中国临床研究
Chin J Clin Res, January 2026, Vol.39, No.1
Cite as: Dong R, He SY, Li MD. Research advances in diabetic foot ulcer [J]. Chin J Clin Res, 2026, 39(1):22-27.
DOI: 10.13429/j.cnki.cjcr.2026.01.004

Research advances in diabetic foot ulcer

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Abstract: Diabetic foot ulcers（DFU）are a common complication in patients with diabetes, severely impacting their quality of life and increasing the risk of amputation. While hyperglycemia, neuropathy, poor circulation, and infection are all influencing factors to the development of DFU. Among them, hyperglycemia is the most significant one, as prolonged hyperglycemia can induce neuropathy, poor circulation, and infection. Therefore, it is crucial to explore how hyperglycemia leads to DFU and the roles of neuropathy, poor circulation, and infection in this process. In recent years, researchers have conducted in-depth investigations into the pathological mechanisms, clinical diagnosis, and treatment strategies for DFU. Although significant progress has been made compared to the past, numerous challenges remain in the early identification and effective management of DFU, particularly in understanding precise pathogenesis, establishing diagnostic criteria, developing individualized treatment plans, and finding specific pharmacological therapies. In light of this, this article provides a systematic review of DFU, focusing on its pathogenesis, diagnostic methods, and treatment options (including the integration of conventional therapies and emerging technologies), with the aim of offering valuable insights for clinical practice.
Keywords: Diabetes; Diabetic foot ulcer; Heal; Negative pressure therapy; Stem cell therapy; Debridement

Diabetes is a type of metabolic disease caused by insulin secretion deficiency or impairment of its biological effects, characterized by high prevalence and severe complications [1]. With the aging of the population, changes in lifestyle, and the increase in obesity rates, diabetes has become a global public health issue. According to the latest report from the International Diabetes Federation, the number of diabetes patients worldwide has exceeded 500 million, and it is expected to continue growing in the coming decades [2]. Diabetic foot ulcer (DFU) is a serious complication in diabetic patients, caused by long-term hyperglycemia leading to neuropathy, peripheral vascular disease, and immune dysfunction, which results in foot infection, ulceration, or gangrene [3]. DFU not only significantly reduces patients' quality of life but also often leads to amputation or even death, with a five-year mortality comparable to that of some malignant tumors [4]. Although certain progress has been made in wound management, revascularization, biomaterials, stem cell, and exosome therapy in recent years, the treatment of DFU still faces challenges such as poor efficacy, high recurrence rate, and lack of unified and effective treatment strategies. Therefore, summarizing the research progress of DFU systematically is of great significance for further promoting the optimization of clinical treatment and the exploration of new therapies [5-6].

1 Epidemiology

The epidemiological characteristics of DFU are influenced by multiple factors such as era, region, and lifestyle. Early studies showed that its prevalence was 4% to 10%, but it has increased significantly in recent years and now stands at 15% to 25%, indicating that the disease burden is gradually worsening [2]. There are significant differences across different regions. In developed countries, the amputation rate has decreased due to well-established screening and care systems. In contrast, in developing countries, due to limited medical resources and insufficient patient compliance, the proportion of severe ulcers is relatively high. Dietary structure also affects the incidence trend of DFU. High-sugar and high-fat diets have increased the risk in Asia and the Middle East, while the Mediterranean diet has a certain protective effect. Overall, although treatment standards have improved in some regions, DFU remains a major global public health burden.

2 Pathophysiological mechanisms of DFU development

The formation and progression of DFU result from the synergistic effects of multiple pathological mechanisms, with core processes including vascular injury, neuropathy, immune dysregulation, and metabolic disorders [7].

2.1 Vascular injury

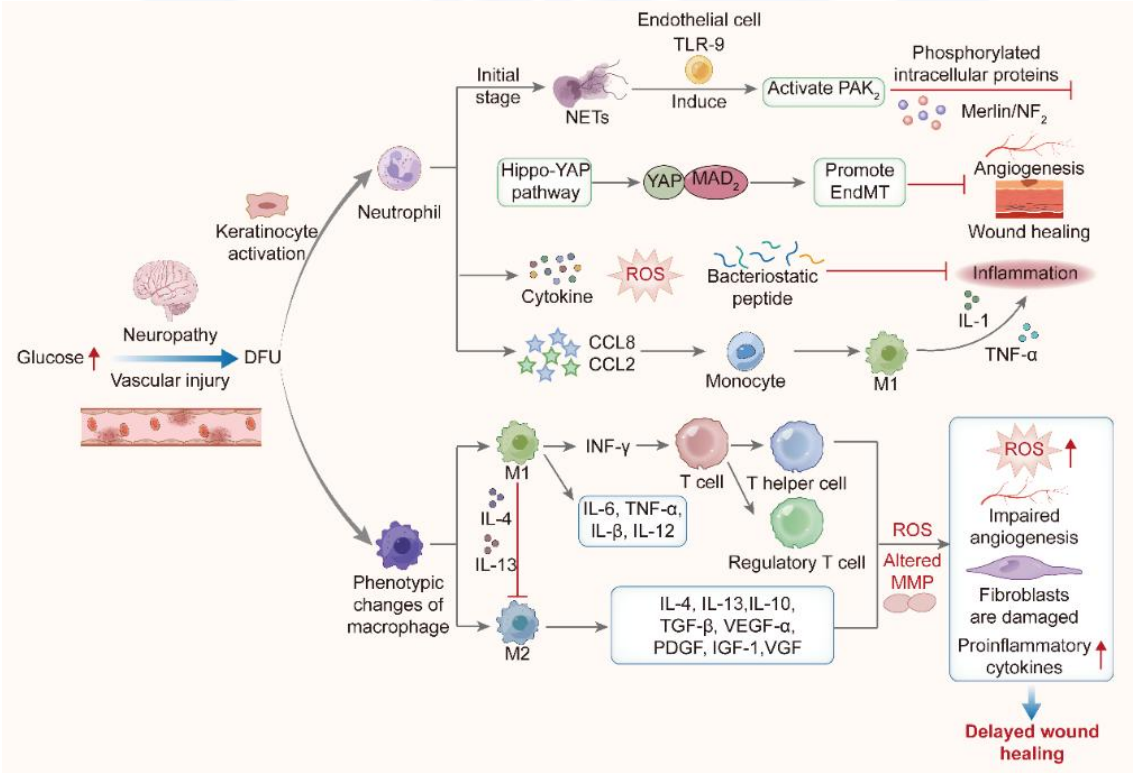
Long-term hyperglycemia first lays the foundation for DFU formation by damaging the structure and function of macro and micro vessels. At the macroscopic level, peripheral arterial disease (PAD) caused by atherosclerosis and thrombosis leads to restricted lower extremity perfusion [8]. At the microvascular level, endothelial dysfunction and basement membrane thickening cause capillary hypoperfusion and hypoxia-ischemia [9]. At the molecular level, insulin signaling impairment, deposition of advanced glycation end products (AGEs), and oxidative stress in a hyperglycemic environment activate transcription factors such as nuclear factor kappa-B (NF-κB) and activator protein-1 (AP-1), exacerbating vascular inflammation [10]. This ultimately delays wound repair and increases the risk of gangrene [11-12].

2.2 Neuropathy

Diabetic neuropathy is also crucial in the development of DFU. Persistent hyperglycemia inhibits neurofilament protein synthesis, disrupts axonal structure, and exacerbates oxidative stress and energy metabolism disorders through the AGE/receptor for AGE (RAGE) pathway and mitochondrial dysfunction, leading to neuronal degeneration [13]. Sensory loss makes minor traumas easy to overlook, and combined with autonomic dysfunction, promotes the development of local injury and infection [14].

2.3 Immune dysregulation

Immune system abnormalities run through all stages of DFU and are important factors in maintaining its chronic inflammation. In a hyperglycemic environment, the phagocytic capacity of monocyte-macrophages decreases, limiting the efficiency of early inflammation clearance [9], while the continuous elevation of inflammatory factors such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) traps the wound in a chronic inflammatory state [15-16]. Dysregulation of the immune system is key to maintaining the chronic inflammatory environment of DFU [17-18]. Among these, macrophages remain in the M1 phenotype due to abnormalities in forkhead box protein O1 (FOXO1) [19] and the AGE/RAGE pathway, secreting pro-inflammatory factors and impairing matrix remodeling [20]. Meanwhile, excessive activation of RAGE-mediated NF-κB, mitogen-activated protein kinase (MAPK), and phosphatidylinositol 3-hydroxy kinase (PI3K)/AKT signaling induces oxidative stress, cell apoptosis, and abnormal expression of matrix metalloproteinase (MMP), further impairing tissue repair capacity. Neutrophils overrelease reactive oxygen species (ROS) and form abnormal neutrophil extracellular traps (NETs) [21], which can induce endothelial-mesenchymal transition through the TLR9/Hippo/YAP/SMAD2 pathway [22], inhibiting angiogenesis and delaying repair. overactivation of natural killer cells amplifies tissue damage through interferon-γ (IFN-γ) and perforin. Changes in the distribution of Langerhans cells suggest their potential role in local immune regulation [23]. **Figure 1** illustrates the processes by which immune cells delay wound repair.

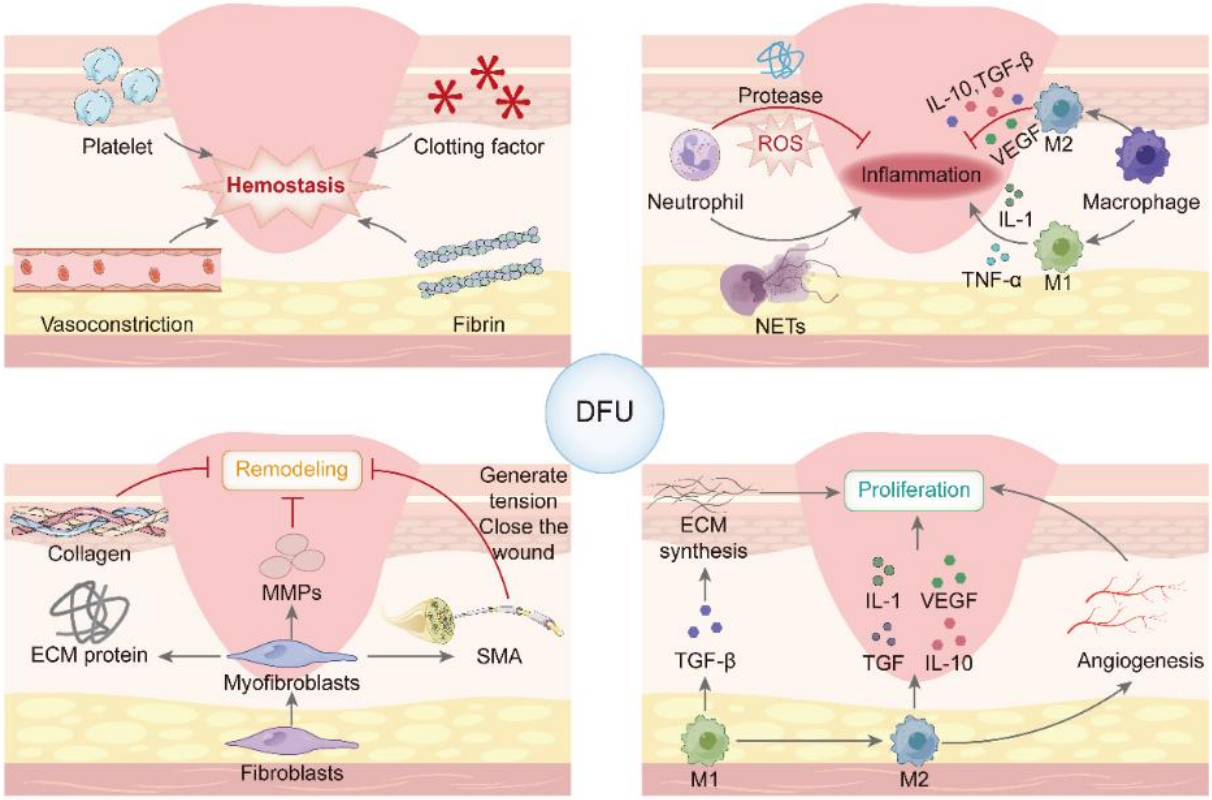


Note: the diabetic wound environment induces neutrophils to form NETs. NETs activate p21-activated kinase 2 (PAK2) in endothelial cells via the membrane receptor TLR-9. PAK2 phosphorylates the intracellular protein Merlin/NF2, thereby inhibiting the Hippo/YAP signaling pathway. This triggers the binding of YAP to the transcription factor SMAD2, which then translocates together from the cytoplasm to the nucleus, further inducing endothelial-mesenchymal transition. As a result, angiogenesis is inhibited and wound healing is delayed. In DFU wounds, this process impairs the phenotypic transformation of macrophages, blocking the transition from a pro-inflammatory to an anti-inflammatory state and leading to chronic inflammation. It also elevates ROS levels, increases pro-inflammatory cytokines, and exacerbates fibroblast damage, which in turn impairs wound healing and prolongs the inflammatory state. CCL = C-C motif chemokine ligand; TGF-β = transforming growth factor-β; VEGF-α = vascular endothelial growth factor-α; PDGF = platelet-derived growth factor; IGF = insulin-like growth factor; VGF = angiogenesis growth factor.

Fig.1 Process of immune cells delaying wound repair

3 Wound healing process of DFU

The wound healing process of DFU is significantly delayed compared to normal wounds, and its pathological basis involves multiple impairments in the hemostasis, inflammation, proliferation, and remodeling phases [24]. During the hemostasis phase, hyperglycemia, AGE, and oxidative stress jointly alter platelet reactivity and coagulation function [25], forming abnormal and non-degradable blood clot structures. These not only disrupt the scaffold required for cell migration and growth factor release but also exacerbate local ischemia and hypoxia [26]. In the inflammation phase, diabetes-related immune dysregulation impairs the recruitment and phenotypic transformation of neutrophils and macrophages. Sustained elevation of pro-inflammatory mediators (such as IL-β, IL-6, TNF-α) and ROS leads to a state of "inflammatory stasis". Sustained overexpression of TNF-α inhibits keratinocyte migration and M2 macrophage polarization, thereby hindering re-epithelialization and angiogenesis [27]. This inflammatory response is further amplified by microbial biofilms and hypoxic metabolism. During the proliferation phase, the transition of macrophages from the M1 to M2 phenotype is blocked, resulting in imbalanced levels of TGF-β and VEGF, as well as limitations of extracellular matrix (ECM) deposition and angiogenesis [28]. Abnormal activation of TGF-β signaling induces fibrosis and disordered matrix cross-linking, while an imbalance in the ratio of matrix metalloproteinases (MMPs) to their tissue inhibitors impairs tissue repair capacity. In the remodeling phase, excessive oxidative stress and proteolysis [29] cause ECM degradation, keratinocyte apoptosis, the decline of synthetic and migratory abilities of fibroblasts [30], and impaired mature collagen formation [31], ultimately delaying wound closure. Fibroblast dysfunction forms the core pathological basis for the non-healing nature of DFU through multiple mechanisms[32]. **Figure 2** illustrates the wound repair process in DFU patients.



Note: SMA = smooth muscle actin.

Fig.2 Process of wound repair in DFU patients

4 Advances in DFU diagnosis

DFU refers to full-thickness skin defects occurring below the ankle joint in diabetic patients, often accompanied by peripheral neuropathy and/or PAD. Guidelines from the International Working Group on the Diabetic Footand the American Diabetes Association both recommend a multi-dimensional diagnostic system, which comprehensively evaluates the ulcer location, size, depth, and results of the bone probing test. This is combined with neurological function tests (e.g., 10g monofilament examination, vibration threshold testing) and perfusion indicators (ankle-brachial index, toe pressure, transcutaneous oxygen pressure), with imaging and microbiological examinations supplemented when necessary. Patients who meet the diagnostic criteria for diabetes and present with typical foot lesions can be diagnosed with diabetic foot, while ulcers caused by other etiologies need to be excluded. Although various grading systems have been applied for risk assessment and treatment guidance, there remains a lack of consistency in diagnostic standards. Challenges include inconsistent definitions of infection, distortion of the ankle-brachial index due to arterial

calcification, non-standardized thresholds for perfusion indicators, and limited reproducibility of assessment methods. In the future, unified diagnostic criteria should be established, integrated with objective biomarkers and multi-center validation, to promote the standardization and precision of diabetic foot diagnosis.

5 Advances in the treatment of DFU

Current conventional clinical treatments for DFU include blood glucose control and infection management, surgical debridement, application of wound dressings to maintain a moist wound environment and manage exudate, local wound decompression, management of PAD, negative pressure wound therapy, and oxygen therapy. These adjunctive therapies for DFU can improve wound healing rates to a certain extent, but the overall healing outcomes remain unsatisfactory. Furthermore, most of the current reported data are derived from small randomized controlled trials, which carry a high risk of bias. Given the complex pathophysiology of DFU and individual patient variations, multidisciplinary collaboration has increasingly become a primary treatment modality for DFU. **Table 1** summarizes the commonly used treatment methods for DFU.

Tab.1 Treatment for DFU wound healing

Treatment methods	Description	Advantages
Wound care and debridement	Remove necrotic tissue and purulent exudate from wounds, and provide comprehensive nursing care	Regulate inflammation, control infection, and maintain optimal moisture levels for wound recovery; reduce infection risk and create a favorable environment for new tissue growth
Antibiotic therapy	Selection of antibiotic is based on infection type, pathogen susceptibility, and the patient's clinical status	Combine traditional antibiotics with emerging therapies (e.g., monoclonal antibodies, phage therapy) to address antibiotic resistance
Negative pressure wound therapy and pressure redistribution techniques	Apply negative pressure to enhance wound blood circulation and reduce swelling	Effectively lower wound infection rates and improve healing quality; optimize pressure distribution and reduce direct pressure on wounds
Stem cell therapy	Utilize stem cells from various tissue sources, peripheral blood mononuclear cells, and exosomes derived from mesenchymal stem cells	Secrete bioactive factors to repair damaged tissue, regulate immune responses, and promote regeneration; exosomes mediate intercellular communication, immune regulation, tissue repair, and antioxidant and anti-inflammatory effects
Biomaterials	Design and manufacture materials with specific biocompatibility and bioactivity	3D-printed biomaterial scaffolds effectively mimic the extracellular matrix and promote cell adhesion and growth
Hydrogels	Porous structure, high water absorption capacity, and excellent biocompatibility; permeable to cells, nutrients, and bioactive molecules	Regulate hyperglycemia, monitor wound status, and respond to pH changes; possess antibacterial properties and the ability to reduce ROS levels
Gene therapy	Evolve from single growth factor delivery to multi-target gene/cell combination strategies; functions by repairing or replacing defective genes	Modify mesenchymal stem cells via CRISPR/Cas to enhance secretion of pro-repair factors, anti-apoptotic ability, and local viability; enable sustained/controllable local expression and multi-factor synergistic intervention; modified cells provide structural and signaling support
Chinese medicine therapy	Chinese medicines and numerous plants can promote DFU wound healing processes	Different plants exhibit unique anti-inflammatory and antibacterial properties; activate various growth factors, cytokines, and chemokines

Note: CRISPR/Cas, the system of Clustered Regularly Interspaced Short Palindromic Repeats and their associated proteins.

5.1 Wound care and debridement

Wound care and debridement are core components of traditional DFU treatment. By removing necrotic tissue and purulent exudate, debridement reduces infection risk, decreases bacterial load, and promotes granulation tissue formation, thereby accelerating the healing process [33]. Meanwhile, comprehensive nursing measures such as inflammation control, infection management, and moisture maintenance are critical for optimizing wound repair [34]. In recent years, hydrosurgical debridement has attracted attention for its ability to efficiently remove necrotic tissue using high-pressure water jets, and it outperforms traditional methods in reducing postoperative infections. However, the selection of a specific debridement approach still requires individualized assessment based on patient conditions and wound characteristics [33]. Nevertheless, choosing an appropriate debridement method necessitates personalized evaluation according to the patient's specific circumstances and wound features.

5.2 Selection and application of antibiotic therapy

Antibiotic therapy plays a vital role in wound management, particularly in preventing and treating infections. Traditionally, broad-spectrum antibiotics have been widely used to treat various infections, but with the growing problems of antibiotic resistance, reasonable antibiotic selection has become increasingly important [35]. Studies indicate that antibiotic choice should be based on the type of infection, pathogen susceptibility, and the patient's clinical status. In some cases, the application of molecular diagnostic tools can help clinicians adjust antibiotic treatment regimens earlier, thereby improving treatment efficacy [36]. In addition, traditional antibiotics must be combined with novel treatment strategies, such as emerging therapies like monoclonal antibodies and phage therapy, to address the escalating challenge of antibiotic resistance. Therefore, developing rational antibiotic usage guidelines and conducting continuous monitoring and evaluation can effectively reduce infection risk and improve patient outcomes.

5.3 Negative pressure wound therapy and pressure redistribution techniques

Negative pressure wound therapy, as an emerging wound treatment modality, has demonstrated favorable outcomes in promoting wound healing. By applying negative pressure, this technique enhances blood circulation in the wound bed, reduces edema, and thereby accelerates the healing process [37]. Studies have shown that negative pressure wound therapy can effectively decrease wound infection rates and improve healing quality, particularly in the management of complex wounds and chronic ulcers [38]. In addition, pressure redistribution techniques, an integral component of negative pressure wound therapy, optimize pressure distribution and reduce direct mechanical stress on the wound, thereby lowering the risk of wound deterioration. In recent years, with continuous advancements in negative pressure wound therapy devices, new canister-free negative pressure systems have been gradually introduced into clinical practice. These systems can better maintain stable negative pressure and reduce saturation of wound exudate, thereby enhancing therapeutic efficacy [39]. In summary, the combination of negative pressure wound therapy and pressure redistribution techniques offers a novel strategy for wound management and merits further promotion and application in clinical settings.

5.4 Biomaterial applications

In recent years, biomaterials have undergone rapid, multi-directional development in the field of DFU treatment. Multifunctional dressings centered on hydrogels have been extensively studied due to their moisture retention, controlled release, and cell/growth factor loading capabilities. They have shown superior healing effects compared to traditional dressings in animal studies and some clinical trials [40]. Materials such as ECM-mimetic scaffolds, nanofibers, and bioglass, by improving the local microenvironment, promoting cell adhesion and angiogenesis, have been proven to accelerate granulation tissue formation and reduce scarring in *in vivo* models. Recently, the advancement of 3D printing technology has enabled scaffolds to mimic the natural ECM structure more effectively, and promote cell attachment and proliferation. Hydrogels with immunomodulatory properties can accelerate diabetic wound healing by regulating hyperglycemia, responding to pH changes, exerting antibacterial effects, reducing ROS levels, and promoting angiogenesis [41]. Currently, hydrogels have exhibited great potential in the field of wound healing, especially in the treatment of diabetic wounds. Their porous structure, high water absorption capacity, and excellent biocompatibility make them ideal candidates for wound dressings. Hydrogels are categorized into natural and synthetic types, providing diverse options for biomedical applications.

5.5 Potential of stem cell therapy

Stem cell therapy has emerged as a promising alternative treatment for DFU. Studies have shown that stem cell transplantation can suppress inflammation and promote the polarization of M1 macrophages to the M2 phenotype by secreting chemokines and paracrine signals, thereby accelerating tissue repair. Multiple cell types, including adipose-derived mesenchymal stem cells (AD-MSCs), human umbilical cord stem cells, bone marrow stem cells, and peripheral blood mononuclear cells, have demonstrated potential to promote DFU healing, with AD-MSCs being the most widely used. Additionally, mesenchymal stem cell-derived exosomes (MSC-Exos) have emerged as a potential novel therapeutic target due to their role in diabetic wound healing. Exosomes are nanoscale vesicles containing components such as DNA, messenger RNA, microRNA (miRNA), circular RNA, metabolites, lipids, cytoplasmic proteins, and cell surface proteins. They mediate intercellular communication and play a critical role in the diabetic wound healing process [42]. MSC-Exos carry bioactive factors such as miRNAs, proteins, and lipids to regulate macrophage polarization, inhibit inflammatory responses, reduce oxidative stress, and activate signaling pathways including PI3K/AKT and TGF-β/Smad. They modulate host-microbe interactions, antiviral immunity, immune homeostasis, central and peripheral immune regulation, and receptor-ligand signal transduction, while also participating in cell differentiation and migration. These effects collectively promote angiogenesis, fibroblast proliferation, and re-epithelialization, covering multiple key stages of wound healing. With low immune rejection, high biosafety, and robust tissue repair capabilities, MSC-Exos are being regarded as a potential alternative to traditional therapies. Furthermore, numerous animal experiments and in vitro studies have confirmed that MSC-Exos can significantly accelerate wound healing in diabetic models, enhance angiogenesis and collagen deposition. Notably, exosomes derived from different sources (umbilical cord, adipose tissue, bone marrow, menstrual blood, etc.) exhibit differences in functional properties and miRNA profiles, providing a basis for personalized preparation. Therefore, MSC-Exos are expected to become a revolutionary treatment for DFU [43].

5.6 Gene therapy

In recent years, research on gene therapy for DFU has evolved from single growth factor delivery to multi-target gene/cell combination strategies and precise regulatory approaches. VEGF/FGF gene delivery, aimed at promoting angiogenesis and improving the local microenvironment, has been shown to accelerate granulation tissue formation and re-epithelialization in animal models and several early-phase human studies, indicating its potential value in enhancing local blood flow.

Gene therapy, leveraging technologies such as CRISPR/Cas, has shown promising prospects in repairing or replacing defective genes. Engineering mesenchymal stem cells or other repair cells to enhance their secretion of pro-repair factors, anti-apoptotic capacity, and local survival has demonstrated superior efficacy compared to wild-type cells in multiple diabetic wound models, suggesting that the "cell + gene editing" approach holds significant development potential [44-45]. Compared to traditional topical medications or single-dose protein administration, the advantages of gene therapy lie in its ability to achieve sustained or controllable

local expression, enable multi-factor synergistic intervention, and provide both structural and signaling support through engineered cells. However, the field still faces challenges such as vector safety [46], control of expression duration, immune responses, and large-scale production. More high-quality randomized controlled trials and long-term follow-up studies are urgently needed to confirm its clinical effectiveness and scalability.

5.7 Chinese medicine treatment

Relevant studies have demonstrated that numerous plants, including Chinese medicinal herbs, exhibit wound-healing capabilities and are now widely used in clinical practice, even serving as alternatives to conventional medicine in some cases. A variety of plant-derived active components have shown remarkable wound-healing effects in DFU treatment, and they have gradually garnered clinical attention due to their anti-inflammatory, antibacterial, and cell regeneration-promoting properties. Research indicates that plants such as *Prunus salicina, Opuntia spp., Taxillus chinensis, Mimosa spp., Astragalus membranaceus, Nerium oleander,* and *Aloe vera* [47] can accelerate wound repair by promoting collagen synthesis, enhancing blood flow, inhibiting pro-inflammatory cytokines, and stimulating fibroblast proliferation. Among these, herbs like *Aloe vera* and *Salvia miltiorrhiza* stand out for their prominent anti-inflammatory, anti-apoptotic, and oxidative stress-improving effects, attributed to their abundant bioactive ingredients. In addition, citrus peel extracts have shown efficacy in lowering blood glucose and promoting wound healing, while olive oil and its combination with honey have also been proven to facilitate DFU wound repair [48]. In summary, plant extracts, with their advantages of multi-target action and low adverse reaction rates, provide potential alternative and adjunctive options for DFU treatment.

5.8 Prevention of DFU

DFU is a common and severe complication in diabetic patients, characterized by high morbidity and disability rates; therefore, prevention and management are of critical importance. Lifestyle interventions and patient education are the primary strategies. By raising awareness among patients and their families about risk factors and self-management, emphasizing foot examinations [49], appropriate footwear selection, foot hygiene, a balanced diet, and moderate exercise [50], the risk of DFU can be effectively reduced, and overall health can be improved. Meanwhile, strengthening patients' knowledge of blood glucose monitoring and foot care helps enhance their self-efficacy and prevent ulcer development [51]. Recent research has also explored wearable sensors and remote monitoring systems for real-time tracking of foot temperature, pressure, and skin status, providing technical support for early warning and individualized prevention.

5.9 Management of DFU

In DFU management, a comprehensive, multidisciplinary collaborative model has become the mainstream trend. This model integrates the expertise of specialists from endocrinology, surgery, nursing, nutrition, podiatry, and other fields. Through collaboration, regular communication, and individualized interventions [52], it enables systematic, whole-process management of patients. This not only improves treatment efficiency but also promotes early identification and prevention of DFU, thus playing a significant role in reducing incidence rates and improving patient prognosis [53]. The integration of systematic management, precise intervention, and novel biotechnology is emerging as the core direction for the advancement of DFU treatment.

6.Summary

Although current treatments for DFU have achieved certain progress, they still have obvious limitations. For example, traditional pharmacological therapies and surgical interventions often show poor efficacy in some patients, with prolonged recovery processes and high recurrence rates [54]. This highlights the necessity of future research: evaluating multiple interventions for high-risk populations, integrating digital health technologies, and clarifying potential pathological mechanisms and biomarkers to guide more effective strategies. Emerging approaches such as novel biomaterials, stem cell therapy, and bioengineered skin—including biological scaffolds, stem cells, exosomes, extracellular matrices, growth factors, and platelet-rich plasma—as well as individualized, multidisciplinary, and technology-assisted protocols, are expected to advance the comprehensive management of DFU and improve patient outcomes [55].

Conflict of Interest None

Author Contributions

Conceptualization and design: Dong Run, Li Mingdong; Data collection and organization: Dong Run, He Siyi; Data analysis: Dong Run, He Siyi; Figure and table preparation: Dong Run; Manuscript drafting: All authors; Manuscript revision: Dong Run, He Siyi; Dong Run and He Siyi contributed equally to the writing of this article

Acknowledgments

We thank Hainan General Hospital and Hainan Medical University for the academic support provided during the implementation of this research.

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Submission Received: 2025-07-05 /**Revised:** 2025-11-08

·研究进展·

糖尿病足溃疡的研究进展

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摘要：糖尿病足溃疡（DFU）是糖尿病患者常见的并发症，严重影响患者的生活质量并增加截肢风险。高血糖、神经病变、血液循环不良和感染均是DFU发生的影响因素，但高血糖是最主要的，长期高血糖可诱导神经病变、血液循环不良和感染，探讨高血糖是如何导致DFU以及神经病变、血液循环不良和感染意义重大。近年来，研究者们对DFU的病理机制、临床诊断以及治疗策略进行了深入探讨，虽较前取得了明显进展，但在DFU的早期识别和有效管理上仍存在诸多挑战，特别在精准的发病机理、诊断标准构建、个体化治疗方案及特异性药物治疗方面仍存在诸多不足。为此，本文将从发病机制、诊断方法、治疗选择（包括传统疗法与新兴技术的结合）对DFU进行系统综述，旨在为临床实践提供参考。

关键词：糖尿病；糖尿病足溃疡；愈合；负压治疗；干细胞治疗；清创

中图分类号：R587.2　**文献标识码：**A　**文章编号：**1674-8182（2026）01-0022-06

Research advances in diabetic foot ulcer

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Abstract: Diabetic foot ulcers (DFU) are a common complication in patients with diabetes, severely impacting their quality of life and increasing the risk of amputation. While hyperglycemia, neuropathy, poor blood circulation, and infection are all influencing factors to the development of DFU. Among them, hyperglycemia is the most significant one, as prolonged hyperglycemia can induce neuropathy, poor circulation, and infection. Therefore, it is crucial to explore how hyperglycemia leads to DFU and the roles of neuropathy, poor circulation, and infection in this process. In recent years, researchers have conducted in-depth investigations into the pathological mechanisms, clinical diagnosis, and treatment strategies for DFU. Although significant progress has been made compared to the past, numerous challenges remain in the early identification and effective management of DFU, particularly in understanding precise pathogenesis, establishing diagnostic criteria, developing individualized treatment plans, and finding specific pharmacological therapies. In light of this, this article provides a systematic review of DFU, focusing on its pathogenesis, diagnostic methods, and treatment options (including the integration of conventional therapies and emerging technologies), with the aim of offering valuable insights for clinical practice.

Keywords: Diabetes; Diabetic foot ulcer; Heal; Negative pressure therapy; Stem cell therapy; Debridement

糖尿病是一类由胰岛素分泌缺陷或其生物学作用受损引起的代谢性疾病，具有高患病率和严重并发症的特点[1]。随着人口老龄化、生活方式的改变及肥胖发生率的增加，糖尿病已成为全球性公共健康问题。据国际糖尿病联盟最新报告，全球糖尿病患者人数已超过5亿，并预计在未来数十年持续增长[2]。糖尿病足溃疡（diabetic foot ulcer，DFU）是糖尿病患者因长期高血糖导致神经病变、周围血管病变及免疫功能低下，引起足部感染、溃疡或坏疽的一种严重并发症[3]，DFU不仅显著降低患者生活质量，并且常导致截肢甚至死亡，其五年死亡率可与部分恶性肿瘤相当[4]。尽管近年来在创面管理、血运重建、生物材料、干细胞及外泌体治疗等方面取得了一定进展，但DFU的治疗仍面临疗效不佳、复发率高及缺乏统一有效治疗策略等困境。因此，系统总结DFU的研究进展，对于进一步推动临床治疗优化及新疗法探索具有重要意义[5-6]。

DOI：10.13429/j.cnki.cjcr.2026.01.004

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出版日期：2026-01-20

QR code for English version

1 流行病学

DFU的流行病学特征受年代、地区及生活方式等多因素影响。早期研究显示其患病率为4%~10%，而近年来有较大幅度的上升，目前为15%~25%，提示该疾病负担逐渐加重[2]。不同地区差异显著，发达国家因筛查和护理体系完善，截肢率有所下降，而发展中国家则因医疗资源有限及患者依从性不足，严重溃疡比例较高。饮食结构亦影响DFU的发生趋势，高糖高脂饮食导致亚洲和中东地区风险升高，而地中海饮食有一定保护作用。总体来看，尽管部分地区治疗水平改善，但DFU依旧是全球范围内重要的公共健康负担。

2 DFU发生的病理生理机制

DFU的形成与演变源于多种病理机制的协同作用，其核心环节包括血管损伤、神经病变、免疫失衡及代谢紊乱等[7]。

2.1 *血管损伤* 长期高血糖首先通过损伤大血管与微血管结构和功能，为DFU形成奠定基础。长期高血糖通过影响大血管及微血管结构功能，为溃疡发生提供了病理基础。宏观层面上，动脉粥样硬化及血栓形成引起的外周动脉疾病（peripheral arterial disease，PAD）导致下肢灌注受限[8]。微血管方面，内皮功能障碍与基底膜增厚造成毛细血管灌注不足与缺氧缺血[9]。在分子水平上，高糖环境下的胰岛素信号障碍、晚期糖基化终末产物（advanced glycation end products，AGEs）沉积和氧化应激激活核因子κB（nuclear factor kappa-B，NF-κB）、激活蛋白-1（activator protein-1，AP-1）等转录因子，加重血管炎症[10]，最终延缓创面修复并增加坏疽风险[11-12]。

2.2 *神经病变* 糖尿病性神经病变在DFU的发生中同样至关重要。持续的高血糖抑制神经丝蛋白合成，破坏轴突结构，并通过AGE/AGE受体（receptor for AGE，RAGE）通路及线粒体功能紊乱加剧氧化应激和能量代谢障碍，造成神经元退行性改变[13]。感觉缺失使轻微外伤易被忽视，加上自主神经功能障碍，促进了局部损伤和感染的发生[14]。

2.3 *免疫失衡* 免疫系统异常贯穿DFU的各阶段，是维持其慢性炎症的重要因素。高糖环境下，单核-巨噬细胞吞噬能力下降，早期炎症清除效率受限[9]而肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）、白细胞介素（interleukin，IL）-6等炎性因子的持续升高使伤口陷入长期炎症状态[15-16]。免疫系统的紊乱是维持DFU慢性炎症环境的关键[17-18]，其中巨噬细胞因叉头框蛋白O1（forkhead box protein O1，FOXO1）[19]及AGE/RAGE通路异常而持续停留在M1型，分泌促炎因子并损伤基质重塑[20]。与此同时，RAGE介导的NF-κB、丝裂原激活的蛋白激酶（mitogen-activated protein kinase，MAPK）和磷酸肌醇3激酶（phosphatidylinositol 3-hydroxy kinase，PI3K）/AKT信号过度活化诱导氧化应激、细胞凋亡及基质金属蛋白酶（matrix metalloproteinase，MMP）异常表达，进一步削弱组织修复能力；中性粒细胞过度释放活性氧（reactive oxygen species，ROS）和形成异常中性粒细胞胞外捕获网（neutrophil extracellular traps，NETs）[21]，可通过TLR9/Hippo/YAP/SMAD2通路诱导内皮-间质分化[22]，抑制血管再生，延迟修复；自然杀伤细胞过度激活通过γ干扰素（interferon-γ，IFN-γ）及穿孔素放大组织损伤；朗格汉斯细胞分布改变则提示其在局部免疫调控中的潜在作用[23]。图1展示了免疫细胞延缓伤口修复的相关过程。

3 DFU伤口愈合的过程

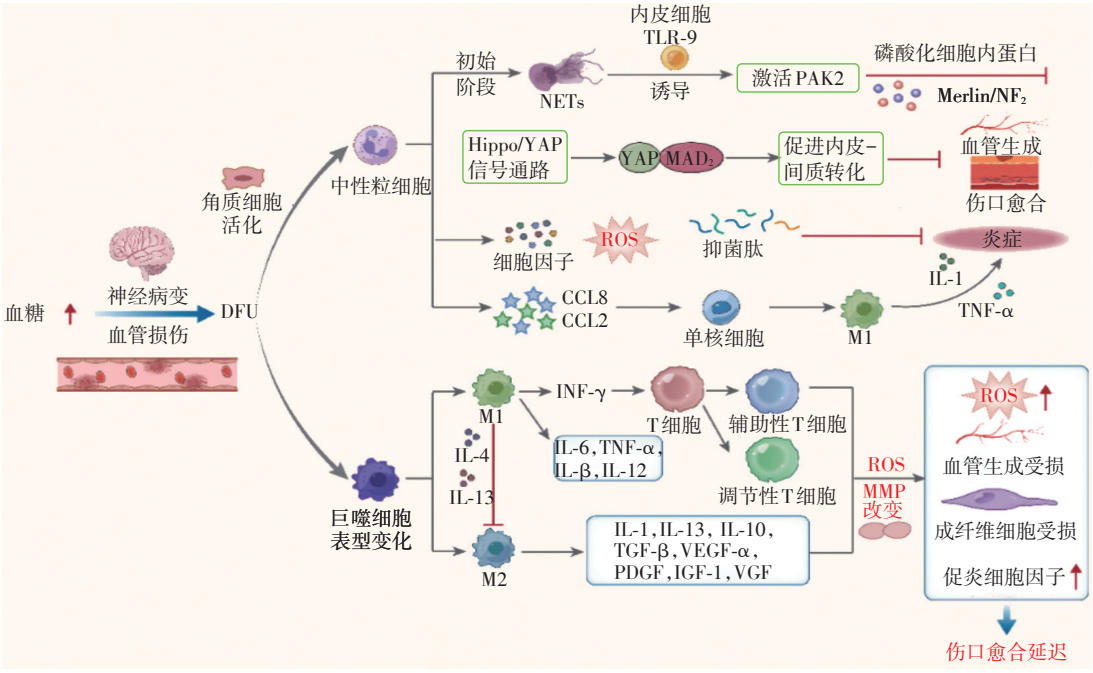
DFU的伤口愈合过程较正常创面明显延迟，其病理基础涉及止血、炎症、增殖及重塑各阶段的多重障碍[24]。止血期中，高血糖、AGE及氧化应激共同改变血小板反应性和凝血功能[25]，形成异常且难以降解的血块结构，不仅破坏细胞迁移与生长因子释放所需的支架，还加剧局部缺血与缺氧[26]。炎症期中，糖尿病相关的免疫失衡导致中性粒细胞与巨噬细胞募集及表型转化受阻，促炎介质[如IL-β、IL-6、TNF-α]和ROS持续升高，形成“炎症停滞”状态。TNF-α的长期高表达抑制角质形成细胞迁移与M2型巨噬细胞极化，从而阻碍再上皮化和血管生成[27]，并在微生物生物膜及缺氧代谢作用下进一步放大炎症反应。在增殖期，巨噬细胞由M1向M2表型转化受阻，导致TGF-β和VEGF水平失衡，细胞外基质（extracellular matrix，ECM）沉积及血管生成受限[28]。TGF-β信号异常激活引起纤维化及基质交联紊乱，而MMP/MMP组织抑制因子比例失衡则削弱组织修复。重塑期中，过度的氧化应激与蛋白水解作用[29]导致ECM降解及角质形成细胞凋亡，成纤维细胞合成与迁移能力下降[30]，成熟胶原难以形成[31]，最终延缓创面闭合。成纤维细胞功能障碍通过多重机制构成DFU难愈合的核心病理基础[32]。图2展示了DFU患者伤口修复过程。

4 DFU的诊断进展

DFU是糖尿病患者踝关节以下出现的全层皮肤缺损，常伴周围神经病变和/或PAD。国际糖尿病足工作组和美国糖尿病协会指南均建议采用多维度诊断体系，综合评估溃疡部位、大小、深度及探针触骨试验结果，结合神经功能检测（如10 g单丝试验、振动阈值测试）与灌注指标（踝肱指数、趾压、经皮氧分压），必要时辅以影像学与微生物学检查。凡符合糖尿病诊断标准并伴典型足部病变者可确诊为糖尿病足，需排除其他原因所致溃疡。尽管多种分级系统已用于风险评估与治疗指导，但诊断标准仍缺乏一致性。感染定义不统一、动脉钙化导致踝肱指数失真、灌注指标阈值尚未标准化，且评估方法重现性有限。未来应建立统一的诊断标准，结合客观生物标志物与多中心验证，推动糖尿病足诊断的标准化与精准化。

5 DFU的治疗进展

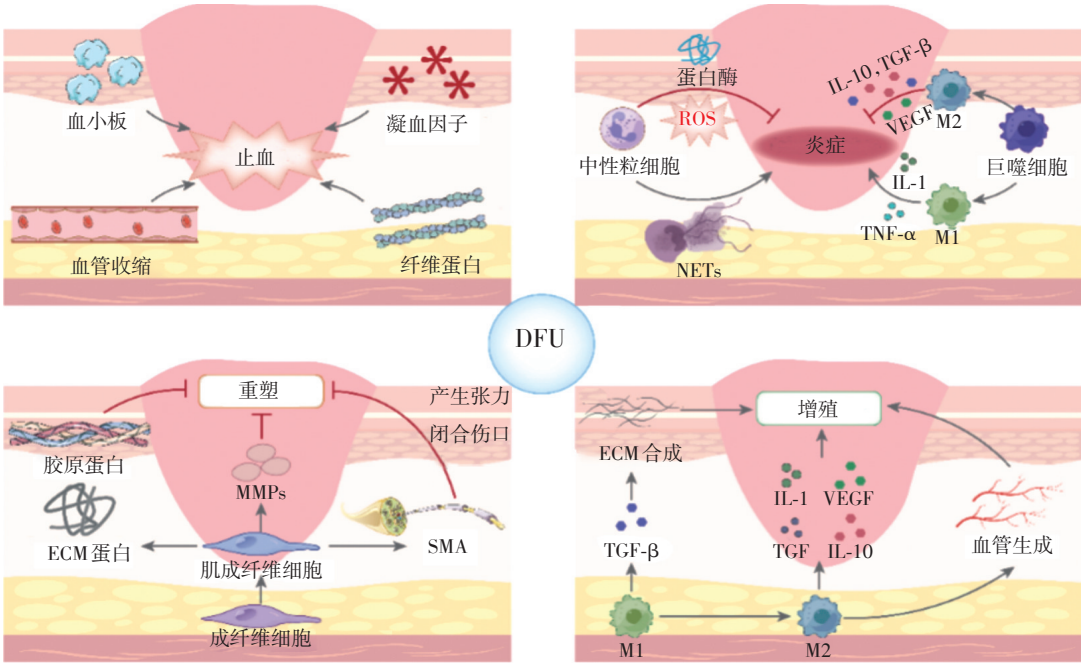
目前临床DFU的常规治疗方法包括控制血糖及感染、外科清创、应用伤口敷料湿润伤口环境及控制渗出物、局部伤口减压、管理PAD、负压疗法以及氧疗等，这些针对DFU的辅助疗法在一定程度上有利于提高伤口愈合率，但痊愈率仍不容乐观，且目前报道的大部分数据都是小的随机对照试验，具有较高的偏倚风险。由于DFU病情的复杂性及个体化差异，多学科协作已日益成为DFU主要的治疗手段。表1列出DFU常用治疗方法。



注：糖尿病伤口环境促使中性粒细胞形成NETs。NETs通过膜受体TLR-9在内皮细胞中激活p21活化激酶2(PAK2)。PAK2磷酸化细胞内蛋白Merlin/NF2，抑制Hippo/YAP信号通路。促使YAP与转录因子SMAD2结合，随后从细胞质共同转移到细胞核，进一步诱导内皮-间质转化，从而阻碍血管生成并延迟伤口愈合。在DFU伤口中，影响巨噬细胞表型的转化，阻碍从促炎状态过渡到抗炎状态，形成慢性炎症。促使ROS水平升高，促炎细胞因子增多，成纤维细胞受损加重，进而导致伤口愈合受损和炎症状态延长。CCL为C-C基序趋化因子配体；TGF-β为转化生长因子-β；VEGF-α为血管内皮生长因子-α；PDGF为血小板衍生生长因子；IGF为胰岛素样生长因子；VGF为血管生成生长因子。

图1　免疫细胞延缓伤口修复过程

Fig.1　Process of immune cells delaying wound repair



注：SMA为平滑肌肌动蛋白。

图2　DFU患者伤口修复过程

Fig.2　Process of wound repair in DFU patients

5.1　*创面护理与清创术*　创面护理与清创术是DFU传统治疗的核心环节，清创通过去除坏死组织和脓性分泌物可降低感染风险、减少细菌负荷并促进肉芽组织形成，从而加速愈合过程[33]。同时，综合护理措施如炎症控制、感染管理及湿度维持对优化创面修复至关重要[34]。近年来，水力清创因其通过高压水流高效去除坏死组织，在降低术后感染方面优于传统方法而受到关注，但具体选择仍需结合患者状况及创面特征进行个体化评估[33]。然而，选择适当的清创方法仍需根据患

表1 DFU伤口愈合的治疗方法
Tab.1 Treatment for DFU wound healing

治疗方法	描述	优势
伤口护理与清创	清除伤口坏死组织及脓性分泌物并给予综合护理	调节炎症、控制感染并维持适宜的湿度水平确保创伤恢复的最佳条件；降低感染风险，为新组织的生长创造有利环境
抗生素治疗	抗生素的选择可以基于感染类型、病原体敏感性以及患者的临床状况	传统抗生素与采用单克隆抗体、噬菌体疗法等新兴疗法结合，应对抗生素耐药性
负压治疗和压力分散技术	施加负压以促进伤口血液循环并减轻肿胀	有效降低伤口感染发生率和提高愈合质量；优化压力分布并减轻伤口的直接压力
干细胞疗法	各种组织来源的干细胞、外周血单个核细胞和间充质来源干细胞衍生外泌体	分泌生物活性因子修复受损组织、调节免疫反应并促进组织再生；外泌体具有细胞间通讯、免疫调节、组织修复与再生以及抗氧化和抗炎作用
生物材料	具有特定生物相容性和生物活性材料的设计与制造	3D打印技术使生物材料制造的支架能够更有效地模拟细胞外基质；促进细胞黏附和生长
水凝胶	多孔结构、高吸水能力和出色的生物相容性；细胞、营养物质和生物活性分子能够渗透	调节高血糖、监测伤口状态、对pH值变化做出反应；具有抗菌、降低ROS水平等能力
基因治疗	单一生长因子递送演进为多靶点基因/细胞联合策略；基因治疗通过修复或替换有缺陷的基因来发挥作用	CRISPR/Cas等改造间充质干细胞，增强其分泌促修复因子能力、抗凋亡能力和局部存活性；实现局部持续或可控表达、实现多因子协同干预；改造细胞同时提供结构与信号支持
中医治疗	中药和大量植物都具有促进DFU伤口愈合过程的能力	不同的植物展现出独特的抗炎和抗菌特性；激活多种生长因子、细胞因子和趋化因子

注：CRISPR/Cas为成簇规律间隔短回文重复序列及其相关蛋白系统。

者的具体情况和创面的特点进行个性化评估。

5.2 *抗生素治疗的选择与应用* 抗生素治疗在创伤管理中扮演着至关重要的角色，尤其是在预防和治疗感染方面。传统上，广谱抗生素被广泛应用于各种感染的治疗，但随着抗生素耐药性的增加，合理选择抗生素变得愈发重要[35]。研究指出，抗生素的选择应基于感染的类型、病原体的敏感性以及患者的临床状况。在某些情况下，分子诊断工具的应用能够帮助临床医生更早地调整抗生素治疗方案，从而提高治疗的有效性[36]。此外，传统的抗生素使用方式必须与新的治疗策略相结合，例如使用单克隆抗体、噬菌体治疗等新兴疗法，以应对日益严峻的抗生素耐药问题。因此，制定合理的抗生素使用指南并进行持续的监测和评估，能够有效降低感染风险并改善患者预后。

5.3 *负压治疗与压力分散技术* 负压治疗作为一种新兴的创面治疗方法，在创面愈合中显示出良好的效果。该技术通过施加负压，促进创面血液循环，减少肿胀，进而加速愈合过程[37]。研究表明，负压治疗能够有效降低创面感染率，并改善愈合质量，尤其是在复杂创伤和慢性创面管理中[38]。此外，压力分散技术也是负压治疗的一部分，通过优化压力分布，减轻对创面的直接压力，从而降低创面损伤的风险。近年来，随着负压治疗设备的不断改进，新的无罐负压系统逐渐被引入临床，其能够更好地维持负压并减少创面渗出液的饱和，从而提高治疗效果[39]。总之，负压治疗与压力分散技术的结合，为创面管理提供了新的思路，值得在临床中进一步推广和应用。

5.4 *生物材料应用* 近年生物材料在DFU治疗领域呈多方向快速发展：以水凝胶为核心的多功能敷料因其保湿、控释与可负载细胞/因子能力被广泛研究并在动物与部分临床研究中显示出优于传统敷料的愈合效果[40]。以ECM仿生的支架、纳米纤维与生物玻璃等材料，通过改善微环境、促进细胞黏附与血管再生，已在体内模型中证明可加速肉芽组织形成并降低瘢痕化。近来，三维打印技术的发展使支架可以更好地模拟ECM，促进细胞附着和生长，而具有免疫调控功能的水凝胶则通过调节高血糖、响应pH变化、抗菌、降低ROS水平及促进血管生成，加速了糖尿病伤口愈合[41]。目前，水凝胶在伤口愈合领域，特别是在糖尿病伤口的治疗中表现出了巨大的潜力。它们的多孔结构，高吸水性和生物相容性使其成为伤口敷料的合适选择。水凝胶分为天然和合成两类，为生物医学应用提供了多种选择。

5.5 *干细胞疗法的潜力* 干细胞治疗已成为DFU的一种有前景的替代方案，研究表明干细胞移植可通过分泌趋化因子和旁分泌信号抑制炎症、促进巨噬细胞M1向M2转化，从而加速组织修复。多种细胞类型，包括脂肪间充质干细胞、人脐带干细胞、骨髓干细胞及外周血单核细胞，均显示出促进DFU愈合的潜力，其中脂肪间充质干细胞应用最为广泛。另外，间充质干细胞来源外泌体(mesenchymal stem cell-derived-exosomes，MSC-Exos)在糖尿病伤口愈合中的潜在作用使其作为新型治疗靶点成为可能性。外泌体是一种纳米级囊泡，含有DNA、信使RNA、微小RNA(micro RNA，miRNA)、环状RNA、代谢物、脂质、细胞质和细胞表面蛋白等成分，参与细胞间通信，在糖尿病伤口愈合过程中发挥重要作用[42]。MSC-Exos通过携带miRNA、蛋白和脂质等生物活性因子，调控巨噬细胞极化、抑制炎症反应、减轻氧化应激并激活PI3K/AKT、TGF-β/Smad等信号通路，调控宿主-微生物作用、病毒免疫、平衡免疫、调节中枢与外周免疫、调控受体-配体信号转导，参与细胞分化、细胞迁移，从而促进血管新生、成纤维细胞增殖与上皮化，覆盖了创面愈合的多个关键环节。具有较低的免疫排斥反应、更高的生物安全性和更强的细胞修复能力，正被视为潜在替代方案。另外，大量动物实验与体外研究证实MSC-Exos可显著

加速糖尿病模型伤口愈合、提高血管生成与胶原沉积，且不同来源（脐带、脂肪、骨髓、月经血等）外泌体在功能特性与 miRNA 谱上存在差异，为个性化制备提供依据。因此，MSC-Exos 有望成为 DFU 治疗的革命性手段[43]。

5.6　基因治疗　近年来，DFU 的基因治疗研究从单一生长因子递送逐步演进为多靶点基因/细胞联合策略与精准调控手段。以促进血管再生和改善局部微环境为目的的 *VEGF/FGF* 基因递送在动物模型及若干人体早期研究中显示可加速肉芽组织形成与上皮化，提示对改善局部血流具有潜在价值。基因治疗借助 CRISPR/Cas 等技术在修复或替换缺陷基因方面已展现出良好前景，改造间充质干细胞或其他修复细胞以增强其分泌促修复因子、抗凋亡能力和局部存活性，已在多个糖尿病伤口模型中显示出优于野生型细胞的疗效，提示“细胞 + 基因编辑”路径具有重要发展潜力[44-45]。相较于传统外用药物或单次蛋白给药，基因治疗的优势主要体现在能够实现局部持续或可控表达、实现多因子协同干预、并通过改造细胞同时提供结构与信号支持。然而该领域仍面临载体安全性[46]、表达时限控制、免疫反应与规模化生产等挑战，亟需更多高质量随机对照试验与长期随访以证实临床有效性与可推广性。

5.7　中医药治疗　相关研究表明，众多植物包括传统中药也具有促进伤口愈合的能力，目前已广泛应用于临床，并在某些情况下可替代传统医学。多种植物来源的活性成分在 DFU 治疗中展现出显著的伤口愈合作用，因其抗炎、抗菌和促进细胞再生等特性而在临床应用中逐渐受到关注。研究表明，大叶李、仙人掌属、钝叶寄生、含羞草属、黄芪、夹竹桃及芦荟等[47]均可通过促进胶原合成、增强血流、抑制促炎因子及刺激成纤维细胞增殖来加速伤口修复，其中芦荟和丹参等药物因其丰富的生物活性成分在抗炎、抗凋亡及改善氧化应激方面具有突出作用。此外，柑橘类果皮提取物在降低血糖和促进愈合方面亦表现出疗效，而橄榄油及其与蜂蜜的联合应用也被证实有助于 DFU 伤口修复[48]。综上，植物提取物凭借其多靶点、低不良反应发生率等优势，为 DFU 治疗提供了潜在的替代和辅助方案。

5.8　DFU 的预防　DFU 是糖尿病患者常见且严重的并发症，具有高发病率和致残率，因此预防与管理至关重要。生活方式干预和教育是首要环节，通过提高患者及其家属对风险因素和自我管理的认知，强调足部检查[49]、合理鞋具选择、足部卫生、健康饮食和适度锻炼[50]，可有效降低 DFU 风险并改善整体健康状况。同时，强化患者的血糖监测和足部护理知识，有助于提升自我效能感并预防溃疡发生[51]。最新研究还探索了可穿戴传感器与远程监测系统，用于足部温度、压力及皮肤状态的实时追踪，为早期预警与个体化预防提供了技术支撑。

5.9　DFU 的管理　在 DFU 管理方面，综合、多学科协作模式已成为主流趋势。多学科团队管理模式整合了内分泌科、外科、护理、营养及足病等多领域专家的力量，通过协作、定期沟通与个体化干预[52]，实现对患者的系统化、全程化管理，不仅提高了治疗效率，还促进了 DFU 的早期识别与预防，从而在降低发生率和改善预后方面具有重要价值[53]。系统化管理、精准干预与新型生物技术的结合正成为 DFU 治疗发展的主要方向。

6　总　结

当前治疗 DFU 的方法虽然取得了一定进展，但仍存在明显的局限性。例如，传统的药物治疗和外科干预往往对某些患者效果不佳，且恢复过程漫长，复发率高[54]。这凸显了未来研究的必要性：评估针对高危人群的多种干预措施、整合数字健康技术、阐明潜在的病理机制和生物标志物，以指导更有效的策略。新型生物材料、干细胞疗法、生物工程皮肤等新兴方法，包括生物支架、干细胞、外泌体、细胞基质、生长因子和富血小板血浆，以及个体化、多学科和技术辅助的方案，有望推动 DFU 的综合管理并改善患者预后[55]。

利益冲突　无

作者贡献　构思与设计：董润、李明东；数据收集与整理：董润、何思懿；数据分析：董润、何思懿；图表绘制：董润；稿件撰写：所有作者；稿件修订：董润、何思懿；董润和何思懿对本文撰写贡献相等

志谢　感谢海南省人民医院和海南医科大学在本研究工作实施过程中提供的学术帮助

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收稿日期:2025-07-05 **修回日期**:2025-11-08 **编辑**:叶小舟