Review Article

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Advanced Bioengineered and Molecularly Targeted Strategies in Diabetic Wound Healing: A Literature Review

Internal Medicine Section

MANSOUR ALANAZI[1], DHAIFALLAH ALENIZI[2], SHEREEN MOHAMED OLAMA[3], RAED ALRUWAILI[4], ANSHOO AGARWAL[5], BADER ALANAZI[6]

ABSTRACT

Diabetic Foot Ulcers (DFUs) represent a major complication of Diabetes Mellitus (DM), associated with significant morbidity, elevated risk of lower limb amputation and substantial healthcare costs. Conventional wound management strategies frequently prove inadequate given the complex pathophysiology of diabetes-associated impaired tissue repair, driving a paradigm shift towards advanced bioengineered, molecular and nanotechnology-based therapeutic approaches. The present literature review comprehensively evaluates the evidence for six major therapeutic domains: bioengineered skin substitutes, growth factor therapies, nanotechnology-based drug delivery systems, regenerative medicine modalities {Mesenchymal Stem Cell (MSC) therapy, exosome therapy, Platelet-Rich Plasma (PRP) and gene therapy}, Hyperbaric Oxygen Therapy (HBOT) and emerging multimodal smart platforms. Bioengineered skin substitutes- including Apligraf, Dermagraft and EpiFix- demonstrated superior wound closure rates compared to conventional dressings across multiple Randomised Controlled Trials (RCTs) and meta-analyses. Becaplermin {recombinant Platelet-Derived Growth Factor (PDGF) –BB}, the sole Food and Drug Administration (FDA)-approved molecularly targeted agent for DFUs, achieved complete wound healing in 48% of patients versus 25% in the placebo group (p=0.007). Nanotechnology platforms demonstrated transformative antibacterial, antioxidant and sustained drug delivery potential, although a significant translational gap between preclinical and clinical evidence persists. Regenerative medicine modalities- including MSC therapy, exosome-based therapies, PRP and HBOT- each demonstrated clinically meaningful benefits in refractory or high-risk DFUs. No single therapeutic modality fully addresses the multifactorial pathological deficiencies of diabetic wound healing. An evidence-based, patient-stratified, multimodal approach- integrating bioengineering, molecular biology, nanotechnology and regenerative medicine- represents the optimal strategy for improving clinical outcomes in DFUs. A Wagner-grade-stratified treatment algorithm is proposed to facilitate evidence-based clinical decision-making.

Keywords: Diabetic foot, Mesenchymal stem cells, Nanoparticles, Platelet-rich plasma, Regenerative medicine, Tissue engineering

INTRODUCTION

The DM is among the non communicable diseases with the fastest rate of global growth. According to the International Diabetes Federation (IDF), an estimated 537 million adults were living with diabetes in 2021, a figure projected to reach 783 million by 2045. Impaired wound healing constitutes one of the most debilitating complications of diabetes, contributing substantially to morbidity, hospitalisation and lower limb amputation [1]. An estimated 19-34% of individuals with diabetes will develop a DFU during their lifetime, with an annual global incidence of approximately 9.1 million new cases [2].

Under normal physiological conditions, wound healing proceeds through four overlapping, well-coordinated phases: haemostasis, inflammation, proliferation and remodelling [3]. Each phase involves a precisely timed sequence of cellular and molecular events. Macrophages coordinate the transition from proinflammatory to pro-repair states; fibroblasts produce and deposit collagen; keratinocytes drive re-epithelialisation; and endothelial cells support angiogenesis. The Extracellular Matrix (ECM) functions as a dynamic scaffold throughout all stages [2,3].

This finely regulated healing cascade is severely disrupted in the diabetic microenvironment. Advanced Glycation end products (AGEs), formed as a consequence of chronic hyperglycaemia, impair protein function and disrupt cellular signalling [3]. Oxidative stress generated by excess glucose metabolism overwhelms endogenous antioxidant defences, causing direct cellular damage and perpetuating the inflammatory phase [4]. Microvascular and macrovascular diseases limit tissue perfusion and oxygen supply, whereas peripheral neuropathy reduces sensory perception and raises the risk of repeated microtrauma [5]. When taken as a whole, these processes produce a wound environment marked by persistent inflammation, poor angiogenesis, decreased growth factor bioavailability, inadequate collagen synthesis and increased vulnerability to biofilm-forming infections [5,6].

Conventional wound management techniques- including wound debridement, pressure offloading, moisture-balancing dressings, infection control and glycaemic optimisation- provide essential foundational care but frequently prove insufficient for complex, non healing diabetic ulcers [6]. The increasing prevalence of antibiotic-resistant infections further compounds treatment challenges [7]. By comprehensively integrating the evidence across six key therapeutic areas, the current literature review fills a critical translational gap.

Molecular Pathophysiology of Impaired Diabetic Wound Healing

An understanding of the molecular mechanisms underlying impaired diabetic wound healing is essential for designing targeted therapies. The disruption affects all four phases of healing [Table/Fig-1]. Chronic hyperglycaemia leads to non enzymatic glycation of proteins and lipids, generating AGEs that activate Receptor for AGE (RAGE) receptors on fibroblasts, macrophages and endothelial cells [3]. RAGE activation triggers downstream Nuclear Factor Kappa B (NF-κB) signalling, amplifying proinflammatory cytokine production {tumour necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6} and prolonging the inflammatory phase. Reactive Oxygen Species

Healing phase	Key cells/Molecules	Normal duration	Diabetic impairment mechanism
Haemostasis	Platelets, fibrin, clotting factors	Minutes to hours	Impaired platelet function; reduced thromboxane A2; hyperglycaemia-driven endothelial dysfunction [3]
Inflammatory	Neutrophils, macrophages, IL-1β, TNF-α, IL-6	2-5 days	Prolonged inflammation; excess ROS; elevated AGEs activating NF-κB; impaired macrophage polarisation (M1 dominance) [3,4,8]
Proliferative	Fibroblasts, keratinocytes, VEGF, EGF, PDGF, TGF-β	5-21 days	Reduced fibroblast activity; impaired VEGF signalling; poor angiogenesis; decreased collagen deposition; growth factor deficiency [3,8]
Remodelling	Myofibroblasts, MMPs, collagen I & III, TIMP	21 days-2 years	Excessive MMP-2 and MMP-9 activity; deficient TIMP; poor collagen cross-linking; chronic non healing state [8]

[Table/Fig-1]: Phases of wound healing: normal progression versus diabetic impairment.

(ROS) generated by excess glucose metabolism overwhelm endogenous antioxidant enzymes, resulting in oxidative damage to cellular membranes, Deoxyribonucleic Acid (DNA), and wound repair proteins [4,8].

Growth factor deficiency at wound sites is paradoxical in diabetes: despite elevated systemic levels, PDGF, Vascular Endothelial Growth Factor (VEGF), Epidermal Growth Factor (EGF), Transforming Growth Factor-beta (TGF-β) and Insulin-like Growth Factor 1 (IGF-1) are markedly downregulated in diabetic wound tissue [8]. Protease hyperactivity {particularly Matrix Metalloproteinase (MMP)-2 and MMP-9}, AGE-mediated growth factor inactivation and reduced receptor expression on target cells collectively account for this phenomenon. Angiogenic failure is mediated by downregulation of VEGF-A and impairment of its downstream phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) signalling cascade [8]. Polymicrobial biofilm formation occurs within 24-72 hours of wound colonisation; biofilm-embedded bacteria demonstrate 100-1,000-fold greater antibiotic resistance compared to their planktonic counterparts [7,8].

Advances in Diabetic Wound Management

Bioengineered skin substitutes: Bioengineered skin substitutes are designed to replicate the cellular composition, structural architecture and signalling environment of native skin. Available products include living cell-based bilayer constructs, acellular dermal matrices, placental membrane allografts and emerging three-dimensional (3D) bioprinted constructs [9-11]. A comparative analysis of available options is presented in [Table/Fig-2] [4,9-12]. Apligraf (Organogenesis, USA) consists of a stratified neonatal keratinocyte epidermal layer overlying a bovine collagen type I dermal matrix seeded with neonatal human dermal fibroblasts; complete wound closure was achieved in 56% of treated patients compared with 38% in the standard care group at 12 weeks ($p<0.05$) [11].

Dermagraft employs a bioabsorbable polyglactin mesh seeded with neonatal human dermal fibroblasts and was associated with significantly higher odds of complete healing compared with gauze dressing {Odds Ratio (OR) 1.71, 95% Confidence Interval (CI) 1.09-2.67} in a prospective RCT [10].

EpiFix (MiMedx, USA) is a dehydrated human amnion/chorion membrane (dHACM) allograft delivering more than 200 regulatory proteins, including PDGF-AA, VEGF, EGF and TGF-β, as well as tissue inhibitors of metalloproteinases and achieved 97% complete closure versus 0% in the standard care arm at four weeks [12]. Three-dimensional bioprinting represents the current frontier of skin replacement technology, with Phase II clinical trials ongoing.

Growth factor therapies: Growth factor therapies replenish the depleted signalling milieu of diabetic wounds through ligand-receptor-mediated, phase-appropriate mechanisms [13]. The principal growth factors are summarised in [Table/Fig-3] [14-17]. Becaplermin (recombinant human PDGF-BB, 0.01% topical gel) is the only growth factor agent with FDA approval for the treatment of chronic DFUs. Becaplermin activates downstream Ras/Mitogen-Activated Protein Kinase (MAPK) and PI3K/Akt pathways upon binding to PDGFRβ, driving fibroblast chemotaxis, proliferation and ECM synthesis [14]. Becaplermin carries a boxed warning regarding malignancy risk with three or more tubes of use. Sustained-release formulations using microspheres and hydrogel carriers are under clinical investigation [15]. VEGF-A is the principal angiogenic regulator and a key therapeutic target in ischaemic diabetic wounds; controlled-release delivery systems including collagen sponges, injectable hydrogels and VEGF gene-loaded lipid nanoparticles have been developed [16,17]. Evidence summaries are presented in [Table/Fig-3].

Nanotechnology-based drug delivery systems: Nanotechnology platforms offer precise spatial and temporal control over therapeutic agent delivery to the wound microenvironment. Key platforms and their evidence profiles are summarised in [Table/Fig-4] [18-23]. Silver nanoparticles (AgNPs) demonstrate broad-spectrum antibacterial activity mediated by silver ion release, ROS generation and direct membrane disruption [18]. Zinc Oxide Nanoparticles (ZnO NPs) enhance keratinocyte migration and VEGF expression and provide complementary antioxidant and pro-regenerative properties [19]. Electrospun nanofibre scaffolds fabricated from biodegradable polymers provide a biomimetic substrate for cell adhesion and directed migration [20-22]. Cellulose acetate nanofibres functionalised with chitosan/cerium oxide nanoparticles achieved approximately 95% wound closure in 15 days [22]. Stimuli-responsive nanogel systems capable of releasing therapeutic cargo in response to wound-specific microenvironmental cues (pH, glucose concentration, MMP activity, or temperature) represent the most advanced application of nanotechnology in this field [20]. Abdel-Gawad R et al., found that AgNP hydrogel (cellulose) improved wound healing in Streptozotocin (STZ)-induced diabetic rats [23]. Evidence summaries are presented in [Table/Fig-4].

Product	Category	Components	Mechanism	Clinical evidence	Limitations
Apligraf	Bilayer (living cells)	Bovine collagen + neonatal fibroblasts + keratinocytes	GF secretion; ECM deposition; re-epithelialisation	RCT: 56% closure vs 38% standard care ($p<0.05$) [9-11]	Cold storage; short shelf life; high cost
Dermagraft	Dermal (living cells)	Polyglactin scaffold + neonatal fibroblasts	Fibroblast-secreted GFs; collagen synthesis; angiogenesis	Prospective RCT: Higher closure rates vs gauze (OR 1.71) [10]	Single use; expensive; limited availability in LMICs
Acellular allograft	Acellular allograft (dHACM)	Dehydrated human amnion/chorion membrane	Anti-inflammatory cytokines; PDGF-AA, EGF, VEGF, TGF-β delivery	RCT: 97% vs 0% complete closure at 4 weeks [12]	Variable biologic processing; storage requirements
Integra	Acellular dermal matrix	Cross-linked bovine collagen + GAG + silicone layer	Scaffolding for fibroblast migration; neodermis formation	Prospective study: 94% successful engraftment [4]	Two-stage procedure; infection risk under silicone layer

[Table/Fig-2]: Comparative analysis of bioengineered skin substitutes for diabetic wound management [4,9-12].

Growth factor	Primary source	Target cells	Key actions	Delivery systems	Clinical outcome data
PDGF (Becaplermin)	Platelets, macrophages	Fibroblasts, smooth muscle cells	Chemotaxis; fibroblast mitogenesis; ECM deposition; granulation	Topical gel (0.01%); sustained-release microspheres	RCT: 48% complete healing vs 25% placebo (p=0.007) [14]
VEGF	Endothelium, macrophages	Endothelial cells	Angiogenesis; vascular permeability; endothelial migration	Hydrogel scaffolds; gene-delivery nanoparticles; collagen sponges	In vivo: 3× increase in microvessel density; faster closure in STZ models [16]
EGF	Platelets, macrophages	Keratinocytes, fibroblasts	Epithelialisation; keratinocyte migration; collagen synthesis	Electrospun nanofibres; topical spray; bioprinted scaffolds	RCT: Significant re-epithelialisation vs control (p<0.01) [17]
TGF-β	Platelets, T-cells	Fibroblasts, macrophages	Collagen synthesis; myofibroblast differentiation; anti-inflammatory switch	Collagen matrices; alginate beads; gene therapy vectors	Pre-clinical evidence: Improved collagen I/III ratio and wound tensile strength [15]
IGF-1	Liver, fibroblasts	Keratinocytes, endothelial cells	Cell survival; anti-apoptotic; angiogenesis; glucose uptake	IGF-1-loaded hydrogels; MSC-secreted paracrine	In vivo (animal model): Enhanced angiogenesis in diabetic rats [15]
FGF-2	Fibroblasts, endothelium	Fibroblasts, endothelial cells	Fibroblast and endothelial proliferation; angiogenesis; wound contraction	Alginate microspheres; fibrin hydrogels; nanoparticles	Phase II RCT: Significantly reduced ulcer area at 12 weeks (p=0.003) [16]

[Table/Fig-3]: Growth factors in diabetic wound therapy: sources, mechanisms, delivery systems and clinical evidence [14-17].

Nanoplatform	Size range	Loaded agents	Mechanism of action	In-vivo evidence	Key advantages
AgNPs	1-100 nm	Ag ions; curcumin co-loading	ROS generation; membrane disruption; anti-biofilm	Complete wound closure within 15 days; 95% antibacterial in STZ rats [18]	Broad-spectrum antimicrobial; low resistance risk
ZnO NPs	10-200 nm	ZnO core; growth factors	Antioxidant; antibacterial; promotes keratinocyte migration	Accelerated closure; VEGF upregulation; enhanced re-epithelialisation [19]	Pro-regenerative; low mammalian cell toxicity at therapeutic doses
Polymeric nanoparticles	50-300 nm	Antibiotics; VEGF; curcumin; siRNA	Sustained controlled release; protect cargo from degradation	Reduced bacterial load; 2× faster closure vs free drug [20]	Tunable release kinetics; biodegradable matrices
Electrospun nanofibres	100 nm-10 µm	GFs; antimicrobials; MSCs	ECM-mimicking scaffold; cell attachment; directional migration	~95% wound closure in 15 days; enhanced collagen deposition [21,22]	High surface area; customisable; supports cell infiltration
AgNP hydrogel (cellulose)	Various	AgNPs; carboxymethyl cellulose	Sustained silver release; antimicrobial matrix	Wound healing in STZ-induced diabetic rats [23]	Biodegradable matrix; ease of application
Stimuli-responsive nanogels	50-500 nm	Exosomes; antimicrobials; antioxidants	pH/glucose-triggered release; smart drug delivery	Enhanced antibacterial + anti-inflammatory + angiogenic effects [20]	Context-specific release; reduced off-target effects

[Table/Fig-4]: Nanotechnology platforms for diabetic wound therapy: evidence summary [18-23].

Regenerative medicine approaches: Regenerative medicine approaches aim to restore intrinsic healing capacity through replacement or supplementation of dysfunctional cellular components and molecular signals. Comparative data are presented in [Table/Fig-5]. MSCs, derived from bone marrow, adipose tissue, or umbilical cord Wharton's jelly, exert their therapeutic effects predominantly through paracrine secretion of growth factors {VEGF, IGF-1, hepatocyte growth factor, Stromal Cell-Derived Factor-1 alpha (SDF-1α)} and immunomodulatory cytokines, rather than through direct differentiation [24]. In a clinical trial evaluating allogeneic adipose-derived MSC therapy for DFUs, the treatment group demonstrated 73% complete closure compared with 48% in controls [25]. MSC-seeded silk fibroin-chitosan scaffolds demonstrated synergistic healing benefits in diabetic rat wound models [26]. Exosomes secreted by MSCs carry pro-angiogenic microRNAs (miR-21, miR-126), reduce oxidative stress and facilitate macrophage polarisation from proinflammatory M1 to pro-repair M2 phenotypes [27,28]. Wharton's jelly MSC-derived exosomes produced significant improvements in tissue regeneration in a clinical study of DFU patients [28,29].

The PRP delivers a physiologically balanced cocktail of growth factors (PDGF, VEGF, TGF-β, EGF and IGF-1) directly to the wound site; its autologous origin obviates immunological concerns [30-32]. Gene therapy approaches targeting VEGF, PDGF-B, TGF-β, or Hypoxia-Inducible Factor-1 alpha (HIF-1α) delivery are under active preclinical and early-phase clinical investigation [33,34]. A Cochrane systematic review of wound dressings found that HBOT was associated with significantly higher odds of wound healing at six weeks [35]. HBOT achieves tissue oxygen tensions of 250-300 mmHg and promotes angiogenesis, fibroblast proliferation, collagen synthesis and neutrophil antimicrobial activity [35]. Evidence summaries are presented in [Table/Fig-5] [5,24,25,28-31,33-35].

Emerging multimodal and smart wound platforms: The next generation of diabetic wound therapies increasingly integrates multiple active components into single smart platforms. Key emerging paradigms include: nanoparticle-functionalised bioengineered scaffolds delivering concurrent antimicrobial, anti-inflammatory and pro-angiogenic signals; pH/glucose-responsive hydrogels incorporating exosomes and antimicrobial nanoparticles; electrically conductive scaffolds harnessing endogenous wound electric fields; and Artificial Intelligence (AI)-assisted wound monitoring platforms [36]. Curcumin-functionalised AgNPs and ZnO NPs have demonstrated significantly improved diabetic wound healing outcomes in STZ models [37,38]. Plant-derived exosome-like nanovesicles represent a natural, low-immunogenicity delivery vehicle [38]. Negative Pressure Wound Therapy (NPWT) applies sub-atmospheric pressure (-80 to -125 mmHg) to reduce wound oedema, stimulate granulation tissue formation, eliminate exudate and reduce bacterial burden; a meta-analysis demonstrated significantly improved outcomes with NPWT compared with conventional dressings in DFU patients [5].

Evidence-based Treatment Algorithm

Given the heterogeneity of diabetic wounds, a single universal treatment protocol is neither appropriate nor evidence-supported. The treatment algorithm presented in [Table/Fig-6] stratifies therapeutic approaches according to Wagner wound classification [39], infection status and vascular supply, with evidence levels graded according to the Oxford Centre for Evidence-Based Medicine (OCEBM) framework [5,6,8-10,14,16,18,19,24,25,27-

Modality	Mechanism	Best evidence	Stage	Key limitations	Future directions
MSC therapy	Differentiation + paracrine GF secretion; angiogenesis; immunomodulation	Clinical trial: 73% closure in ADSC group vs 48% control [24,25]	Phase I-III trials	Cost; immune rejection; lack of standardisation	Exosome-mediated MSC therapy; 3D bioprinting with MSCs
Exosome therapy	Macrophage polarisation M1→M2; miRNA delivery; angiogenesis; anti-oxidant	Clinical: Wharton's jelly MSC-exosomes improved tissue regeneration [28,29]	Phase I-II trials; preclinical	Isolation standardisation; dosing; manufacturing scalability	Smart hydrogel-exosome platforms; engineered exosomes
Gene therapy	VEGF/PDGF gene delivery; RNAi silencing; restores impaired signalling	In vivo: VEGF gene delivery tripled microvessel density [33,34]	Pre-clinical to early Phase I	Safety; off-target gene integration; high cost	Non-viral nanosystems; CRISPR for pathway restoration
PRP Therapy	PDGF, VEGF, TGF-β, EGF from activated platelets; inflammation modulation	RCT: >90% ulcer area reduction in high-risk DFU patients [30,31]	Phase II-III RCTs; meta-analyses	Variable preparation protocols; platelet count variability	Standardised PRP kits; PRP combined with bioprinted scaffolds
HBOT	Increases tissue pO_2; ROS modulation; angiogenesis; fibroblast stimulation	Cochrane review: significantly higher odds of healing with HBOT at six weeks [35]	Phase III RCTs; established adjunct	Expensive; specialised centres; 90-min sessions	Portable HBOT devices; combination with topical oxygen therapy
NPWT	Reduces oedema; promotes granulation; removes exudate; mechanical stretch	Meta-analysis: Improved DFU outcomes vs conventional dressings [5]	Established; Phase III evidence	Infection risk; discomfort; device dependency	Smart monitoring sensors; bioactive NPWT interfaces

[Table/Fig-5]: Comparative assessment of regenerative medicine modalities for diabetic wound healing [5,24,25,28-31,33-35].

Wound classification	Wagner grade	Infection status	First-line strategy	Adjunct/advanced therapy	Evidence level (OCEBM) and Refs
Superficial epidermal ulcer	Grade 1	None	Hydrocolloid/foam dressing + glycaemic control + offloading	Topical EGF spray if stagnant >2 weeks	Level 1 [6,36]
Partial thickness with necrosis	Grade 2	Mild	Sharp debridement + topical antibiotics + alginate dressing	PDGF gel (becaplermin); bioengineered scaffold	Level 1 [9,10,14]
Deep ulcer to tendon/ capsule	Grade 3	Moderate	Systemic antibiotics + surgical debridement + NPWT	Tissue-engineered substitute (Apligraf/Dermagraft); VEGF-loaded scaffold	Level 1-2 [5,9,10,16]
Ischaemic/poorly vascularised	Grade 3-4	Variable	Vascular surgery consultation + revascularisation + HBOT	MSC therapy; VEGF gene therapy; NPWT post-revascularisation	Level 2 [24,25,33,35]
Osteomyelitis/ bone involvement	Grade 4	Severe	i.v. antibiotics + bone debridement/resection; glycaemic optimisation	Local antibiotic delivery systems; bioactive bone scaffolds	Level 2-3 [8,18,19]
Gangrene (partial/ complete foot)	Grade 5	Severe/septic	Emergency surgical intervention; amputation if non-salvageable	Post-amputation stump closure: PRP + skin substitute	Level 1 [30,31,36]
Chronic non healing (>12 weeks)	Any grade	Any	Multimodal: debridement + NPWT + infection control + metabolic optimisation	Exosome therapy; 3D bioprinted scaffold; stem cell injection	Level 2-3 [24,25,27-29]

[Table/Fig-6]: Evidence-based treatment decision algorithm for diabetic wound management stratified by Wagner Grade [39]; Evidence levels per OCEBM [40] [5,6,8-10,14,16,18,19,24,25,27-29,33,35].

29,33,35], using numeric Levels 1-5 informing first-line and adjunct therapy selection. The algorithm is intended to complement rather than replace current international standards (IWGDF, IDSA). Wound bed preparation- comprising debridement, infection management and glycaemic optimisation- underpins all advanced therapeutic strategies. Multidisciplinary team input is recommended for Wagner Grade 3 and above.

DISCUSSION

The present literature review provides a comprehensive translational framework synthesising the current evidence base for improved therapeutic methods in diabetic wound healing across six major categories. The main conclusion is consistent and therapeutically significant: an evidence-based, patient-stratified, multimodal approach is ideal, as no single therapy modality is adequate [35,36].

Bioengineered skin substitutes have the highest level of clinical evidence, as evidenced by numerous RCTs and meta-analyses showing noticeably greater wound closure rates compared to traditional bandages. The results for Apligraf, Dermagraft and EpiFix are in line with and expand upon previously published reviews by Frykberg RG and Banks J [36]. These products' clinical significance stems from their ability to deliver a sustained, physiologically appropriate cocktail of growth factors and ECM components [9,10,12].

As the only FDA-approved molecularly targeted treatment for DFUs, becaplermin shows strong evidence. Becaplermin carries a boxed warning regarding malignancy risk with three or more tubes of use [13,14]. Nevertheless, the 48% versus 25% complete closure rate compared with placebo remains a landmark finding [14]. The pharmacokinetic constraints of topical growth factor treatment may be addressed by new sustained-release delivery systems [15-19].

The largest translational gap between preclinical and clinical evidence is found in the nanotechnology sector [20-25]. Although stimuli-responsive nanogel systems, electrospun nanofibre scaffolds, ZnO NPs and AgNPs have shown remarkable outcomes in murine STZ models, there is still a dearth of solid Phase II and III clinical trial evidence [27-34]. Safety problems related to nanoparticle cytotoxicity, biodistribution and possible genotoxicity need to be thoroughly investigated [20].

Refractory DFUs can benefit clinically from MSC treatment, exosome-based therapies, PRP and HBOT. Given its autologous nature and comparatively low cost, PRP therapy is a desirable alternative in resource-constrained settings; however, heterogeneity is introduced by the variation in preparation techniques and platelet concentrations [31,32,36].

The Wagner-grade-stratified therapy algorithm combines data across therapeutic domains and stratifies recommendations by wound severity, infection state and vascular supply [37-40]. This strategy is consistent with precision medicine ideas [4,35].

The results of the present review have a number of health policy ramifications. Diabetic foot illness disproportionately affects low- and middle-income nations, where access to bioengineered skin substitutes, MSC therapies and HBOT is significantly restricted. PRP

therapy, derivable from autologous blood with minimal apparatus, merits prioritisation in resource-constrained situations [6,36]. There is an urgent need for the creation of regulatory frameworks for sophisticated wound care products, specifically exosome-based therapies and 3D bioprinted constructions [27,29].

Limitation(s)

The present literature review has several limitations. Significant variation is present across the included studies regarding patient populations, wound categorisation systems, therapeutic methods, outcome measures and follow-up lengths. This heterogeneity prevented meta-analysis and required narrative synthesis. The majority of existing evidence compares individual advanced therapies to standard care rather than to one another; head-to-head comparative trials are largely lacking. The follow-up durations in several included trials were brief (12-16 weeks), constraining inferences about the durability of wound closure. The limitation of included studies to English-language publications may have resulted in language bias and publication bias cannot be disregarded.

Recommendations

Clinical practice recommendations: Rigorous wound bed preparation- including sharp debridement, infection assessment with biofilm disruption strategy, glycaemic optimisation targeting glycated Haemoglobin (HbA1c) below 53 mmol/mol (7%) and appropriate offloading- is recommended prior to consideration of any advanced therapy. For neuropathic or mixed-aetiology DFUs failing to achieve 50% area reduction after four weeks of conventional therapy, bioengineered skin substitutes (Apligraf, Dermagraft, EpiFix) are recommended. Becaplermin (recombinant PDGF-BB) gel is recommended as adjuvant therapy for full-thickness DFUs, for a maximum of 20 weeks. NPWT is recommended as a primary modality for moderately exuding post-surgical or post-debridement diabetic wounds and as a bridge therapy prior to skin grafting or bioengineered substitute application. HBOT is recommended as an adjuvant for ischaemic DFUs in appropriately equipped facilities, particularly for Wagner Grade 3-4 wounds. PRP therapy is recommended for Grade 1-3 DFUs refractory to standard management.

Research and development recommendations: Standardisation of PRP preparation protocols is needed to reduce therapeutic variability. Head-to-head RCTs comparing bioengineered skin substitutes against each other are urgently required. Scale-up of stimuli-responsive nanotechnology platforms from preclinical to Phase II-III clinical trials, with comprehensive long-term safety profiling, represents a critical translational priority. Multicentre RCTs with standardised characterisation and dosing for MSC and exosome therapies are required. Prospective cost-effectiveness analyses of AI-powered wound monitoring platforms are warranted. Access equity research is necessary, given that the burden of diabetic wounds is highest in low- and middle-income countries.

CONCLUSION(S)

The pathological process of diabetic wound healing is driven by diabetes-induced cellular dysfunction, growth factor deficiency, angiogenic failure, chronic biofilm infection and compromised immunological regulation. The present literature review demonstrates that bioengineered skin substitutes represent the highest level of evidence among advanced wound care modalities, with multiple RCTs and meta-analyses confirming superior wound closure rates. Becaplermin provides compelling evidence as the sole FDA-approved molecularly targeted treatment. Nanotechnology platforms demonstrate transformative potential, though a significant translational gap between preclinical and clinical evidence persists. Regenerative medicine modalities- MSC therapy, exosome therapy, PRP and HBOT- offer clinically significant advantages for refractory wounds. The optimal therapeutic approach is inherently multimodal, tailored to patient and wound characteristics and guided by a systematic, evidence-based decision framework.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Internal Medicine, Northern Border University, Arar, Saudi Arabia.
2. Professor, Department of Dermatology, Northern Border University, Arar, Saudi Arabia.
3. Professor, Department of Internal Medicine, Northern Border University, Arar, Saudi Arabia; Rheumatology Department, Mansoura University, Egypt.
4. Associate Professor, Department of Internal Medicine, Northern Border University, Arar, Saudi Arabia.
5. Professor, Department of Anatomy, Northern Border University, Arar, Saudi Arabia.
6. Assistant Professor, Department of Internal Medicine, Northern Border University, Arar, Saudi Arabia.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Shereen Mohamed Olama,
Professor, Department of Internal Medicine, Northern Border University, KSA;
Rheumatology Department, Mansoura University, Egypt.
E-mail: olamasm@yahoo.com

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