A Synergistic Multi-Modality Treatment Approach to Address the Key Drivers of Wound Chronicity

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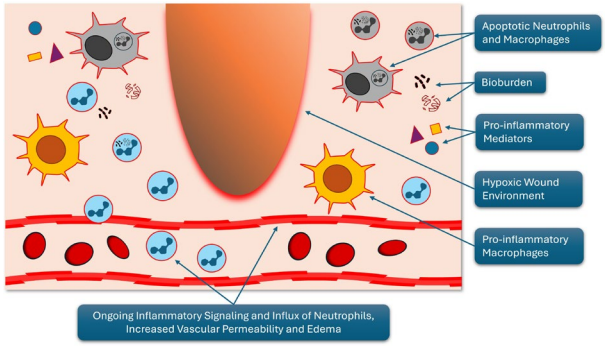
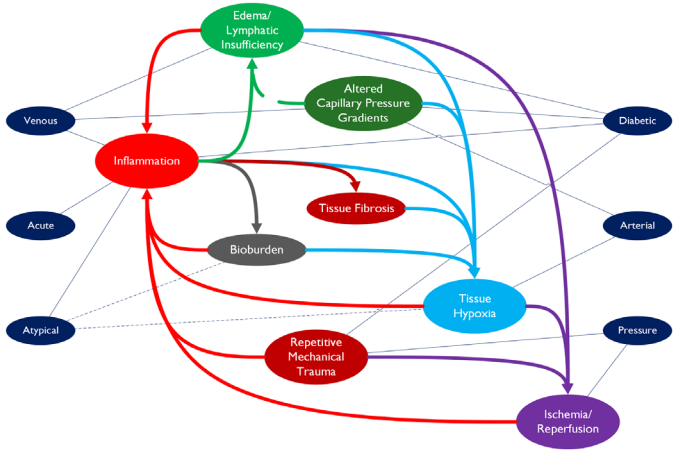
Background: Chronic wounds remain a major clinical and economic burden, affecting millions worldwide. Despite advances in wound care, many wounds fail to heal due to persistent inflammation, tissue hypoxia, edema and lymphatic dysfunction, often exacerbated by ischemia–reperfusion injury, bioburden and tissue fibrosis.

The Inflammatory Wound Environment

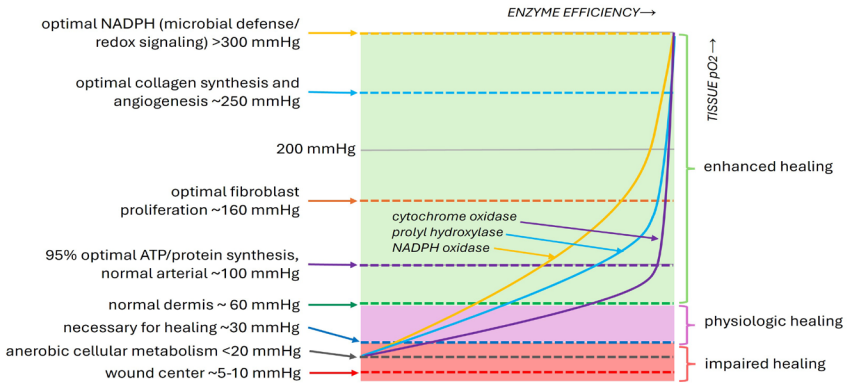


These interrelated mechanisms are further compounded by comorbidities such as obesity, diabetes, and vascular disease. Interventions that concurrently address multiple drivers of wound chronicity hold significant therapeutic potential.

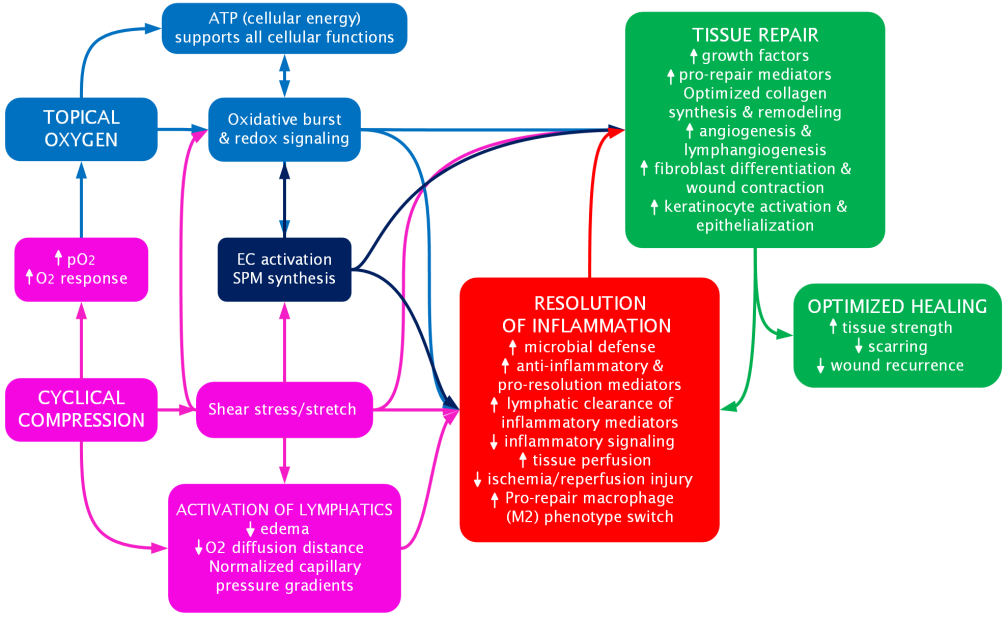
The Common Pathophysiology of Chronic Wounds



The effect of Tissue Oxygen Tension on Wound Healing



Multi-Modality Topical Oxygen Therapy (ITOT)* Mechanism of Action



pO2, partial pressure of oxygen; EC, endothelial cell; SPM, specialized pro-resolving lipid mediators; NADPH, nicotinamide adenine dinucleotide phosphate; ATP, adenosine triphosphate; M2, pro-repair macrophage phenotype.

Multi-Modality Topical Oxygen Therapy: Topical oxygen and cyclical compression promote wound healing through synergistic cellular and molecular mechanisms. Topical oxygen increases tissue oxygen tension to fuel ATP production, enhance microbial defense via oxidative burst, activate redox signaling, and optimize collagen synthesis and crosslinking. Cyclical compression increases the partial pressure (pO_2) of topical oxygen and activates lymphatic function, improving clearance of inflammatory mediators, reducing edema, decreasing diffusion distance for oxygen, normalizing capillary pressure gradients, and restoring perfusion. Compression-induced shear stress/shear stretch activates endothelial cells (ECs) and stimulates the biosynthesis of specialized pro-resolving mediators (SPMs). This initiates a cascade of anti-inflammatory and pro-resolution signaling, including polarization of macrophages toward the reparative M2 phenotype and acceleration of inflammation resolution. In parallel, M2 macrophages, SPMs, and ECs upregulate growth factors and reparative cytokines that direct wound repair and remodeling. Activated ECs stimulate angiogenesis and lymphatic angiogenesis, while fibroblasts drive collagen synthesis, ECM production, and myofibroblast differentiation, enabling wound contraction. Keratinocyte activation promotes epithelialization, and during remodeling, fibroblast activity enhances collagen fiber organization. Collectively, these pathways promote efficient resolution of inflammation, improved perfusion, increased tissue strength, reduced scarring, and lower wound recurrence.

Clinical studies demonstrate that ITOT significantly increases healing rates, reduces healing time, lowers recurrence, and decreases hospitalizations and amputations in chronic wounds. Cost-effectiveness analyses further indicate improved quality-adjusted life years (QALYs) and reduced long-term expenditures.

Conclusion: Chronic wounds persist due to a self-sustaining cycle of hypoxia, edema, and inflammation. By integrating oxygen delivery with cyclical compression, ITOT directly addresses the multifactorial barriers to repair, promoting durable healing and reducing complications. This multi-modality approach represents a promising therapeutic advance in the management of refractory lower extremity wounds, with broad implications for improving outcomes and quality of life and reducing healthcare costs.

*TWO2, AOTI, Inc, Oceanside, CA; Lohr JM, et al. A synergistic multimodality treatment approach to address the key drivers of wound chronicity. J Vasc Surg Venous Lymphat Disord. 2026 Jan;14(1):102348. doi:10.1016/j.jvsv.2025.102348