Pharmacological Modulations of Angiogenesis in Diabetic Surgical Wound

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Abstract:

The phenomenon of impaired angiogenesis significantly contributes to the delayed healing of wounds in individuals diagnosed with diabetes, particularly in the context of surgical interventions. In this regard, the pharmacological modulation of angiogenesis emerges as a viable strategy aimed at addressing these challenges by facilitating adequate neovascularization at the sites of injury. Recent advancements in drug delivery systems have introduced innovative methodologies, including the application of lipid nanoparticle-formulated protein transduction domains integrated into gelatin hydrogel dressings. This review explores the pathophysiology of angiogenesis failure in diabetic surgical wounds, evaluates pharmacological strategies to enhance angiogenesis. A rational, surgery-focused therapeutic algorithm is proposed. Beyond pharmacological interventions, optimizing systemic factors such as glycemic control, infection prevention, and tissue oxygenation remains critical for surgical outcomes. Current evidence highlights that while some angiogenic agents demonstrate promise in preclinical and early clinical studies, translation to routine surgical practice is limited by safety concerns, high cost, and heterogeneous trial results. In general, improving angiogenesis via novel pharmacological and biomaterial approaches shows great potential for advancing surgical wound healing in diabetes, with continued research necessary to enhance effectiveness, safety, and clinical application.

Keywords: Diabetic wound healing, Pathophysiology, Angiogenesis cascade, Pharmacological modulations, Drug delivery and biomaterials, Therapeutic algorithm.

1 Introduction:

Patients with diabetes mellitus face a higher risk of postoperative wound complications due to chronic microvascular damage and impaired tissue repair [1,2]. A key deficit is disrupted angiogenesis, which limits oxygen and nutrient delivery to healing tissue and promotes persistent inflammation, leading to non-healing wounds [3,5]. Many available therapies show inconsistent results because they target only single defects, while diabetes simultaneously impairs hypoxia signalling, nitric oxide production, endothelial progenitor cell function, extracellular matrix stability, and increases advanced glycation end-products [4,7,8,9]. As these abnormalities interact, isolated treatments such as growth factors, metabolic drugs, standard dressings, or negative-pressure therapy often fail to fully restore angiogenesis. Moreover, most evidence comes from chronic diabetic foot ulcers, which differ from surgical wounds in oxygen needs, biomechanics, and timing of vascular regrowth. These limitations highlight the need for strategies that address multiple pathways. This review summarizes angiogenic failure in diabetic surgical wounds evaluates current and emerging pharmacological approaches.

Figure 1: Diabetic wound

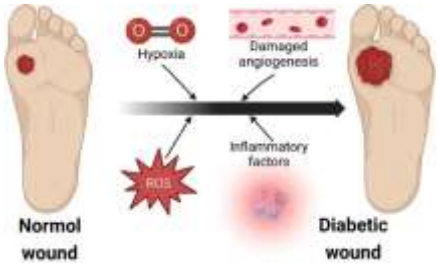

Figure 2: Formation of diabetic wound from normal wound

Table 1: Types of Diabetic Wounds [5]

TYPES	DESCRIPTION & LOCATION
Neuropathic wounds	Result from peripheral neuropathy, leading to a loss of sensation. They are commonly found on pressure points of the feet.
Ischemic wounds	Caused by peripheral arterial disease and poor blood circulation, typically located on the toes or the outer edges of the foot.
Neuro-ischemic wounds	A combination of both neuropathic and ischemic components, frequently occurring on the heels or other areas of the feet.
Charcot wounds	A severe complication beginning with a soft-tissue fracture or dislocation, typically affecting the bones and joints of the foot or ankle.

2 Pathophysiology of Angiogenesis failure in Diabetic Surgical wounds:

The failure of proper blood vessel formation (angiogenesis) represents a central pathological mechanism underlying poor healing of surgical wounds in diabetic patients. This impairment stems from multiple interconnected cellular and molecular disruptions caused by the diabetic metabolic environment.

Key Pathophysiological Mechanisms**:**

2.1 Hypoxia Signalling Disruption

The hypoxia-inducible factor-1 alpha (HIF-1α) pathway, which normally coordinates vascular responses to low oxygen, becomes dysfunctional in diabetes. Persistent hyperglycemia increases prolyl-hydroxylase enzyme activity, leading to excessive degradation of HIF-1α. This results in reduced production of crucial angiogenic factors including vascular endothelial growth factor (VEGF) and stromal cell-derived factor-1 (SDF-1). Consequently, the wound environment fails to initiate adequate angiogenic signalling despite tissue hypoxia [4,16].

2.2 Endothelial Dysfunction

Diabetes induces endothelial nitric oxide synthase (eNOS) dysfunction, reducing nitric oxide bioavailability. Nitric oxide deficiency impairs endothelial cell migration, proliferation, and vasodilation capacity. Advanced glycation end-products (AGEs) accumulate in vascular tissues, promoting oxidative stress and inflammation through receptor-mediated pathways. These changes collectively disrupt the endothelial cell functions necessary for new blood vessel formation [7].

2.3 Progenitor Cell Impairment

Endothelial progenitor cells (EPCs), which normally contribute to vascular repair, show functional deficiencies in diabetes. Oxidative stress and inflammatory mediators reduce EPC mobilization from bone marrow. Impaired homing capability limits EPC recruitment to wound sites. Circulating EPCs demonstrate reduced proliferative and migratory capacity [8,9].

2.4 Microenvironment Alterations

Chronic inflammation characterized by elevated pro-inflammatory cytokines (TNF-α, IL-6) creates an anti-angiogenic environment. Increased matrix metalloproteinase (MMP) activity excessively degrades extracellular matrix components. Matrix degradation disrupts the structural scaffold required for endothelial cell organization into functional vessels. Proteolytic cleavage of angiogenic factors and their receptors further compromises neovascularization [10,24].

Integrated Pathophysiological Sequence:

The diabetic metabolic environment initiates a cascade where hyperglycemia-driven oxidative stress and AGE accumulation impair both HIF-1α stability and eNOS function. This disrupts angiogenic signalling and nitric oxide-mediated vascular responses simultaneously [5]. Concurrent EPC dysfunction diminishes the cellular reserve available for vascular repair, while the pro-inflammatory, protease-rich wound microenvironment actively inhibits vessel maturation and stability. These parallel pathological processes collectively cause insufficient and poor-quality neovascularization [9], ultimately resulting in impaired wound healing with reduced tissue perfusion and oxygenation. This comprehensive understanding of angiogenesis failure mechanisms (Fig. 1) provides the rationale for developing targeted therapeutic approaches that address multiple components of this complex pathophysiology [6].

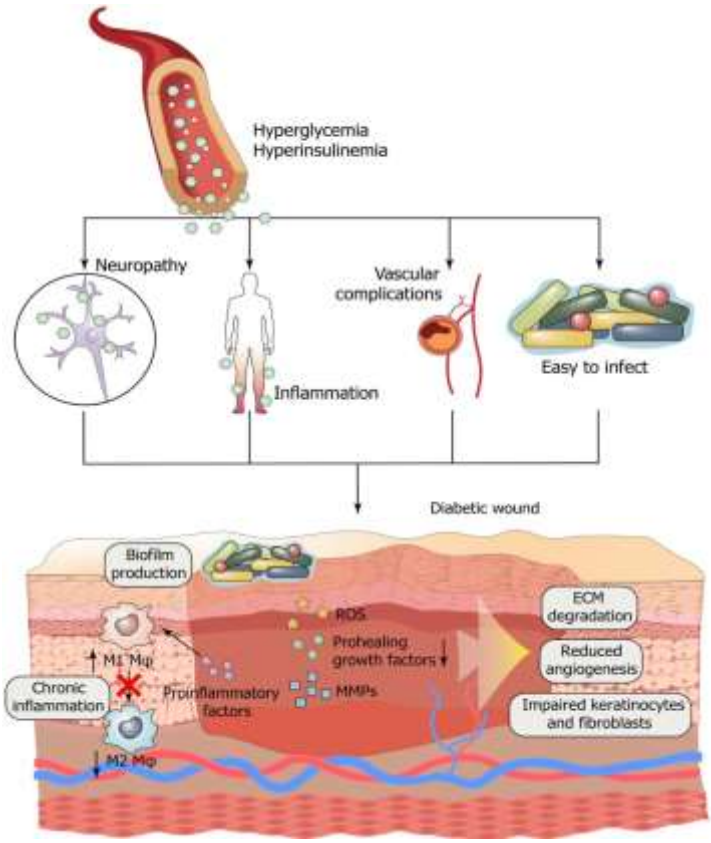

Figure 3: Pathophysiology of angiogenesis failure in diabetic surgical wounds

3 Angiogenesis cascade:

Angiogenesis is a co-ordinated, multi-step process essential for new blood vessel formation. It unfolds through a precise sequence of cellular and molecular events [5,10,24]:

3.1 Initiation

Angiogenic growth factors bind to specific receptors on the surface of endothelial cells within existing parent vessels (venules).

3.2. Intracellular Signalling

This growth factor-receptor binding activates specific intracellular signalling pathways within the endothelial cells.

3.3. Vessel Permeabilization

Activated endothelial cells release proteolytic enzymes that degrade the basement membrane surrounding the parent vessel.

3.4 Cell Proliferation

Endothelial cells begin to proliferate and extend outward sprouts through the dissolved areas of the basement membrane.

3.5 Cell Migration

The sprouting endothelial cells migrate into the wound matrix. This movement is guided by cell surface adhesion molecules called integrins (including αvβ3, αvβ5, and αvβ1).

3.6 Matrix Remodelling

Matrix metalloproteinases (MMPs) are secreted to break down the surrounding extracellular matrix, clearing a path for the advancing vascular sprouts.

3.7 Tube Formation

The migrating endothelial cells organize into hollow, tubular structures that connect with one another, forming primitive vascular loops.

3.8 Vessel Differentiation

These initial loops begin to differentiate, developing into the afferent (arterial) and efferent (venous) limbs of the new circulation.

3.9 Maturation and Stabilization

New vessels are stabilized through the recruitment of mural cells (pericytes and smooth muscle cells), which provide structural support.

3.10 Perfusion Establishment

Blood flow commences through the newly formed, mature, and stable vessel.

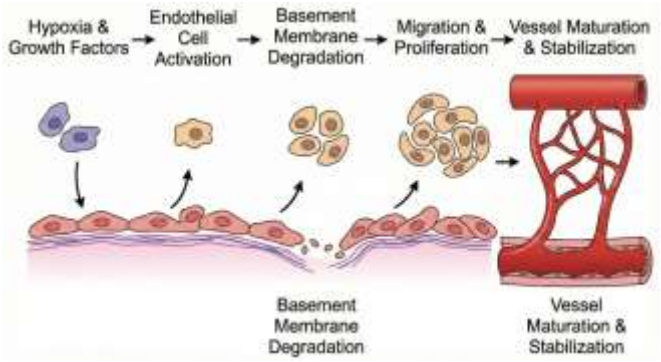

Figure 4: Angiogenesis cascade

4 Pharmacological Strategies to Modulate Angiogenesis:

Pharmacological intervention aims to correct the specific molecular and cellular deficits that impair angiogenesis in the diabetic wound environment clinical therapies to emerging investigational agents.

4.1 Established Pharmacological Therapies;

4.1.1 Topical Growth Factor Therapy

Platelet-derived growth factor-BB (PDGF-BB/Becaplermin:

Mechanism:

A recombinant growth factor applied as a topical gel (0.01%). It promotes the chemotaxis and proliferation of fibroblasts and inflammatory cells, stimulates granulation tissue formation, and enhances angiogenesis [11,12].

Status:

FDA-approved for the treatment of diabetic foot ulcer. Its pro-healing rationale makes it a candidate for off-label use in surgical wounds with adequate perfusion.

4.1.2 Systemic Metabolic Modulators

These drugs, primarily used for glycemic control, have pleiotropic effects that indirectly promote a more favourable environment for angiogenesis.

Metformin

Mechanism**:**

Activates the AMP-activated protein kinase (AMPK) pathway, which in turn upregulates endothelial nitric oxide synthase. This improves nitric oxide bioavailability and enhances the function of endothelial progenitor cells (EPCs), thereby supporting vascular repair [13].

GLP-1 Receptor Agonists (e.g., Liraglutide, Semaglutide)

Mechanism:

Exert potent anti-inflammatory effects and have been shown to have direct pro-angiogenic properties, improving microvascular circulation and outcomes in diabetic wounds [14].

DPP-4 Inhibitors (e.g., Sitagliptin, Saxagliptin)

Mechanism:

Inhibit the degradation of endogenous glucagon-like peptide-1 (GLP-1) and, crucially, Stroma Cell-Derived Factor-1 (SDF-1). By preserving SDF-1 levels, they enhance the recruitment and homing of progenitor cells to the wound site [15].

4.2 Emerging Pharmacological Strategies;

4.2.1 HIF-1α Stabilizers

These agents target the core defect in the hypoxic signalling response.

Deferoxamine (DFO) : An iron chelator that inhibits prolyl-hydroxylase activity, preventing HIF-1α degradation. This leads to increased expression of downstream targets like VEGF, effectively restoring the hypoxic angiogenic drive [16,17].

Prolyl-Hydroxylase Inhibitor (e.g., Roxadustat)

Developed for anaemia, these small molecules directly stabilize HIF-1α and are under investigation for their potential to accelerate wound vascularization and closure [18].

4.2.2 Nitric Oxide Donors

Mechanism:

These therapies deliver nitric oxide directly to the wound bed to compensate for its deficiency. Formulations include topical gels, creams and innovative hydrogel-based delivery systems that provide sustained release.

Effects:

Nitric oxide donors improve local blood flow, possess anti-microbial properties and directly stimulate endothelial cell proliferation and migration, leading to enhanced angiogenesis [19].

4.2.3 Topical Statins

Mechanisms:

Statins like simvastatin, when applied topically, have been shown to promote angiogenesis through multiple pathways, including:

- Activation of the PI3K/Akt/eNOS pathway
- Upregulation of VEGF expression
- Mobilization of endothelial progenitor cells from the bone marrow [20]

Advantage: Topical application avoids systemic side effects and delivers the drug directly to the wound site.

4.2.4 Mesenchymal Stem Cell-Derived Exosomes (MSC-Exos)

Mechanism:

These nano-sized extracellular vesicles act as natural delivery vehicles for a cargo of pro-angiogenic microRNAs, mRNAs, and proteins [22,23] (e.g., VEGF, FGF)

Delivery:

Incorporated into advanced dressings like hydrogels or biomaterials scaffolds to protect them and ensure sustained release at the wound site.

Effect:

MSC-Exos modulate the wound micro environment, reduce inflammation, and robustly stimulate the formation of new, functional blood vessels [21].

5 Angiogenic stimulators and inhibitors:

Wound healing relies on a careful balance of angiogenic stimulators (like FGF-1, FGF-2, TGF-α/β, PGE2, TNF-α, VEGF, and EGF) and angiogenic inhibitors (such as thrombospondin-1, TIMPs, interferons, angiostatin, and endostatin). Key Angiogenic Stimulators:

5.1 Fibroblast Growth Factors (FGFs)

The FGF family consists of 23 small polypeptides, each with about 140 amino acids. FGF-1 (aFGF-acidic fibroblast growth factor) and FGF-2 (bFGF-basic fibroblast growth factor) are the main players when it comes to angiogenesis. They work by signalling through FGF receptors (from FGFR-1 to FGFR-4), which are high-affinity tyrosine kinase receptors. These factors bind strongly to ECM (Extra Cellular Matrix) glycosaminoglycans like heparan sulphate, which helps in a couple of ways: They increase stability and protect against degradation and they limit how far they can diffuse, letting the ECM serve as a sort of reservoir and FGFs promote endothelial cell growth, movement, and differentiation, acting in an autocrine or paracrine manner. FGF-2, in particular, boosts endothelial migration via integrin receptors during the formation of granulation tissue [5,10].

5.2 Vascular Endothelial Growth Factor (VEGF)

VEGF works by increasing the permeability of blood vessels, which allows fibrinogen and fibronectin to leak out and form provisional ECM. It's mainly triggered by low oxygen levels. The VEGF family includes VEGF-A, B, C, D, E, and placental growth factor. VEGF-A has seven isoforms (121–206 amino acids) created through alternative splicing; the key ones are VEGF121, 165, 189, and 206. While all these isoforms function similarly, they differ in how they bind to ECM and heparin. VEGF specifically stimulates endothelial cells, leading to: Proliferation, Sprouting, Increased permeability in micro vessels, Regulation of integrin receptors. It also helps keep those endothelial cells alive by inducing Bcl-2 [5,16].

5.3 Transforming Growth Factor-β (TGF-β)

TGF-β brings neutrophils, macrophages, and fibroblasts into the mix, playing a crucial role in angiogenesis by managing: Cell growth, Movement, Formation of capillary tubes and ECM deposition [5].

5.4 Angiopoietins

These factors act on Tie-2 receptors: Ang-1: promotes vessel stability as an agonist and Ang-2: an antagonist that helps with vessel remodelling. There are also Ang-3 (in mice) and Ang-4 (in humans), though their functions aren't fully understood [5,10].

5.5 Mast Cell Tryptase

This enzyme breaks down ECM components and releases growth factors bound to the ECM. It also indirectly activates matrix metalloproteinases. Mast cell tryptase encourages capillary growth and the proliferation of endothelial cells, although this effect can be blocked by tryptase inhibitors [10].

Table 2: Angiogenic Stimulators and Inhibitors [5]

STIMULATORS	INHIBITORS
aFGF (FGF-1)	Thrombospondin-1
bFGF (FGF-2)	Tissue inhibitors of matrix metalloproteinases
TGF-α	Interferon alpha/beta/gamma
TGF-	Angiostatin
PGE2, TNF-	Endostatin
VEGF, EGF	

6 Proposed therapeutic algorithms for clinical practice:

A systematic, phased approach is essential for optimizing healing outcomes in diabetic surgical wounds. This algorithm progresses from fundamental systemic management to advanced targeted therapies, emphasizing evidence-based practice while acknowledging future directions.

6.1 Phase I: Creating a Permissive Environment (Before Algorithms)

For angiogenic therapies to be effective, it is essential to first release the "brakes" that limit vessel growth. This begins with vascular clearance, which is mandatory for establishing noticeable pulses or biphasic Doppler signals. Additionally, if the transcutaneous oxygen pressure (TcP O_2) is below 30 mmHg, angiogenesis cannot occur, making revascularization-either endovascular or via bypass-a prerequisite [24,25]. Furthermore, glycaemic permissiveness plays a critical role; elevated blood sugar levels can lead to non-enzymatic glycation of the basement membrane, resulting in excessive thickening that obstructs the passage of new capillaries. Therefore, it is crucial to aim for a perioperative blood glucose level of less than 180 mg/dL to facilitate effective migration of endothelial cells [1,29].

6.2 Phase II: The Therapeutic Algorithm (Decision Tree)

This phase of wound management begins 48 to 72 hours post-surgery, once haemostasis has been successfully achieved. The first step involves evaluating the wound bed, referred to as the angiogenic baseline, which is crucial for determining the appropriate course of action. It is essential to classify the surgical site into one of three categories: Category A, which is characterized by a deep, cavitary defect with moderate exudate; Category B, which presents a shallow, granular defect with stalling edges; and Category C, which features an ischemic or pale bed that exhibits poor potential for granulation. This classification process is vital for guiding subsequent treatment strategies and optimizing wound healing outcomes [29].

6.2.1 Pathway A: Mechanical Induction (For Deep Defects)

The primary goal of this intervention is to boost Vascular Endothelial Growth Factor (VEGF) levels through a technique known as micro-deformation. The main method employed is Negative Pressure Wound Therapy (NPWT) with instillation [26]. In this setting, continuous suction is maintained at -125 mmHg, which creates a mechanical strain that stretches the cells' cytoskeleton within the wound bed. This stretching sends out biochemical signals, a process known as mechano-transduction, that encourages the surrounding cells to produce increased levels of VEGF. To enhance the effectiveness of this therapy, saline or an antiseptic may be instilled into the wound for a specified dwell time, such as 10 minutes of soaking, followed by 2 hours of negative pressure application. This approach not only promotes VEGF production but also aids in clearing away "slough," which can obstruct capillary buds and impede the healing process.

6.2.2 Pathway B: Chemotactic Recruitment (For Stalled/Shallow Wounds)

The primary goal of this intervention is to attract endothelial cells through the use of specific chemical signals. The main intervention involves the application of Recombinant Human Platelet-Derived Growth Factor (rh-PDGF), which can be administered via a topical gel, such as Becaplermin, once daily [11,12]. In diabetic wounds, the natural release of PDGF is often diminished, which impairs the healing process. By applying rh-PDGF, we can enhance the recruitment of macrophages and fibroblasts to the wound site. These cells play a crucial role in the healing process by producing the collagen matrix that is essential for the formation of new blood vessels, ultimately facilitating improved recovery in diabetic wounds.

6.2.3 Pathway C: Oxygen Gradient Manipulation (For Hypoxic Beds)

The primary goal of our intervention is to tackle diffusion barriers, and we propose Hyperbaric Oxygen Therapy (HBOT) as the main intervention. The protocol involves administering HBOT for 90 minutes at a pressure of 2.0 to 2.4 Atmospheres Absolute (ATA), five days a week. It is essential to note the paradox in this treatment: while some level of hypoxia is necessary to trigger the production of Vascular Endothelial Growth Factor (VEGF), sufficient oxygen is still required to facilitate the construction of collagen tubes that form new blood vessels. HBOT effectively creates a steep oxygen gradient that supports fragile, newly formed capillaries, preventing their collapse. Additionally, we offer a topical option, Topical Oxygen Therapy (TOT), which provides continuous diffusion of oxygen directly onto the wound bed through a portable device. This alternative can be particularly beneficial for patients who may not be suitable for systemic HBOT [24].

6.3 Phase III: The Scaffold (For Refractory Cases)

If Pathways A, B, or C do not achieve a 50% reduction in wound size within four weeks, it is essential to consider a different approach. One effective intervention is the use of Acellular Dermal Matrices (ADM) or Bioengineered Skin. The rationale behind this approach lies in the observation that tissues in diabetic patients often lack the necessary extracellular matrix (ECM) structure, which is critical for supporting the growth of new blood vessels. To facilitate this process, a meshed ADM—derivable from bovine, porcine, or human sources—can be applied. This ADM functions as a collagen scaffold that promotes capillary ingrowth from the edges of the wound, a mechanism referred to as "bridging" [27].

7 Conclusion:

Diabetic surgical wounds remain difficult to treat because multiple defects in angiogenic signalling-such as reduced HIF-1α activity, endothelial dysfunction, and depletion of endothelial progenitor cells-limit the formation of new blood vessels needed for healing [28]. A growing range of pharmacological options now targets different parts of this impaired pathway, including metabolic drugs, recombinant growth factors, HIF-1 stabilizers, nitric-oxide–based therapies, and biologics such as stem-cell–derived exosomes. When combined with careful systemic optimization, these targeted interventions have the potential to significantly enhance vascular regeneration and improve surgical outcomes. However, meaningful progress will require well-designed clinical trials focused specifically on surgical wounds in diabetic patients, as most current evidence comes from chronic ulcer studies. Strengthening this research base is essential for integrating newer therapies into standard surgical practice and achieving more reliable healing in this high-risk population [29,30].

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