The Future of Wound Care Diagnostics: Biomarkers

Joseph Boykin, Jr., MD, FACS

Wound healing is influenced by a combination of well-documented environmental and biological factors that have an impact on patient recovery. Currently, no effective diagnostic tools to assess the critical biological activities or impairments within the wound that, in turn, may direct clinicians to the most appropriate and cost effective wound treatment protocols exist — treatment protocols designed to address wound healing range in effectiveness and are not based on the biologic activity of each unique wound. In many cases, wound care practitioners feel as if they are flipping a coin when selecting wound therapies. Many times, the trial-and-error processes used for clinical wound management lead to significant expense and prolong patient morbidity.

If clinicians were able to assess the biological factors affecting the wound, they would have a clearer concept of what constitutes appropriate therapy. One way to do this is to use biomarkers of wound healing to assess the state of readiness of a wound for healing. A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological or biochemical features that can be used to assess the progress of disease or the effects of treatment. Currently, approximately 14 known biomarkers are under investigation for use as either a diagnostic tool or therapy for the treatment of chronic or difficult-to-heal wounds.

In the effective treatment of wounds, diagnostic tests utilizing biomarkers would be used to predict and manage wound outcomes and would play a critical role in determining the cause of a wound, assessing its status in healing and helping identify any comorbidities or complications that may contribute to healing delay. These tests also would be helpful in the development of effective management plans using proven wound protocols.

**Nitric oxide**. One biomarker being investigated as a diagnostic test for wound healing is nitric oxide (NO). Nitric oxide is formed from the amino acid L-arginine and oxygen by three distinct isoforms of nitric oxide synthase (NOS). The inducible isoform (iNOS) is synthesized in the early phase of wound healing by inflammatory cells (mainly macrophages) and is a critical co-factor in wound healing. 1

NO is a pivotal biological factor for wound repair and is an important regulator of wound inflammation, epidermal cell migration, wound angiogenesis, collagen deposition, and wound tensile strength. The stable, end-oxidation products of NO (called nitrate, or NOx) can be measured in tissues and fluids to determine NO bioactivity in wounds. The early results of these determinations in clinical settings appear to offer promise for the use of NO as a noninvasive diagnostic indicator of wound healing. 2-4

A current hypothesis regarding the role of NO assumes that when wound NO bioactivity is significantly below normal biological levels for wounds — or the optimal range that promotes healing — normal wound repair mechanisms are impaired. Therefore, by measuring wound NO bioactivity (using NOx), we may be able to predict wound outcomes for difficult-to-heal wounds, monitor the effectiveness of selected “wound healing” therapies, and develop “novel” topical wound treatments or dressings based on their ability to enhance wound NO bioactivity.

**Matrix metalloproteinase**. Another biomarker that, like NO, plays a critical role in the healing process is matrix metalloproteinase (MMP). MMPs are a family of zinc endopeptidases capable of degrading all the components of the extracellular matrix. 5-7 MMPs are key players in every phase of healing: they eliminate damaged protein, destroy the provisional extracellular matrix, facilitate migration to the center of the wound, remodel the granulation tissue and modulate angiogenesis and the activity of some growth factors. 3

In the course of normal wound healing, MMP levels decrease and the closure progresses. However, in chronic non-healing wounds (eg, venous ulcers, pressure ulcers, and diabetic foot ulcers), an excessive build up of MMPs often occurs, especially in the inflammatory phase of healing. The excessive, imbalanced production of MMPs in the wound environment impairs the normal wound repair process and stalls healing. To initiate the successful recovery of wound repair, therapies are needed to address the imbalanced MMP production. One such proven therapy currently in use is 3M™ (St. Paul, MN) Tegaderm™ Matrix with PHIT™ technology. This technology helps decrease total wound MMP production through the use of four cations that naturally occur in the

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Dr. Boykin is Medical Director, Wound Healing Center, Burn Program and Hyperbaric Medicine HCA Retreat Doctors’ Hospital, Richmond, Va. He has received grant and research support and is a member of the speaker’s bureau for 3M Health Care, St. Paul, MN. This information was presented as an Exhibit Hall educational session by 3M Health Care (St. Paul, MN) at the Symposium on Advanced Wound Care, Dallas, TX, April 2009.
body. In vitro studies have demonstrated that MMP activity is reduced when increasing amounts of this technology surround the cells responsible for MMP production in the wound. Once the excessive MMP production is corrected, the wound environment may become more balanced, thus hastening wound healing.

**Patient/provider potential.** For both researchers and practitioners alike, this is an exciting time in the field of wound management. With increased attention on biomarkers such as NO and MMPs and on their roles in facilitating both the evaluation and treatment of chronic wounds, clinicians will have more therapies and diagnostics at their disposal. From a patient treatment perspective, great strides are being made in the ability to provide clinicians and patients with the information needed to pinpoint the causes of wound healing impairment and, in turn, implement proven wound management protocols that may result in faster healing and significant time and cost savings.

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**References**