Journal of Applied Pharmaceutical Research
Volume 13 Issue 1, Year of Publication 2025, Page 1 – 13
DOI: https://doi.org/10.69857/joapr.v13i1.812

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Review Article

JOURNAL OF APPLIED PHARMACEUTICAL RESEARCH | JOAPR
www.japtronline.com ***ISSN: 2348 – 0335***

NEW INFORMATION ON THE ETIOLOGY AND BIOLOGICAL TARGETS OF WOUNDS ASSOCIATED WITH DIABETES

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Article Information
Received: 13th November 2024
Revised: 17th January 2025
Accepted: 5th February 2025
Published: 28th February 2025

Keywords
Wound healing, Diabetes, Pathological changes, Molecular targets, Inflammation.

ABSTRACT
Background: Wound healing is a complex process that advances through inflammation, proliferation, and remodelling phases. Diabetes precipitates numerous ailments that obstruct practically all of these reparative processes. **Methodology:** We performed a literature search on ScienceDirect and PubMed databases using various keywords, including "Diabetes Wound Healing." The search was refined by applying relevant filters to obtain the most pertinent articles for this review article's objective. **Results:** Patients with diabetes may incur wounds during or after medical interventions. The wound healing process comprises remodelling, proliferation, and inflammation. Diabetes impedes nearly all of these healing processes through various pathological changes. This study primarily examines the molecular pathways of inflammatory substances, including growth stimulants and other factors that hinder wound healing. It also examines molecular targets and the current advancements in wound care and complete healing. **Conclusion:** Based on our investigation, we identified several practical approaches for treating wound inflammation and proposed that combining these strategies may yield the most significant results in our research domain.

INTRODUCTION

Diabetes is still a major issue, according to recent studies on its occurrence and impact. The number of Americans diagnosed with diabetes in 2018 was 34.2 million, with an additional 88 million with prediabetes. Consequently, the CDC estimates that healthcare costs amounted to $237 billion [1]. As many as a quarter of all diabetics will develop foot ulcers or another type of diabetic lesion [2]. At least one-third of the whole budget goes toward treating these wounds, which can be quite expensive due to diabetes and associated complications [3]. Diabetes is associated with several pathological changes that impair wound healing. Poor blood circulation and damage to the vasculature are consequences of chronic hyperglycemia. Diabetics may have trouble identifying things because of neuropathy and peripheral vascular dysfunction. In diabetic wounds, there is swelling, a lower number of new blood vessels, problems with the migration of keratinocytes, and a slower growth of fibroblasts [4]. Infection, wound dehiscence, and chronic, nonhealing wounds are among the complications that can arise in diabetic individuals' wounds due to these changes.

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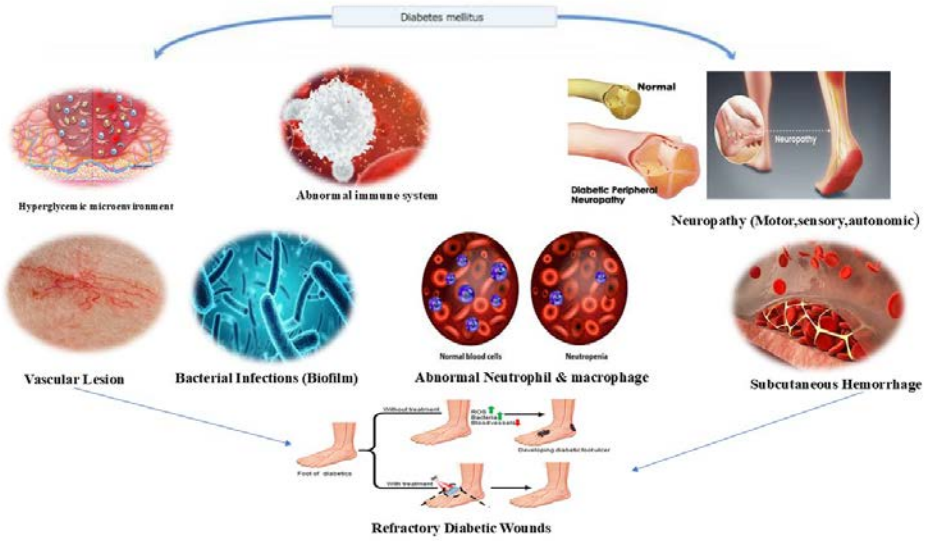

Figure 1: Normal wound healing is disturbed

Effects of Diabetes on Healing

Complex wounds heal in three steps: contraction, proliferation, and inflammation. That and remodelling typically occur. Blood clots and immune cell infiltration characterise inflammation. Strong angiogenesis and reepithelialisation characterise proliferation [5]. Late proliferation, scarring, wound maturation, and remodelling occur [6]. Diabetes blocks most of these healing pathways.

Diabetes-related wound inflammation

Diabetic wounds have a more extended inflammatory stage than nondiabetic wounds. This proinflammatory state may slow healing and cause persistent wounds [7]. M1 macrophages are phagocytic and proinflammatory during wound healing. In diabetic wounds, macrophages generate too many inflammatory cytokines [9]. However, anti-inflammatory, angiogenesis-promoting, and ECM-producing M2 macrophages replace them. Diabetic wounds have more inflammatory macrophages than anti-inflammatory ones [8]. Neutrophils release inflammatory mediators, free radicals that increase oxidative stress, and cytotoxic enzymes. Oxidative stress slows pathological healing and damages tissue in diabetic wounds [10].

Neutrophils that hunt bacteria overproduce neutrophil extracellular traps (NETs). Diabetic wounds increase NET production, causing inflammation and slowing recovery. Another molecular change that increases wound inflammation in diabetes is miRNA. Diabetics and non-diabetics showed equal healing miRNA levels in healthy skin. MiRNA expression changed after the wound, suggesting it may be involved in inflammation that isn't acting effectively. Epigenetics and transcription factors. Diabetes wounds have harmful inflammation and dysregulation. Many studies on humans and animals show that chronic inflammation slows diabetic wound healing. Long-term inflammation delays healing, increasing chronic wound risk.

Increasing healing-promoting growth factors and reducing inflammation in diabetic mice enhanced wound healing. [14]. Additionally, research links it to abnormal hypertrophic and keloid scars [11–13]. Diabetics must reduce inflammation during healing to avoid scarring. Most wound healing occurs during proliferation when blood flow is restored [15]. Angiogenic and antiangiogenic factors like VEGF, PEDF, and angiogenesis-1 keep the vasculature in healthy skin steady. When blood oxygen levels drop too low after an injury, the body produces more angiogenic factors and fewer antiangiogenic ones. Inadequate angiogenesis, which can take numerous forms, is a significant cause of wound healing failure. Vascular maturation and pruning in diabetic wounds require platelet-derived growth factor (PDGF) later in wound remodeling. Because macrophages produce few proangiogenic factors, diabetic wounds may initially lack them. Capillary maturation factors are downregulated, while antiangiogenic factors are upregulated.

Additional variables include matrix metalloproteinases and miRNAs, which limit angiogenesis [16]. Damage to vascular

maturation factors slows wound healing. This stabilizes the newly created capillary bed. Lack of maturation factors slows wound healing and increases the risk of chronicity [5]. Diabetes vascular alterations and oxygen deprivation limit leukocyte migration into the wound, increasing infection risk [17].

Diabetes injury scar tissue

Scarring, maturation, and remodeling are natural wound-healing processes. Scarring results from wound contracture and collagen degradation. Fibroblasts secrete scar collagen and ECM. Collagen fiber density and the lack of hair follicles and sebaceous glands show that a skin scar is new and not from the original tissue [18]. Medical research shows that diabetes wounds heal with physically different scars and produce less collagen. A scar with less contractile strength and more collagen can't mend adequately due to its lower tensile strength [19]. Fibroblasts, senescent cells that cannot divide, may slow diabetic wound healing. When diabetic wound contraction is insufficient, granulation and reepithelialization speed healing. The diabetes scar matrix cannot withstand shear and tensile pressures [20].

After Surgery: Diabetes and Wound Healing Recovery Issues

As previously indicated, diabetes increases the risk of wound infections, dehiscence, and scarring. Diabetics encounter in most surgical subspecialties; surgical site infection is more common than postoperative glucose increase. Diabetes raises infection risk via more channels than hyperglycemia [21]. Obesity and other common comorbidities increase the risk of superficial and deep incisional surgical infections [22]. Diabetes patients undergoing abdominal panniculectomies are at risk for wound dehiscence, infections, readmission, sepsis, and extended hospital stays. Diabetics who use mesh reinforcing for abdominal wall repairs are more likely to get infections [23]. Diabetes can slow down the healing of breast reconstruction because it can cause ischemia, dehiscence, nipple-areolar complex cesses, and faster flap necrosis [24]. Diabetes can cause surgical site infections in cosmetic breast surgery [25]. Patients with diabetes are getting implants. More problems occur with mastopexy [26]. In another trial of breast, body, and face cosmetic treatments, diabetes increased the risk. The same study indicated that torso treatments caused more wound issues than face or breast surgeries. Diabetes wounds look different, but the reason is unknown [27]. Diabetes patients who have hand surgery are more prone to developing infections, stiffness, and poor wound healing [28]. The trigger finger and carpal tunnel openings show this, but the latter is less evident [29–31]. Diabetics had lengthier hospital stays and infections after face fractures [32].

Diabetes-related injuries and health

Nutrition strongly influences surgical wound healing and infection risk in type 2 diabetes [33]. The subjective global nutritional status rating predicts worse wounds in poorly treated wounds. We use the Wagner grading to assess the severity of diabetic ulcers. [34]. The anabolic stage of wound healing requires a better diet. To catabolize wound healing, anabolic hormones increase insulin resistance and reduce diabetes [35]. Diabetes metabolic problems include protein loss, hyperglycaemia, a negative nitrogen balance, increased resting energy demand, and malnutrition risk. Diabetics with wounds, fat breakdown, and microalbuminuria lose more protein and lean body mass than those without wounds. These approaches show diabetic wound regeneration requires more nourishment than regular wound healing. To improve diabetic patients' nutritional status, analyse lean body mass loss, identify macro- and micronutrient deficits, and create a diet that meets these needs. In wounds not caused by diabetes, whey protein supplementation restores cytokine levels, aiding cutaneous wound healing [36].

Diabetes begins with weakened skin, resulting in poor wound healing. Collagen is one of two unaffected features of diabetic skin. Advanced glycation end products (AGEs) cause oxidative stress, ageing, and skin stiffness, and they build up faster in diabetic skin [37]. Diabetes patients are less likely to recover from wounds due to these skin abnormalities. Wounds enhanced dietary AGEs' negative effects in diabetic mice models, causing persistent inflammation and delayed healing [38]. Diabetes patients must minimise AGE-rich foods while healing wounds since they naturally create more. Diabetes patients with injuries must reduce meat and fatty food intake and avoid frying, grilling, and roasting to reduce AGE intake [39].

Mechanistic comprehension

Diabetes' slow healing process may cause a wound that won't heal, in addition to psychological suffering and despair. This can cause septicemia, gangrene, osteomyelitis, cellulitis, and walking problems. Diabetics decreased wound healing is well established, but the disease's cause remains unknown. Only

coordinated biochemical mediators activated by inflammatory cells and pathways can restore health. Cellular and metabolic alterations have been associated with diabetic wound healing failure. Wound healing involves many cell types. These include endothelium, B, T, fibroblast, monocyte, macrophage, and keratinocyte. These cells produce and regulate growth factors and cytokines. As monocytes grow into macrophages, they secrete pro-inflammatory cytokines such as IL-1β2, TNF-α3, IL-64, IGF-16, and TGF-β7. Diabetes sufferers and non-diabetics may relate. This crucial stage produces neutrophils, T cells, B cells, keratinocytes, fibroblasts, IL-10, mast cells, and endothelial cells. These cells participate in producing TGF-β, IGF-1, and VEFG [40]. Macrophages help healing. Oxidative stress and hyperglycemia alter epigenetics, affecting macrophage polarisation and control. Dysregulated macrophage polarisation may delay wound healing [41-42].

Diabetes inhibits wound healing due to a complex chemical process, according to research. Studies show that diabetes in animal models decreases growth factor synthesis, keratinocyte and fibroblast migration and proliferation, neutrophil and macrophage activity, and other wound healing processes. People with diabetes also have trouble healing because their blood vessels are narrow, their metabolism is off, their oxygen levels are low because of changes in the red blood cell membrane and haemoglobin glycation, and their internal systems don't work right [45]. Blood vessel constriction limits wound oxygenation, causing hypoxia. Second, haemoglobin glycation causes nutritional and oxygen deficits, which hinder healing. UPR8 drives endoplasmic reticulum unfolded protein accumulation in response to hypoxia or glucose scarcity. After skin or tissue injury, this UPR produces inflammatory mediators and activates them. DWs produced greater pro-inflammatory chemokines and exhibited prolonged UPR activation [46]. Diabetic microvascular problems produce local ischemia, which slows wound healing. MiRNAs9, a family of non-coding RNAs with 19–24 nucleotides, are involved in various physiological processes. Scientists have linked miRNA alterations to many illnesses and poor wound healing [47].

When oxygen levels are low, MiR-210 targets E2f3 to limit keratinocyte growth during wound healing [48]. By targeting globin transcription factor 2 and VEGFR210, MiR-200b reduces angiogenesis [49]. MiRNAs influence angiogenesis, re-epithelialization, fibroblast migration, keratinocyte migration, inflammation, and epithelization in diabetic wounds [50-51]. There were higher levels of matrix metalloproteinase-9 in the serum [52], fewer nerves in the epidermis, a poor barrier function, changes in the expression of neuropeptides in the skin, less inflammation, collagen buildup, and changes in the ratio of different types of collagens [53-55].

Free radicals, oxidative stress, and chemical signaling process

Charts 1 and 2 show essential evidence that has developed in recent decades, aiding several processes. When PKC pathways are blocked, hyperfiltration happens, and AGEs are made. These AGEs cause neuropathy through the Maillard reaction, polyol, hexosamine, diacylglycerol pathways, and nitric oxide. Oxidative stress and mitochondrial reactive oxygen species production accelerate these processes [56]. Oxidative stress worsens diabetes and wound healing. The transcription factor NRF212 controls cell motility, apoptosis, proliferation, differentiation, and oxidative stress adaptation [57].

High hyperglycemia and oxidative stress activate NRF2, facilitating damage repair. In a study by Long et al., turning on NRF2 through indirect and direct methods lowered oxidative stress caused by diabetes. It changed gene expression for TGF-β, cell migration, and proliferation [58]. Diabetes is associated with the expression of the stress-inducible gene ATF-313 and metabolic and B-cell dysfunction [59]. The irregular pro-inflammatory response activates ATF-3 and iNOS, causing oxidative stress and slowing healing. Badr et al. showed that improper cellular differentiation and remodelling hinder healing [60]. Caspase-3, -8, and -9 activity, free radical levels, ATF-3, and iNOS expression are abnormally upregulated. The body heals with HβD 1, 2, and 3 and proinflammatory cytokines like MIP1α14, MIP-215, and KC16. These cytokines kill germs and cause leukocytokines to build up.

Neutrophils, monocytes, macrophages, and dendritic cells transform into leukocytes. Research shows that soluble and membrane-bound CX3CL117 attract fibroblasts and macrophages [34–36]. It's too bad that Badr et al. found that losing MIP1, MIP-2, and CX3CL1 lowers STAT318 levels, AKT/PKB, and NF-κB activation. Lower amounts of HβD 1, 2, and 3 were observed. Combining these factors makes diabetic wound healing harder [61]. Diabetic peripheral neuropathy inhibits wound healing by inhibiting the autonomic nervous

system. This condition affects both sensory and motor nerves. Unfortunately, excessive protein kinase activation and aberrant nerve cell protein glycation produce nerve dysfunction and ischemia. The culprit is excessive blood sugar and oxidative stress [62]. Patients with sensory neuropathy, which reduces or eliminates pain, develop diabetic sores faster. Due to painlessness, diabetic wounds bleed more. Altering Akt/mTOR inhibits diabetic wound healing. Huang et al. developed a diabetes-induced rat model [63]. According to Lima et al., AKT, IR/IRS/PI3K, and IR/SHC/ERK are insulin-signaling pathways that aid wound healing. Turning on these pathways speeds up the healing of diabetic wounds, encourages angiogenesis, raises the production of VEGF and SDF1a tissue, and phosphorylates eNOS [64]. In wound healing, matricellular proteins link ECM proteins to cell surface receptors and interact with them, according to research.

Al-420 contributes to the matricellular protein in keratinocyte migration, angiogenesis, and reepithelialization. When AL-4 binds to integrin β1, it can start signalling SRC, ERK, AKT, and JAK1/STAT3 signalling pathways. By activating STAT3, injured tissue may suffer angiogenesis, keratinocyte NO production, and iNOS21 overexpression. Injury significantly increases AL-4 expression, which is generally low in healthy skin. Diabetes patients' diminished AL-4 expression slows healing by affecting angiogenesis and re-epithelialization [65].

Immune System Function

Healthy innate immune system control is crucial to recovery. Only innate immune responses and inflammation can start after TLRs22 activation. Diabetics' immune systems and inflammatory responses are compromised by TLRs-2 downregulation in damaged tissue. Reduced chemotactic action delays inflammatory cell recruitment [66–69]. Diabetes impairs the immune system and slows wound healing, making people more susceptible to infections. Developing biofilms in bacteria that touch the wound site contributes to diabetic wounds. Biofilm microorganisms impede healing by defending against the immune system and antibiotics. Most diabetic lesions lead to lower limb amputations [70].

Immune cells perform several activities, including inflammation. Monocytes, T lymphocytes, B lymphocytes, and mast cells are examples. Diabetics may have decreased host immunity due to cell dysregulation. High levels of pro-inflammatory cytokines like TNF-α and IL-6 in diabetes lead to insulin resistance, hyperinflammation, and disruption of the inflammatory cascade. An increase in effector T cells may cause higher TNF-α levels. The TCR-V2 range grew in diabetic wound patients while the frequency of naïve T cells decreased (Maura et al.). We have too many effector T cells [71]. Higher AGE levels can impact immunity by causing cytokine production, such as TNF-α and IL-6. Cell function disruption by AGEs may slow healing, increase immunological responses, and cause death. This may stop collagen production [72]. Angiogenic mast cells emit VEGF, TGF-1, and FGF [48]. Numerous studies show that mast cells, macrophages, endothelial cells, and fibroblasts help heal wounds. It promotes matrix remodelling, disrupting the wound's pro- and anti-angiogenic balance [73-81].

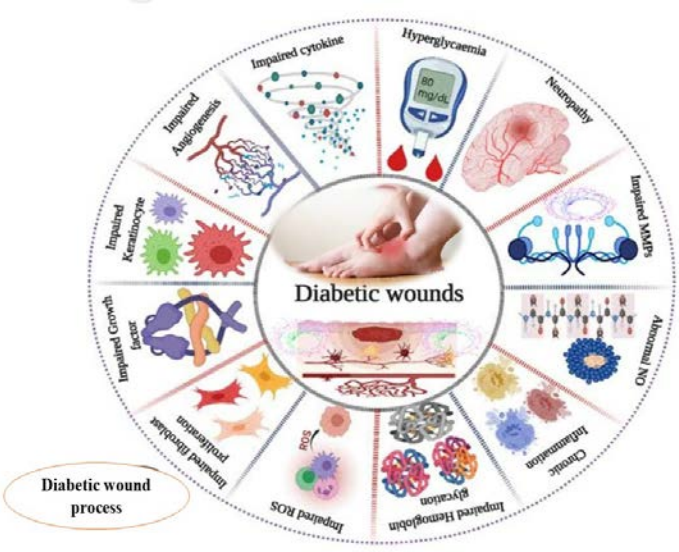

Figure 2: Causes of Diabetic Wounds

Delays in wound healing can be attributed to growth factors. Growth factors are crucial to initiate and sustain the various phases of wound healing. Figure 3 illustrates this. Several problems, like decreased expression of growth factor receptors or increased growth factor degradation, worsen wound healing in people with diabetes. Platelets release PDGF, an important serum mitogen. It encourages connective tissue growth, matrix synthesis, and cell proliferation. A key cell type in the wound area, macrophages, continue to secrete PDGF during the late inflammatory phase. PDGF's unique features attract macrophages and inflammatory cells. It aids in the partial synthesis of collagen, proteoglycans, and glycosaminoglycans.

It speeds up the healing process by encouraging fibroblast migration and proliferation, angiogenesis, the creation of a temporary extracellular matrix, and protein synthesis in the

granulation phase of tissue. A decrease in PDGF synthesis and its receptors in wounds caused by diabetes suggests that PDGF plays a role in wound healing. Numerous PDGF clinical trials have demonstrated faster recoveries. BFGF28 has an impact on many different biological processes. Among these processes are the following: migration of cells, proliferation of endothelial cells, growth and multiplication of fibroblasts, and metabolism of the extracellular matrix.

The increased rate and intensity of granulation tissue growth aids the healing process. VEGF, one of the strongest angiogenic cytokines in the skin, may significantly affect angiogenesis and vasculogenesis, the two processes that slow down wound healing the most. Capillary endothelial cells move and divide to make this process happen. Proteases break down the extracellular matrix of capillaries that were already there. Applying VEFG to diabetic wounds increases capillary density, improving circulation and metabolism.

When blood flow returns to the wounds, they heal more quickly. This transport of oxygen and nutrients enables the reparative cells to develop and function properly. Granulation tissue production relies on it and plays a crucial role in regulating wound revascularisation and permeability. The activation of the VEFG receptor-1 leads to inflammation, whereas the activation of the VEFG receptor-2 induces angiogenesis. These two receptors regulate the effects of VEGF. Diabetes impairs wound healing, and low VEGF levels in local wounds are a hallmark of the disease. Researchers have found that wounds don't heal because VEGF receptor patterns aren't working right. Low VEGF mRNA levels, high VEGFR-1, and low levels of VEGFR-2 mark these.

The process by which platelets attach to EGF receptors makes EGF, which improves cell migration, motility, angiogenesis, proliferation, and the matrix's ability to heal itself. Two peptides are required to form IGF: IGF-1 and IGF-2. IGF-1 helps wounds heal by increasing the number of keratinocytes and fibroblasts, cell granulation, and re-epithelialization.

If you have diabetes, your body may not make enough IGF-1, which can cause problems with cell granulation. A wound's affinities are controlled by its pH. Wounds in humans and animals with diabetes took longer to heal due to reduced amounts of TGF-β and IGF-1 [78, 79].

Factor β leads to transformation

Growth factors change to speed up the healing process after a wound. The inflammatory cells that tumor growth factors attract and activate include growth factors, neutrophils, macrophages, lymphocytes, keratinocytes, and fibroblasts. In addition to enhancing angiogenesis, vascularization, and ECM synthesis, these drugs decrease ECM degradation. In wound healing conditions, TGF-β levels are lower when diabetes is present. Several experiments have shown that the promoter regions of the genes that make MMP have an inhibitory element that lowers gene expression and depends on TGF-β1. More MMP expression leads to more growth factor breakdown, while fewer TGF-β levels lead to less.

The genes that bind to TGF-e and make matrix metalloproteinase (MMP) are controlled by transcription factors Smad-2, Smad-3, and Smad-4. TGF-1 enhances collagen production by activating Smad-2 and Smad-3. Decreased TGF-1 levels attract more activated inflammatory cells, which extends the repair process of DWs from the inflammatory phase to the proliferation phase. Previously, researchers believed that excessive levels of TGF-3 primarily caused low TGF-1 levels in diabetics. Collagen production decreased, and macrophage activity increased in the final analysis. Diabetics have an extended inflammatory phase and elevated reactive oxygen species due to their increased macrophage activity. Diabetic wounds heal more slowly and imperfectly due to an imbalance in the expression of these growth factors or their absence altogether [80-81]

The role of myeloprotegerins in postponed wound healing

The extracellular matrix and enzymes from the matrix metalloproteinase family, which are involved in angiogenesis, make it easier for wounds to heal, change shape, and start to form new cells. Collagens, proteoglycans, and elastin have recently been the subject of an upsurge in research due to the significance of wound healing.

According to the study, changes in growth factor synthesis, cytokines, and other molecular components primarily cause inadequate wound healing in diabetics. These abnormalities and imbalances in gene expression in all key cells make the repair process less effective. Since the inflammatory stage and chronic nonhealing wounds cannot coexist, the former typically manifests during the latter.

Numerous molecular factors and targets have radically altered wound care for diabetics. We can classify these management approaches based on the molecular targets that control their functions. PDGF, EGF, VEFG, FGF, KGF, and TGF-α are some growth factors that can directly connect with stem cells, autologous fibroblasts, or keratinocytes.

We have previously discussed the relevance and purpose of these objectives in the preceding sections. These objectives include regulating growth factors, collagen production and breakdown, matrix metalloproteinase (MMP), nitric oxide levels, and cytokines that promote or inhibit inflammation. It's still unclear what role this enzyme plays in wound healing, but it may help keratinocytes move away from the basement membrane. This lets macrophages and neutrophils destroy the matrix as they remove dead or damaged tissue. Researchers have found that high metalloprotease (MMP) levels in chronic wound fluid are a sign of diabetic wounds.

These levels are about sixty times higher than those in acute wound fluid. This spike in protease activity hinders the body's natural ability to heal itself and expedites tissue disintegration. There can be several factors at work here. One is that increased glucose levels immediately affect matrix metalloproteinases (MMPs), changing their expression and abundance. Another is that persistently high levels of inflammatory and profibrotic cytokines are associated with downregulated TIMP expression. Finally, the production of complex glycation products indirectly affects MMPs. Because of this, they remove growth factors, receptors, matrix proteins, and other components necessary for wound healing [82-83].

Biological Targets

Research on the molecular mechanisms by which diabetes impairs wound healing has increased dramatically in recent years. Researchers have found that an imbalance in the production of molecular parts like growth factors and cytokines is why diabetics' wounds don't heal properly.

Because of these abnormalities and imbalances in gene expression in all important cells, the healing process is less effective. To that end, chronic nonhealing wounds can only appear during the inflammatory phase and never simultaneously. Identifying numerous molecular factors and targets has radically altered wound care for diabetics.

We can classify these management approaches based on the molecular targets that control their functions. PDGF, TGF-α, EGF, VEFG, FGF, and KGF are growth factors that work directly with stem cells, autologous fibroblasts, and keratinocytes. The preceding sections have already covered the relevance and purpose of these objectives. Among these goals are controlling nitric oxide levels, matrix metalloproteinase (MMP), inflammatory and non-inflammatory cytokines, and collagen-making and breaking down. One biochemical target that many drugs may directly influence is key factors linked to angiogenesis.

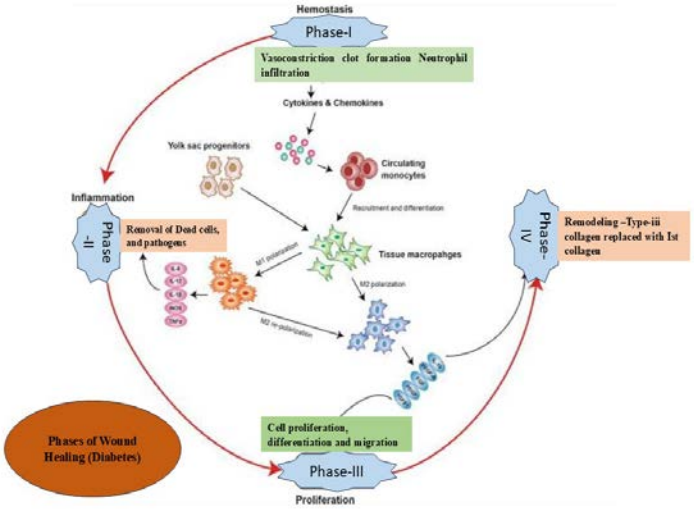

Figure 3: The primary mechanism that causes Diabetic Wounds to heal more slowly

Experimental studies

In a clinical trial involving photodynamic therapy, Tardive et al. (2014) discovered that the probability of amputation was 0.029 times more significant in the treatment group compared to the control group. Park et al. (2018) did a phase III multicenter, double-blind, randomised, placebo-controlled trial to test the safety and effectiveness of a new growth factor therapy spray containing rhEGF for treating diabetic wounds.

73.2% of people in the rhEGF group (compared to 50.6% of people in the placebo group) finished the healing process, which is a significant difference ($p = 0.001$). In addition, irrespective of HbA1c levels, the rhEGF-treated group exhibited a quicker repair rate ($p = 0.029$). Compared to the placebo group, the rhEGF group shortened the median durations for 50% reductions in ulcer size and complete wound healing. Asadi et al. (2017)

conducted a low-intensity cathodal direct current study using a single-blind, placebo-controlled design. The study's findings suggest that electric stimulation can speed up the healing of ischemic ulcers by setting off healing factors like VEFG and HIF-1α in the wound. Soleimani et al. (2017) conducted a study to explore the benefits of flaxseed oil, an omega-3 fatty acid. People with diabetic wounds who took omega-3 fatty acid supplements for 12 weeks saw improvements in their plasma TAC, serum hs-CRP, ulcer size, insulin metabolic markers, and glutathione levels [84,85]. The trial was double-blind, randomized, and placebo-controlled. **Table 1** summarizes the results of several recent clinical studies that aimed to improve the healing time of diabetic wounds.

Future strategies for treatment

Peripheral neuropathy, peripheral vascular disease, and foot problems or illnesses are major contributors to diabetic wounds. Despite technological advances, such as using bioengineered skin cells and traditional care, insulin's reported rate of wound healing has remained below 50%. New medicines that target cytokines, inflammatory mediators, the extracellular matrix, matrix metalloproteinase, the epidermis, genetics, vasculature, and stem cell therapy have made it possible for diabetic wound assessment to improve.

Diabetic wounds have prompted a flurry of research into potential treatments. Stem cell therapy, platelet-rich plasma, substance P, sphingosine 1-phosphate, laser therapy, shockwave treatment, and therapies generated from natural products are all part of the techniques. A safer and more successful treatment for diabetic wounds must be developed using these strategies, as shown in Table 1. Clinical trials have only tested these treatments on humans, but research is still ongoing.

Table 1: List of diabetic wound clinical trial studies[86]

Study	Total No. of Patients	Type of Study	Intervention and Comparison	Outcomes
Alhawari et al.	10	Prospective clinical trial	Autologous PRP injections vs. platelet-poor plasma	Improved wound healing ($p < 0.05$)*
Gupta et al.	60	Randomized controlled trial	PRP dressings vs. normal saline dressings	Healing rate or percentage ulcer area reduction ($p = 0.3$)
Malekpour et al.	90	Randomized controlled trial	PRP gel vs. silver sulfadiazine ointment	Increased the healing rate ($p = 0.0$)*
Elsaid et al.	24	Randomized controlled trial	PRP gel dressings vs. saline dressings	Reduced wound size and contribute to faster healing times($p < 0.00$)*
Xie et al.	48	Clinical study	Autologous platelet-rich gel vs. standard wound care	Shorter hospital stays ($p < 0.05$)*
Yarahmadi et al.	25	Double-blind, parallel-group clinical trial	PRP-fibrin glue dressings combined with oral vitamins E and A vs PRP-fibrin glue with a placebo	Improved wound healing ($p = 0.019$)*
Kartika et al.	30	Open label, randomized controlled trial	Autologous platelet-rich fibrin (A-PRF) plus hyaluronic acid (HA) vs. A-PRF alone vs. sodium chloride	A-PRF + HA significantly improved wound healing ($p < 0.05$)*
Smith et al.	18	Feasibility-randomized controlled trial	Fat grafting with or without PRP vs. standard podiatric care	No significant differences

***Significant difference**

CONCLUSION

Peripheral neuropathy, peripheral artery disease, and foot illnesses are among the several risk factors that could result in diabetic wounds, according to research by S. Patel et al. (2019).

Despite the extensive use of standard care and technological advancements such as bioengineered skin cells, the wound healing rates for diabetics have allegedly remained around 50%. Research into diabetic wounds is witnessing the rapid emergence of novel, non-conventional therapeutic techniques. Some things fall into this group: extracellular matrix, angiogenesis stimulators, gene and stem cell treatments, cytokine inhibitors and stimulators, and skin replacements.

The treatment of diabetic wounds has been the subject of a surge in recent years. Serious complications might arise when wounds take longer to heal in people with diabetes. Numerous studies have examined various factors that can lead to poor wound healing. The condition is common in people with diabetes. Improvements in the management of wound healing in diabetes have been made possible by new therapeutic approaches and materials. Various methods based on growth factors, dual growth factors, anti-inflammatories, cytokines, matrix metalloproteinase (MMP), angiogenesis, extracellular matrix (ECM), stem cells, and natural products have been investigated and tested by researchers with varying degrees of success. Crucial is mastering the basic method and coming up with newer carriers.

Combination therapy may become an important area of research in the future for the management of damaged wounds. Diabetic wounds recover at a faster rate as a result. Additional research into diabetic wound healing medications that target specific phases is necessary. It could be helpful to evaluate the level of recovery more precisely.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Anubhav Dubey and Niladry S Ghosh wrote the original draft. They also contributed to supervising and looking after administration. Mamta Kumari contributed to analyzing literature and working on methodologies. Anubhav Dubey and Mamta Kumari were involved in collecting data, data curation, and accessing various resources.

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