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AN UPTO DATE REVIEW: IN SIGHTS OF DIABETIC WOUND HEALING

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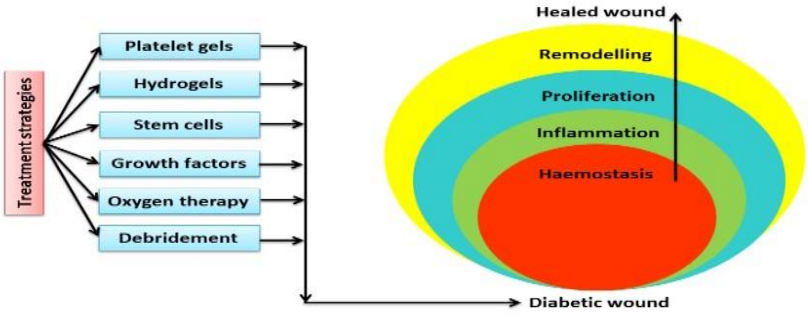
Abstract
Diabetes mellitus is a chronic metabolic condition characterized by persistent hyperglycemia, which has a detrimental impact on long-term health. The prevalence of diabetes mellitus is increasing, leading to a rise in the number of individuals experiencing impaired wound healing associated with this condition. Diabetic wounds often result in lower limb amputations, causing significant financial burden. The healing of these wounds is particularly challenging due to the hyperglycemic environment that promotes the growth of biofilms. This review provides an overview of recent advancements in the understanding of the pathophysiology of diabetic wounds, with a focus on neuropathy, impaired angiogenesis, compromised barrier function, and subsequent polymicrobial infections. The elucidation of these mechanisms contributes to a better understanding of the complexities involved in diabetic wound healing. Furthermore, this review discusses current treatment approaches as well as potential future strategies aimed at addressing the diverse pathologies associated with diabetic wounds. By targeting specific aspects of the wound healing process, these interventions aim to promote more efficient and effective healing, ultimately reducing the need for amputations and improving patient outcomes. Given the alarming increase in the prevalence of diabetes, it is crucial to stay updated on the advancements in our understanding of diabetic wound pathophysiology and the development of novel therapeutic approaches. Continued research and innovation in this field hold promise for improving the management and outcomes of individuals with diabetic wounds, thus alleviating the burden associated with this debilitating complication.



Keywords: diabetes mellitus, diabetic wounds, hyperglycemia, impaired wound healing, pathophysiology.

INTRODUCTION

Diabetes mellitus (DM), characterized by inadequate insulin production or response in the body, has emerged as a global health threat (1). According to the International Diabetes Federation, there were 537 million diagnosed cases of diabetes worldwide in 2021, with projections estimating a rise to 783 million by 2045. In the context of India, there were 74 million reported cases of diabetes in 2021, and it is projected to reach 124 million by 2045, making India a diabetes hotspot (2).

One of the complications associated with diabetes is impaired wound healing, which is particularly relevant in the treatment of diabetic wounds (DW). The impaired healing process in diabetic individuals is often attributed to the triopathy phenomenon, characterized by immunopathy, neuropathy, nephropathy, and vasculopathy (3,4). Approximately 30% of individuals with diabetes experience wound complications during their lifetime. Standard treatment for DW includes measures such as blood glucose control, wound depressurization, debridement, advanced dressing techniques, and surgical interventions. However, despite these interventions, DW pathogenesis remains multifactorial, with long-term inflammation and elevated oxidative stress being key factors hindering proper wound healing (5).

In addition to the delayed wound healing, DW also increases the risk of infections, and lower extremity amputations are performed every 30 seconds worldwide on individuals with diabetes. The altered molecular environment in DW contributes to delayed healing and chronic inflammation. Impaired angiogenesis, resulting from inadequate vascular supply to the wound site, has been observed in DW.

Furthermore, abnormal neutrophil response to injury has been implicated in the chronicity and tissue damage associated with DW (6,7). Neutrophils are known to form extracellular traps (NETs) by releasing chromatin granules and proteins, creating an extracellular matrix that binds and destroys bacteria.

This process, called NETosis, leads to the death of neutrophils and the release of nuclear materials within NETs. Intriguingly, previous studies have revealed that both angiogenesis and NETosis pathways are regulated by protein kinase C-βII (PKC-βII), an enzyme with a pivotal role in DW(10-13). PKC-βII has been implicated in the downregulation of the angiogenic pathway involving Akt (protein kinase B)/endothelial nitric oxide synthase (eNOS) in diabetic patients (10,11). Therefore, the focus of this current review is to provide a comprehensive analysis of the structure of PKC-βII, along with the available Protein Data Bank (PDB) structures. The objective is to facilitate drug discovery efforts targeting PKC-βII, ultimately aiming to improve the efficacy of treatments for DW.

2. Pathophysiology of Diabetic Wound Healing

2.1 Hyperglycemia

Hyperglycemia, a characteristic feature of diabetes mellitus (DM), plays a significant role in impairing wound closure and contributing to the development of diabetic foot ulcers (DFUs) through various mechanisms. While hypoglycemia has also been associated with vascular complications in diabetes (14), the focus of the literature and this section is primarily on the detrimental consequences of hyperglycemia in relation to DFUs. Hyperglycemia, a state of high blood sugar, diminishes the functionality of crucial antioxidant enzymes like glutathione peroxidase and superoxide dismutase. This impairment results in elevated quantities of reactive oxygen species (ROS) and consequent oxidative harm (17). Elevated ROS levels can adversely affect blood flow, metabolism, and structure of peripheral nerves, making the skin more susceptible to injury and infection, thus impeding wound healing. It is crucial to manage hyperglycemia carefully in individuals with diabetes.

2.2 Neuropathy

Besides elevating the propensity for the development of diabetic foot ulcers (DFUs), each specific form of neuropathy, including sensory, motor, and/or autonomic, possesses the ability to hinder DFU healing in an autonomous manner. Neuropathic skin showcases diminished neuronal density and exhibits decelerated rates of wound healing (15). Apart from conventional therapies such as antibiotics, debridement, and wound cleansing to enhance wound closure in diabetic and neuropathic patients (16), prevention strategies are not commonly employed, as current neuropathy treatments primarily focus on alleviating foot pressure and controlling itching (16). Moreover, neuropathy can impact various physiological processes, including digestion, urination, and circulation. The central nervous system, consisting of the spinal cord and cerebral cortex, receives sensory information from the rest of the body through peripheral nerves. Any condition affecting the nerves outside the brain and spinal cord is referred to as peripheral neuropathy, presenting a wide range of potential symptoms. Treatment options for peripheral neuropathy can vary significantly based on the individual and may address underlying causes, specific forms of neuropathy, or symptomatic relief.

2.3. Microvascular Complications

2.3.1. Peripheral Arterial Disease

Patients with diabetic foot ulcers (DFUs) often present with peripheral arterial disease (PAD), which exacerbates outcomes and increases the risk of limb amputation (17, 18). A crosssectional study reported that 43% of DFU cases were associated with PAD (17). Revascularization techniques have demonstrated that eligible patients who undergo reperfusion of the ulcer area have reduced risks of death and amputation (19-21). PAD manifests as various clinical syndromes, with the lower limbs being most commonly affected. It is imperative to comprehend the implications of PAD and implement appropriate management strategies for these patients. Even in cases where symptoms are absent, clinically silent disease indicates heightened vascular morbidity and mortality.

2.3.2. Hypoxia

Differential gene expression is observed in various skin cell populations under hypoxic conditions. A recent study utilizing flow-mediated skin fluorescence to monitor skin hypoxia revealed lower levels in DFUs, which were associated with poorer healing prognosis and increased risk of complications (22). Hypoxemia or hypoxia arises from inadequate oxygen levels in the body, posing a hazardous situation. Inadequate oxygen supply to the brain, liver, and other organs can lead to damage within minutes of symptom onset. Hypoxemia refers to low oxygen levels in the blood, while hypoxia refers to low oxygen levels in the tissues. Both conditions may coexist and are collectively referred to as hypoxia.

2.3.3. Anemia

Research has indicated that anemia is a prevalent condition among individuals with diabetes, particularly in the presence of DFUs (23-28). A meta-analysis revealed a positive correlation between

the severity of anemia and DFU severity, which could be utilized as a predictor of mortality and amputation (29). Approximately one-third of the global population, totaling around 5.5 billion people, suffer from anemia. This particular medical condition exerts its influence on approximately 35% of females, 51% of expectant females, 40% of individuals falling within the age range of 0 to 12 years, and 18% of males on a global scale. These concerning statistics are observed in both developed and developing nations a like. The leading factors contributing to anemia worldwide are iron deficiency, thalassemia and hemoglobinopathies, folate deficiency, and parasitic diseases, all of which have a significant prevalence.

2.4. Barrier Disruption and Infection

2.4.1. Transepidermal Water Loss (TEWL)

The preservation of an optimal skin barrier and the defense against infections and water evaporation are contingent upon the harmonious interplay of various components, including lipids, intercellular connections, antimicrobial peptides, and enzymes. As individuals age, the overall moisture level of the outermost layer of the skin, known as the stratum corneum, experiences a gradual decline (30), studies focusing on the stratum corneum's surface have demonstrated similarities between young and old skin (31). Although some studies have reported no significant changes in transepidermal water loss (TEWL) (32-34), others have observed an increase (33, 35). Notably, diabetic skin exhibits similarities to aged skin, such as reduced lipid content, decreased hydration of the stratum corneum, and increased advanced glycation end-products (AGEs). Skin hydration has been identified as a significant predictor of wound healing, as observed prior to interventions such as recanalization (36), and has been found to correlate with microcirculation (37).

2.4.2. Antimicrobial Peptides

Preserving the structural and functional integrity of the skin, as well as maintaining water homeostasis is critical for preventing infections. The production of antimicrobial peptides (AMPs) represents one of the immune defense mechanisms of healthy skin, aimed at controlling the population of pathogens and maintaining a healthy skin microbiome. Upregulation of human β-defensin expression has been observed in diabetic foot ulcers (DFUs); however, subsequent AMP production has been suggested to be inadequate for regulating microbial activity (38). Recent research has explored the potential use of AMPs to promote wound healing.

2.4.3. Bacterial Diversity

Emerging evidence suggests that the gut and skin microbiomes of individuals with diabetes are dysbiotic, potentially contributing to the onset and progression of diabetes (39). Studies have indicated a higher prevalence of colonization by S. aureus and S. epidermidis on diabetic skin (40). The augmented occurrence of infections in individuals with diabetic foot ulcers (DFUs) and the subsequent dissemination of infection to the bones and bloodstream can be ascribed to the elevated prevalence of Staphylococcus aureus colonization on both intact diabetic skin and DFUs. To address this issue, innovative treatment approaches have prioritized the localized administration of drugs through diverse release mechanisms. This emphasis on topical drug delivery stems from the limited efficacy of systemic antibiotics in accessing chronic wound sites, especially in the presence of bacterial biofilms (41, 42).

2.4.4. pH and Microbiome

The complex interaction between the host and microbiome is facilitated by the significantly more alkaline wound environment observed in DFUs compared to acute wounds. Alkaline pH conditions have been shown to promote biofilm formation in various bacterial strains, including Pseudomonas (43). Moreover, pH has demonstrated differential effects on bacterial resistance to antibiotics (44).

2.5. Inflammation and Immune System Deficiency in Chronic Wounds

The process of wound healing involves four interconnected phases: hemostasis, inflammation, proliferation, and remodeling (45, 46). However, chronic wounds, such as non-healing diabetic foot ulcers (DFUs), are characterized by disruptions in each stage of wound healing, leading to impaired tissue repair (47). Studies have revealed that macrophage overexpression of tumor necrosis factor (TNF) and downregulation of transforming growth factor-1 (TGF-1) result in elevated levels of interleukin-10 (IL-10), decreased collagen production, and increased tissue damage (47). Additionally, the dysregulation of the p38 mitogen-activated protein kinase signaling pathway has been implicated in the failure of cells to transition from an inflammatory to a proliferative state (48). Moreover, patients with diabetes exhibit reduced phagocytic activity, as well as leukocyte dysfunction, leading to impaired immune cell function (49, 50).

2.6. Psychological Impacts of Diabetes Mellitus

The impact of a diabetic foot ulcer (DFU) diagnosis on a patient's quality of life has yielded conflicting findings, despite the well-known negative effects of diabetes mellitus (DM) on mental health, self-esteem, and family cohesion (51). Interestingly, studies suggest that individuals with DFUs do not experience significantly worse mental health outcomes compared to those without DFUs (51, 52). Furthermore, even patients who undergo substantial transtibial amputations have reported improvements in their overall quality of life (53). In certain cases, psychotherapy administered during hospitalization has shown promise in reducing anxiety, depression, and problem areas related to diabetes management (54).

3. Available Treatment Strategies

3.1. Debridement

Debridement, an integral component of standard wound treatment, serves various purposes, encompassing the reduction of bacterial burden and presence of biofilms, as well as the enhancement of immune system efficiency (55). Surgical debridement, recognized as a gold standard in caring for diabetic foot ulcers (DFUs), is postulated to facilitate healing by eliminating non-viable tissue and potentially synergizing with co-administered treatments (56, 57). While conclusive evidence regarding the effectiveness of surgical debridement in wound healing is currently lacking (58), further investigations into debridement modalities have revealed that surgical debridement is associated with shorter healing times (59). In cases where biofilms infiltrate deeper wound layers, adjunctive dressing may be necessary, and studies employing porcine models and human subjects have demonstrated that enzymatic debridement, an alternative debridement method, can decrease wound size, inflammation, and promote the formation of granulation tissue (55, 60).

3.2. Hyperbaric Oxygen Therapy

Recent scientific studies indicate that the application of hyperbaric oxygen therapy (HBOT) shows potential advantages for the treatment of patients diagnosed with Wagner grade 3 and 4 ulcers (61). This treatment approach has been associated with notable enhancements in various physiological markers, including reductions in HbA1c levels, leukocyte counts, and serum creatinine levels (62). It is important to note, however, that the current body of evidence regarding HBOT remains limited due to the scarcity of high-quality clinical trials investigating its efficacy. Nevertheless, prolonged utilization of HBOT has demonstrated several beneficial effects, such as decreased recruitment and adhesion of neutrophils, enhanced oxygen delivery to damaged tissues, alleviation of inflammation, and accelerated wound healing in individuals suffering from diabetic ulcers (60, 63). Recent investigations have highlighted the efficacy of topical oxygen therapy, as an alternative to HBOT, in fostering DFU healing and fostering an aerobic wound microbiota (64, 65).

3.3. Negative Pressure Therapy and Off-Loading

The impact of negative pressure wound therapy (NPWT) on blood flow and tissue oxygenation has yielded conflicting results in various research studies. Within the realm of extensively investigated

and trialed therapies for diabetic foot ulcers (DFUs), off-loading has emerged as the established methodology. Off-loading encompasses the reduction of pressure on the foot, specifically targeting high plantar foot pressure, which has shown to be beneficial in the prevention of ulcer formation (66). In a recent comprehensive review and meta-analysis, certain components of footwear have been identified as efficacious in lowering plantar pressures. These include metatarsal additions, apertures, and arch profiles, all of which have demonstrated effectiveness in reducing plantar pressures (67). Surgical off-loading, supported by multiple studies, has been shown to significantly improve healing outcomes and reduce amputation rates in individuals with DFUs compared to non-surgical care (68).

3.4. Growth Factor-Based Therapies

Growth factors, such as keratinocyte growth factor (KGF)-2, platelet-derived growth factor (PDGF), basic fibroblast growth factor (FGFb), and epidermal growth factor (EGF), have been extensively studied as potential therapeutic interventions for promoting wound healing in individuals with diabetes. Numerous studies utilizing small animal models have demonstrated the promising efficacy of these growth factors in addressing diabetic wound healing (69, 70) due to their involvement in various stages of wound healing, which are often dysregulated in chronic wounds. Among growth factor-based treatments, only one topical growth factor-based treatment, Becaplermin (0.01% Regranex® gel), has been authorized by the US Food and Drug Administration for promoting healing of diabetic foot ulcers (DFUs) (71)–(72). One of the challenges in utilizing growth factors for wound closure is ensuring their prolonged local bioavailability and continuous interaction with receptors. However, wounds pose a harsh microenvironment rich in proteases and peptidases, which can degrade growth factors, compromising their stability, chemical integrity, and bioavailability (73), (74).

3.5. Hydrogels/Matrices/Dressings and Skin Substitutes

Dressings, when utilized in conjunction with supplementary therapies, are frequently employed to manage diabetic foot ulcers (DFUs). Research conducted on both mouse models and human subjects has provided evidence that the application of extracellular matrix and stromal vascular fraction gels in combination not only facilitates the wound healing process but also promotes the synthesis of collagen and the formation of new blood vessels (neoangiogenesis) (75), (76). The use of bioengineered skin substitutes with living cells has yielded high-quality clinical data (77). Meta-analyses comparing skin substitutes to standard care have shown that the use of skin substitutes reduces the time required for wound healing and lowers the rate of amputation in DFUs (78)–(79).

3.6. Platelet Gels and Platelet-Rich Plasma (PRP)

Extensive research and documentation spanning more than thirty years have thoroughly examined the utilization of autologous platelet-rich plasma (PRP) and platelet gel products, revealing their remarkable capacity to expedite the healing process of persistent wounds. This therapeutic efficacy can be attributed to the abundant presence of diverse growth factors within PRP, namely Platelet-Derived Growth Factor (PDGF), Transforming Growth Factor-1 (TGF1), and Epidermal Growth Factor (EGF). These growth factors exhibit a range of intricate functions, including the promotion of tissue regeneration, stimulation of cellular proliferation and differentiation, facilitation of degranulation, and augmentation of chemotaxis (65)–(80). Moreover, PRP exhibits antimicrobial properties, further contributing to its beneficial effects on wound healing. The combined action of growth factors and antimicrobial actions of PRP creates an optimal environment for tissue repair and regeneration. Comparative studies have demonstrated that platelet products, such as PRP, yield superior healing outcomes and are better accepted by patients when compared to standard saline dressings, which have traditionally been used as the conventional therapy for non-healing Diabetic Foot Ulcers (DFUs) (81).

3.7. Stem Cells

Stem cell therapy has emerged as a promising approach for the treatment of DFUs, garnering significant interest in recent years. Studies investigating different modalities of stem cell therapy have

shown positive healing outcomes in humans. One approach involves the utilization of autologous micro-fragmented adipose tissue injections. This technique utilizes adipose tissue derived from the patient's own body, which is processed to obtain a concentrated population of adipose-derived stem cells. These micro-fragmented adipose tissue injections have demonstrated promising results in promoting wound healing and tissue regeneration (82).Additionally, combination treatments utilizing mesenchymal stem cells (MSCs) derived from the umbilical cord have also shown positive outcomes in DFU management (83). MSCs possess unique regenerative properties and can differentiate into various cell types involved in tissue repair. These characteristics make them an attractive therapeutic option for promoting wound healing and improving clinical outcomes. Recent meta-analyses of randomized controlled trials investigating autologous stem cell therapy for DFUs have reported lower amputation rates and improved wound healing, further supporting the potential of stem cellbased interventions in the management of DFUs.

4. Diagnostic Measures

4.1. Biomarkers

The assessment of diabetic foot ulcer (DFU) healing progress and prognosis relies on the identification of biomarkers. Various specimens, including tissue biopsies, blood samples, and wound exudate fluid, can be utilized for studying DFU biomarkers. Inflammatory biomarkers have been associated with the onset of osteomyelitis in certain studies (84), as well as the monitoring of therapeutic response (85). Additional studies have demonstrated that procalcitonin serves as a predictor for DFU severity, the development of osteomyelitis, and the risk of amputation (86)-(87). However, the reliance on experienced nuclear physicians for prediction analysis poses a limitation, as their expertise can vary significantly depending on the extent of their training (88).

4.2. Biosensors and Imaging

Recent advancements in guidelines pertaining to the prevention of Diabetic Foot Ulcers (DFU) have emphasized the significance of regular monitoring of foot skin temperature. This practice is employed to identify early signs of inflammation and facilitate prompt intervention measures to avert the development of ulcers (89). In addition to its preventive capabilities, thermal monitoring has exhibited considerable efficacy in accurately predicting the healing progress of DFU wounds. Ongoing scientific investigations are actively exploring innovative approaches, such as the integration of sensors into dressings, to furnish real-time feedback regarding both wound temperature and pH levels. These advancements aim to enhance the overall monitoring and management of DFU, providing valuable insights into the wound healing process (90).

5. Conclusions

Although substantial progress has been made in comprehending the underlying mechanisms of diabetic wound healing, several gaps persist in our clinical comprehension of diabetic wound management. Enhanced awareness of the diverse aspects of wound conditions holds the potential to facilitate expedited, simplified, and cost-effective diagnostic procedures. The application of intelligent wound dressings, hydrogels, and other cutting-edge technologies presents an opportunity for enabling personalized care and treatment for individuals with diabetic wounds. Vigilant surveillance and timely interventions employing these advanced technologies possess the potential to avert the progression of non-healing wounds, even in cases where patients fail to grasp the gravity of their wound conditions. Given the escalating population of individuals afflicted with diabetes, the significance of effectively managing chronic wounds is on the rise. Consequently, additional research efforts are imperative to expedite the healing process of diabetic wounds and optimize the resulting outcomes.

CONFLICT OF INTEREST

Authors declare by stating that they have no conflict of interest.

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