Chronic cutaneous wounds are a social and economic burden to the United States, affecting roughly 6.5 million patients. Over $25 billion dollars is spent annually to treat this condition; and the toll it takes on the economy will only continue to grow as the global population ages, the incidence of obesity and diabetes increases, and the cost of healthcare rises. With this in mind, efforts have been made to obtain a better understanding of the biological mechanisms occurring within these chronic wound beds in hopes of shedding light on inadequacies with our current treatment choices as well as stimulating ideas for possible new approaches or modalities. The purpose of this article is to summarize the molecular changes occurring within the beds of chronic ulcers, and to review the current role of one of the cornerstones in wound care therapy, debridement, and what evidence-based medicine has taught us about its efficacy.

Why Chronic Wounds Are Chronic

As practicing physicians, our goal is to obtain complete wound closure as quickly and as cost-effectively as possible. We routinely hear that a chronic wound must be converted to an acute wound in order for it to progress sequentially through the phases of healing. However, these intractable ulcers fail to follow defined timeframes, and the steps needed in achieving closure are complex and multi-factorial. Wounds of chronic nature are often characterized by resident cells that have undergone phenotypic changes. These phenotypic changes result in a modification of the physiology of the wound bed and alter these cells’ effectiveness in participating in the biochemical mechanisms.

The environment and the inflammatory response of a chronic wound are much different than those of an acute wound. Alterations in protease regulation, cytokine release, fibroblast morphology, and the composition of the extra-cellular matrix are all thought to play a role in the impairment of wound healing. When protease regulation becomes disrupted in non-healing ulcerations, mal-distribution or elevated levels of matrix metalloproteinase (MMPs) are often noted within the fluid of chronic venous leg and pressure ulcers. These MMPs alter fundamental cell processes like apoptosis, angiogenesis, migration, and proliferation through their action on the extra-cellular matrix, and negatively impact wound contraction and closure. For instance, serine proteases such as neutrophil elastase are present in higher amounts in chronic venous leg ulcer fluid and this results in increased degradation of fibronectin, an integral component in the extra-cellular matrix.

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Debridement and the Current State of Play

Here are the latest developments in this rapidly changing area.

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An inverse relationship exists between levels of pro-inflammatory cytokines and wound healing potential. Studies have shown that as TNF-alpha, IL-1B, and TGF-B1 decrease, the wound begins to progress through the phases of tissue repair and epithelialize. In these chronic wounds, macrophage function is stifled, subsequently preventing recruitment of fibroblasts and keratinocytes to the area of injury.

Another potential cause of wound chronicity is alteration in fibroblast morphology and proliferation. The shape change is believed to be due to the presence of certain pro-inflammatory cytokines which create an enlarged polygonal cell contour that is much different than the normal spindle-shaped fibroblast. It is possible that this morphogenesis limits the fibroblast’s response to growth factors.
and compromises its motility and ability to reorganize the extra-cellular matrix environment. “In a study comparing fibroblasts from chronic venous leg ulcers and pressure wounds to patient-matched normal skin fibroblasts, the non-healing wound sites exhibited decreased fibroblast proliferation and collagen production.” This may further contribute to prolonged healing.

Keratinocyte adhesion and movement play a critical role in allowing a cutaneous lesion to reach complete closure. The activity of these cells is dependent on the extra-cellular matrix and the cytokines located in the wound environment. Ultimately these two factors determine the phenotype of the keratinocyte. In acute wounds, keratinocytes express a5B1 integrin that permits migration of the cell. However, this integrin’s expression is markedly reduced in recalcitrant wounds.9

Other Factors That Affect Healing

Identifying reasons why a wound has become stagnant is of utmost importance, as it is only after this is accomplished that you can fully address the problem. Evaluating the molecular chronic wound environment is only part of the picture. Besides the biochemical changes discussed previously, there are a number of different disease-specific deterrents to wound healing. Peripheral vascular disease, malnutrition, and infection are just a few of the more common pathologies.

Oxygen is a necessary element for completion of vital steps in the phases of healing. Its absence or limited supply, as is the case with vascular disease, threatens the body’s ability to respond to injury. Cellular hypoxia hampers hydroxylation of lysine and proline, thereby preventing collagen fibril crosslinking. When oxygen is at a deficit, leukocyte oxidative phosphorylation becomes less effective and bacteria are not destroyed. This, in turn, lowers the threshold for infection.10

In cases where patients are malnourished and their diets lack certain minerals and vitamins, wound failure will result. Vitamins such as ascorbic acid (Vitamin C) and retinoic acid (Vitamin A) function as cofactors and cellular signals. They are needed in stabilizing and modulating collagen crosslinks and engaging in cellular metabolism.11

Infection is a process whereby bacteria invade healthy tissue to elicit an immune response. They can form biofilms and cause protraction of the inflammatory phase, whereby excess cytokines and proteases are released. Healthy granulation tissue subsequently gets degraded, tissue growth factors are destroyed, and the deposition of collagen is hindered.11 Capable of modifying their genotype and phenotype, these microorganisms often develop multi-drug resistance, making them even more difficult to combat. Bacterial bio-burden increases the metabolic load placed on the wound bed;12 and endotoxins located in the cell wall of some gram negative bacteria further complicate the situation as they prevent the migration of fibroblasts/keratinocytes from the periphery into the ulcer.

This begs the question, how do we as physicians create a more ideal healing environment? Taking both the micro and macro wound environment into account, the answer is not merely one action but rather a multitude of treatment responses. These include providing adequate perfusion to the wound, management of bio-burden, debridement, nutritional supplementation, pressure mitigation, and the management of underlying disease state such as diabetes and venous insufficiency. The remainder of this article, however, will focus on debridement and why it is considered the cornerstone in wound care therapy.

Debridement

Debridement is defined as the removal of devitalized, necrotic tissue or foreign bodies from a wound. Optimum debridement should achieve a balance between the removal of necrotic tissue and the preservation of healthy tissue, while not jeopardizing subsequent healing.13 Chronic wounds are likely to require serial debridements rather than a single intervention. The underlying pathogenic abnormalities in chronic wounds cause a continual build-up of necrotic tissue, and regular debridement is necessary to reduce the necrotic burden and achieve healthy granulation tissue.

Debridement reduces wound contamination and controls excessive bacterial load, thereby assisting in the reduction of tissue destruction. Dead spaces that may otherwise harbor bacterial growth must be exposed during debridement. Removing senescent and non-migratory cells from the ulcer edge may stimulate the wound healing cascade by allowing for improved availability of growth factors as the necrotic tissue will no longer act as a physical barrier to growth factor re-

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New Debridement Modalities

Advances in molecular science have given us insight into how a chronic wound behaves and have allowed for us to develop new debridement techniques. A recent multi-center, prospective study published in the Journal of Wound Care looked at a new monofilament fiber product known as Debrisoft (Activa Health Care, UK) and evaluated its debridement efficacy and ability to achieve complete granulation tissue at the bed of pressure, diabetic, and venous leg ulcerations. The 10 x 10cm polyester product is designed to remove and trap exudates, slough, hyperkeratotic tissue, and debris from superficial wounds by applying mild pressure in a circular motion over the affected site. Bahr, et al. found that the product was 93.4% effective in debridement, that the average time for each debridement session was 2.51 minutes, and that all patients reported no to minimal, short-lived discomfort when Debrisoft was utilized.19

An agent of particular interest to the plastic and reconstructive surgery community is the Debrase Gel Dressing (DGD) by MediWound Ltd. DGD is a bromelain-based enzymatic mixture derived from the stem of a pineapple plant. After application for four hours, the proteolytic enzymes are said to dissolve necrotic cutaneous tissue from humans and animals with high specificity. Because it is often difficult to differentiate the viable tissue and the eschar interface due to subtle irregularities in depth and involvement, the surgical concern is damaging healthy tissue during the process of sharp debridement and manipulation. DGD appears to be both rapid and selective and can be used in place of surgical debridement in some instances.

Recent porcine burn studies have shown that DGD rapidly digests eschars, while preserving healthy tissue.20 The DGD is currently being assessed in burn wounds and may have some application in treatment of intractable eschar pressure wounds.

With the advent of products like the Versajet, hydro-surgery has become an adjunct to many podiatrists’ armamentarium. The stream of pressurized saline functions as a knife and assists the operator in removing debris from areas of abnormal contour or sites that are difficult to reach. In 2008, a study from the International Wound Journal compared hydro-surgery debridement to scalpel debridement with pulse lavage on a total of forty-one patients with lower extremity ulcers. Caputo and his counterparts devised this controlled, randomized trial as a way of assessing clinical efficacy of this newer technique over a 12-week period, and measured the length of time required to perform each debridement method. While the Versajet proved to be quicker and minimized the surgical duration, both groups exhibited similar median times to wound closure.21

Another relatively new wound debridement modality is pulsed, non-thermal, low frequency ultrasound. This method delivers a mechanical pressure wave via acoustic vibrations through a coupling medium. The physiological effect created by low frequency ultrasound is enhanced in-
flammatory response and tissue repair. The pressure wave deforms cell membranes (radiation force), generates microscopic bubbles that expand and contract within tissues (cavitation), and creates eddy currents around these bubbles (microstreaming). This energy rotates and twists the already destabilized cell membranes, leading to increased permeability and altered cell activity.\(^2\) Signal transduction pathways are stimulated and promote angiogenesis, facilitate leukocyte adhesion, and produce growth factors, nitric oxide, and prostaglandins.\(^2\)

Herberger, et al. discussed the efficacy, tolerability, and patient benefit of ultrasound-assisted wound treatment versus surgical debridement in a paper published by the Journal of Dermatology. In this prospective, randomized, controlled clinical trial evaluating 67 subjects, they found that both groups had improved wound status and quality of life, while also noting reduction in perceived pain. Over 85% of patients in each treatment group experienced more than minimal benefit (24). Similar findings were noted in a study of 19 patients with chronic leg ulcers by Tan and colleagues, where they concluded that six individuals obtained symptomatic relief in pain and odor, seven achieved complete ulcer resolution, and eight exhibited no response to the ultrasound therapy.\(^2\)

**How Much to Debride and How Often to Debride**

Wound debridement was recognized as a vital adjunct in the care of patients with chronic ulcers through Steed’s landmark article that demonstrated a lower rate of healing in centers that performed less frequent debridements and improved rate of healing in centers that performed more frequent debridements.\(^2\) While evidence supports the practice of chronic wound debridement because of its positive impact on healing outcomes,\(^2\)\(^,\)\(^2\)\(^,\)\(^2\) questions remain unanswered about the frequency of debridement and the extent of peripheral wound tissue removal necessary to promote healing.

In an initial report involving three patients, Brem and co-workers found that biopsies from non-healing edges of chronic wounds exhibited distinct pathogenic morphology and impairment of fibroblast migration as compared to biopsies from adjacent non-ulcerated areas that exhibited normalization of morphology and normal migration capacity.\(^2\) The authors recommended a more aggressive removal of the non-healing edge to allow for the exposure of cells within the wound that are biologically capable of responding to wound-healing stimuli. However, the study involved a very Continued on page 150
small number of patients and used gene transcription data obtained from microarrays as a guide for the level of debridement, making this rather difficult for most clinicians to adapt to their clinical practice.

A retrospective analysis of two level-1 therapeutic studies investigated whether a correlation existed between diabetic foot ulcers and venous leg ulcers for serial wound debridement and rates of closure and healing. Cardinal and colleagues found a significantly higher reduction (34%) in wound mean surface area in individuals who underwent surgical debridement, and discovered higher rates of closure (29%) at the centers where repetitive debridement was performed compared to (15%) non-serial debridement centers. The authors were, however, unable to conclude that higher closure rates equated to more serial debridements per patient, and because of the retrospective nature of the analysis, were unable to control the variability in debridements, techniques, and aggressiveness.

Conclusion

The healing dynamics of chronic wounds are altered by physiological impairments that result in delayed healing and severe morbidity. Debridement is one of the cornerstones in the healing of chronic ulcers. As our understanding of chronic wound healing advances and new debridement modalities continue to emerge, it is important to recognize what truly constitutes appropriate, standardized debridement, and to help improve the efficacy and facilitate healing.

References


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