# Bone-origin repair in diabetic foot ulcers: Mechanisms of callus formation and endocrine effects in healing (Review)

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**Abstract.** Diabetic foot ulcers (DFUs) represent a severe complication of diabetes mellitus, affecting ~1/3 of diabetic patients during their lifetime and imposing substantial clinical and economic burdens globally. While conventional understanding attributes DFU pathogenesis primarily to peripheral neuropathy, vascular insufficiency and infection, emerging evidence reveals that bone involvement plays a previously underappreciated but important role in wound chronicity. The present review introduces the concept of 'bone-origin repair', a therapeutic framework that leverages the skeleton's intrinsic regenerative and endocrine capacity to support soft-tissue healing in bone-adjacent DFUs. Diabetes profoundly impairs bone health through cortical thinning, bone marrow stromal cell exhaustion and disrupted callus biology, creating a permissive environment for ulceration and delayed healing. Beyond structural compromise, bone functions as a multifunctional endocrine organ secreting bioactive molecules (osteokines) including osteocalcin (OCN), sclerostin, fibroblast growth factor-23 and receptor activator of nuclear factor-κB ligand/osteoprotegerin that regulate systemic metabolism, angiogenesis and immune function. In diabetic patients, dysregulated osteokine secretion, characterized by reduced OCN and elevated sclerostin, establishes a catabolic milieu that impairs wound healing capacity. Controlled bone injury triggers substantial osteokine release, with platelet-derived growth factor-BB reaching distant wound sites to accelerate healing through enhanced angiogenesis and re-epithelialization. This bone-wound crosstalk operates via a coordinated endocrine loop involving macrophage polarization, type-H vessel formation and neurovascular coupling. While promising, bone-origin repair requires careful patient selection, exclusion of active osteomyelitis and integration with standard DFU care. The present review synthesizes current understanding of bone-DFU pathophysiology, examines the molecular mechanisms underlying the endocrine influence of the bone on wound healing and discusses the translational potential of bone-targeted strategies as adjunctive therapies in diabetic wound management.

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*Key words:* diabetic foot ulcers, bone-origin repair, osteokines, bone marrow stromal cells, wound healing

**Contents**



## 1. Introduction

According to the International Diabetes Federation, ~588.7 million individuals globally are living with diabetes in 2024, representing a prevalence of 11.1% (1). This figure is projected to rise substantially, reaching 852.5 million cases and a prevalence of 13.0% by 2050. The burden of diabetes is most pronounced in middle-income countries, which account for 452.9 million cases in 2024, followed by high-income countries with 114.1 million and low-income countries with 21.8 million cases (2). DFUs represent one of the most debilitating complications of diabetes mellitus, affecting 15-25% of diabetic patients during their lifetime and contributing to >85% of non-traumatic lower limb amputations (3). Globally, DFUs impact ~18.6 million individuals annually, with lifetime ulcer risk ranging from 19 to 34%, recurrence rates reaching 65% at 3-5 years and 5-year mortality rates of 50-70% following initial ulceration (4). The burden of DFUs extends beyond individual morbidity to encompass substantial healthcare costs, with annual expenditures ranging from $9 to 13 billion in the United States alone (5). Despite advances in multidisciplinary care and evidence-based interventions, amputation rates associated with DFUs continue to rise in some regions, particularly among young and racial/ethnic minority populations (4).

The pathophysiology of DFUs involves a complex interplay of peripheral neuropathy, peripheral arterial disease (PAD),

chronic inflammation and impaired tissue regeneration (6). Peripheral neuropathy, affecting ~60% of diabetic patients, contributes to sensory loss and abnormal foot mechanics that increase ulcer risk (7,8). Vascular insufficiency secondary to PAD further compounds healing impairment by limiting oxygen and nutrient delivery to affected tissues (9). The diabetic microenvironment is characterized by persistent hyperglycemia, advanced glycation end-product (AGE) accumulation, oxidative stress and immune dysregulation, factors that collectively sustain a pro-inflammatory state dominated by cytokines such as TNF-α, IL-1β and IL-6, which impair angiogenesis and delay repair (3).

While considerable attention has been directed toward soft-tissue pathology in DFUs, bone involvement remains frequently overlooked despite mounting evidence of its important role in wound healing and ulcer recurrence (7,10). In diabetic patients, the skeleton undergoes profound metabolic and structural alterations including cortical thinning, reduced bone mineral density, impaired bone marrow stromal cell function and dysregulated bone remodeling (11). These changes not only increase susceptibility to foot deformities and mechanical stress but also compromise the capacity of the bone to support overlying soft-tissue repair. Beyond endogenous repair mechanisms, bone regeneration research has increasingly explored biomimetic scaffolds and immunomodulatory fiber-based approaches (12-14).

Emerging evidence has fundamentally redefined the understanding of bone from a passive structural scaffold to a multifunctional endocrine organ (15-17). Bone cells, osteoblasts, osteocytes and osteoclasts, secrete a constellation of bioactive molecules termed 'osteokines' that exert systemic effects on distant organs through endocrine, paracrine and autocrine mechanisms (15). These bone-derived factors, including OCN, sclerostin, FGF-23, receptor activator of nuclear factor-κB ligand/osteoprotegerin (RANKL/OPG) and lipocalin-2 (LCN2), regulate energy metabolism, vascular biology, immune function and tissue repair capacity (18). OCN, in its undercarboxylated form, stimulates insulin secretion from pancreatic β-cells and enhances insulin sensitivity in peripheral tissues (19,20). Sclerostin, secreted predominantly by osteocytes, inhibits Wnt/β-catenin signaling and suppresses bone formation (21). The endocrine dimension of bone extends beyond mineral homeostasis to influence wound healing processes through modulation of angiogenesis, macrophage polarization and extracellular matrix (ECM) remodeling (22).

The concept of 'bone-origin repair' defined as the targeted recruitment of intrinsic reparative programs within the bone microenvironment through deliberate and controlled local bone stimulation, represents an emerging therapeutic framework that may be applicable to carefully selected cases of DFU (23). Building on principles derived from bone marrow stimulation techniques (microfracture, drilling), periosteal distraction and cortical transverse transport, this approach aims to harness the regenerative and endocrine capacity of the skeleton to secondarily support soft-tissue healing in bone-adjacent ulcers (24). However, this concept remains exploratory and requires clearly defined clinical boundaries to prevent conceptual overreach and inappropriate application in settings of active osteomyelitis, structural instability or advanced Charcot neuroarthropathy (25). The present review synthesizes current understanding of bone pathology in diabetic foot disease, examines the molecular and cellular mechanisms underlying callus formation and its impairment in diabetes, explores the endocrine functions of bone relevant to wound healing and discusses the translational potential of bone-targeted strategies as adjunctive therapies in diabetic wound management. By integrating insights from osteoimmunology, vascular biology and regenerative medicine, the present review aims to provide a comprehensive framework for understanding and potentially exploiting the bone-wound axis in clinical practice.

## 2. DFU microenvironment that resists repair

*Metabolic-vascular-immune triangle in diabetes*. DFUs are open wounds that occur in individuals with type 1 or type 2 diabetes, commonly in the setting of peripheral neuropathy, poor glycemic control and PAD (26). These ulcers represent one of the most frequent and severe complications of diabetes, affecting ~1/3 of patients during their lifetime. Globally, ~18.6 million individuals are affected each year including ~1.6 million cases in the United States and~50% of DFUs become infected, with ~20% of infected cases progressing to partial or total foot amputation (27).

The development of DFUs is driven by factors such as neuropathy, vascular insufficiency, trauma and impaired immunity (28). Neuropathy contributes to sensory loss and abnormal foot mechanics, increasing ulcer risk (29) and affects ~60% of diabetic patients (8). Vascular disease further impairs circulation and delays healing (30). Foot deformities and visual impairment, particularly in older adults, elevate the likelihood of unnoticed injuries (31). These risks are exacerbated by hyperglycemia and prolonged diabetes duration (32). In this setting, chronic hyperglycemia serves as the upstream metabolic abnormality linking vascular dysfunction and immune dysregulation in the diabetic wound microenvironment (33-35).

Chronic hyperglycemia activates alternative metabolic pathways, such as the polyol and hexosamine pathways, which contribute to the overproduction of reactive oxygen species and the formation of AGE products, both of which are key mediators of cellular damage in diabetes (36). AGEs accumulate in hyperglycemic environments through non-enzymatic reactions between reducing sugars and proteins, lipids or nucleic acids (37). These AGEs exert their pathological effects primarily through interaction with the receptor for AGE (RAGE), a multiligand pattern recognition receptor expressed on endothelial cells, macrophages and fibroblasts (38). Binding of AGEs to RAGE triggers intracellular signaling cascades, including NF-κB, MAPK and JAK/STAT pathways (39,40). These cascades upregulate pro-inflammatory cytokines such as TNF-α and IL-6, promote oxidative stress via NADPH oxidase activation and suppress reparative cell behaviors (41-43).

Metabolic injury then converges with vascular and immune dysfunction. In chronic wounds such as DFUs, persistent inflammatory signaling impairs fibroblast migration, disrupts ECM turnover and compromises angiogenesis (44). At the same time, AGE-related redox imbalance and inflammatory activation sustain chronic inflammation and oxidative stress (45,46), while diabetic wound healing is further impaired

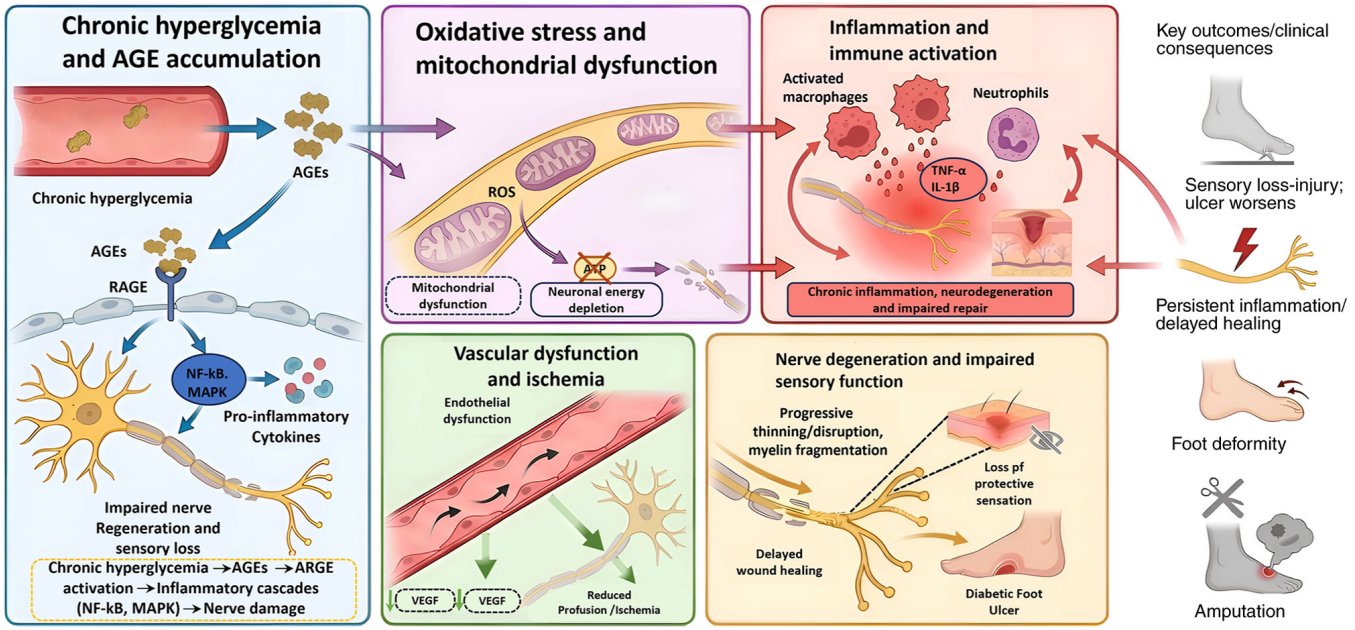


Figure 1. Chronic hyperglycemia and AGE accumulation in diabetic foot ulcers: Impaired healing and nerve damage. Chronic hyperglycemia leads to AGE accumulation, triggering RAGE activation and inflammatory cascades that impair nerve function and regeneration. Figure shows how oxidative stress, mitochondrial dysfunction and vascular dysfunction exacerbate nerve degeneration and sensory loss. The resulting impaired healing contributes to foot deformity, increased infection risk and the potential for amputation. AGEs, advanced glycation end products; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor.

through AGE-RAGE-associated mechanisms (40,47). Rather than acting sequentially, these metabolic, vascular and immune abnormalities reinforce one another: Metabolic stress damages endothelial and stromal function, vascular insufficiency worsens tissue hypoxia and repair failure, and chronic inflammation further compromises microvascular integrity and tissue regeneration. Together, these processes create a wound environment that predisposes to ulceration and delays healing (Fig. 1).

*Bone involvement: Cortical thinning, marrow stromal exhaustion, osteomyelitis risk*. Bone involvement in DFUs is frequently overlooked, yet it plays an important role in maintaining the structural integrity of the foot and supporting the regenerative processes of the wound bed. In individuals with diabetes, both metabolic and mechanical factors compromise the bone-soft tissue unit, creating an environment that fosters chronic wound formation and hinders effective healing (48,49).

*Cortical thinning*. Cortical thinning in DFU is a key pathological feature driven by a complex interplay of metabolic, neurological and vascular factors (50). Hyperglycemia negatively affects bone health by impairing the function of osteoblasts and osteocytes, the primary cells involved in bone formation and maintenance (51). This metabolic disturbance disrupts normal bone metabolism by decreasing the production of ECM components and hindering mineralization (52). Beyond reducing bone formation and increasing fragility, it accelerates the apoptosis and senescence of osteoblasts, further contributing to bone loss (53). By perturbing the delicate balance between bone-forming osteoblasts and bone-resorbing osteoclasts, diabetes impairs bone remodeling and contributes to cortical bone thinning and reduced bone mineral density (54).

Araújo *et al* (52) demonstrated that high-glucose conditions substantially disrupt the bone ECM. Specifically, glucose exposure promotes increased collagen deposition but results in a disorganized fibril structure and deficient collagen crosslinking. This structural deterioration yields a more brittle, less resilient matrix, ultimately compromising mechanical strength and increasing fracture risk (52). Bone quality is heavily dependent on collagen crosslinking, which occurs via enzymatic lysyl oxidase pathways or non-enzymatic processes that generate AGEs. For instance, the AGE pentosidine is a known marker of increased fracture risk in elderly patients with type 2 diabetes (55). Although AGEs typically interfere with primary mineralization, a positive association has also been reported between collagen crosslink ratios and mineral layer thickness in trabecular bone (56). Furthermore, excessive non-enzymatic crosslinking impairs cancellous bone quality in osteoporotic patients, independent of mineral content (57). Collectively, these findings suggest that abnormal collagen crosslinking, particularly in the setting of AGE accumulation, weakens the structural integrity of the bone matrix and contributes to bone fragility.

Neuropathy, a prevalent complication in DFU, further exacerbates cortical thinning (58). These sensory and motor deficits lead to abnormal mechanical loading of the foot, driven by altered gait mechanics and loss of protective sensation, which ultimately impairs bone remodeling responses (59). Beyond mechanical stress, compromised neural signaling disrupts the intricate neurovascular regulation of local blood flow and nutrient delivery, hindering the bone's ability to repair and maintain its structural integrity (60). Similarly, autonomic dysfunction can dysregulate circulatory responses, diminishing the supply of oxygen and nutrients essential for maintaining skeletal health (61).

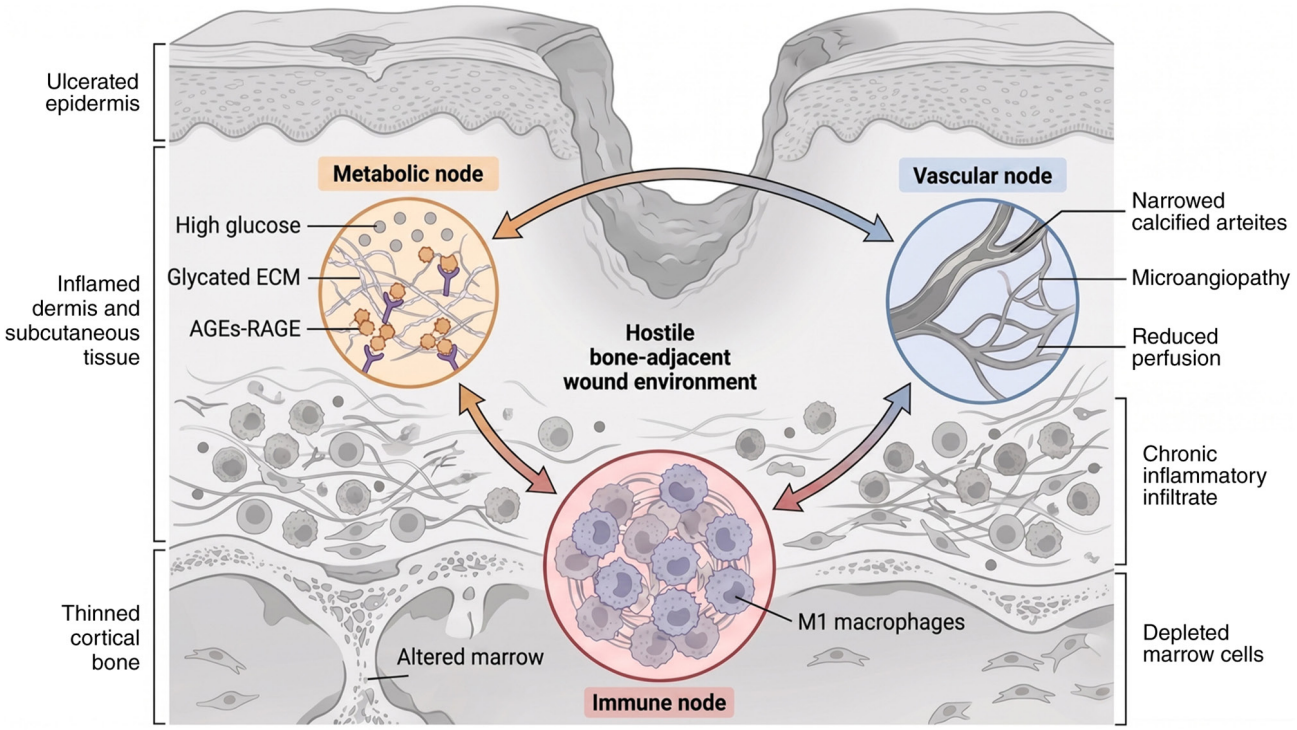


Figure 2. Hostile bone-adjacent wound environment in DFUs. The diagram outlines how high glucose, glycated ECM and AGEs-RAGE signaling (metabolic node) contribute to wound dysfunction. Vascular impairment (vascular node) is characterized by narrowed calcified arteries, microangiopathy and reduced perfusion, which hinder proper blood flow to the wound. The immune response (immune node) is dominated by M1 macrophages and a depletion of marrow stromal cells, which further contributes to the cycle of chronic inflammation and poor healing. AGEs, advanced glycation end products; ECM, extracellular matrix; M1, classically activated pro-inflammatory macrophage phenotype; RAGE, receptor for advanced glycation end products.

PAD, a frequent comorbidity in DFU, substantially exacerbates cortical thinning by compromising the local blood supply (62). Reduced vascularity limits the delivery of oxygen, growth factors and nutrients essential for osteoblast function and bone matrix synthesis (63). The resulting chronic ischemia impairs bone repair processes and promotes a catabolic environment within bone, thereby accelerating cortical loss (64). Collectively, the interplay of hyperglycemia, AGEs, neuropathy and PAD creates a vicious cycle that progressively depletes cortical bone mass, increasing bone fragility and the risk of further complications in patients with DFU (Fig. 2).

*Marrow stromal exhaustion*. Beyond impaired remodeling, diabetes perturbs the bone marrow stem/progenitor niche, reducing the availability and fitness of osteogenic progenitors. Osteogenesis is severely hindered in diabetic individuals by osteoblast dysfunction and the exhaustion of bone marrow stromal cells (BMSCs), both of which are key for bone regeneration (65). In the context of DFU, this BMSC exhaustion contributes to impaired repair and delayed wound healing (66-68), further compromising overall bone health (69). Aging further compounds this issue, driving a lineage shift whereby BMSCs preferentially differentiate into adipocytes rather than osteoblasts, a hallmark of age-related bone loss (70,71). Key to this balance are CXCL12-abundant reticular (CAR) cells, which regulate the transition between osteogenesis and adipogenesis (72). Disruptions in CAR-hematopoietic cell communication promote marrow adipogenesis through the direct conversion of CXCL12+ preadipocyte-like cells into lipid-laden marrow adipocytes (72). This suggests a cell-nonautonomous mechanism in which CXCL12-dependent physical coupling with hematopoietic cells helps prevent premature adipocytic differentiation.

The chronic inflammation, oxidative stress and compromised microenvironment surrounding the ulcer create a hostile setting for BMSCs, which are essential for bone regeneration (73). Pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6 and IL-8, secreted by immune cells such as macrophages and neutrophils, activate inflammatory pathways such as NF-κB and MAPK, thereby promoting BMSC senescence (74-76). This impairs the ability of BMSCs to proliferate and differentiate into osteoblasts, while the upregulation of cell-cycle inhibitors p16INK4a and p21CIP1 serves as a marker of cellular aging (77). Simultaneously, oxidative stress generated by immune-cell activity produces reactive oxygen species, including $O^{2-}$, $H_2O_2$, and $OH^{\bullet}$. These reactive oxygen species damage cellular components, particularly mitochondria (78-80) and further impair BMSC function (81,82). Dysregulation of Nrf2, a key regulator of antioxidant defenses, exacerbates this oxidative damage and further limits the regenerative capacity of these cells (83).

The DFU microenvironment is further compromised by hypoxia and nutrient deprivation (3). While poor vascularization initially activates hypoxia-inducible factor-1α(HIF-1α) signaling (84,85), prolonged oxygen deficiency eventually impairs BMSC metabolism (86). These local deficits are compounded by systemic metabolic disturbances that reduce the availability of essential glucose and amino acids, depriving BMSCs of the substrates required for repair (87). Together with chronic inflammation and oxidative stress, these stressors

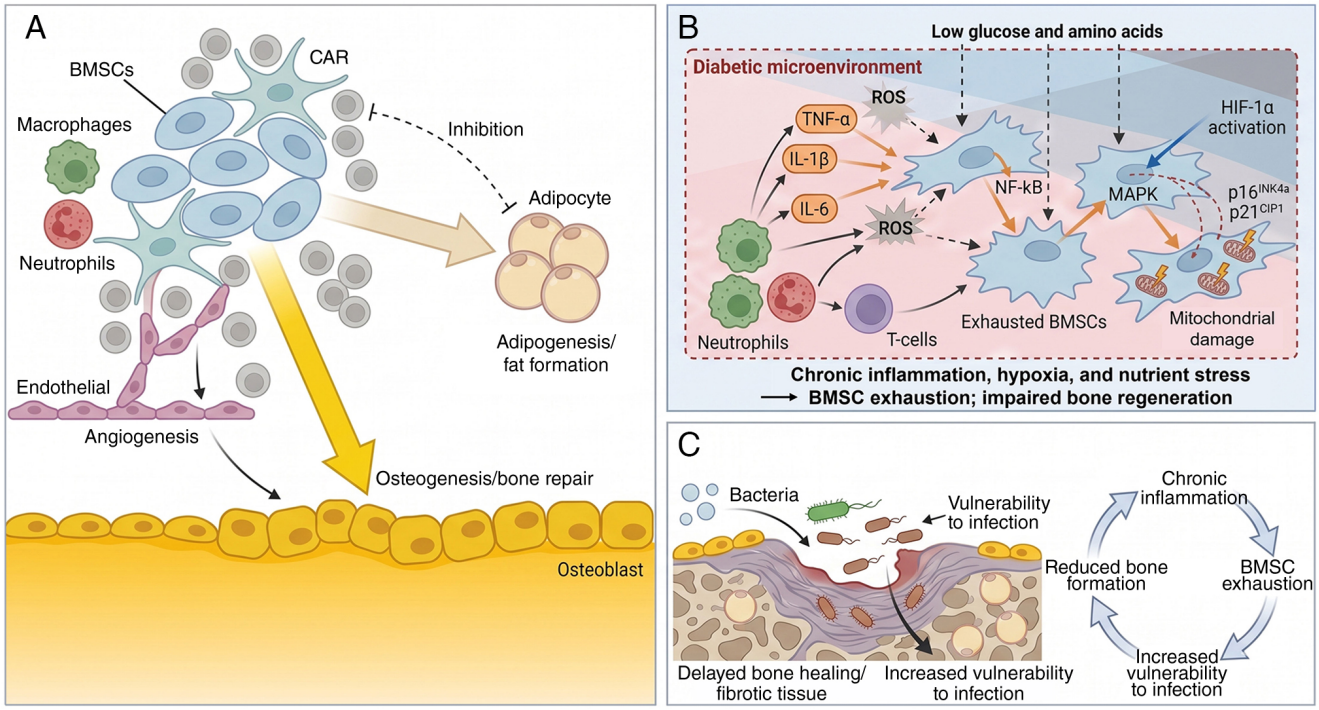


Figure 3. BMSC-driven bone formation vs. BMSC exhaustion in the diabetic foot ulcer microenvironment. (A) In the healthy marrow niche, BMSCs support osteogenesis, angiogenesis and bone repair through interactions with stromal, vascular and immune cell populations. (B) In the DFU microenvironment, chronic inflammation, hypoxia, oxidative stress and nutrient deprivation induce BMSC exhaustion through inflammatory and stress-related signaling pathways, resulting in loss of regenerative capacity. (C) BMSC exhaustion contributes to impaired bone regeneration, delayed healing, increased susceptibility to infection and persistent chronic inflammation. BMSCs, bone marrow mesenchymal stromal/stem cells; CAR, CXCL12-abundant reticular cells; DFU, diabetic foot ulcer; HIF-1α, hypoxia-inducible factor-1α; ROS, reactive oxygen species.

establish a feedback loop in which BMSC exhaustion diminishes the regenerative potential of bone tissue. Consequently, bone repair becomes less efficient, further weakening the capacity of diabetic bone to support local healing. Ultimately, BMSC exhaustion in DFUs impairs bone regeneration and may increase vulnerability to further complications, including infection (Fig. 3).

*Progression from DFU to osteomyelitis*. Diabetic foot osteomyelitis (DFO) represents a severe complication affecting 20-68% of patients with diabetic foot ulcers, considerably increasing the risk of lower-extremity amputation (88). While neuropathy and vascular insufficiency create the general conditions for ulcer formation (89), impaired wound healing and microbial persistence, diabetes-related changes in bone may further increase susceptibility to osteomyelitis (90). Cortical bone deterioration, driven by intracortical remodeling, can thin the cortex from within through cavitation and coalescing pores, increasing cortical porosity and compromising bone strength and structural integrity (91-93). Consistent with this, regions with lower cortical thickness and higher cortical porosity represent structurally and mechanically weaker sites within bone (94). In parallel, marrow stromal dysfunction may impair the local supportive capacity of the marrow microenvironment (95-98). In this context, BMSC exhaustion/senescence is associated with impaired self-renewal and reduced osteogenic differentiation, thereby diminishing osteogenic repair capacity (99). Once DFU extends into deep soft tissue adjacent to bone (100), these bone-specific abnormalities may leave the subjacent bone less able to withstand and recover from contiguous bacterial insult, thereby facilitating progression to established infection (100).

The progression from superficial ulceration to bone infection follows a predictable cascade driven by the unique pathophysiological environment of the diabetic foot. Superficial DFUs typically begin as neuropathic ulcerations that, when left untreated or inadequately managed, provide a direct pathway for bacterial invasion (101). Loss of protective sensation due to peripheral neuropathy allows repetitive microtrauma to go unnoticed, while impaired immune function and chronic hyperglycemia create conditions favorable for bacterial proliferation and biofilm formation (3).

Bacteria penetrate compromised soft tissues, initially colonizing the wound bed before extending into subcutaneous tissues and eventually reaching the underlying bone (102). This progression is accelerated by PAD, which reduces perfusion and oxygen delivery required for effective immune cell function (103). In addition, the polymicrobial nature of the majority of DFIs, commonly involving Staphylococcus aureus, Pseudomonas aeruginosa and anaerobic species, further complicates the infectious process (104,105). Once bacteria establish infection within bone tissue, they form resilient biofilms that resist both host immune responses and antibiotic penetration, leading to chronic, difficult to treat osteomyelitis (106,107). Diagnosis of DFO remains challenging because systemic inflammatory markers may be absent or minimal in diabetic patients despite severe bone infection (108). A positive probe to bone test in the setting of a chronic ulcer is highly suggestive of underlying osteomyelitis and often necessitates aggressive intervention, including surgical debridement and prolonged

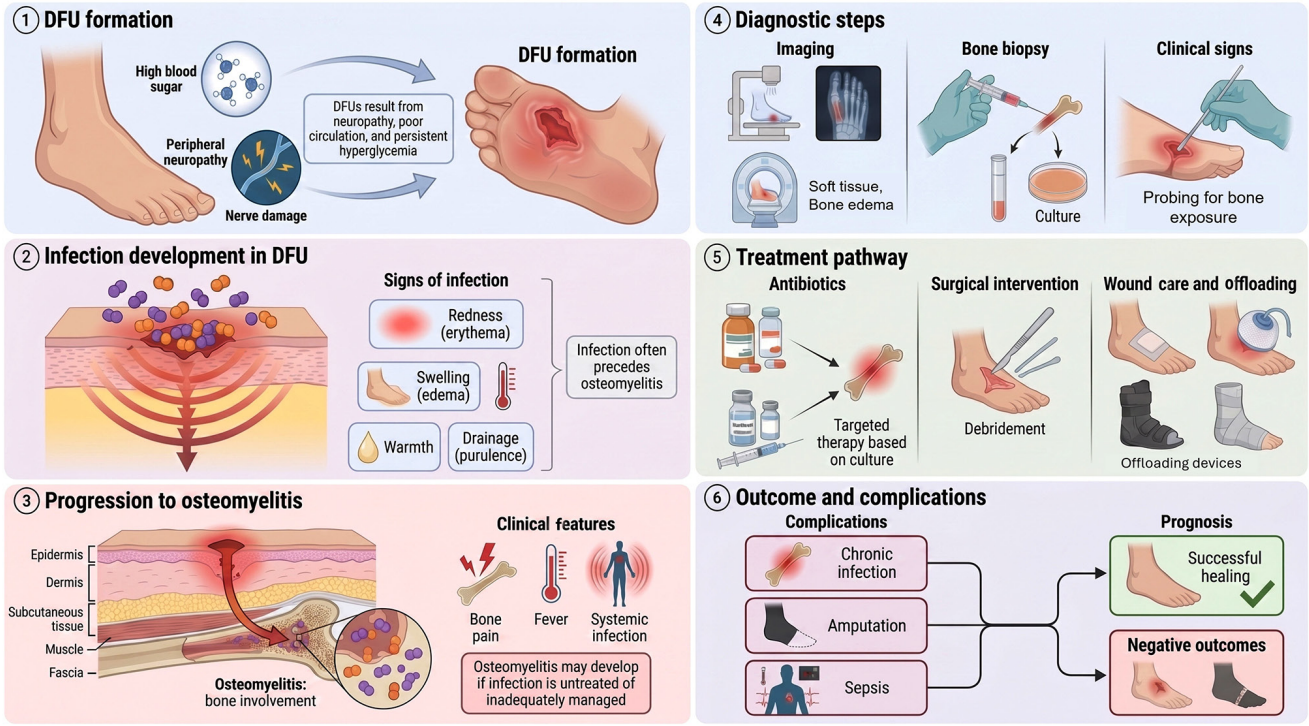


Figure 4. Progression from DFU to osteomyelitis. The stages of DFU formation, from (1) the initial effects of high blood sugar and peripheral neuropathy, (2) to infection development and signs of infection and (3) eventual progression to osteomyelitis. The (4) treatment pathway encompasses diagnostics, antibiotics, surgical intervention and wound care, while the (5) outcomes and complications emphasize the potential for chronic infection, amputation or sepsis, with (6) corresponding positive or negative prognoses. DFU, diabetic foot ulcer.

antimicrobial therapy, to prevent progression to major amputation (109). This progression highlights the importance of early intervention, revascularization and appropriate infection control as part of the wound healing strategy (Fig. 4). It also defines an important practical boundary for bone-origin repair, since suspected osteomyelitis should first undergo appropriate diagnostic evaluation, confirmed osteomyelitis should be treated before bone-targeted intervention is considered (102) and any subsequent reconstruction should follow only after infection control has been achieved (110).

## 3. Bone-origin repair, concept and boundaries

In bone-adjacent DFUs, the underlying skeleton should be viewed not merely as a passive structural substrate, but as a compartment with inherent regenerative and signaling capacity (111). In the present review, bone-origin repair refers to a hypothesis-driven, localized strategy in which controlled stimulation of the cortical, subcortical unit beneath or near a DFU is intended to trigger a confined, callus-like response that may secondarily support soft-tissue healing (112). At present, this remains an emerging conceptual framework rather than a validated clinical strategy. It is not proposed as a blanket indication for bone-targeted intervention, but as a potential adjunctive strategy to be applied under carefully defined clinical conditions.

At the clinical level, these conditions are best understood as provisional candidate scenarios rather than established indications. The concept is most plausible in chronic, bone-adjacent DFUs in which sensory loss and abnormal foot mechanics indicate a strong neuropathic/mechanical component (113,114), especially when ulceration develops over deformity or other sites of repetitive stress (31) and the underlying bone-soft tissue unit is likely to be structurally compromised by cortical thinning or impaired bone support (115,116). By contrast, ulcers dominated by active osteomyelitis, critical ischemia, severe structural instability or advanced Charcot neuroarthropathy should not be considered candidates for bone-targeted stimulation until those conditions have been appropriately excluded or treated (6,117,118).

A key factor in the clinical translation of bone-origin repair is patient stratification by ulcer phenotype. Conceptually, this framework is most plausible in neuropathic or neuropathic-predominant DFUs, where sensory loss, deformity and repetitive mechanical pressure are central drivers of tissue breakdown (31). In these settings, the underlying bone-soft tissue unit is exposed to chronic stress, leading to structural vulnerabilities that may be more relevant to a bone-targeted reparative concept (59,119). Conversely, in ischemic or neuro-ischemic ulcers, limited macrovascular and microvascular perfusion likely constrains both the local callus response and any downstream soft-tissue benefit (120). Consequently, vascular optimization remains a prerequisite, and severe ischemia represents a poor candidate state for primary bone-targeted stimulation (121). DFUs with mixed neuropathic and ischemic features require the greatest caution, as the coexistence of abnormal mechanical loading and perfusion deficits makes both mechanistic attribution and therapeutic outcomes more difficult to predict (6).

Mechanistically, the proposed core of bone-origin repair is that controlled local bone stimulation activates intrinsic reparative programs within the bone microenvironment (122).

Procedures such as micro-drilling or osteoperforation analogs create localized cortical or subchondral injuries intended to recruit progenitor populations, initiate a callus-like healing cascade, and modulate local vascular and immune signaling (123,124). In principle, this confined response could enhance regional perfusion, mobilize reparative mesenchymal cells and alter the periosteal microenvironment in ways that secondarily support the metabolic and regenerative requirements of the overlying ulcer bed (125,126). This hypothesis is biologically grounded in the capacity of bone injury responses to recruit MSCs (127,128), osteoprogenitors (129) and associated reparative cellular programs (130,131).

However, the evidence level must be clearly distinguished: At present, direct evidence that inducing a peri-ulcer callus causes DFU healing is lacking. Tibial cortex transverse transport (TTT) is a corticotomy-based distraction procedure (132) and the currently cited efficacy evidence derives from clinical studies (133-135) in severe or recalcitrant DFUs rather than from mechanism-specific trials (136). Consequently, clinical experience with TTT provides only indirect support for the broader principle that targeted manipulation of bone biology can influence distal soft-tissue outcomes. In these studies, TTT has been associated with improved healing, limb salvage, ankle-brachial index, skin temperature and distal microvascular density (137,138). These observations are consistent with bone-driven neovascular and reparative signaling, but they do not establish peri-ulcer callus formation itself as the proven causal mechanism of wound closure.

Clarifying the boundaries of bone-origin repair is essential to prevent conceptual overreach. First, it is not a proposal for blanket osteogenesis under all DFUs. Several ulcers overlie weakened, deformed or infected bone (for example, Charcot neuroarthropathy, osteopenic metatarsals and DFO). In such settings, indiscriminate drilling or corticotomy risks fracture, destabilization or spread of infection (139-141). Any bone-targeted maneuver must be contingent on prior evaluation and, where necessary, treatment of osteomyelitis and structural instability. Second, bone-origin repair is not synonymous with unchecked or ectopic ossification. The aim is to induce a confined, self-limited callus response within cortical and subcortical bone, not to generate heterotopic bone in fascia, tendons or dermis, which would likely exacerbate pressure concentrations and impair joint mobility (142,143). Lessons from distraction osteogenesis highlight that while sustained mechanical tension can robustly stimulate osteogenesis and angiogenesis, it also carries risks of infection, fracture and aberrant mineralization if poorly controlled (144,145). Third, bone-origin repair is not a substitute for foundational DFU care. Revascularization, infection control (including management of DFO), pressure off-loading and meticulous wound debridement remain primary determinants of outcome (146,147). The promising results of TTT and similar procedures have been achieved in the setting of optimized conventional management, indicating that bone-targeted approaches should be understood as adjunctive strategies layered onto standard care rather than replacements for it (137). Finally, bone-origin repair is not a single, fixed protocol; the depth, spatial distribution and timing of bone stimulation are likely to require patient-specific titration based on bone quality, vascular status and ulcer characteristics.

*Integration with existing DFU standard treatments.* Bone-origin repair, if translated into clinical practice, should be layered onto standard DFU management rather than introduced in parallel without prior optimization of vascular, infectious and mechanical factors (148,149). Current DFU management is based on systematic assessment of perfusion, infection and mechanical loading, followed by regular wound evaluation, serial debridement, appropriate moist dressings and pressure off-loading. When PAD is present, revascularization should be performed when indicated, whereas adjunctive therapies such as negative pressure wound therapy are generally considered only after standard care has been optimized and wound healing remains inadequate (149). In practical terms, revascularization and infection assessment come first: Ischemic or neuro-ischemic ulcers should undergo prompt vascular evaluation and revascularization when indicated before elective bone-targeted stimulation is considered (150,151), while clinically uninfected ulcers should not receive antibiotics solely to promote healing and suspected or confirmed infection should undergo guideline-based antimicrobial and, when necessary, surgical management before any bone procedure is contemplated (152,153). Local wound care should continue throughout, including regular inspection, debridement and appropriate dressings; negative pressure wound therapy may be considered mainly for post-operative wounds or selected cases, but not as a substitute for infection control or vascular optimization (154). Mechanical protection also remains essential, with ongoing off-loading or protected weight-bearing determined by ulcer location, foot stability and procedural extent; any progression in loading after a bone-targeted intervention should be individualized and deferred until both soft-tissue and structural conditions are clinically stable (155,156).

## 4. Callus biology

Callus formation is the central tissue response through which mechanically competent bone is restored after injury (157). This process represents a sophisticated orchestration of cellular recruitment, phenotypic switching and matrix deposition that recapitulates developmental ossification programs (157,158). Therefore, understanding callus biology at molecular and cellular resolution is important for identifying how diabetes disrupts fracture healing and for developing targeted interventions to restore bone-origin repair capacity in diabetic foot ulcers.

*Cellular cast.* Following a controlled cortical or subcortical injury, callus formation proceeds through overlapping phases of inflammation, soft callus formation, hard callus maturation and remodeling. Each phase is defined by a characteristic 'cellular cast' (159). Early on, platelets and neutrophils dominate the hematoma, providing hemostasis and releasing a first wave of chemokines and growth factors. Monocytes subsequently differentiate into macrophages, which are key regulators of the switch from inflammation to repair (160); their phenotype transitions from predominantly pro-inflammatory to pro-reparative as healing progresses and that disruption of this switch leads to delayed or abnormal callus formation (160,161).

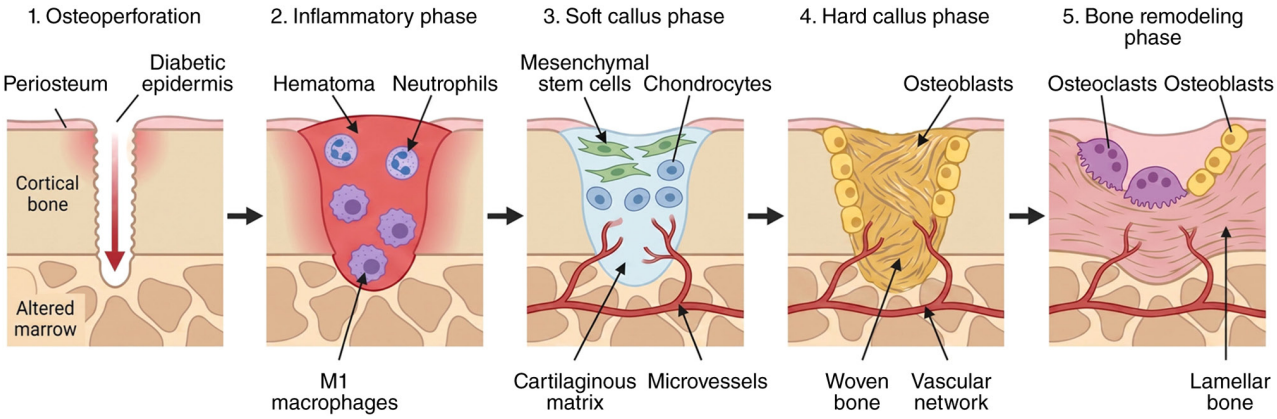


Figure 5. Stages of callus formation after osteoperforation. The sequential stages of bone healing after (1) osteoperforation begin with (2) the inflammatory phase, where M1 macrophages and neutrophils infiltrate the area. (3) The healing process progresses to the soft callus phase, with mesenchymal stem cells and chondrocytes forming a cartilaginous matrix. The (4) hard callus phase leads to woven bone formation and vascular network development. Finally, the (5) bone remodeling phase replaces woven bone with lamellar bone through the coordinated action of osteoclasts and osteoblasts. M1, classically activated pro-inflammatory macrophage phenotype; MSCs, mesenchymal stem cells.

Mesenchymal stromal cells (MSCs) are recruited from periosteum, endosteum and bone marrow and migrate into the hematoma, where they proliferate and differentiate along chondrogenic and osteogenic lineages (128). After the early inflammatory events, fracture repair progresses into the soft-callus stage (162). This stage usually begins a few days following the fracture. During this time, MSCs migrate to the injury site and differentiate into chondrocytes and osteoblasts. These newly formed cells generate a fibrocartilaginous callus, which plays a vital role in stabilizing the fractured bone. The soft callus functions as a temporary support structure, connecting the broken bone fragments and creating a foundation for subsequent bone repair (163). As the healing process advances, the soft callus is slowly converted into a hard callus during the stage referred to as hard callus formation (Fig. 5) (164). During this stage, osteoblasts deposit osteoid, which subsequently mineralizes to create a woven bone scaffold. At the same time, osteoclasts resorb both cartilage and immature bone, contributing to callus remodeling and restoration of normal bone architecture (163).

The developing callus becomes highly vascularized, with endothelial cells and pericytes working together to form and stabilize new blood vessels. Recent studies have also identified a specialized subset of endothelial cells, known as 'type H' cells, which are associated with osteoprogenitor cells and may serve as key regulators of angiocrine signaling during bone repair (165,166). In addition to these classical bone and vascular cells, immune cell subsets, including macrophages, T cells and innate lymphoid populations, contribute to callus quality (167). Macrophages play pivotal roles throughout healing, with M1 macrophages dominating early inflammation and M2 macrophages promoting resolution and osteogenesis (168). Osteoimmunology studies indicate that macrophages regulate both osteoblast and osteoclast activity throughout bone repair, and that sustained pro-inflammatory macrophage phenotypes or defective efferocytosis can impair callus maturation (161,167,169). These osteal macrophages are located adjacent to osteoblasts and regulate bone formation through efferocytosis and paracrine signaling (170). Taken together, these observations suggest that immune and stromal cell behavior is likely to be an important determinant of callus quality in any bone-targeted reparative response.

*Key signaling pathways and matrix cues*. Callus formation is orchestrated by an integrated network of signaling pathways. Members of the TGF-β and bone morphogenetic protein (BMP) families are among the earliest and most prominent (171). They drive MSC recruitment, proliferation and differentiation, and regulate the balance between chondrogenesis and osteogenesis; canonical Smad-dependent TGF-β/BMP signaling is essential for normal bone repair and perturbation of these pathways has been linked to non-union and impaired callus quality (172,173).

The Wnt/β-catenin pathway is another major regulator, promoting osteoblast differentiation and maturation while suppressing excessive chondrogenesis (174). Human fracture-callus studies have shown active Wnt signaling in normally healing callus and altered Wnt activity in non-union tissue, underscoring its relevance to callus competence (175,176). Hedgehog and Notch pathways interact with both BMP/TGF-β and Wnt networks, fine-tuning progenitor cell fate and the timing of endochondral ossification. These pathways do not operate in isolation; rather, they form a densely interconnected 'signal grammar' in which changes in one pathway propagate through others, affecting cell recruitment, proliferation and differentiation (177).

The HIF-VEGF axis couples angiogenesis with osteogenesis through oxygen-sensing mechanisms. HIF-1 regulates bone homeostasis and angiogenesis by controlling VEGF expression, with the HIF-1/RANKL/Notch1 pathway bidirectionally regulating macrophage differentiation into osteoclasts under different conditions (178). VEGF serves as the master regulator of vascular development and is required for effective angiogenic-osteogenic coupling, with dose-dependent effects on mesenchymal progenitor differentiation and angiocrine functions of endothelium (179). Notch signaling exhibits stage-specific functions, with Notch1-4 receptors controlling osteoblast differentiation, matrix mineralization and osteoclast recruitment through crosstalk with Wnt/β-catenin, BMP and RANKL/OPG pathways (180).

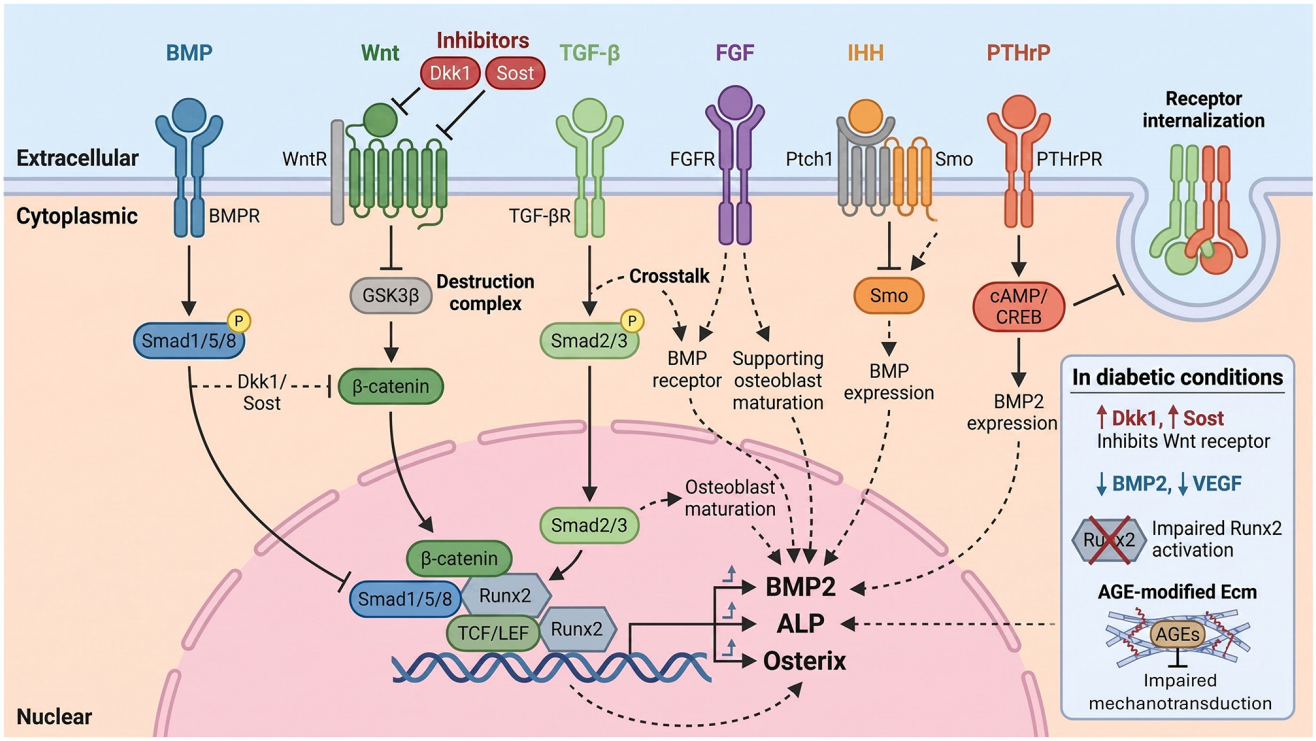


Figure 6. key signaling pathways involved in bone formation. In diabetic conditions, dysregulation of these pathways occurs due to increased Dkk1, Sost and AGE-modified ECM, leading to impaired osteogenesis, reduced BMP2 and VEGF, along with dysfunction in Runx2 activation. These factors collectively contribute to poor bone healing and delayed tissue repair in DFUs. AGE, advanced glycation end product; ALP, alkaline phosphatase; BMP, bone morphogenetic protein; BMP2, bone morphogenetic protein 2; BMPR, bone morphogenetic protein receptor; Dkk1, dickkopf-related protein 1; ECM, extracellular matrix; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; GSK3β, glycogen synthase kinase 3β; IHH, Indian hedgehog; LEF, lymphoid enhancer-binding factor; P, phosphorylation; Ptch1, patched 1; PTHrP, parathyroid hormone-related protein; PTHrPR, parathyroid hormone-related protein receptor; Runx2, runt-related transcription factor 2; Smo, smoothened; Sost, sclerostin; TCF, T-cell factor; VEGF, vascular endothelial growth factor.

The ECM adds a further layer of regulation: Its composition, stiffness and degree of cross-linking influence integrin signaling, mechanotransduction and the way cells interpret growth-factor cues. Glycation-related changes and altered collagen cross-linking can therefore have direct consequences for callus architecture and mechanics, beyond their effects on bone cells per se (181,182). ECM stiffness regulates MSC differentiation through mechanotransduction pathways, while glycation-induced matrix modifications alter mechanical properties and cellular interactions (183). The bone ECM guides specific tissue formation at implantation sites through osteoinductive, osteoconductive and osteogenic signals (Fig. 6) (183).

*Angio-osteo coupling in the callus*. Angiogenesis and osteogenesis are tightly coupled during bone regeneration (179). Newly formed vessels are not only conduits for oxygen and nutrients but also active participants in regulating callus development through 'angiocrine' signals (184). Studies of skeletal vasculature have shown that endothelial cells can directly influence osteoprogenitor proliferation and differentiation via VEGF signaling and other paracrine factors, and that osteoblast-derived HIF-1α-VEGF activity is required to initiate and sustain this angiogenic-osteogenic cascade (63,179,185,186). Vascular-skeletal coupling represents a fundamental requirement for successful callus maturation. Type H vessels, characterized by high CD31 and Endomucin expression, possess unique ability to induce osteogenesis through factors including Platelet-derived growth factor-BB (PDGF-BB), SLIT3, HIF-1α, Notch and VEGF (184,187). PDGF-BB is one of a family member of transmembrane glycoproteins encoded by four genes A, B, C and D. These specialized capillaries support perivascular osteoprogenitor cells and thereby control bone formation, with blood vessels serving as both structural templates around which bone development occurs and conduits delivering essential minerals, growth factors and progenitor cells (179).

Within the callus, spatial organization of vessels and bone-forming cells is non-random (179). VEGF produced by inflammatory cells, MSCs, osteoblasts and hypertrophic chondrocytes promotes endothelial proliferation and sprouting, while reciprocal signals from endothelial cells enhance osteoblast and osteoclast activity (188). Osteoblast-derived VEGF plays key roles at multiple fracture healing stages, promoting macrophage recruitment and angiogenic responses during inflammation, coupling angiogenesis with osteogenesis in areas of intramembranous ossification and stimulating blood vessels and osteoclasts for cartilage resorption during endochondral ossification (189). The intimate bidirectional communication between endothelial cells and bone cells involves angiocrine functions where endothelium regulates osteoprogenitors, while immune cells recruited by the vascular microenvironment modulate both angiogenesis and osteogenesis (190).

Pericytes serve dual functions as vascular stabilizers and osteoprogenitor reservoirs. Bone-specific microvascular pericytes, tightly affiliated with capillaries, exhibit multilineage

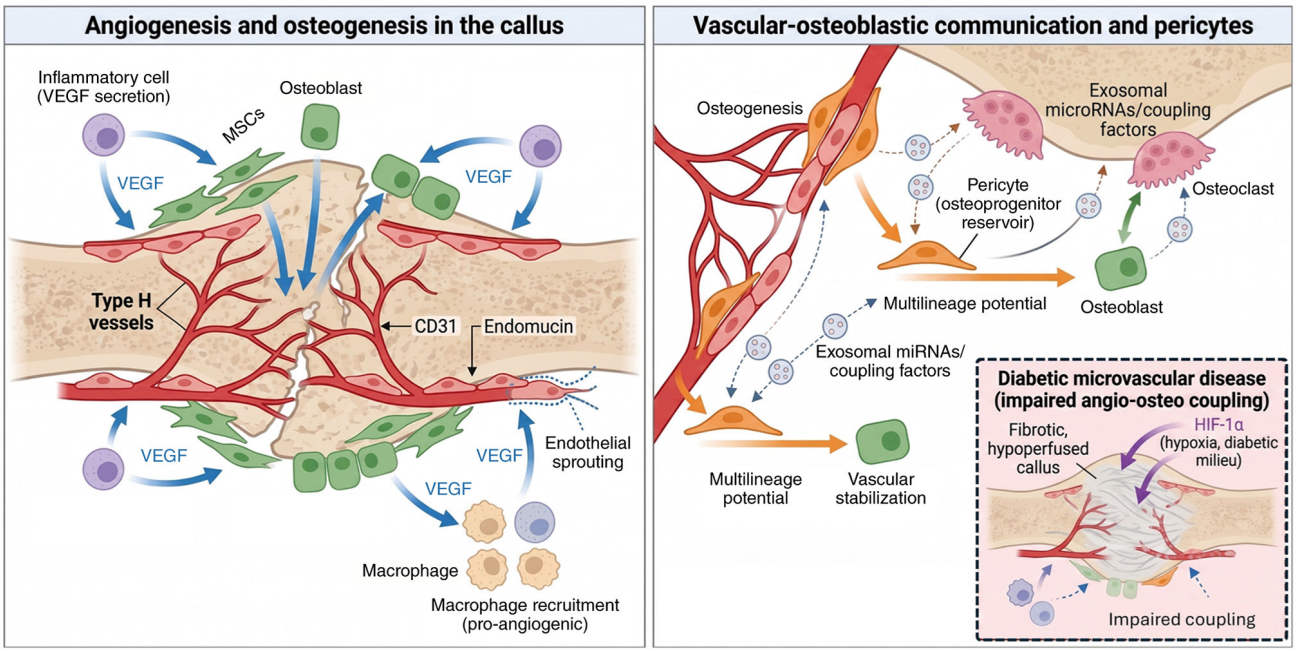


Figure 7. Angio-osteo coupling in the callus and diabetic disruption. Angiogenesis and osteogenesis are tightly coupled during bone regeneration in the callus. Endothelial cells, osteoblasts and osteoclasts communicate through reciprocal signaling, with VEGF playing a central role in both angiogenesis and osteogenesis. Specialized blood vessels, such as Type H vessels, support osteoprogenitor cells and facilitate bone formation by secreting factors such as PDGF-BB, SLIT3 and Notch. Pericytes serve as both vascular stabilizers and osteoprogenitor reservoirs, contributing to bone remodeling. In the diabetic microvascular environment (red dashed box), this coupling is impaired, leading to under-perfused or fibrotic callus formation. Dysregulated HIF-VEGF signaling may hinder effective angiogenesis and osteogenesis, contributing to delayed bone healing in diabetic foot ulcers. HIF-1α, hypoxia-inducible factor-1α; miRNAs, microRNAs; MSCs, mesenchymal stromal/stem cells; VEGF, vascular endothelial growth factor.

potential and constitute the cellular reserve for bone formation, remodeling and repair (191). Coupling factors and exosomal microRNAs mediate crosstalk between osteoclasts, osteoblasts, vessel-specific endothelial cells and perivascular pericytes, playing central roles in angiogenesis-osteogenesis coupling essential for bone remodeling (192). Perfusion geometry within the callus determines nutrient delivery and waste removal, with adequacy of vascular supply being critically dependent on successful angiogenesis, as fracture healing can be prevented by inhibiting angiogenesis (193).

In bone-origin repair applied beneath DFUs, the interaction between angiogenesis and osteogenesis is a factor to be taken into account. The hope is that a localized callus response can augment perfusion in an otherwise ischemic, microangiopathic environment. However, it is equally plausible that, in advanced diabetic microvascular disease, the ability of bone to mount an effective angiogenic response is constrained, leading to under-perfused or fibrotic callus (194). The balance between these two outcomes likely depends on the degree of vascular compromise and the integrity of HIF-VEGF signaling in diabetic bone (Fig. 7) (34,195).

*Diabetic modifiers of callus kinetics and quality*. Diabetes mellitus exerts multifactorial effects on bone regeneration, and these are expected to shape any callus induced by bone-origin repair under a DFU (196,197). Hyperglycemia, AGE accumulation, oxidative stress, low-grade inflammation and vascular damage converge to impair osteoblast differentiation, increase osteoclast activity and alter the function of osteocytes and MSCs (181,196,198). AGEs alter matrix mechanical properties, disrupt molecular conformation, impair enzyme activity and interfere with receptor functioning (199,200). Through interaction with RAGE, these molecules trigger pro-inflammatory signaling and oxidative stress that fundamentally derails normal callus kinetics (201). MSCs exposed to hyperglycemic or AGE-rich environments show impaired proliferation and osteogenic differentiation, increased adipogenic drift and enhanced senescence, while osteoblasts exhibit reduced matrix production and increased susceptibility to apoptosis (182,202).

On the immune side, diabetes alters macrophage plasticity, prolonging pro-inflammatory phenotypes and delaying the transition toward pro-reparative subsets (203). In bone, this can translate into a prolonged inflammatory phase within the callus, with excessive production of reactive oxygen species and pro-inflammatory cytokines that interfere with osteoblast and chondrocyte function (204). Aged and diabetic macrophages show increased sensitivity to inflammatory signals, and failure of M1-to-M2 repolarization leads to persistent inflammation, increased osteoclast activation and decreased osteoblast formation (168). Proper macrophage polarization is essential for successful bone healing, as M2 macrophages promote tissue regeneration while prolonged M1 dominance inhibits repair (205). Microangiopathy compounds these cellular defects by reducing perfusion to fracture sites, with decreased blood supply increasing impaired healing incidence from 10 to 15 to 46% (206). The diabetic microenvironment exhibits reduced VEGF responsiveness, impaired endothelial function and diminished Type H vessel abundance (207).

*Quantifiable endpoints and biomarker candidates*. To facilitate future research design and clinical trial endpoint selection,

studies of callus biology in diabetic bone repair should incorporate quantifiable measures across structural, vascular, histologic and circulating domains (208-210). Structural evaluation may include longitudinal CT or micro-CT to quantify callus volume and mineral density (211,212), thereby characterizing the three-dimensional composition and maturation of the regenerative unit. Vascular assessment may include serial local perfusion measurements using laser Doppler-based methods or angiographic techniques to track angiogenic recovery (213). Where tissue-level analysis is feasible, quantification of $CD31^{hi}$/$Emcn^{hi}$ type-H vessels may provide a useful marker of angiogenic-osteogenic coupling (187,214-216). In parallel, serial measurement of PDGF-BB and other candidate osteokines may help characterize temporal circulating response patterns (214,217). At present, such circulating profiles should be interpreted as exploratory biomarkers rather than validated surrogate endpoints.

## 5. Endocrine effects of bone on DFU healing

Over the past two decades, bone has been redefined from a purely structural tissue to a multifunctional endocrine organ. Osteoblasts, osteocytes and, to a lesser extent, osteoclasts secrete bioactive factors, collectively termed osteokines, that regulate energy metabolism, vascular biology and immune function (218). In the context of DFUs, a key distinction must be made between two levels of bone-derived signaling: Systemic endocrine effects mediated by circulating factors, and local paracrine or autocrine effects occurring within the bone-wound microenvironment (15,219-221). While both may be relevant in the diabetic state, their evidence levels and mechanistic implications are not equivalent. Accordingly, the following discussion distinguishes between osteokines that are more plausibly involved as functional mediators of repair and those that may currently be more effectively interpreted as associated biomarkers.

*Bone as an endocrine organ*. The recognition of bone as an endocrine organ has fundamentally reshaped the understanding of skeletal biology beyond its traditional structural and mineral storage functions (15,218). Bone cells, osteoblasts, osteocytes and osteoclasts, secrete a constellation of bioactive molecules termed 'osteokines' that exert systemic effects on distant organs through endocrine, paracrine and autocrine mechanisms (222). These bone-derived factors represent key mediators associating skeletal metabolism to wound healing, with particular relevance in the diabetic context where both systems are profoundly dysregulated (222).

OCN, the primary non-collagenous protein in the bone matrix, exists in two major forms with distinct biological associations: The carboxylated form, which facilitates mineralization and the undercarboxylated (ucOCN) form (15), which has been implicated in systemic metabolic regulation (223). While experimental murine models indicate that ucOCN can potently stimulate insulin secretion and peripheral sensitivity (19,224), its endocrine role in humans remains a subject of ongoing debate (225-228). Human clinical data generally show an inverse association between circulating OCN and glycemic indices, such as HbA1c and fasting glucose, but these associations are not uniform and often do not establish ucOCN as a definitive causal mediator (223,226). This clinical discrepancy is illustrated by reports of patients with type 2 diabetes exhibiting lower circulating OCN levels than healthy controls (7.07±3.80 ng/mlvs. 20.41±13.50 ng/ml), alongside inverse associations with glycemic markers (223). Consequently, in the context of DFU pathogenesis, OCN is best interpreted as a plausible metabolic mediator whose reduction in diabetes may reflect altered bone-endocrine function, rather than a fully validated driver of soft-tissue repair.

Sclerostin, encoded by the SOST gene and predominantly secreted by osteocytes, is a potent inhibitor of canonical Wnt/β-catenin signaling (15). By binding to LRP5/6 co-receptors on osteoblasts, it suppresses bone formation, shifting the remodeling balance toward an anti-anabolic state (229).

Beyond these local skeletal effects, circulating sclerostin has been associated with metabolic dysfunction; however, its role as a systemic endocrine mediator remains less clearly defined than its established paracrine action in bone (230). While elevated sclerostin levels in diabetes may contribute to a compromised bone environment (231), direct evidence associating sclerostin to DFU healing remains limited (232,233). Pharmacological inhibition of sclerostin is under clinical investigation, with monoclonal antibodies, including romosozumab, blosozumab, and BPS804 (setrusumab), being explored for their potent anabolic effects (234-237).

FGF-23, produced by osteoblasts and osteocytes, represents a bone-derived endocrine factor that regulates phosphate metabolism primarily through renal actions (238). FGF-23 targets the kidney's proximal tubule, the parathyroid gland and the cardiovascular system; while its primary role is phosphate homeostasis, it has also been implicated in inflammatory and vascular pathways relevant to tissue repair (239,240). In diabetes, however, interpretation of circulating FGF-23 is complicated by the frequent coexistence of chronic kidney disease (CKD), making it difficult to distinguish direct endocrine effects from CKD-related biomarker elevation (15,241-244). Thus, FGF-23 is better interpreted as a context-dependent systemic biomarker rather than an established causal mediator of DFU repair.

By contrast, the RANKL/OPG axis constitutes a fundamental regulatory system linking bone remodeling with immune activation (245). The RANKL/OPG ratio, regulated by osteoblasts and osteocytes, influences immune cell subsets (for example, T cells and dendritic cells) and endothelial cells, contributing to osteoimmune crosstalk within the wound microenvironment. In diabetes, this ratio is elevated, promoting excessive osteoclastogenesis and inflammatory cytokine production (246-249). While RANKL-neutralizing antibodies (for example, denosumab) represent potential strategies to rebalance this signaling, their relevance to DFU remains unproven (250,251). Therapeutic extrapolation must remain cautious regarding potential risks, including increased infection susceptibility, suppression of necessary bone remodeling and impaired skeletal adaptation in the biomechanically complex diabetic foot (252).

LCN2, secreted by osteoblasts, influences energy metabolism by suppressing appetite in the brain and has been linked to inflammatory processes (253). LCN2, can bind bacterial siderophores and has been implicated in matrix degradation; subtly altered LCN2 signaling might therefore affect

Table I. Bone-derived factors in diabetic wound healing: targets, effects and therapeutic strategies.

| Bone-derived factor | Primary source | Target tissues/cells | Net effects on wound healing | Diabetic alterations | Therapeutic angles | (Refs.) |
|---|---|---|---|---|---|---|
| Osteocalcin (ucOCN) | Osteoblasts | Pancreatic β-cells, adipocytes, muscle and endothelial cells | Enhanced insulin sensitivity, improved glucose metabolism, angiogenesis promotion and fibroblast activation | Reduced (7.07 vs. 20.41 ng/ml in T2DM) | PTH analogues (increased secretion), vitamin K supplementation and exercise interventions | (20,223) |
| Sclerostin | Osteocytes | Osteoblasts (LRP5/6), adipocytes and vascular cells | Inhibits Wnt/β-catenin signaling, suppresses bone formation and may impair angiogenesis | Elevated in T2DM | Romosozumab (anti- sclerostin mAb), Blosozumab and BPS804 | (234-237) |
| FGF-23 | Osteoblasts/ Osteocytes | Kidney (proximal tubule), parathyroid gland and cardiovascular system | Phosphate homeostasis, indirect vascular effects and potential inflammatory modulation | Variable alterations reported | FGF-23 blocking antibodies (experimental) and targeting FGF receptor signaling | (15, 241-243) |
| RANKL/ OPG Ratio | Osteoblasts/ Osteoclasts | Osteoclast precursors, immune cells (T cells, DCs) and endothelial cells | Osteoclastogenesis regulation, immune cell activation and inflammatory cytokine production | Elevated ratio (increased RANKL, decreased OPG) | Denosumab (RANKL inhibitor) and OPG supplementation (experimental) | (246-249) |
| Lipocalin-2 (LCN2) | Osteoblasts | Brain (hypothalamus), adipose tissue and inflammatory cells | Appetite suppression, energy metabolism regulation and inflammatory modulation | Context-dependent changes | Under investigation | (254,256, 261-263) |
| PDGF-BB | Osteoclast precursors/ injury | Fibroblasts, endothelial cells and pericytes | Angiogenesis (Type H vessels), fibroblast activation and KGF secretion → keratinocyte migration | Reduced release capacity | Recombinant PDGF-BB topical, bone injury-triggered release, osteokine-loaded hydrogels | (18,220) |

the protease-antiprotease balance and ECM turnover within chronic DFUs, although this remains speculative.

LCN2 also known as neutrophil gelatinase-associated lipocalin, is secreted by osteoblasts (253-255), and various immune cell types (256,257), and has been implicated in energy metabolism, innate immunity (256) and inflammatory signaling (253,258). In the context of bone-derived endocrine signaling, its interpretation remains highly context-dependent. While LCN2 can bind bacterial siderophores (259), and has been associated with matrix remodeling (256,259), its specific causal relevance to DFU repair is not yet established. In diabetes, current evidence suggests that circulating LCN2 levels may reflect a systemic dysmetabolic or inflammatory state rather than act as a primary driver of wound healing (256,260), particularly because its metabolic and immune effects are not consistently unidirectional. Accordingly, LCN2 is best interpreted as a context-dependent osteokine with biomarker relevance, while its direct therapeutic modulation for DFU remains under investigation (254,256,261-263).

PDGF-BB, released locally following bone injury, acts on fibroblasts, endothelial cells and pericytes (220,264). Among the osteokines discussed here, PDGF-BB is more plausibly positioned as a direct paracrine mediator than as an accompanying biomarker, because bone-injury-triggered PDGF-BB signaling is mechanistically linked to angiogenesis, fibroblast activation and improved diabetic wound repair (265,266). PDGF-BB also influences osteoclast precursor behavior, further supporting its role in coordinating reparative responses across bone-associated tissues (220,264). In the diabetic state, impaired PDGF-BB release from bone may compromise this reparative influence on distal soft tissues (220). While topical recombinant PDGF-BB is an established clinical therapy, strategies to leverage bone-derived release mechanisms or

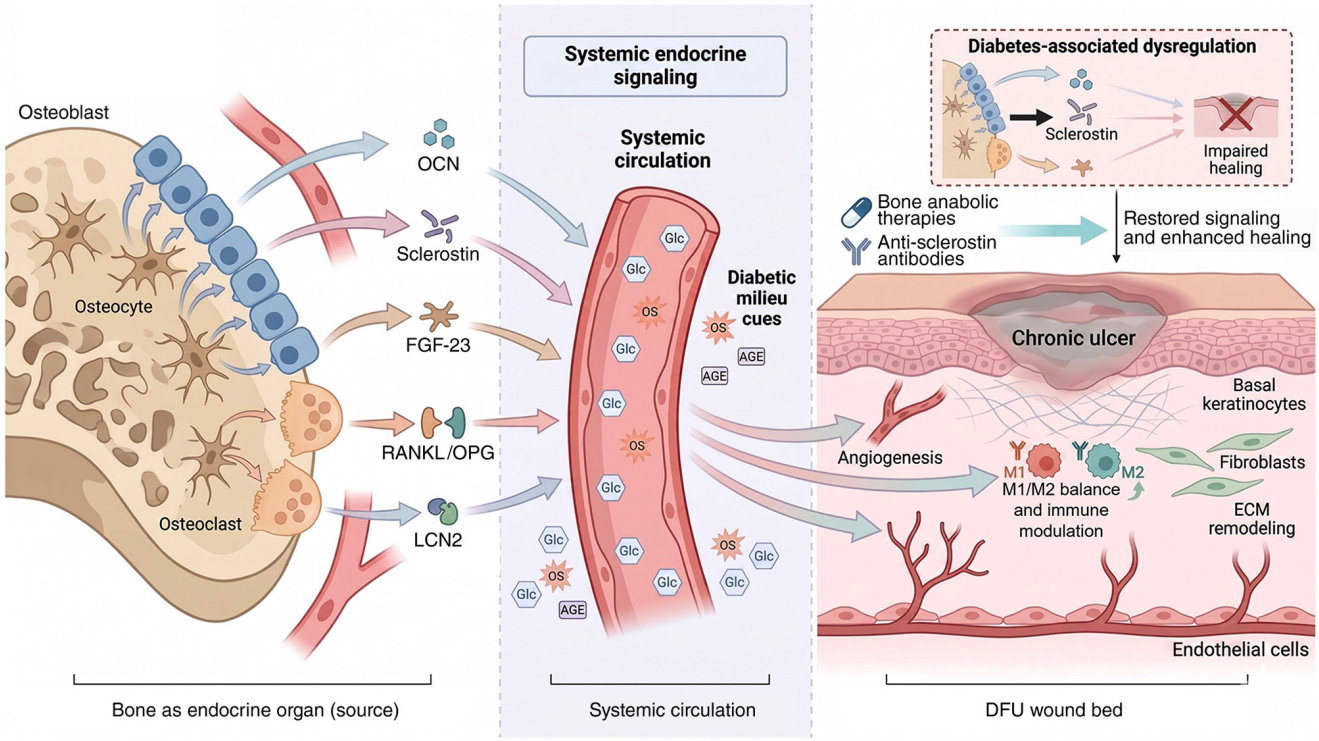


Figure 8. Bone-derived endocrine signaling and associated biomarkers in the diabetic foot ulcer microenvironment. Bone cells release osteocalcin, sclerostin, FGF-23, RANKL/OPG and lipocalin-2 into the systemic circulation, where these signals interact with diabetes-related metabolic cues. Within the diabetic foot ulcer wound bed, these bone-derived factors are best interpreted as candidate signals and associated biomarkers that may influence angiogenesis, immune modulation and extracellular matrix remodeling. The upper-right inset illustrates diabetes-associated dysregulation, whereas the therapeutic overlay is presented as investigational rather than established clinical efficacy. AGE, advanced glycation end product; DFU, diabetic foot ulcer; ECM, extracellular matrix; FGF-23, fibroblast growth factor 23; Glc, glucose; LCN2, lipocalin 2; M1/M2, classically activated/pro-inflammatory and alternatively activated/pro-reparative macrophage phenotypes; OCN, osteocalcin; OPG, osteoprotegerin; OS, oxidative stress; RANKL, receptor activator of NFκB ligand.

targeted delivery platforms remain of interest and should be regarded as investigational within the specific framework of bone-origin repair (267).

To further illustrate the systemic roles of bone-derived signals in diabetic wound healing, Table I summarizes the primary sources, target tissues, functional effects, diabetes-associated alterations and emerging therapeutic strategies for key osteokines implicated in this endocrine network.

*Diabetic context and therapeutic levers*. The diabetic milieu fundamentally disrupts bone endocrine function, creating a pathological feedback loop wherein skeletal dysfunction exacerbates systemic metabolic derangements that further impair wound healing. Understanding these disease-specific alterations and identifying therapeutic strategies to restore beneficial bone-wound crosstalk represents a frontier in diabetic wound management. The complex interaction between bone-derived signals (osteokines) and diabetic wound healing plays a key role in the pathophysiology of DFU (7,220). Osteoblasts, osteocytes and osteoclasts secrete various osteokines, including OCN, sclerostin, FGF-23, RANKL/OPG and LCN2, which exert systemic effects on metabolism, angiogenesis and immune regulation (Fig. 8) (229,268).

Diabetes is associated with broad alterations in osteokine secretion that may influence both systemic metabolism and the local bone-wound microenvironment (223). Type 2 diabetic patients exhibit reduced circulating OCN levels, specifically the undercarboxylated form, showing substantial inverse associations with glycemic control (223,269,270). Elevated circulating sclerostin, increased FGF-23, frequently confounded by coexisting CKD, dysregulated LCN2 profiles (260,271,272) and a shifted RANKL/OPG balance (273) collectively suggest a catabolic and pro-inflammatory endocrine/paracrine milieu. Although the patterns imply that not only is the bone of the diabetic patient structurally weakened, but it is also endocrinologically abnormal, the relative contribution of each osteokine to the failure of DFU repair remains unequal and, in some cases, needs further mechanistic explanations.

Additional therapeutic considerations involve attempts to modulate OCN biology, for instance, through vitamin K supplementation to optimize carboxylation status, or interventions aimed at reducing bone marrow adiposity (274). However, within the DFU context, such strategies remain biologically plausible but clinically unvalidated, particularly given the unresolved debate surrounding the causal role of undercarboxylated OCN in human metabolic repair (275). Furthermore, while the emerging field of bone-targeted drug delivery, utilizing bisphosphonates or bone-binding peptides, may offer opportunities to localize osteoactive agents (276), its efficacy and potential unintended consequences in the diabetic foot remain insufficiently studied. Finally, the deliberate induction of controlled bone remodeling to trigger osteokine release is a provocative concept (220); its clinical translation would require strict integration with established standards of care, including infection control, vascular assessment and mechanical off-loading (277).

## 6. The bone-origin repair loop

Preclinical evidence suggests that controlled bone injury can activate a bone-skin signaling response in diabetic mice, with PDGF-BB identified as a key circulating mediator associating tibial bone defects to accelerated foot wound healing (220). In humans, interventional studies of TTT in severe or recalcitrant DFUs have reported improved healing, limb salvage, distal perfusion, and small-vessel density, but these clinical data do not yet establish that callus formation itself is the proven causal mechanism of wound closure (132,278). These findings are reinforced by a systematic review and meta-analysis of 7 studies involving 818 participants that found pooled healing and limb-salvage rates of 0.96 and 0.98, respectively, together with significant improvements in ankle-brachial index and skin temperature (137). However, these clinical outcomes do not yet establish that bone-injury-induced callus is itself the proven causal mechanism of wound closure, and TTT must still be interpreted alongside its reported risks, including fracture at the transport site and pin-site infection.

The temporal cascade proceeds as PDGF-BB mediates keratinocyte growth factor secretion from wound-site fibroblasts via PDGFR signaling, thereby accelerating re-epithelialization (220). Additional preclinical evidence suggests that neurovascular signaling also contributes to bone repair, as increased β2-adrenergic signaling has been associated with enhanced callus neovascularization in fracture healing models (279,280).

## 7. Points of controversy and counterevidence

Several points of controversy and counterevidence should be acknowledged to maintain a balanced perspective on the bone-origin repair framework. First, the current human literature regarding osteokine directionality, particularly for OCN, sclerostin, FGF-23 and LCN2, remains heterogeneous (229,281,282). In several population studies, these associations may reflect broader systemic metabolic or inflammatory states rather than direct causal effects on wound repair (283,284). Second, interpretation of FGF-23 in the diabetic population is substantially confounded by the high prevalence of CKD, which can considerably alter circulating levels and complicate mechanistic attribution to bone signaling alone (285). Third, the clinical utility of bone-targeted stimulation may be limited in severely ischemic feet, where impaired macro- and microcirculation could restrict both local callus formation and any downstream soft-tissue benefit. Collectively, these considerations reinforce that the bone-origin repair framework should presently be viewed as a hypothesis-generating concept whose specific mediators, clinical indications and therapeutic limits require prospective validation.

## 8. Conclusion and future prospective

The convergence of metabolic dysfunction, neuropathy and vascular disease in diabetes creates profound skeletal alterations (including cortical thinning, bone marrow stromal cell exhaustion and impaired callus biology) that directly compromise the bone-soft tissue unit and contribute to ulcer chronicity. Beyond these structural deficits, the recognition of bone as a dynamic endocrine organ secreting bioactive osteokines has fundamentally reshaped the understanding of systemic factors influencing wound repair.

The diabetic bone microenvironment is characterized by dysregulated osteokine secretion patterns, with reduced levels of beneficial factors such as OCN and elevated levels of inhibitory molecules such as sclerostin, creating a catabolic and pro-inflammatory milieu that impairs wound healing capacity both locally and systemically. Hyperglycemia, AGE accumulation, oxidative stress and chronic low-grade inflammation converge to impair osteoblast function, alter macrophage polarization, compromise angiogenesis and reduce the regenerative potential of mesenchymal progenitors within bone marrow. These cellular and molecular disruptions translate into prolonged healing times, increased infection risk and elevated amputation rates in diabetic patients with foot ulcers.

However, key caveats must be emphasized. Bone-origin repair is not a universal solution for all DFUs. Patient selection is paramount, active osteomyelitis, severe structural instability, advanced Charcot neuroarthropathy and critical ischemia represent absolute contraindications to bone-targeted interventions. The concept should be understood as an adjunctive strategy layered onto optimized conventional management (revascularization, infection control, pressure off-loading and meticulous debridement) rather than a replacement for foundational care. The depth, spatial distribution and timing of bone stimulation likely require patient-specific titration based on bone quality, vascular status and ulcer characteristics. Furthermore, the risk of complications, including fracture, infection spread, ectopic ossification and over-lengthening, necessitates rigorous clinical protocols and multidisciplinary expertise. Therapeutic targeting of the bone-wound axis offers multiple avenues, including anabolic bone agents, anti-sclerostin antibodies and optimization of OCN bioactivity. Large-scale clinical trials are urgently needed to validate safety and efficacy. The bone-wound axis represents a frontier bridging osteoimmunology and regenerative medicine that may unlock new limb salvage opportunities, though this promise requires rigorous validation, careful patient selection and multidisciplinary expertise.

Looking forward, precision medicine approaches that phenotype individual patients' osteokine profiles and tailor interventions accordingly may become feasible, offering personalized strategies to harness skeletal endocrine function for improved diabetic wound outcomes. Single-cell sequencing technologies, advanced imaging modalities and biomarker discovery platforms will be instrumental in identifying which patients are most likely to benefit from bone-targeted approaches. Large-scale, well-controlled clinical trials are urgently needed to validate the safety and efficacy of bone-origin repair strategies, establish standardized protocols and define optimal patient selection criteria.

To focus future investigation, several testable research questions emerge: i) Can controlled peri-ulcer bone stimulation induce measurable local callus formation and improve soft-tissue healing beyond optimized standard DFU care alone? ii) Which ulcer phenotypes are most likely to benefit from this strategy, particularly neuropathic-predominant vs. ischemic or mixed presentations? iii) Which structural, vascular or circulating biomarkers most reliably reflect biologically meaningful

activation of the bone-soft tissue unit? iv) Can candidate bone-derived mediators such as PDGF-BB be prospectively associated with downstream wound-healing outcomes in human DFU?

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SC and XC drafted the manuscript, edited and revised the manuscript. XC designed the review. All authors read and approved the final version of the manuscript. Data authentication not applicable.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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