The Role and Therapeutic Potential of Angiogenesis and Adipose Tissue Metabolic Remodeling in Diabetic Foot Ulcer Healing: A Preprint

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Date: 2026-03-19T14:35:21+00:00

Abstract

Diabetic foot ulcer (DFU) is one of the most severe and devastating chronic complications of diabetes, imposing a heavy burden on global healthcare systems. The fundamental reason for the difficulty in DFU healing lies in the fact that it is not merely a localized lesion, but rather a local manifestation of systemic metabolic disorders. This paper systematically elucidates the critical roles of two core pathological processes—angiogenesis impairment and adipose tissue metabolic remodeling—in DFU healing, as well as the interconnections between them.

Under diabetic conditions, glucotoxicity, accumulation of advanced glycation end products, and dysregulation of growth factor signaling collectively hinder local angiogenesis, specifically manifesting as endothelial progenitor cell dysfunction, imbalance between pro- and anti-angiogenic factors, and extracellular matrix metabolism disorders. Simultaneously, adipose tissue undergoes pathological remodeling, characterized by adipocyte hypertrophy, chronic inflammation, and dysregulation of the adipokine profile, which establishes a systemic pro-inflammatory microenvironment through the release of pro-inflammatory cytokines and free fatty acids.

These two mechanisms do not exist in isolation but are intertwined through the "adipose-vascular axis" : adipose tissue inflammation exacerbates endothelial dysfunction and angiogenic failure, while insufficient local blood supply further worsens adipose tissue hypoxia and dysfunction, forming a vicious cycle that ultimately leads to persistent wound inflammation, energy crises in repair cells, and healing arrest. Based on these mechanisms, this paper reviews multimodal therapeutic strategies targeting this vicious cycle, including systemic interventions to improve adipose tissue function at its source and local methods to promote vascular regeneration. In the future, multi-target and individualized combination therapy regimens that integrate systemic metabolic regulation with local

regenerative medicine are expected to break through existing bottlenecks and provide new pathways for the cure of DFU.

Full Text

Preamble

Review and Monograph: The Role and Therapeutic Potential of Angiogenesis and Adipose Tissue Metabolic Remodeling in Diabetic Foot Ulcer Healing

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Abstract

Diabetic Foot Ulcer (DFU) is one of the most severe chronic complications of diabetes, characterized by high disability and mortality rates. The healing process of DFU is complex and involves multiple biological stages, among which impaired angiogenesis and dysfunctional adipose tissue metabolic remodeling are key factors contributing to delayed wound healing. Recent studies have demonstrated that promoting angiogenesis can significantly improve the local microenvironment of the ulcer, while the metabolic remodeling of adipose tissue —particularly the phenotypic transformation of adipocytes and the secretion of adipokines—plays a crucial regulatory role in the inflammatory response and tissue repair. This article reviews the specific mechanisms of angiogenesis and adipose tissue metabolic remodeling in DFU healing and explores their potential as therapeutic targets, aiming to provide new strategies and theoretical foundations for the clinical treatment of DFU.

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1. Introduction

Diabetic Foot Ulcer (DFU) represents a significant global health challenge, often leading to lower-limb amputations and a substantial reduction in the quality of life for patients with diabetes. The pathophysiology of DFU is multifaceted, involving peripheral neuropathy, peripheral arterial disease, and a persistent inflammatory state. At the cellular level, the failure of the wound to transition from the inflammatory phase to the proliferative phase is a hallmark of chronicity.

Two critical processes have emerged as central to understanding and treating DFU: angiogenesis and adipose tissue metabolic remodeling. Angiogenesis, the formation of new blood vessels from pre-existing ones, is essential for supplying oxygen and nutrients to the healing tissue. Simultaneously, the adipose tissue surrounding the wound site is no longer viewed merely as an energy storage organ but as a dynamic endocrine organ that undergoes significant metabolic

shifts in response to injury. This review focuses on the interplay between these two processes and their combined impact on the DFU healing trajectory.

2. The Role of Angiogenesis in DFU Healing

Angiogenesis is a fundamental requirement for successful wound repair. In healthy individuals, the process is tightly regulated by a balance of pro-angiogenic and anti-angiogenic factors. However, in the hyperglycemic environment of DFU, this balance is severely disrupted.

2.1 Mechanisms of Impaired Angiogenesis

Hyperglycemia leads to the accumulation of Advanced Glycation End-products (AGEs), which induce oxidative stress and endothelial dysfunction.

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Angiogenesis and Adipose Tissue Metabolic Remodeling in the Healing of Diabetic Foot Ulcers and Their Therapeutic Potential

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Abstract Diabetic foot ulcer (DFU) represents one of the most severe and devastating chronic complications of diabetes mellitus, imposing a substantial burden on healthcare systems worldwide. The refractory nature of DFU stems from its characterization not merely as a localized lesion, but as a local manifestation of systemic metabolic dysregulation. This review systematically examines the pivotal roles of impaired angiogenesis and adipose tissue metabolic remodeling—two interrelated core pathologic processes—in the nonhealing phenotype of DFU and explores their intricate interdependence.

In the diabetic state, hyperglycemia-induced toxicity, accumulation of advanced glycation end products (AGEs), and dysregulation of growth factor signaling cascades collectively impair local neovascularization. These abnormalities manifest as endothelial progenitor cell (EPC) dysfunction, an imbalance between proangiogenic and antiangiogenic factors, and extracellular matrix (ECM) remodeling dyshomeostasis. Concurrently, adipose tissue undergoes pathologic remodeling characterized by adipocyte hypertrophy, chronic low-grade inflammation, and an altered adipokine secretory profile, thereby establishing a systemic proinflammatory milieu through the release of inflammatory mediators and free fatty acids (FFAs).

These two pathogenic mechanisms do not operate independently but are intimately linked through an "adipose-vascular axis." Adipose tissue inflammation exacerbates endothelial dysfunction and impairs angiogenesis, while insufficient local blood supply further worsens adipose tissue hypoxia and dysfunction, creating a vicious cycle. This cycle ultimately leads to persistent wound inflammation, an energy crisis in reparative cells, and healing arrest. Based on these mechanisms, this paper reviews multi-modal therapeutic strategies targeting this vicious cycle, including systemic interventions to improve adipose tissue function and local methods to promote vascular regeneration. In the future, integrating systemic metabolic regulation with local regenerative medicine through multi-target, individualized combination therapies is expected to break through existing bottlenecks and provide new pathways for the cure of DFU.

[Keywords] Diabetic foot; Ulcer; Angiogenesis; Adipose tissue; Adipokines; Insulin resistance; Adipose-derived stem cells; Exosomes; Treatment

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Introduction

Diabetic foot ulcer (DFU) is a major chronic complication of diabetes, characterized by high disability and mortality rates. The fundamental reason for the difficulty in DFU healing lies in the fact that it is not merely a local wound issue but a localized manifestation of systemic metabolic disorders. Among the various pathological factors, impaired angiogenesis and metabolic remodeling of adipose tissue have emerged as two core links that significantly influence the healing process.

1. Mechanisms of Impaired Angiogenesis in DFU

Effective wound healing requires a robust angiogenic response to supply oxygen and nutrients to the regenerating tissue. However, in the diabetic environment, several factors converge to inhibit this process:

- **Endothelial Dysfunction:** Chronic hyperglycemia and the accumulation of advanced glycation end products (AGEs) lead to oxidative stress, which impairs the function of endothelial progenitor cells (EPCs) and mature endothelial cells. This reduces their ability to migrate, proliferate, and form stable capillary structures.
- **Growth Factor Imbalance:** There is a marked imbalance between pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), and anti-angiogenic factors. Dysregulated signaling cascades prevent the initiation of the vascular repair program.
- **Extracellular Matrix (ECM) Instability:** The diabetic state alters the composition and degradation of the ECM, which serves as the structural scaffold for new vessels. Excessive protease activity leads to premature degradation of the matrix, hindering stable vessel formation.

2. Adipose Tissue Metabolic Remodeling and Systemic Impact in DFU

Adipose tissue is no longer viewed merely as an energy storage organ but as a complex endocrine organ that plays a vital role in systemic metabolism. In diabetes, adipose tissue undergoes "pathological remodeling":

- **Adipocyte Hypertrophy and Inflammation:** Adipocytes increase in size and become dysfunctional, secreting a range of pro-inflammatory cytokines (e.g., TNF-α, IL-6). This creates a chronic, low-grade systemic inflammatory state.
- **Adipokine Dysregulation:** The secretion profile of adipokines is shifted, with a decrease in protective factors like adiponectin and an increase in detrimental factors like leptin and resistin. This shift contributes to systemic insulin resistance and further impairs the healing environment.

3. The Intertwining of Angiogenesis Impairment and Adipose Tissue Metabolic Remodeling

The relationship between angiogenesis and adipose tissue is bidirectional, forming what can be termed the "adipose-vascular axis."Inflammation within adipose tissue releases free fatty acids (FFAs) and inflammatory mediators that directly damage the vascular endothelium and inhibit angiogenesis. Conversely, impaired local microcirculation leads to hypoxia within the adipose tissue surrounding the wound, which triggers further inflammatory responses and metabolic dysfunction in adipocytes. This reciprocal aggravation creates a vicious cycle that traps the DFU in a non-healing, inflammatory phase.

4. Therapeutic Potential of Targeting Angiogenesis and Adipose Metabolism in DFU

Breaking the vicious cycle between metabolic dysfunction and impaired vascularization is key to improving DFU outcomes. Current and emerging therapeutic strategies include:

- **Systemic Metabolic Regulation:** Targeting adipose tissue function through pharmacological means (e.g., insulin sensitizers) or lifestyle interventions to reduce systemic inflammation.
- **Local Regenerative Medicine:** Utilizing adipose-derived stem cells (ADSCs) and their derivatives, such as exosomes, to promote local angiogenesis and modulate the wound microenvironment. These therapies offer the potential to deliver pro-angiogenic signals while simultaneously dampening inflammation.
- **Multi-target Combined Therapy:** Future treatments should aim to integrate systemic metabolic control with local advanced wound care. Individualized protocols that address both the systemic "soil" (metabolism)

and the local "seed" (vascular regeneration) are likely to provide the most effective clinical outcomes.

In conclusion, understanding the interplay between angiogenesis and adipose tissue remodeling provides a more holistic view of DFU pathogenesis. By targeting the adipose-vascular axis, clinicians and researchers can develop more effective, multi-dimensional strategies to overcome the challenges of diabetic wound healing.

Chinese General Practice, 2026. [Epub ahead of print].

Compromised local perfusion further aggravates adipose tissue hypoxia and functional derangement, thereby perpetuating a vicious cycle. This interconnected pathology ultimately culminates in persistent wound inflammation, impaired cellular energy metabolism in reparative cells, and arrested healing progression. Based on these mechanistic insights, this review evaluates multimodal therapeutic strategies targeting this pathogenic cycle, including systemic interventions that ameliorate adipose tissue dysfunction at its source and localized approaches that promote vascular regeneration. Future directions should focus on integrating systemic metabolic modulation with regional regenerative medicine through multi-targeted, personalized combination regimens, potentially overcoming current therapeutic limitations and offering novel pathways for DFU healing.

Keywords: Diabetic foot; Ulcer; Angiogenesis; Adipose tissue; Adipokines; Insulin resistance; Adipose-derived stem cells; Exosomes; Therapeutic strategies

The sharp rise in the global prevalence of diabetes has made diabetic foot ulcer (DFU) one of the increasingly severe public health challenges. Approximately 15% to 25% of patients with diabetes will develop a foot ulcer during their lifetime. Among these, up to 24% of non-healing DFUs may eventually lead to lower limb amputation, and the five-year mortality rate for these patients even exceeds that of several common cancers [**?**]. Each stage of the aforementioned pathological process constitutes a "multiple hit" that ultimately impairs angiogenesis.

Traditional treatment for DFU focuses on debridement, pressure offloading, revascularization, and infection control [**?**]. However, even with the application of the most advanced standards of care, a significant number of ulcers remain refractory to healing. This highlights the urgent need to explore deeper underlying pathological mechanisms.

1.1 Hyperglycemia and Advanced Glycation End Products (AGEs)

Wound healing is a highly coordinated and dynamic process consisting of four distinct stages: hemostasis, inflammation, proliferation, and remodeling. During the proliferative phase, efficient angiogenesis is essential, as it delivers oxygen, nutrients, immune cells, and growth factors to the wound bed while si-

multaneously removing metabolic waste. However, in a diabetic environment, this process is severely impaired. Concurrently, diabetes is fundamentally a systemic metabolic disease characterized by the dysfunction and metabolic remodeling of adipose tissue (AT) [**?**]. Adipose tissue is no longer viewed simply as a passive energy storage organ, but rather as a highly active endocrine and immune organ. In diabetic patients, the adipokine secretion profile shifts from an anti-inflammatory and insulin-sensitizing state toward a pro-inflammatory and insulin-resistant state. This systemic metabolic inflammatory environment subsequently influences distal wound healing processes through the circulatory system [**?**].

The toxic effects of advanced glycation end products (AGEs) are driven by two primary mechanisms: (1) Persistent hyperglycemia: This disrupts normal intracellular metabolic pathways, leading to the overproduction of mitochondrial reactive oxygen species (ROS) and resulting in severe oxidative stress [**?**]. High levels of ROS not only directly damage endothelial cell DNA, proteins, and lipids but also function as second messengers that interfere with multiple critical signal transduction pathways. (2) Advanced glycation end products: These are products of the non-enzymatic glycosylation of proteins and lipids under high glucose concentrations. AGEs impair angiogenesis through two main routes. One involves receptor binding, which activates downstream inflammatory pathways such as NF-κB, leading to the massive release of pro-inflammatory cytokines.

This creates a pro-inflammatory microenvironment that inhibits endothelial cell function and induces apoptosis [**?**]. Another mechanism involves the cross-linking of extracellular matrix (ECM) proteins: AGEs undergo irreversible cross-linking with proteins such as collagen and elastin. This process leads to the thickening and stiffening of the vascular basement membrane, which physically obstructs the budding and migration of endothelial cells, thereby preventing neovascularization from effectively penetrating the tissue [**?**].

1.2 Dysregulation of Growth Factor Signaling Pathways

In diabetic foot ulcers (DFU), the expression, function, and environmental context of growth factors are all significantly impaired [**?**] . These abnormalities are primarily manifested in the following aspects:

1. VEGF Signaling Pathway "Resistance" In the normal wound healing process, angiogenesis is a highly coordinated, multi-step process. This process is primarily regulated upstream by hypoxia-inducible factor-1α (HIF-1α) and precisely controlled by a network of key growth factors, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and angiopoietins (Ang). Among these, VEGF is primarily responsible for stimulating the proliferation, migration, and increased permeability of endothelial cells, while angiopoietin-1 (Ang1) binds to the Tie-2 receptor to promote vascular stabilization.

However, the expression pattern of VEGF in DFU wounds is abnormal. Although some studies suggest that overall VEGF levels may be elevated, there is often a delay in peak expression or a reduction in its duration. More importantly, a severe state of "VEGF resistance" exists. Due to oxidative stress and chronic inflammation, the critical downstream signaling pathway—phosphatidylinositol 3-kinase/protein kinase B/endothelial nitric oxide synthase (PI3K/Akt/eNOS)—is impaired. This leads to reduced activity of endothelial nitric oxide synthase (eNOS), preventing VEGF from effectively performing its functions in promoting vasodilation and angiogenesis. Under these conditions, the negative effects of VEGF, such as significantly increased vascular permeability leading to tissue edema and microcirculation disorders, become dominant.

2. Imbalance Between Pro-angiogenic and Anti-angiogenic Factors
The equilibrium between factors that promote and inhibit blood vessel formation is fundamentally disrupted in the diabetic wound environment.

In the diabetic microenvironment, the expression of anti-angiogenic factors is significantly upregulated. While PDGF is primarily responsible for recruiting pericytes to envelop nascent blood vessels—providing structural support and functional stability—chronic hyperglycemia and its derived pathophysiological changes disrupt these processes. For instance, angiopoietin-2 (Ang-2) is highly expressed under the stimulation of chronic inflammation. As an antagonist to Ang-1, Ang-2 binds to the Tie-2 receptor, thereby undermining vascular stability and leading to vessel leakage and regression.

Another critical anti-angiogenic factor, thrombospondin-1 (TSP-1), also shows increased expression in diabetic conditions. TSP-1 inhibits angiogenesis by directly suppressing endothelial cell proliferation and inducing apoptosis. Furthermore, soluble vascular endothelial growth factor receptor-1 (sFlt-1) acts as a decoy receptor, binding to and neutralizing the activity of VEGF, which further impairs the angiogenic process.

[Figure 1: see original paper]

The imbalance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) also plays a pivotal role. In diabetic wounds, pro-inflammatory cytokines stimulate neutrophils and macrophages to oversecrete MMPs (particularly MMP-8 and MMP-9), while the expression of TIMPs (such as TIMP-1) remains relatively insufficient [**?**]. This excessive proteolytic activity degrades the provisional extracellular matrix (ECM) scaffolds and essential growth factors (such as VEGF and FGF). Consequently, the fragile structures of nascent blood vessels are destroyed, preventing them from achieving stability and maturation.

Table 1: Changes in key angiogenic factors and their impact in diabetic foot ulcers

Factor	Role in Normal Healing	Changes in DFU	Consequences
VEGF	Promotes endothelial cell proliferation, migration, and survival; increases vascular permeability.	Delayed or shortened expression; functional resistance (impaired downstream signaling).	Blunted angiogenic response; vascular hyper-permeability leading to edema.
FGF	Promotes proliferation of endothelial cells and fibroblasts.	Decreased expression levels.	Impaired cell proliferation and weakened angiogenic capacity.
Ang-1	Stabilizes mature vessels; promotes pericyte coverage.	Decreased expression levels or inhibited activity.	Vascular instability; prone to leakage and regression.
Ang-2	Assists in vascular remodeling under physiological conditions.	Increased expression levels.	Antagonizes Ang-1, disrupting vascular stability.
TSP-1	Inhibits excessive angiogenesis during the late stages of healing.	Persistently elevated expression levels.	Premature inhibition of endothelial cell function; induction of apoptosis.
sFlt-1	Regulates VEGF activity.	Increased expression levels.	Neutralizes VEGF, weakening its pro-angiogenic effects.

Note: VEGF = vascular endothelial growth factor; FGF = fibroblast growth factor; Ang-1 = angiopoietin-1; Ang-2 = angiopoietin-2; TSP-1 = thrombospondin-1; sFlt-1 = soluble VEGF receptor-1.

1.3 Endothelial Progenitor Cells (EPCs)

Endothelial progenitor cells (EPCs) are bone-marrow-derived cells that, under physiological conditions, can be mobilized into the peripheral blood and home to sites of ischemia or injury to participate in angiogenesis and vascular repair.

However, in patients with diabetes, EPC dysfunction is primarily characterized by a significant reduction in quantity. This decrease in circulating EPCs is largely attributed to pathological changes in the bone marrow microenvironment and defects in mobilization signaling pathways.

Simultaneously, these pathological processes disrupt the signals and pathways essential for cell migration and communication. (2) Abnormalities in fibronectin (FN) and collagen [**?**]: The composition and quality of the extracellular matrix (ECM) are also altered. The synthesis of essential ECM proteins, such as FN, is reduced or subject to abnormal degradation. Furthermore, newly deposited collagen exhibits disordered alignment and excessive cross-linking, failing to provide a healthy microenvironment conducive to angiogenesis.

1.5 Chronic Inflammation and Immune Cell Infiltration

Diabetic wounds fail to transition smoothly from the inflammatory phase to the proliferative phase, as persistently present inflammatory cells secrete large quantities of substances that impair angiogenesis. The primary manifestations include: (1) M1 macrophage polarization [**?**]: Macrophages in diabetic wounds tend to adopt a pro-inflammatory M1 phenotype. These M1 macrophages continuously produce tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), matrix metalloproteinases (MMPs), and increased reactive oxygen species (ROS), which directly inhibit endothelial cell function and degrade the extracellular matrix (ECM). (2) Neutrophil extracellular traps (NETs) [**?**]: Activated neutrophils release NETs through a specific form of inflammatory cell death known as NETosis. Although intended to capture and kill pathogens, the excessive formation of NETs in chronic wounds creates a physical barrier to healing. Furthermore, NETs are enriched with cytotoxic and pro-inflammatory molecules that further damage endothelial cells. Impaired angiogenesis in diabetic foot ulcers (DFU) is not caused by a single factor, but rather by a vicious cycle driven by hyperglycemia involving growth factor dysregulation, ECM destruction, cellular dysfunction, and persistent inflammation. This cycle ultimately results in the formation of sparse, structurally abnormal, and functionally defective blood vessels within the DFU wound. These vessels typically exhibit irregular lumens, lack complete pericyte coverage, and possess excessive permeability. Consequently, they fail to effectively improve tissue perfusion and instead exacerbate tissue edema and hypoxia, ultimately leading to tissue necrosis, repair failure, and chronic, non-healing ulcers.

(2) Functional impairment: The environment of hyperglycemia, oxidative stress, and inflammation leads to a severe decline in the function of surviving endothelial progenitor cells (EPCs), including impaired migration, proliferation, adhesion, and differentiation into mature endothelial cells. Their ability to home to the wound site is also significantly weakened, rendering them unable to provide sufficient "seed" cells for neovascularization [**?**].

1.4 ECM Abnormalities and Proteolytic Imbalance

Normal extracellular matrix (ECM) provides a temporary scaffold and essential biomechanical signals for cell migration and angiogenesis. In diabetic wounds, however, ECM metabolism is severely imbalanced. This imbalance is primarily manifested in the dysregulation between matrix metalloproteinases (MMPs) and their corresponding tissue inhibitors of matrix metalloproteinases (TIMPs).

2. Adipose Tissue Metabolic Remodeling and Systemic Impact in DFU

Adipose tissue functions as a highly active endocrine and immune organ, and its dysfunction plays a central role in the pathogenesis of type 2 diabetes. Metabolic remodeling of adipose tissue under diabetic conditions is primarily characterized by adipocyte hypertrophy, ectopic lipid deposition, chronic low-grade inflammation dominated by macrophage infiltration, and dysregulation of the adipokine secretion profile [**?**]. This systemic metabolic disorder exerts a profound long-distance influence on the local healing microenvironment of diabetic foot ulcers through endocrine, immune, and metabolic pathways. Consequently, it serves as a critical systemic factor contributing to the refractory nature of these wounds.

2.1 From Healthy to Pathological Adipose Tissue

(2) Leptin Resistance: Although leptin levels may be elevated, central and peripheral tissues are prone to developing leptin resistance. In healthy physiological states, leptin possesses pro-angiogenic properties and promotes keratinocyte proliferation. However, the loss of leptin signaling due to resistance prevents these beneficial effects from being realized. Furthermore, chronically high leptin levels are associated with systemic inflammatory states.

Healthy adipose tissue, particularly subcutaneous fat, functions normally by maintaining insulin sensitivity; its primary role is to store energy and release fatty acids when required. It secretes beneficial adipokines, such as adiponectin (APN), which exerts anti-inflammatory, insulin-sensitizing, and pro-angiogenic effects, and leptin (LEP), which suppresses appetite and promotes energy expenditure. Conversely, under the influence of diabetes and in the context of energy excess and genetic susceptibility, adipose tissue undergoes pathological remodeling. The core driver of this remodeling is adipocyte hypertrophy.

(3) Elevated Levels of Pro-inflammatory Adipokines:

- **TNF-α**: This cytokine inhibits the tyrosine phosphorylation of insulin receptor substrate (IRS), thereby exacerbating local insulin resistance. It also induces apoptosis in endothelial cells and keratinocytes and upregulates the expression of matrix metalloproteinases (MMPs), which leads to the degradation of the extracellular matrix (ECM).
- **IL-6**: Promotes systemic inflammation and acute phase responses.

Once adipocytes reach their maximum storage capacity, several pathological issues are triggered:

(1) **Hypoxia**: Hypertrophic adipocytes lead to a relative deficiency in blood supply, inducing a state of hypoxia. This condition amplifies the acute-phase response, promotes the hepatic production of C-reactive protein (CRP), inhibits the secretion of adiponectin, and disrupts insulin signaling pathways, thereby inducing the expression of HIF-1α. (2) Cell Death and Inflammation: Hypoxia and endoplasmic reticulum (ER) stress trigger adipocyte death, which releases danger signals that recruit circulating monocytes to infiltrate the adipose tissue. (3) Macrophage Polarization: Infiltrating monocytes polarize into M1-type macrophages under the influence of local pro-inflammatory factors. These macrophages, in turn, secrete large quantities of TNF-α and interleukin-6 (IL-6). (4) MCP-1: This chemokine continuously recruits monocytes and macrophages to the wound site, sustaining localized inflammation. (5) Resistin: This factor promotes the production of inflammatory cytokines and directly impairs insulin action.

2.2.2 Systemic Inflammation and Immune Regulation

Pathological adipose tissue serves as the primary source of systemic chronic low-grade inflammation. These processes involve the secretion of pro-inflammatory cytokines, such as Interleukin-6 (IL-6), which establish a self-perpetuating vicious cycle. (4) Fibrosis: While healthy adipose tissue undergoes mild extracellular matrix (ECM) remodeling to maintain metabolic homeostasis, pathological expansion results in severe fibrosis. This process leads to the fibrosis of adipose tissue, which further exacerbates its functional impairment.

Inflammatory factors reach the wound site through the systemic circulation, distorting the wound microenvironment—which should naturally be "reparative"—into a state of "persistent inflammation."Currently, the mechanisms underlying impaired wound healing include the following:

(1) **Imbalance in Macrophage Polarization**: Systemic inflammatory signals (such as TNF-α and IL-6) direct macrophage polarization within the wound toward a pro-inflammatory M1 phenotype rather than a reparative M2 phenotype. The persistent presence of M1 macrophages hinders the transition of the healing process from the inflammatory phase to the proliferative phase [**?**].

Characteristics of healthy adipose tissue versus pathological adipose tissue

Feature	Healthy Adipose Tissue	Pathological Adipose Tissue (Diabetic State)
Cell Size	Normal size, high hyperplastic potential	Excessive hypertrophy

Feature	Healthy Adipose Tissue	Pathological Adipose Tissue (Diabetic State)
Vascularization	Well-vascularized, adequate blood supply	Insufficient vascularization, leading to hypoxia
Macrophages	Primarily alternatively activated (M2 type); anti-inflammatory state	Massive infiltration of classically activated (M1 type) macrophages forming "crown-like structures" ; pro-inflammatory state

(2) **Persistent Neutrophil Infiltration** [**?**]: Inflammatory factors prolong the lifespan of neutrophils, causing them to continuously release reactive oxygen species (ROS) and proteases within the wound. This sustained activity further damages tissue and prevents the formation of healthy granulation tissue.

2.2.3 Lipotoxicity and Ectopic Lipid Deposition

When the storage capacity of adipose tissue becomes saturated, lipids overflow and deposit in non-adipose organs (such as the liver, muscle, and even the skin), a phenomenon known as ectopic lipid deposition. This process leads to an increase in circulating free fatty acids (FFAs) and triggers significant physiological shifts.

The transition is characterized by a distinct shift in the adipokine profile: adiponectin (APN) levels decrease significantly, while leptin (LEP) levels rise, often leading to leptin resistance. Furthermore, there is a marked increase in pro-inflammatory mediators, including resistin, tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and interleukin-1β (IL-1β). Collectively, these changes drive systemic insulin resistance and chronic low-grade inflammation.

2.2 How Pathological Adipose Tissue Affects DFU Healing

Pathological adipose tissue acts as a "maladaptive signaling factory," secreting a variety of bioactive substances—including adipokines, inflammatory cytokines, and free fatty acids—into the systemic circulation. These factors systematically downregulate the regenerative and repair capacities of distal tissues.

2.2.1 Adipokine Dysregulation: Functional Reversal of Key Messengers

(1) A decrease in adiponectin levels represents the most significant adipokine alteration in diabetes [**?**]. Adiponectin exerts multiple beneficial effects on

wound healing, including pro-angiogenic, anti-inflammatory, and insulin-sensitizing activities. Its deficiency in diabetic foot ulcers (DFU) directly deprives the wound of a potent endogenous signal essential for promoting healing.

Elevated levels of free fatty acids (FFAs) lead to several adverse effects: (1) Direct cytotoxicity: High concentrations of FFAs, such as palmitate, can be taken up by local endothelial cells, fibroblasts, and keratinocytes in the wound, triggering lipotoxicity. Lipid overload induces endoplasmic reticulum stress and mitochondrial dysfunction, which in turn activates apoptotic pathways leading to cell death. Simultaneously, mediated by pattern recognition receptors such as Toll-like receptor 4 (TLR4), FFAs activate pro-inflammatory signaling pathways. This further exacerbates local inflammation and oxidative stress, directly hindering re-epithelialization and angiogenesis [**?**]. (2) Impairment of insulin signaling: The accumulation of FFA metabolic intermediates, such as ceramides and diacylglycerol, can activate protein kinase C (PKC) and stress-activated protein kinase (SAPK). These molecules interfere with insulin signal transduction and aggravate local insulin resistance, rendering cells unable to effectively utilize glucose for energy production [**?**].

2.2.4 Local Dermal Adipocyte Dysfunction Adipocytes exist within the dermal layer of the skin and play a dynamic role in wound healing. Following an injury, dermal adipocytes undergo dedifferentiation, transforming into fibroblast-like cells. These cells facilitate early-stage repair by secreting antimicrobial peptides (such as cathelicidin) and various growth factors. However, the high-glucose and inflammatory environment also impairs the function of these local adipocytes. Impaired angiogenesis is intricately intertwined with the metabolic remodeling of adipose tissue; both factors may inhibit the ability of adipocytes to dedifferentiate and secrete beneficial factors. This weakens their positive role during the early stages of wound healing, thereby exacerbating healing obstacles at the local level [**?**].

3. The Intertwining of Angiogenesis Impairment and Adipose Tissue Metabolic Remodeling

Adipose tissue metabolic remodeling serves as a critical bridge connecting the systemic disease state of diabetes with the local pathological manifestations of Diabetic Foot Ulcers (DFU). This process involves adipocyte metabolic dysfunction, the release of inflammatory cytokines, and the disruption of insulin signaling pathways, creating a circular mechanism that continuously amplifies pathological damage. (1) Self-perpetuation of chronic inflammation [**?**]: Adipose tissue inflammation leads to the release of inflammatory factors, which inhibits angiogenesis and results in tissue hypoxia. This hypoxia further exacerbates inflammation within the adipose tissue and the local wound area, leading to even more severe inhibition of angiogenesis. This constitutes a self-reinforcing inflammatory loop.

Consequently, a tight correlation is formed between systemic pathological changes and local wound healing impairments. Viewing DFU as a local manifestation of a systemic metabolic disease suggests that starting with the improvement of systemic adipose tissue function—by regulating lipid metabolic homeostasis, enhancing adipokine secretion, and reducing chronic inflammation—could be pivotal. (2) The vicious cycle of insulin resistance [**?**]: Adipose tissue inflammation and lipotoxicity induce systemic insulin resistance, which exacerbates hyperglycemia. This leads to the production of more Advanced Glycation End-products (AGEs) and Reactive Oxygen Species (ROS), damaging endothelial cell function and intensifying inflammation. This results in impaired angiogenesis and subsequent adipose tissue hypoxia, further deteriorating adipose tissue function and insulin sensitivity.

When acting synergistically within diabetic foot ulcers (DFUs), these factors construct a multi-layered, devastating pathological microenvironment that severely impedes the healing process.

First, at the metabolic level, they collectively trigger an "energy crisis." The scarcity of microvessels leads to a severe deficiency in the delivery of oxygen and glucose. Simultaneously, systemic vascular dysfunction results in inadequate local blood flow, further compromising the transport of oxygen and nutrients essential for tissue repair. Concurrently, metabolic remodeling of adipose tissue induces chronic inflammation, insulin resistance, and lipid metabolism disorders. These two pathological processes are intricately intertwined and closely linked within the DFU context, exacerbating the deterioration of the ulcer tissue microenvironment, delaying healing, and increasing the risk of recurrence. This synergy significantly enhances the refractory nature of DFUs, leaving critical repair cells—such as fibroblasts and keratinocytes—in a state of "starvation" and functional inhibition due to lipotoxicity and insulin resistance, which impair the effective utilization of available energy substrates.

Second, at the immunological level, these factors combine to create an "inflammatory stalemate." Pro-inflammatory cytokines originating from pathological adipose tissue (such as TNF-α and IL-6) are continuously delivered through the systemic circulation, further fueling the local inflammatory response and preventing the wound from progressing toward the proliferative phase of healing.

3.1 Reciprocal Influence of Angiogenesis and Adipose Remodeling

(1) The process by which adipose tissue inflammation triggers vascular damage involves multiple mechanisms [**?**]. Under inflammatory conditions, adipose tissue releases pro-inflammatory cytokines such as TNF-α and IL-6. Once these factors enter the systemic circulation, they are continuously delivered to the wound site. Simultaneously, local hypoxia and necrotic tissue persistently release endogenous "danger signals." This dual stimulation prevents wound macrophages from transitioning from a pro-

inflammatory, destructive M1 phenotype to an anti-inflammatory, reparative M2 phenotype, causing the healing process to become permanently "stalled" in a state of chronic inflammation. (3) At the molecular signaling level, this results in "signaling chaos" : pro-angiogenic signals (such as VEGF) lose their functionality due to receptor resistance and expression inhibition, while anti-angiogenic signals (such as Ang-2 and TSP-1) become dominant. These cytokines inhibit the activity of eNOS, thereby reducing nitric oxide production and impairing vasodilation capacity. Concurrently, they promote endothelial cell apoptosis, disrupt the vascular endothelial barrier, and upregulate the expression of adhesion molecules such as VCAM-1 and ICAM-1. This enhances leukocyte adhesion and migration, leading to a chronic inflammatory state that exacerbates systemic endothelial dysfunction. Furthermore, these inflammatory factors significantly inhibit the mobilization, homing, and repair functions of endothelial progenitor cells, thereby reducing the capacity for vascular regeneration and maintenance. (2) Insufficient angiogenesis further leads to the deterioration of adipose tissue function [**?**]. At the cellular level, the ultimate result is comprehensive functional impairment: endothelial cells, fibroblasts, keratinocytes, and immune cells—situated within an extreme microenvironment characterized by hypoxia, inflammation, toxic energy substrates, and aberrant signaling—universally exhibit dysfunction, accelerated senescence, and massive apoptosis, ultimately leading to tissue repair failure and ulceration.

The maintenance of subcutaneous adipose tissue health is highly dependent on an adequate blood supply and the continuous delivery of oxygen and nutrients. Under the pathological conditions of diabetic microangiopathy, the capillary network is significantly damaged, and adipose tissue perfusion decreases sharply.

4. Therapeutic Potential of Targeting Angiogenesis and Adipose Metabolism in DFU

Targeted intervention strategies that integrate the core mechanisms of diabetic foot ulcer (DFU) recalcitrance—specifically addressing impaired angiogenesis and the metabolic remodeling of adipose tissue—demonstrate significant therapeutic potential. Chronic tissue hypoxia is a primary driver of this condition. This pathological state not only directly accelerates the apoptosis and necrosis of adipocytes but also triggers a robust local inflammatory cascade. This cascade promotes extensive macrophage infiltration and the massive release of pro-inflammatory cytokines. Collectively, these pathological alterations significantly disrupt the normal secretory profile of adipokines, ultimately leading to impaired wound healing.

4.1 Source Regulation: Targeting Adipose Remodeling to Improve Systemic Environment

This strategy aims to correct systemic metabolic and inflammatory disorders, thereby creating a favorable macro-environment for wound healing. Specific methods include:

1. Improving Adipose Tissue Function and Insulin Sensitivity Application of Novel Hypoglycemic Agents: The roles of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) [**?**] and sodium-glucose co-transporter 2 inhibitors (SGLT2is) [**?**] extend far beyond simple blood glucose regulation. These agents significantly reduce body weight and visceral fat volume, directly improving the inflammatory state and functional capacity of adipose tissue.

2. Specialized Therapeutic Interventions Photobiomodulation Therapy: As discussed in [**?**], this approach utilizes specific wavelengths of laser light to stimulate mitochondrial function. This stimulation upregulates cellular energy production and the expression of factors such as vascular endothelial growth factor (VEGF), effectively promoting angiogenesis and epithelialization. This method offers the advantages of being both non-invasive and safe.

Hyperbaric Oxygen Therapy: According to [**?**], this therapy increases the partial pressure of blood oxygen, which indirectly upregulates the expression of hypoxia-inducible factor 1-alpha (HIF-1α) and its downstream target, VEGF. This process stimulates angiogenesis while simultaneously enhancing the bactericidal capacity of leukocytes and the clinical efficacy of antibiotics.

4.3 Multimodal Combination and Future Prospects: Breaking the Vicious Cycle

The multimodal and sequential combined application targeting the intertwined processes of angiogenesis and adipose metabolism may better align with the complex pathophysiology of diabetic foot. This approach reduces the release of pro-inflammatory cytokines and free fatty acids (FFAs) at the source. Consequently, this not only improves systemic insulin resistance but also indirectly alleviates the inhibition of vascular endothelial function.

Two primary classes of pharmacological agents highlight the potential of this strategy:

1. **Thiazolidinediones (TZDs):** For example, pioglitazone [**?**] acts as an agonist for the peroxisome proliferator-activated receptor γ (PPARγ). These agents promote adipocyte differentiation, reduce cellular hypertrophy and inflammation, and increase the secretion of adiponectin. Although their clinical use is sometimes limited by side effects, their underlying mechanism demonstrates that targeting adipocyte differentiation and function is a viable therapeutic strategy.

In the clinical treatment of ulcers, practical efforts may be directed toward the following areas:

1. Combination of Systemic Intervention and Local Treatment A synergistic approach combining systemic and local therapies may help break the pathological cycle of non-healing ulcers. For example, systemic metabolism and inflammatory profiles can be improved using SGLT2 inhibitors (SGLT2i) or GLP-1 receptor agonists (GLP-1RA), while ADSC-derived exosome hydrogels or combined growth factor therapies are applied locally to the wound site to promote repair [**?**].

2. Development of Intelligent Delivery Systems The development of smart delivery systems utilizing advanced biomaterials—such as thermosensitive or pH-responsive hydrogels—can significantly enhance therapeutic outcomes. These systems enable the controlled and sustained release of growth factors, exosomes, or anti-inflammatory drugs, thereby maintaining high local effective concentrations and improving overall treatment efficiency [**?**].

3. Targeting Specific Adipokines and Inflammatory Pathways Targeting specific molecular pathways offers a promising avenue for precision therapy: - **Adiponectin Mimetics:** The development of small-molecule adiponectin receptor agonists aims to directly replenish the beneficial signaling pathways that are deficient in patients with Diabetic Foot Ulcers (DFU). These mimetics are designed to simulate the anti-inflammatory and insulin-sensitizing effects of adiponectin, potentially reversing the chronic inflammatory state of the wound.

Insulin sensitization and pro-angiogenic effects currently represent highly attractive research directions [**?**]. (2) Specific anti-inflammatory therapy: By targeting key inflammatory mediators—for instance, through the use of anti-TNF-α antibodies (such as etanercept) [**?**] or IL-1β inhibitors (such as canakinumab) [**?**]—it is expected that the systemic and local inflammatory stalemate can be broken. To avoid the risk of systemic infection associated with generalized immunosuppression, the development of localized drug delivery systems, such as sustained-release hydrogels, represents a critical focus for future research [**?**].

4.2 Local Repair: Directly Targeting Angiogenesis Impairment

This strategy acts directly on the local wound site to stimulate neovascularization, addressing the core issue of ischemia. Specific approaches include: (1) Growth factor therapy. Recombinant human platelet-derived growth factor (rhPDGF-BB, Becaplermin) is an FDA-approved drug for DFU [**?**], though its efficacy as a monotherapy is limited. Future trends involve developing combination therapies using multiple growth factors (such as VEGF, FGF, and Angiopoietin-1) to simulate a more physiological angiogenic process and promote the formation of a mature, stable vascular network. (2) Individualized and precision medicine: Future treatments must be stratified and personalized

based on the specific type of DFU (ischemic, neuropathic, or neuroischemic) and the patient' s specific metabolic profile (e.g., inflammatory cytokine levels and adipokine profiles). For instance, pro-angiogenic therapy should be intensified for patients with severe ischemia, while local anti-inflammatory strategies should be combined for those with hyperactive inflammation.

Future research in the treatment of diabetic foot ulcers should focus on: (1) further elucidating the sophisticated regulatory networks of the vascular-adipose-immune axis in wound healing [**?**]; (2) conducting large-scale, multicenter randomized controlled clinical trials to confirm the efficacy and safety of new therapies; and (3) promoting multidisciplinary collaboration that integrates materials science, nanotechnology, gene editing, and artificial intelligence to develop a new generation of intelligent healing systems [**?**].

Gene therapy [**?**]: By introducing genes encoding pro-angiogenic factors (such as VEGF and HIF-1α) into local wound cells via plasmid or viral vectors, sustained and controlled expression of these factors can be achieved. The refractory nature of diabetic foot ulcers is rooted in systemic metabolic disorders and multiple defects in the local microenvironment. Pathological impairment of angiogenesis and metabolic remodeling of adipose tissue are two interconnected and mutually reinforcing core pathological links.

Hyperglycemia and adipose tissue-driven chronic inflammation collectively destroy the angiogenic processes and reparative microenvironment essential for wound healing. Breaking this vicious cycle represents a novel approach to DFU treatment. Advanced regenerative medicine strategies—targeting pro-angiogenesis, correcting adipose metabolism and adipokine imbalances, and utilizing adipose-derived mesenchymal stem cells (ADSCs) and their exosomes—represent highly promising new therapeutic directions. Through multi-target, individualized comprehensive intervention strategies that simultaneously regulate angiogenesis and systemic metabolism, we hope to ultimately overcome the challenge of diabetic foot ulcers and benefit millions of patients worldwide. (2) Cell-based and cell-free therapies. Cell therapy primarily involves the application of ADSCs, which are "star cells" in regenerative medicine due to their ease of acquisition, high yield, and strong proliferative capacity; local transplantation of ADSCs can comprehensively improve the healing microenvironment [**?**]. Cell-free therapy mainly refers to exosome therapy. As the primary paracrine component of ADSCs, exosomes possess lower immunogenicity and tumorigenic risk and are easier to store and standardize, making them a promising "cell-free cell therapy." Engineered exosomes can further enhance targeting and repair efficacy [**?**].

Author Contributions: Shang Junliang was responsible for the conception, design, and writing of the paper, and is overall responsible for the article; Xu Xuying was responsible for the revision, quality control, and proofreading of the paper; all authors have confirmed the final manuscript.

Conflicts of Interest: The authors declare no conflicts of interest.

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