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Research Progress on Healing Mechanism of Diabetic Foot Ulcer

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Abstract

Diabetic foot ulcers are a prevalent complication that can significantly impact quality of life and necessitate high-level amputations. Hence, early diagnosis and treatment, elucidation of pathogenesis, and targeted countermeasures assume paramount importance. Wound healing entails a complex process wherein various components such as inflammatory cells, extracellular matrix, and immune cells intricately interact with each other. Due to the vulnerability of the skin to damage, inadequate or impaired wound healing has emerged as an urgent clinical challenge requiring resolution. This paper provides a comprehensive overview of the pathogenesis, diagnosis, and treatment of diabetic foot ulcers in order to offer theoretical guidance for specific interventions.

Keywords

Diabetes, Diabetic Foot Ulcer, Wound Healing, Machine Made

1. Introduction

The prevalence and incidence of diabetes is increasing rapidly, and it is the complications of diabetes that pose a major threat to patients, one of the common chronic complications is ischemic ulcer (DFU), which results in reduced oxygen supply and required nutrients for the ulcer. The skin of diabetic patients is easily damaged, and the epidermal cells on the wound cannot produce the necessary factors such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) required to promote healing [1]. This results in damage that is difficult to heal, seriously affecting the quality of life and health of patients. The treatment of diabetic foot ulcer has become one of the important topics in clinical medicine. With the progress of scientific research, experts began to pay attention to transcription factors, angiogenesis, neuropeptides, etc., in order to

improve the treatment effect of diabetic foot ulcers.

2. Diagnostic Criteria and Research Progress

2.1. Diagnostic Criteria

The World Health Organization defines diabetic foot as: lower extremity infection, ulceration and (or) deep tissue destruction induced by diabetic patients with various neuropathy and peripheral vascular lesions of different degrees [2]. The lesions may involve joints, tendons and surrounding soft tissues [3]. Existing evidence has confirmed that MRI is the best imaging method for the diagnosis of soft tissue, muscle, joint and bone lesions [4]. Although there is no universal standard for clinical diagnosis, the grade classification proposed by Wagner *et al.* is one of the most commonly used methods. This method divides foot lesions into different types and levels based on the degree and depth of tissue necrosis. This classification method is concise and easy to remember, and has been widely used in clinical practice. However, the main disadvantage of this classification method is that it ignores the influence of pathophysiological factors such as ischemia and infection.

2.2. Treatment Methods and Progress

Foot ulcers in diabetic patients are a chronic disease, so wound repair takes a long time. In the course of treatment, chronic wounds need to be transformed into acute wounds to promote rapid recovery of ulceration. Treatment methods can generally be divided into two kinds: traditional Chinese and Western medicine and traditional Chinese medicine [5]. Basic treatment includes active response to various risk factors, such as the use of insulin glargine, control of hypertension, prevention of myocardial infarction and cerebrovascular disease, and can also be treated by lifting the circulatory system of the foot and using vasodilators. If necessary, bypass surgery may be considered. However, in the case of the lower limb artery is basically blocked, it is particularly easy to lead to bacterial infection, and the treatment is more difficult.

2.2.1. Debridement

Patients with chronic diabetes may need surgery to deal with the infection [6]. The purpose of surgery is to remove potential sources of infection and promote healing of the ulcer. The procedure usually involves removing dead tissue and making sure the wound is healthy and exposed. Traditional treatments include excision and debridement with scissors and scalpel.

2.2.2. Trauma Dressing

Selecting a suitable wound dressing is crucial for the treatment of patients with chronic diabetes, helping to maintain a moist environment on the wound [7], preventing the absorption of seepage, and promoting tissue regeneration. Trauma dressings commonly used in medicine include transparent dressings.

2.2.3. Negative Pressure Wound Healing

Negative pressure therapy is a common treatment for chronic diabetic foot ulcers. In terms of treatment strategy, it is necessary to fully clear the ulcerating wound and destroy the infected necrotic tissue. In order to promote wound healing, closed negative pressure drainage system was used to repair the wound. For open wounds, it is necessary to cover the appropriate dressing and connect the suction system. Normative negative pressure is then applied for attraction [8] to promote wound healing. During treatment, the dressing should be changed in time to prevent infection. The treatment of chronic foot ulcers requires changing the dressing every 2 - 3 days.

2.3. Mechanism of Slow Healing of Diabetic Foot Ulcer

2.3.1. Hyperglycemia

AGEs (advanced glycation end products) are the products of excessive non-enzyme-catalyzed reactions of sugars, proteins, fats, nucleic acids and amino acids in the body [9]. People with diabetes accumulate excessive amounts of blood sugar in the body due to long-term high blood sugar. Excessive accumulation of AGEs will inhibit the function of mononuclear macrophages and reduce their ability to secrete cytokines. Endothelial cells play a role in the formation of blood vessels during wound healing and proliferation. Because the protein binds to AGEs on the membrane surface, it may inhibit the proliferation of endothelial cells, and may also induce apoptosis. AGEs may also affect the survival rate of fibroblasts. At the same time, some studies have shown that AGEs may also have certain effects on growth factors [10]. Maurizio found that glycosylation of fibroblast growth factor (FGF-2) may be increased in hyperglycemic mice compared to normal glycemic mice ($P \leq 0.001$), and may significantly reduce the in vitro chemotactic of FGF-2 and its in vivo angiogenic properties. This suggests that high blood sugar may affect the glycation of certain growth factors, which may cause them to lose their normal function.

2.3.2. Abnormal Inflammatory Response

A notable feature of diabetes is the prolonged duration of the inflammatory response after chronic low-level inflammation, which is not conducive to wound healing. Chronic low level inflammatory response is a manifestation of immune system dysfunction in diabetic patients. Because neutrophils begin to gather near the wound at the beginning of the inflammatory phase, their activity is reduced in diabetic foot patients, so diabetic patients are more susceptible to infection and lead to wound deterioration. Clinical and experimental studies have shown that neutrophils in diabetic mice have defects in chemotaxis, phagocytosis and bactericidal ability. Another type of macrophage that plays an important role in inflammation does not function properly in people with diabetes. Recent studies by Mirza *et al.* have shown that the increase of inflammatory cytokine interleukin-1β (IL-1β) and the inhibition of IL-1β pathway can promote wound healing [11], which may be achieved by regulating the transformation of macrophage M1/M2.

2.3.3. Impaired Angiogenesis

The formation of blood vessels is important for tissue repair, as well as providing nutrition and support for other cells. However, in patients with diabetes, angiogenesis is severely inhibited, in which a decrease in vascular endothelial growth factor (VEGF) is a key factor. EPCs are involved in endothelial cell repair, secretion of angiogenic factors, and protection of the integrity of damaged endothelial cells. Non-enzymatic glycosylation of the vascular basement membrane caused by hyperglycemia impairs the migration ability of EPCs and thus affects vascular regeneration. In addition, oxygen supply is essential for angiogenesis. Under normal circumstances, local hypoxia induces hypoxia-inducible factor-1 (HIF-1) expression, which in turn regulates a variety of cellular processes, including angiogenesis, metabolism, and apoptosis. In diabetic wounds, the expression of HIF-1α and its target genes is reduced, resulting in impaired angiogenesis and delayed wound healing.

2.3.4. Extracellular Matrix

Extracellular matrix (ECM) is an important component of diabetic foot wound healing. It provides a scaffold for cell interactions that help promote tissue growth and regeneration. In the process of diabetic wound healing, the activity of MMPs increases while the content of TIMPs decreases, resulting in the imbalance of the ratio of MMPs to TIMPs. The levels of MMP-1, MMP-8, and MMP-9 were elevated in long-term unhealed wounds, while the levels of TIMP were relatively low. Compared to normal wounds, the amount of MMP-8 from neutrophils in diabetic wounds may be as high as 50 - 100 times. In the diabetic wound environment, selective inhibition of MMP-9 may help accelerate healing. Regulation of MMP levels may help promote the healing of diabetic wounds. Overall, the imbalance between MMPs and TIMPs increases the degradation of the extracellular matrix, leading to abnormal collagen synthesis and affecting cell migration ability associated with proliferation.

2.4. Research Progress on the Mechanism of Wound Healing

2.4.1. Signal Transduction Pathway

Studies have shown that the factors that promote the healing of diabetic foot ulcer are related to inhibiting apoptosis, promoting fibrocyte proliferation, promoting angiogenesis, accelerating epithelialization, etc., which involve the regulation of multiple signal transduction pathways and various cytokines [12].

2.4.2. Angiogenesis and Wound Healing

The main components of granulation are fibroblasts and new capillary beds. VEGF is a specific vascular growth factor that binds and activates VEGFR-2, a specific receptor on the surface of endothelial cells, and promotes endothelial growth. Yu Zeyang *et al.* [13] found in the experiment of diabetic foot ulcer model rats. After effective intervention, the expressions of VEGF, VEGFR2, mRNA and protein in wound tissue are up-regulated, which may be the mechanism of wound healing. In the study of Luo Liya *et al.* [14], it was found that the effect on ulcer

tissue inflammation and lymphatic vessel repair was due to the insufficient vitality and decreased number of macrophages secreting VEGF. In normal tissues, VEGF can promote and induce angiogenesis and promote cell migration [15] [16]. Therefore, VEGF is a key factor in wound healing.

3. Conclusion

Diabetic foot is one of the most common complications in people with diabetes, and the main goal of treatment is to maintain blood sugar levels and reduce foot symptoms. Among them, diabetic foot ulcer is one of the typical manifestations of this complication. The key to treatment is to keep blood sugar levels stable; Secondly, surgical removal of necrotic tissue is the main means to control infection and promote tissue healing. In recent years, Zeng Naxin *et al.* [17] found that diabetic neuropathy leads to reduced relaxation of foot muscles and ligaments. Periosteum stretch can effectively promote wound healing and tissue regeneration by adjusting foot muscles, tissues and posture, thereby changing foot burden, reducing local pain, alleviating inflammatory response, and increasing blood circulation and metabolism. The emergence of new surgical methods provides more possibilities for the treatment of chronic wounds. With the continuous improvement and development of experimental techniques in molecular biology, immunology, genetics and other fields, more and more factors affecting wound healing have been revealed. These scientific advances offer more possibilities for healing intractable wounds. We look forward to new breakthroughs and progress in the future, and believe that there will be better ways to heal intractable wounds.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Bechara, N., Gunton, J.E., Flood, V., Hng, T. and McGloin, C. (2021) Associations between Nutrients and Foot Ulceration in Diabetes: A Systematic Review. *Nutrients*, **13**, Article 2576. https://doi.org/10.3390/nu13082576

[2] Zhang, SR. (2019) Comparative Analysis of X-Ray, CT and Low-Field MRI Images of Diabetic Foot. *World Latest Medical Information Abstracts*: *Continuous Electronic Journal*, **19**, 183-184.

[3] Li, M.L. and Sang, S. (2021) Application Value of MRI in the Diagnosis of Diabetic Foot (DF) Ulcers. *New World of Diabetes*, **24**, 186-189.

[4] Wang, J., Tang, W.W., Chen, D.W., *et al.* (2020) A Case of Catheter-Related Right Atrial Thrombosis in a Diabetic Foot Patient Treated with Hemodialysis. *Chinese Journal of Diabetes*, **12**, 1027-1029.

[5] He, F.L., Xiao, C., Long, N.J. and Liu, L.J. (2022) Effect and Mechanism of Ginkgo Biloba Extract Injection on Wound Recovery in Rats with Diabetic Foot Ulcer Model. *Journal of Guangxi Medical University*, **39**, 67-73.

[6] Wei, J.H. and Zhou, H.D. (2021) Research Progress on the Mechanism of Wound Healing in Diabetic Foot Ulcer. *Youjiang Medicine*, **49**, 621-624.

[7] Wu, L., Guo, H., Yang, Y.S. and Xu, X.Y. (2021) Study on the Mechanism of Action of Huiyang Shengji Ointment in the Treatment of Diabetic Foot Ulcer. *Beijing Journal of Traditional Chinese Medicine*, **40**, 956-962.

[8] Zhan, H.S. (2021) Clinical Observation of Negative Pressure Sealing Drainage Combined with Astragalus Injection in the Treatment of Diabetic Foot Ulcer. Guangxi University of Chinese Medicine.

[9] Wang, Z., Li, L., Du, R., Yan, J., Liu, N., Yuan, W., *et al.* (2016) CML/RAGE Signal Induces Calcification Cascade in Diabetes. *Diabetology & Metabolic Syndrome*, **8**, Article No. 83. https://doi.org/10.1186/s13098-016-0196-7

[10] Huang, Q.Z. (2014) Protective Effect of GLP-1 Analogs on Kidneys of Rats with Type 2 Diabetes and Its Possible Mechanism. Fujian Medical University.

[11] Lei, T., Sun, D.X., Zhou, J., Wei, H.L., Zhang, X.L., *et al.* (2019) Study on the Mechanism of Action of Panax Notoginseng/Bletilla Striata Sponge in Promoting Wound Healing in Rats with Diabetic Foot Ulcer Based on Wnt/β-Catenin Signaling Pathway. *China Pharmacy*, **30**, 483-487.

[12] Marquard, F.E. and Jücker, M. (2020) PI3K/AKT/mTOR Signaling as a Molecular Target in Head and Neck Cancer. *Biochemical Pharmacology*, **172**, Article 113729. https://doi.org/10.1016/j.bcp.2019.113729

[13] Tan, W.S., Arulselvan, P., Ng, S., Taib, C.N.M., Sarian, M.N. and Fakurazi, S. (2020) Healing Effect of Vicenin-2 (VCN-2) on Human Dermal Fibroblast (HDF) and Development VCN-2 Hydrocolloid Film Based on Alginate as Potential Wound Dressing. *BioMed Research International*, **2020**, 1-15. https://doi.org/10.1155/2020/4730858

[14] Luo, L.Y., Cai, Y.L., Wei, Z.R., *et al.* (2021) Effect of Vitamin D on the Expression of Vitamin D Receptor, Peroxisome Proliferator-Activated Receptor γ, and Vascular Endothelial Growth Factor in Tissues of Patients with Diabetic Foot Ulcers. *Chinese Journal of Diabetes*, **29**, 426-432.

[15] Iranparast, S., Assarehzadegan, M., Heike, Y., Hossienzadeh, M. and Khodadadi, A. (2014) Wilms' Tumor Gene (WT1) Expression Correlates with Vascular Epithelial Growth Factor (VEGF) in Newly Acute Leukemia Patients Undergoing Chemotherapy. *Asian Pacific Journal of Cancer Prevention*, **15**, 9217-9223. https://doi.org/10.7314/apjcp.2014.15.21.9217

[16] Maehana, S., Nakamura, M., Ogawa, F., Imai, R., Murakami, R., Kojima, F., *et al.* (2016) Suppression of Lymphangiogenesis by Soluble Vascular Endothelial Growth Factor Receptor-2 in a Mouse Lung Cancer Model. *Biomedicine & Pharmacotherapy*, **84**, 660-665. https://doi.org/10.1016/j.biopha.2016.09.083

[17] Zeng, N.X., Zeng, Z., You, Y., *et al.* (2021) Lateral Tibial Periosteum Distraction for the Treatment of Chronic Ischemic Diseases of the Lower Limbs. *Chinese Journal of Orthopaedics*, **41**, 1607-1613.