International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 14, No. 2, 2026

Advances in the Application of Growth Factors in Chronic Diabetic Wounds

Jinhui Jiang [1], Peijian Huang [1], Yi Li [1], Ying Guan [1], and Qiang Tang [2, *]

[1] Clinical Medical College, Youjiang Medical University for Nationalities, Baise Guangxi, 533000, China
[2] Department of Burn and Plastic Surgery, Affiliated Hospital of Youjiang Medical University for Nationalities, Baise Guangxi, 533000, China

*** Corresponding author:** Qiang Tang

Abstract: Growth factors are important signal substances that control tissue repair, and they offer new ideas for treating this kind of disease, this paper sorts out the working principles and current uses of common growth factors including epidermal growth factor and vascular endothelial growth factor, it analyzes the main roles of different growth factors in cell increase and blood vessel formation, and also points out the problems of weak stability and short survival time of single growth factor, meanwhile, it sums up the cooperative effects when multiple growth factors are used together, and discusses the application progress of new delivery methods like nanotechnology and 3D bioprinting, at present, related studies still have limitations such as not enough clinical trial data and no confirmed long-term safety, future research needs to explore its working principles more deeply, finish clinical verification and make personalized treatment plans, so as to push the clinical application and standardized use of growth factors in treating chronic diabetic wounds, and help improve the recovery condition of patients.

Keywords: Chronic Diabetic Wounds; Growth Factors; Wound Healing; Combination Therapy.

1. Introduction

In recent years, the number of people with diabetes around the world has kept going up, data from the International Diabetes Federation shows that there were 537 million diabetes patients all over the world in 2021, during the development of the disease, people who have diabetes often get long-term wounds, and diabetic foot ulcers are the most common among these problems [1]. Diabetic chronic wounds are caused by vascular damage due to high blood sugar, nerve lesions that affect nutrient delivery, imbalanced inflammatory responses, and decreased cell proliferation and migration capabilities, creating a pathological microenvironment that hinders healing[2]. These long-term wounds need a long time to get better, they carry high risks of getting infected, and patients can easily suffer from bad problems like amputation, such wounds take up 1.5% to 3% of all surgery patients in hospitals, and this number is going up every year, this situation adds more pressure to people with diabetes and makes their life quality become lower, the normal treatment ways used in hospitals now, such as cleaning wounds, fighting infections and changing dressings, cannot really improve the bad inner environment of the wounds, so the results of these treatments are not good enough. Growth factors, as key signaling molecules regulating cell proliferation, differentiation and tissue repair, can activate the signaling pathways related to wound healing, promote angiogenesis, epithelialization and matrix remodeling, providing a new strategy for the treatment of diabetic chronic wounds [3]. In-depth study of the mechanisms and effects of various growth factors holds significant clinical value in overcoming current treatment limitations and developing new therapeutic approaches. At the same time ,It also provides a theoretical basis for improving the prognosis of diabetic patients and reducing the incidence of complications [4].

This paper sorts out and concludes the working principles and practical application status of several common growth factors in the healing of diabetic chronic wounds, which mainly include epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF); this study distinguishes the main functional differences among various growth factors, and these functions cover cell proliferation promotion, angiogenesis induction and immune regulation, all of which can improve the abnormal microenvironment of wound tissues; the paper also focuses on sorting out the clinical application limitations of single growth factor treatment, including unstable properties and short effective duration; for instance, wound proteases can easily break down EGF, and VEGF may also trigger irregular angiogenesis at local wound sites [5]. This article summarizes the synergistic mechanisms and clinical efficacy differences when common growth factors are combined with other wound treatment methods for the treatment of chronic diabetic wounds [6]. More, given the advancements in novel delivery strategies such as nanotechnology and 3D printing in enhancing the bioavailability of growth factors, this article examines the current limitations of the research [7]. Ultimately, this will provide theoretical references for the subsequent formulation of personalized treatment plans, promote the clinical transformation and standardized application of growth factors in the treatment of chronic wounds in diabetes, and help reduce amputation rates and improve prognosis [8].

2. Overview of Chronic Diabetic Wounds

2.1. Pathogenesis

The formation and progression of chronic diabetic wounds result from the combined effects of various inducing factors and physiological changes in the human body, and the whole pathological process is quite complicated; long-term high blood glucose levels can cause a variety of physiological disorders in the human body, which serves as the major cause of this disease. Persistent hyperglycemia can activate the

polyol metabolism pathway in the body and promote the massive production of advanced glycation end products; these products can bind to receptors on the surface of vascular endothelial cells, reduce the production of nitric oxide and accelerate the release of various inflammatory factors, thereby leading to thickened vascular walls and narrowed vascular lumens. When such vascular lesions occur, local blood circulation around the wound will be blocked, oxygen and essential nutrients cannot be delivered normally to the wound area, and this condition will further hinder the self-repair and healing of wounds [9]. At the cellular level, sustained high blood sugar can suppress the proliferation and migration of fibroblasts and keratinocytes; it also weakens the capacity of these two cell types to produce extracellular matrix proteins, including collagen. [10]. Besides, diabetic patients usually suffer from abnormal inflammatory responses; they have a reduced capacity to eliminate inflammatory cells and maintain high levels of pro-inflammatory factors, which keeps the wound in a long-lasting inflammatory stage and prevents the wound from entering the proliferation and repair stage smoothly [11]. the proteinase activity at the wound site will increase abnormally, which will excessively break down growth factors and extracellular matrix, continuously slowing down the healing process of the wound.

2.2. Wound Characteristics

Chronic diabetic wounds differ greatly from normal wounds in pathological characteristics; they usually show disordered healing processes and unsatisfactory clinical recovery effects. The healing progress of chronic diabetic wounds is disturbed at every stage. In the inflammatory stage, high blood sugar causes abnormal activation of macrophages, reduces the removal efficiency of pathogens and necrotic tissues, and keeps pro-inflammatory factors at a high level, therefore maintaining a persistent chronic inflammatory state and delaying the transition to the proliferative stage [12]. During the proliferative phase, fibroblast cannot work properly, collagen synthesis is restricted, and granulation tissue fails to grow well; in the wound remodeling stage, the imbalance between matrix metalloproteinases and their corresponding inhibitors can block scar maturation, which easily causes unstable scar tissue. Clinically, chronic wounds in diabetic patients are highly susceptible to infection and thus deserve widespread attention; insufficient local blood supply limits the infiltration of immune cells and damages the skin's protective barrier, which further facilitates bacterial colonization and increases the risk of wound infection. Furthermore, infection can easily spread to deeper tissues, forming abscesses and even osteomyelitis [9]. Slow healing is a typical characteristic. While ordinary wounds typically heal in 2-4 weeks, chronic diabetic wounds often take more than 8 weeks to heal, and in some severe cases, they may not heal for months or even years. Furthermore, Furthermore, the recurrence rate of these wounds is very high. Even if they temporarily heal, due to the lack of fundamental improvement in vascular and nerve damage, the wounds are prone to reopen under the influence of minor trauma, pressure or infection, seriously affecting the quality of life of the patients and even leading to adverse consequences such as amputation [13].

3. Application of common growth factors in diabetic chronic wounds

3.1. Growth Factors Promoting Cell Proliferation and Re-epithelialization

3.1.1. Epidermal Growth Factor (EGF)

Studies by Li Xinjie, Huang Lijuan, and others have shown that after binding to epidermal growth factor receptor (EGFR) on target cells, EGF induces receptor dimerization and activates the Ras-Raf-MEK-ERK and PI3K-Akt pathways, thereby driving cell proliferation and differentiation and regulating matrix synthesis to accelerate re-epithelialization[14]. In addition, EGF enhances cell migration and activates the EGFR-AKT/mTOR pathway, upregulates the expression of proliferating cell nuclear antigen (PCNA) and cyclin-dependent kinase 4 (CDK4), inhibits apoptosis, and promotes wound healing[15].

Clinicians generally apply recombinant human epidermal growth factor gel or topical liquid medications to treat mild diabetic foot ulcers; this common therapeutic approach can raise the wound healing speed by 30% to 40% and reduce the overall healing duration by roughly 10 to 14 days [16]. Following Ilizarov tibial transverse bone transport surgery, the application of recombinant human epidermal growth factor to the wound can regulate serum levels of factors such as vascular endothelial growth factor and basic fibroblast growth factor, increase the ankle-brachial index and skin temperature of the affected limb, and reduce pain [17]. For complicated diabetic foot wounds with pus infection and exposed joint capsules, topical epidermal growth factor treatment after ultrasonic debridement can accelerate granulation tissue regeneration; this method can prepare the wound for subsequent autologous skin grafting and reduce the possibility of amputation. EGF plays an essential role in wound repair; reduced EGF expression may induce inflammatory cell accumulation and further ulcer enlargement. Moreover, elevated MMP-9 levels can aggravate wound inflammation and destroy the basement membrane and extracellular matrix structure.

3.2. Growth Factors Promoting Angiogenesis and Improving Blood Supply

3.2.1. Vascular Endothelial Growth Factor (VEGF)

VEGF acts as a key regulatory molecule that controls vascular formation in diabetic wounds; it specifically binds to VEGFR-2 located on endothelial cell surfaces, which triggers receptor dimerization and intracellular tyrosine phosphorylation. This process further recruits the p85 regulatory subunit of PI3K and turns on the PI3K/AKT signaling pathway. The activated AKT can suppress pro-apoptotic proteins, increase the expression of cyclin D1 to facilitate cell cycle progression and endothelial cell proliferation, and adjust cytoskeleton arrangement to speed up endothelial cell migration toward the ischemic wound region [18].

Related research by Zhang Long, Mao Defen and other scholars has proven that VEGF is vital for angiogenesis and epithelial repair; yet in chronic wound conditions, hypoxia, infection and other adverse factors often lead to inadequate VEGF expression, which causes poor local blood supply and restricts epithelial cell migration. Meanwhile, the sustained high expression of the pro-inflammatory factor TNF-α can intensify local inflammatory reactions and destroy the

microenvironment required for wound repair [19]. Recent studies have shown that high concentrations of VEGF can enhance capillary permeability, promote the entry of large molecules such as fibrinogen from plasma into the extracellular matrix and form fibrin gel, which then serves as a temporary matrix to support the endogenous growth of angiogenesis and stromal cells [20].

Exogenous VEGF features a short half-life and is prone to degradation in the body, so repeated dosing is necessary to sustain its therapeutic effect; this situation raises overall treatment expenses and increases the difficulty of clinical operation. Furthermore, chronic wounds possess a complicated microenvironment, so single VEGF treatment can only achieve limited therapeutic outcomes. More in-depth studies are therefore required to explore the synergistic effects between VEGF and other growth factors or biomaterials, as well as to identify the most appropriate dosage and delivery approach [21].

3.2.2. Fibroblast Growth Factor-2 (FGF-2/bFGF)

bFGF serves as an important multifunctional regulatory substance; it can modulate blood vessel formation and gather various repair cells at wound sites. Existing research has found that TGF-β1 and bFGF work together to increase the PD-L1 level in fibroblasts; when bFGF is co-cultured with activated macrophages, it can also help M1-type PD-L1 convert into the M2 type, and lower the secretion of inflammatory substances [22]. bFGF can boost the expression of vascular endothelial growth factor; it speeds up wound recovery and protects surrounding tissue matrices, which helps burn wounds heal better. Several research findings indicate that bFGF-loaded hydrogel possesses favorable extracellular matrix characteristics; it is able to provide a suitable microenvironment to support cell differentiation, cell proliferation and other vital cellular activities [23].

At present, there are several mature preparations of basic fibroblast growth factor (bFGF) available for the treatment of chronic wounds. Among them, recombinant human basic fibroblast growth factor gel is the most widely used formulation in clinical practice. To enhance the therapeutic effect, new delivery carriers are constantly being developed. bFGF is a peptide with a relatively short half-life in the body and is easily degraded by proteases. Its transdermal absorption efficiency is low, making it difficult to effectively penetrate deep into the wound to exert its effects. Moreover, the acidic environment of the wound can disrupt its molecular structure, further reducing its activity [24].

3.2.3. Angiopoietin-1 (Ang-1)

Angiopoietin-1 (Ang-1), a key pro-angiogenic factor, can specifically bind to the Tie2 receptor on the surface of vascular endothelial cells, activate the PI3K/Akt and ERK1/2 signaling pathways, inhibit endothelial cell apoptosis and enhance their adhesion stability, promote angiogenesis maturation and remodeling, and improve blood supply to diabetic wounds [25]. Multiple studies have proven that angiotensin-1 (Ang-1) can adjust vascular permeability to lessen wound exudation; it can also recruit pericytes to wrap vascular endothelial cells via chemotaxis, and therefore improve the structural stability of newly formed blood vessels. The healing capacity of diabetic wounds is closely linked to the expression level of Ang-1, yet this protein has a short in-vivo half-life and can be easily broken down by proteases, which greatly restricts its clinical use [26-27].

VEGF, bFGF and Ang-1 are essential substances that facilitate blood vessel regeneration in diabetic wound tissues; despite their similar overall effects, these factors vary greatly in their specific working mechanisms and functional priorities. All of these molecules can activate signaling pathways like PI3K/Akt, which helps endothelial cells survive and supports the formation of new blood vessels. VEGF mainly takes charge of starting angiogenesis, it can drive endothelial cell proliferation and migration to kick off vascular regeneration; this growth factor also comes with obvious drawbacks, as it may trigger vascular leakage and irregular cell growth, and its short in-vivo retention time makes multiple drug applications indispensable in clinical treatment. bFGF combines angiogenesis promotion, chemotactic cell repair, and mild anti-inflammatory effects, making it more widely applicable, but it has poor transdermal permeability and is easily inactivated by the acidic wound environment. Ang-1 is responsible for the maturation, stability, and structural integrity of new blood vessels, reducing exudation, but its angiogenesis promotion rate is slow when used alone, and it also suffers from easy degradation and a short half-life.

3.3. Growth Factors Promoting Matrix Synthesis and Tissue Remodeling

3.3.1. Platelet-Derived Growth Factor (PDGF, including PDGF-AA and PDGF-BB)

After binding to PDGFR-alpha/beta on target cells, the PDGF-AA and PDGF-BB isoforms activate the PI3K-Akt and MAPK pathways, thereby promoting fibroblast proliferation and type I and III collagen synthesis. They also activate MMP-2/9 and enhance cellular proliferation, migration, and angiogenic capacity. In addition, MT1-MMP can activate the PDGF-beta/PDGFR-beta pathway to maintain the stability of newly formed vessels[28]. Studies have shown that PDGF can promote wound healing and tissue repair while also contributing to neovessel stabilization.

Clinically, PDGF hydrogel preparations have been widely used in the treatment of diabetic foot ulcers, and sustained release of PDGF effectively promotes tissue regeneration at the wound site. Antioxidants released from hydrogels efficiently mitigate reactive oxygen species (ROS), induce M2 macrophage polarization, and, together with growth factors that enhance cell migration and angiogenesis, produce synergistic effects during wound healing, thereby significantly increasing the healing rate[29]. However, PDGF has poor stability, requires low-temperature storage, and is readily degraded by proteases. In addition, its penetration into deeper wound tissues is limited, reducing its efficacy in deep wounds[30].

3.3.2. Insulin-Like Growth Factor-1 (IGF-1)

Under diabetic conditions, hyperglycemia reduces insulin-like growth factor-1 (IGF-1) levels, inhibits Akt pathway activation and neural regeneration and repair, weakens its pro-repair effects, and forms a vicious cycle with hyperglycemia that impedes wound healing[31]. Animal experiments have shown that IGF-1 at a concentration of 1.5 mg/L exerts optimal healing-promoting effects on skin ulcers in diabetic rats through autocrine and paracrine mechanisms. A study by Yang H and colleagues demonstrated that the GelMA/PNS/Alg@IGF-1 composite hydrogel, with a dual-barrier structure, enables gradient and sequential release of IGF-1, protects its bioactivity, promotes angiogenesis, and improves diabetic wound repair, indicating substantial potential for clinical translation[32].

However, IGF-1 has a short half-life and is readily degraded in the diabetic wound environment, which is

characterized by high oxidative stress and elevated protease activity. Direct administration therefore has difficulty maintaining an effective local concentration and cannot continuously support healing. Moreover, because glycemic regulation is impaired in diabetic patients, IGF-1 administration may induce hypoglycemia unless carbohydrate intake or glucose-lowering treatment is adjusted in a timely manner; severe hypoglycemia may even be life-threatening.

Both PDGF and IGF-1 promote matrix synthesis, tissue remodeling, and wound repair by activating the PI3K-Akt pathway, and both share the limitations of short half-life, susceptibility to proteolytic degradation in the wound bed, and relatively low bioavailability. PDGF primarily stimulates fibroblast proliferation, collagen synthesis, and neovessel stabilization, thereby improving granulation tissue quality; its clinical formulations are relatively mature, but it is limited by poor stability, the need for refrigerated storage, and insufficient penetration into deep wound tissue. IGF-1, by contrast, is more focused on correcting the hyperglycemia-suppressed reparative microenvironment and facilitating coordinated vascular and neural repair. Although its pro-healing efficacy is evident, it is highly prone to inactivation in the oxidative and protease-rich diabetic wound environment, and its use requires strict blood glucose monitoring because of the risk of hypoglycemia.

3.4. Immunomodulatory and Anti-inflammatory Growth Factors

3.4.1. Interleukin-10

Studies have shown that interleukin-10 (IL-10) can inhibit the release of pro-inflammatory cytokines via the JAK-STAT pathway and enhance the expression of anti-apoptotic factors through the PI3K/Akt pathway[33]. It can also regulate cell metabolism by inhibiting mTOR activity through the STAT-DDIT4 pathway, while simultaneously inhibiting antigen-presenting cell activation and improving tissue inflammation-related vascular abnormalities [34]. Decreased levels of the anti-inflammatory factor IL-10 weaken the body's ability to regulate inflammatory responses, creating a vicious cycle of "high inflammation and low repair [35-36].

Currently, there are few mature, marketed products specifically for the treatment of diabetic wounds using IL-10; most are still in the research and experimental stage, and exist primarily in the form of drug-loaded compound formulations and gene-modified cell preparations.

4. Combined Application of Multiple Growth Factors

Single growth factors in the treatment of diabetic chronic wounds are easily affected by the wound microenvironment, resulting in limited efficacy and a single target. However, the combined application of multiple growth factors can significantly improve treatment outcomes by synergistically covering the entire repair process [37]. The combination of different growth factors can create complementary effects in cell proliferation, angiogenesis, and immune regulation. Studies by Xu Jiasheng et al. have shown that when proliferative growth factors (such as EGF) are combined with acidic fibroblast growth factor (aFGF), EGF accelerates epithelial cell proliferation and differentiation, while aFGF promotes tissue repair and regeneration, shortening wound healing time [38]. A study conducted by Wang Huiying's team adopted a combined therapy of topical recombinant human epidermal growth factor (rhEGF) and red-blue light irradiation for diabetic foot treatment; the research findings proved that this combined approach can effectively speed up wound healing, lower the body's inflammatory factor levels, and greatly reduce the occurrence of postoperative scarring and pigmentation [39]. Another study from Wang Yang indicated that the combination of Shengji Yuyi ointment and recombinant bovine basic fibroblast growth factor (bFGF) gel can relieve ulcer symptoms in diabetic patients, ease wound pain, and effectively improve patients' overall living conditions [40].

5. Challenges and Future Perspectives

The poor stability and low delivery efficiency of growth factors are major bottlenecks in clinical applications. VEGF, bFGF, PDGF, and IGF-1 are all polypeptides with short in vivo half-lives, easily degraded by matrix metalloproteinases highly expressed in wounds; moreover, they are mostly traditional topical formulations with limited transdermal depth, making it difficult to act on deeper layers of the wound [24]. Diabetic wounds form an acidic microenvironment; this condition can destroy the molecular structure of therapeutic drugs and weaken their biological activity, so external drugs struggle to sustain effective concentrations at wound sites. Patients thus need frequent medication, which raises treatment costs and increases clinical operation difficulty, and fails to support continuous wound repair. In addition, one single growth factor only acts on a single target, so it cannot work through the whole wound healing cycle. Diabetic chronic wounds bring multiple pathological changes in the body, such as vascular injury, nerve damage, persistent inflammation and insufficient matrix synthesis; a single growth factor is unable to improve all these abnormal symptoms at the same time. Even if multiple growth factors are used together, there are no unified standards for their matching proportion, administration time and dosage, which makes it hard to achieve optimal treatment outcomes.

Emerging new technologies offer a viable way to solve the existing limitations of growth factor therapy; in the field of nanotechnology, nanoparticles and nanofiber carriers can shield growth factors from degradation by proteases. For example, Zhao and his team prepared PDA-modified PLGA nanofiber scaffolds; after being cross-linked with bFGF, these scaffolds can retain the biological activity of growth factors and achieve slow drug release, and the outer PDA coating can also improve the adsorption efficiency and structural stability of loaded bFGF [41]. 3D bioprinting technology can prepare methacrylamide gelatin hydrogel scaffolds loaded with fibroblasts. The cells secrete growth factors to endow them with activity, and the porous structure simulates the microenvironment, facilitating cell infiltration [42]. These technologies can significantly enhance the bioavailability of growth factors and provide new therapeutic strategies for chronic diabetic wounds.

Future breakthroughs in growth factor therapy for diabetic chronic wounds mainly rely on improvements in three areas, including deeper mechanism exploration, clinical verification and personalized treatment strategies. Mechanism studies need to focus on the interactive relationships in the growth factor signaling network; for example, researchers can explore how IGF-1 and VEGF work together to regulate vascular and nerve repair at the molecular level, so as to find new effective therapeutic targets. Multi-center and long-term

follow-up clinical trials are also required to confirm the safety and therapeutic effect of PDGF combined with nanocarriers in diabetic patients with different disease conditions. Doctors can adjust personalized treatment schemes according to patients' genetic characteristics and wound microenvironment, such as changing the dosage of EGF based on detected MMP-9 levels. With the continuous development of modern technology, the combination of growth factors with 3D bioprinted scaffolds or gene editing treatment is expected to realize accurate wound repair and lower the amputation risk of diabetic patients. The large-scale clinical promotion of this therapy in the future can greatly improve the recovery effect of diabetic wounds and help reduce the overall medical burden.

Acknowledgments

Funding: This work was supported by the National Natural Science Foundation of China (No. 82160907).

References

[1] GBD 2021 Diabetes Collaborators. (2023). Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *The Lancet*, *402*(10397), 203–234. https://doi.org/10.1016/S0140-6736(23)01301-8.

[2] Okonkwo, U. A., Chen, L., Ma, D., Barakat, H., & Milne, T. (2020). Compromised angiogenesis and vascular integrity in impaired diabetic wound healing. *PLOS ONE*, *15*(4), e0231962. https://doi.org/10.1371/journal.pone.0231962.

[3] Zhang, Y., Hei, F., Xiao, Y., Liu, Z., & Li, Q. (2024). Acidic fibroblast growth factor inhibits reactive oxygen species-induced epithelial-mesenchymal transdifferentiation in vascular endothelial cells via the miR-155-5p/SIRT1/ Nrf2/ HO-1 pathway to promote wound healing in diabetic mice. *Burns & Trauma*, *12*, tkae010. https://doi.org/ 10. 1093/ burnst/ tkae010.

[4] Huang, G., Sui, M., Zhu, H., & Liu, Y. (2025). Pharmacoeconomic evaluation of recombinant human acidic fibroblast growth factor in the treatment of diabetic foot ulcers. *Chinese Journal of New Drugs*, *34*(12), 1313–1321.

[5] Zhang, F., Zhang, H., Wang, S., et al. (2025). A dynamically phase-adaptive regulating hydrogel promotes ultrafast anti-fibrotic wound healing. *Nature Communications*, *16*(1), 3738. https://doi.org/10.1038/s41467-025-58829-7.

[6] Li, M., Chen, X., Chen, P., & Lin, W. (2025). Efficacy of human epidermal growth factor gel combined with collagen sponge in the treatment of chronic refractory wounds. *Journal of Fujian Medical University*, *59*(3), 187–191, 197.

[7] Wang, P., Berry, D., Moran, A., & Smith, J. (2020). Controlled growth factor release in 3D-printed hydrogels. *Advanced Healthcare Materials*, *9*(15), e1900977. https://doi.org/ 10. 1002/ adhm.201900977.

[8] An, H., Li, S., Wang, P., & Zhou, L. (2024). A study on the treatment of diabetic foot wounds with a novel negative-pressure drainage device combined with basic fibroblast growth factor. *China Medical Cosmetology*, *14*(1), 26–29.

[9] Chinese Diabetes Society. (2021). Guideline for the prevention and treatment of type 2 diabetes mellitus in China (2020 edition). *Chinese Journal of Diabetes Mellitus*, *13*(4), 315–409.

[10] Ruan, Q., Zhang, S., Xi, M., & Wang, Y. (2024). Interaction between fibroblasts and keratinocytes in wound-edge skin tissue of patients with diabetic foot and its mechanism. *Chinese Journal of Burns and Wound Repair*, *40*(8), 762–771.

[11] Dai, F., Zhang, J., Chen, F., et al. (2024). A multi-responsive hydrogel combined with mild heat stimulation promotes diabetic wound healing by regulating inflammation and enhancing angiogenesis. *Advanced Science*, *11*(46), e2408783. https://doi.org/10.1002/advs.202408783.

[12] Dasari, N., Jiang, A., Skochdopole, A., & Armstrong, D. G. (2021). Updates in diabetic wound healing, inflammation, and scarring. *Seminars in Plastic Surgery*, *35*(3), 153–158. https:// doi. org/ 10.1055/s-0041-1731495.

[13] Wang, G., Yue, R., & Gong, G. (2023). A case-control study of recurrence risk factors after healing of diabetic foot ulcers. *Chinese General Practice*, *26*(15), 1857–1862.

[14] Cortvrindt, C., Speeckaert, R., Delanghe, J. R., & Speeckaert, M. M. (2022). Urinary epidermal growth factor: a promising next-generation biomarker in kidney disease. *American Journal of Nephrology*, *53*(5), 372–387. https://doi.org/ 10. 1159/ 000523996.

[15] Hong, W. (2024). Mechanistic study of long non-coding RNA XIST in promoting proliferation and migration of HaCaT cells in diabetic ulcer wounds through competitive binding to miR-126-3p and regulation of EGFR [Master's thesis]. Nanchang University.

[16] Zhao, D. Y., Su, Y. N., Li, Y. H., Yu, T. Q., Li, J., & Tu, C. Q. (2020). Efficacy and safety of recombinant human epidermal growth factor for diabetic foot ulcers: a systematic review and meta-analysis of randomised controlled trials. *International Wound Journal*, *17*(4), 1062–1073. https://doi.org/ 10.1111/ iwj. 13348.

[17] Qiu, H., Wang, Q., Yu, L., & Zhang, T. (2023). Efficacy of recombinant human epidermal growth factor combined with Ilizarov transverse tibial bone transport in the treatment of Wagner grade 2–4 diabetic foot and its effects on serum wound repair-related factors. *Journal of Qiqihar Medical University*, *44*(6), 537–542.

[18] Baek, J. Y., Kwak, J. E., & Ahn, M. R. (2024). Eriocitrin inhibits angiogenesis by targeting VEGFR2-mediated PI3K/AKT/mTOR signaling pathways. *Nutrients*, *16*(7), 1091. https:// doi.org/10.3390/nu16071091.

[19] Zhang, L., Chen, L., Wang, L., & Huang, X. (2023). Effects of PRP gel and rhGM-CSF gel in the treatment of chronic refractory wounds and their influence on wound repair factors. *Guangxi Medical Journal*, *45*(4), 403–407.

[20] Yan, H., Zhao, Y., Liu, H., & Chen, J. (2025). Experimental study of hepatocyte growth factor/vascular endothelial growth factor 165 dual-gene therapy accelerating healing of full-thickness skin wounds. *Chinese Journal of Aesthetic Medicine*, *34*(5), 1–5.

[21] Zha, W. (2023). Study on VEGFA mRNA lipid nanoparticles promoting diabetic wound healing [Master's thesis]. Southeast University.

[22] Qiu, W. (2019). Study on the role and mechanism of FGF-2 synergizing with TGF-beta1 to upregulate fibroblast PD-L1, regulate wound inflammation, and promote healing [Master's thesis]. Army Medical University.

[23] Chen, X., Wu, X., Lin, H., & Zheng, Y. (2022). Effects of gelatin methacryloyl hydrogel loaded with silver and recombinant human basic fibroblast growth factor on rabbit deep second-degree burn wounds. *Chinese Journal of Burns and Wound Repair*, *38*(7), 640–649.

[24] Xia, Y., Zhang, B., Huang, Y., & Wang, H. (2025). Effects of basic fibroblast growth factor combined with neutral oxidizing potential water dressing on the repair of second-degree burn wounds. *Chinese Journal of Aesthetic Medicine*, *34*(9), 56–59.

[25] Kim, I., Kim, H. G., So, J. N., Kim, J. H., Kwak, H. J., & Koh, G. Y. (2000). Angiopoietin-1 regulates endothelial cell survival

through the phosphatidylinositol 3'-kinase/Akt signal transduction pathway. *Circulation Research*, *86*(1), 24–29. https: // doi.org/10.1161/01.RES.86.1.24.

[26] Badr, G., El-Hossary, F. M., Lasheen, F. E. M., et al. (2023). Cold atmospheric plasma induces the curing mechanism of diabetic wounds by regulating the oxidative stress mediators iNOS and NO, the pyroptotic mediators NLRP-3, Caspase-1 and IL-1beta, and the angiogenesis mediators VEGF and Ang-1. *Biomedicine & Pharmacotherapy*, *169*, 115934. https://doi.org/ 10. 1016/j.biopha.2023.115934.

[27] Nie, X. (2021). Role of the Ang-1/Tie-2 pathway in transverse tibial bone transport-promoted wound angiogenesis in patients with severe diabetic foot [Master's thesis]. Guangxi Medical University.

[28] Lehti, K., Allen, E., Birkedal-Hansen, H., et al. (2005). An MT1-MMP-PDGF receptor-beta axis regulates mural cell investment of the microvasculature. *Genes & Development*, *19*(8), 979–991. https://doi.org/10.1101/gad.1276205.

[29] Kim, J., Bong, K. W., Cho, J. K., & Song, S. C. (2025). Thermo-responsive hydrogel via sustained co-delivery of TA and PDGF to modulate the diabetic microenvironment and accelerate diabetic wound healing. *Journal of Materials Chemistry B*, *13*(24), 7090–7105. https://doi.org/10. 1039/ D5TB00286A.

[30] Yuan, G., Guo, X., Ran, X., & Zhang, Y. (2015). Clinical efficacy and safety evaluation of recombinant human platelet-derived growth factor gel in chronic diabetic foot ulcers. *Chinese Journal of Clinical Pharmacology*, *31*(6), 424–428.

[31] Zhang, C., Fei, C., Fu, L., & Li, M. (2022). Correlation of FGF-2, Lp-PLA2, and IGF-1 levels with disease severity in patients with diabetic foot. *Laboratory Medicine*, *37*(9), 826–830.

[32] Yang, H., Chen, Y., Rong, Y., et al. (2025). Multifunctional hydrogel targeting senescence to accelerate diabetic wound healing through promoting angiogenesis. *Journal of Nanobiotechnology*, *23*(1), 177. https://doi.org/10.1186/ s12951 -025-02856-8.

[33] Saraiva, M., Vieira, P., & O'Garra, A. (2020). Biology and therapeutic potential of interleukin-10. *Journal of Experimental Medicine*, *217*(1), e20190418. https://doi.org/ 10. 1084/ jem.20190418.

[34] Ip, W. K. E., Hoshi, N., Shouval, D. S., Snapper, S., & Medzhitov, R. (2017). Anti-inflammatory effect of IL-10 mediated by metabolic reprogramming of macrophages. *Science*, *356*(6337), 513–519. https://doi.org/10. 1126/ science. aal3532.

[35] Farrell, E., Fahy, N., Ryan, A. E., et al. (2016). vIL-10-overexpressing human MSCs modulate naive and activated T lymphocytes following induction of collagenase-induced osteoarthritis. *Stem Cell Research & Therapy*, *7*(1), 74. https://doi.org/10.1186/s13287-016-0328-6.

[36] Xu, F., Liang, P., & Liao, R. (2023). Mechanism of Yiqi Shengji mixture in repairing chronic refractory wounds in rats based on the Wnt/beta-catenin signaling pathway. *Global Traditional Chinese Medicine*, *16*(3), 453–459.

[37] Writing Group of the Expert Consensus on the Application of Growth Factors in the Treatment of Second-Degree Burn Wounds (2024 Edition). (2025). Expert consensus on the application of growth factors in the treatment of second-degree burn wounds (2024 edition). *Chinese Journal of Injury Repair and Wound Healing (Electronic Edition)*, *20*(4), 277–283.

[38] Xu, J., Min, D., Guo, G., Liao, X., & Fu, Z. (2018). Experimental study of epidermal growth factor and acidic fibroblast growth factor in the treatment of diabetic foot wounds. *Experimental and Therapeutic Medicine*, *15*(6), 5365–5370. https://doi.org/10.3892/etm.2018.6069.

[39] Wang, H., Fu, X., Zhao, H., & Liu, J. (2025). Observation on the efficacy of topical recombinant human epidermal growth factor combined with red-blue light in second-degree burn wounds. *Chinese Journal of Aesthetic Medicine*, *34*(10), 51–54.

[40] Wang, Y., Liu, T., Li, W., & Chen, S. (2024). Clinical study of Shengji Yupi ointment combined with recombinant bovine basic fibroblast growth factor gel in the treatment of superficial chronic ulcers. *Modern Drugs and Clinical Practice*, *39*(5), 1294–1298.

[41] Zhao, J., Han, F., Zhang, W., Yang, Y., You, D., & Li, L. (2019). Toward improved wound dressings: effects of polydopamine-decorated poly(lactic-co-glycolic acid) electrospinning incorporating basic fibroblast growth factor and ponericin G1. *RSC Advances*, *9*(57), 33038–33051. https://doi.org/10.1039/C9RA06577A.

[42] Sun, H., Wang, L., Cui, A., & Zhang, Q. (2024). In vitro pro-angiogenic effects of 3D-printed gelatin methacryloyl hydrogel scaffolds loaded with fibroblasts. *Chinese Journal of Tissue Engineering Research*, *28*(22), 3484–3489.