Bioengineered Alternative Tissues in Diabetic Wound Healing

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KEYWORDS

• Diabetic foot ulcer • Graft • Biological tissue • Wound healing • Chronic wound

KEY POINTS

- New methods of wound care are at the forefront of limb salvage and can lead to improved methods for treatment of diabetic foot ulcers.
- The use of bioengineered alternative tissues does not preclude the need for maximizing perfusion, regular debridement, and off-loading.
- Bioengineered alternative tissues are subdivided into dermoinductive and dermoconductive products based on their properties, and there are benefits associated with each.
- The appropriate selection of a bioengineered alternative tissue product is dictated by the requirement of the wound.
- Research supports that the use of bioengineered alternative tissues increases the rate of healing.

INTRODUCTION

Diabetic Foot Ulcers

According to the World Health Organization, diabetes mellitus is one of the leading causes of death in the world, along with ischemic heart disease, stroke, chronic obstructive pulmonary disease, and human immunodeficiency virus/acquired immunodeficiency syndrome.[1] At present, 382 million people are living with diabetes, 26 million of whom are in the United States, and by 2035 there is estimated to be nearly 417 million.[2] The disease prevalence is increasing and it has a great impact on society, costing US$471 billion in 2012.[1,2]

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Several complications associated with diabetes challenge the course and outcomes of patients as well as the health care system. Among these are heart disease, blindness, retinopathy, renal disease, neuropathy, and lower-limb amputation.[3] Increased morbidity and mortality has been seen with the presence of diabetic peripheral neuropathy, which leads to diabetic foot ulceration (DFU). The risk of foot ulceration is as high as 25% in diabetic patients and is the leading cause of hospitalization in this population.[4] Diabetic patients who develop foot ulcerations in their lifetimes are at higher risk of death, lower-extremity amputation, contralateral lower-extremity amputation, and reulceration.[5] A study in 2014 found cumulative incidences of 26.6% for DFU, 5.8% for lower-extremity amputation, and 14.0% for death in 644 diabetic patients.[6] It also concluded that DFU has an independent impact on lower-extremity amputation and mortality.

Diabetic wound healing and limb salvage has received attention over the last decade because DFUs can have severe end results. Researchers and clinicians have addressed how to advance wound healing by decreasing the time to wound closure, improving the cost-effectiveness of treatment options, and improving limb salvage rates. Over the last several years many new wound healing products have become available. New technologies are designed to heal complicated DFUs that may have previously led to partial or complete limb loss. Among these are bioengineered alternative tissue (BAT) products.[7,8]

Despite the development of these products, fundamental principles still apply to the healing of DFUs. Perhaps the most important element in DFU care is maximizing perfusion to the lower extremity. Without adequate blood flow to the tissues, wounds do not heal, regardless of the therapies used. Regular sharp debridement is also necessary to reduce bioburden. In addition, off-loading of DFUs on the plantar aspect of the foot is vitally important to healing. The use of BAT products should be reserved for recalcitrant wounds that have stalled. They should not be used if the wound is progressing by applying the fundamental principles discussed earlier. Further, mindless serial application without a definitive treatment plan for closure is not recommended because of the high cost. Thus, BAT products should be carefully considered before application. There are many different BAT products available to the wound care provider. This article discusses only some of these products. Further, there is a paucity of comparative efficacy/effectiveness clinical trials. Thus, it is not possible to conclude that one product or product category is superior to another.

BIOENGINEERED ALTERNATIVE TISSUES

Several different types of BATs exist that are intended to assist in wound closure whether as a definitive coverage or as part of a staged process (**Table 1**). Kim and colleagues[7] in 2007 introduced the terminology for BATs to help clarify some of the confusion in the literature with advanced wound care products.[8] The terms dermoinductive and dermoconductive have helped to categorize BATs and aid in proper use of these materials (**Fig. 1**). These terms are adopted from the orthopedic model of characterizing bone materials into osteoinductive and osteoconductive categories. Thus, dermoinductive is analogous to osteoinductive, in which cells or other protein factors are imbedded into the material. Dermoconductive is analogous to osteoconductive, in which the products serve as scaffolds with no active agents integrated.

Dermoinductive refers to the BAT products that provide cells, such as fibroblasts and keratinocytes that provide growth factors into the wound. These cells are essential for skin development and wound healing.[9] They induce the activation of new tissue (granulation tissue) within a wound. These products were previously termed living