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Overview of the Repair Mechanisms and Clinical Research Progress in Diabetic Skin Ulcers

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Abstract: ***Diabetic skin ulcers are a significant complication impacting diabetic patients' quality of life. This review examines repair mechanisms, including ferritin deposition, platelet-rich plasma, and stem cell therapy, while highlighting breakthroughs in nanotechnology and cytokine-based treatments. These innovations promise to revolutionize clinical approaches, offering improved healing and reduced complications. The findings lay a robust foundation for future research and clinical applications.***

Keywords: diabetic foot ulcers, nanotechnology, stem cell therapy, cytokine therapy, wound healing

1. Introduction

Diabetes, a global chronic illness, endangers health and well-being through its widespread prevalence, high disability rates, and costly medical expenses [1-3]. Recent data released by the World Health Organization and the International Diabetes Federation reveals that diabetes has become a pressing global health concern, with a staggering 9.3% of the world's population—affecting more than 463 million individuals as of 2019. If current trends continue, experts predict this number will climb to 10.2% by 2030, potentially impacting close to 700 million people by 2045. The sharp rise underscores the urgent need for widespread intervention and awareness [4]. In China, the scenario is similarly severe, with around 11% of the population affected by diabetes, and a significant number undiagnosed, worsening the difficulties in managing the condition [5, 6].

Diabetes mellitus, often termed the "insidious harvester of life", not only threatens the patient's survival, but also triggers a series of complications like dominoes [7]. In contemporary medicine, diabetic skin ulcers are a puzzle, especially foot ulcers. The vicious cycle of high blood glucose levels makes the skin tissue of these patient's brittle and can cause trauma. These apparently insignificant wounds often turn into persistent chronic ulcers with little success even with various treatments [8, 9]. As the most representative of diabetes-related skin ulcers, diabetic foot ulcers (DFUs) often lead to accelerated tissue necrosis. These wounds are not only highly susceptible to bacterial invasion, but also deteriorate at an alarming rate, leaving the physician helpless [10, 11]. Consequently, investigating the repair processes of diabetic skin ulcers and assessing successful treatment options is crucial for easing patient discomfort, decreasing disability prevalence, and minimizing mortality rates.

The rapid changes in science and technology have revolutionized the field of medicine, and have led to a deeper understanding of the repair mechanisms of diabetic skin ulcers. With the emergence of cutting-edge technologies and breakthrough discoveries, clinical therapeutic approaches have shown unprecedented innovation. This review is based on the current situation, deeply analyzing the latest research progress from molecular mechanism to clinical practice, and attempting to provide medical workers with inspiring thoughts and practical clinical guidance through systematic sorting and in-depth interpretation, so as to optimize the diagnostic and treatment system of diabetic skin ulcers and improve the quality of life of patients.

2. Repair Mechanisms of Diabetic Skin Ulcers

2.1 Ferroptosis

2.1.1 The Role of Ferroptosis in Diabetic Skin Ulcers

The uniqueness of iron oxidation as a newly revealed mechanism of cell death is reflected in the two main features of lipid peroxidation and excessive oxidative stress [12]. It is of interest that the iron metamorphosis pathway is most likely involved in the pathologic process of diabetic skin ulcers when the organism is in a hyperglycemic environment [13]. The intracellular environment under hyperglycemic conditions undergoes significant changes, with iron ions and reactive oxygen species (ROS) levels climbing, and this imbalance triggers a series of chain reactions: a massive accumulation of lipid peroxides, which ultimately leads to the destruction of the cell membrane structure, and the cell is headed for the fate of death [14, 15]. Through in-depth observation of skin tissue samples from patients with diabetic skin ulcers, researchers found a thought-provoking phenomenon: not only did the content of lipid peroxidation products and iron ions in the tissues of these patients exceed the normal level, but at the same time, the activity of antioxidant enzymes showed a significant decrease in the trend, which is a strong evidence that iron oxidation plays an indispensable role in the development of diabetic skin ulcers [16]. indispensable role in the development of diabetic skin ulcers [16].

2.1.2 The Regulatory Mechanism of Platelet-Rich Plasma (PRP)

Platelet-rich plasma (PRP), a substance rich in growth factors and cytokines, holds great promise for treating diabetic skin ulcers [17, 18]. To understand how it works, PRP influences the body by adjusting the levels of GPX4 and SLC7A11, two important components of our antioxidant enzyme system. GPX4 stands out for its ability to neutralize harmful lipid peroxides, which helps maintain cell membrane integrity and prevents a type of cell death called ferroptosis that's caused by iron overload [19]. Moreover, PRP reduces the production of lipid peroxides by inhibiting ACSL4, a key enzyme in lipid peroxidation, further protecting against ferroptosis [20, 21]. On a molecular level, PRP activates the Nrf2/SLC7A11/GPX4 signaling pathway, strengthening the cell's antioxidant defenses and reducing oxidative stress [22, 23]. These complex molecular mechanisms work together to accelerate ulcer healing, providing a new therapeutic option for treating diabetic skin ulcers clinically.

2.1.3 The Regulatory Mechanism of Secretory Autophagosomes (SAPs)

The emergence of secreted autophagosomes (SAPs) as innovative nanomedicines has sparked a revolution in diabetic wound therapy [24]. Diving deeper into how they work, it's remarkable that SAPs play a crucial and irreplaceable role in repairing damaged skin cell viability by regulating iron metabolism in a groundbreaking way [25]. Interestingly, in high glucose environments, SAPs effectively prevent the accumulation of Fe^{2+} caused by endoplasmic reticulum stress, thanks to their unique regulatory mechanism [26]. More strikingly, SAPs also stimulate exosomal secretion, through which excess Fe^{2+} is excreted from the cells, significantly alleviating cytotoxicity while lowering the concentration of iron ions, presenting a dual therapeutic advantage [27].

Excitingly for the research community, SAP demonstrated excellent results in counteracting hyperglycemic damage to critical skin repair cells such as human dermal fibroblasts (HDF) and human umbilical vein endothelial cells (HUVEC). This innovative nanomedicine not only boosts cell proliferation but also facilitates cell migration, which is a key component of wound healing. Building on this discovery, researchers have created a groundbreaking wound dressing called Gel-SAP by seamlessly integrating SAPs with gelatin-methyl methacrylate (GelMA) hydrogel [27]. The experimental data are exciting: the dressing achieved remarkable results in restoring skin repair cell function and promoting diabetic wound healing, a landmark breakthrough in this field.

2.2 Cytokine

2.2.1 Inflammation Regulation

Inflammatory cytokines play a central role in regulating the healing process of diabetic skin ulcers, and their mechanism of action is fascinating [28]. These tiny "commanders" are finely orchestrated through a complex network of molecular signals, controlling every aspect of wound repair like an invisible hand guiding the rebuilding process of life. Intriguingly, pro-inflammatory factors such as interleukin-1β, interleukin-6, and tumor necrosis factor-α are rapidly awakened at the onset of ulceration, not only triggering a cascading inflammatory response, but also mobilizing an army of immune cells, which act as a trained scavenger force, efficiently removing pathogenic microorganisms and dead tissues from wounds [29-32]. These pro-inflammatory factors act as if they were the architects of life, constructing vital pathways to deliver nutrients and oxygen to damaged tissues by stimulating neovascularization. It should not be overlooked that an excessive inflammatory response often interferes with the normal healing process of the ulcer. Under such circumstances, anti-inflammatory factors such as interleukin-10 and transforming growth factor-β appear in a timely manner to prevent further tissue damage by inhibiting excessive inflammatory responses, thus creating favorable conditions for tissue repair and regeneration [33]. It is thought-provoking that the delicate balance between these inflammatory factors plays a decisive role in the healing of diabetic skin ulcers, and any subtle imbalance may lead to a blockage of the healing process. It is thus clear that precisely regulating the expression and activity of inflammatory cytokines and maintaining their dynamic balance in clinical treatment is undoubtedly a key strategy for promoting ulcer healing and improving patient prognosis.

2.2.2 Angiogenesis

The importance of angiogenesis as a central mechanism of diabetic skin ulcer repair cannot be overstated. When the vascular system of the ulcer region suffers a severe blow under the influence of hyperglycemia intertwined with inflammatory response, the vicious cycle of insufficient blood supply exacerbates the dilemma of wound healing [34]. The regulatory role of cytokines is particularly critical in this pathologic state.

Vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) are the two main drivers of angiogenesis [35]. VEGF is like the "conductor" of angiogenesis. It stimulates the growth of new blood vessels by controlling several biological processes, such as the proliferation, migration, and formation of lumens in vascular endothelial cells. When there are ischemic and hypoxic conditions in diabetic skin ulcers, the body usually responds by producing more VEGF [36]. Meanwhile, FGF helps ensure the formation and stability of new blood vessels by regulating the growth activities of vascular endothelial cells and smooth muscle cells. Together, they establish a vascular network that supports wound healing [37, 38].

In this complex process of revascularization, different cytokines like platelet-derived growth factor (PDGF) also have their own important roles [33]. These molecules work together through a complicated signaling network, creating a detailed plan for angiogenesis. With this understanding, it's clear that carefully controlling the expression of these cytokines is a crucial way to speed up wound healing and improve patients' quality of life in clinical settings.

2.2.3 Cell proliferation

In the process of healing diabetic skin ulcers, two main growth factors, epidermal growth factor (EGF) and platelet-derived growth factor (PDGF), are very important for cell proliferation. They work through different but connected pathways. EGF mainly focuses on regulating epidermal cells,

speeding up the recovery of epithelial tissue by stimulating cell proliferation and differentiation [39]. This careful control helps form new epithelial layers over the wound, protecting it and preparing it for further healing. On the other hand, PDGF affects more cell types, like fibroblasts and smooth muscle cells, to support the formation and maturation of granulation tissue, which is crucial for effective wound repair [33]. These two growth factors don't just make cells divide and grow, they also control how cells move, change, and even die through a complicated signaling system. Working together, they help build a complete healing structure for wounds.

2.3 Stem Cells

2.3.1 Adipose-Derived Stem Cells (ADSCs)

Adipose-derived stem cells (ADSCs) exhibit multidimensional therapeutic potential in the healing process of diabetic skin ulcers, and their mechanisms of action are complex and interrelated [40]. Notably, these cells have the ability to secrete a variety of bioactive substances, including key factors such as vascular endothelial growth factor (VEGF), bFGF, and TGF-β, which play an indispensable role in the physiological processes of neovascularization, tissue regeneration, and wound repair [41]. Remarkably, microvesicles (MVs) released from ADSCs showed unique advantages in promoting cell proliferation and tissue repair. Under the special condition of high glucose environment, ADSCs showed remarkable regulatory effects: by reducing the endoplasmic reticulum stress-induced production of free ferrous ion (Fe^{2+}), and at the same time, by exocytosis to excrete excessive Fe^{2+} out of the cell, the cellular damage caused by Fe^{2+} was effectively mitigated [40]. More importantly, ADSCs also showed excellent immunomodulatory ability, which could not only inhibit the infiltration process of inflammatory cells, but also regulate the secretion level of inflammatory factors, and ultimately create a microenvironmental atmosphere conducive to tissue regeneration.

2.3.2 Bone Marrow-Derived Stem Cells (BMSCs)

Bone marrow stem cells (BMSCs), as an amazing class of cell populations with amazing multidirectional differentiation potential, are not only capable of evolving into various cellular forms such as osteoblasts, chondrocytes, and adipocytes, but also play an indispensable role in the process of diabetic skin ulcer repair. Of interest, these cells are directly involved in the process of tissue regeneration at the ulcer site by transforming into fibroblasts and endothelial cells [42]. Surprisingly, BMSCs are not simply transformed cells, but they also act as "factories" for growth factors and cytokines, secreting key substances such as HGF and IGF-1, which drive cell proliferation and migration and accelerate the pace of ulcer healing. In my opinion, nothing is more striking than the excellent immunomodulatory capacity demonstrated by BMSCs, which reduces the production of inflammatory factors by inhibiting the proliferation and activation of immune cells, such as T and B cells, thus creating a microenvironmental atmosphere conducive to tissue regeneration and ulcer healing [43].

2.3.3 Umbilical Cord Blood-Derived Stem Cells (UCBSCs)

As a unique cell therapy resource, umbilical cord blood stem cells (UCBSCs) have shown significant advantages in the field of allogeneic transplantation due to their low immunogenicity, which greatly reduces the rejection reaction of the body. It's important to note that UCBSCs play a key role in creating new blood vessels by releasing factors like VEGF and Ang-1. This improves blood flow to the ulcer, ensuring enough nutrients and oxygen for tissue healing [44]. Further studies show that UCBSCs can also control inflammation, creating a good environment for ulcer healing. They do this by reducing both inflammatory factors and the number of inflammatory cells [45].

2.3.4 Exosomes

Exosomes are small sacs released by cells that are filled with important molecules like proteins, mRNAs, and miRNAs. These tiny messengers play a big role in many biological processes. When these molecules enter target cells, they start a series of complex regulatory pathways that help heal diabetic skin ulcers [46]. Exosomes that contain VEGF and bFGF are particularly good at making endothelial cells grow and move, speeding up the formation of new blood vessels. Exosomes with TGF-β help make ulcerated tissues stronger by boosting the growth of fibroblasts and the production of collagen [47]. Amazingly, these tiny vesicles also have the unique ability to regulate the immune system, both by modulating innate and adaptive immune responses and by suppressing excessive inflammatory responses, thereby creating favorable conditions for tissue repair. In my opinion, this multiple biological function of exosomes makes them ideal for the treatment of diabetic ulcers.

2.4 Immune Regulation

2.4.1 Macrophage Immunomodulation

Macrophages, as key regulators in the repair process of diabetic skin ulcers, regulate the repair and reconstruction of tissues through multiple mechanisms, removing damaged cellular debris while precisely regulating the inflammatory response. It is worth delving into the fact that during physiologic wound healing, macrophages undergo a dynamic transformation from pro-inflammatory M1-type to inflammation-suppressive M2-type, a phenotypic shift that is decisive for effective tissue repair [48]. Unfortunately, the wound microenvironment in diabetic patients severely interferes with this phenotypic polarization process, resulting in a persistent failure of inflammation to subside, which in turn impedes wound healing [49]. In-depth studies have revealed that the regulation of macrophages by the nuclear receptor PPARγ is significantly impaired in the diabetic state. Notably, PPARγ activation is able to promote wound healing through a bidirectional regulatory mechanism: upregulation of healing-related gene expression on the one hand, and inhibition of pro-inflammatory cytokine production on the other [50]. The underlying cause of the reduced PPARγ activity is the activation of inflammasomes by the sustained production of IL-1β, and the application of PPARγ agonists is effective in reversing this pathologic process.

2.4.2 Immunomodulation by Phytochemicals

Natural active substances such as flavonoids, saponins, phenolic compounds, and polysaccharides contained in the plant kingdom play an integral role in various aspects of wound repair, and they influence the healing process through unique and complex mechanisms of action [51, 52]. Of

interest, these nature-derived chemicals and their derivatives exhibit remarkable immunomodulatory abilities, encompassing macrophage migration, nitric oxide synthase inhibition, lymphocyte and T-cell stimulation, cytokine activation, and natural killer cell enhancement, as well as playing a pivotal role in the regulation of NF-κB, TNF-α, and apoptosis. Remarkably, flavonoids construct a line of defense for pancreatic β-cells against cytokine-mediated apoptosis through the activation of the PI3-kinase pathway [50].

The repair of diabetic skin ulcers is a sophisticated biological symphony of iron metabolism, cytokine regulation, stem cell therapy, and immunomodulation, and the inhibition of iron metabolism by PRP and SAP, together with cytokine-mediated inflammation regulation, promotion of neovascularization, and stimulation of cellular proliferation, constitute an effective therapeutic system. In this repair process, stem cells such as ADSCs, BMSCs and UCBSCs injected a powerful impetus for ulcer healing through multiple pathways such as secretion of growth factors, directed differentiation and regulation of immune response. Impressive research has revealed that exosomes contain bioactive molecules with great potential to improve the immune system and regulate cell function. This discovery has brought new hope to the field of ulcer healing. As we explore these intricate molecular mechanisms, we see how they are closely connected, forming a complex biological network that offers a promising approach for treating diabetic skin ulcers.

3. Advances in Clinical Research

3.1 Traditional Treatments

In the treatment of diabetic skin ulcers, traditional therapies have always been a key part, even though they're not perfect. In modern medical practice, this well-established treatment plan includes things like cleaning the wound, caring for it with dressings, and preventing infections [53]. Wound debridement is the most important step in the whole treatment process. It involves removing dead tissue, foreign objects, and pus, and creating a good environment for the wound to heal [54]. Notably, when performing debridement operations, healthcare professionals must strictly adhere to the principle of asepsis in order to eliminate any possible cross-infection potential. In the process of daily care, a reasonable dressing change program can be regarded as an important weight for the success of treatment. Healthcare professionals have to choose the right dressing for each wound based on its characteristics. This not only protects the wound but also helps new tissue grow. Given that many diabetic patients have weaker immune systems, treating infections is a very important part of the overall treatment plan [55]. This requires clinicians to develop a personalized antibiotic use plan based on the results of drug sensitivity tests. At the same time, strengthening the overall conditioning and immunity enhancement of patients should not be overlooked. Undeniably, although traditional treatment methods have accumulated rich experience in clinical practice, their efficacy is often unsatisfactory, especially in the face of complex or severe ulcers, it is often difficult to achieve the expected therapeutic goals

3.2 Modern Treatments

3.2.1 Nanotechnology Applications

Nanotechnology, as a revolutionary means of diabetic foot ulcer treatment, is playing an irreplaceable role in multiple dimensions with its unique microscopic advantages. By using nanocarriers to deliver glucose-lowering drugs like metformin or insulin, this advanced drug delivery system can control blood sugar levels in the area affected by neuropathy and also help reduce neuropathy symptoms [56, 57]. It's important to note that nanomaterials are very effective in treating peripheral vascular diseases. They can help grow new blood vessels and produce collagen by slowly releasing vasodilators like nitric oxide, which speeds up wound healing [58]. Additionally, nanomaterials are good at controlling inflammation. They can reduce the overproduction of inflammatory markers like TNF-α, which helps create a better environment for tissue repair [59, 60]. Moreover, nanomaterials are really good at fighting infections. They can get rid of biofilms, lower the activity of enzymes that harm tissue, and raise the pH level of wounds. All these things help stop germs from growing and spreading, which lowers the chance of getting an infection. For instance, using antibacterial nanoparticles or nanoenzyme cascade catalytic systems can break up biofilm structures, making antibiotics work better and penetrate deeper [61]. Although nanotechnology has made significant progress in the treatment of DFU, it still faces some challenges. For instance, the action pathways of nanomaterials are relatively singular, requiring a combination of local and systemic administration to improve efficacy; the therapeutic stages of nanomaterials are mostly limited to a certain stage of wound healing, necessitating the development of nanomaterials that can regulate the entire wound healing process; at the same time, the adverse biological effects of nanomaterials also need further research to ensure their safety.

3.2.2 Wound Dressings

Wound dressings play a crucial role in the treatment of diabetic skin ulcers. Traditional dressings, such as gauze and bandages, are inexpensive and readily available but require frequent changes and may adhere to the wound, failing to provide a moist environment. Microneedle patches, characterized by their painless and minimally invasive nature, achieve direct drug delivery, significantly enhancing bioavailability and accelerating the wound healing process [62]. Sponge dressings, with their high porosity and strong water absorption, effectively manage wound exudate, maintaining a clean and dry wound environment. The bioactive substances they contain further facilitate the healing process [63]. Hydrogel dressings replicate the extracellular matrix, offering an optimal environment for cell growth and movement [64]. Biological dressings have shown extraordinary therapeutic efficacy in the contemporary medical field, through its unique moisturizing mechanism, effectively avoiding the phenomenon of dry scabs on the surface of the wound, and at the same time, forming a natural barrier to bacterial invasion; more critically, this kind of dressings can constantly deliver all kinds of growth factors and biologically active substances to the trauma surface, thus stimulating the newborn of local blood vessels and accelerating the formation of granulation tissues and repairs. With the rapid development of science and technology, the

emergence of three-dimensional bioprinting technology has undoubtedly brought about a revolutionary breakthrough in the field of tissue engineering, this precision printing process is not only able to perfectly replicate the extremely complex tissue scaffolding structure, but also to provide a tailor-made ideal micro-environment for cell growth and differentiation [65]. This significantly enhances tissue repair and blood vessel formation, paving the way for tailored therapies in managing DFU. Advanced, intelligent dressings with multifunctional capabilities can dynamically adjust drug delivery in response to shifts in the wound's microenvironment—such as pH levels and temperature—ensuring targeted and effective treatment [66, 67]. These new types of wound dressings have unique features and combined benefits, providing a more tailored and comprehensive approach to treating DFUs. However, research on these advanced dressings is still in the early stages. There is a pressing need to speed up both basic research and clinical trials to confirm their effectiveness and safety.

3.2.3 Stem Cell Therapy

Stem cell therapy has shown remarkable potential in the treatment of DFU, and the medical community is excited by the unique repair mechanisms of various stem cells. When stem cells, such as BMSCs, are injected into the body via subcutaneous or intramuscular routes, these miraculous cells are guided by specific signaling molecules to precisely target the traumatized area. Amazingly, once at the target site, these "medical elites" begin their "repair engineering" by secreting a steady stream of bioactive substances such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and other bioactive substances, which trigger an intricate chain reaction of tissue repair [42]. These critical growth factors uniquely stimulate dermal fibroblasts to proliferate and migrate, creating a neovascularization network at the wound site, resulting in a significant acceleration of the repair process. It is worth exploring that G-CSF, as a unique signaling molecule, can subtly activate and regulate endogenous peripheral blood stem cells in the bone marrow microenvironment, leading to their release into the circulatory system. This sophisticated physiological regulatory mechanism actually builds a stronger intrinsic support network for wound healing [68]. Stem cell transplantation has revolutionized the treatment of DFU, and this breakthrough has excited the entire medical community. Through in-depth observation and clinical practice, it is not difficult to find that stem cell transplantation has shown amazing therapeutic effects in improving the blood circulation of the affected limbs, which not only allows patients suffering from pain to regain their lives, but also dramatically shortens the healing cycle of the wounds. As a medical practitioner who has studied this technology for many years, I feel compelled to emphasize that among the many types of stem cells, adipose-derived stem cells (ADSCs) are writing a unique therapeutic saga in the field of clinical application due to their excellent biological properties. As a revolutionary discovery in the field of regenerative medicine, these cells have amazing isolation properties and amazing propagation speed, and hardly trigger any rejection in the human body. What is worth exploring is that these amazing cells are able to independently produce a variety of growth factors that are essential for the body's repair, including TGF-β, which has a significant tissue rebuilding function, and IGF-1, which promotes cell proliferation, and plays an indispensable role in the process of repairing damaged tissues. This breakthrough discovery undoubtedly opens up a brand-new research direction for regenerative medicine and provides new hope for mankind to overcome difficult diseases [69]. As key players in immune system regulation and anti-inflammatory responses, these substances not only bring new ideas to the treatment of DFU, but also provide an ingenious solution to the healing process of this intractable disease, giving us a glimpse into the infinite possibilities of future medical treatments.

3.2.4 Cytokine Therapy

Epidermal growth factor (EGF), as a "magical messenger" in the biological world, has attracted the attention of researchers with its unique physiological activity. In the field of cell proliferation regulation, it is like a precise "conductor", especially good at scheduling the growth rhythm of keratinocytes and fibroblasts, the two "musicians". Amazingly, this tiny molecule not only shows remarkable application prospects in the field of nerve repair, but also can optimize the local microcirculation system to provide continuous nutritional support for damaged tissues, which can be called the "guardian angel" of cell repair and regeneration. These combined effects show how valuable EGF is in the healing process of DFUs [70]. VEGF encourages the multiplication of endothelial cells, facilitates the development of new blood vessels, boosts vascular permeability, and creates a supportive framework for endothelial migration and vessel formation, which are vital for DFU healing [36]. Additionally, basic fibroblast growth factor (bFGF) works to counteract the overaccumulation of advanced glycation end products (AGEs) on receptors, effectively breaking the cellular "stalemate" caused by AGE buildup. This, in turn, fosters vascular regeneration, granulation tissue development, and epithelialization, further aiding wound recovery [71]. In addition, platelet-derived growth factor (PDGF), as a mitogen, plays an important role in wound healing [72]. Its representative preparation, becaplermin, has been widely used in the treatment of refractory injuries and has significantly shortened the healing time of DFU. Although other growth factors such as insulin-like growth factor (IGF), transforming growth factor (TGF), and nerve growth factor (NGF) are still in the experimental research stage for the healing process of DFU, they have shown positive therapeutic potential [33].

3.2.5 Traditional Chinese Medicine

Traditional Chinese medicine (TCM) therapies have accumulated certain experience in the treatment of diabetic skin ulcers. Studies have shown that the main pathogenesis of this condition lies in four major pathological factors: "deficiency", "stasis", "dampness", and "heat". By combining internal and external TCM treatments for ulcers, the healing of ulcers can be promoted, and the clinical cure rate can be improved [73, 74]. However, the clinical studies on TCM treatment of diabetic skin ulcers have a relatively small sample size, and the evaluation standards for clinical efficacy are not unified. Further research is needed in the future.

4. Summary and Outlook

Diabetic skin ulcers, especially DFU, have become an undeniable global public health issue. This article systematically reviews the repair mechanisms and clinical research progress of diabetic skin ulcers, covering multiple aspects from molecular mechanisms to clinical treatments. In terms of repair mechanisms, multiple mechanisms such as ferroptosis, cytokine regulation, stem cell therapy, and immune modulation work together in the healing process of diabetic skin ulcers. For example, platelet-rich plasma promotes ulcer healing by upregulating the expression of antioxidant enzymes and downregulating the expression of lipid peroxidase enzymes to inhibit ferroptosis. Stem cell therapy provides new cell sources and microenvironments for ulcer healing by secreting growth factors, differentiating into necessary cell types, and regulating immune responses. In the field of clinical research, traditional treatments such as debridement, dressing changes, and anti-infection therapy still play an important role. However, modern treatment methods such as the application of nanotechnology, the development of new dressings, stem cell therapy, and cytokine therapy also show broad application prospects. These new methods have significant advantages in improving treatment outcomes, shortening healing time, and reducing amputation rates.

Looking to the future, with the continuous in-depth of medical research and the rapid development of science and technology, we are expected to have a more comprehensive understanding of the repair mechanisms of diabetic skin ulcers and develop safer and more effective new treatment methods. This will bring blessings to diabetic patients, alleviate their suffering, and improve their quality of life. At the same time, we also need to further strengthen basic research, improve clinical trials, and promote the continuous progress of the treatment field of diabetic skin ulcers. This review highlights the intricate repair mechanisms and clinical advancements in diabetic skin ulcers. Innovations in nanotechnology, stem cell therapy, and cytokine applications offer promising solutions. Ongoing research will further enhance treatment efficacy and improve patient outcomes globally.

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