

The role of nitric oxide in diabetic foot ulcer healing: A review

Marta García-Madrid, PhD¹
¹Medical Scientific Liaison, Convatec, Spain

Introduction

- The marked tendency of diabetic foot ulcers (DFUs) toward chronicity often leads to their progression into hard-to-heal wounds, and despite optimal standard of care (SoC) management, only approximately one-third achieve healing within 12 to 24 weeks¹
- Beyond well-recognized systemic and local risk factors, poor DFU healing reflects a complex interplay between systemic dysfunction, the wound microenvironment, and impaired tissue repair mechanisms²
- Evidence suggests that dysregulation of nitric oxide (NO) signaling, among others, may contribute to DFU chronicity, as diabetes-associated hyperglycemia reduces NO bioavailability³
- NO is an endogenous antimicrobial and antibiofilm molecule produced by the mammalian innate immune response to microorganisms that holds promise in advanced wound care⁴

Objective

This review analyzed the potential of NO to improve healing outcomes in DFUs by addressing:
(i) physiological functions in wound healing; (ii) mechanisms of dysregulated wound healing in diabetes mellitus (DM); and
(iii) emerging strategies targeting NO-related pathways

Results

Physiological role of endogenous nitric oxide in wound healing

Preclinical studies consistently demonstrate that NO supports DFU healing by targeting ^{4,5}

- ◆ **Inflammatory phase:** Exhibiting antimicrobial and antibiofilm activity, thereby limiting wound bioburden and reducing oxidative stress
- ◆ **Proliferative phase:** Promotion of fibroblast, keratinocyte, and endothelial cell activity
- ◆ **Maturation phase:** Supporting organized matrix remodeling and sustained wound closure

Key biological drivers of impaired healing in DFUs⁶⁻⁸

BIOLOGICAL DOMAIN	IMPACT ON WOUND HEALING
Metabolic and oxidative stress	Impaired reparative cell function and tissue regeneration
Vascular dysfunction	Endothelial dysfunction and impaired perfusion contribute to tissue hypoxia
Chronic inflammation and immune dysfunction	Persistent inflammatory microenvironment and delayed transition to the proliferative phase

Nitric oxide-related DFU management strategies

- ◆ Independently, research has explored a range of NO-related strategies for DFU management, including dressings, hydrogels, microneedles, and portable devices⁹⁻¹⁴
- ◆ Evidence is predominantly preclinical¹² with only a limited number of medical devices evaluated in clinical studies involving patients with DFUs^{13,14}
- ◆ A novel medical device that generates NO within a dressing reported superior healing outcomes compared to SoC dressings, including greater wound area reduction and higher rates of complete healing at 12 weeks¹³

Conclusion

The critical role of NO in DFU healing has stimulated significant research interest in NO-based strategies. NO is a promising antimicrobial agent that is emerging as a novel and effective option for DFUs, particularly since these wounds are so prone to infection

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