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Update on Collagens: What You Need to Know and Consider

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The prevalence of chronic wounds remains a concern for wound care providers. Additional therapies that promote wound healing continue to be on the forefront of wound care. Selecting treatment modalities should be based on current evidence and a critical analysis of that evidence. However, evidence in wound care in the form of randomized controlled trials is lacking. This article describes collagen, its use in wound care, and current evidence for review.

INTRODUCTION

The treatment and ultimate healing of chronic wounds present challenges to the wound care provider. These challenges pose a significant burden to the health care system both here in the United States and globally. A chronic wound is defined as a wound that does not progress through the normal phases of wound healing and is of long duration (i.e., ≥6 weeks) or has frequent recurrences (Shah & Chakravarthy, 2015). The presence of chronic wounds has reached epidemic proportions, with an estimated 6.5 million people in the United States experiencing chronic wounds and an excess of $50 billion spent every year on chronic wound treatments (Pourmoussa, Gardner, Johnson, & Wong, 2016; Wu et al., 2017). As populations increase and individuals live longer, the incidence of chronic wounds will surely increase. In addition, chronic wounds predispose to loss of limb, reduced quality of life, increased pain and suffering, and even death.

The use of modern treatment concepts, especially in the form of active wound dressings, is essential to increase the efficiency of care and the promotion of wound closure. The primary function of any wound dressing is to provide an optimal healing environment. Because the latter is influenced by a number of factors due to the wide variety of wounds, it is impossible for just one ideal wound dressing to exist.

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COLLAGEN'S ROLE IN WOUND HEALING

Over 90% of all chronic wounds are a result of either diabetic and venous ulcers or pressure injuries (Pourmoussa et al., 2016). Regardless of the etiology, the current standard of care for treating chronic wounds includes debridement, reducing bioburden, controlling edema, off-loading pressure points, redistributing pressure, controlling moisture, and using suitable compression dressings for venous ulcers. In spite of this treatment, many chronic wounds do not heal. Collagen promotes wound healing and is needed for each and every phase of wound healing. Therefore, its efficacy as an adjunct to wound healing may have merit.

Collagen is a triple helix protein molecule of soft tissue and is the most abundant structural and functional protein of the extracellular matrix (ECM). It serves as a scaffold in connective tissue. Collagen was once thought of as only structural support, but now it has become evident that collagen controls many cellular functions including cell shape and differentiation, migration, and synthesis of a number of proteins (Rangaraj, Harding, & Leaper, 2011). When utilized as an adjunctive wound therapy, collagen stimulates and recruits immune cells and fibroblasts.

As previously stated, collagen is needed for every phase of wound healing and has multiple functions. Collagen stimulates cellular differentiation, angiogenesis, and mitogenesis to produce a structural scaffold in tissues. Collagen types I, II, and III are the main types of collagen found in connective tissue and constitute 90% of collagen present in the body. Collagen type I compromises approximately 70% of collagen in the skin with type III being 10%, and trace amounts of types IV, V, VI, and VII forming the remainder (Rangaraj et al., 2011; Uitto, Olsen, & Frazio, 1989). Without collagen wounds would not heal.

Collagen controls cellular functions for protein synthesis and ECM deposition. Cellular migration of keratinocytes, fibroblasts, monocytes, macrophages, and neutrophils occurs during interaction with the collagen proteins, particularly type I. Collagen is produced by fibroblasts. Fibroblasts, the main connective tissue cells present in the body, are a type of cell responsible for making the ECM

and collagen (Xue & Jackson, 2015). Collagen, glycosaminoglycans, proteoglycans, elastin, fibronectin, laminin, and other cellular components form the ECM (Xue & Jackson, 2015). Collagen aids in the uptake and bioavailability of fibronectin that assembles into fibrils attaching cells to the ECM. Together, this ECM and collagen form the structural framework and play an important role in tissue repair.

Collagen also plays a major role in scar tissue formation, contraction, and remodeling, which contributes to a tensile strength of 20% of normal at 3 weeks after injury, and gradually reaches a maximum of 80% of normal skin (Desmouliere, Redard, Darby, & Gabbiani, 1995). In early wound healing, type III collagen is laid down first, with the proportion of type I collagen increasing with scar formation and remodeled with maturation. Collagen also influences wound contraction. The pattern of collagen fiber organization has been documented by polarized light microscopy (Berry, Harding, Stanon, Jasani, & Ehrlich, 1998). Early granulation tissue collagen fibers were noted to be thick. Myofibroblasts, the cells responsible for wound contraction and development of fibrotic changes, were associated with thick collagen fibers. Fibroblasts were associated with both fine and thick collagen fibers, suggesting that wound contraction involves a volume change and that normal dermal and adipose tissues are pulled into the defect by forces generated within the fibroblasts (Berry et al., 1998). Thus, without collagen, wounds would not undergo contraction.

Degradation of the ECM is an essential component of wound healing and scar formation. Matrix metalloproteinases (MMPs), composed of collagen, elastin, laminin, and fibronectin catalyze and degrade ECM molecules. These MMPs include collagenases, gelatinases, stromelysins, matrilysins, and membrane-type MMPs and are classified into groups based on their substrate specificity. Collagen induces collagenase (Xue & Jackson, 2015). Collagenase is involved in the normal turnover of connective tissue and collagen that is resistant to the other proteases. Collagenolysis is an important physiologic process responsible to a large extent for the repair of wounds and the processes of tissue remodeling, where undesired accumulations are removed as new connective tissue is laid down.

At the time of injury, platelets aggregate around exposed collagen. Platelets then secrete factors that interact and stimulate the intrinsic clotting cascade, strengthening the aggregate into a stable hemostatic plug (Xue & Jackson, 2015). Blood platelets also release granules, which then release a variety of growth factors and cytokines such as platelet-derived growth factor, insulin-like growth factor, epidermal growth factor, and transforming growth factor-β (Xue & Jackson, 2015). These growth factors initiate the inflammatory phase of wound healing by mobilizing neutrophils, eosinophils, and monocytes to the site of injury (Xue & Jackson, 2015). Proteolytic enzymes are then secreted by inflammatory cells (neutrophils, eosinophils, and macrophages) that migrate to the wound injury. Proteolytic enzymes degrade the ECM and give rise to many protein fragments during wound healing. The degradation products, including collagen, have a chemotactic effect and recruit other cells to the site. Cytokines released during this phase of healing directly influence the deposition of collagen in the wound by fibroblasts and decrease regulation of tissue inhibitors of matrix metalloproteinases (TIMPs) (Xue & Jackson, 2015). An optimal ratio of MMPs and TIMPs is crucial for wound healing and the integrity of the ECM. Collagen is a functional unit of wound healing in each phase of the wound healing cycle by the nature of its many functions and processes.

COLLAGEN WOUND PRODUCTS

The chronic wound environment is hostile to fibroblast-produced collagen; therefore, clinicians must change the wound microenvironment (Berry et al., 1998; Hochstein & Bhatia, 2014; Xue & Jackson, 2015). As previously noted, collagen performs multiple functions in the healing wound. The use of collagen-based dressings allows clinicians to provide this necessary substance externally so that the natural balance of the wound bed can be restored. The availability of human collagen as a raw material for the production of wound dressings is very expensive and limited. An alternative would be recombinant human collagen. Because large quantities of these collagens cannot be produced in a cost-effective way, raw materials of animal origin are used instead.

External collagen also has multiple functions. There are a variety of collagen dressings and products that employ different carriers of the collagen including amorphous gels and pastes, gel-impregnated dressings, polymers, oxidized regenerated cellulose (ORC), and ethylene diamine tetraacetic acid (Hochstein & Bhatia, 2014). In addition, there are collagen dressings/products that contain antimicrobials such as silver or polyhexamethylene biguanide (PHMB). The multiple forms of collagen make it an option for use with many different wound types based on wound assessment. The collagen within these products is derived from bovine, porcine, equine, or avian sources that have been purified in order to render them nonantigenic. Also, collagen products can contain different concentrations and type of collagen (Hochstein & Bhatia, 2014). Some contain type I or native collagen whereas others also contain denatured collagen. Native collagen is a natural three-dimensional structure that may provide a more natural environment for fibroblasts and better targets for MMPs than denatured or processed collagen (Hochstein & Bhatia, 2014). Processed or denatured collagen may provide a readily available source of amino acids for tissue reconstruction and a higher number of exposed active sites to divert MMPs and keep them from degrading and digesting the newly formed collagen.

Understanding the functions of collagen in wound healing aids in recognizing the benefits of external collagen as a wound care treatment. External collagen provides the wound with an alternative source of collagen that can be degraded by high levels of MMPs as well as elastase in chronic wounds. It is known that these two classes of enzymes are involved in the imbalance between collagen breakdown and deposition (Shah & Chakravarthy, 2015). Collagen can serve as a decoy or sacrifice so that endogenous native collagen can continue to inhibit or deactivate the MMPs and elastase that are present in chronic wounds (Hochstein & Bhatia, 2014). It is known that chronic wounds are stalled in the inflammatory phase of wound healing and will not progress to healing unless the inflammation is resolved. During the inflammatory phase, the wound is attempting to cleanse itself of necrotic tissue, mostly collagen and debris by utilizing these digestive enzymes. The major classes of enzymes responsible for this activity are the MMPs. Diverting these MMPs from newly formed collagen in the ECM by providing external collagen can abate the inflammation in chronic wounds and restore balance in collagen degradation and deposition.

Chronic wound environments are hostile to fibroblast-produced collagen. Collagen produced by fibroblasts stimulates cellular migration and new tissue development. The use of a collagen dressing allows the natural balance in the wound bed to be restored to increase fibroblast production and permeation of collagen (Shah & Chakravarthy, 2015). External collagen can also aid in the uptake and bioavailability of fibronectin. Fibronectin is a glycoprotein that connects cells with collagen fibers by binding the integrin receptors in the ECM causing reorganization of the cell's cytoskeleton and facilitating cell movement. It is also vital for regulating neovascularization of granulation tissue during the resolution of tissue injury toward healing (Xue & Jackson, 2015). Collagen also preserves leukocytes, macrophages, fibroblasts, and epithelial cells, all of which are necessary for wound healing. External collagen can also assist in the maintenance of the chemical and microenvironment of a chronic wound so that healing can progress (Xue & Jackson, 2015).

The many functions of collagen in wound healing are apparent and well established. The hostile wound environment in chronic wounds impedes many of these normal functions, preventing progression through the phases of wound healing. Adjuvant treatment with external collagen may help reestablish collagen's normal functions and restore the integrity of the ECM.

REVIEW OF THE LITERATURE

The problem with research in wound care is the lack of well-developed and conducted randomized controlled trials (RCTs). This phenomenon prevents clinicians from making decisions based on the best type of evidence. Unfortunately, most published evidence is in the form of case series, recommendations, consensus panels, and product-specific trials, many sponsored by the manufacturer of the product. Due to this lack of high-quality evidence, clinicians often have to rely on experience and expertise to make treatment decisions. Nonetheless, a critical analysis of the literature is warranted and a brief review will be provided.

A systematic review is a rigorous synthesis of research findings on a particular research question, using systematic sampling and data collection procedures and formal protocols (Polit & Beck, 2018). Chicone, de Carvalho, and Paggiaro (2018) conducted a systematic review to analyze RCTs on the use of ORC/collagen dressings for the treatment of diabetic foot ulcers. After evaluating 3016 studies for methodological similarities, the authors found only three studies were eligible for the inclusion in the review. Of these three studies, one RCT was considered at high risk of bias. The results of meta-analysis of the other two studies showed no significant improvement in wound healing rates with the use of ORC/collagen compared with standard care. The authors concluded there was not enough high-quality evidence to support ORC/collagen for the treatment of diabetic foot ulcers (Chicone et al., 2018). This further emphasizes the need for additional, well-conducted, RCTs comparing the use of collagen treatments with standard care.

Kloeters, Unglaub, de Laat, van Abeelen, and Ulrich (2016) conducted a prospective and randomized evaluation of the protease-modulating effect of ORC/collagen matrix in the treatment of pressure injuries. The researchers compared ORC/collagen (n = 23) to foam dressing (n = 10). A total of 33 patients with pressure injuries were enrolled in the study and followed up for 12 weeks after treatment. Wound assessments were performed, photographs taken, and wound exudate collected on admission into the study and at 5 days, 14 days, and then every 14 days during the study period. The researchers measured levels and activity of elastase and plasmin in the wound exudate and found that wounds treated with ORC/collagen matrix showed a significantly faster healing rate correlated with decreased activity of elastase and plasmin in wound exudate ($p \leq .05$). Wound surface reduction was 65% after 12 weeks in the ORC/collagen group compared with only 41% in the control group ($p \leq .05$). The authors also reported no signs of infection or intolerance to the ORC/collagen (Kloeters et al., 2016). A limitation of this study was the small sample size. Further research with a larger sample is needed.

Lintzeris et al. (2018) presented a case series of nine wounds on eight patients with multiple comorbidities who failed previous treatments. The authors utilized a purified collagen matrix with PHMB to control biofilm formation, sequester proteolytic enzymes, and provide a biocompatible scaffold to support healing. Wound etiologies included three pressure injuries, one diabetic foot ulcer, one venous

ulcer, two postsurgical wound dehiscences, one ulcer secondary to calciphylaxis, and one traumatic wound secondary to hematoma. The chronic wounds had been present on average 9.2 weeks prior to the first application of the collagen matrix. The collagen was applied weekly after conventional wound care and debridement. Compression and offloading were applied where appropriate. On average, patients received 5.8 applications of the collagen matrix. Of the six wounds that healed, the average time to closure was 10 weeks after the first application. The remaining three wounds that did not heal showed improved appearance with 100% granulation tissue and surface area reduction of 61.4% (Lintzeris et al., 2018). All chronic wounds were contaminated or colonized with bacteria. Heavy bioburden impedes wound healing. The authors concluded that this case series demonstrated that the use of a collagen matrix with PHMB and good wound care improved the wound bed environment and supported closure of wounds recalcitrant to other modalities (Lintzeris et al., 2018). The authors acknowledged partial funding from the manufacturer for analysis and writing assistance. This case series, albeit small, does support the efficacious use of collagen in a variety of chronic wound etiologies and comorbidities, but should be viewed with caution.

Shah and Chakravarthy (2015) conducted a case series utilizing 100% bovine native collagen and standard care that included the use of systematic or topical antimicrobials in patients with chronic and persistent wounds that failed to heal in spite of prior conservative treatments using submucosal intestinal matrix, ORC/collagen, or skin substitute. This series included 20 patients with 21 chronic wounds of various sizes ranging from 0.6 to 101.4 cm^2. The total duration of treatment with the bovine collagen was up to 12 weeks. The authors reported complete wound healing in 15 patients with healing times ranging from 13 to 68 days. Two additional patients achieved wound healing at 107 and 114 days using a combination of the bovine collagen and other therapies. One patient did not respond to treatment. The authors concluded that by changing their wound care treatment of these chronic wounds and adding 100% native type I collagen, they achieved an 83.3% wound closure rate. They concluded that collagen may be a worthwhile option to explore in chronic wounds resistant to conservative treatment (Shah & Chakravarthy, 2015). Notably, this study was sponsored by the manufacturer of the collagen product.

This is only a brief review of the evidence on the use of collagen as an adjuvant to wound therapy. The challenge for the clinician is to analyze and interpret these findings when making treatment decisions about the use of collagen for chronic wounds. Currently, practice decisions may be heavily based on clinician experience and expertise. As the push for evidence-based practice continues, additional research will definitely be needed.

CONCLUSION

There is ample evidence of the many benefits of collagen on wound healing. However, there is a lack of rigorous research studies to support the use of external collagen in chronic wounds. The clinician is cautioned to critically analyze the literature prior to implementing these therapies into practice and to recognize that it may be necessary to rely heavily on experience and expertise.

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