Stimuli-Responsive Nanocomposite Hydrogels for Diabetic Foot Ulcer Management: Microenvironment Modulation and Therapeutic Synergy

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Abstract: Diabetic foot ulcer (DFU) is a debilitating complication of diabetes mellitus, featuring chronic non-healing wounds, recurrent infections, and a high risk of lower-limb amputation. Its multifactorial pathogenesis involves hyperglycemia-induced immune dysfunction, impaired neutrophil and macrophage activity, and persistent activation of inflammatory pathways such as NF-κB, while a wound microenvironment rich in reactive oxygen species, pathogenic colonization, and chronic inflammation severely limits conventional therapies. Nanocomposite hydrogels offer a promising multifunctional platform for DFU management, as nanomaterial incorporation enhances mechanical strength, self-healing, adhesion under moist conditions, and stimuli responsiveness. Bioactive functionalization enables synergistic antibacterial, antioxidant, and anti-inflammatory effects, with controlled drug release and modulation of the wound microenvironment. Formulations containing silver nanoparticles, curcumin, tannic acid, honey-derived components, exosomes, or anti-inflammatory drugs have demonstrated accelerated tissue repair in preclinical studies. Continued multidisciplinary advances in design, bioactivity optimization, and in vivo evaluation may expedite clinical translation and improve patient outcomes while reducing amputation risk.

Keywords: Diabetic Foot Ulcer; Nanocomposite Hydrogel; Pathogenesis; Wound Healing; Antibacterial; Antioxidant; Anti-Inflammatory

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by impaired glucose metabolism and frequently accompanied by complications affecting the cardiovascular system, retina, kidneys, and nervous system. Diabetic foot ulcer (DFU) is a major chronic complication in diabetic patients, arising primarily from peripheral neuropathy, peripheral arterial disease, and other related factors, ultimately leading to foot infections, ulceration, and even deep tissue destruction. Without timely intervention, DFU can progress to conditions requiring limb amputation. Epidemiological studies have shown that the global prevalence of DFU is approximately 6.3%, with affected patients facing a high risk of amputation within the first year following infection—about 34.1%—and a mortality rate of 5.5% [1].

DFU is characterized by persistent non-healing wounds, recurrent infections, and compromised skin integrity, and it represents the leading cause of lower-limb amputation worldwide. This complication imposes a substantial physical, emotional, and economic burden on patients, their families, and society at large. Achieving rapid and successful DFU wound closure requires a comprehensive therapeutic approach involving patient education, rigorous glycemic control, wound debridement, application of advanced dressings, offloading therapy, surgical interventions, and other adjunctive treatments currently used in clinical practice. Over the past few decades, a major breakthrough in DFU management has been the development and clinical adoption of novel wound dressings [2]. Although various types of dressings are now widely used, their clinical efficacy remains a matter of some debate [3]. Among these, hydrogel-based dressings are the most frequently employed for managing DFU in all stages [4].

However, traditional hydrogels, due to their highly hydrophilic nature, are inherently limited in their ability to adsorb hydrophobic molecules, thereby constraining their range of therapeutic functions. To address these limitations, nanocomposite hydrogels have been developed by incorporating hydrophobic functional groups into polymer matrices through chemical or physical modification. These composite systems are formed by embedding nanoparticles or nanostructures into cross-linked polymer networks via physical entrapment or covalent bonding. Such nanocomposites possess several advantages, including their capacity to serve as drug carriers, responsiveness to external stimuli, and enhanced adsorption of hydrophobic contaminants [5]. Owing to the combined properties of hydrogel matrices and encapsulated nanoparticles, nanocomposite hydrogels achieve synergistic functionalities unattainable by conventional hydrogels, thereby offering remarkable potential for wound repair applications [4].

This review provides an overview of the pathogenesis of DFU, the physicochemical properties of nanocomposite hydrogels, and their applications in DFU wound healing, with the aim of providing novel and effective material strategies for improving DFU treatment outcomes.

2. Pathogenesis of Diabetic Foot Ulcer (DFU)

Diabetic foot ulcer (DFU) refers to ulceration and deep tissue destruction of the foot in patients with diabetes, associated with distal lower limb neuropathy and varying degrees of peripheral vascular disease, with or without infection. To date, the pathogenesis of DFU has not been fully elucidated. Li et al. [6] suggested that hyperglycemia-induced dysfunction of neutrophils and macrophages may be contributing factors, whereas Guo et al. [7] reported that a history of smoking, neuropathy, vascular disorders, peripheral arterial disease, and long-term poor blood pressure control are also associated with the disease (Figure 1).

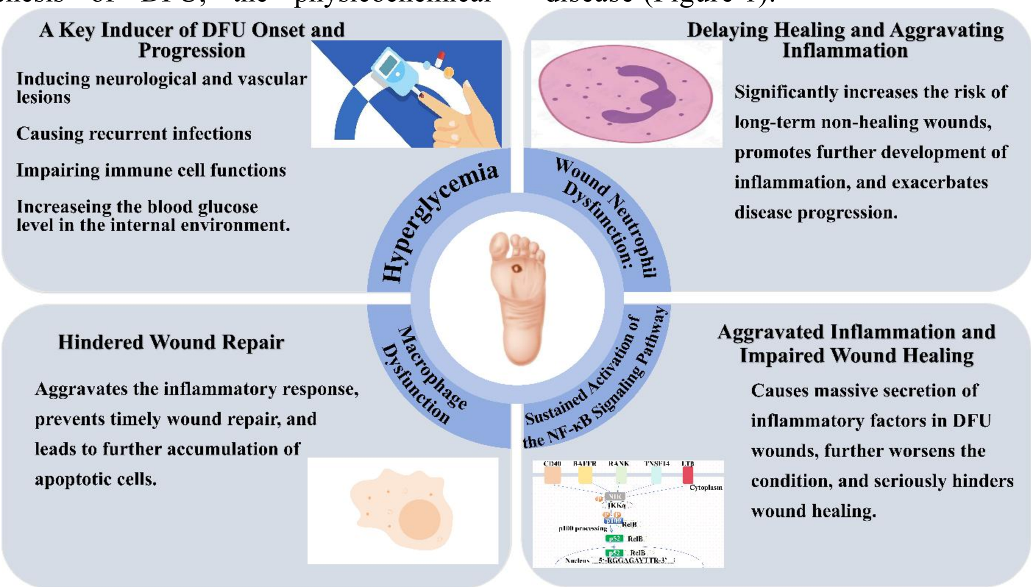

Figure 1. Pathogenesis of Diabetic Foot Ulcer

2.1 Impact of Hyperglycemia

Hyperglycemia and hypertension are key pathological factors leading to nerve dysfunction and consequent neuropathic changes, which play a critical role in the development of DFU. Liu et al. [8] demonstrated that under hyperglycemic conditions, the functions of various immune cells are compromised. For instance, neutrophil phagocytic activity is impaired; M1 macrophages exhibit prolonged activation and continuously produce large amounts of proinflammatory cytokines, thereby creating a proteolytic microenvironment; and hyperglycemia suppresses normal T-cell differentiation, leading to immunodeficiency. These alterations collectively predispose DFU wounds to recurrent and severe bacterial infections. Zhou et al. [9] further reported that DFU is a chronic condition in which repeated infections—triggered by persistent hyperglycemia and anaerobic pathogens—cause progressive ulceration and tissue destruction. Given that the lower limb vasculature plays a major role in systemic circulation, any vascular occlusion or stenosis can severely impair perfusion, leading to tissue hypoxia and even cellular necrosis.

2.2 Neutrophil Dysfunction in the Wound

According to He et al. [10] inflammatory responses mediated by immune cells are critical to wound healing and constitute an early acute reaction following tissue injury. Neutrophils, considered the first line of defense in wounds, are the earliest immune cells to migrate to injured tissue during the inflammatory phase. They clear necrotic cells and invading pathogens through oxidative metabolism and formation of neutrophil extracellular traps (NETs)—net-like structures composed of DNA and proteins that can immobilize and destroy pathogens. Neutrophils also release antimicrobial peptides, secrete pro-inflammatory cytokines, and facilitate angiogenesis as well as proliferation and activation of keratinocytes and fibroblasts, thereby recruiting additional immune cells such as monocytes to the injury site. Ruan et al. [11] found that in DFU patients, chronic hyperglycemia downregulates the expression of CXCR2 on neutrophils and impairs chemotactic signals mediated by formyl peptide receptors, leading to delayed migration and inadequate production of antimicrobial agents. These defects increase the risk of chronic non-healing wounds, exacerbate inflammation, and promote disease progression.

2.3 Macrophage Dysfunction

Macrophages play a vital role in maintaining tissue homeostasis by regulating tissue regeneration and antigen presentation. Upon receiving recruitment signals from activated neutrophils, monocytes migrate to the wound site and differentiate into macrophages. These cells contribute to wound repair by clearing apoptotic neutrophils and exerting anti-inflammatory effects, thereby facilitating tissue remodeling. As reported by He et al. [10], macrophages can polarize between the pro-inflammatory M1 phenotype (responsible for antimicrobial activity and inflammation) and the anti-inflammatory/pro-repair M2 phenotype (which releases growth factors and promotes tissue regeneration). In DFU, persistent hyperglycemia significantly alters both the number and phenotype of macrophages at the wound site. Impaired M1-to-M2 polarization prolongs the pro-inflammatory state, resulting in continuous secretion of cytokines such as TNF-α and interleukins by M1 macrophages, thereby aggravating tissue inflammation. Simultaneously, reduced M2 polarization delays healing, leading to accumulation of apoptotic cells and further tissue damage.

2.4 Persistent Activation of the NF-κB Signaling Pathway

Nuclear factor kappa-B (NF-κB) is a transcription factor involved in inflammation, immune response, apoptosis, and cellular stress responses. In mammals, the NF-κB family comprises RelA (p65), RelB, c-Rel, NF-κB1 (p105/p50), and NF-κB2 (p100/p52). NF-κB activation occurs via two distinct pathways: the canonical (classical) and non-canonical (alternative) signaling pathways. The canonical pathway—mediated primarily by the p65/p50 heterodimer—is typically triggered by external stimuli such as inflammatory cytokines (e.g., TNF-α, interleukins secreted by macrophages), pathogen-associated molecular patterns, and oxidative stress. These stimuli activate the IκB kinase (IKK) complex, which phosphorylates and degrades IκB (inhibitor of NF-κB), thereby facilitating NF-κB nuclear translocation and transcription of target genes, including pro-inflammatory cytokines, to eliminate pathogens and repair tissue damage. However, Guo et al. [12] found that sustained NF-κB activation increases pro-inflammatory cytokine secretion in DFU wounds, aggravating local inflammation, worsening the clinical course, and further delaying wound healing.

3. Properties of Nanocomposite Hydrogels

3.1 Mechanical Properties

Conventional hydrogels typically exhibit relatively weak mechanical strength, which markedly limits their applications in many fields. To overcome this limitation, various strategies have been proposed to enhance their mechanical properties [13,14]. Among these, the incorporation of nanomaterials into hydrogel matrices has proved to be an effective approach for strengthening nanocomposite hydrogels [15]. Nanomaterials generally possess exceptionally high mechanical strength and large specific surface area, which allows efficient dissipation of externally applied stress. Furthermore, the introduction of reactive functional groups on nanomaterials facilitates strong interactions with polymer chains, leading to a dual crosslinking structure—both polymer–polymer and nano–polymer crosslinks. This dual network significantly increases the compressive strength of the hydrogels, mitigates fracture in the polymer network, and ultimately improves their mechanical performance [16].

Unmodified nanomaterials often have poor compatibility with polymer matrices. Surface functionalization with hydroxyl, amino, or other reactive groups can significantly improve the interfacial compatibility and thus enhance the mechanical properties of nanocomposite hydrogels. For example, Sowan et al. [17] introduced dynamic covalent chemistry (DCC) reactive groups at the interface between silica nanoparticles and polymer resin, thereby improving stress relaxation, increasing toughness, and reducing polymerization shrinkage stress. In dental restorative materials, Sowan et al. [18] further utilized thiol–thioester (TTE) exchange reactions at the resin–filler interface, achieving a 30% reduction in shrinkage stress alongside mechanical improvements, including a 60% increase in Young's modulus and a 35% increase in toughness. Similarly, Li et al. [19] functionalized SiO_2 nanoparticles with boronic acid/ boronate ester dynamic covalent bonds (DCBs) and incorporated them into an alginate matrix; compared to control hydrogels, the nanoparticle-reinforced hydrogels displayed improved stiffness and deformation resistance, both of which were dependent on the nanoparticle concentration.

3.2 Self-Healing Properties

Self-healing hydrogels possess the ability to restore their mechanical properties after damage, thereby extending their service life and improving their stability during application [20,21]. As a result, the development of self-healing hydrogels has become a prominent research focus. Notably, nanocomposite hydrogel systems exhibit superior self-healing performance, primarily due to the dynamic interactions between their constituent components.

Incorporating nanomaterials can efficiently enhance the self-healing capacity of hydrogels, with the extent of improvement largely dependent on the types of interfacial interactions present. For example, graphene oxide (GO) nanosheets contain hydroxyl, epoxy, and other functional groups capable of forming hydrogen bonds with polymer chains. Pereira et al. [22] incorporated GO nanosheets into a Schiff-base hydrogel synthesized from a benzaldehyde-functional amphiphilic polyacrylamide crosslinker and ethylene glycol chitosan. Rheological characterization revealed that the self-healing efficiency improved dramatically—from 60% in the pristine hydrogel to over 99% upon GO addition. This enhancement can be attributed to additional dynamic physical interactions between the GO surface groups and polymer chains, which further optimized the Schiff-base-mediated dynamic crosslinking network.

The dynamic responsiveness of nanomaterials also enables adaptive regulation of self-healing in hydrogels. For instance, in pH-responsive systems, Behjat et al. [23] demonstrated that introducing tannic-acid-modified ZIF-8 nanoparticles at concentrations of 5–15 wt% into a borax-crosslinked poly (vinyl alcohol) matrix increased the self-healing efficiency to 65.45–85.27%. Beyond pH responsiveness, nanomaterials can impart thermo-, photo-, electro-, and other stimulus-responsiveness, thereby enabling tunable healing properties in the hydrogel.

3.3 Adhesive Properties

Certain components in nanocomposite hydrogels allow them to adhere to plastics, glass, and biological tissues—an essential property for their utility in wound dressings, wearable sensors, and related biomedical or engineering applications. Conventional hydrogels generally have weak adhesive strength and detach easily in moist environments. Incorporating nanomaterials can significantly enhance adhesion by forming strong interfacial bonds between surface functional groups and the hydrogel matrix.

To address the limitations of traditional thermo-sensitive hydrogels—namely weak adhesion, poor retention in moist environments, and unsuitability for irregular wound shapes—Wang et al. [24] developed a composite incorporating Ce^{3+}/TA/UTI nanoparticles with F127-lipoic acid (F127-LA) micelles. Coordination between Ce^{3+} and F127-LA enabled a gradual viscosity increase at physiological temperature (37 °C), allowing injectable coverage of irregular wounds without spreading. Upon UV irradiation, disulfide bonds in F127-LA underwent exchange reactions to form a covalently crosslinked solid hydrogel. The low-swelling property prevented detachment in wet environments, while UV curing created a topological interlocking interface with tissues. Moreover, thiol groups in the hydrogel could undergo thiol–disulfide exchange with tissue thiols/disulfides, resulting in an adhesion strength exceeding 30 kPa. Even after prolonged PBS immersion, the hydrogel remained firmly attached, effectively sealing the wound.

3.4 Stimuli-Responsiveness

Stimuli-responsive hydrogels can undergo reversible physical or chemical changes in response to external stimuli such as light, heat, electric fields, or magnetic fields. These properties, and the ability to tailor them, offer broad potential for biomedical, environmental, and engineering applications. Although some single-component hydrogels display limited stimulus-responsiveness, most cannot provide controllable responses under practical conditions [25].

To address the challenge of limited control over drug release parameters in conventional polymer nanoparticles—particularly under the complex conditions of the biological microenvironment—Chen et al. [26] designed a spiropyran (SP)-based organic–inorganic hybrid nanogel (NG). This was synthesized via emulsion polymerization using upconversion nanoparticles, SP, acrylic acid, and N,N′-bis(acryloyl)cystamine (BAC) as precursors, producing a multi-stimuli-responsive crosslinked carrier. The nanogel enabled fine-tuning of drug release rates. Using doxorubicin hydrochloride as a model drug, results showed controllable release within 24 h under single stimuli such as near-infrared (NIR) light, acidic pH, or reducing agents; under a triple mild stimulus (NIR + pH 6 + 4 mM reducing agent), the release efficiency was further increased. Such effective, controllable drug release provides new opportunities for designing advanced stimuli-responsive nanomedicine carriers. Furthermore, incorporation of two-dimensional nanomaterials into hydrogels can enhance their multi-stimulus responsiveness, underscoring their significant potential in biomaterials and flexible electronics.

4. Applications of Nanocomposite Hydrogels in DFU Wound Healing

4.1 Antibacterial Function of Nanocomposite Hydrogels in Wound Healing

The persistently hyperglycemic microenvironment in DFU wounds promotes bacterial colonization and proliferation [27]. Effective early-stage antibacterial intervention is critical for preventing refractory DFU wounds from progressing to more severe stages [28]. Many hydrogels display intrinsic antibacterial properties, enabling them to inhibit bacterial growth, reduce infection risk, and thereby support wound healing. For example, Liang et al. [29] demonstrated that certain natural hydrogels possess inherent antibacterial activity, such as chitosan hydrogels, whose amino groups interact electrostatically with negatively charged bacterial membranes, disrupting their integrity and leading to bactericidal effects. In addition, cationic polymers such as polyethyleneimine and ε-polylysine (E-polylysine, EPL) are highly effective synthetic antibacterial hydrogel materials. EPL is a natural polypeptide with broad-spectrum antibacterial properties. Sun et al. [30] developed a Gelatin Methacryloyl (GelMA) composite hydrogel loaded with EPL-based antimicrobial peptides and observed significant antibacterial efficacy.

Beyond using inherently antibacterial polymers, hydrogel antibacterial activity can be enhanced by incorporating antimicrobial agents such as drugs, metallic nanoparticles, or natural extracts [31-33]. For instance, silver ions, antibiotics, and antimicrobial peptides can be loaded into hydrogels to achieve sustained, controlled antibacterial release, maintaining prolonged antimicrobial action at the wound site.

4.2 Antioxidant Function of Nanocomposite Hydrogels in Wound Healing

Excessive accumulation of reactive oxygen species (ROS) in DFU wound tissue induces chronic oxidative stress and inflammation, making timely ROS scavenging during the wound proliferation phase particularly important [34]. Hydrogels can be functionalized with antioxidant nanomaterials to release these agents locally, thereby lowering ROS levels at the wound site.

Qi et al. [35] reported that cellulose acetate nanofiber hydrogels loaded with curcumin exhibited significantly enhanced free radical scavenging ability compared to controls. Honey-based hydrogels, owing to phenolic compounds in honey, also possess antioxidant capacity; Song et al. [36] further improved this by integrating metal chelators into honey hydrogel formulations, enabling the suppression of lipid peroxidation and effective clearance of free radicals and peroxyl radicals. Tannic acid, a natural antioxidant [37], has similarly been employed as an active component—Duan et al. [38] observed that increasing tannic acid content in silk fibroin hydrogels progressively strengthened antioxidant capacity at 37 °C, thereby reducing oxidative radicals in the wound bed and promoting tissue repair.

A limitation of traditional hydrogels is the uncontrolled release of antioxidant agents. This can be addressed by designing microenvironment-sensitive smart hydrogels that combine stimuli-responsiveness with antioxidant components, enabling on-demand release and precise redox balance regulation in the wound. Such designs not only improve therapeutic efficacy but also reduce potential side effects to surrounding healthy tissue, providing a more optimized solution for chronic wound management.

4.3 Anti-Inflammatory Function of Nanocomposite Hydrogels in Wound Healing

In chronic wounds, excessive and prolonged inflammatory responses result from dysregulated cytokine release, thereby impeding tissue repair [39]. Anti-inflammatory hydrogels based on delivery of bioactive molecules are among the most extensively studied strategies for modulating the wound environment. These systems achieve inflammation control via local delivery of cytokines, exosomes, genes, or anti-inflammatory drugs.

Drug-loaded hydrogels provide sustained anti-inflammatory effects via controlled release; exosome-loaded hydrogels regulate intercellular communication to improve the inflammatory microenvironment; gene delivery hydrogels allow targeted regulation of inflammation-related gene expression; and cytokine-loaded hydrogels modulate immune cell function to promote inflammation resolution and tissue regeneration.

For instance, Chen et al [40] developed a hydrogel enabling transdermal delivery of ibuprofen, showing promising potential as a local ibuprofen delivery system in vitro. Wathoni et al. [41] fabricated physically crosslinked hydrogel film dressings from the natural polysaccharide sacran, which maintained wound moisture, reduced production of inflammatory cytokines such as IL-5, IFN-γ, and TNF-α in atopic dermatitis model mice, and accelerated wound closure. Saleh et al. [42] engineered an adhesive hydrogel loaded with miRNA nanoparticles that adhered to the wound site for localized immune modulation, significantly downregulated pro-inflammatory markers, and, as confirmed by histological and qPCR analyses, promoted improved wound healing outcomes.

5. Conclusion and Outlook

Diabetic foot ulcer (DFU), a severe chronic complication of diabetes, is driven by pathological features such as immune cell dysfunction caused by hyperglycemia and persistent activation of the NF-κB signaling pathway. These factors contribute to recurrent wound infections, impaired healing, and a substantial burden on both patients and society. Conventional dressings and standard hydrogels are hindered by limitations—including poor mechanical strength, weak adhesion, and single functionality—making them inadequate for addressing the complex and dynamic requirements of DFU repair.

Nanocomposite hydrogels, created by integrating nanoparticles into a polymer matrix, not only overcome the intrinsic shortcomings of traditional materials but also achieve synergistic performance enhancement. Mechanically, the high specific surface area of nanomaterials, together with dynamic crosslinking interactions, significantly improves their compressive strength and resistance to deformation. Self-healing properties, enabled by dynamic interactions between nanoparticles and polymer chains, allow efficient recovery after damage. Adhesion is strengthened through robust interfacial interactions between nano-components and tissue, effectively addressing detachment in moist environments. Moreover, stimulus-responsiveness endows these hydrogels with the ability to release therapeutic agents in an on-demand manner, offering opportunities for precision therapy.

In DFU management, nanocomposite hydrogels can sterilize wounds via physical antimicrobial effects and through the controlled release of antimicrobial agents. Additionally, they can incorporate antioxidant components to scavenge excess reactive oxygen species (ROS) and deliver anti-inflammatory drugs to modulate immune cell function and alleviate chronic inflammation. Together, these mechanisms enable comprehensive modulation of the wound microenvironment, demonstrating significant therapeutic potential.

Nevertheless, challenges remain in the development of nanocomposite hydrogels. On one hand, compatibility between certain nanomaterials and polymer matrices requires optimization, as high nanoparticle loading can lead to aggregation, potentially compromising biosafety and material stability. On the other hand, most current studies are confined to the laboratory stage; their long-term biodegradability, in vivo biocompatibility, and cost-effective large-scale production require further investigation.

Future research may focus on: (1) developing nanocomposite hydrogels with multiple dynamic crosslinking networks to further enhance mechanical properties and environmental adaptability; (2) designing intelligent, multi-stimuli-responsive drug delivery systems tailored to the DFU wound microenvironment for coordinated antibacterial, antioxidant, and anti-inflammatory effects; and (3) strengthening clinical translation through animal studies and clinical trials to validate safety and efficacy, ultimately promoting nanocomposite hydrogels as novel, practical DFU dressings and providing optimized solutions to the current challenges in DFU treatment.

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