Current Understanding of The Mechanisms Underlying Diabetic Wounds

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Abstract:

Diabetic wounds, a severe consequence among diabetic patients, significantly contribute to disability and mortality. A significant part of this work on the pathophysiology of diabetic wound healing has mostly focused on processes driven by chronic inflammation, hyperglycaemia and dysfunctions in microcirculation. As per the recent research, defensins could have an important part in the initiation and maintenance of diabetic wound healing. Chronic, non-healing process, particularly in the lower limbs, are the result of diabetes's obstruction of various stages of the wound healing. Diabetes-related hyperglycemia disrupts the regular operation of vital cells such fibroblasts, keratinocytes and endothelial cells that participate in the healing of serious wounds. Mononeuropathy, commonly seen in diabetic individuals, impairs diabetic wound healing by reducing pain sensitivity, making injuries go unnoticed and worsening progressively. Diabetic wounds are also more risk of infection due to a weakened immune response, further delaying healing and increasing the risk of severe complications like amputation or gangrene. Recent study into the molecular and cellular processes of diabetic wound healing has led to the development of new treatment approaches, including stem cell therapy, growth factors and bioengineered skin substitutes to promote tissue regeneration. In addition, advanced treatments like nanotechnology and gene therapy offer targeted interventions for better healing outcomes. Managing diabetic wounds functionally requires a comprehensive strategy involving glucose control, infection management, and modern wound care practices. Ongoing study is very crucial for discovering innovative therapies that improve the standard of care and patient outcomes in diabetes.

Keywords: Diabetic Wound, Pathophysiology, Hyperglycaemia, Fibroblasts, Keratinocytes, Gene Therapies, Nanotechnology.

1. Introduction:

Diabetes mellitus is a group of conditions that affect metabolism by chronic high blood sugar, resulting from either insufficient insulin production or the body's inability to use insulin successfully. Gradually, it can lead to complications like neuropathy, retinopathy, kidney damage, cardiovascular issues, and diabetic foot ulcers [1]. Diabetic wounds are especially prevalent and tough to treat, often becoming severe and life-threatening if not managed punctually. Diabetes is the major chronic metabolic disorder in many countries, with its frequency rising due to lifestyle factors such as minimize

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physical activity, increased obesity high blood pressure, high cholesterol, genetics, and aging [2]. The healing procedure is significantly impaired in diabetic patients, as elevated blood sugar levels harm blood vessels and nerves, slowing down the healing of wounds and enhance the risk of infections and other complications [3]. A significant trouble is neuropathy, characterized by nerve deteriorates that may result in diminished sensation in the wound of feet. This complicates the detection and supervision of small injuries. Moreover, vascular dysfunction might impede blood circulation, hindering the movements of nutrients and oxygen to the impacted region, thereby prolonging the wound healing process. Diabetic sores, especially on the feet, can progress chronic and, if inadequately handled, may outcome in amputation [4]. Individuals with diabetes must emphasize foot care to avert injury and consequences. Routine examinations, diligent foot assessments, and the use of suitable footwear are essential procedures for preventing complications. Effective diabetes control, which entails sustaining blood glucose levels within a designated range, is essential for facilitating wound healing. Collaboration with healthcare experts to design a specific treatment plan is crucial for optimal care. Over the past 30 years, the World Health Organization (WHO) has noted a significant increase in the prevalence of type 2 diabetes in countries with different income levels [5]. Juvenile or insulin-dependent diabetes, type 1 diabetes is a chronic condition brought on by the pancreas' inability to produce insulin. For people with diabetes to survive, treatment—especially insulin—must be easily accessible and reasonably priced. By 2025, the global goal is to stop the rise in diabetes and obesity. About 422 million people worldwide suffer with diabetes, primarily in very low- and poor middle-income countries. An approximately population of 1.5 million die from diabetes every year, and both its incidence and prevalence have steadily increased in recent decades from Figure 1 [6].

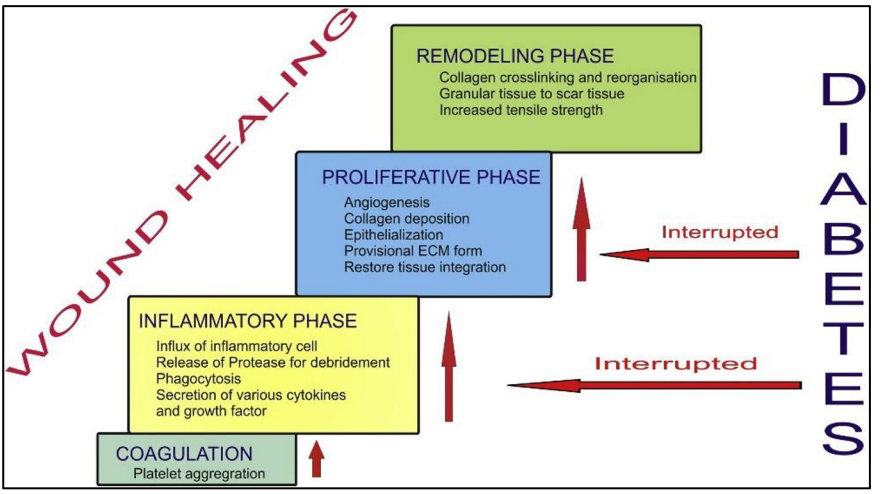

Figure 1: Disruption of the typical healing process of wounds in diabetics [1]

1.1. **Hyperglycemia:** Hyperglycemia hinders wound healing and encourages the development in individuals with diabetes mellitus (DM) of diabetic foot ulcers (DFUs) through a number of factors, including as peripheral neuropathy, skin cell dysfunction, and atherosclerosis. Research mostly focuses on the detrimental impact of hyperglycemia on the onset and diabetic foot ulcer (DFUs) development, even if hypoglycemia is associated with vascular problems in diabetes [7]. By decreasing blood

flow and impeding the supply of nutrients to wounds, hyperglycemia speeds up atherosclerosis and prevents healing. Through pressure-induced vasodilation, a skin defense mechanism, it has also been shown to impair the endothelial cell activity, which is essential for diabetic foot ulcer healing. In addition to affecting endothelial cells, hyperglycemia interferes with vital re-epithelialization activities like synthesis of protein, keratinocyte, proliferation and fibroblast migration. Many keratinocyte proteins involved in re-epithelialization, such as cytoskeletal proteins keratin (K2, K6, K10) and the laminin-5 α3 chain precursor protein (LM-3A32), are synthesized less frequently in people with diabetic foot ulcers. Re-epithelialization is hampered by a decrease in LM-3A32 because it affects keratinocyte survival and differentiation [8].

Because glutathione peroxidase and superoxide dismutase, two antioxidant enzymes, are less active when blood sugar levels are high, free radical damage results, which hinders the healing of wounds. This could help explain why elevated levels of the receptors for advanced glycation end products (AGEs), which are markers of skin aging, are associated with persistent hyperglycemia. Additionally, through a variety of mechanisms, including as the hexosamine, polyol, protein kinase C, and the pathways leading to advanced glycation end products (AGE), hyperglycemia increases the production of reactive oxygen species (ROS). In the early phases of wound healing, reactive oxygen species are essential but, in later stages, excessive ROS generation may be harmful. Increased levels of reactive oxygen species (ROS) jeopardize peripheral nerve structural integrity, metabolic processes, and vascular supply, which may result in malfunctions in sensory, motor, and autonomic functions. The probability of getting a diabetic foot ulcer (DFU) is considerably grow by each of these deficits. Simultaneously, elevated blood glucose levels impede wound healing by improving the skin's vulnerability to injury and infection [9].

1.2. Neuropathy: In addition to raising the chance of developing diabetic foot ulcers (DFUs), sensory, motor, and autonomic neuropathy also significantly hinder DFU recovery. Skin that is dry and damaged is the result of autonomic neuropathy, which reduces sweat gland function. This improves the risk of infection and pruritus, which both hinder the relieve of wounds [10]. Although the exact cause is uncertain, pruritus is linked to diabetic neuropathy. At the same time, motor neuropathy increases pressure on the foot's plantar region, resulting in tissue ischemia and necrosis. Decreased neural density and delayed healing are characteristics of neuropathic skin. In addition to controlling blood sugar, people can prevention dry skin and itching by avoiding by hot water and using moisturizers, especially those without colouring or fragrances. The use of antibiotics for infections, debridement, and wound irrigation are further therapies to improve wound healing in individuals with diabetes and neuropathy. According to recent research, the development of diabetic neuropathy may be influenced by hyperlipidemia, particularly hypertriglyceridemia [11]. This implies that drugs that reduce cholesterol may be able to avoid or even undo nerve fibres damage. Since current neuropathy therapies mostly focus on reducing foot pressure and addressing pruritus, this approach is not frequently used. In diabetics, neuropathy mostly affects neurons that depend on nerve growth factor (NGF), and exogenous NGF therapy has shown promise. It has been demonstrated to improve keratinocyte turnover, leukocyte chemotaxis, wound contraction, and, in certain cases, lead to clinically improved healing [12]. Some other micro-vascular complications related in wound healing are:

1.2.1. Hypoxia: People with diabetes mellitus (DM) frequently develop diabetic foot ulcers (DFUs) in hypoxic environments due to poor circulation. Different skin cell types have distinct gene expression profiles under these circumstances. According to a cell culture study keratinocytes and dermal fibroblasts showed alterations in gene expression related to cellular metabolism proteins, while endothelial cells and differentiated macrophages increased the expression of genes associated with angiogenesis, cytokines, and growth factors. Recent research using flow-mediated skin fluorescence to evaluate skin hypoxia have shown that less oxygen levels in diabetic foot ulcers (DFUs) are associated with poorer healing results and a higher risk of complications. To address these hypoxic conditions, hyperbaric oxygen remedy has become a popular treatment for DFUs. However, despite its ordinary use, research is ongoing to better understand the exact mechanisms through which hyperbaric oxygen therapy influences gene expression in diabetic foot ulcers (DFUs) [13].

1.2.2. Anemia: Latest studies have emphasized the high occurrence of anemia in individuals with diabetes mellitus (DM), mostly among those with diabetic foot ulcers (DFUs) [14]. Although, there is still debate regarding the relationship between anemia and the outcome of diabetic foot ulcers. According to a meta-analysis, higher anemia severity was associate to higher DFU severity and could predict higher amputation and life threatening. According to retrospective cohort studies, anemia is actively associated with higher death rates, more severe infections, larger and deeper ulcers, and grown risk of amputation [15]. Anaemia was also linked to slow wound healing, higher sever rates, and worse mortality in observational studies conducted in Nigeria. On the other hand, anemia has been shown in a number of studies to be a negligible predictor of clinical outcomes in patients with diabetic foot ulcers (DFU) [16]. Further research is necessary to clarify the equivocal importance of anemia as a factor that predicts the healing of diabetic foot ulcers.

1.2.3. pH and Microbiome: According to one study, diabetics' intertriginous areas had a slightly higher skin pH, even though intact skin has a pH of frequently did not differ significantly between diabetics and non-diabetics. Diabetic foot ulcers (DFUs) have a wound environment that is greater alkalinity compared to acute wounds, which affects the intricate relationships between the microbiota and the host. Experiments with many bacterial species, including Pseudomonas, revealed that alkaline pH conditions promote biofilm development [17]. Moreover, pH has been demonstrated to affect bacterial resistance to antibiotics. Given that antibiotic resistance testing is usually performed at physiological pH, the modified bacterial sensitivity under the atypically alkaline conditions of diabetic foot ulcers must be meticulously evaluated when prescribing therapies for infected wounds [18].

1.2.4. In Chronic Wounds, Inflammation and Immune System Deficiencies: The acute wound healing measure involves four overlapping stages like hemostasis, inflammation, proliferation, and remodeling. In individuals with diabetes, chronic wounds such as diabetic foot ulcers (DFUs) occur due to abnormalities in these stages. DFUs differ from critical wounds by having a prolonged inflammatory phase, with an accumulation in the wound bed, macrophages and neutrophils. Proinflammatory cytokines like TNF-α, IL-1, IL-6, and C-reactive protein further provoke the chronic inflammation and bacterial growth also hinders healing [19]. A crucial challenge in diabetic foot ulcers (DFUs) is persistent hypoxia, which is aggravated by poor

angiogenesis and ongoing inflammation, leading to an increase in reactive oxygen species (ROS) that hinder healing. Furthermore, the downregulation of development factor like TGF-β reduces collagen synthesis and fibroblast proliferation. The overexpression of TNF-α and reduce TGF-β1 levels lead to elevated IL-10, decrease collagen formation, and worsened tissue damage [20]. Research suggested that the p38 MAPK signaling pathway may stop DFUs from progressing to the proliferative phase, worsening the inflammatory reciprocation. A key factor in this is minimize expression of MALAT1, a long non-coding RNA that affects angiogenesis by lowering VEGF levels and improve inflammation. Restoring MALAT1 expression in diabetic models has shown development in wound healing by enhancing fibroblast activity. Macrophage dysfunction also plays a hypercritical role in chronic inflammation, as they fail to transition properly from the pro-inflammatory M1 phenotype to the healing M2 phenotype. Additionally, impaired neutrophil function and altered cytokine production contribute to the severity of DFUs, with higher neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) proposed as potential biomarkers for DFU severity [21,22].

2. Diagnostic Measures Biomarkers:

The development of biomarkers is essential for evaluating the healing progress and prognosis of diabetic foot ulcers (DFUs). Biomarker analysis can be conducted on tissue biopsies, serum, or wound exudate, but the quality of the samples is critical for obtaining reliable results. One study noted that low-quality tissue samples from DFUs can interfere with biomarker analysis and make clinical trial design more challenging. Inflammatory markers, like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), are frequently investigated in connection with osteomyelitis linked to DFUs [23]. While some studies suggest a link between these markers and osteomyelitis or therapy response, their overall effectiveness remains debated. Procalcitonin has been proposed as a marker for DFU severity and amputation risk, but it has shown limited value in distinguishing between infected and uninfected DFUs. Additionally, ESR and CRP may be unreliable in patients with sensory neuropathy. A clinical trial using WBC-SPECT/CT for diagnosing osteomyelitis showed promise but was dependent on the expertise of nuclear physicians [24].

3. Current Treatment and Techniques for DFU Management:

Diabetic wounds are often classified as chronic due to their prolonged healing times, sometimes exceeding three months, and their deviation from normal healing processes. This leads to reduced mobility and increased treatment costs, highlighting the need for more efficient healing methods. In order to lower the risk of limb amputations, diabetic wound prevention and treatment are essential [25]. Initial evaluation typically involves a physical exam to assess the wound's size, depth, location, and tissue type, followed by a vascular assessment and infection testing. The "TIME" philosophy—focused on tissue debridement, infection management, moisture balance, and wound edge care—guides treatment. The primary goal is to promote rapid healing and prevent amputations, with key strategies including identifying at-risk individuals, offering appropriate care, and preventing recurrence. While traditional treatments such as photobiomodulation, shockwave therapy, nanomedicine, TENS, debridement, and

hyperbaric oxygen therapy are used, challenges remain in terms of healing speed, treatment progress, and preventing recurrence [26].

3.1. Wound Debridement and Dressing: Chronic diabetic foot ulcers (DFUs) often contain nonviable tissue at their edges, which hinders the healing process. For optimal healing, the wound bed needs to be moist, well-vascularized, free of nonviable tissue, and infection-free. In order to treat cellular and molecular abnormalities and get the bed ready for reepithelialization, wound debridement is crucial [27]. This process removes necrotic, fibrous, senescent, and nonviable tissue, including biofilm, which can block healing by harboring bacterial or fungal colonies resistant to treatments. Biofilm forms when microorganisms adhere to the wound surface and produce a protective matrix. New debridement methods aim to eliminate biofilms using topical treatments, negative pressure therapy, and ultrasound. Low-frequency ultrasound is effective for cleaning wounds but may require multiple sessions for diabetic ulcers [28]. Various debridement methods, such as hydrotherapy, enzymatic, and sharp surgical techniques, help accelerate healing by removing dead tissue while preserving healthy tissue. Larval therapy has also been used successfully, though it can cause local irritation and discomfort [29].

3.2. Transcutaneous Electrical Nerve Stimulation: One non-invasive treatment option is transcutaneous electrical nerve stimulation (TENS) that applies electrical stimulation to promote healing in chronic wounds. Clinical and animal studies have demonstrated TENS's effectiveness in enhancing local blood circulation and increasing wound temperature, which aids healing. TENS supports wound epithelialization, contraction, and angiogenesis, and boosts phagocytosis, growth factor expression, and fibroblast migration [30]. It also promotes protein synthesis by fibroblasts, reduces edema, and improves vascular perfusion at the wound site. The optimal frequency for healing is 2 Hz, with treatment typically lasting 15 minutes per day for five days. Studies have demonstrated that TENS raises important growth factors such as platelet-derived growth factor-A (PDGF-A), fibroblast growth factor-2 (FGF-2), and epidermal growth factor (EGF). By blocking proinflammatory cytokines like IL-1β, TNF-α, and IL-6, it also has anti-inflammatory effects. However, TENS's use is limited by the need for specific stimulation parameters, making it less suitable for managing large wounds [31].

3.3. Nanomedicine: Nanoparticle (NP) technology has shown promising potential for treating chronic diabetic wounds. By delivering both bioactive components, such as growth factor, peptides, cytokines, nonbioactive materials and stem cells, like oxygen and metal ions, nanoparticles support the healing system [32]. Current advancements in nanoparticle-based matrices have demonstrated their effectiveness in encourage wound healing by stimulating cell regeneration, improving angiogenesis, enhancing collagen formation and modulating inflammation. Nanoparticles, due to their little size and distinctive properties, are particularly beneficial for chronic diabetic wounds. They enhance drug delivery openly to the wound area, minimize side effects, and enable controlled release, resulting in more effective healing than conventional cure [33].

Nanotechnology allows for targeted medication transportation, enhancing drug stability and minimizing side effects. Different nanoparticles, such as gold, silver, chitosan, and

curcumin, have been thoroughly studied for their potential in healing diabetic wounds. For instance, microspheres containing recombinant human epidermal growth factor (rhEGF) and thermosensitive hydrogels with curcumin have shown promising results in accelerating wound healing. Furthermore, a combination of L-carnosine and curcumin has been effective in reducing infections in diabetic ulcers [34]. The antibacterial properties of nanoparticles, especially gold and silver, further help lower infection possibilities. However, challenges remain in the widespread use of nanotechnology, together with inconsistencies in preparation methods, the absence of clear biosafety guidelines, and unresolved issues applied to nanoparticle biocompatibility, biodegradability, and controlled drug release. Addressing these issues is pivotal to fully harness the potential of nanoparticles in chronic wound healing [35].

3.4. Shockwave Therapy (SWT): Advance research suggests that extracorporeal shock wave therapy (ESWT) can significantly enhance soft tissue healing and is effective in treating diabetic foot ulcers (DFUs). ESWT has proven to be both effective and safe for control chronic wounds in both short-term and long-term use. In research with 67 patients who received six treatments consisting of 500 shocks at 4 Hz and 0.11 mJ/mm^2 energy flux density, positive outcomes were observed in the therapy of both diabetic and non-diabetic foot ulcers, although the benefits decreased over time [36]. ESWT was found to raise macrophage function, increasing extracellular signal-regulated kinase (ERK) activity, which is very important for wound healing [37]. While current study does not fully support the routine use of shock wave therapy in wound healing, it has shown promise for individuals with chronic DFUs lasting 30 days or more. Main side effects include bruising, pain, nausea, and infections, highlighting the need for further investigation into the causes of diabetic wounds to optimize therapeutic effectiveness [38].

3.5. Hyperbaric Oxygen Therapy and Topical Oxygen Therapy: Neuronal injury, tissue hypoxia, and reduced microcapillary perfusion are common and main issues in diabetes mellitus (DM). Hyperbaric oxygen therapy (HBOT), known for over 20 years for its ability to boost tissue oxygenation, has proven effective in treating chronic diabetic foot ulcers (DFUs). HBOT reduces edema, enhances fibroblast proliferation, stimulates collagen synthesis, improves tissue perfusion, alleviates hypoxia, modifies inflammatory cytokines, and promotes neoangiogenesis [39]. It has shown advantage in wound healing and lowering amputation risk, and may enhance survival in diabetics with DFUs. Moreover, its use is limited due to insufficient scientific confirmation supporting its safety and effectiveness. Likewise, topical oxygen therapy (TOT), once overlooked due to lack of empirical support, has been shown to significantly enhance oxygen levels in the wound bed, speeding up healing. TOT uses pressurized or continuous diffusion devices to deliver oxygen and must be merge with proper wound care. It may be an alternative treatment for some diabetic DFUs, but not all wounds will respond to it [40].

3.6. Photo biomodulation (PBM): Technological advancements in photonics and biophotonics have enabled the effective use of light in treating diabetic foot ulcers (DFUs). In diabetic patients, photobiomodulation (PBM), formerly known as low-level laser therapy (LLLT), has been demonstrated to accelerate wound healing. Mester made the initial discovery of PBM in 1968 after noticing that mice's hair growth was stimulated by low-power laser light [41]. Since then, in vitro and in vivo research has

made use of lasers, light-emitting diodes (LEDs), and broadband light to treat chronic wounds. PBM is an effective therapy for DFUs, offering benefits like infection reduction, pain relief and enhanced standard of living for individuals with diabetes. The treatment works by using light energy to activate atoms and molecules within cells without causing a significant temperature increase. PBM promotes angiogenesis, aids in extracellular matrix (ECM) formation, and helps regulate the inflammatory phase of healing. Factors like energy density, wavelength, and application duration determine the treatment's effectiveness [42]. Red light penetrates deeper than other colors, while infrared and near-infrared light penetrate even further. Studies have shown that LED-based PBM encourages angiogenesis and early-stage wound healing, with no reported negative side effects. However, further investigation is required to ascertain the ideal dosage and comprehend PBM's full effects at the tissue, cellular, and molecular levels.

4. Conclusion

Over the past few years, research in the area of diabetic wound care has grown exponentially. Diabetes frequently causes impaired wound healing, which can have disastrous effects on those who suffer from the disease. Several studies have revealed that a number of variables contribute to poor healing in diabetes. Significant progress has been achieved in managing wound healing in diabetes using a variety of novel therapeutic techniques and products. With differing degrees of success, various natural products have been tried, including growth factor, dual growth factor, cytokine modulators, anti-inflammatory drugs, MMP inhibitors, angiogenesis stimulators, extracellular matrix stimulators, stem cells, and others. Conventional methodologies have been surpassed by recent studies that use a combinational strategy. It gives researchers hope that they will learn the fundamentals and experience the latest developments in the outline of innovative carriers. Future research on the treatment of impaired wounds may focus heavily on combination treatments. Consequently, it helps diabetic wounds recover faster. To identify distinct agents that may work at different stages of diabetic wound healing, extensive investigation is required. Improving clinical techniques and systems can help determine the degree of healing.

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