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Diabetic Wound Healing: Interplay of Genetic Predisposition, Environmental Exposures, Lifestyle Choices, and Ethnicity in Therapeutic management

Sharon Benita Stephen[1], Rashmi Pauline[1], Saranya Velmurugan[1], Gowtham Kumar Subbaraj[1#]

[1] Faculty of Allied Health Sciences, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam – 603103, Tamil Nadu, India.

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ABSTRACT:
Diabetic wound healing is a complex process influenced by various factors including genetic predisposition, environmental exposures, lifestyle choices, and ethnicity. This review explores the intricate interplay of these elements in the treatment of diabetic wounds. Genetic predispositions, such as variations in genes involved in inflammation and angiogenesis, can significantly impact an individual's susceptibility to diabetic wound complications. Environmental exposures, including pollutants and microbial pathogens, further exacerbate wound healing challenges in diabetic patients. Lifestyle choices such as diet, exercise, and smoking habits play a crucial role in modulating wound healing outcomes. Additionally, ethnicity contributes to variations in wound healing rates and responses to treatment due to genetic and cultural factors. Understanding these multifaceted influences is essential for tailoring effective diagnostic and therapeutic approaches for diabetic wound management. Integrating personalized medicine strategies with culturally sensitive healthcare practices can enhance outcomes and reduce the burden of diabetic wounds on affected individuals and healthcare systems.

1.0. Introduction

Diabetic wounds are injuries that occur in individuals with diabetes and are slow to heal due to several factors that impair the healing process [1, 2]. Diabetes leads to numerous pathological alterations that disrupt nearly every aspect of the healing process, such as chronic elevation of blood sugar levels, which harms blood vessels and impedes adequate blood flow, as well as peripheral vascular disease and neuropathy, complicating the identification of wounds [3]. Diabetic wounds commonly exhibit heightened inflammation, reduced angiogenesis, impaired keratinocyte migration, and diminished fibroblast proliferation, leading to heightened risks of complications such as infections, wound reopening, and the persistence of non-healing chronic wounds [4]. Wounds in diabetic individuals are frequently marked by heightened inflammation, reduced formation of new blood vessels, impaired movement of keratinocytes, and diminished growth of fibroblasts, leading to heightened risks of complications such as infections, wound reopening, and the transition to chronic non-healing wounds [5,6]. Individuals with diabetes face a 15-fold higher risk of undergoing amputations due to foot wounds or ulcers [7]. To prevent severe diabetic sores or wounds, catching and treating wounds early is the most important thing to do, and there are things individuals can do to support their body's healing processes, such as managing blood sugar, eating a healthy diet, and doing regular self-checks [8]. Diabetic wounds can take longer to heal, and the incidence of delayed healing process in diabetic patients is increasing globally due to lack of preventive and therapeutic measures. It is estimated that impaired healing of diabetic wounds affects approximately 25% of all patients with diabetes mellitus, often resulting in lower limb amputation, with subsequent high economic and psychosocial costs [9]. The hyperglycemic environment promotes the formation of biofilms and makes diabetic wounds difficult to treat. Factors that may increase the risk of infection as shown

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in Figure 1, include impaired sweating, dry and cracked skin, toenail infections, and foot abnormalities [10].

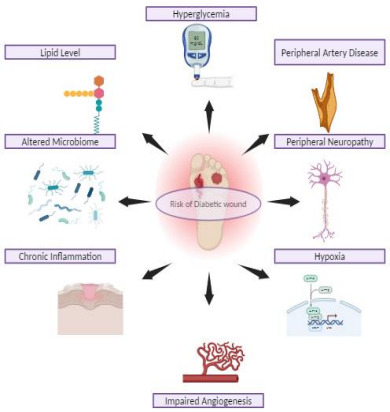

Figure 1: Multifactorial risks associated with chronic diabetic wound

Diabetes could impede wound healing by diminishing the synthesis of growth and reparative hormones, limiting the formation and restoration of new blood vessels, compromising the integrity of the skin barrier, and diminishing collagen synthesis [11]. Individuals facing impaired wound healing from diabetes-related nerve and blood vessel effects may also encounter complications like heart disease, kidney issues, and eye-related issues [12]. Monitoring wounds and taking preventive measures are crucial for individuals with diabetes to minimize the risk of complications during wound healing [13]. The first four grades categorize wounds according to their depth, whereas grades 4 and 5 evaluate the seriousness of gangrene and decreased blood supply in the foot. These latter stages pose a serious threat to the limb and frequently necessitate amputation as shown in Figure 2. Genes play a crucial

2.0. Genetic predisposition and Diabetic wound healing

Genetic and environmental factors have been studied in relation to wound healing, revealing various polymorphisms associated with chronic wound microbiome composition and healing outcomes. Notably, literatures focused on the association between genetic variations and chronic wound microbiomes, specifically identifying the TLN2 and ZNF521 genes as influential in bacterial colonization patterns and healing rates [20]. Other genetic role in wound healing, and their expression can significantly impact the healing process. Several studies have highlighted the importance of gene therapy and the identification of wound healing driver genes for the development of effective wound healing therapeutics. During the wound healing process, researchers have observed heightened expression of particular genes related to tissue repair, angiogenesis, and immune response [14]. Gene therapy, including the delivery of growth factors and the use of genetically modified cells, has been explored as a potential approach to enhance wound healing [15,16]. Additionally, research has identified potential hub genes associated with skin wound healing, such as IL1B, IL-6, and various chemokines, which play key roles in the regulation of the inflammatory response and tissue repair [17,18]. Understanding the genetic mechanisms underlying wound healing is essential for the development of targeted therapeutic interventions to promote effective and timely healing [19].

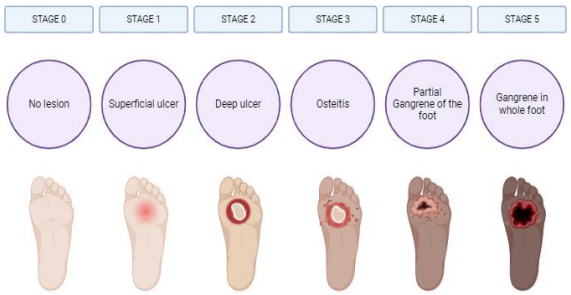

Figure 2: Illustrates, the stages of diabetic wounds based on the presence of ischemia or infection.

polymorphisms have been connected to the development and healing of venous ulcers, including TNFα-308A, FGF-R2, HFE, Erβ, and coagulation factor XIII [21]. Additionally, inherited genetic diseases like Down syndrome and Ataxia-telangiectasia can contribute to impaired wound healing [22].

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3.0. Environmental Exposure and their impact on diabetic wound healing

Environmental factors, including age, diabetic condition, and genetic heritage, play a crucial role in determining the pace and effectiveness of wound healing [23]. Overall, understanding the complex interaction between genetic and environmental factors in wound healing can aid in the development of personalized medicine approaches and improved therapeutic strategies [24]. Gene expression modifications in diabetic wounds significantly contribute to the impaired healing process observed in diabetic patients. The elevated glucose levels characteristic of diabetes result in modifications in gene expression associated with compromised angiogenesis, neuropathy, inadequate chronic inflammatory response, barrier dysfunction, and subsequent polymicrobial infections in diabetic wounds [25]. These changes contribute to the complexity of diabetic wound healing and the challenges associated with treating these wounds effectively. Understanding the genetic mechanisms underlying these changes is crucial for developing targeted treatment strategies to address the multiple causes of impaired healing in diabetic wounds [26]. Research has also highlighted the importance of gene therapy and identifying wound healing driver genes to enhance the healing process in diabetic wounds [27]. By focusing on gene expression changes and molecular mechanisms, researchers aim to develop more effective diagnostic and treatment strategies to improve outcomes for individuals with diabetic wounds [28]. Genetic testing and personalized medicine are paving the way for advancements in diabetic wound healing. Molecular wound diagnostics are being developed to enable personalized medicine approaches in treating diabetic wounds [29]. The aim is to monitor wounds using theragnostic wound dressings, which can provide real-time information about the wound's status and tailor treatment strategies like foam dressings, alginate dressings or hydrogel dressing [30,31]. Impaired wound healing can result from various factors, which can broadly be classified as either local or systemic. Local factors encompass oxygenation, infection, and the presence of foreign bodies, while systemic factors encompass age, gender, sex hormones, stress, ischemia, obesity, nutrition, alcohol consumption, and smoking [32,33].

4.0. Lifestyle Factors and Behaviours

Proper nutrition plays a crucial role in the wound healing process as shown in Table 1. Research indicates that macronutrients like carbohydrates and fats are essential for activities like fibroblast and leukocyte functions, hormone secretion, and growth factor production [34]. Micronutrients also contribute significantly to wound healing, with deficiencies potentially impairing the process [35]. Malnutrition, especially in elderly individuals and those with conditions like diabetes, can hinder wound healing by affecting nutrient absorption and metabolism [36]. A significant correlation exists between micronutrients and chronic wounds, where malnutrition encompasses either deficiencies, excesses, or imbalances in energy and nutrient intake, all of which can hinder the process of wound healing [37]. Protein and energy requirements for chronic wound patients may increase significantly to support the healing process [38] And also, the effect of essential fatty acid supplementation on wound healing remains controversial, with omega-3 supplementation alone showing harmful effects but beneficial outcomes when combined with omega-6 [39]. On the other hand, changes in lifestyle factors also affect wound healing, a well-balanced diet rich in proteins, carbohydrates, vitamins A, B, C & E, iron, zinc are crucial for skin health and wound healing

[40]. Smoking and excessive alcohol consumption can delay wound healing by reducing oxygen supply and impairing scar tissue quality [41]. Changes in body weight and insufficient consumption of essential nutrients such as proteins, fluids, energy, and vitamins can impact the process of wound healing [42]. Engaging in physical activity offers numerous advantages for wound recovery, such as expediting healing, decreasing oxidative harm, and enhancing emotional well-being [43].

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Table 1: Nutritional factors associated with the process of wound healing

Nutrient	Functions	Sources
Protein and amnio acids that make up protein	The multifaceted role of a substance in the body, which facilitates muscle, ligament, and skin development, transports essential nutrients like lipids, vitamins, and minerals, ensures oxygen delivery, fosters a favourable nitrogen balance, and contributes to the synthesis of enzymes crucial for wound healing and repair.	Meat, eggs, milk, cheese, yogurt, legumes, nuts, seeds.
Energy	This nutrient provides energy, safeguards against undesired loss of mass, and is essential for building molecules, generating nitrogen, and producing collagen.	Protein, carbohydrates, fat.
Fluid	Functions as a solvent for various nutrients, aids in regulating body temperature, and facilitates the transportation of nutrients and waste products.	Water, milk, juice, coffee, tea, soda, punch, broth, beverages.
Vitamin A	Synthesizing proteins, supporting immune function, and maintaining epithelial tissues.	Deep green and yellow fruits and vegetables, beef liver, fortified milk.
Vitamin C	Necessary for the creation of collagen and the uptake of iron.	Critus juices and fruits, fortified juices, tomatoes, strawberries, potatoes, broccoli, peppers, mangos, collard greens, cabbage.
Zinc	Acts as a co-factor in the production of collagen and various cellular metabolic processes, while also supporting immune function.	Nuts, dried fruits, dried beans, whole-grain cereal, organ meats.
Copper	This nutrient maintains the integrity of the skin, blood vessels, and connective tissue, while also contributing to various enzymatic processes within the body.	Liver, fish, nuts, seeds.
Iron	Red blood cells provide assistance by transporting oxygen and aiding in collagen formation, thereby bolstering immune system health.	Liver, meat, fish, poultry, fortified breads and cereals.

Physical activity has the potential to decrease inflammation, a significant factor hindering timely healing, and it may lower the presence of inflammatory indicators in the bloodstream, thus fostering swifter recovery. Moreover, exercise can diminish oxidative harm, a critical consideration for demographics like seniors and individuals with diabetes, who might experience heightened levels of harmful free radicals [44,45,46]. However, there are limitations to the evidence supporting the use of exercise in wound healing. The available evidence indicates that exercise could enhance wound healing, quality of life, and physical abilities among adults dealing with venous leg ulcers. However, these conclusions stem from a limited number of trials, which are hampered by notable methodological flaws [47]. There is currently no evidence to support the use of exercise regimens to improve wound healing, and more research is needed to determine the optimal exercise regimens for different types of wounds [48]. Proper foot care and hygiene practices are paramount in wound healing, particularly in preventing and managing foot ulcers. Daily foot inspection is crucial to detect early signs of trouble, especially for individuals with conditions like diabetes [49]. Keeping the feet clean, bandaged, and avoiding walking barefoot are essential preventive measures. Off-loading techniques, such as wearing special footgear or using braces, help reduce pressure on ulcers, promoting faster healing [50]. Proper footwear selection is vital to support foot health and prevent ulcers. Maintaining optimal blood glucose levels, regular foot examinations, and seeking prompt medical attention for any foot issues are key in preventing complications like infections and amputations [51]. Additionally, gentle cleansing with soap and water, appropriate wound dressings, and avoiding harsh topical agents aid in wound healing. Overall, a comprehensive approach to foot care

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involving daily inspection, proper hygiene practices, suitable footwear choices, and timely intervention is crucial for effective wound management and prevention of foot ulcers [52].

5.0. ***Ethnic Disparities in Wound Healing***

Racial and ethnic disparities in wound healing, particularly in the context of pressure ulcers, are a significant concern influenced by various factors. Studies highlight the importance of addressing disparities through tailored healthcare strategies [53]. Research emphasizes the need for healthcare organizations to focus on eliminating disparities by collecting racial and ethnic information, monitoring healing outcomes by race and ethnicity, and implementing disparity reduction processes supported by leadership. Additionally, having a diverse nursing workforce competent in cross-cultural approaches is crucial for improving outcomes for minority populations [54]. Understanding predictors of non-healing, such as deficits in daily living activities and pressure ulcer severity, is essential to reduce disparities, especially among Black nursing home admissions. These findings underscore the necessity of targeted interventions to achieve equity in healthcare for minority populations [55].

6.0. Therapeutic Management strategies for diabetic wound healing

The treatment of diabetic wound healing entails the use of both supportive care and pharmaceutical therapies. Considering their ability to heal slowly, often more than three months. Diabetes wounds are classified as chronic because they fail to follow the typical wound-healing pattern. Following a physical examination to ascertain the extent of the wound, a vascular examination is performed to look at the location, size, depth, and type of tissue impacted by the wound [56]. Furthermore, determining the presence of infection depends critically on sampling the wound's edge. The loss of mobility and the high expense of treatment increase the need for an efficient and rapid wound healing [57].

6.1. Pharmacological Interventions

Pharmacological strategies include antibiotics to prevent and treat infections, growth factors like platelet-derived growth factor (PDGF) to promote wound healing, anticoagulants to prevent thrombosis, analgesics to manage pain and improving patient outcomes and reducing the risk of complications [58]. It is crucial to maintain optimal blood sugar levels and practice proper foot care, such as wearing appropriate footwear and keeping feet clean and dry, to prevent and manage diabetic wounds [59]. Additionally, hyperbaric oxygen therapy boosts oxygen levels for faster healing, and nutritional supplements support collagen production. Proper diabetes management, wound dressings, surgical interventions, lifestyle modifications like exercise and a balanced diet, all contribute to successful diabetic wound healing [60].

6.2. Surgical Approaches

Standard wound care practices involve a combination of debridement, dressing selection, infection control, offloading pressure, and promoting tissue perfusion. Debridement is the removal of non-viable tissue from the wound to promote healing [61]. Dressings should be selected based on the type of wound, moisture balance, and exudate management. Infection control measures, such as proper hand hygiene and the use of antimicrobial agents, are essential to prevent or treat infections. Offloading pressure from the wound is crucial to prevent further damage and promote healing. Moreover, promoting tissue perfusion through proper positioning, elevation, and compression can help improve blood flow to the affected area [62].

6.3. Advanced wound care technologies

Wound care therapies and technologies encompass a range of innovative approaches to promote healing. This includes the use of growth factors and skin substitutes, which can stimulate tissue regeneration and accelerate the wound healing process [63]. Negative pressure wound therapy is another advanced technique that involves applying negative pressure to the wound bed, promoting blood flow and reducing edema. Biologic therapies, such as stem cell treatments or bioengineered skin substitutes, represent cutting-edge interventions that aim to enhance the body's

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natural healing mechanisms. These emerging interventions hold promise for addressing complex wounds and promoting optimal healing outcomes [64]. Multidisciplinary teams play a crucial role in wound care by fostering collaboration among various healthcare professionals, including physicians, nurses, podiatrists, and other specialists. This collaborative approach allows for comprehensive assessment and management of complex wounds, drawing on the expertise of each team member to provide holistic care [65]. Physicians contribute their medical knowledge and expertise in diagnosing underlying conditions, while nurses play a key role in wound assessment, dressing changes, and patient education. Podiatrists bring specialized knowledge in foot care and diabetic wound management, enhancing the team's ability to address specific wound-related issues. By working together, these multidisciplinary teams can develop tailored treatment plans that optimize patient outcomes and promote effective wound healing [66].

7.0. Future Direction and Research

Future directions in wound care research are focused on several key areas to enhance treatment outcomes and address challenges in wound healing. Studies are exploring the use of advanced wound dressings through bibliometric analysis to understand current research trends and global perspectives [67]. Additionally, there is a growing emphasis on elucidating and enhancing local antimicrobial defense mechanisms to improve wound healing outcomes, particularly in chronic wounds that pose significant public health concerns. The integration of technology, such as digital solutions and predictive analytics, is expected to play a crucial role in easing provider workloads, improving patient quality of life, and enhancing overall wound care practices [68]. Research in transcriptomics is shedding light on genes and protein pathways dysregulated in diabetic foot ulcers, paving the way for the development of biologically based compounds to accelerate wound healing in these patients [69]. Overall, the future of wound care is moving towards a more comprehensive, technology-driven approach that aims to optimize patient care, streamline workflows, and advance treatment modalities for better outcomes [70]. Wound healing as major future goal in gene editing and regenerative medicine, this offers innovative solutions by manipulating genes or using stem cells to repair damaged tissues. Optimizing lifestyle interventions for wound healing involves considering individual habits and conditions to enhance the body's natural healing processes [71].

8.0. Conclusion

Diabetes adversely acts on the phases of normal wound healing phases, i.e., hemostasis, inflammatory phase, proliferative phase, re-epithelialization and remodeling phase, and poses a big burden on the quality of life of a diabetic individual. Diabetic wound care management plays a pivotal role in improving healing outcomes and enhancing the quality of life for individuals with chronic wounds. The challenges posed by skin wounds and compromised wound healing underscore the importance of advancing research in wound care to address public health concerns and reduce healthcare expenses associated with complex treatments. By tapping into the power of technology, such as digital solutions and predictive analytics, healthcare providers can streamline workflows, ease workloads, and ultimately improve patient quality of life. Patient assessments are crucial in tailoring personalized treatments and optimizing wound care interventions to meet individual needs effectively. Embracing innovative therapies, enhancing research efforts, and addressing the social determinants of health disparities are essential components in the quest for better wound healing outcomes and overall well-being.

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Conflict of Interest

The authors declare that there is no competing of interest regarding the publication of this article.

Authors Contribution

All authors contributed to this work, read and approved the final draft.

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Data Availability

The data that supports the study are openly available upon request.

Ethical Approval

No ethical approval was required because this study was obtained from already published case vs. control studies. Since the present study was categorized as meta-analysis, patient consent forms are not required.

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