ARE ALL COLLAGEN DRESSINGS THE SAME?

Knowing the Difference Makes All the Difference

By Ronald Sherman, DPM, MBA
The Division of Vascular Surgery and Endovascular Therapy at
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The Importance of Collagen

The extracellular matrix (ECM) is a three-dimensional gel-like structure that surrounds cells in all tissues of the body. Fundamentally, the ECM is composed of water, polysaccharides, and proteins.[1]

ECM proteins play a significant role in each phase of wound healing. They can stimulate cell proliferation and differentiation, guide cell migration, and modulate cellular responses. When the ECM is dysfunctional, wound healing is delayed.[2]

Collagen is the most abundant protein in the interstitial ECM and provides the structure or scaffold for wounds to heal. It provides tensile strength and plays a role in other cellular processes such as adhesion and migration.[3] To date, 28 types of collagen have been identified.[1] Collagen type I is the dominant form found in almost all tissues, especially in tendons and skin. Type I collagen is the classic collagen molecule consisting of three polypeptide chains in a characteristic triple-helical configuration.[4] The other forms of collagen are found in defined areas (e.g., type II collagen occurs in cartilage and the cornea, whereas collagen type III is the principal form within the walls of blood vessels).[3]

Collagen's Critical Role

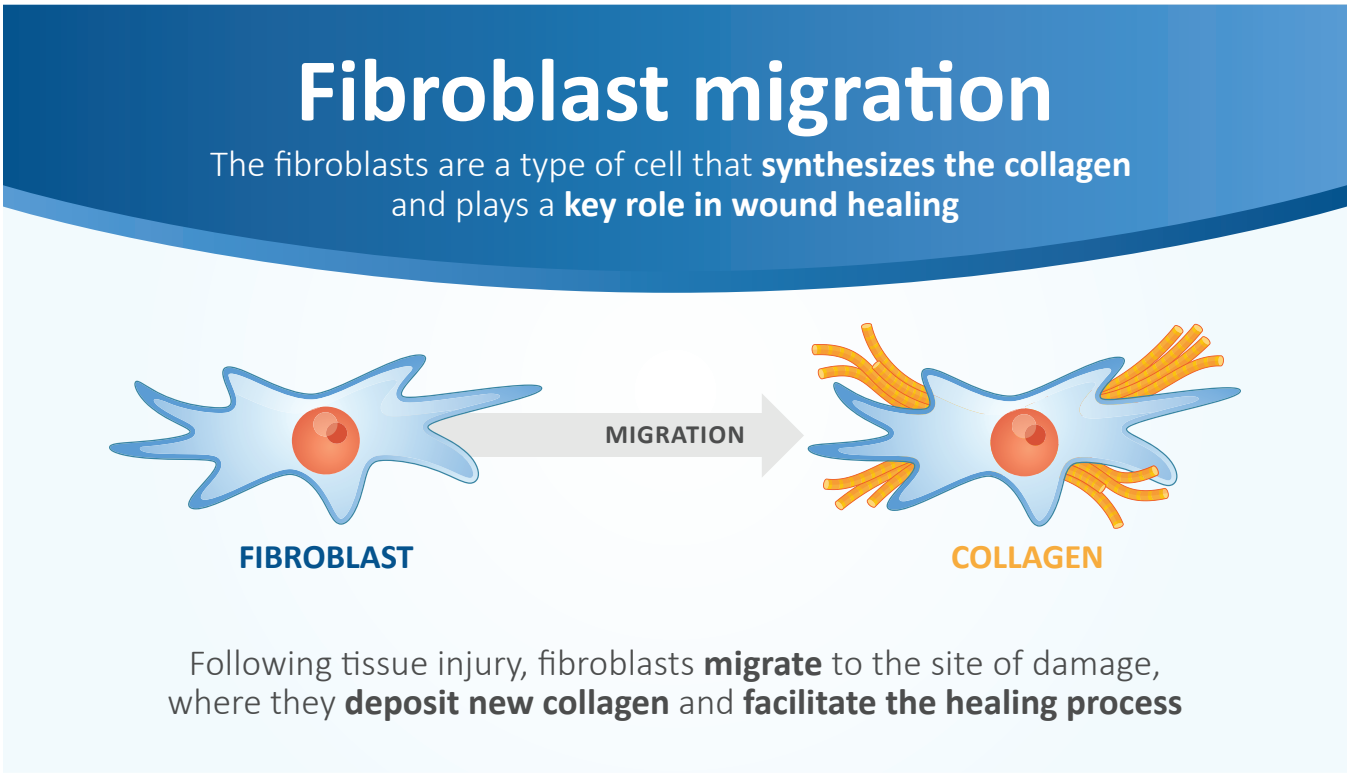
It is now evident that collagen plays a critical role in all phases of wound healing because of its chemotactic role[5]:

- **Hemostasis:** After an injury, the interaction between broken collagen and platelets leads to the activation of the clotting cascade.[5]
- **Inflammation:** Proteases break and revise the collagen into small fragments, stimulating the migration of inflammatory cells to the wound bed.[5]
- **Proliferation:** Collagen can also stimulate the migration of:
  - **Fibroblasts** > deposition of endogenous collagen
  - **Vascular endothelial cells** > formation of granulation tissue
  - **Keratinocytes** > re-epithelization[5]
- **Remodeling:** Collagen fibers become matured and become rearranged and aligned, creating a bridge between the edges of the damaged tissue.[6]

What are Fibroblasts?

Fibroblasts are one of the most abundant cells in connective tissues. They play a critical role in regulating the turnover of ECM under normal conditions. When tissues are injured, fibroblasts migrate about the injured region, deposit new collagen, and eventially differentiate into myofibroblasts, highly contractile cells that are able to produce ECM proteins, especially collagen, and can facilitate the wound closure.[7] (See Box 1.)

Box 1. Fibroblast Migration



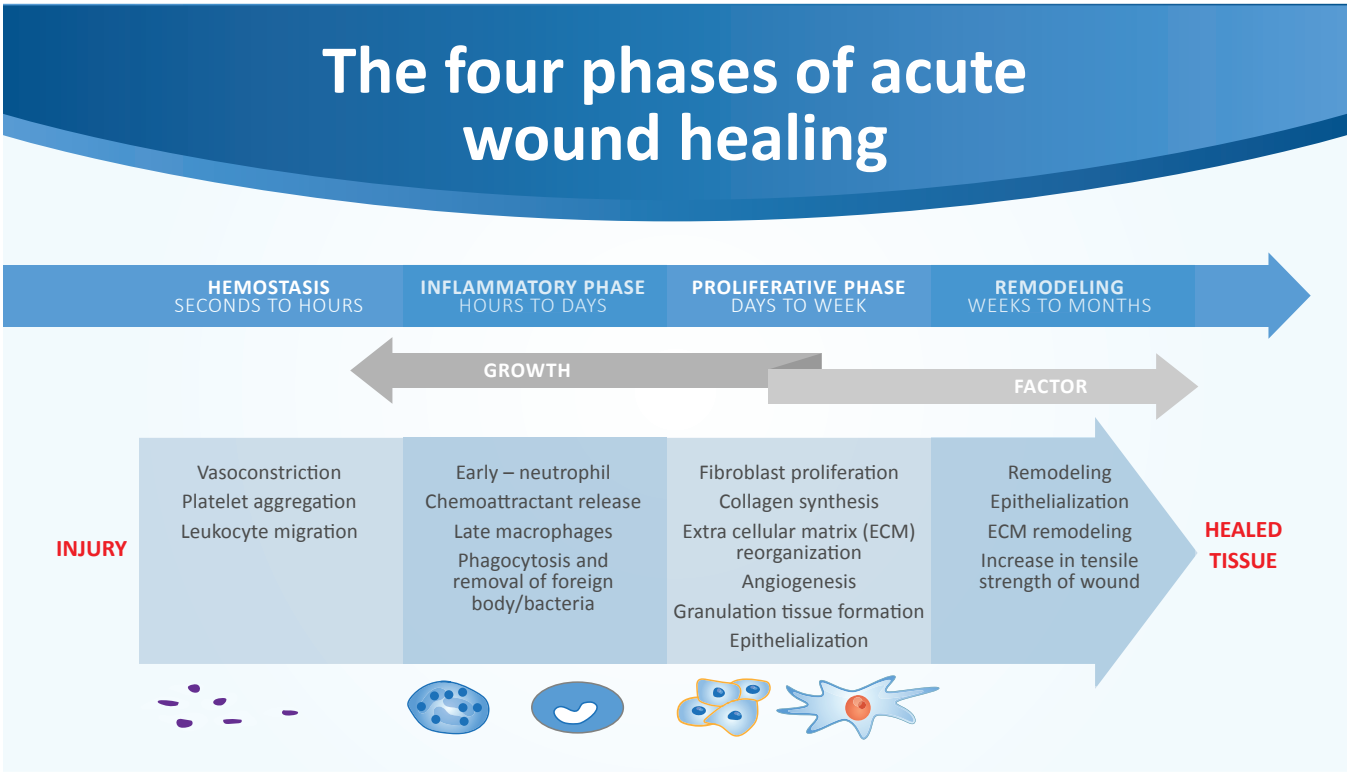
What are Proteases?

Proteases are enzymes that break down proteins. The major proteases involved in wound healing are the matrix metalloproteinases (MMPs) and elastase.[8] MMPs preferentially break down ECM proteins such as collagen. Elastase can convert pro-MMPs (the natural precursor of MMPs) to active MMPs.[9]

Proteases are essential for normal wound healing. In physiological healing, they help debride and cleanse the wound bed from the damaged ECM so that new tissue can form and wound closure can easily occur.[10]

In chronic wounds, proteases levels are out of control and elevated. When MMPs and elastase reach high levels for a prolonged time, the fragile balance between tissue breakdown and repair is altered, and wounds do not progress to healing. Excessive wound proteases can destroy the newly formed ECM, thus leading to prolonged inflammation and impaired healing.[9] (See Box 2.)

Box 2. The Four Phases of Acute Wound Healing



What Impact Does Collagen Have?

In physiological healing, proteases cleanse the wound from the damaged ECM and facilitate the migration of fibroblasts[11] that are able to synthesize collagen and new ECM. Under normal conditions, fibroblasts and proteases maintain tissue homeostasis by regulating the turnover of ECM.

Chronic wounds are characterized by decreased collagen deposition and increased collagen breakdown. The recruitment of fibroblasts in the wound bed is delayed, and the expression of the collagen gene in fibroblasts is suppressed. In addition, proteases levels are abnormally elevated. When MMPs and elastase reach high levels for a prolonged time, they begin to degrade the newly formed collagen.[9]

The Benefits of Collagen

Collagen dressings provide multiple benefits to wound healing, particularly in difficult-to-heal wounds. In chronic wounds, collagen dressings can reboot the healing process. These dressings can help regulate the turnover of ECM and re-establish the tissue homeostasis. The excess of MMPs is a key contributor to wound chronicity.

The majority of collagen dressings on the market can reduce MMPs and elastase levels in the wound environment by acting as a sacrificial substrate. These dressings give MMPs an alternative attractive collagen source and leave the endogenous native collagen available for normal wound healing.[5]

In addition to this mechanism, some collagen dressings can provide a biodegradable scaffold to the wound bed. They can stimulate the migration, nesting, and proliferation of fibroblasts and can boost the deposition of new human collagen fibers and granulation tissue.[5]

Knowing the Difference Makes All the Difference

The *Integrity* of Collagen Makes a Difference

In the manufacturing process, collagen integrity can be easily denatured, altered, or destroyed. The functionality of native collagen is hardly reproduced by the manufacturing process. Most of the marketed products have a preponderance of denatured collagen, defined as collagen that has largely lost its triple-helical formation.[12] Some of the benefits of the collagen can be lost if the collagen is largely denatured in the manufacturing process.[9] For example, denatured collagen does not easily interact with the host tissue, and fibroblasts do not migrate significantly.[12]

Thanks to advanced extraction methods and new purification technologies, some collagen dressings contain higher quantities of native collagen. Scientific evidence demonstrated that the capacity of the collagen to interact with biological tissues depends on the retention of the native structure.[12]

Native collagen dressings present a suitable three-dimensional structure that can provide a natural biodegradable scaffold for the migration and anchorage of fibroblast and can support cell adhesion and growth.[9,12]

The ideal pore size of a collagen dressing has a restricted size range. Pores too large or too small may not be suitable for sustaining interaction and cell movement during the healing process.[12] Native collagen dressings maintain regular pore sizes and can facilitate cell adhesion and fibroblast migration.[13] (See Boxes 3 and 4.) For these reasons, choosing a collagen dressing that has maintained its native structure is significant to the healing process.

The *Type* of Collagen Makes a Difference

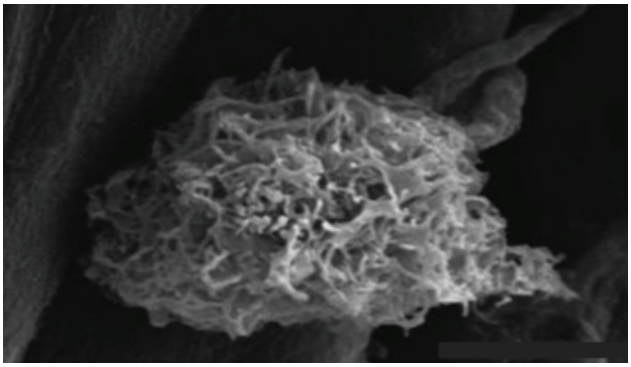
The second factor to consider when choosing a dressing is the type of collagen. Collagen type I is the dominant form in the skin and accounts for approximately 70% of the total amount of collagen in the dermis.[14] Dressings containing only type I collagen are thought to be better recognized by our body.

The *Content* of Collagen Makes a Difference

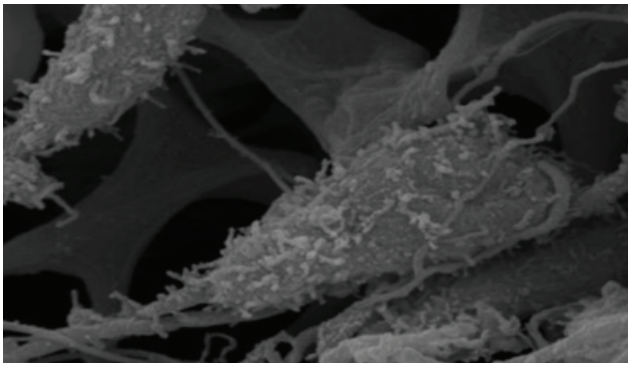
The third factor to keep in mind is the collagen content of the pad. An excess of MMPs can damage the wound healing process. Collagen dressings can inactivate MMPs by giving them an alternative source of collagen. Dressings with high collagen content can easily sacrifice a part of their amount of collagen to feed and inactivate MMPs and elastase. The remaining part of the dressing can act as a biodegradable scaffold and can stimulate the migration and proliferation of fibroblasts in the wound bed. Collagen provides the most profound attraction for the longest time. The longer, the better.

"An ideal dressing should keep the native structure and contain high amount of type I collagen."

Box 3. Native Collagen Structure



Box 4. Denatured Collagen Structure



Skin Repair Versus Skin Regeneration

Wound healing is reached by repair or regeneration.[15]

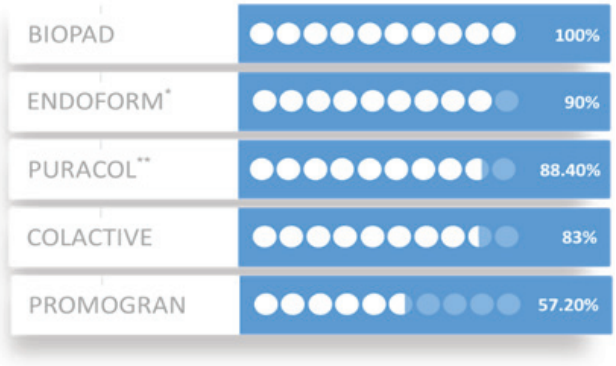
- **Skin Repair:** The deposition of connective tissue is a key phase to re-establish continuity of the skin.[6] The wound heals by fibrosis and scar formation.[15]
- **Skin Regeneration:** New tissue completely restores damaged parts to their original morphology and functionality.[16]

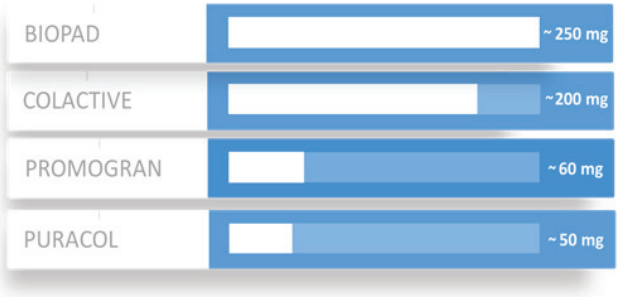
"Biodegradable scaffolds can promote tissue regeneration and create a bridge to connect edges of the wound."[17]

A Solution That Can Make a Difference

BioPad is a 100%[12] pure native equine Type I collagen primary wound dressing for the management of chronic non-healing wounds to help in wound closure. (See Box 5.) BioPad is prepared as a sponge-shaped device that transforms into a soft gel allowing contact with the entire wound bed. This collagen does not contain any fillers, just pure collagen to stimluate proliferation of the ECM to construct more collagen in the formation of granulation tissue.

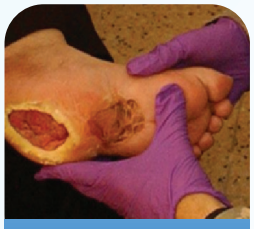
Box 5. Collagen Content of Most Widely Used Wound Healing Dressings



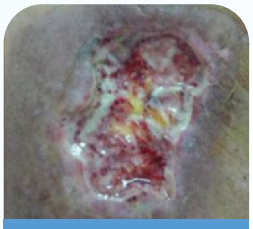


BioPad can be used in hyperbaric chambers and/or with negative pressure wound therapy and is indicated for the following wounds (see Box 6):

Box 6. BioPad Indications



Partial-thickness Wounds
Full-thickness Wounds
Surgical Wounds
Traumatic Wounds
Draining WOunds
Podiatric Wounds
Other Bleeding Surface Wounds



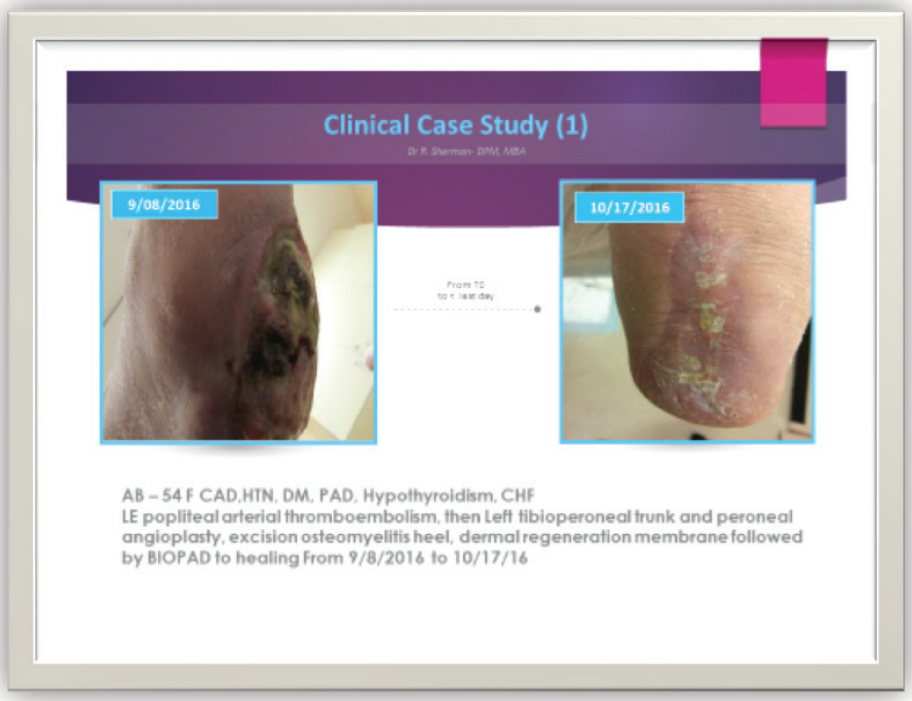
Pressure Ulcers
Venous Insufficiency Ulcers
Diabetic Ulcers

Dehisced Surgical Incisions
Post-laser Surgery

Donor Sites
Lacerations

Clinical Cases

Clinical Case Study #1



Clinical Case Study #2

Clinical Case Study #3

Conclusion

Collagen dressings were thought to assist in wound healing by primarily attracting fibroblasts to enhance the structural support and protein scaffolds within the extracelluar matrix. This attraction and comfortable nesting of fibroblasts enhance the foundation and progression of wounds. Collagen also interacts with a variety of cell functions that include cell differentiation and shape, chemotaxis, and the additional synthesis of various proteins. The role of collagen is also understood to assist in the attraction and reduction of MMPs in chronic wounds to commence actual healing. Research has shown that collagen possesses a hydrophilic property that aids in the uptake of pro-inflammatory stimuli and reduces sensescent cells conducive to healing seen in the acute wound process.

An ideal collagen dressing choice should include:

a. Native intact structure (not denatured, not altered, or cross-linked)

b. The highest amount of collagen content

c. Type I collagen composition

BioPad 100% pure collagen is an effective choice in the clinician's arsenal of wound healing products. It has been shown to accelerate wound healing when chosen for the right wounds as indicated.

About the Author

Dr. Ronald Sherman is the podiatric surgeon in the Division of Vascular Surgery and Endovascular Therapy at Johns Hopkins Multidisciplinary Diabetic Foot and Wound Service. He is a principal clinican at Johns Hopkins Multidisciplinary Diabetic Foot and Wound Service, focusing on healing unresponsive foot ulcerations and reconstruction of diabetic wounds.

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