International Journal of Research and Applied Innovations (IJRAI)

| ISSN: 2455-1864 | www.ijrai.org | editor@ijrai.org | A Bimonthly, Scholarly and Peer-Reviewed Journal |

|| Volume 9, Issue 2, March-April 2026||

DOI:10.15662/IJRAI.2026.0902005

Next-Generation Therapeutic Interventions Driving Regeneration in Diabetic Wound Healing

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Publication History: 03.02. 2026 (Received); 08.03.2026 (Revised); 12.03. 2026 (Accepted); 15.03.2026 (Published).

ABSTRACT: Chronic inflammation, angiogenesis, neuropathy, oxidative stress, and an imbalance of microbes are some of the complications that affect the healing process, hence the challenge in the healing of diabetic wounds across the globe. However, it is not possible to achieve the healing process through the regeneration of tissues using conventional methods. The article highlights the need for regenerative methods rather than the conventional methods of treating the complications that affect the healing process of diabetic wounds, as it is the need of the hour to heal the wounds completely, i.e., both structurally and functionally. New biomaterials, such as smart hydrogels, ECM-mimicking scaffolds, and nanofibers, are some of the regenerative methods that are being adopted in the healing of diabetic wounds. Exosomes and stem cell therapy are also being adopted in the healing of diabetic wounds, as they reduce the level of inflammation and promote angiogenesis in the wound area. Also, the molecular dysfunctions that affect the healing process are being corrected through RNA-based therapy and gene editing tools. Personalized care for the healing of diabetic wounds, as well as the results, are being improved through innovations such as 3D bioprinting, electroceut.

KEYWORDS: Diabetic wound healing, Regenerative therapeutics, Smart biomaterials, Stem cell based therapies, Gene-editing technology

I. INTRODUCTION

In diabetes mellitus, wound healing is pathologically delayed or an impaired repair process induced by chronic hyperglycemia that disrupts the normal body healing processes (1). Haemostasis, inflammation, proliferation, and remodelling are the four consecutive phases of wound healing that take place in healthy individuals. Conversely, continuously high blood glucose levels damage blood vessels and nerves, weaken immunological defences and reduce the delivery of oxygen to tissues in diabetics. Ultimately, this delays or prevents proper healing due to decreased angiogenesis, prolonged inflammation, and defective collagen synthesis. Diabetes mellitus is a chronic metabolic disorder that increases blood glucose levels and results in sustained hyperglycemia. Diabetic patients have chronic wounds since their wound-healing ability is compromised. Despite years of scientific and technological developments, wound care in diabetic patients is still a clinical problem (2).

1.1 Types of diabetes mellitus

Type 1 Diabetes Mellitius (T1DM)

An absolute lack of insulin results from the destruction of the pancreatic beta cells that produce insulin in type 1 diabetes mellitus (T1DM), a chronic autoimmune disease. Because the body is unable to produce insulin, which is necessary for cells to absorb glucose for energy, this condition causes hyperglycemia, or elevated blood sugar levels. Auto antibodies that target pancreatic beta cells and lymphocytic infiltration are immune-mediated destruction events that lead to type 1 diabetes. Genetic susceptibility is important, particularly when it comes to certain human leukocyte antigen (HLA) genes (particularly HLA-DR3 and HLA-DR4). The autoimmune response may be triggered by environmental factors like viral infections. Hyperglycemia and clinical diabetes result from insulin secretion falling below levels required for normal glucose homeostasis when 80–90% of beta cells are destroyed (3).

1.2 Type 2 Diabetes Mellitius (T2DM)

Hyperglycemia induced by the body's inadequate utilization of insulin (insulin resistance) and relative deficiency of insulin are characteristics of type 2 diabetes mellitus (T2DM), a long-term metabolic disease. It is primarily induced by a combination of inadequate compensatory insulin secreted by pancreatic beta cells and insulin resistance, which is when muscle, fat, and liver cells fail to respond to insulin as required. The disorder frequently manifests gradually and

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is frequently associated with poor diet, obesity, genetics, and physical inactivity. Neuropathy (tingling or numbness in extremities), fatigue, blurred vision, increased thirst, frequent urination, and wounds that heal slowly are some of the symptoms. Cardiovascular disease, retinopathy that results in blindness, kidney failure, and poor blood flow that may necessitate limb amputations are examples of long-term complications. Insulin resistance and pancreatic β-cell impairment are two components that together establish the pathophysiology of Type 2 Diabetes Mellitus (T2DM). The central locations of insulin resistance are fat, liver, and muscle, all of which cannot respond in a proper manner to normal amounts of insulin. Blood glucose is increased due to the liver releasing extra glucose and muscle and fat cells taking up less glucose (4).

II. EPIDEMIOLOGY

Since it is becoming more widespread, diabetes mellitus has now become a major worldwide public health issue. As of 2024–2025, about 589 million people aged 20–79 years lived with diabetes, and by the year 2050, it is predicted to increase to 853 million. In 1990, an estimated 7% of adults across the world had diabetes, by 2022, it increased to 14%, a sharp increase driven by ageing populations, urbanisation, and diet lifestyle. Over 80 percent of the people with diabetes live in low- and middle income nations (LMICs), and they are disproportionately affected by the disease. The fastest growth in diabetes prevalence is occurring in these regions, and also gaps in diagnosis and treatment are significant. For instance, nearly 60% of adults with diabetes globally are not treated, and the majority of them are from LMICs. The Eastern Mediterranean, Africa, and South-East Asia have some of the lowest coverage rates of treatment and highest rates of prevalence (5).

III. GLOBAL PREVALENCE AND BURDEN OF DIABETIC WOUNDS

Prevalence is site specific, as it has been estimated to range between 3% and 13% on continents such as North America, Africa, Asia, Europe, and Oceania. Diabetic foot complications affect millions of individuals globally, accounting for a high disability adjusted life years (DALYs) or years lived with disability (YLDs). High rates of recurrence are also one of the issues with the treatment; between 40% and 40% of patients experience recurrence of the ulcers within one year, while 60% do so within three years. Diabetic foot ulcers also cause major economic burden as billions of dollars are used annually globally for medical care (6). They are a leading cause of morbidity, mortality, and economic load worldwide.There is a high percentage of individuals with diabetes who experience diabetic wounds, particularly diabetic foot ulcers. An estimated 19% to 34% of diabetics will develop a foot ulcer during their lifetime, per studies. International Diabetes Federation (IDF) declares that occurs in approximately 6.3% of all adults with diabetes globally. But there are considerable regional differences in the prevalence within this group (7).

3.1 Pathophysiology of impaired wound healing in diabetes.

The perturbing actions of hyperglycemia on cellular function, leading to oxidative stress, hyperinflammatory responses, and impaired growth factor activity, are responsible for wound impairments in diabetes. Microvascular injury, which reduces blood flow to the wound, and peripheral neuropathy, which leads to loss of sensation and augmented injury,enhance the impairments. In addition, chronic inflammation and immune dysfunction decelerate healing, and decreased angiogenesis and disrupted extracellular matrix hinder repair and normal tissue formation (8). Figure 2 illustrates the dynamic cellular and molecular events involved in the wound healing process.

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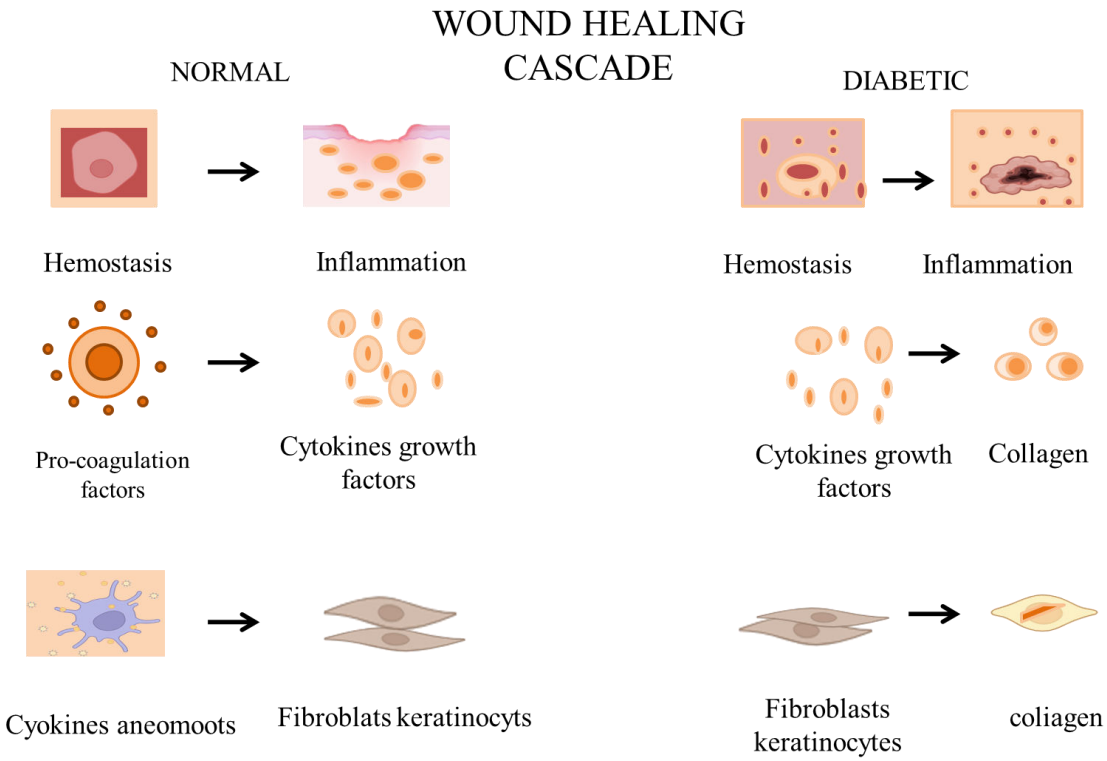

Figure 2: Wound Healing Cascade: Cellular and Molecular Phases of Wound Healing.

IV. PATHOPHYSIOLOGICAL BASIS OF IMPAIRED DIABETIC WOUND HEALING

4.1 Hyperglycemia induced oxidative stress.
When blood glucose is too high to neutralize reactive oxygen species (ROS), the body undergoes hyperglycemia induced oxidative stress, which kills cells and leads to a variety of diabetic complications, including diabetic retinopathy, nephropathy, and cardiovascular disease. The process employs several pathways, such as the hexosamine pathway, advanced glycation end products (AGEs), dysregulation of protein kinase C (PKC), and the overproduction of ROS by mitochondrial dysfunction. The pathogenesis of diabetic complications is promoted by oxidative stress, as well as inflammation, apoptosis, and endothelial dysfunction (9), (10).

4.2 Chronic inflammation and dysregulated cytokine response.
Sustained and misguided immune activation is a characteristic of persistent inflammation and an imbalanced cytokine response, which may lead to system sickness, disease progression, and ongoing tissue injury. A state of long-term inflammation is generated when cytokines, or signalling molecules that organize immune reactions, become de,regulated, either with excessive pro-inflammatory mediators or with insufficient anti-inflammatory signals. Chronic illnesses such as cardiovascular disease, type 2 diabetes, cancer, and neurodegenerative diseases have been associated with this dysregulation, which may arise due to a range of stimuli such asinfections or autoimmune diseases. It also has the ability to lead to extensive organ damage. Normal Immune Response, Pro-inflammatory cytokines are produced in reaction to a primary injury or infection to neutralize the insult and initiate the process of healing. Chronic Inflammation: Chronic inflammation causes lasting tissue damage if it persists or is initiated by an inappropriate stimulus(11).

4.3 Impaired angiogenesis and vascular dysfunction
Age, disease (e.g., diabetes and systemic sclerosis), and stress have been linked to decreased angiogenesis, or the formation of new blood vessels, and vascular dysfunction, or decreased health of blood vessels. All of these lead to poor tissue perfusion, which worsens cardiovascular disease, neurodegenerative disease, and impaired wound healing. Impaired angiogenesis due to factors that result from aging, such as endothelial dysfunction and reduced expression of

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vascular endothelial growth factor (VEGF), can be addressed by therapeutic intervention aimed at improving endothelial health and stimulating VEGF expression. Ageing One of the primary risk factors for cardiovascular diseases that occur with ageing is loss of function in the ability to form new blood vessels(12).

4.4 ECM remodeling and fibroblast dysfunction.

Fibroblast dysfunction is defined by inappropriate or excessive fibroblast activity, and this leads to problematic ECM alterations. Remodelling of the ECM is the dynamic process of constructing, degrading, and reorganizing the extracellular matrix, and it is mainly directed by the fibroblasts. Dysregulated fibroblasts can produce excess extracellular matrix proteins (fibrosis), be unable to repair tissue properly (delayed healing), or hasten the progression of diseases such as cancer or chronic wounds.MMP/TIMP Disharmony, Excessive matrix metalloproteinases (MMPs) and diminished tissue inhibitors of metalloproteinases (TIMPs) are commonly observed in diabetic ulcers. Tissue repair is impaired by such disharmony, resulting in excessive ECM breakdown(13).

4.5 Neuropathy and infection susceptibility

Neuropathy makes one more susceptible to infection due to the fact that nerve damage, which is a symptom of most neuropathies, weakens proper bodily defenses and function, resulting in problems such as compromised sensation, decreased mobility, and skin disruption that provide portals of entry for infectious agents. Infection will also destroy nerves directly or induce autoimmune reactions that destroy nerve cells, generating or exacerbating neuropathy. Treatment of the root cause of the neuropathy, together with active wound management and proper hygiene, is essential in preventing and controlling secondary infection.Peripheral neuropathy is one of the most important diabetic complications with a significant contribution to impaired wound healing. Motor neuropathy leads to foot deformity, including claw toes or Charcot foot, and this will increase the pressure points and skin breakdown(14).

Table 1: Key molecular and cellular alterations in diabetic wound healing.

Sr. No.	Category	Normal Wound Healing	Diabetic Wound Healing (Alterations)	Functional Consequence	References
1.	Inflammation	Controlled and self-limiting inflammatory response with balanced cytokine levels	Prolonged inflammation with excessive production of TNF-α, IL-1β, and IL-6	Sustained inflammation, tissue damage, and delayed healing	(15)
2.	Oxidative Stress	Moderate ROS levels act as signaling molecules to promote repair	Excessive ROS generation and reduced antioxidant enzymes (SOD, catalase, GPx)	Oxidative injury to cells and ECM; impaired tissue regeneration	(16)
3.	Angiogenesis	VEGF and HIF-1α activation stimulate new blood vessel formation	Decreased VEGF and HIF-1α expression; endothelial dysfunction	Reduced neovascularization and poor oxygen delivery	(17)
4.	Angiogenesis	VEGF and HIF-1α activation stimulate new blood vessel formation	Decreased VEGF and HIF-1α expression; endothelial dysfunction	Reduced neovascularization and poor oxygen delivery	(18)
5.	Fibroblast Function	Active fibroblast migration, proliferation, and collagen deposition	Decreased fibroblast activity and impaired ECM synthesis	Weak granulation tissue and reduced tensile strength	(19)

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6.	Keratinocyte Function	Efficient migration and proliferation for re-epithelialization	Impaired keratinocyte migration and differentiation	Delayed wound closure and fragile epidermal barrier	(20)
7.	Growth Factors	Adequate expression of PDGF, TGF-β, EGF, and IGF-1	Down-regulated growth factor synthesis and activity	Disrupted cell signaling and impaired wound progression	(21)
8.	Immune Cells (Macrophages/ Neutrophils)	Timely macrophage transition from pro-inflammatory (M1) to pro-repair (M2) phenotype	Persistent M1 macrophages and reduced M2 polarization	Chronic inflammation and inadequate tissue remodeling	(22)

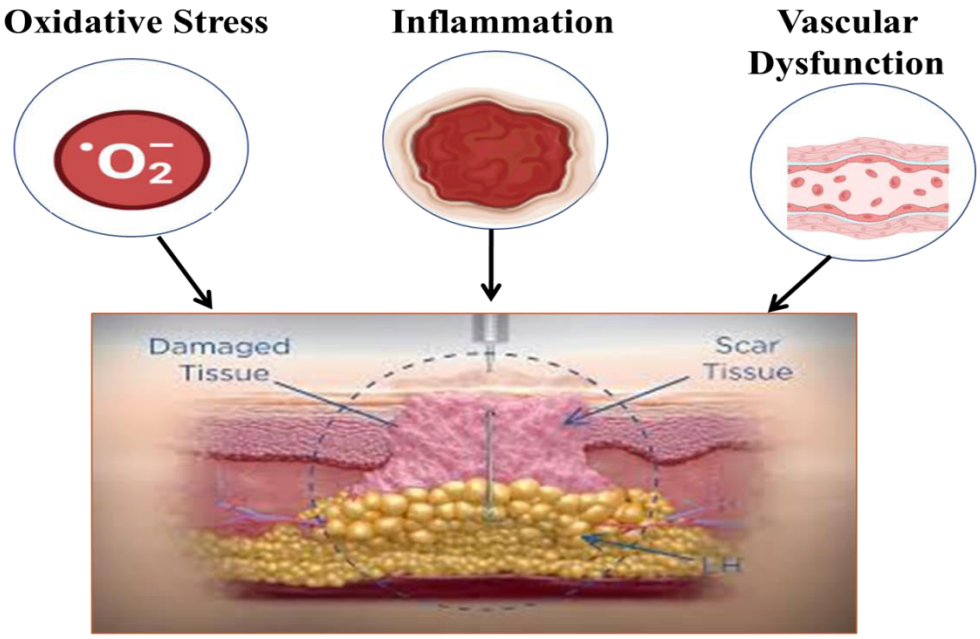

Figure 3: Interplay of oxidative stress, inflammation and vascular dysfunction in diabetic wounds.

V. CONVENTIONAL THERAPEUTIC APPROACHES

5. 1 Debridement techniques

Debridement of the wound on a regular basis is required to remove biofilm, slough, and dead tissue. Granulation tissue growth and re-epithelialization are encouraged by debridement, which converts a chronic wound into an acute wound. Autolytic, mechanical, enzymatic, and surgical debridement techniques are commonly employed. Due to compromised immunity, diabetic ulcers are highly susceptible to microbial colonization. Topical antiseptics, systemic antibiotics (if needed), and strict aseptic wound care measures control infection. Appropriate antimicrobial choice is ensured by culture-guided therapy(23).

5.2 Debridement techniques

Autolytic, biological, enzymatic, mechanical, and sharp (surgical) methods are some of the debridement methods employed to eliminate dead or devitalised tissue in a wound. From invasive procedures such as surgical debridement with scalpels to natural mechanisms like autolysis, it is up to the patient and the type of wound. Achieved using occlusive or semi, occlusive dressings (transparent films, hydrogels, and hydrocolloids), painless, gentle, and selective. suitable for patients who cannot tolerate forceful treatments.Local application of proteolytic enzymes topically (e.g,

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papain urea, collagenase) dissolves only necrotic tissue, leaving healthy tissue intact. Suits patients who cannot undergo debridement surgery("TODJ-13-27" no date)(24).

5.3 Dressings and topical agents

Topical dressings and drugs are critical for diabetic healing of wounds since they accelerate the healing of longstanding ulcers, promote tissue regeneration, and inhibit infection. In selecting drugs in diabetes therapy, choice depends on clinical endpoints and wound types. Several topical agents are useful for the care of diabetic wounds. Topical application of metformin induces collagen synthesis and reduces apoptosis in diabetic wounds, accelerating healing. Platelet derived growth factors (PDGFs), especially in the form of becaplermin gel, by stimulating cell migration and tissue development, have been somewhat helpful in achieving closure. There are other biologics like human umbilical cord (HUC) extracts, fibroblast growth factor (FGF), and recombinant human epidermal growth factor (hEGF), which have shown the potential to enhance healing rates as well as minimize side effects, often outperforming conventional care(25) .

5.4 Offloading and infection control

Infection prevention and effective offloading are intimately connected. Offloading accelerates healing of the wound by reducing pressure and shear forces, which reduces the risk of bacterial colonisation and infection. As proper offloading avoids hospitalisations and amputations due to infection complication, evidence-based recommendations postulate non-removable knee-high offloading devices as the reference standard for the management of neuropathic plantar foot ulcers. In order to avoid aggravating complications, offloading methods have to be adjusted in the presence of active infection or ischaemia .In the treatment of neuropathic ulcers, start with non-removable knee-high appliances unless otherwise specified; alternative is removable appliances or specialized footwear. Monitor circulatory or infection complications; offloading must not exacerbate ischaemia or worsen an infection. Educate patients in self-management and repositioning, e.g, minimizing wheelchair use and pressure relief use(26).

5.5 Standard pharmacological agents (antibiotics, growth factors)

Routine pharmacologic therapies for healing diabetic wounds, especially diabetic foot infections (DFIs), are growth factors that support tissue repair and specific antibiotics depending on the nature and severity of the infection. Because they don't promote healing or arrest infection in uninfected ulcers, antibiotics are not applied to non infected wounds, but are vital for infected diabetic foot ulcers. General antibiotics for DFIs target aerobic Gram-positive bacteria like streptococci and Staphylococcus aureus (including MRSA), and occasionally aerobic Gram-negative and anaerobic bacteria in more severe or polymicrobial infections. Depending on the severity of infection, empirical antibiotic therapy often integrates broad-spectrum beta-lactams such as carbapenems, fluoroquinolones, or piperacillin-tazobactam with agents such as vancomycin for MRSA coverage(27).

Table 2: Current standard therapies and clinical outcomes

Sr. No.	Therapy / Intervention	Mechanism of Action	Standard Regimen / Application	Reported Clinical Outcomes	References
1.	Optimized Glycemic Control (Insulin / Oral Hypoglycemics)	Improves microvascular perfusion and leukocyte function; reduces advanced glycation end-product (AGE) formation	Tight glycemic control (HbA1c ≤ 7%) via insulin or oral agents	Accelerated wound closure; reduced infection rate	(12)
2.	Sharp/Surgical Debridement	Removes necrotic tissue and biofilm; promotes granulation tissue formation	Performed weekly or biweekly depending on wound status	Enhanced healing rate and reduced infection	(13)
3.	Offloading (Total Contact Cast, Specialized Footwear)	Reduces mechanical pressure and shear stress on ulcer site	Use of total contact cast or removable walker	60–90% ulcer healing rate within 12 weeks	(14)
4.	Moist Wound Dressings	Maintains moist environment for epithelial	Dressing changes 2–3× weekly	Improved healing time vs.	(15)

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	(Hydrocolloid, Hydrogel, Foam)	migration		dry dressings	
5.	Topical / Systemic Antibiotics	Reduces microbial load and infection	Based on wound culture and sensitivity; systemic for infected ulcers	Infection control, prevention of sepsis	(16)
6.	Negative Pressure Wound Therapy (NPWT)	Applies subatmospheric pressure to remove exudate and stimulate angiogenesis	Continuous or intermittent suction (−75 to −125 mmHg)	40–60% reduction in healing time	(17)
7.	Growth Factor Therapy (e.g., Recombinant PDGF-BB, Becaplermin gel)	Stimulates fibroblast proliferation and angiogenesis	Topical gel applied once daily	~43% complete healing vs. 29% with placebo	(18)
8.	Hyperbaric Oxygen Therapy (HBOT)	Increases oxygen tension and neovascularization	90–120 min sessions, 5× weekly, for 30–40 sessions	Improved healing and lower amputation risk	(19)

VI. EMERGING THERAPEUTIC STRATEGIES

6.1 Biologics and Growth Factors (VEGF, PDGF, EGF, FGF, HGF)

Growth factors are proteins that regulate cellular activities such as growth, differentiation, and healing, and they are a usual component of biologics, which are complex therapeutic materials derived from living organisms or their products. VEGF, PDGF, EGF, FGF, and HGF are some examples. These biologics are used for significant clinical applications, particularly tissue engineering, cancer therapy, regenerative medicine, and the management of certain blood disorders.Vascular endothelial growth factor, or VEGF, promotes the process of angiogenesis, which is required for tissue healing and wound repair. It mainly supports the growth of new blood vessels by affecting endothelial cells. Platelet-Derived Growth Factor, or PDGF, induces proliferation and division of cells, especially in blood vessels and connective tissue. Aside from being essential in tissue repair, it can act in concert with other growth factors such as VEGF and HGF to induce cell migration and proliferation(28).

6.2 Stem Cell and Exosome Based Therapies

In regenerative medicine, exosome and stem cell-based therapies are advancing rapidly and offer potential alternatives or supplements to traditional stem cell therapies. Stem cell, derived exosomes, which are small vesicles released by stem cells, transport growth factors, cytokines, miRNAs, and other bioactive molecules that facilitate tissue repair, reduce inflammation, and modulate immune responses. These exosomes, without posing the risk of immunological rejection or tumorigenesis associated with cell transplantation, can imitate the regenerative properties of their parental stem cells. By 2025, advanced stem cell-derived exosome therapies will feature highly purified exosomes that are derived from certain mesenchymal stem cells, personalised exosome preparations based on patient biomarkers, and applications in joint repair, rejuvenation of skin, healing of wounds, and hair regrowth(29).

6.3 Gene Therapy and RNA-based Approaches

Current advanced treatment methods such as gene therapy and RNA-based therapies modulate or modify DNA or RNA in cells to treat diseases at the molecular and genetic level. To cure genetic disorders, gene therapy normally involves altering the DNA within patients cells, often employing techniques such as gene transfer, gene editing, or gene silencing. To combat the root causes of diseases, including genetic and certain non-genetic disorders, it tries to change, insert, or delete genetic material. Delivering genes, growth factors, proteins, peptides, stem cells, or exosomes to the wound site is the goal of gene therapy in diabetic wound healing. These tactics aim to modify inflammatory responses, promote angiogenesis, and increase cellular proliferation all of which are frequently abnormal in diabetic wounds(30).

6.4 Nanotechnology in Drug Delivery and Wound Dressings

One of the innovative methods of enhancing the healing process and therapeutic outcomes is through the application of nanotechnology in drug delivery and wound dressing. Nanotechnology employs materials in the nanoscale (1–1000 nm) due to their unique properties that render them effective for medical use, especially in wound care and targeted and localized drug delivery.As delivery vehicles for drugs, nanoparticles (NPs) protect therapeutic drugs from degradation

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and enable precise localization to affected areas. The efficacy of drugs is enhanced and the incidence of side effects in the body is reduced by this localized delivery. Hydrogels, liposomes, and micelles are some of the nanomaterials that offer improved bioavailability, stability, and controlled drug release. Through the delivery of growth factors, antimicrobial drugs, and other bioactive agents directly to the wound area, nanotechnology-based drug delivery systems for burn and chronic wounds hasten recovery, reduce the risk of infection, and minimize scarring(10).

6.5 Biomaterials and 3D Scaffolds for Regeneration

By providing a supporting framework that is very similar to the natural extracellular matrix (ECM) of the skin, biomaterials and 3D scaffolds play a critical role in enhancing diabetic wound healing. By facilitating cellular attachment, proliferation, and differentiation, all key processes necessary for wound healing, these scaffolds allow tissue regeneration to be efficient. The accurate fabrication of such scaffolds with tunable architecture, e.g,pore size and mechanical properties, to closely approximate the physiological characteristics of skin is enabled by utilization of 3D printing and bio printing technologies. The wound healing process in diabetic ulcers, such as diabetic foot ulcers, is complex and often hindered by inadequate vascularization and chronic inflammation(17).

6.6 Antioxidant and Anti-inflammatory Interventions

The aim of antioxidant and anti-inflammatory therapy is to minimize the adverse effects of oxidative stress and overactive inflammation, the causal origin of many acute and chronic diseases. Oxidative stress, resulting from an imbalance between the body's antioxidant defenses and the production of reactive oxygen species (ROS), will result in cell damage. While inflammation is an adaptive immune response to damage or infection, when it is dysregulated it can become long-lasting and result in the formation of disease. Reactive oxygen species (ROS) neutralisation, ROS are highly reactive molecules which can damage lipids, proteins, and DNA within cells, leading to oxidative stress and inflammation. Antioxidants directly neutralise ROS. (such as. Figure 3 represent the concept of precision medicine integrating genetic profiling, immunotherapy, cell-based therapy, and targeted pharmacological interventions(19).

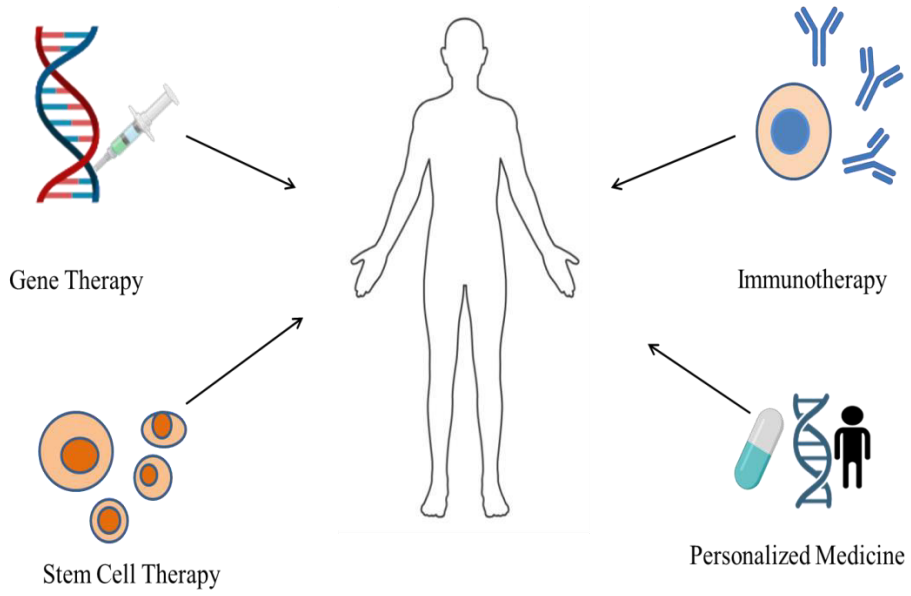

Figure 3: Schematic representation of advanced therapeutic interventions.

VII. CONCLUSION

Chronic hyperglycemia, oxidative stress, inflammation, angiogenesis, neuropathy, extracellular matrix dysfunction, and increased risks of infections are some of the factors that make the wound healing process in diabetes patients a complex clinical challenge. Even though these factors seldom assure complete tissue regeneration, the conventional therapeutic interventions are useful in the initial stages of wound healing. Instead of addressing the symptoms, the next-generation regenerative therapies aim at restoring the natural tissue structure and function. Some of the next-generation regenerative therapies include stem cell and exosome therapies, gene and RNA therapies, bio-printed skin substitutes,

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bioactive hydrogels, smart biomaterials, and drug delivery using nanotechnology. The management of diabetes wound healing is also changing due to the advent of integrative therapies such as AI-based wound care management, photobiomodulation, electroceutical dressing, and antioxidants. Even though the next-generation regenerative therapies are promising, challenges such as cost, standardization, regulation, and patient variation still exist.

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