tissue-engineered skin substitutes; this technology, which emerged from treating burn wounds when it was impractical or impossible to harvest enough graft tissue to treat the burn, has evolved considerably since that time. This review will focus on tissue-engineered skin substitutes and their application in the treatment of chronic wounds.

Synthetic Skin Substitutes

A bioprosthetic skin substitute generally refers to a material consisting of a biologically derived substance that may be combined with another material to allow for its application to a wound. There currently are more than 50 skin substitutes on the market, with many more under development. These skin substitutes represent a biocompatible extracellular matrix template that allows for the migration of cells from neighboring, ostensibly healthy tissue, encompassing either biomaterial (ie, noncellular matrices containing important proteins but no cellular components derived from cadaveric, animal, or synthetic sources) or cellular (ie, tissues harvested from human or animal origin) categories of products. However, there are materials that contain components of each. Overall, these dressings are expensive to manufacture and apply, which to some degree has prevented their widespread adoption, but they remain useful and even cost effective in selected situations.

Acellular Human Dermis—Acellular human dermis products generally are derived from cadaveric skin tissue that has been treated with various detergents, enzymes, and antibacterial and/or antimicrobial agents to ensure that there is no immunogenicity or potential harm. These materials serve as biocompatible scaffolds for cellular and vascular growth into the wound bed and allow for secondary tissue regeneration. Additionally, they can contain collagen, elastin, proteoglycans, and other proteins, which may in turn modulate the wound healing process. Examples of acellular human dermis wound dressings are provided in the Table.

Animal-Derived Matrix or Material—Several companies have taken the approach of using an

Skin Substitutes for Wound Healing

Wound Dressing	Manufacturer
Acellular Human Dermis	
AlloDerm	LifeCell Corporation
AlloSkin	AlloSource
DermACell	Arthrex, Inc
GammaGraft	Promethean LifeSciences, Inc
Graftjacket	Kinetic Concepts, Inc
Matrix HD	RTI Surgical, Inc
TheraSkin	Soluble Systems, LLC
Animal Derived	
Biobrane ^a	Smith & Nephew, Inc
Endoform ^b	Hollister Wound Care LLC
EZ Derm ^a	Mölnlycke Health Care
Integra ^a	Integra LifeSciences Corporation
Oasis Wound Matrix ^b	Smith & Nephew, Inc
PriMatrix ^b	TEI Biosciences
TransCyte ^{a,c}	Smith & Nephew, Inc
Human Derived	
Apligraf	Organogenesis, Inc
Dermagraft	Shire Regenerative Medicine, Inc

^aUses a synthetic matrix coated with animal collagen or polypeptides.

^bUses an animal-derived extracellular matrix.

^cTransCyte also contains neonatal fibroblasts.

animal-derived extracellular matrix or a synthetic matrix coated with animal collagen or polypeptides, mostly porcine and/or bovine (Table). Both materials aim to provide structural support in the form of a matrix on which new tissue and vasculature can form

while providing proteins and/or growth factors that can modulate wound healing.

Human-Derived Products—Materials that incorporate fibroblasts derived from human sources, generally from neonatal foreskin tissue, have been an interesting development in the field of skin substitutes. One such product, Dermagraft (Shire Regenerative Medicine, Inc), also incorporates an extracellular matrix and a bioabsorbable polyglactin mesh. The major benefit is that the fibroblasts are able to directly generate growth factors, collagen, cytokines, and glycosaminoglycans to contribute to healing in the wound environment. This approach has proven quite efficacious in treating wounds such as diabetic foot ulcers⁸; however, a few theoretical yet unproven risks include rejection of and hypersensitivity to this material due to trace amounts of bovine serum.

The other major skin substitute in this class is Apligraf (Organogenesis, Inc), an allogenic, cultured, bilayered skin equivalent. With this material, a dermal layer of cultured human fibroblasts and bovine type I collagen is combined with an epidermal layer of cultured human keratinocytes, generating a material approximating the normal skin architecture. This material can then be absorbed in a similar fashion to a graft and is able to directly generate a robust wound-healing environment. Although it does not contain appendageal or vascular elements, Apligraf has been shown to substantially increase blood flow by more than 70% to the base of diabetic foot ulcers.⁹

Efficacy of Skin Substitutes

Several randomized controlled trials (RCTs) have assessed the efficacy of a number of these skin substitutes. Apligraf is widely studied, with multiple RCTs analyzing a total of more than 500 patients with diabetic foot ulcers and venous leg ulcers. Studies have reported a significant ($P < .05$) difference in healing time in patients treated with Apligraf versus the control, though other dressings (eg, nonadherent gauze, Unna boot) also were used in both groups.¹⁰⁻¹² In one study, the difference in median time to wound closure for Apligraf versus control was quite impressive (61 vs 181 days).¹¹

Similarly, numerous trials have been conducted in hundreds of patients with diabetic foot ulcers who were treated with Dermagraft. Studies have reported either a statistical difference or trend toward increased healing,¹³⁻¹⁵ with nearly double the number of wounds showing complete healing in the treatment group compared to control in one study.¹³

Another product that has undergone multiple RCTs assessing its efficacy in treating venous leg ulcers and diabetic foot ulcers is the Oasis Wound Matrix (Smith & Nephew, Inc) animal-derived

extracellular matrix, which has been shown to significantly ($P < .05$) improve the proportion of wounds healed at 12 weeks in multiple studies.¹⁶⁻¹⁸ Some other products have been tested in smaller trials, and ongoing studies are being conducted. It has not been proven if these results can be extended to similar skin substitutes, but the outlook is encouraging. Ideally, further research will generate an environment in which several products are available and can compete on a cost-efficient basis to allow for more widespread application of these novel skin substitutes.

Cost-effectiveness

Numerous studies analyzing the cost of chronic wound treatment with biosynthetic skin substitutes have been conducted. Given the substantial economic burden of chronic wounds in general, including costly inpatient admissions, skilled nursing for dressing changes, and material costs, it is important to note that marked improvement in overall healing time likely has the greatest effect on total cost of treatment; however, this outcome has to be balanced with the high cost of some of these skin substitutes. For example, with a cost of approximately \$1000 for a single 7.5-cm, circular disk of Apligraf, which has a shelf life of only 15 days, and approximately \$1500 per application of Dermagraft, there has to be a justifiable benefit of purchasing and using these expensive products.¹⁹ Although there still is much to be determined, recent cuts in Medicare reimbursement for wound care²⁰ will likely force the companies making these materials to adapt to a changing economic reality. Notwithstanding, these skin substitutes have proven to be effective treatment modalities to promote wound healing. A comprehensive review of the use of bioengineered skin substitutes for the treatment of therapy-resistant chronic wounds showed notable cost savings over the course of 1 year compared to traditional wound care. However, it is important to note that this review included cases that had failed to improve with several months of standard wound care.²¹ Some smaller individual studies reported similar findings of cost-effectiveness in using skin substitutes to treat facial burns (Biobrane [Smith & Nephew, Inc])²² and diabetic foot ulcers (Apligraf and Dermagraft).^{23,24} A potential caveat is that there currently is insufficient data to advocate the use of these skin substitutes as first-line treatment.

Conclusion

Skin substitutes represent a promising area of chronic wound care that will undoubtedly become more useful to the medical community as the growing US population begins to age, especially given the rising prevalence of underlying factors such as diabetes

mellitus. Preventing the progression of chronic ulcers and encouraging a faster healing process have the potential to greatly impact the number of amputations performed on a regular basis in the elderly population due to chronic wounds. Furthermore, appropriate and judicious use of skin substitutes in chronic wounds has the potential to lead to a direct decrease in cost of care. Familiarity with the components and appropriate usage of skin substitutes will help dermatologists stay at the leading edge of wound care in the future.

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