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# Diabetes and Wound Healing: Pathophysiology, Complications, and Emerging Therapies

**Naeem Hamza[1]*, Krish Shah[1] , Yasmin Schukur[1], Diana Roibu[1], Naeema Zainaba[1] and Felix Nandor Richard Bragg[1]**

[1]Iuliu Hatieganu University of medicine and pharmacy cluj Napoca, Romania

***Corresponding Author:** Naeem Hamza, Iuliu Hatieganu University of medicine and pharmacy cluj Napoca, Romania.

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## Abstract

Diabetic wound healing represents a paradigm of therapeutic recalcitrance, wherein hyperglycaemia disrupts the orchestrated progression of hemostasis, inflammation, proliferation, and remodeling phases, culminating in chronic ulceration and amputation risk. This narrative review synthesizes pathophysiological mechanisms underpinning these deficits, emphasizing protracted inflammation via M1 macrophage dominance and cytokine surfeit (TNF-α, IL-6, IL-1β), oxidative/nitrosative disequilibria from mitochondrial superoxide excess and polyol/AGE/hexosamine fluxes, and cellular impairments in fibroblasts (senescence, migratory arrest), keratinocytes (re-epithelialization failure), and endothelial cells (angiogenic paucity). Vascular sequelae—microvascular (retinopathy, nephropathy, neuropathy with 60–85% ulcer attribution) and macrovascular (atherothrombosis)—exacerbate hypoxia via HIF-1α proteasomal sabotage, while motor neuropathy fosters deformities and gait derangements amplifying plantar shear. Emergent factors include biofilm-mediated persistence (68–77% DFU prevalence), MMP/TIMP imbalance eroding ECM integrity, and epigenetic "metabolic memory" via histone/DNA modifications and non-coding RNAs sustaining M1 skew and angiogenic suppression. Multifactorial interventions—glycaemic intensification (HbA1c <7%), protease modulation, biofilm disruption, and epigenetic editors—yield 25–76% risk attenuation across trials, yet gaps in longitudinal epigenomic profiling and personalized CRISPR therapeutics persist. Bridging these informs precision strategies to restore redox homeostasis, phenotypic plasticity, and vascular dynamism, mitigating the $15–30 billion annual DFU burden.

**Keywords:** Diabetes, Wound healing, Pathophysiology, CRISPR, DFU, Macrophages

## Introduction

Wound healing represents a tightly regulated biological process encompassing three key phases—inflammation, proliferation, and remodelling—that synchronize in healthy tissues to facilitate timely and complete wound closure. As articulated in the literature, "Independent of the cause of injury, wound healing is characterized by three established phases that are synchronized in time and activity until complete wound closure. The three stages are namely the inflammatory, proliferation, and remodelling phase.[1]" In diabetes, however, this orderly progression is profoundly disrupted, with prolonged inflammation emerging as a hallmark feature that impedes healing and promotes chronic wound formation: "It is recognized that increased and sustained inflammation leads to suboptimal wound healing and subsequent fibrotic development.[1]"

Compounding these issues, hyperglycaemia, oxidative stress, and impaired cellular responses further exacerbate the abnormalities, frequently culminating in delayed closure, heightened infection risk, and recurrent ulceration—particularly in the lower extremities.

## Overview of Normal Wound Healing Mechanisms

### Phases of Wound Healing

Normal wound repair proceeds through a series of overlapping phases that ensure coordinated tissue restoration. This process constitutes a complex, temporally and spatially regulated cascade encompassing hemostasis, inflammation, proliferation, and remodeling [2].

Hemostasis Upon tissue injury, hemostasis promptly halts bleeding through a multifaceted response. Vasoconstriction rapidly reduces blood flow, followed by platelet adhesion to exposed subendothelial surfaces and activation of the coagulation cascade, culminating in fibrin clot formation. This clot establishes a provisional extracellular scaffold that supports subsequent cellular migration and infiltration [2]. Platelets, upon activation, degranulate to liberate more than 300 bioactive mediators, encompassing growth factors such as epidermal growth factor and platelet-derived growth factor, cytokines including interleukins 1 and 6, transforming growth factor-beta, platelet factor 4, and various chemokines that orchestrate immune cell recruitment [3]. Beyond hemorrhage control, this phase lays the foundational matrix and initiates signalling pathways critical for downstream repair processes.

Inflammation The inflammatory phase commences concurrently with hemostasis resolution, serving to eradicate contaminants and prepare the wound bed for reconstruction. Neutrophils predominate as initial responders, infiltrating the site to phagocytose pathogens and debris while liberating reactive oxygen species, proteases, and antimicrobial peptides to sterilize the environment [4]. Subsequently, monocytes enter the wound, differentiating into macrophages that orchestrate phase transition. These cells engulf apoptotic neutrophils through efferocytosis and secrete an array of growth factors to dampen inflammation and promote repair [3]. This phase is indispensable for pathogen clearance and modulation of the microenvironment to favour proliferative activities.

Proliferation The proliferative phase focuses on tissue reconstitution, involving orchestrated cellular proliferation, migration, and matrix deposition. Fibroblasts, endothelial cells, and keratinocytes collaborate to generate granulation tissue, rich in collagen and other extracellular matrix constituents, which bridges the wound defect [3]. Angiogenesis, driven by endothelial cell sprouting and capillary network formation, ensures adequate oxygenation and nutrient delivery to the avascular wound core [5]. Concurrently, keratinocytes migrate across the provisional fibrin scaffold to re-epithelialize the surface, restoring barrier integrity [6].

Remodeling Advanced glycation end-products (AGEs), which accumulate in hyperglycaemic diabetic environments, modify collagen cross-linking and diminish tissue pliability, thereby compromising extracellular matrix dynamics and impairing cellular adhesion and migration during remodeling. Although the extracellular matrix's pivotal function in orchestrating wound repair is extensively characterized, specific mechanistic disruptions by AGEs in diabetic contexts warrant further elucidation[7].

## Key Cellular Players

Multiple cell populations interact dynamically across healing phases to drive resolution.
Platelets: They initiate hemostasis as primary responders but extend their influence throughout repair. They bind to injured endothelium, exocytose alpha-granule contents comprising growth factors and chemokines and polymerize fibrin to form a migratory scaffold [3]. This multifaceted role bridges coagulation with inflammatory signalling, priming the site for regenerative cascades [3].

Neutrophils: These cells dominate early inflammation, rapidly mobilizing to the injury for robust antimicrobial activity. Through phagocytosis and discharge of reactive oxygen species alongside proteases, they neutralize threats and degrade necrotic material [4]. While essential for infection containment, persistent neutrophil activation can prolong inflammation and hinder progression to repair [3].

Macrophages: Their function as versatile coordinators, adopts an initial pro-inflammatory M1 phenotype for debris clearance before polarizing to an M2 reparative state. They facilitate inflammatory resolution via efferocytosis of apoptotic neutrophils and elaboration of growth factors like transforming growth factor-beta and platelet-derived growth factor, thereby shifting the milieu toward proliferation and matrix synthesis [3,7]. This phenotypic adaptability underpins efficient phase transitions.

Fibroblasts and Endothelial Cells Fibroblasts serve as principal architects of the extracellular matrix, synthesizing collagens, fibronectin, and proteoglycans to foster granulation tissue and enable wound contraction through myofibroblast differentiation [3,4]. Endothelial cells, meanwhile, propagate neovascularization by proliferating into tubular structures, sustaining metabolic demands in the healing bed [5].

## Role of Growth Factors and Extracellular Matrix (ECM)

Growth factors and the ECM synergize to direct cellular orchestration in wound repair. Cells including platelets discharge key mediators—such as platelet-derived growth factor, transforming growth factor-beta, vascular endothelial growth factor, fibroblast growth factor, and epidermal growth factor—that stimulate chemotaxis, proliferation, and extracellular matrix production across proliferative and remodeling stages [2]. The ECM, comprising collagens, fibronectin, proteoglycans, and glycosaminoglycans, furnishes structural scaffolding alongside biochemical cues that regulate cellular adhesion, migration, differentiation, and proliferation, culminating in functional tissue restoration [8,9]. These reciprocal interactions not only summon cells to the injury but also calibrate their behaviours to achieve precise spatiotemporal repair.

## Why Diabetes Impairs Wound Healing

In contrast to the orchestrated progression of normal wound healing, diabetes mellitus profoundly disrupts the temporal and spatial coordination of repair phases, culminating in chronic non-healing wounds. This impairment arises from multifaceted pathophysiological derangements, including protracted inflammation, deficient neovascularization, peripheral neuropathy with aberrant mechanical loading, and deposition of advanced glycation end-products (AGEs) that compromise matrix integrity and cellular signalling [10,11].

Delayed Inflammatory Response Optimal wound resolution hinges on swift recruitment of neutrophils and macrophages, coupled with a seamless phenotypic shift from pro-inflammatory M1 macrophages to reparative M2 states, which facilitates debris clearance and proliferative

initiation [3,7]. In diabetic milieus, however, hyperglycaemia fosters dysregulated innate immunity, manifesting as persistent neutrophil influx and macrophage polarization defects that sustain a maladaptive inflammatory milieu. This prolongation impedes efferocytosis—the phagocytosis of apoptotic cells—and exacerbates protease-mediated tissue degradation, thereby stalling transition to granulation tissue formation and predisposing lesions to chronicity.

Impaired Angiogenesis: The process of angiogenesis underpins tissue regeneration by establishing a perfusive microvascular lattice, predominantly governed by endothelial cell activation and vascular endothelial growth factor (VEGF) signalling [5]. Diabetic hyperglycaemia engenders endothelial dysfunction through oxidative nitrosative stress and diminished nitric oxide bioavailability, curtailing VEGF receptor phosphorylation and downstream Akt/eNOS pathways. Consequently, capillary sprouting and lumenization are attenuated, yielding hypoxic wound beds deficient in nutrients and oxygen, which perpetuate stalled re-epithelialization and matrix deposition.

Neuropathy and Altered Biomechanical Loading Diabetic peripheral neuropathy attenuates nociceptive feedback, fostering repetitive subclinical trauma from unperceived pressure gradients during ambulation. This sensory deficit, compounded by autonomic vasomotor instability, amplifies shear and compressive forces on plantar soft tissues, precipitating micro-injuries and callus formation that erode dermal integrity. Biomechanically, heightened peak plantar pressures correlate with reduced tissue hardness and elasticity, exacerbating ulceration susceptibility and impeding mechanotransduction signals essential for fibroblast activation and extracellular matrix remodeling.

Impact of Advanced Glycation End-Products (AGEs) Chronic hyperglycaemia catalyses non-enzymatic glycation of long-lived proteins, yielding AGEs that cross-link collagen fibrils, thereby rigidifying the extracellular matrix and diminishing its pliability. These modifications impair fibroblast adhesion, migration, and collagenolytic activity during remodeling, while receptor-mediated signalling via RAGE elicits pro-inflammatory cascades that further attenuate healing [7]. In diabetic wounds, AGE accumulation thus fosters fibrotic scarring with contracted, disorganized matrices, perpetuating biomechanical dysfunction and cellular senescence.

**Clinical Significance**

Diabetic foot ulcers (DFUs) epitomize the dire sequelae of impaired wound healing, afflicting 15% to 25% of diabetic individuals over their lifetime and exacting a profound socioeconomic toll. Epidemiologically, DFUs exhibit a global prevalence of approximately 6.3%, with annual incidence rates of 2% among at-risk cohorts, disproportionately burdening low- and middle-income regions where access to podiatric care lags. Economically, DFU management incurs direct costs exceeding $15 billion annually in the United States alone, encompassing hospitalizations, debridement, and offloading interventions, while indirect burdens from productivity losses amplify this to over $30 billion. Alarmingly, 14% to 24% of DFUs precipitate major lower-extremity amputations, with 5-year post-amputation mortality rivalling that of many malignancies [13-16].

These ulcers frequently coalesce with comorbidities such as obesity, peripheral artery disease (PAD), and chronic kidney disease (CKD), which synergistically erode healing trajectories. Obesity exacerbates inflammatory adipokine profiles and venous stasis, PAD induces ischemic gradients that thwart perfusion, and CKD impairs leukocyte function alongside uremic toxins that stifle granulation. Racial and socioeconomic disparities further stratify outcomes, with Black and

Hispanic patients facing 1.5- to 2-fold higher amputation risks attributable to delayed presentations and undertreatment of these confounders [17-19].

Collectively, the literature affirms that efficacious repair demands synchronized orchestration of platelets, neutrophils, macrophages, fibroblasts, endothelial cells, growth factors, and extracellular matrix constituents across phases [12]. In diabetes, this harmony fractures under immune dysregulation, vasculopathy, neuropathy, and matrix glycation, underscoring the imperative for targeted molecular inquiries and multidisciplinary trials to mitigate these deficits [10,11].

## Pathophysiology of Impaired Wound Healing in Diabetes

### Hyperglycaemia and Cellular Dysfunction

#### Effects on Fibroblasts

Fibroblasts are indispensable mesenchymal effectors in wound repair, facilitating extracellular matrix (ECM) synthesis, deposition of structural proteins such as collagen and fibronectin, and orchestration of proliferative and remodeling phases through migration to the injury site and differentiation into contractile myofibroblasts [20]. In physiologic contexts, fibroblasts function as immunomodulatory sentinels, maintaining quiescence under homeostasis but activating upon detection of damage- or pathogen-associated molecular patterns to propagate pro-inflammatory signalling, thereby recruiting leukocytes and modulating innate responses via cytokine and chemokine networks [21]. Hyperglycaemia in diabetes, however, precipitates fibroblast senescence, characterized by blunted proliferative capacity, diminished migratory kinetics, and aberrant ECM production, which collectively impair granulation tissue formation and prolong inflammatory stasis [22]. High-glucose milieus inhibit fibroblast migration by repressing basic fibroblast growth factor-mediated c-Jun N-terminal kinase phosphorylation, while elevating interleukin-7/interleukin-7 receptor expression to paracrine-suppress angiogenesis through endothelial dysfunction [23,24]. Senescent fibroblasts further exacerbate delays by exosomally transferring microRNA-497 to endothelial cells, thereby curtailing autophagy via ATG13 suppression and hindering vascular repair [25]. Proliferative deficits are compounded by lactate accumulation in chronic diabetic wounds, mirroring high-glucose-induced metabolic shifts that curtail cell cycle progression [26]. Notably, subtype-specific impairments emerge: in type 1 diabetes, collagen deposition—quantified via hydroxyproline accrual—is reduced by approximately 40% independent of glycaemic control (HbA1c), attributable to intrinsic fibroblast hypoproliferation without elevated collagenase activity, whereas type 2 diabetes sustains normative synthesis [27]. These aberrations foster fibrotic maladaptation in comorbid tissues, such as myocardial remodeling via advanced glycation end-product/receptor for advanced glycation end-product signalling and transforming growth factor-β/Smad activation, amplifying matrix metalloproteinase dysregulation and pro-fibrotic leukocyte recruitment to perpetuate chronic ulceration and organ fibrosis [28].

#### Keratinocyte Dysfunction

Keratinocytes predominate the epidermal compartment, driving re-epithelialization through orchestrated proliferation, differentiation, migration, and angiogenic stimulation to restore barrier integrity while elaborating growth factors (e.g., epidermal growth factor, keratinocyte growth factor, fibroblast growth factor-2), cytokines, chemokines, and matrix metalloproteinases in paracrine/autocrine loops that interface with stromal fibroblasts and macrophages [29]. In diabetic hyperglycaemia, keratinocytes manifest profound dysfunctions encompassing retarded migration, adhesion deficits, and proliferative arrest, which attenuate epidermal regeneration and sustain proteolytic ECM degradation, culminating in non-healing ulcers [29]. Hyperglycaemic

exposure downregulates phosphorylated focal adhesion kinase and α2β1 integrin, impeding translocation across glycated substrates, while interleukin-22 deficits from dysregulated mononuclear cells curtail matrix metalloproteinase-3 secretion essential for locomotion [30]. Apoptotic propensity escalates via upregulated Bcl-2, caspase-3, and Fas ligand/Fas pathways induced by matrix metalloproteinase-9, diminishing viable progenitor pools; concurrently, suppressor of cytokine signalling-3 overexpression obstructs cytokine-driven growth signals, and reactive oxygen species overload—via epidermal growth factor receptor/extracellular signal-regulated kinase-mediated interleukin-8 excess—amplifies neutrophil influx and oxidative burden [31]. Dysbalanced matrix metalloproteinase/tissue inhibitor of metalloproteinase equilibria and thrombospondin-1 overexpression further stifle vascular endothelial growth factor biosynthesis through Akt suppression and epigenetic hypomethylation, exacerbating hypoxia and infection susceptibility [32]. These interconnected impairments underscore keratinocytes' centrality in diabetic wound chronicity, with allogeneic/autologous keratinocyte therapies (e.g., Apligraf) demonstrating accelerated closure in trials by reinstating migratory and proliferative competence [33].

**Endothelial Cell Damage**

Endothelial cells (ECs) maintain vascular homeostasis via nitric oxide (NO)-dependent vasodilation, antithrombotic shielding, and selective permeability, yet diabetes elicits EC dysfunction through synergistic hyperglycaemia and insulin resistance, fostering microvascular hypoperfusion and macrovascular atherothrombosis that impair wound neovascularization [34]. Hyperglycaemia predominates as the instigator, activating diacylglycerol-protein kinase C isoforms and polyol pathways to uncouple endothelial NO synthase, diverting L-arginine flux toward superoxide overproduction and engendering peroxynitrite-mediated nitrosative stress that quenches NO bioavailability [35]. This cascade elevates adhesion molecule expression (e.g., vascular cell adhesion molecule-1), oxidized low-density lipoprotein infiltration, and advanced glycation end-product formation, precipitating leukocyte transmigration and plaque progression [36]. Insulin resistance amplifies these via phosphatidylinositol 3-kinase/Akt attenuation, curtailing endothelial NO synthase phosphorylation and augmenting endothelin-1 vasoconstriction, while adipokine dysregulation (e.g., tumor necrosis factor-α, resistin) and free fatty acid surfeit incite dyslipidaemia and caveolae disruption [37]. Microalbuminuria heralds severity, correlating with superoxide antagonism of NO in type 1 diabetes and paralleling endothelial-to-atherosclerotic trajectories in type 2 [38]. Reactive oxygen species overproduction—mitochondrially sourced under hyperglycaemia—fuels this via NAD(P)H oxidase and uncoupled endothelial NO synthase activation, yielding peroxynitrite that nitrates biomolecules, activates nuclear factor-κB inflammation, and oxidizes lipids to sustain a pro-thrombotic, hypoxic wound milieu [39]. Antioxidant modalities (e.g., N-acetylcysteine) partially ameliorate by scavenging superoxide and preserving NO tone, highlighting the nexus of oxidative/nitrosative disequilibria in diabetic vasculopathy [40].

**Role of AGEs in Cross-Linking ECM Proteins, Leading to Tissue Rigidity**

Advanced glycation end-products (AGEs) accrue via non-enzymatic Maillard condensation of reducing sugars with protein amines, evolving from labile Schiff/Amadori products to stable cross-links (e.g., pentosidine, carboxymethyl-lysine) under protracted hyperglycaemia, thereby infiltrating durable ECM constituents like collagen and elastin to rigidify tissue architecture [41]. These modifications augment intermolecular bridging, elevating fibril density, thermal resilience, and matrix metalloproteinase resistance while eroding solubility, elasticity, and degradability, manifesting as vascular stiffening, myocardial diastolic compromise, and skeletal brittleness via osteoblast suppression [42]. In diabetic pathogenesis, AGE-receptor for AGE ligation propagates

oxidative/inflammatory cascades through Janus kinase/signal transducer and activator of transcription and nuclear factor-κB, inducing transforming growth factor-β/connective tissue growth factor elaboration to transdifferentiate fibroblasts into myofibroblasts and skew ECM toward excessive type I/III collagen accrual [43]. Wound healing falters as glycated scaffolds impair endothelial adhesion (e.g., laminin/fibronectin to type IV collagen), curtail migratory cues, and sustain leukocyte chemotaxis, yielding avascular, fibrotic scars that thwart granulation and re-epithelialization [44]. Fibrotic sequelae amplify in nephropathy (mesangial expansion, basement membrane thickening) and cardiomyopathy (interstitial hypertrophy), where cross-links thicken glomerular/tubulointerstitial matrices and diminish compliance [45]. Therapeutic AGE inhibitors (e.g., aminoguanidine) or breakers attenuate these in models by restoring pliancy and curbing inflammation, positioning the AGE-receptor for AGE axis as a pivotal target for mitigating diabetic rigidity and reparative deficits [46].

**Chronic Inflammation**

A. Persistent Pro-Inflammatory Cytokines: Tumor Necrosis Factor-α (TNF-α), Interleukin-6 (IL-6), and Interleukin-1β (IL-1β)

In diabetic wounds, a maladaptive pro-inflammatory milieu persists due to dysregulated macrophage activation, wherein M1-polarized macrophages predominate and resist phenotypic transition to reparative M2 states. This imbalance sustains elevated secretion of TNF-α, IL-6, and IL-1β, fostering a self-perpetuating inflammatory cascade that impedes progression to proliferative and remodeling phases [47]. TNF-α, primarily elaborated by activated macrophages and adipocytes, recruits neutrophils via chemoattraction and amplifies M1 polarization through TNFR2-mediated mitogen-activated protein kinase and nuclear factor-κB signalling, while high concentrations induce apoptosis in fibroblasts, keratinocytes, and endothelial cells, thereby curtailing extracellular matrix deposition and angiogenesis. IL-6, derived from T lymphocytes, macrophages, and adipose tissue, dose-dependently escalates with hyperglycaemia to stimulate acute-phase responses, neutrophil mobilization via interleukin-8 and monocyte chemoattractant protein-1 induction, and further M1 skewing, correlating with wound chronicity and systemic insulin resistance. IL-1β, processed via NALP3 inflammasome activation in monocytes and macrophages, autoregulates its production and drives leukocyte emigration while promoting insulin resistance; levels in diabetic foot ulcers inversely correlate with healing, remaining elevated through day 10 post-injury in diabetic models [47]. Collectively, these cytokines prolong leukocyte infiltration, enhance matrix metalloproteinase-mediated degradation, and inhibit re-epithelialization, manifesting as stalled granulation and heightened ulceration risk. Therapeutic modulation, such as interleukin-1 receptor antagonism with anakinra or neutralizing antibodies, attenuates downstream TNF-α and IL-6 expression, restores M1/M2 equilibrium, and accelerates closure in db/db murine models and human trials, underscoring cytokine blockade as a viable strategy to mitigate chronicity [47].

B. Oxidative Stress: Reactive Oxygen Species Accumulation and Antioxidant Depletion

Oxidative stress constitutes a pivotal driver of diabetic complications, arising from disequilibrium between reactive oxygen species (ROS) overproduction and antioxidant defenses, exacerbated by chronic hyperglycaemia and mitochondrial dysfunction (49). Hyperglycaemia fuels ROS generation—principally superoxide anions ($O_2^{-}\bullet$), hydrogen peroxide ($H_2O_2$), and hydroxyl radicals (•OH)—via enhanced glycolysis and Krebs cycle flux, yielding excess NADH/$FADH_2$ that overloads the electron transport chain; this uncouples oxidative phosphorylation, amplifying mitochondrial superoxide output and propagating a vicious cycle of cellular damage. Concomitant pathways amplify this burden: the polyol pathway diverts glucose to sorbitol via aldose reductase, depleting NADPH essential for glutathione regeneration; advanced glycation end-product (AGE)

formation from glycated proteins engenders dicarbonyl-mediated free radicals; protein kinase C isoforms, activated by diacylglycerol accumulation, heighten vascular permeability and cytokine elaboration; and hexosamine flux elevates O-linked glycosylation of transcription factors, sustaining inflammation. Antioxidant systems—superoxide dismutase, catalase, and glutathione peroxidase—become overwhelmed, with glutathione peroxidase inactivation via glycation further eroding ROS scavenging. DNA strand breaks from excess ROS activate poly(ADP-ribose) polymerase-1, depleting $NAD^+$ and inhibiting glyceraldehyde-3-phosphate dehydrogenase, thereby shunting glycolytic intermediates into polyol, PKC, and AGE pathways, intensifying oxidative/nitrosative insult. In wound contexts, this manifests as endothelial apoptosis, impaired fibroblast proliferation, and matrix cross-linking rigidity, perpetuating hypoxia and chronic ulceration; lactate buildup from anaerobic glycolysis in hypoxic beds mirrors these shifts, curtailing cell cycle progression via metabolic acidosis [48]. Mitigation via antioxidants or AGE inhibitors restores redox homeostasis and ameliorates tissue injury in preclinical models.

C. Dysregulated Macrophage Polarization in Diabetic Wound Healing

Macrophages orchestrate wound repair via phenotypic plasticity, transitioning from pro-inflammatory M1 states during early inflammation to pro-reparative M2 states in proliferation and remodeling [49]. In physiologic healing, M1 macrophages—elicited by interferon-γ, lipopolysaccharide, granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor—facilitate pathogen clearance and debris phagocytosis via Janus kinase/signal transducer and activator of transcription, interferon regulatory factor, Notch, and phosphatidylinositol 3-kinase/Akt pathways, secreting tumor necrosis factor-α, interleukin-1β, interleukin-6, interleukin-12/23, nitric oxide, and chemokines (CXCL-9/10) while upregulating antigen presentation and complement activation. M2 polarization, induced by interleukin-4/13, interleukin-10, glucocorticoids, and transforming growth factor-β, counters this by elaborating interleukin-10 and promoting extracellular matrix synthesis, angiogenesis, and efferocytosis through mannose receptor and arginase-1 expression. In diabetic wounds, hyperglycaemia and advanced glycation end-products sustain M1 dominance via nuclear factor-κB hyperactivation and Notch1 upregulation, impairing M1-to-M2 shift and yielding persistent inflammation, diminished collagen accrual, and avascular granulation (49). MicroRNAs (e.g., miR-146a inhibiting Toll-like receptor 4/nuclear factor-κB; miR-145a-5p suppressing M1 markers) and long noncoding RNAs (e.g., GAS5 reduction favoring M2; XIST enhancing interleukin-33/miR-19b-mediated repair) emerge as regulators, with dysregulation exacerbating imbalance. This polarization skew fosters reactive oxygen species-induced damage, abrogates vascular endothelial growth factor signaling, and heightens ulceration propensity; targeted interventions—such as phosphatidylinositol 3-kinase/Akt agonists, Notch inhibitors (e.g., DAPT), or mesenchymal stem cell-derived exosomes—restore M2 predominance, bolstering phagocytosis, neovascularization, and closure in streptozotocin-induced models [49].

## Vascular Impairment

### Microvascular Complications

Microvascular sequelae of diabetes predominantly afflict insulin-independent glucose uptake sites—the kidney, retina, and peripheral nerves—rendering them susceptible to hyperglycaemia-mediated insults, including endothelial cytotoxicity, oxidative stress via superoxide excess, sorbitol polyol accumulation, and advanced glycation end-product deposition [50]. These converge to derange perfusion, escalate permeability, deposit extravascular proteins, and dysregulate coagulation, culminating in organopathy. Diabetic retinopathy ensues from retinal capillary derangement: basement membrane hypertrophy, permeability surges yielding microaneurysms and hemorrhages, and ischemia-driven neovascularization with vitreous

traction, progressing to proliferative stages in up to 48% of type 1 cases after 15 or more years [50]. Nephropathy, impacting 30–50% of type 2 diabetics over their lifetime, manifests glomerular hyperfiltration evolving to mesangial expansion, basement membrane thickening, interstitial fibrosis, and podocyte effacement under dual glycaemic/hypertensive duress; microalbuminuria (>30 mg/24h), heralding endothelial barrier breach and filtration surfeit, portends overt proteinuria and end-stage renal disease while increasing cardiovascular mortality 2- to 3-fold—managed via angiotensin-converting enzyme inhibitors/angiotensin receptor blockers targeting <130/80 mmHg blood pressure to retard progression by 20–40% [51]. Neuropathy encompasses distal symmetric sensorimotor deficits (asymptomatic in up to 50%), autonomic dysautonomia, and mononeuropathies, precipitated by vasa nervorum ischemia, oxidative nitrosation, and impaired neurotrophic support; sensory attenuation—vibration/proprioception loss in long fibers—fosters unrecognized trauma, callus formation, and Charcot arthropathy, synergizing with ischemia to precipitate foot ulceration and 60–85% of non-traumatic amputations [52]. Multifactorial intensification (glycaemic HbA1c <7%, lipid optimization) curtails incidence by 25–76% across trials [50].

**Macrovascular Complications**

Hyperglycaemia and insulin resistance synergize to accelerate macrovascular atherogenesis in diabetes, manifesting as coronary heart disease, cerebrovascular events, and peripheral arterial disease through intertwined metabolic-inflammatory cascades [53]. Insulin resistance, often obesity-attendant, liberates free fatty acids that ligate Toll-like receptors, attenuate phosphatidylinositol 3-kinase/Akt signalling to curtail glucose transporter-4 translocation and endothelial nitric oxide synthase activation—yielding nitric oxide paucity and endothelial dysfunction—while nuclear factor-κB transactivation elicits pro-atherogenic cytokines/adhesion molecules. Hyperglycaemia amplifies this via mitochondrial superoxide surge, activating protein kinase C isoforms that heighten permeability, vasoconstrictor endothelin-1 elaboration, and thromboxane $A_2$ dominance over prostacyclin; ancillary fluxes—polyol (NADPH depletion), advanced glycation end-product/receptor ligation (nuclear factor-κB reinforcement), and hexosamine (O-linked glycosylation of Sp1)—sustain oxidative/inflammatory loops. This prothrombotic milieu, compounded by platelet hyperaggregability from dysinsulinemia-induced calcium accrual, destabilizes plaques via foam cell accrual and matrix metalloproteinase excess. Coronary ramifications include 2–4-fold myocardial infarction risk escalation, with diabetics evincing 1.5–2-fold higher post-revascularization mortality/stent thrombosis; cerebrovascularly, ischemic stroke odds ratio approximates 2.3, with 2-fold recurrence/disability amplification; peripherally, ankle-brachial index <0.9 doubles claudication/amputation hazards, medial calcification confounding diagnostics [51]. Multifactorial interventions—glycaemic (HbA1c <7%), lipid (LDL <1.8 mmol/L), and antihypertensive (<130/80 mmHg)—mitigate events by 20–50%, augmented by glucagon-like peptide-1 agonists/sodium-glucose cotransporter-2 inhibitors for cardioprotection [53].

**Hypoxia in Wound Beds**

Diabetic wound hypoxia, intensified relative to normoglycemic lesions, stems from angiogenic deficits and perpetuates a non-resolving milieu, wherein adaptive hypoxia-inducible factor-1 (HIF-1) signalling falters under hyperglycaemic duress [54]. Normoxic prolyl hydroxylase domain enzymes hydroxylate HIF-1α for von Hippel-Lindau-mediated ubiquitination/degradation; hypoxia stabilizes HIF-1α, enabling nuclear translocation, HIF-1β dimerization, and hypoxia response element binding to transcriptionally upregulate vascular endothelial growth factor, glucose transporter-1, erythropoietin, stromal cell-derived factor-1, and stem cell factor—fostering endothelial progenitor cell recruitment, neovascularization, and granulation. In diabetes,

hyperglycaemia aberrantly sustains prolyl hydroxylase activity, enforcing HIF-1α proteasomal turnover even in low-oxygen states; methylglyoxal, a glycolytic byproduct, exacerbates via two prongs: heat-shock protein 40/70/CHIP recruitment for ubiquitin-independent degradation, and p300 coactivator modification impeding HIF-1β dimerization/transactivation. This attenuates vascular endothelial growth factor/stromal cell-derived factor-1/stem cell factor expression, curtailing capillary sprouting, endothelial survival, and perfusion while mitochondrial reactive oxygen species from prolyl hydroxylase overload sustains endothelial injury/inflammation [54]. Outcomes include avascular stasis, necrotic propensity, infection susceptibility, and ulcer recidivism; preclinical restoration via HIF-1α stabilization (e.g., dimethyloxalylglycine) or methylglyoxal scavengers augments granulation and closure in db/db models [54].

**Neuropathy**

Diabetic peripheral neuropathy, the most prevalent diabetic complication (prevalence 30–50%), manifests heterogeneous sensory (numbness, paraesthesia, hyperalgesia/allodynia), motor (weakness/atrophy), and autonomic (orthostasis, gastroparesis) deficits, often insidious with nocturnal pain exacerbation and culminating in ulceration/amputation [55]. Chronic hyperglycaemia precipitates a metabolic cascade—insulin resistance, dyslipidaemia, endoplasmic reticulum/mitochondrial oxidative stress—yielding mitochondrial superoxide surfeit that galvanizes polyol (aldose reductase-mediated sorbitol accrual/NADPH drain), advanced glycation end-product (protein cross-linking/receptor for advanced glycation end-product inflammation), protein kinase C (permeability/cytokine surge), and hexosamine (transcriptional dysregulation) pathways, eroding redox poise and microvascular integrity [55]. This engenders vasa nervorum hypoperfusion, neurotrophic factor (nerve growth factor/brain-derived neurotrophic factor) depletion, axonal degeneration, Schwann cell demyelination, and macrophage-mediated cytokine/chemokine efflux, disproportionately afflicting distal sensory fibers (myelinated Aδ/C unmyelinated) for vibration/temperature/proprioception loss. Protective sensation ablation begets repetitive microtrauma from unperceived pressure/shear, fostering callosities, fissures, and Charcot neuroarthropathy amid ischemia/infection synergy—initiating 85% of foot ulcers. Glycaemic intensification (HbA1c reduction >1%) retards progression by 60% in nascent cases; symptomatic palliation employs duloxetine/gabapentinoids (number needed to treat 6 for 50% relief), with holistic podiatric surveillance/preventive offloading averting 50–70% of amputations [55].

**Motor Neuropathy: Foot Deformities and Altered Gait Mechanics**

Diabetic neuropathy manifests as a distal, symmetrical, length-dependent degeneration of somatic and autonomic nerves, with motor involvement exacerbating fall propensity, gait instability, and postural sway despite predominant sensory deficits [56]. Motor neuropathy induces weakness and atrophy of intrinsic foot musculature, engendering imbalance that, compounded by neuropathic arthropathy, precipitates diabetic neuro-osteoarthropathy (Charcot foot)—a progressive, irreversible cascade of weight-bearing osteoarticular destruction, midfoot effacement ("rocker-bottom" deformity), and claw toe malalignments [56]. Quantitative assessments via isokinetic dynamometry reveal deficits in ankle dorsiflexors/plantar flexors and knee extensors/flexors across type 1 and type 2 diabetes cohorts, attributable to denervation, intramuscular lipogenesis, and mitochondrial bioenergetic impairment, evincing a distal-proximal atrophy gradient; severe manifestations entail near-total distal denervation with neurogenic sarcomere disarray [56]. Neuromuscular junctional perturbations commence with demyelination, attenuated acetylcholine quanta, and terminal dysmorphology, evolving to motor unit attrition and hypertrophic reinnervation with aberrant firing patterns; concomitant gamma motor neuron injury attenuates spindle Ia/Ib afferent feedback, blunting stretch reflexes and volitional

precision, thereby undermining gait kinematics [56]. Corticospinal tract demyelination and volumetric attenuation further impair descending drive, fostering incoordination and disequilibrium [56]. These perturbations redistribute plantar loading to metatarsal prominences, synergizing with sensory attenuation to provoke subclinical shear/pressure insults, culminating in callus hyperkeratosis, fissuring, and ulceration susceptibility amid ischemia and microbial ingress—positioning motor neuropathy as a cardinal antecedent to diabetic pressure ulcer chronicity [56].

## Additional Pathophysiological Factors

### Biofilm Formation

Biofilms comprise polymicrobial consortia encased in an extracellular polymeric substance matrix of polysaccharides, proteins, lipids, and nucleic acids, conferring adherence to host tissues or foreign substrates while impeding antimicrobial ingress and immune effector access [57]. Implicated in 60–80% of chronic infections, including diabetic foot ulcers (DFUs), biofilms facilitate antibiotic resistance gene horizontal transfer and evade phagocytosis, engendering recalcitrant, recurrent suppurations [57]. In DFUs, biofilms—predominantly polymicrobial assemblages of Gram-negative opportunists (e.g., Pseudomonas aeruginosa, Escherichia coli, Acinetobacter baumannii) and Gram-positive pathogens (Staphylococcus aureus, Enterococcus faecalis)—exploit necrotic debris and immunosenescence to transition from planktonic to sessile phenotypes, perpetuating a proinflammatory niche via quorum sensing-mediated virulence [57]. Neutrophil/macrophage aggregates liberate reactive oxygen species and proteases, paradoxically amplifying matrix metalloproteinase-9-driven extracellular matrix proteolysis and angiogenesis inhibition while biofilm-embedded persisters elude clearance [57]. Prevalence attains 68–77% in biopsied DFUs, correlating with neuropathy, osteomyelitis, ulcer duration exceeding 30 days, Wagner grade ≥2, necrosis, and surface area >4 $cm^2$; P. aeruginosa quorum sensing proteases further thwart leukocyte infiltration [57]. Diagnosis hinges on tissue biopsy (gold standard) over swabs, augmented by confocal laser scanning/electron microscopy or peptide nucleic acid-fluorescence in situ hybridization for matrix visualization; clinical proxies encompass iridescent exudate, recalcitrant slough, or gelatinous regrowth post-debridement [57]. Management adheres to biofilm-based wound care paradigms: iterative sharp/surgical debridement with topical antiseptics (e.g., silver nanoparticles, polyhexamethylene biguanide) to disrupt aggregates, transitioning to maintenance antimicrobials and advanced modalities (negative pressure therapy, bioengineered substitutes) upon granulation; adjuncts like bacteriophages, antimicrobial peptides, phytochemicals (quercetin), or photodynamic therapy synergize with systemic agents to curtail recurrence and foster closure [57].

### Dysregulated Protease Activity

Matrix metalloproteinases (MMPs)—zinc-dependent endopeptidases—mediate extracellular matrix proteolysis across hemostasis (debridement), proliferation (angiogenic scaffolding), and remodeling (collagen maturation), counterpoised by tissue inhibitors of metalloproteinases (TIMPs) that enforce spatiotemporal restraint [58,59]. In diabetes, hyperglycaemia, oxidative surfeit, and advanced glycation end-product accrual dysregulate MMP/TIMP stoichiometry, elevating MMP-1/2/8/9 alongside TIMP-1/2/3 attenuation, yielding unchecked ECM catabolism, growth factor sequestration, and inflammatory perpetuation [58,59]. Neutrophil-elaborated MMP-8 surges 50–100-fold in chronic DFUs, while MMP-9 predominates in hypoxic/inflammatory milieus to degrade fibronectin/laminin, abrogate re-epithelialization, and amplify interleukin-6/tumor necrosis factor-α loops; MMP-2 facilitates keratinocyte locomotion yet exacerbates fibrosis when imbalanced [58,59]. This disequilibrium—evident in MMP-9/TIMP-1 ratios >10 in non-healing ulcers—thwarts granulation, sustains protease-rich exudates, and correlates with

Wagner grade escalation, osteomyelitis, and amputation [58,59]. Peripheral neuropathy compounds vulnerability by delaying lesion detection, permitting unchecked proteolysis to excavate deeper breaches amid unperceived plantar shear [58]. Photobiomodulation restores equilibrium by repressing MMP-1/2/9 transcripts and augmenting TIMP-2 in diabetic models, underscoring therapeutic targeting (e.g., selective MMP-9 inhibitors, doxycycline) to recalibrate remodeling and avert chronicity [58,59].

**Epigenetics**

Chronic hyperglycaemia imprints a "metabolic memory" in diabetic wounds, sustaining reparative deficits via epigenetic reprogramming—histone tailoring, cytosine methylation, non-coding RNA orchestration, and $N^6$-methyladenosine ($m^6A$) epitranscriptomics—that aberrantly governs hemostasis, inflammation, proliferation, and extracellular matrix dynamics without genomic alteration [60]. Histone perturbations skew macrophage ontogeny toward pro-inflammatory M1 phenotypes: methyltransferases MLL1/Setdb2 enforce H3K4me3/H3K9me3 at Toll-like receptor 4/nuclear factor-κB loci, amplifying interleukin-6/tumor necrosis factor-α while SETD2-mediated H3K36me3 attenuates AKT/mTOR-driven keratinocyte mitogenesis; SET7/9 targets hypoxia-inducible factor-1α for angiogenic sabotage, whereas EZH2/JMJD3 toggles H3K27me3 on Runx1/VEGFA to modulate endothelial repair [60]. Acetyltransferases/deacetylases (MOF/HDAC2/5/8) acetylate H4K16 or suppress HO-1/Sirt1, fostering interleukin-1β pyroptosis and M1 dominance; sirtuin ablation elevates H3K27ac at cytokine promoters, while lactylation links glycolytic flux to reparative gene repression [60]. DNA methylation via DNMT1 hypermethylates Notch1/PU.1/KLF4/Ang-1/TGF-β, curtailing macrophage accrual, M2 skew, and endothelial barrier integrity; TET2/TDG-mediated demethylation of MMP-9 unleashes proteolysis, impeding closure [60]. Non-coding RNAs interweave: microRNA-146a/129-2-3p/497 dampen Toll-like receptor 4/nuclear factor-κB for M2 transition, whereas microRNA-195-5p/205-5p/155 repress VEGFA/FGF-7; long non-coding RNA H19/GAS5/MALAT1/XIST sponge microRNA-29b/150-5p/1914-3p to liberate CTGF/SOX9/COL1A1 for angiogenesis/fibroblast activation, with circular RNA-Snhg11/0001052/ADAM9 modulating hypoxia-inducible factor-1α/autophagy [60]. $m^6A$ dynamics amplify: METTL3/14 methylate STAT1/VEGF-C for M1 bias/lymphangiogenesis, FTO destabilizes PPAR-γ, and YTHDC1/SQSTM1 curbs keratinocyte autophagy [60]. These interconnected aberrations—protracted M1 persistence, angiogenic paucity, keratinocyte stasis, and matrix excess—underpin non-healing diathesis; CRISPR epigenome editors (dCas9-p300/TET1), histone deacetylase inhibitors, or exosomal non-coding RNA payloads herald precision rectification [60].

**Future Directions and Challenges**

Cytokines are key inflammatory mediators produced during infection, functioning to stimulate target cells and increase interleukin (IL) levels. This process can contribute to the development of type 2 diabetes mellitus (T2DM), refractory wound repair, and insulin resistance. Yan et al. (2014) developed a non-invasive diagnostic tool combining gas chromatography and mass spectrometry (GC-MS) for early T2DM detection, designed to be cost-effective for resource-limited settings. This tool identifies isopropanol and 2,3,4-trimethylhexane in exhaled breath, achieving a sensitivity of 97.9% and specificity of 100%. Similarly, Scirica et al. (2017) examined cardiac biomarkers in T2DM, finding elevated high-sensitivity troponin T (hs-cTnT) levels indicative of cardiac stress, which correlates with increased DFU risk. Inflammatory markers such as C-reactive protein (CRP) and IL-6 play predictive roles in diabetic foot ulcer (DFU) progression, severity, and non-healing risk. Strong correlations exist between elevated CRP ($r = 0.839$) and IL-6 ($r = 0.728$) levels and poor wound healing outcomes, consistent with findings from Mohamed et al. (2024). Although emerging biomarkers show promise for detecting T2DM, assessing DFU

severity, or predicting non-healing, traditional markers like HbA1c, fasting glucose, and cardiac troponins remain essential for risk stratification and disease monitoring [68, 69].

IL-10 represents a potential biomarker for promoting healing. This anti-inflammatory cytokine is synthesized by macrophages, dendritic cells, Th2 cells, and activated regulatory T cells, with low expression in keratinocytes and endothelial cells at diabetic wound edges, which may limit excessive inflammation. Studies in streptozotocin-induced diabetic (STZ) rats demonstrate that elevated IL-10 disrupts immune responses, delaying healing, suggesting a mechanistic link between IL-10 levels and wound outcomes [61,71,72].

Transforming growth factor-beta (TGF-β) regulates collagen synthesis and tissue remodeling. In diabetic wounds, reduced TGF-β expression is consistently associated with delayed healing. In non-diabetic individuals, TGF-β promotes fibroblast proliferation, extracellular matrix production, and angiogenesis. In T2DM, TGF-β downregulation fosters chronic inflammation and impairs regeneration, resulting in delayed wound closure. Research by Nirenjen et al. (2023) and Li et al. (2020) supports TGF-β as a biomarker: elevated levels correlate with enhanced fibroblast activity and collagen deposition, whereas low levels indicate impaired repair and adverse outcomes in diabetic wounds.

**Genetic and Metabolic Profiling for Tailored Therapies**

Personalized diabetes management is crucial for optimizing DFU healing. Genetic profiling identifies DNA variants predicting disease susceptibility or treatment response. Heritability of T2DM ranges from 25% to 72% [65]. The rs13266634 polymorphism in SLC30A8 influences T2DM risk and therapeutic efficacy, underscoring the value of individualized strategies [65]. Pharmacogenetic studies highlight KCNJ11 mutations, which encode the Kir6.2 subunit of ATP-sensitive potassium channels, affecting insulin secretion and drug responsiveness (Billings and Florez, 2010) [65]. Genetic testing enables targeted preventive interventions, such as lifestyle modifications, to mitigate disease onset in at-risk individuals [65].

Barriers to Implementing Advanced Therapies

- **Cost and reimbursement**: Economic feasibility in resource-limited settings.
- **Regulatory hurdles**: Approval processes for novel biologics and devices.
- **Clinician training**: Ensuring adoption of cutting-edge techniques.

When evaluating precision medicine, implementation barriers must be addressed. An umbrella review by Aguilera-Cobos et al. (2023) analyzed 71 studies on advanced therapy medicinal products (ATMPs) [66], identifying cost-related challenges in 14. For instance, Provenge faced bankruptcy due to manufacturing scale-up issues. Regulatory obstacles are exemplified by Glybera, a gene therapy withdrawn for insufficient post-marketing data. The European Medicines Agency's conditional marketing authorization can expedite access when comprehensive data are pending. Clinician attitudes also hinder adoption; younger providers exhibit more favourable views toward insulin pumps ($r = -0.26$, $P < 0.001$) and continuous glucose monitoring ($r = -0.14$, $P = 0.02$) than older counterparts ($r = -0.23$, $P = 0.001$). Both groups prioritize cost reduction, improved insurance, and education to enhance device adherence [68].

The Role of Technology

- AI and machine learning: Predicting wound healing trajectories and infection risk.
- Wearable sensors: Real-time monitoring of wound pH, temperature, and moisture.
- Telemedicine: Remote wound assessment and management in underserved areas.

Machine learning (ML) has transformed DFU outcome forecasting, accurately predicting resolution up to 16 weeks into treatment. Renard et al. (2022) analyzed photographs from 2,291 visits involving 281 ulcers across 155 patients, developing an ML model reliant on hand-crafted imaging features (e.g., ulcer measurements and patterns), with supplementary clinical inputs like nutrition and size influencing predictions. This approach requires minimal computational resources, enabling deployment on smartphones or tablets for remote use, workload reduction, and misdiagnosis prevention. ML also facilitates DFU classification by type and severity, supporting personalized interventions and early detection.

ML aids in amputation risk prediction for DFUs, where procedures are indicated for severe infection, gangrene, or necrosis to avert sepsis or mortality. One study applied XGBoost and gradient-boosted trees to predict lower extremity amputations (LEAs) during hospitalization, achieving high accuracy for major LEAs (AUC-ROC = 0.82), moderate for minor LEAs (0.637), and fair for any LEA (0.756). Key predictors included white blood cell count, comorbidity score, red blood cell count, eosinophil levels, and necrotic eschar [73].

Wearable sensors are advancing non-invasive wound monitoring by integrating pH and temperature detection for real-time infection alerts. Smart dressings with self-healing properties or triggerable drug delivery support remote management and efficiency. Challenges include limited sensitivity to subtle pH/temperature shifts in early infection and the need for multi-biosensor integration. Future innovations should enhance accuracy, sensitivity, and incorporate 3D wound mapping.

**Global Health Perspectives**

- Disparities in wound care outcomes across populations**:** Black and Hispanic populations; rural areas [76,77,78].
- Strategies for scaling affordable interventions in low- and middle-income countries (LMICs) [79]**.**
- Public health initiatives**.**

DFU treatment varies by race and ethnicity. Centers for Disease Control and Prevention data indicate White individuals are more likely to receive revascularization, limb preservation, or timely amputations than Black or Hispanic patients, who present at later stages with higher hospitalization risks [76.77]. Research disparities persist; Athonvarangkul et al. (2023) studied far-infrared energy for peripheral circulation in a cohort of 32 participants (27 White, 5 non-White). These inequities stem from historical socioeconomic barriers limiting care access. Future studies must prioritize diverse representation [76].

Rural-urban divides exacerbate outcomes: 65% of rural counties face health professional shortages, rising to 83% in predominantly Black areas [78]. Multidisciplinary limb teams are urban-centric, leaving rural sites underserved in vascular and infectious disease expertise. Black patients experience gangrenous DFUs at nearly twice the rate of White patients, highlighting needs for expanded ambulatory care and specialists.

In LMICs, multidisciplinary teams—including podiatrists, endocrinologists, and wound care nurses—are essential for DFU management amid resource constraints. Podiatrist involvement reduces major amputations by 56–85% through routine exams, education, and foot care [79]. Endocrinologists optimize glycaemic control, lowering recurrence and ulceration risks via comorbidity management and medication guidance [79]. Wound care nurses mitigate infection and amputation risks through early assessments and evidence-based protocols [79].

## Conclusions

The confluence of metabolic, inflammatory, vascular, and epigenetic aberrations in diabetes coalesces to engender a non-resolving wound milieu, wherein sustained hyperglycaemia perpetuates a self-amplifying cycle of oxidative insult, proteolytic excess, hypoxic stasis, and immunosenescence—manifesting as stalled granulation, recurrent ulceration, and limb-threatening sequelae. Pivotal insights delineate macrophage M1/M2 disequilibrium and cytokine cascades as therapeutic linchpins, amenable to interleukin-1 blockade or phosphoinositide 3-kinase agonists; endothelial/keratinocyte dysfunctions underscore angiopoietin-like 4/microRNA-497 inhibition for reparative resuscitation; and biofilm/MMP dysregulation advocates iterative debridement with selective inhibitors (e.g., doxycycline for MMP-9). Epigenetic reprogramming—via HDAC/DNMT antagonists or exosomal non-coding RNAs—harbingers reversal of "metabolic memory," restoring HIF-1α/VEGFA signaling and ECM pliancy. Notwithstanding, translational lacunae abound: subtype-specific (type 1 vs. 2) disparities in fibroblast hypoproliferation, paucity of human epigenomic cohorts, and underpowered trials on multimodal adjuncts (photobiomodulation, bacteriophages) necessitate rigorous, stratified investigations. Future paradigms must integrate omics-driven biomarkers for risk stratification, harnessing CRISPR epigenome editors and bioengineered scaffolds to recalibrate the diabetic wound niche. By dismantling these barriers, we may curtail the 14–24% amputation trajectory and socioeconomic toll, advancing toward resilient, regenerative healing paradigms.

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