The Use of Human Amnion/Chorion Membrane in the Clinical Setting for Lower Extremity Repair: A Review

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KEYWORDS

• Amniotic membrane • Dehydrated human amnion/chorion membrane
• Growth factors • Wound care

KEY POINTS

- Amniotic membrane composed of amnion and chorion has been recognized for its use as a facilitator of wound healing for more than 100 years.
- Amniotic membrane–based products have various therapeutic applications in the foot and ankle, including the treatment of chronic wounds, fasciitis, and tendonitis.
- Several products containing various components of amniotic membrane are available, but for most there are limited clinical and scientific data.
- Dehydrated human amnion/chorion membrane contains an array of growth factors known to play critical roles in the physiologic processes of normal healing and tissue regeneration.

INTRODUCTION

Normal wound healing occurs in a well-orchestrated and predictable sequence of events including hemostasis, inflammation, proliferation, and remodeling. These interrelated physiologic processes create a reparative microenvironment characterized by high initial levels of growth factors and other soluble mediators of cell signaling;

Disclosures: Dr Zelen: The Professional Education and Research Institute of which he is Medical Director has received funding from MiMedx for completion of studies related to dHACM; Dr. Snyder: Has provided consultative services to MiMedx. Dr. Serena has served as a principal investigator for MiMedx and has received research funds. Dr. Li has provided consultative services to MiMedx.

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Clin Podiatr Med Surg 32 (2015) 135–146
http://dx.doi.org/10.1016/j.cpm.2014.09.002 **podiatric.theclinics.com**
0891-8422/15/$ – see front matter

controlled levels of proteases and bacteria; and functional fibroblasts, keratinocytes, and vascular endothelial cells.[1]

Cell-mediated regeneration of extracellular matrix (ECM), the largest component of dermal skin layer, remains an integral part of this complex dynamic.[1] In acute wounds the provisional wound matrix composed of fibrin and fibronectin provides a scaffold to direct cells into the site of injury, which then participates in secreting ECM. The ECM forms communications signals with cells and between cells through a process known as dynamic reciprocity.[1]

Angiogenesis, the formation of new blood vessels, is another critical process to normal wound repair.[2] Activated by growth factors released by platelets, inflammatory cells, and fibroblasts, vascular endothelial cells sprout and form new capillary channels in the wound bed. Together with the provisional matrix, these angiogenic vessels comprise the granulation tissue heralding a successfully healing wound. Many advanced wound healing modalities, ranging from negative pressure to growth factor therapy to living skin equivalents, are designed to stimulate angiogenesis and accelerate wound repair.

More recently, regenerative mechanisms have been elucidated in wound healing. A variety of stem cells may play a role in wound repair, including mesenchymal stem cells, adipose stromal cells, and endothelial progenitor cells.[3–5] These cells are mobilized, recruited, and homed to sites of injury by soluble mediators generated by the wound healing cascade. A growing number of regenerative therapies in development exploit these stem cells as a novel wound healing strategy.

In contrast, chronic, or delayed healing, wounds are characterized by an aberrant and hostile wound microenvironment, including persistent inflammation, cell senescence, growth factor deficiencies, bioburden, and increased levels of destructive proteases.[1] These factors impede angiogenesis, granulation, and epithelialization.[1,6] Despite multiple causes of chronic wounds (eg, diabetes, venous insufficiency, peripheral arterial disease, and pressure) virtually all chronic wounds share one or more of these common pathologic features.

Many advanced wound management interventions are clinically used to support or promote healing of chronic wounds. These interventions include recombinant growth factors, living skin equivalents, negative pressure therapy, low-frequency ultrasonography, and more recently products derived from amniotic membrane. This article reviews recent scientific data and clinical findings related to amniotic membrane in wound healing.

AMNIOTIC MEMBRANE AS A THERAPEUTIC INTERVENTION

Human amniotic membrane is a reproductive tissue representing the innermost lining of the placenta. Two distinct layers, the amnion and chorion, become fused at approximately 3 months of gestation (**Fig. 1**). These layers serve to protect the fetus during growth in the uterus. Among the key functions of amniotic membrane are:

- Its immunologically privileged state
- Reservoir of multiple growth factors involved with tissue growth and regeneration
- Antiinflammatory properties

Such properties confer remarkable therapeutic potential for amniotic membrane for wound healing, tissue repair, and regenerative therapy.[7–11] Native human amnion/chorion membrane contains growth factors, such as epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), keratinocyte growth factor (KGF), vascular EGF (VEGF), transforming growth factors (TGFs); nerve growth factor (NGF), and