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THERAPEUTIC CHALLENGES IN THE MANAGEMENT OF DIABETIC FOOT ULCERS: A CRITICAL REVIEW ON CURRENT AND EMERGING TREATMENT STRATEGIES

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ABSTRACT

Diabetic foot ulcers (DFUs) remain one of the most severe and costly complications of diabetes mellitus, contributing substantially to morbidity, mortality, and lower-limb amputations worldwide. The pathogenesis of DFUs is multifactorial, involving peripheral neuropathy, ischemia, immune dysfunction, persistent inflammation, and microbial biofilm formation, all of which disrupt the normal wound-healing cascade. Although conventional management strategies—such as systemic antibiotics, debridement, offloading, and moist wound dressings—form the cornerstone of DFU care, their clinical effectiveness is often limited by antimicrobial resistance, poor patient adherence, delayed healing, and high recurrence rates. These limitations highlight the need for therapeutic approaches that address both infection control and the underlying pathophysiological abnormalities of diabetic wounds.

Recent advances in biomaterial science have led to the development of innovative wound care strategies, including nanofiber-based dressings, hydrogel systems, growth factor delivery platforms, and cell- or exosome-loaded scaffolds. These emerging technologies aim to modulate the wound microenvironment, enhance angiogenesis, provide controlled drug release, and promote tissue regeneration. However, despite encouraging preclinical outcomes, challenges related to biological instability, mechanical durability, scalability, safety, and regulatory approval continue to impede clinical translation. This review critically evaluates the global burden, pathophysiological mechanisms, and current therapeutic limitations in DFU management, while systematically discussing emerging biomaterial-based wound care strategies. By synthesizing existing evidence, this article underscores the need for clinically translatable, multifunctional wound dressings supported by well-designed clinical trials to improve long-term outcomes in patients with diabetic foot ulcers.

Keywords: Diabetic foot ulcer; Diabetes mellitus; Chronic wound healing; Peripheral neuropathy; Peripheral arterial disease; Biofilm formation; Antimicrobial resistance; Debridement; Offloading techniques; Advanced wound dressings; Biomaterials; Nanofibers; Electrospinning; Core–shell nanofibers; Drug delivery systems; Hydrogels; Composite hydrogels; Angiogenesis; Tissue regeneration.

1. INTRODUCTION

Diabetic foot ulcers (DFUs) are a common and highly morbid consequence of long-standing and poorly controlled diabetes mellitus. Among the estimated 537 million individuals living with diabetes worldwide, approximately 19–34% are expected to develop a DFU during their lifetime. DFUs represent a leading cause of diabetes-related hospital admissions and are the primary precursor to lower-extremity amputations. Nearly 20% of patients with DFUs require minor or major limb amputation, and approximately 10% die within one year of initial ulcer diagnosis [1].

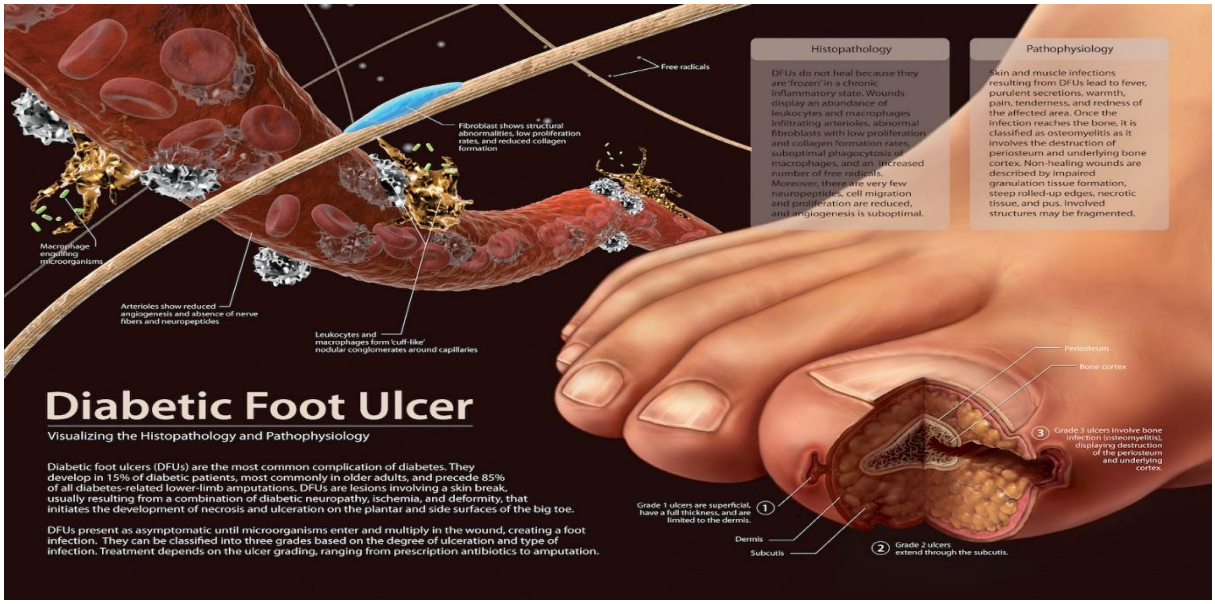
The prevalence of DFUs varies across geographical regions, with the highest rates reported in North America (13.0%), followed by Africa (7.2%), Asia (5.5%), Europe (5.1%), and Oceania (3.0%) [2]. Socioeconomic and demographic factors further influence disease burden. In 2021, the global prevalence of diabetes was estimated at 10.5%, with higher prevalence observed in urban populations (12.1%) compared to rural regions (8.3%), and in high-income countries (11.1%) compared to low- and middle-income countries (5.5%) [2]. These disparities contribute to unequal access to preventive care and timely DFU management, thereby increasing the risk of complications.

DFUs are associated with substantial mortality, with long-term outcomes comparable to several malignancies. Australian cohort data demonstrate a 5-year mortality rate of 24.6% among individuals with DFUs, increasing to 45.4% at 10 years

[2]. Mortality is primarily driven by chronic kidney disease, cardiovascular disease, sepsis, and multi-organ failure. Patients with neuropathic ulcers exhibit lower mortality rates compared to those with ischemic or infected ulcers, highlighting the prognostic importance of ulcer aetiology.

Morbidity in DFU patients is predominantly related to infection. Diabetic foot infections complicate approximately 60% of DFUs and represent a major cause of emergency department visits and hospitalizations [1]. Persistent or relapsed infections are common, with up to 25% of patients demonstrating unresolved infection after 10–20 days of treatment. In severe infections and osteomyelitis, amputation rates may reach nearly 90% [1].

The economic burden of DFUs is considerable. Global healthcare expenditure related to diabetes has reached USD 966 billion, reflecting a 316% increase over the past 15 years [2]. DFUs account for a significant proportion of these costs due to prolonged hospital stays, repeated surgical interventions, and long-term wound care. In the United States, Medicare expenditures for DFU treatment exceed USD 6 billion annually, with DFUs implicated in over 80% of major and 96% of minor lower-limb amputations [2].



2. PATHOPHYSIOLOGY OF DIABETIC FOOT ULCERS

The pathophysiology of DFUs is complex and multifactorial, involving metabolic dysregulation, neuropathy, angiopathy, and impaired immune responses. The interaction between diabetic immunopathy, neuropathy, and vascular dysfunction promotes ulcer formation, infection, and delayed healing [3].

2.1 Diabetic Neuropathy

Peripheral neuropathy is the most common complication of diabetes and contributes to more than 60% of DFUs [3]. Sensory neuropathy results in loss of protective sensation, increasing susceptibility to unrecognized trauma. Motor neuropathy causes intrinsic muscle atrophy and foot deformities, such as claw toes and hammer toes, leading to abnormal pressure distribution. Autonomic neuropathy reduces sweat and sebaceous gland function, resulting in dry, fissured skin prone to breakdown and infection. The combined effects of sensory, motor, and autonomic neuropathy lead to callus formation, subcutaneous haemorrhage, and eventual ulceration [4].

2.2 Ischemia and Peripheral Arterial Disease

Diabetes is increasingly recognized as a vascular disease. Endothelial dysfunction, characterized by reduced nitric oxide bioavailability and increased smooth muscle proliferation, promotes atherosclerosis and vascular narrowing. Hyperglycaemia also increases fibrinogen and plasminogen activator inhibitor levels, impairing fibrinolysis. Hyperlipidaemia and hypertension further exacerbate vascular dysfunction, resulting in reduced tissue perfusion, ischemia, and impaired wound healing [5].

2.3 Infection and Biofilm Formation

Infection is a frequent complication of DFUs and significantly delays wound healing. Approximately 60% of DFUs develop clinically significant infections, which may be superficial, deep, or involve osteomyelitis. Common pathogens include *Staphylococcus aureus*, *Streptococcus* species, and Gram-negative bacilli, with MRSA complicating 15–32% of infections [5]. Biofilm formation enables bacterial persistence by reducing antibiotic penetration and evading host immune responses, thereby contributing to chronic infection and antimicrobial resistance [3].

Normal wound healing is a coordinated process involving haemostasis, inflammation, proliferation, and remodelling. In diabetic wounds, this process is disrupted from the outset. Chronic hyperglycaemia impairs microvascular circulation, exacerbates ischemia, and prolongs the inflammatory phase [6]. Neutrophil and macrophage dysfunction, particularly impaired macrophage polarization, leads to excessive inflammation and delayed transition to the proliferative phase. Collagen synthesis, extracellular matrix remodelling, and angiogenesis are significantly impaired, increasing susceptibility to infection and chronic non-healing ulcers [7].

3. CONVENTIONAL MANAGEMENT THERAPIES FOR DIABETIC FOOT ULCERS

3.1 Systemic Antibiotic Therapy

Diabetic foot infections (DFIs) progress along a continuum ranging from contamination to localized infection and, ultimately, systemic involvement. Early intervention at the stage of local infection or biofilm formation is critical to prevent clinically overt infection and severe complications. Host-related factors significantly influence the microbiome composition of DFUs, thereby affecting therapeutic outcomes [8].

The selection of systemic antibiotics is guided by infection severity, prior antibiotic exposure, and the likelihood of resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) [9]. Multiple comparative studies and systematic reviews have evaluated the efficacy and safety of commonly used antibiotics in DFIs.

Fluoroquinolones, particularly moxifloxacin, demonstrated comparable clinical resolution rates to piperacillin–tazobactam (TZP) or amoxicillin–clavulanic acid (AMC), with pooled analyses showing no statistically significant differences in treatment outcomes (RR ≈ 1.0). However, moxifloxacin was associated with a higher incidence of adverse events compared with TZP/AMC [9].

Similarly, ertapenem (ETP) showed non-inferior efficacy to TZP ± vancomycin across several trials, although subgroup analyses suggested reduced effectiveness in severe infections. Tigecycline failed to meet non-inferiority criteria when compared with ETP + vancomycin and was consistently associated with higher adverse event rates, particularly gastrointestinal disturbances [9]. In osteomyelitis-associated DFIs, ETP + vancomycin achieved significantly higher clinical resolution rates than tigecycline.

Comparisons between ampicillin–sulbactam and cefoxitin revealed no statistically significant differences, although cefoxitin showed higher cure rates in osteomyelitis subsets. Overall, evidence suggests that while multiple antibiotic regimens demonstrate

similar efficacy, safety profiles and resistance patterns are critical determinants in therapy selection [9,10].

3.2 Adverse Drug Events and Safety Concerns

Antibiotic-associated adverse events remain a major limitation in DFI management. Tigecycline and linezolid were linked to significantly higher adverse event rates compared to carbapenems and β-lactam/β-lactamase inhibitor combinations. In contrast, daptomycin demonstrated a more favourable safety profile than vancomycin and semi-synthetic penicillin. Carbapenem-based regimens combined with anti-pseudomonal agents generally resulted in fewer adverse effects than anti-pseudomonal penicillin [9,10].

3.3 Antimicrobial Resistance and Biofilm Formation

Antimicrobial resistance (AMR) represents a growing challenge in DFU management. High resistance rates have been reported among common DFU pathogens, including quinolone resistance in *Enterobacterales* (29.3%), carbapenem resistance in non-fermenting Gram-negative bacteria (22.2%), and multidrug resistance (MDR) in *Acinetobacter* spp. (up to 63.6%). MRSA accounted for 21.1% of *S. aureus* isolates, while vancomycin-resistant *Enterococcus* (VRE) was identified in 7% of cases [11,16]. Biofilm formation further exacerbates AMR by protecting bacterial communities through extracellular polymeric substances, efflux pumps, and persisted cells, collectively reducing antibiotic penetration and efficacy [12]. Over 50% of DFU isolates are capable of biofilm formation, with many exhibiting resistances to multiple antibiotic classes [15]. These factors contribute to persistent infections, delayed healing, increased risk of amputation, and escalating healthcare costs [13, 14].

3.4 Debridement Techniques in DFU Management

Debridement is a cornerstone in DFU care, as it removes necrotic tissue, reduces microbial burden, disrupts biofilms, and promotes wound healing. The European Wound Management Association recognizes surgical, mechanical, enzymatic, chemical, and autolytic debridement as validated approaches [17].

Surgical and Mechanical Debridement

Surgical (sharp) debridement remains the standard of care for infected, deep, or non-healing DFUs. Randomized controlled trials have demonstrated significantly reduced healing time and higher healing rates compared with conventional wound care, although differences in complication and relapse rates were not always statistically significant [17,18]. In diabetic foot osteomyelitis, surgical debridement or bone resection can be curative, although selected cases may be managed conservatively with antibiotics alone.

Autolytic and Enzymatic Debridement

Autolytic debridement employs moisture-retentive dressings such as hydrogels to facilitate endogenous enzymatic breakdown of necrotic tissue. While effective in wound size reduction, evidence suggests no clear superiority in achieving complete healing when compared with alternative approaches [17,18].

Enzymatic debridement agents, including bromelain-based formulations and collagenase ointments, have shown promise in reducing biofilm burden and promoting wound area reduction. Collagenase is well-supported by randomized trials across various chronic wounds but is associated with higher rates of local adverse events such as pain and cellulitis [17,19].

3.5 Limitations of Debridement Evidence

The overall quality of evidence comparing debridement techniques remains low due to

small sample sizes, methodological weaknesses, and heterogeneity in outcome measures. Consequently, definitive conclusions regarding the superiority of specific debridement methods cannot be drawn [17,19].

4.OFFLOADING TECHNIQUES

Diabetic foot ulcers (DFUs) are defined as full-thickness wounds occurring distal to the ankle in individuals with diabetes mellitus and represent a significant cause of morbidity and lower-limb amputation worldwide [20]. The development of DFUs is multifactorial, with peripheral neuropathy, elevated plantar pressure, foot deformities, and impaired wound healing playing central roles. Long-standing diabetes frequently leads to peripheral neuropathy, resulting in loss of protective sensation. This sensory deficit allows repetitive mechanical stress to occur without patient awareness, predisposing the plantar soft tissues to progressive injury and ulceration [21].

Plantar pressure refers to the magnitude and distribution of forces acting between the plantar surface of the foot and the ground during standing and ambulation. Persistently elevated plantar pressure is a key biomechanical factor contributing to both the formation of diabetic foot ulcers and delayed wound healing [22]. Excessive focal pressure and shear stress impair local microcirculation, promote tissue ischemia, and perpetuate inflammation, thereby disrupting the normal wound-healing process. Consequently, strategies aimed at reducing or redistributing plantar pressure are essential in DFU management.

Offloading is defined as the reduction, redistribution, or elimination of mechanical load from the ulcerated area of the foot to promote tissue repair. In patients with diabetic neuropathy, subjective perception of pain or discomfort is unreliable due to reduced sensory feedback. As a result, patients are often unable to judge whether adequate pressure relief has been achieved during standing or walking [23]. Subjective comfort therefore does not accurately reflect effective pressure reduction at the ulcer site.

International guidelines on diabetic foot care emphasize the importance of objective biomechanical assessment when evaluating offloading interventions [24]. Objective pressure measurement techniques are required to quantify pressure reduction at the ulcer site, compare the efficacy of different offloading modalities, optimize individualized treatment strategies, and correlate biomechanical outcomes with ulcer healing rates. Such objective assessments are critical for both clinical decision-making and research applications.

Offloading modalities used in DFU management may be broadly categorized into non-removable devices, removable devices, surgical offloading procedures, and adjunctive padding techniques. Among these, total contact casting (TCC) is widely recognized as the gold standard for offloading plantar diabetic foot ulcers. TCC involves the application of a well-moulded, minimally padded cast that closely conforms to the contours of the foot and lower leg. By increasing the total contact area between the foot and the cast, TCC effectively reduces peak plantar pressures at the ulcer site [25]. In addition, restriction of ankle and foot motion minimizes shear forces and repetitive trauma during gait. The non-removable nature of TCC enforces patient adherence, which significantly contributes to its superior healing outcomes. Numerous randomized controlled trials and systematic reviews have demonstrated higher ulcer-healing rates with TCC compared to removable offloading devices [26]. However, its use is limited by the need for skilled application, difficulty in frequent wound inspection, and contraindications such as active infection, severe peripheral arterial disease, or excessive wound exudation.

Specialized footwear represents a more practical approach to offloading, particularly for long-term management and prevention of

ulcer recurrence. Therapeutic shoes, custom-moulded insoles, rocker-bottom soles, and orthotic inserts are designed to accommodate foot deformities and redistribute plantar pressure away from high-risk areas. These devices alter gait mechanics and reduce localized pressure over bony prominences [27]. Although specialized footwear improves comfort and allows regular wound monitoring, its clinical effectiveness is highly dependent on patient adherence. Evidence indicates that inconsistent use significantly reduces healing outcomes when compared with non-removable offloading systems [28].

Removable cast walkers (RCWs), offloading boots, and other pressure redistribution devices serve as intermediate options between TCC and therapeutic footwear. When worn as prescribed, RCWs can achieve plantar pressure reduction comparable to TCC [29]. However, the removable design often results in reduced compliance, as patients may remove the device during daily activities, thereby limiting its therapeutic benefit. Felted foam padding is frequently used as an adjunctive offloading technique, particularly in resource-limited settings. While effective in reducing focal pressure, this method requires frequent replacement and careful application to maintain consistent offloading [30].

Despite their proven benefits, offloading techniques are associated with several limitations. Non-compliance remains the most significant challenge, especially with removable devices. Offloading interventions may also impair mobility, increase fall risk, and negatively impact quality of life. Improper fitting or prolonged use without adequate monitoring can lead to secondary complications, including skin breakdown and the development of new ulcers. Therefore, selection of an offloading modality should be individualized based on ulcer characteristics, vascular status, infection risk, and patient lifestyle [24].

In summary, effective offloading is essential for the healing and prevention of diabetic foot ulcers. While total contact casting remains the most effective modality, alternative strategies such as specialized footwear and removable pressure redistribution devices play important roles in comprehensive DFU management. Ongoing research is increasingly focused on smart offloading systems and pressure-sensing technologies to enable objective monitoring and improve patient adherence.

5. MOIST WOUND DRESSINGS

Moist wound healing is a fundamental principle in the management of diabetic foot ulcers, as it creates an optimal environment for cellular migration, angiogenesis, and extracellular matrix formation [31]. Chronic DFUs are commonly characterized by prolonged inflammation, impaired growth factor activity, reduced angiogenesis, and delayed epithelialization. Moist wound dressings are designed to maintain adequate hydration at the wound surface while effectively managing exudate, thereby preventing desiccation and limiting tissue necrosis. Commonly used moist dressings in DFU care include foam dressings, hydrocolloids, and alginate dressings, each possessing distinct physicochemical properties suited to different wound conditions.

Foam dressings are frequently employed in the management of moderately to heavily exuding diabetic foot ulcers. These dressings are typically composed of polyurethane or silicone-based materials with a porous structure that enables efficient absorption of wound exudate while maintaining a moist wound interface [32]. By controlling excess moisture, foam dressings reduce the risk of per wound maceration, which is particularly relevant in patients with diabetes who have fragile skin. In addition, foam dressings provide thermal insulation and mechanical cushioning, offering protection against external trauma and pressure. Their semi-permeable structure allows gaseous

exchange while acting as a barrier to microbial penetration. However, foam dressings lack inherent antimicrobial properties and may require adjunctive antimicrobial therapy when used in infected wounds.

Hydrocolloid dressings are composed of hydrophilic substances such as gelatine, pectin, and carboxymethylcellulose incorporated into an adhesive matrix. Upon contact with wound exudate, these components absorb fluid and form a gel that maintains a moist wound environment and facilitates autolytic debridement [33]. In diabetic foot ulcers with low to moderate exudation, hydrocolloids support removal of necrotic tissue and promote granulation tissue formation. Their occlusive or semi-occlusive nature reduces external contamination and limits moisture loss. However, hydrocolloid dressings are generally contraindicated in infected DFUs, as their occlusive properties may promote anaerobic bacterial growth. Additionally, strong adhesion to surrounding skin may result in skin stripping and irritation during dressing removal, particularly in elderly or neuropathic patients.

Alginate dressings are derived from naturally occurring polysaccharides obtained from brown seaweed and are particularly suitable for heavily exuding diabetic foot ulcers. These dressings interact with wound exudate through an ion-exchange mechanism, forming a hydrophilic gel that maintains moisture while facilitating absorption of excess exudate [34]. Alginate dressings also exhibit mild haemostatic properties, making them useful following sharp debridement. Their ability to conform to irregular wound beds ensures close contact with the ulcer surface and supports granulation tissue formation. However, alginate dressings require secondary dressings for fixation and moisture retention. Furthermore, their use in dry or minimally exuding wounds may lead to desiccation and delayed healing.

Despite their clinical utility, moist wound dressings present several limitations in DFU management. Dressing adherence to the wound bed or per wound skin is a common concern, particularly with hydrocolloids and inadequately hydrated alginates, leading to pain and tissue trauma during removal. Infection risk is another important limitation, as a moist environment can promote microbial proliferation if exudate is poorly controlled or dressing changes are delayed [35]. Moreover, while moist dressings support physiological wound healing, they do not address underlying pathological factors such as ischemia, neuropathy, hyperglycaemia, or persistent mechanical stress. Consequently, delayed or incomplete healing may occur when moist wound dressings are used in isolation without adequate offloading and multidisciplinary care.

In conclusion, foam, hydrocolloid, and alginate dressings play an important role in creating an optimal wound environment for diabetic foot ulcer healing. Their effectiveness depends on appropriate wound selection, regular monitoring, and integration into a comprehensive DFU management strategy. Recent research is increasingly directed toward the development of advanced moist dressings incorporating antimicrobial agents and bioactive compounds to overcome current limitations and improve clinical outcomes.

6. ADVANCED WOUND CARE APPROACHES

6.1 Nanofibers in Advanced Wound Care

Nanofibers are ultrafine continuous fibres with diameters typically below 1000 nm, characterized by a high surface-area-to-volume ratio, interconnected porosity, and tuneable mechanical properties. Their structural similarity to the extracellular matrix (ECM) makes them highly suitable for biomedical applications, particularly wound healing and tissue regeneration. Nanofibers can be fabricated from natural polymers (e.g., collagen, gelatine, chitosan), synthetic polymers (e.g., PCL, PLGA, PVA), or composite systems, and can serve as carriers for antimicrobial agents, growth factors,

herbal extracts, and nanoparticles to achieve localized and sustained drug delivery.

In chronic wounds such as diabetic foot ulcers (DFUs), impaired angiogenesis, persistent inflammation, and microbial infection significantly delay healing. Nanofiber-based dressings provide a moist wound environment, enhance cell adhesion and proliferation, promote angiogenesis, and reduce microbial colonization, thereby accelerating tissue regeneration. Consequently, nanofiber dressings are emerging as promising next-generation wound care systems.

6.2 Types of Nanofiber Dressings

1) Electrospun Polymeric Nanofibers

Electrospinning is the most widely employed technique for nanofiber fabrication due to its ability to generate fibres with controlled diameter, morphology, porosity, and alignment. The process involves a high-voltage power supply, a polymer solution-loaded syringe, and a grounded collector. Under an electric field, the polymer jet is stretched and deposited as nanofibers onto the collector.

Electrospun nanofibers have been extensively explored for diabetic wound management due to their high surface area, porosity, and mechanical tunability. They mimic the native ECM and support skin regeneration; however, bacterial contamination and persistent inflammation remain major challenges in chronic wounds. Therefore, incorporation of bioactive agents into Electrospun matrices has been proposed to enhance therapeutic outcomes. Electrospun nanofibers can deliver antibiotics, antibacterial nanoparticles, stem cells, and phytochemicals to promote cell proliferation, migration, and differentiation.

Although electrospun mats act as physical barriers against bacteria, maintaining wound moisture is essential. Hence, hybrid systems combining electrospun nanofibers with hydrogels have been developed to improve moisture retention and wound healing efficacy. Hydrogels with three-dimensional polymeric networks have shown significant potential in diabetic ulcer management [36]

2) Composite Nanofibers Loaded with Bioactive Agents

Composite nanofibers incorporate multiple polymers or nanoparticles to enhance mechanical strength, biological activity, and drug delivery efficiency. These systems enable the encapsulation and controlled release of sensitive therapeutic agents, improving wound healing and regenerative outcomes [37].

3) Coaxial (Core–Shell) and Multilayer Nanofibers

Coaxial electrospinning produces core–shell nanofibers in a single-step process, where the core contains therapeutic agents and the shell acts as a protective barrier.

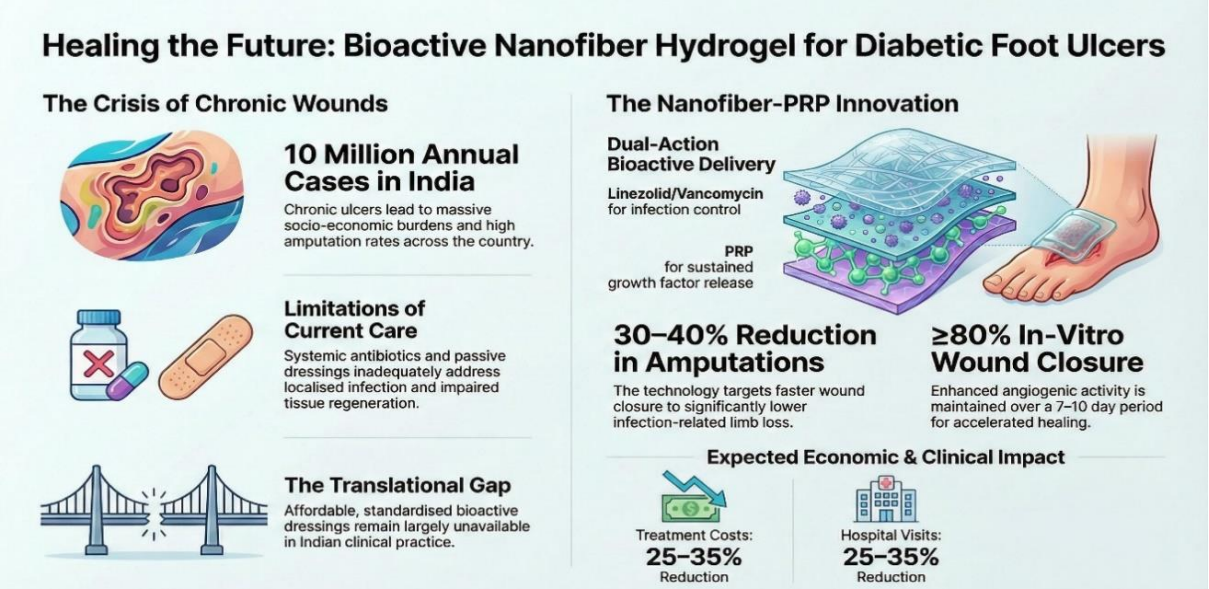
Key advantages include:

Suppression of burst release: The shell controls diffusion and prevents rapid drug leakage.

Protection of labile biomolecules: Growth factors, enzymes, and nucleic acids are shielded from degradation.

Sequential drug delivery: Dual-drug systems can deliver antibiotics initially, followed by sustained release of growth factors for tissue regeneration.

For example, PCL/PVP coaxial fibres demonstrated controlled cisplatin release over 8–9 days, highlighting their potential for sustained drug delivery applications [38].



6.3 Hydrogel Dressings

Hydrogels are three-dimensional polymeric networks capable of retaining large amounts of water, making them suitable for wound dressings. Based on origin, hydrogels are classified as natural or synthetic. They provide structural scaffolds for drug delivery, cytokine release, and cell encapsulation.

Hydrogels exhibit biocompatibility, antibacterial properties, and structural adaptability, reducing amputation rates in DFU patients. Their antioxidative and antibacterial properties promote angiogenesis and cell proliferation, while mitigating hypoxia and oxidative stress. Well-designed hydrogels can inhibit infection, stimulate cell migration and vascularization, and accelerate wound closure [39].

1) Natural Hydrogels

Natural hydrogels are derived from biopolymers and exhibit excellent biocompatibility, biodegradability, and ECM-mimicking properties, making them ideal for wound healing applications. Common natural polymers include collagen, chitosan, alginate, hyaluronic acid, and silk fibroin [40].

Collagen Hydrogels

Collagen is a major ECM protein and provides a scaffold for cell migration and tissue regeneration. Collagen hydrogels also contain bioactive factors that stimulate cell proliferation and differentiation, promoting DFU healing [41].

Chitosan Hydrogels

Chitosan is a biopolymer derived from chitin and is widely used in tissue engineering due to its antimicrobial activity, biocompatibility, low toxicity, and haemostatic properties. It can be chemically modified and fabricated into nanofibers, nanoparticles, hydrogels, and films. Reactive amine and hydroxyl groups allow functionalization and polymer blending [40,41].

Alginate Hydrogels

Alginate, extracted from seaweed, supports cell immobilization and drug delivery. Its hydrophilic nature maintains a moist wound environment, enhances re-epithelialization, and reduces infection risk [40].

Hyaluronic Acid Hydrogels

Hyaluronic acid exhibits anti-inflammatory and antioxidant properties and promotes angiogenesis through CD44 receptor interaction. It enhances collagen deposition and epithelial regeneration, making it valuable for skin repair applications [41].

2) Synthetic Hydrogels

Synthetic polymers such as PEG and PVA offer tuneable physicochemical properties and high molecular weight structures, allowing precise control over mechanical strength and degradation behaviour [42].

3) Composite Hydrogels

Composite hydrogels combine natural and synthetic polymers to balance biocompatibility and mechanical stability. Natural polysaccharides alone often exhibit weak mechanical strength, whereas synthetic polymers show limited biodegradability. Therefore, hybrid hydrogels with optimized polymer ratios have been developed to achieve ideal mechanical and degradation properties [43].

These hydrogels may incorporate nanomaterials or ceramic fillers to reinforce the polymer network, forming interpenetrating polymer networks that enhance structural integrity and biological performance [42].

6.4 Growth Factor– and Cytokine-Loaded Hydrogels

Growth factor (GF)–loaded hydrogels are designed to accelerate wound healing by enhancing angiogenesis, fibroblast proliferation, and extracellular matrix remodelling. However, their clinical performance is often compromised by the intrinsic instability of growth factors in the wound environment**.** Zheng et al. (2023) reported that proteases such as matrix metalloproteinases (MMPs), which are overexpressed in chronic diabetic wounds, rapidly degrade exogenously delivered growth factors, significantly reducing their bioavailability and therapeutic duration [44]

In addition, many growth factors exhibit a short biological half-life and high production cost, limiting their practicality for repeated or long-term treatment. Berry-Kilgour et al. (2021/2022) emphasized that the need for high dosing to compensate for rapid degradation substantially increases treatment cost, creating a major barrier to widespread clinical adoption [45].

Clinical translation is further complicated by heterogeneous therapeutic outcomes. A recent Frontiers (2025) analysis of GF-based therapies in DFU reported significant inter-patient variability in healing response, likely driven by differences in wound chronicity, glycaemic control, and inflammatory burden (Frontiers, 2025). From a materials perspective, Li et al. (2024) highlighted that many hydrogel scaffolds exhibit uncontrolled burst release, leading to supraphysiological local concentrations followed by rapid depletion of growth factors, which undermines sustained therapeutic signalling [46].

Polypeptide-based hydrogels have been proposed as improved carriers due to their bioactivity and tunability; however, Wang et al. (2023) demonstrated that such systems often show poor stability in the acidic wound microenvironment characteristic of chronic DFUs, resulting in premature degradation and loss of structural integrity [47].

6.5 Cell- and Exosome-Loaded Hydrogels

Cell- and exosome-loaded hydrogels represent a more biologically complex strategy, aiming to deliver living cells or cell-derived vesicles capable of modulating inflammation, promoting angiogenesis, and stimulating tissue regeneration. Despite encouraging preclinical data, manufacturing and biological limitations remain substantial.

One major challenge is the low yield and poor scalability of exosome isolation. Gonçalves et al. (2023) reported that current isolation techniques, including ultracentrifugation and size-exclusion chromatography, often produce insufficient quantities of exosomes for clinical use while introducing batch-to-batch variability [48].

Even when successfully delivered, exosome functionality can be compromised by the hostile diabetic wound microenvironment. A Dovepress (2025) review noted that persistent hyperglycaemia and oxidative stress in DFUs may alter exosomal cargo activity and reduce their regenerative signalling capacity (Dovepress, 2025). Similarly, stem cell–based hydrogel systems face challenges related to poor cell survival. An MDPI (2022) review reported that ischemia, hypoxia, and inflammation in DFUs dramatically reduce transplanted cell viability, limiting long-term therapeutic benefit**.**

From a delivery standpoint, Zhang et al. (2024) demonstrated that exosomes are subject to rapid clearance from the wound site, even when embedded within hydrogels, resulting in limited retention and reduced therapeutic exposure time [49]. Furthermore, Liu et al. (2023) highlighted the lack of standardized characterization protocols for stem cell–derived vesicles, which complicates regulatory approval and reproducibility across studies [50].

6.6 Oxygen-Releasing and ROS-Scavenging Hydrogels

Oxygen-releasing and reactive oxygen species (ROS)–scavenging hydrogels are designed to address hypoxia and oxidative stress—two central pathological features of diabetic wounds. While these systems offer targeted microenvironmental modulation, they present important safety and engineering challenges.

Oxygen-evolving hydrogels, particularly those based on peroxide chemistry, carry a risk of hyperoxia-induced tissue damage. Guan et al. (2021) demonstrated that excessive or uncontrolled oxygen release can exacerbate oxidative stress, impair cell viability, and damage newly formed tissue [51]. Chemical instability remains a further concern, as Li et al. (2025) reported that peroxide-based oxygen generators are prone to premature decomposition, leading to unpredictable oxygen release profiles [52].

ROS-scavenging hydrogels face limitations related to finite antioxidant capacity**.** Chen et al. (2023) showed that antioxidant moieties within stimuli-responsive hydrogels can become rapidly saturated in highly oxidative DFU environments, reducing long-term efficacy [53]. From a mechanical standpoint, an Oxford (2025) review emphasized that many oxygen- and ROS-modulating hydrogels exhibit mechanical mismatch with native foot tissue, limiting durability and patient compliance in load-bearing DFUs [54].

Emerging ultrasound-responsive ROS-scavenging systems offer on-demand activation but introduce clinical complexity. A recent PMC (2026) study highlighted that reliance on external ultrasound stimulation increases treatment complexity, equipment dependence, and variability in real-world clinical settings [55].

6.7 Injectable & *In Situ* Forming Systems

Injectable and *in situ* forming biomaterials have emerged as promising platforms for wound management and tissue regeneration due to their minimally invasive administration, ability to conform to irregular wound geometries, and potential for localized, sustained drug delivery (IJPS, 2023). These systems typically undergo sol–gel or liquid–solid transitions in response to physiological triggers such as temperature, pH, ionic strength, or enzymatic activity, enabling depot formation directly at the target site. Despite these advantages, several limitations continue to hinder their clinical translation.

One of the primary challenges associated with injectable *in situ* forming depots is monomer toxicity and chemical deterioration**.** According to the IJPS (2023) review on versatile depot platforms, many polymerizable systems rely on reactive monomers or crosslinking agents that may generate cytotoxic intermediates or byproducts during gelation. Furthermore, exposure to physiological environments can lead to chemical degradation of the polymer network, resulting in compromised mechanical integrity and reduced control over drug release kinetics [56]. Another critical limitation is slow gelation kinetics, which can cause premature leakage of the formulation from the wound site before complete solidification. Advances reviewed in a recent PMC (2024) article reported that delayed sol–gel transitions remain a significant issue, particularly in wounds with high exudate levels or in anatomically mobile regions. Such leakage can reduce therapeutic efficacy and lead to non-uniform drug distribution at the target site **[57]**.

Although stimuli-responsive injectable hydrogels provide adaptability to dynamic wound environments, uncontrolled swelling behaviour poses a substantial drawback. Wang et al. (2022) demonstrated that excessive swelling in smart hydrogels may exert mechanical pressure on wound edges, potentially impairing local tissue perfusion and delaying the healing process. This concern is especially relevant in confined wound spaces where volumetric expansion cannot be readily accommodated [58].

Alginate-based *in situ* forming systems are widely investigated because of their biocompatibility and mild gelation conditions; however, they often **exhibit** limited mechanical strength. Shen et al. (2022) reported that conventional alginate hydrogels are unable to withstand repetitive mechanical stress, making them unsuitable for high-load or weight-bearing areas such as the plantar surface of the foot. Mechanical failure in such regions can result in premature loss of wound coverage and reduced treatment effectiveness [59].

Injectable peptide-based hydrogels represent an emerging class of biomaterials with excellent bioactivity and tuneable self-assembly properties. Nevertheless, their broader application is constrained by complex purification processes and high production costs. Zhang et al. (2023) highlighted that multistep peptide synthesis and stringent purification requirements significantly increase manufacturing costs, limiting scalability and hindering commercialization for routine clinical use [60].

Overall, while injectable and *in situ* forming systems offer substantial advantages for localized wound therapy, persistent challenges related to toxicity, gelation control, swelling behaviour, mechanical robustness, and manufacturing feasibility must be addressed to enable successful clinical translation.

6.8 Bio adhesive Hydrogels

The primary objective of bio adhesive hydrogels is to provide a seamless interface between the dressing and the irregular wound bed, preventing the formation of "dead spaces" where bacteria can proliferate. However, clinical translation faces significant hurdles.

The "Wet-Adhesion" Paradox

Most bio adhesive hydrogels rely on chemical bonds (like Schiff base or catechol-mediated bonding) to stick to the tissue. However, DFU wounds are often characterized by high exudate levels. This constant moisture layer acts as a barrier, preventing the polymer chains from forming stable cross-links with the tissue surface, which leads to early detachment [61].

Secondary Trauma & Tissue Friction

While high adhesion is desired, a critical limitation is secondary injury during dressing removal. If the adhesive strength exceeds the cohesive strength of the newly formed, fragile granulation tissue, removal of the dressing can "strip" the healing layer, effectively resetting the wound to an earlier inflammatory stage [62].

6.9. Conductive Hydrogels

Conductive hydrogels aim to restore the "current of injury"—the natural electrical field of the skin that is disrupted in chronic diabetic wounds. By using materials like PEDOT: PSS, Polyaniline (PANI), or Polypyrrole (PPy), these gels facilitate cell migration (galvanotaxis).

Conductivity Decay in Saline Environments

A major technical limitation is ion interference. Conductive hydrogels often rely on a delicate balance of dopants to maintain electrical flow. In the saline-rich environment of a DFU (high in Na^+ and Cl^- ions), the hydrogel's internal conductivity can be disrupted or "short-circuited," causing a rapid loss of electrical performance within 24–48 hours [63].

Mechanical Rigidity and "Short-Circuiting"

Most conductive polymers are inherently rigid and hydrophobic. When blended into a soft hydrogel matrix to make it "wearable," the resulting material often suffers from mechanical mismatch. Repetitive movement of the foot causes micro-cracks in the conductive network, leading to inconsistent electrical stimulation and potential "hot spots" that can cause localized thermal damage to the skin [63].

7. Platelet-Rich Plasma (PRP) Treatments

Platelet-rich-plasma (PRP) is an autologous blood product with platelet concentration three times that of the whole blood. It produces action upon activation either endogenous or exogenous, which increases the concentration of growth factors and cytokines, leading to accelerated wound healing and tissue repair [64].

Platelet-rich plasma (PRP)–based therapies have been widely explored for wound healing due to their high concentration of autologous growth factors, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor-β (TGF-β). These bioactive components are intended to stimulate angiogenesis, cell migration, and tissue regeneration [65].

Various medical approaches and therapeutic interventions based on the human body itself (i.e., autologous and heterologous) can affect the different levels of healing. Among various therapeutic interventions, the application of platelet rich plasma (PRP) is widely utilized in clinical treatments [66]. However, PRP therapies are inherently limited by biological variability and processing-related challenges that can significantly affect therapeutic outcomes [67].

7.1 Topical PRP Gels and Platelet-Rich Fibrin (PRF)

A fundamental limitation of topical PRP gels and PRF is biological "noise", as the quality and regenerative potential of the treatment are directly dependent on the patient's own blood composition [68]. In patients with chronic conditions such as diabetes mellitus, platelet function is frequently impaired. Long-term diabetic patients often exhibit dysfunctional platelets with reduced growth factor release and altered signalling capacity. As a result, the use of autologous PRP in these populations may effectively deliver "low-quality" growth factors to wounds that are already biologically compromised, limiting therapeutic efficacy [69].

Platelet-rich fibrin (PRF) offers advantages over liquid PRP by forming a natural fibrin matrix that acts as a provisional scaffold for cell migration, anti-inflammatory effect, protection against infections and growth factor retention. However, PRF suffers from limited structural longevity and easily degradable [70]. Miron et al. (2022) reported that PRF matrices often degrade rapidly within the wound bed, frequently dissolving before the completion of the proliferative phase of healing. This premature degradation reduces sustained growth factor availability and may necessitate repeated applications, increasing treatment burden and variability [71].

7.2 Lyophilized PRP and Combination Products

Lyophilized (freeze-dried) PRP formulations have been developed to overcome storage instability and logistical challenges associated with fresh PRP. While lyophilization improves shelf life and standardization, it introduces significant concerns related to loss of bioactivity. The freezing and sublimation steps involved in lyophilization can denature sensitive proteins, including key angiogenic factors such as VEGF. Shiga et al. (2023) demonstrated a marked reduction in biological potency in lyophilized PRP compared to freshly prepared liquid PRP, raising concerns about its regenerative effectiveness [72].

In addition, many commercial lyophilized PRP products require complex reconstitution procedures at the point of care. These formulations are often mixed with carriers such as hyaluronic acid or other hydrogels immediately before application. Such multistep bedside preparation increases the risk of dosing inconsistency, handling errors, and microbial contamination, particularly in non-ideal clinical settings [73]. These practical limitations further complicate the clinical adoption of lyophilized PRP systems despite their logistical advantages.

Overall, while PRP-based therapies remain attractive due to their autologous nature and biological relevance, significant limitations related to patient-dependent variability, rapid degradation, processing-induced bioactivity loss, and clinical handling complexity continue to restrict their reliability and widespread clinical translation.

8. CONCLUSION

Diabetic foot ulcers represent a complex clinical challenge driven by intertwined metabolic, vascular, neurological, and immunological dysfunctions inherent to diabetes mellitus. Despite significant advances in standard wound care practices, including antibiotic therapy, debridement, offloading, and moist dressings, healing outcomes remain suboptimal for a substantial proportion of patients. The persistence of biofilms, rising antimicrobial resistance, impaired angiogenesis, and chronic inflammation continues to limit the effectiveness of conventional therapeutic approaches and contributes to high recurrence and amputation rates.

Emerging biomaterial-based wound care strategies, particularly nanofiber dressings, hydrogel systems, and bioactive delivery platforms, offer promising avenues for addressing the multifaceted pathology of DFUs. These advanced systems have demonstrated the ability to provide localized and sustained delivery of therapeutic agents, improve moisture balance, enhance cellular migration, and promote tissue regeneration. Nevertheless, their successful translation into routine clinical practice is hindered by challenges such as mechanical instability in load-bearing regions, biological variability, manufacturing complexity, cost, and inconsistent clinical efficacy.

Future progress in DFU management will depend on the rational design of multifunctional wound dressings that integrate antimicrobial activity, angiogenic stimulation, mechanical resilience, and patient-friendly application. Equally important is the need for standardized evaluation protocols and large-scale, high-quality clinical trials to establish safety, efficacy, and cost-effectiveness. A multidisciplinary approach combining advances in biomaterials, pharmacotherapy, biomechanics, and personalized medicine will be essential to improve healing outcomes and reduce the global burden of diabetic foot ulcers.

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