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REVIEW

Current and future developments in the treatment of chronic wounds

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Kuen Yeow Chin
Suresh M Anandan*
Karan Koshal*
Prashant Gujadhur*

Department of Plastic Surgery, Wexham Park Hospital, Slough, United Kingdom

*These authors contributed equally to this work

Abstract: Chronic wounds are common and their incidence has been on the increase. They place an enormous burden on health care services and have a major impact on several aspects of patients' wellbeing. It is vital for clinicians to recognize the complexity of the underlying processes leading to the development of a chronic wound. With this knowledge, the key factors that led to their development in each patient can be identified and appropriate steps taken to address modifiable factors. There is currently a wide range of treatments available for treatment of chronic wounds, with a range of exciting new treatments being developed. This paper aims to give an overview of the common etiology and pathophysiology of chronic wounds followed by a discussion of a range of current and future developments in their treatment.

Keywords: chronic wound, wound healing, cutaneous

Introduction

Cutaneous wound healing begins when the integrity of the skin is breached. The body initiates the healing process to re-establish skin continuity so it can carry out its functions, especially as a protective barrier. Wound healing can be divided into four distinct but overlapping steps, ie, hemostasis, the inflammatory phase, the proliferative phase, and wound remodeling.[1] These phases must occur in the proper sequence and time frame for a wound to heal successfully.[2]

The wound healing process, however, can be impaired by multiple factors, which can be divided into systemic (congenital or acquired) and local factors. Individuals with congenital conditions (eg, Ehlers-Danlos syndrome, pseudoxanthoma elasticum, Werner syndrome) have abnormal connective tissue synthesis or regulation, affecting wound healing.[3] Deficiency in essential nutrients (see below), medications like steroids and nonsteroidal anti-inflammatory drugs, systemic factors including endocrine disorders (eg, diabetes mellitus), age, stress, and smoking can impair wound healing. Local factors that affect wound healing include circulation and oxygenation of the wound area, infection, foreign bodies, and venous insufficiency.[2]

Chronic wounds are common and place an enormous burden on health care services. A review by Posnett and Franks[4] predicted a significant increase in the number of patients with chronic wounds in the UK over the next 20 years. One of the main factors is the aging population, because chronic ulceration is higher in the population aged over 65 years. Chronic wounds have a major impact on several aspects of patients' wellbeing. This highlights the importance of achieving a good understanding of the pathophysiology of chronic wounds, and finding new effective treatments.

Correspondence: Kuen Yeow Chin
Department of Plastic Surgery, Wexham Park Hospital, Wexham, Slough, SL2 4HL, United Kingdom
Email andycky@doctors.org.uk

Etiology of chronic wounds

The most common ulcers seen in clinical practice are venous, diabetic, and pressure ulcers.[5–7] In spite of these three distinct causes, the general underlying pathophysiology of difficult-to-heal wounds is believed to be one of tissue hypoxia and repetitive ischemia-reperfusion injury.[8]

Venous ulceration

The prevalence of venous leg ulcers is approximately 1%, and the incidence increases with age. In 2005–2006, the total cost of treating venous leg ulcers in the UK was estimated at £168–£198 million.[9]

Obesity, immobility, venous disease, and congestive cardiac failure (all more common with advancing age) are factors that cause venous hypertension.[10] Sustained venous hypertension leads to chronic venous insufficiency and development of venous ulcers. Venous insufficiency leads to development of edema in the dependent lower limb, which increases the diffusion distance required for nutrients and metabolites to reach the skin, leading to ischemia.[8] Increased venous pressure can be transmitted to the capillaries, leading to capillary distension and leakage of macromolecules like fibrinogen into the extravascular space, forming a precapillary fibrin cuff.[11] Histologically, these fibrotic cuffs envelop dermal capillary vessels, disrupting the exchange of oxygen and nutrients between blood and the dermis of skin as well as entrapping leucocytes and growth factors.[5] Leg elevation and the muscle pump action of walking improve lower limb perfusion, and activated leucocytes orchestrate a reactive oxygen species-mediated reperfusion injury.[10] Repeated hypoxic-reperfusion injury is what prevents healing from taking place.

Diabetic ulceration

About 171 million people worldwide were estimated to have diabetes mellitus in 2000, with a predicted increase to 366 million in 2030.[12] Up to an estimated 25% of diabetic patients in the US will develop diabetic foot ulcer in their lifetime; half of these ulcers will become infected and 20% will undergo amputation of their lower limb.[9] Approximately 24,000 hospital admissions in the UK yearly are for the management of diabetic wounds.[13]

Diabetic ulcer pathophysiology is multifactorial; peripheral vascular disease, peripheral neuropathy, and an impaired immune system from long-term uncontrolled hyperglycemia all contribute to development of a chronic wound.[14] Neuropathic diabetic ulcers develop from repeated trauma and deformity of the foot, which trigger preulcerative callus formation.[5,15] Such feet are then prone to local pressure effects, hypoxia, and tissue necrosis. Neuroischemic ulcers differ in that they also show macrovascular atherosclerosis that further enhances local tissue hypoxia, predisposing the extremities to poor healing. Diabetic patients have at least a 2–3 times higher incidence of atherosclerosis of the lower limbs compared with the nondiabetic population.[16] Endothelial cell dysfunction, smooth muscle cell abnormalities, reductions in endothelium-derived vasodilators, and increased levels of vasoconstrictors (eg, thromboxane A2) in atherosclerotic vessels lead to tissue hypoxia, increased risk of ulcer development, and poor healing.[17] Dysregulation of cellular functions also contributes to the development of diabetic ulcers. Defective leucocyte chemotaxis, phagocytosis, and defective T-cell immunity are responsible for inadequate bacterial clearance. Dysfunction of fibroblasts and epidermal cells leads to delayed or impaired wound healing.[2]

Pressure ulceration

Pressure ulcers define a diverse spectrum of ulceration due to the external compression, shearing, or frictional forces of soft tissues and perforating vessels, especially those overlying a bony prominence.[5] A higher incidence is seen in patients aged over 65 years, females, and those of Caucasian ethnicity. This is especially true if they confer risk factors such as immobility, prolonged intensive care unit stays, and undernourishment.[5] Although the etiology is multifactorial, the pathogenesis is believed to be due to repetitive ischemic-reperfusion injury rather than prolonged ischemia itself.[8]

Despite clear etiologies, it is important to recognize that the development of a recalcitrant wound is multifactorial and clinicians must make use of treatment options targeted to the underlying pathophysiology.[18]

Molecular characteristics of chronic wounds

Research has identified common molecular characteristics of chronic wounds. In general, such ulcers exhibit an exacerbated proteolytic environment.[6] Matrix metalloproteinases are a key group of proteolytic enzymes that promote extracellular matrix debris removal and thereby space for the angiogenesis and cell migration necessary for normal wound healing. Relative to acute wounds, levels of matrix metalloproteinases are found in higher concentrations in the fluids of chronic wounds.[5] It is proposed that the resulting excessive degradation of the extracellular matrix and chemical regulators impairs normal tissue repair.[13]

The interactions of growth hormones in the healing wound are vast and complex, but vital for the progression of the healing cascade.[13] Nonhealing wounds are thought to have reduced growth factor bioavailability either from increased proteolytic degradation or extracellular matrix trapping.[19] Furthermore, reduced levels of transforming growth factor-beta, an anti-inflammatory factor, contribute to the abnormally prolonged inflammatory reaction that is observed in chronic wounds. This leads to a proteolytic environment, which also faces further damage with cellular apoptosis induced by reactive oxygen species.[5,13] Interestingly, it has been suggested that aged fibroblasts are less responsive to transforming growth factor-beta than younger fibroblasts.[5,20] The age-related reduction in proliferation of fibroblasts (ie, replicative cell senescence) is thought to result from reduced growth factor responsiveness of fibroblasts.[13,21] This would imply aging cells within the body are less well equipped for healing to occur, and this may be due to altered gene expression of stress-related genes.[21]

General management

The first step in the management of chronic wounds is obtaining a thorough history and examination to identify the underlying etiology and factors that have led to its development. This knowledge will allow clinicians to guide the patient toward an environment conducive to optimal wound healing.[18] Key questions from the history should include the duration of ulceration and previous treatment strategies. Equally important is the psychosocial history, which may identify factors that perpetuate ulcer formation, eg, financial burden resulting in poor diet and nutrition.

Optimizing the local wound environment

Devitalized necrotic tissue impairs wound healing and promotes bacterial growth.[7] Wound debridement to remove such tissues, leaving behind only healthy tissue with the potential to heal, changes the chronic wound characteristic to one that represents an acute wound.[6] Furthermore, a moist environment is one that is most suited to open wound healing and as such wound dressings are used to maintain such an environment.[14] Both debridement and dressings will be discussed further in the article. Exposed tendons, nerves, vessels, and bones require prompt surgical intervention in an attempt to afford protection from the environment, usually with vascularized soft tissue coverage.[6] Foreign bodies, such as orthopedic devices or vascular stents, are a nidus for infection and generally require prompt removal from the wound environment.[14]

Infection

Open wounds are exposed to the elements and therefore invariably include the presence of organisms.[8] However, not all wounds will require microbiologic analysis or the use of antimicrobials. The terms contamination, colonization, and infection describe the clinical and microbiologic spectrum of interaction between bacteria and host tissue. A contaminated wound is one that is clinically asymptomatic because the host defenses are able to clear away any nonreplicating organisms that may be present.[22] Colonization refers to a wound that is burdened with an increasing number of replicating organisms without host tissue damage.[18] Once a critical bacterial count is reached (critical colonization) healing is impaired.[8] Clinically, a contaminated wound may be malodorous, display serous discharge, granulation tissue, and sometimes a change in wound bed color. An infected wound implies there is some degree of local host tissue damage from the presence of a replicating organism. Quantitative analytical definition of an infected wound is one that contains a bacterial count $>10^5$ colony forming units per gram of tissue/mm^3 of pus.[18] Clinically, the wound may display classic inflammatory characteristics, ie, redness, warmth, pain, and swelling. An infected wound appropriately attracts myeloperoxidase-rich leucocytes that release proteolytic enzymes and superoxide radicals to kill the bacteria. However, this high-protease, high oxidant environment also destroys the surrounding extracellular matrix, growth factors, and cytokines necessary for timely wound healing.[8,18,21] As such, an infected wound will take longer to heal.

Smoking

Cigarette smoking exposes the body to over 4,000 different compounds, many of which are harmful to the body and interfere with the normal dynamics of wound repair.[23] Nicotine, an addictive alkaloid, is a potent vasoconstrictor that reduces nutrient-rich blood from reaching areas undergoing regeneration.[18] Nicotine also increases the adhesiveness of platelets, thereby perpetuating a prothrombotic microvascular environment and further tissue ischemia.[24] Other byproducts, such as carbon monoxide, reduce overall body oxygen transport, and hydrogen cyanide inhibits certain enzymes involved in cellular oxidative metabolism as well as leucocyte function.[23] The overall effect of cigarette smoking is therefore one of relative tissue hypoxia and interruption of the inflammatory phase of wound healing.[23,24]

Nutrition

Any healing wound will require energy and nutrients above that of the basal state to fuel the vast cellular and metabolic

activity it ultimately orchestrates. Certain dietary nutrients are essential for specific stages of the healing process. A deficiency in their supply will therefore prolong if not impede the normal healing process. The antioxidant, vitamin C (ascorbic acid) is a critical cofactor in the synthesis and maintenance of collagen as well as neutrophil migration and angiogenesis.[18] Subclinical deficiency of vitamin C is becoming increasingly identified in at-risk individuals, and there have been recommendations to use oral ascorbic acid supplementation throughout the healing process.[25]

Vitamin A is a key supplement used widely in the perioperative period because of its potent facilitation of normal wound healing. Studies have also shown it to reverse immune suppression induced by steroids or that seen in the postoperative period.[25] Vitamin A is thought to augment the early inflammatory phase of wound healing through a host of different mechanisms, the most significant being its ability to increase the rate of collagen cross-linking.[25] A clinical review of vitamin E concludes that systemic vitamin E could have a negative impact on surgical wounds, similar to glucocorticoids.[25] Furthermore, lipid and water-soluble preparations may have different actions in wounds, and therefore more research is needed into the effects of topical vitamin E on surgical wound healing.

A detailed nutritional history and evaluation can sometimes be overlooked when assessing patients with chronic wounds. A more recent review of nutrition and risk of pressure ulcers in an intensive care unit setting highlights the importance of screening for undernourishment, calculating the resting calorific intake of at-risk patients, and monitoring and supplementing the dietary intake of essential nutrients.[26]

Nonsurgical treatments

A range of conservative treatments has been used to manage nonhealing wounds. With recent technologic advances and a greater understanding of the pathophysiology of chronic wounds, novel therapies such as tissue-engineered substitutes and growth factors, have also been developed.[27] A chronic wound is one that has not adequately re-epithelialized within 6–8 weeks.[28] Regardless of the wound type, general local wound management principles exist for a wide range of chronic wounds.[8] The Wound Healing Society uses the TIME acronym, which is a simple but effective method for defining, communicating, and addressing elements associated with impaired wound healing.[29] The letter "T" refers to tissue, including specific tissue deficits and devitalized or necrotic tissue, "I" stands for inflammation or infection within and surrounding the wound site, "M" indicates the state of moisture balance (ranging from maceration to desiccation) while "E" represents the quality of wound edge (usually heaped up, nonadvancing, and hyperkeratotic in chronic wounds) as well as re-epithelialization.[6]

Basic care

According to Humphreys et al,[30] established conservative treatment modalities for difficult-to-heal wounds include compression therapy, which remains the mainstay for venous ulcers and includes use of compression stockings, hosiery, Unna's boots, and pneumatic compression pumps. Moisturizing of the surrounding skin, control of exudates and eczema, as well as treating any infection, also play an important role. Arterial ulcers are managed by increasing vascularity to the limb through adequate control of any underlying diabetes, hypertension and hypercholesterolemia, as well as advice on smoking cessation and regular exercise. Cilostazol and pentoxifylline have also been shown to improve functional status, ankle-brachial index, and quality of life in patients with arterial ulcers.[6] Neuropathic ulcers are usually treated nonsurgically by good glycemic control in diabetes, appropriate footwear, prompt treatment of infection, and regular assessment of vascular status.[8] Pressure relief, regular repositioning of the patient and skin inspection, use of support surfaces (eg, air-fluidized mattresses), and optimization of nutritional status form the basis of conservatively managing pressure ulcers.

Dressings

Dressings have played an important role in the care of chronic wounds because they promote a moist environment to assist healing. In 1962, Winter[31] demonstrated in animal models that re-epithelialization of a partial thickness wound proceeded 1.5 times faster if the wound was occluded. Although occlusive dressings have not shown such dramatic effects in clinical studies of patients with chronic wounds, they may reduce pain, and are easy to use and cost-effective. Dressings containing hyaluronic acid, which specifically promotes healing, are the only dressings proven so far to contain materials that correct abnormalities in the healing cascade.[13]

Moist dressings

Maintenance of a moist environment is generally accepted as the best topical environment for open wounds.[32] Indeed, many current dressings include debridement and antimicrobial activity with moisture control. These actions combine to make up the components of wound bed preparation.

Ideally, dressings should minimize pain and be easy to use while preventing friction and shear, and protect the periulcer tissue and skin. Vaneau et al[33] recommend the use of hydrogels for the debridement phase, foam at the granulation stage, and either hydrocolloids or low-adherence dressings for the epithelialization phase. Furthermore, a single modality therapy consisting of either a paraffin gauze dressing or a saline-moistened dressing has also been shown to be effective.[32] However, with the exception of hydrocolloid dressings, there is little evidence establishing the superiority of modern dressings in terms of the following general performance criteria: ease of use, pain, ability to absorb and contain exudates, and avoidance of wound trauma on removal.[32]

Antimicrobial therapy

Decreasing bioburden improves control of local and systemic inflammatory mediators. Bacterial concentrations exceeding 10^5 bacteria colony-forming units per gram of tissue or any level of β-hemolytic streptococci have been shown to impair wound healing.[34] *Staphylococcus aureus* is the most commonly identified pathogen in chronic wounds in the US and Europe, while methicillin-resistant *S. aureus* accounts for upwards of 20%–50% of cases.[6] Topical antibiotics (as well as surgical debridement) effectively lower the number of bacteria in chronic wounds and are more effective than systemically administered antibiotics in granulating wounds.[35] However, systemic antibiotics should still be used to treat systemic infection, acute foot infections, and local cellulitis. Use of silver-containing dressings has increased in recent years, with reports of improved healing rates, although not in complete ulcer healing.[36] Topical antibiotics should be discontinued once the bacterial balance has been restored because prolonged use may inhibit wound healing and promote development of resistant organisms.

Intermittent pneumatic compression

Intermittent pneumatic compression can be used as an adjuvant therapy to simple compression. It is effective for managing chronic venous ulcers with severe edema that are resistant to simple compression therapy alone. Compression pressure (20–120 mmHg) is provided at preset intervals to improve venous and lymphatic flow, and is generally used 2 hours a day for a maximum of 6 weeks.[1]

Topical negative pressure therapy

Typically applied after surgical debridement, topical negative pressure therapy consists of the wound having an airtight seal around it where the compartment is connected to an external suction apparatus creating negative pressure through a dressing interface. This allows for removal of excess fluid[37] and improves local dermal perfusion, stimulates angiogenesis, and granulation tissue formation, while decreasing interstitial fluid control, wound exudates, and bacterial load,[1] resulting in faster wound healing rates. However, side effects of such treatment include pain, fluid loss from large wounds, and bleeding. It is contraindicated in patients with frail, thin, or easily bruised skin, and those with neoplasm in the wound floor.[37]

Biosurgery

Biosurgery, through use of sterile maggots, involves the selective digestion of slough and necrotic tissue from wounds without damaging the surrounding healthy tissue.[38] This cost-effective method is best suited to sloughy and infected wounds, and is well tolerated by patients.[39] Contraindications are limited to wounds involving fistulas and those that are close to major blood vessels or vital organs. Limitations include the short shelf-life of maggots, lack of esthetic appeal, and pain at the application site encountered by some patients.[27]

Hyperbaric oxygen

Given that most nonhealing wounds are hypoxic, 100% oxygen given in a pressurized chamber may hasten the wound healing process.[40] This method may be a useful adjunct in the treatment of diabetic ulcers and chronic nonhealing wounds. Nevertheless, its use is currently restricted because special equipment and expertise is required.

Growth factors

The role of growth factors in wound healing is well established.[41,42] They exert influence on various target cells via paracrine and autocrine mechanisms. Identification of the role of individual growth factors in the wound healing process has already led to the development of targeted therapies tested in clinical trials.[43] These growth factors, produced by recombinant DNA technology, attract new cells and increase cell growth at wound sites by targeting individual phases of wound healing. However, clinical results from topical application of growth factors to chronic wounds have not been as remarkable as first hoped due to the complexity of the wound healing process.

Platelet-derived growth factor-BB is currently the only growth factor approved for the treatment of chronic ulcers.[41] Its functions include being mitogenic for smooth muscle cells, endothelial cells, and fibroblasts, being a chemoattractant for

neutrophils and fibroblasts, and enabling fibroblast proliferation and collagen metabolism.[43] Steed et al[44] reported significantly improved ulcer healing rates in patients receiving topical platelet-derived growth factor versus a placebo group. Another randomized controlled trial found that 30 μg/g of platelet-derived growth factor gel daily did not bring about a significant improvement in healing rates versus placebo (36% versus 35%), but 100 μg/g platelet-derived growth factor gel daily led to 50% of ulcers healing by 20 weeks of treatment.[45] Platelet-derived growth factor (eg, becaplermin) has been used to treat noninfected diabetic foot ulcers up to 5 cm² in size and may have some value in treating pressure ulcers.[46] However, there have been recent concerns regarding malignancy with the use of becaplermin.[6] Other growth factors that have been studied include vascular endothelial growth factor, basic fibroblast growth factor, and granulocyte-macrophage colony-stimulating factor. Vascular endothelial growth factor stimulates angiogenesis in granulation tissue and collateral blood vessel formation in peripheral vascular disease.[47] Application of basic fibroblast growth factor causes fibroblast and epithelial cell proliferation, matrix deposition, wound contraction, and angiogenesis, while accelerating granulation tissue formation.[47] However, human trials of topical fibroblast growth factor-2 have not shown a significant advantage over placebo.[48,49] Granulocyte-macrophage colony-stimulating factor mediates epidermal cell proliferation and may have a role in treating infected diabetic foot ulcers.[27] Epidermal growth factor is produced by platelets, macrophages, and monocytes,[49] and its main action is to stimulate epithelial cells to grow across a wound by interacting with the epidermal growth factor receptor on epidermal cells and fibroblasts.[50] Human trials of topical epidermal growth factor have shown increased epithelialization and a shortened wound healing time.[49–51]

With further studies, growth factors could be administered in the future sequentially, in combination, or at timed intervals to closely mimic the normal healing process. The diversity of growth factors and chronic wound types show that such growth factors are potential new treatments if each patient's individual requirements can be identified correctly.[13]

Surgical treatment

The first step in management is to remove local deterrents to healing in the form of devitalized and necrotic tissue which promotes bacterial multiplication and infection, exaggerates inflammation, and acts as a physical barrier to healing.[6,52,53] The term debridement was introduced by Pierre Joseph Desault, the first French professor of clinical surgery, to describe the technique of freshening wound edges by cutting dead-appearing tissue and closing primarily.[54,55] Surgical debridement later became standard practice following the increased survival of patients with military wounds. Consequently, level 1 evidence for the benefit of debridement is lacking because designing such a study would lead to ethical issues.[56] A structured approach to assessment, diagnosis, and management of any type of wound with a patient pathway placing patient needs at the center has been described.[6,57]

Surgical debridement

This is an effective and rapid method for removing nonviable tissue down to and including healthy tissue. The procedure needs anesthesia and may be contraindicated in some patients.

Conservative sharp debridement is removal of dead tissue using scalpel or scissors close to the viable margin. The procedure can be done at the bedside, is rapid, requires no anesthesia, and can be performed by a wide range of practitioners.[57] Debridement may have to be repeated and can be combined with autolytic debridement or negative pressure wound therapy.

The clinical margin of surgical debridement traditionally is appearance of dermal bleeding at the skin margin. Histopathologic analysis of wound edges has been done following debridement, and hyperkeratosis and dermal fibrosis have been found to exist at wound margins. It has been suggested that removal of impaired cells with histologic control would reduce the number of debridements needed and improve healing, and further studies may be needed to define such a margin.[58]

Negative pressure wound therapy

Described initially by Fleischmann et al,[59] it has rapidly proved to be useful in various acute and chronic wounds.[60] It is increasingly being used in wound treatment, although systematic reviews have not established a clear benefit.[61] It has been used to expedite the surgical bed for a skin graft following surgical debridement and to improve skin graft take in edematous wounds. Vuerstaek et al[62] showed that use of negative pressure wound therapy (NPWT) reduced skin graft preparation time by 58% and reduced time to overall healing by 35%. Skin graft take (in patients with chronic leg ulcers) was 92% when NPWT was used as an adjunct compared with 67.4% in controls.[63] Although wound contraction is insignificant, the improved patient comfort, decreased need for regular dressing changes, and less effort required by the

nursing staff make NPWT advantageous for the treatment of pressure sores.[64] NPWT is also a management option for large and complex wounds in difficult areas like the abdomen, perineum, and lower limb with exposed tendons and bones.

Skin substitutes

Primarily intended for extensive burns due to lack of a donor area, a variety of regenerative materials has been developed and used in chronic wounds. Extensive tissue replacement products, referred to recently as biomodulators,[65] have a role in tendon repair, hernia repair, and tissue augmentation, eg, Strattice™ (LifeCell Corporation, Bridgewater, NJ, USA), and Permacol™ (Covidien AG, Mansfield, MA, USA). Skin substitutes can be epidermal, dermal, or combined.[66] A few examples of these skin substitutes are discussed, but do not represent a comprehensive list of all products available on the market.

Epidermal

The cultured epithelial autograft was the first major development in treating extensive burns. A skin biopsy is performed to harvest the patient's keratinocytes that are then cultured in the laboratory in 2–4 weeks. This forms a layer of epidermis and is primarily used for full thickness burns greater than 30%, and has also been used in the treatment of leg ulcers.[65] It is fragile, and hence the results are unpredictable. Epicel® (Genzyme Tissue Repair Corporation, Cambridge, MA, USA) and Laserskin® (Fidia Advanced Biopolymers, Abano Terme, Italy) are the commercial products. Cultured allogenic epidermis (fresh human donor skin, neonatal foreskin) has been used to heal burns and chronic wounds by acting as temporary coverage as host cells eventually replace the cells.[65] They are readily available and cheaper than the cultured epithelial autograft.

Dermal

Inclusion of a dermal component in a skin substitute provides mechanical stability and durability.[52] Dermagraft® (Advanced Biohealing Inc, La Jolla, CA, USA) is a cryopreserved, single layered human fibroblast-derived dermal substitute designed for treatment of diabetic foot ulcers of greater than 6 weeks' duration, including full thickness wounds.[65] This can be applied weekly for up to eight applications over a 12 week period. Transcyte® (Smith and Nephew, London, UK) is another fibroblast-containing construct that uses a silicone-covered nylon mesh for cellular support, and is indicated for temporary coverage of surgically excised burn wounds.[52]

Biobrane® (Dow B Hickam Pharmaceuticals, Sugar Land, TX, USA) is a bilaminar synthetic dressing with an inner layer of nylon mesh that allows fibrovascular ingrowth and has an outer silastic semipermeable and protective layer. This dressing is mostly used to cover partial thickness burns until healing when the dressing lifts off. There is less pain, reduced healing time, and shorter hospitalization.[67]

Integra® (Integra LifeSciences Corporation, Plainsboro, NJ, USA) is a dermal regeneration template consisting of a dermal matrix made of cross-linked bovine collagen and shark-derived chondroitin sulfate, and is covered with a temporary silastic membrane. The wound bed should be surgically debrided and the Integra cut to the defect and applied. Once the dermis is vascularized (by 2–3 weeks) the top silastic layer is removed and a thin autograft applied. This is useful in full thickness burns, full thickness skin defects of acute and chronic wounds, and soft tissue defects.[67]

Alloderm® (Lifecell, Woodlands, TX, USA) is an acellular dermal matrix produced from human cadaveric skin. It can be reconstituted by soaking in crystalloid solution and used immediately in combination with a thin autograft on top for wound coverage. Matriderm® (Dr Suwelack Skin and Health Care AG, Dallas, TX, USA/Eurosurgical, Churchtown, Ireland) is an acellular dermal matrix consisting of bovine collagen and elastin. It is used as a one-step procedure with an autograft for full thickness skin coverage. It has been used to cover partially exposed tendons, and long-term results yield a pliable skin with fewer adhesions.[68]

Combined epidermal and dermal strategy

Apligraf® (Organogenesis Inc, Canton, MA, USA) is a bilayered skin equivalent consisting of a neonatal keratinocyte layer as the epidermis and neonatal fibroblasts in an extracellular bovine and human collagen matrix. It is approved by the US Food and Drug Administration for use in chronic venous and diabetic ulcers.[65] Orcel® (Forticell Bioscience, NY, USA) is another bilayered cellular matrix similar to Apligraf except that it has a porous collagen sponge matrix. It is used to treat epidermolysis bullosa, skin graft donor sites, and chronic wounds.[67]

Future therapies

Cellular communications

Gap junctions are intercellular channels residing in cellular plasma membranes, allowing passage of small molecules like ions (K^+ and Ca^{2+}), second messengers (cyclic adenosine monophosphate and cyclic guanosine monophosphate), and small molecules (glucose) as a way of intercellular communication.[69] As previously explained, wound healing requires coordination of several processes involving different

cell types. Connexins are the building blocks of gap junctions.[69–72] A recent advance in developing new treatment for chronic wounds has focused on modulating intercellular communication by regulating connexin levels.[69,72–75] There are at least 10 different connexins in the epidermis,[71] and they are expressed at different levels during different stages of wound healing.[69,70,76]

Connexin 43 is the most highly expressed connexin in the skin.[69] Its expression at the wound edge falls a few hours to 2 days after wounding, and increases to high levels during the proliferative phase of wound healing.[72] It is suggested that low levels of connexin 43 are required to allow keratinocyte migration and re-epithelialization.[77] There are two treatments that have been developed to target connexin 43 regulation. Topical antisense oligodeoxynucleotide acts by transient knockdown of connexin 43 expression in the epidermis and dermis,[73] with reported effects of enhanced keratinocyte and fibroblast migration and proliferation rates, with reduced amounts of neutrophils and macrophages in the wound.[78,79] Gap27 treatment acts by downregulating connexin 43-mediated signaling, and is also reported to enhance migration and proliferation of keratinocytes and fibroblasts.[80] Altered connexin expression has been shown in diabetic wounds, suggesting a likely link between connexins, diabetes mellitus, and wounds that are difficult to heal.[81]

As current available studies have shown therapeutic potential in this field,[69] with possible further targets to regulate (connexins 26 and 30),[82–84] this may provide clinicians with another treatment option for managing chronic wounds.

Stem cells

Stem cells have the capacity to self-replicate, have long term viability, and multilineage potential.[85,86] Uncommitted mesenchymal stem cells (MSCs) can be found in the bone marrow stroma and connective tissues in various organs of the body,[85] and are capable of differentiating into tissues like bone, cartilage, adipose tissue, and endothelium, depending on their microenvironment.[87,88] MSCs have been found to attenuate the systemic inflammatory response,[89–91] and are postulated to modulate wound healing by differentiating into various cell types (fibroblasts, myofibroblasts, antigen-presenting cells),[92,93] integrate into the wound, and participate in wound repair.[94]

However, only a small percentage of MSCs transplanted into the wound (about 5%) are shown to survive.[95] They have not been shown to transform into keratinocytes or dermal appendage cells,[88] but have been suggested to provide benefit to wound healing through paracrine pathways rather than replacing tissues.[85] The mechanism of delivery of this treatment can be by direct local application of MSCs or with a dermal analog scaffold.[85] Several studies using topical autologous bone marrow MSCs on wounds have reported increased vascularity of the wound bed,[92,96] increased wound epithelialization,[96,97] improved skin graft take,[92,97] and better wound healing.[98–100] Studies have also looked at the potential of skeletal muscle[37,101] and adipose tissue stem cells.[102] Kim et al[103] found that adipose-derived stem cells also help to accelerate wound healing and exhibit antioxidant effects.

Although promising results have been reported using stem cells as a treatment for chronic wounds, crucial aspects of their use, including mechanism of delivery, dosage, and safety, need to be elucidated prior to use outside clinical trials.

Gene therapy

Gene therapy introduces specific genes to target cells altering their inherent genetic coding and thereby enhancing, amending, or negating their biological function by changing the way their products (eg, proteins) are expressed.[104] Genetic material delivery methods can be categorized into virus-dependent (transfection using a viral vector) and nonviral techniques (transduction, eg, microinjection, liposomes, antisense oligonucleotide).[27,105] A gene-activated matrix involves embedding a gene transfer vector into a matrix that is incorporated into the wound, providing exposure of the genetic material to target cells.[27,106,107]

Studies using gene therapy in wound healing have mainly involved genes for growth factors and their receptors.[104,105,108] As discussed above, growth factors act on a range of cell types involved in wound healing to orchestrate the different stages of this process. However, the success of growth factor therapy is limited by problems including a short half-life, low bioavailability, enzymatic inactivation, and need for carrier molecules.[105] Gene therapy may provide a solution by having a more prolonged effect, while gene vectors can produce higher transduction efficiency and be more cell selective.[109] Gene therapy using adenoviral transfer with platelet-derived growth factor in a rabbit model showed improved wound healing,[110] enhancing levels of transforming growth factor-β gene in murine models and showing accelerated healing and increased wound strength.[111] Gene therapy has also been used to enhance the effects of epidermal growth factor[112] and insulin-like growth factor-1 in animal wound healing models,[113] with reports of improved wound healing.

Although gene therapy has shown potential as an attractive approach to help wound healing, it is still in early stages

of development and requires further studies into its stability and safety for therapeutic use.

Conclusion

It is vital for clinicians to recognize the complexity of the underlying processes leading to the development of chronic wounds. With this knowledge, the key factors leading to their development in each patient can be identified and appropriate steps taken to address modifiable factors. There is currently a wide range of treatments available for chronic wounds, with a range of exciting new treatments being developed. Clinicians armed with a good understanding of the wound healing process and pathophysiology of different chronic wound types will be able to choose the treatment that is most suitable for their patient in terms of addressing specific stages of impaired wound healing and also their social circumstances and needs.

Disclosure

The authors report no conflicts of interest in this work.

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