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REVIEW

Wound care matrices for chronic leg ulcers: role in therapy

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Abstract: Chronic leg ulcers are a significant health care concern. Although deep wounds are usually treated by flap transfers, the operation is invasive and associates with serious complications. Skin grafts may be a less invasive means of covering wounds. However, skin grafts cannot survive on deep defects unless high-quality granulation tissue can first be generated in the defects. Technologies that generate high-quality granulation tissue are needed. One possibility is to use wound care matrices, which are bioengineered skin and soft tissue substitutes. Because they all support the healing process by providing a premade extracellular matrix material, these matrices can be termed "extracellular matrix replacement therapies". The matrix promotes wound healing by acting as a scaffold for regeneration, attracting host cytokines to the wound, stimulating wound epithelialization and angiogenesis, and providing the wound bed with bioactive components. This therapy has lasting benefits as it not only helps large skin defects to be closed with thin skin grafts or patch grafts but also restores cosmetic appearance and proper function. In particular, since it acts as a layer that slides over the subcutaneous fascia, it provides skin elasticity, tear resistance, and texture. Several therapies and products employing wound care matrices for wound management have been developed recently. Some of these can be applied in combination with negative pressure wound therapy or beneficial materials that promote wound healing and can be incorporated into the matrix. To date, the clinical studies on these approaches suggest that wound care matrices promote spontaneous wound healing or can be used to facilitate skin grafting, thereby avoiding the need to use invasive surgical tissue transfer strategies.

Keywords: biomaterial, chronic wound, leg ulcer, matrix

Introduction

Chronic leg ulcers are a significant health care concern. Chronic ulcers are wounds that show no tendency to heal after 3 months of appropriate treatment or are not completely healed at 12 months.[1] It is mainly caused by diabetes, neuropathy, arterial insufficiency, venous insufficiency, and pressure.

Wound healing normally proceeds in four phases, namely, hemostasis, inflammation, proliferation, and remodeling.[2] Rapid and appropriate wound healing will generally only occur if these four phases and the physiological events that constitute them occur in the appropriate sequence, timing, and duration. Chronic wounds typically do not follow this organized process.[3]

Wound bed preparation is an essential step in wound treatment. It is defined as management of the wound that accelerates endogenous healing or facilitates the effectiveness of other therapeutic measures.[4–6] The aim of wound bed preparation

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is to convert the molecular and cellular environment of a chronic wound to that of an acute healing wound.[4–6] Some of the widely used methods are wound cleansing, debridement, negative pressure wound therapy (NPWT), and application of moist wound dressings. Debridement is particularly important as it serves to remove the necrotic tissue, excessive bacterial burden, and cellular burden of dead and senescent cells, all of which inhibit wound healing.[7–14] After debridement, pedicled or free-flap transfers are traditionally applied to deep wounds in which bone and/or tendon are/is exposed. However, this operation is invasive and associates with complications, including flap necrosis and infection. These complications are particularly serious problems in elderly people and patients with multiple medical problems and an unfavorable general condition. For these aging or compromised patients, it may be better to use skin grafts, which cover wounds in a less invasive manner. However, skin grafts cannot survive on deep and poorly vascularized defects unless well-vascularized healthy granulation tissue is first generated in the wound. Technologies that promote this are needed. We believe that one possibility is wound care matrices. This section describes how wound care matrices can be used to prepare the wound bed of chronic leg ulcers for subsequent skin grafting.

Wound care matrices

Wound care matrices are bioengineered skin and soft tissue substitutes. Since they all support the healing process by providing a premade extracellular matrix material, they can be termed "extracellular matrix replacement therapies". The matrix acts as a scaffold for regeneration, stimulates wound epithelialization and angiogenesis, and provides the wound bed with bioactive components, thereby accelerating temporary wound closure.[6,15] This therapy has lasting benefits as it not only helps large skin defects to be closed with thin skin grafts or patch grafts, it also restores cosmetic appearance and proper function. In particular, since it acts as a layer that slides over the subcutaneous fascia, it provides skin elasticity, tear resistance, and texture.[16] Numerous therapies and products employing wound care matrices for wound management have been developed recently. The matrices are derived from allogeneic or xenographic tissue, synthetic materials, or a combination of both, and are classified as acellular and cellular materials.[17–19]

One example of a commercially available biosynthetic wound matrix is the collagen-based matrix. It has several advantages as a wound care matrix. First, collagen is the natural substratum for various types of animal cells and is present in tissues in large amounts.[20] Second, the availability of advanced purification techniques means that biocompatible and biodegenerative collagen matrix can be readily extracted from human and animal tissues. These features make the collagen matrix particularly suitable as a component of the artificial tissue substitutes that are used to reconstruct damaged tissues and organs.[21,22]

Several types of collagen-based artificial skin have been reported since the initial description by Yannas and Burke in 1980.[22–25] They include Biobrane® (Smith & Nephew plc, London, UK), Integra® (Siad Healthcare, Milano, Italy), TERUDERMIS (Terumo Corp, Tokyo, Japan), and Pelnac (Smith & Nephew plc, Tokyo, Japan). When these matrix substitutes are placed onto tissue defects, the collagen acts as a scaffold for regeneration. First, sprouting capillaries and fibroblasts migrate into the collagen, thereby resulting in angiogenesis and fibroplasia. Autogenous regenerating tissue then gradually replaces the atelocollagen. Finally, the poorly vascularized deep defect becomes resurfaced with robust granulation tissue that can be easily covered with a simple skin graft.[22–27] Collagen matrices have been reported to effectively facilitate the less invasive reconstruction of severe defects with bone and/or tendon exposure that would previously have required invasive tissue transfer.[26,27] However, it should be noted that they are artificial materials. As such, they may increase the risk of infection and should not be used on clinically diagnosed infected wounds.[28]

Figure 1 illustrates a typical case where a collagen matrix was used to treat a chronic leg ulcer. The patient was a 45-year-old man who suffered from a chronic pyoderma (Figure 1A). The lesion was subjected to surgical debridement followed by application of collagen matrix (Figure 1B and C). Fourteen days later, well-vascularized robust granulation tissue had developed (Figure 1D and E) and a split-thickness skin graft was performed. The patient has remained free of complications in the 3 months since treatment (Figure 1F).

Combination therapies using biomaterials

Several therapies combine wound care matrices with NPWT or incorporate materials that promote wound healing into the matrix. These include a pharmaceutical agent such as prostaglandin E(1),[29] growth factors such as basic fibroblast growth factor (bFGF),[30–32] and cells including bone marrow[17,31–37] and platelet-rich plasma (PRP).[38–42] Ono et al showed that collagen matrix combined with prostaglandin E(1) is effective for preventing wound contracture using an in vivo full-thickness skin defect model.[29] They also showed that collagen matrix

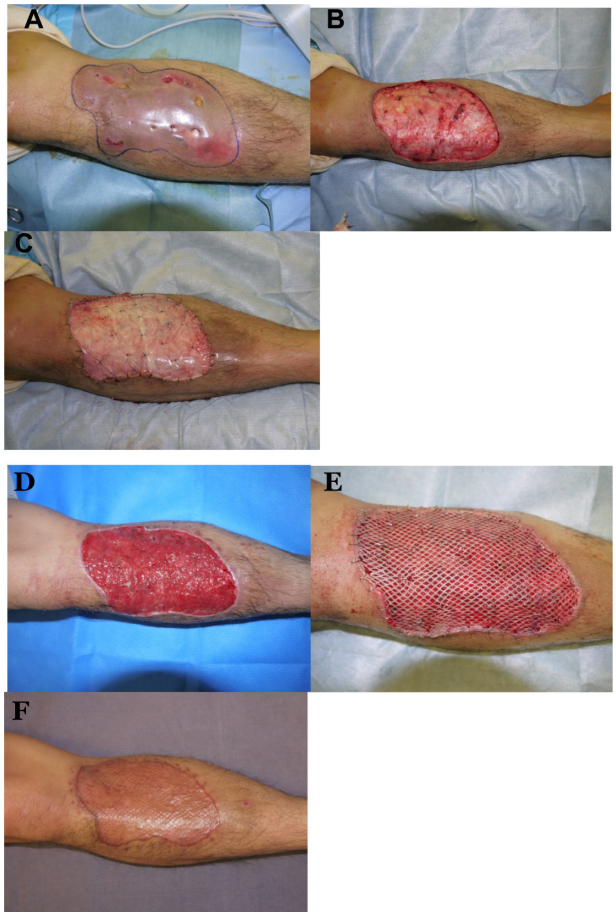

Figure 1 (**A**) Nonhealing chronic pyoderma on the right lower limb before wound debridement. (**B**) After debridement. (**C**) Application of the collagen matrix after debridement. (**D**) Robust granulation tissue 2 weeks after collagen matrix application. (**E**) Split-thickness mesh skin grafting was performed. (**F**) Healed wound 3 months after grafting.

combined with bFGF,[30] transforming growth factor beta,[31] and epidermal growth factor[32] is effective for preventing wound contracture. This section introduces combination therapies using biomaterials that are already in clinical use.

Combination with bone marrow

Bone marrow participates in wound healing by providing multipotential progenitor cells that produce growth factors and orchestrate a cascade of events.[43] Recent evidence suggests that bone marrow may be a source of skin progenitor cells,[44,45] and several experimental[33–36] and clinical[17,33,37] reports show that the topical application of bone marrow cells may promote wound healing. Ichioka et al have developed collagen matrix impregnated with bone marrow. When they applied this material to 53 chronic wounds, successful results were obtained in 44 patients.[46–48] In addition, Mizuno et al combined mononuclear bone marrow cells and allogeneic cultured dermal substitutes to treat intractable ulcers in patients with critical limb ischemia. They injected the mononuclear cells intramuscularly into the lower leg and around the wound area and applied the allogeneic cultured dermal substitute on the wound surface. All six wounds closed completely and the need for amputation was avoided.[49]

Combination with PRP

Platelets enhance wound healing by releasing numerous plasma proteins and various growth factors.[50–52] They stimulate angiogenesis, proliferation and migration, and collagen synthesis. The main growth factors produced by platelets include platelet-derived growth factor,[53] transforming growth factor beta,[54] insulin-like growth factor,[55] endothelial growth factor (EGF), vascular EGF,[56] and fibroblast growth factor (FGF).[57] PRP is defined as plasma that is enriched in platelets.[58,59] PRP can be generated from autologous blood by a minimally invasive procedure that involves a simple centrifugation step.[59–63] Several studies show that PRP has beneficial effects in wound treatment.[38–42] For example, Knighton et al observed that when chronic lower extremity ulcers were treated with platelet-derived wound-healing formula (platelet releasate that is suspended in a collagen base), all exhibited enhanced reepithelialization.[40] Similarly, Minamimura et al found that when 16 chronic limb ulcers were treated with collagen matrix impregnated with PRP, 13 healed successfully.[41,42]

Combination with growth factors

Wound healing may be promoted by the topical application of cytokines such as platelet-derived growth factor, EGF, and bFGF. Of these, bFGF is commercially available. In 1974, Gospodarowicz first isolated FGF from bovine pituitary glands and found that this protein accelerated the proliferation of fibroblasts.[64–66] FGF not only stimulates the fibroblast proliferation[67] but also promotes the proliferation of endothelial cells and keratinocytes and the mitogenesis of mesenchymal cells; consequently, FGF induces angiogenesis, granulation tissue formation, and epithelialization.[64,67,68] Several clinical studies have found that bFGF is safe and effective for the treatment of various wounds, including diabetic ulcers, pressure ulcers, and burns.[69,70] Several experimental studies also showed that bFGF is beneficial for ulcers when it is combined with matrix.[71–74] For example, when the novel artificial dermis consisting of a collagen/gelatin sponge that is capable of sustained bFGF release, developed by Morimoto et al., was used to treat 17 chronic leg ulcers, the wound bed improved in 16 patients.[73,74] Several recent basic research

studies also suggest that bFGF–matrix combinations may promote wound healing.[71,72]

Combination with NPWT

NPWT is a treatment modality that has become widely adopted for a broad range of wound indications since its advent over 15 years ago. The system consists of an electronically controlled pump and foam dressing that drains the wound. An adjustable negative pressure is applied via an airtight adhesive film that covers the wound. NPWT improves wound healing by creating a moist wound-healing environment, reducing tissue edema, removing bacterial products, promoting blood circulation, contracting the wound edges, mechanically stimulating the wound bed, and influencing blood perfusion at the wound edge. All these effects may promote angiogenesis and the formation of granulation tissue.[75–77] There are two ways to use NPWT with wound care matrices: NPWT is used for 1) wound bed preparation before the use of wound care matrices and 2) fixation of wound care matrices. Menn et al used artificial dermis with NPWT for lower extremity reconstruction and concluded that a dermal substitute and NPWT with delayed skin graft application can provide a reasonable tissue-engineered alternative to free-tissue transfer in medically compromised patients.[78]

Conclusion

Wound care matrices can be used to successfully close wounds either by promoting spontaneous healing or by preparing the wound bed for skin grafting, which is a less invasive procedure than surgical tissue transfer. However, we should always bear in mind that topical wound therapeutic management strategies only work effectively on adequately perfused wound beds that have a moist environment without devitalized tissue or a critical bacterial burden.

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Disclosure

The authors report no conflicts of interest in this work.

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