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Impact of reactive oxygen species on bone regeneration in diabetes: Mechanisms and therapeutic strategies

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ABSTRACT

Diabetic bone regeneration is significantly affected by reactive oxygen species (ROS)-induced oxidative stress (OS), which disrupts the balance between osteoclast (OC)-mediated resorption and osteoblast (OB)-mediated formation of bone tissue. This review synthesizes current understanding of how hyperglycemia-driven ROS overproduction dysregulates OB and OC functions, leading to pathological bone remodeling and compromised healing. The key molecular mechanisms involved, such as RANK/RANKL, NF-κB, and MAPK, are discussed, highlighting their role in the ROS-mediated feedback loop that promotes OC differentiation while inhibiting OB survival, differentiation, and activity, worsening bone degeneration. Furthermore, the review addresses ROS-induced cell death pathways (apoptosis, ferroptosis, necroptosis, pyroptosis) along with the pathophysiological changes in the bone marrow microenvironment. Emerging therapeutic strategies to reduce oxidative damage, including antioxidant (AO) therapies and innovative drug delivery systems, offer promise for restoring bone regenerative capacity in diabetic conditions. These innovations aim to restore redox homeostasis, mitigate OS damage, and reactivate endogenous bone regenerative capacity. Understanding these mechanisms provides a foundation for developing targeted interventions to improve clinical outcomes in diabetic bone disease.

1. Introduction

Bone regeneration is a dynamic and complex process fundamental to skeletal maintenance and repair, relying on a precise equilibrium between bone formation by osteoblasts (OBs) and bone resorption by osteoclasts (OCs). In diabetes mellitus (DM), this delicate balance is severely disrupted, leading to compromised bone quality, impaired healing capacity, and a clinically significant increase in fracture risk [1,2]. A substantial body of evidence from epidemiological studies has established that both type 1 (T1DM) and type 2 diabetes (T2DM) are independent risk factors for fractures, even after adjusting for traditional risk factors. Notably, individuals with diabetes exhibit a heightened susceptibility to low-trauma fractures, non-vertebral fractures, and particularly hip and foot fractures [2,3]. A critical paradox in this context is the frequent observation of normal or even elevated areal bone mineral density (BMD) in T2DM, which underscores that the detrimental effects of diabetes on bone strength extend far beyond BMD. Bone strength is a multifactorial property integrally dependent on bone density, bone microstructure (e.g., trabecular connectivity), bone material properties (e.g., collagen cross-linking), and the surrounding microenvironment [4].

A hallmark of diabetic bone disease is a generalized suppression of bone turnover, albeit through distinct mechanisms in T1DM and T2DM that differentially impact bone cells [5,6]. In T1DM, the absolute deficiency of insulin and insulin-like growth factor-1 (IGF-1) primarily impairs osteoblast anabolic function, leading to reduced bone formation. In contrast, the pathophysiology in T2DM is more complex, often involving an interplay of insulin resistance, hyperinsulinemia, and eventual beta-cell dysfunction. While hyperinsulinemia may exert initial anabolic effects, chronic hyperglycemia ultimately becomes the dominant force, promoting oxidative stress and inflammation that suppress OB differentiation and activity while, in advanced stages, potentially enhancing OC resorptive activity. In a previous study on type 2 diabetic model rats, the BMD of the distal femur and lumbar vertebrae in these diabetic rats

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showed varying degrees of reduction compared to non-diabetic rats. This was accompanied by decreased expression of osteoblast-specific genes, including bone morphogenetic protein-2, RUNX2, osteocalcin, and osteopontin, within OBs. Further bone regeneration experiments similarly revealed a significant delay in bone regeneration in diabetic rats compared to normal rats [7]. Another study indicated that diabetes induces an oxidative stress microenvironment in the body, particularly in bone tissue. Under ROS conditions, osteoblasts exhibited significantly higher levels of DNA oxidative damage markers than the control group, directly inhibiting osteoblast function, impairing bone formation, and suppressing bone mineralization [8]. Additionally, under high glucose concentrations, osteoclast differentiation and activity were also reduced, leading to decreased degradation of the bone matrix. In vivo experiments further confirmed that diabetes inhibits osteoclastogenesis, thereby suppressing bone matrix degradation during bone regeneration [9]. In summary, bone regeneration function is impaired in diabetes due to the combined effects of oxidative stress and the high glucose environment.

Central to this hyperglycemia-induced bone dysfunction is the excessive generation of reactive oxygen species (ROS) and the resultant state of chronic oxidative stress (OS) [3]. ROS act as pivotal intracellular messengers that disrupt the key signaling pathways governing bone remodeling. For instance, OS inhibits the canonical Wnt/β-catenin pathway, a critical driver of osteoblastogenesis, and simultaneously activates pro-osteoclastogenic pathways such as RANKL/RANK/OPG and downstream effectors like NF-κB and MAPK, thereby tilting the balance towards excessive bone resorption [10–13]. Furthermore, hyperglycemia drives the non-enzymatic formation and accumulation of advanced glycation end-products (AGEs) in the bone matrix. AGEs, upon engaging their receptor (RAGE), not only directly impair bone material quality by creating aberrant collagen cross-links but also amplify ROS production and pro-inflammatory cytokine release, creating a vicious cycle that perpetuates a pro-resorptive, anti-anabolic bone marrow microenvironment [14,15].

Beyond osteoblasts, osteoclasts, and osteocytes, bone regeneration in diabetes is governed by a broader cellular consortium that includes bone-marrow mesenchymal stem cells (BMSCs), osteocytes, chondrocytes and immune lineagesresiding in or trafficking through the marrow. Hyperglycemia-driven ROS/AGE-RAGE signaling perturbs BMSC self-renewal, mitochondrial fitness, and lineage allocation, often diverting osteoprogenitors toward adipogenesis while accelerating senescence [16,17]. Under diabetic conditions, aberrant signaling pathways characterized by upregulation of sclerostin in osteocytes and increased apoptosis lead to bone loss [18,19]. In chondrocytes, elevated TNF-α levels and oxidative stress-induced alterations in MAPK, PI3K/Akt/IGF, and Smads/BMP-7 signaling pathways enhance cartilage matrix degradation and disrupt cartilage structure [20,21]. In parallel, redox-dependent remodeling of the marrow immune niche—notably NOX2/iNOS-high M1 macrophages, NET-forming neutrophils, and Th17-skewed T cells—amplifies RANKL availability and inflammasome activity, reinforcing osteoclastogenesis and suppressing osteoblastogenesis [22–25]. These axes act synergistically with the OB/OC/osteocyte circuitry reviewed below, arguing that precision redox modulation must also normalize progenitor and immune compartments to restore bone homeostasis in diabetes.

This review will delve into the multifaceted role of ROS in disrupting bone regeneration in diabetes, with a specific focus on the molecular mechanisms by which ROS alter OB and OC function. We will systematically explore the signaling pathways involved in ROS-induced bone loss and critically evaluate emerging therapeutic strategies, including antioxidant therapies and innovative ROS-responsive drug delivery systems, which hold promise for restoring bone homeostasis and improving skeletal outcomes in diabetic patients.

2. Impact of ROS-induced OS on bone regeneration

Mounting evidence underscores the detrimental impact of ROS-induced OS on bone regeneration, implicating both OBs and OCs in a milieu conducive to bone resorption [26]. Bone regeneration is contingent upon a meticulously orchestrated sequence of OB formation and subsequent OC-mediated bone resorption. OBs, predominantly differentiated from BMSCs, are instrumental in the osteogenic process, overseeing the synthesis, secretion, and mineralization of the bone matrix, which contains multiple intermediary metabolites of OBs [27]. Osteocytes, representing the terminal differentiation stage of OBs, are enmeshed within the bone matrix, evolving during the ultimate phases of bone formation [28]. These cells establish a communicative nexus with both OBs and OCs, responding to various signals, including hormonal and mechanical stimuli, to precipitate skeletal remodeling [29]. OCs, unique in their role as the sole bone-resorbing cells, are tissue-specific multinucleated macrophages that originate from monocytes or macrophage precursors situated on or adjacent to the bone surface [30]. OBs, terminally differentiated osteoblasts embedded within the mineralized bone matrix, constitute over 90 % of all bone cells and act as the primary mechanosensors and endocrine regulators of bone remodeling [31]. These cells form an extensive lacunar-canalicular network, allowing them to communicate with each other, as well as with osteoblasts on the bone surface and osteoclast precursors. Through the secretion of key signaling molecules such as sclerostin (an inhibitor of the Wnt/β-catenin pathway), RANKL, and OPG, osteocytes precisely orchestrate the balance between bone formation and resorption. In diabetic conditions, the function of osteocytes is severely compromised by ROS-induced oxidative stress, leading to dysregulated signaling that significantly contributes to impaired bone regeneration [32]. The interaction between OCs and OBs is essential to the process of bone regeneration, which OS significantly impedes through several mechanisms: i) an escalation in OC production and an enhancement of their bone-resorbing function [33]; ii) a redirection of osteoblastic progenitor cell differentiation towards a lipogenic lineage at the expense of the OB lineage [34]; iii) a reduction in OB activity, coupled with an increase in OB and osteocyte apoptosis [35].

Overall, ROS-induced OS impairs the coordinated actions of OBs and OCs, disrupting the bone regeneration by promoting bone resorption, reducing OB activity, and shifting progenitor cell differentiation away from the osteoblastic lineage. This imbalance between bone formation and resorption is a key factor in the diminished bone regeneration observed in diabetic conditions, where OS plays a central role in complicating skeletal remodeling and healing.

2.1. Promoting the role of OCs in osteogenesis

In diabetic bone regeneration, the role of OCs in osteogenesis is notably altered due to the hyperglycemia-ROS feedback loop, which disrupts the balance between bone resorption and formation [33]. Under normal physiological conditions, the activity of OCs is balanced with that of OBs, the cells responsible for bone formation. This balance is crucial for proper bone regeneration, as the bone resorption mediated by OCs clears out old or damaged bone matrix, making way for new bone tissue to be formed by OBs, involving bone remodeling [36]. However, in diabetes, OS driven by hyperglycemia significantly alters OC activity and disrupts this delicate balance [4].

In diabetic conditions, elevated levels of ROS enhance OC differentiation and activity, leading to an increase in bone resorption. ROS activate signaling pathways such as the NF-κB and JNK pathways, both of which promote osteoclastogenesis by upregulating the expression of RANKL. Jiang et al. [37] reported that RANKL could be effected by DNA methylation level of the RANKL promoter mediated by DNA methyltransferase 3a (Dnmt3a) through nuclear factor erythroid 2-related factor 2 (Nrf2) (Fig. 1A). RANKL is essential for OC differentiation and activation, and its increased expression in diabetic environments leads

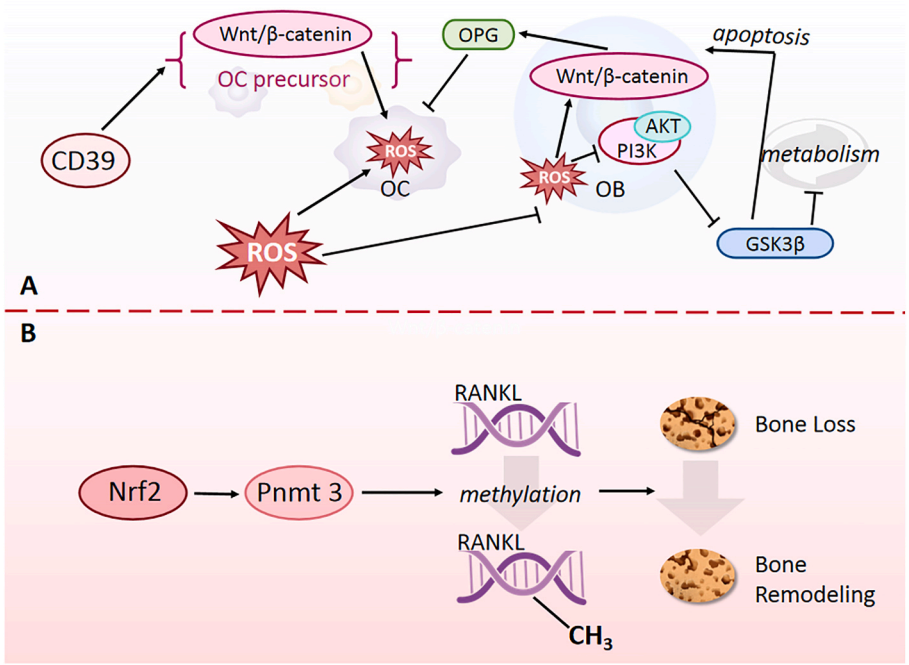

Fig. 1. A) Nrf2 regulates the DNA methylation level of the RANKL promoter through Dnmt3a, thereby influencing RANKL expression [37]. B) An increase in ROS concentration hinders OB differentiation. ROS can affect the Wnt/β-catenin signaling pathway in OBs, inducing them to express OPG, which inhibits OC differentiation. β-catenin activates the transcription of osteogenic markers to promote OB activity. Wnt proteins prevent the degradation of β-catenin, maintaining OC precursor cells [38–40].

to excessive OC activity. This heightened resorptive activity outpaces the compensatory bone formation typically driven by OBs, resulting in net bone loss [41].

Despite their primary role in bone resorption, OCs also play a role in osteogenesis by releasing growth factors embedded in the bone matrix during the resorption process [42]. These factors, such as transforming growth factor-beta (TGF-β) and insulin-like growth factors (IGFs), are essential for the recruitment and activation of OBs and MSCs, which contribute to new bone formation [43,44].However, in diabetes, the excessive and unregulated activity of OCs overwhelms this positive feedback mechanism, leading to an imbalance where bone resorption far exceeds bone formation [45].

In summary, while OCs play an important role in bone remodeling and regeneration under normal conditions, the hyperglycemia-ROS feedback loop in diabetes promotes excessive OC activity, leading to an imbalance in bone remodeling. The enhanced resorption driven by OCs, combined with the impaired bone-forming capacity of OBs, results in net bone loss and diminished bone regeneration. Understanding the altered role of OCs in diabetic bone regeneration provides critical insights into how OS and inflammation contribute to skeletal complications in diabetes and highlights the need for therapeutic strategies aimed at restoring balance between bone resorption and formation.

2.2. Inhibition of OBs in osteogenesis

OBs are the principal cells responsible for synthesizing and mineralizing the bone matrix, playing a crucial role in osteogenesis [6]. However, in diabetic bone regeneration, increased levels of ROS significantly inhibit OB function [46]. Elevated ROS concentrations impede OB differentiation and disrupt the metabolic processes necessary for bone formation by adversely affecting key enzymes (Fig. 1B) [38]. This oxidative environment poses substantial challenges to OBs, as demonstrated by in vitro studies on BMSCs. Prolonged exposure to high ROS levels has been correlated with a diminished capacity for osteogenic differentiation, evidenced by decreased expression of critical osteogenic markers such as Runt-related transcription factor 2 (Runx2), and reduced alkaline phosphatase (ALP) activity, which are essential for bone formation [47].

Conversely, studies have shown that reducing ROS levels in BMSCs enhances osteogenic functionality. By mitigating OS, BMSCs are better able to differentiate into OBs, restore bone mass, and improve bone microarchitecture, as observed in models of ovariectomized (OVX) rats [48]. This suggests that controlling ROS levels can potentially reverse the inhibitory effects on OBs and promote bone regeneration.

Excessive ROS, whether derived from external sources or internal metabolic processes, inflict damage on the lipids, proteins, and other cellular components essential for OB functionality. In the pathological context of diabetes, critically elevated ROS levels not only impair OB differentiation but also lead to OB apoptosis or necrosis. This disruption of OB viability results in diminished bone formation and contributes to the compromised bone regeneration observed in diabetic conditions [48].

The negative consequences of ROS on OB survival and bone formation highlight the critical role of OS in inhibiting osteogenesis in diabetic bone regeneration. These insights underscore the importance of targeting oxidative damage through therapeutic interventions aimed at reducing ROS levels, enhancing OB viability, and restoring the bone-forming capacity of OBs. By mitigating OS, it may be possible to improve osteogenesis and bone regeneration in diabetic patients, addressing one of the key challenges in managing diabetes-related bone disorders.

2.3. ROS-OBs interactions regulate the formation and differentiation of OCs

The interactions between ROS and OBs play a crucial role in regulating the formation and differentiation of OCs in diabetic bone regeneration. The osteoprotegerin (OPG)/RANK/RANKL signaling axis is at the center of this regulatory mechanism, forming a biochemical link between OBs and OCs [49]. OBs produce essential cytokines that promote OC genesis and differentiation, but they also have the ability to inhibit this process under certain conditions. OBs are responsible for

expressing two key cytokines critical for OC differentiation: colony-stimulating factor 1 (Csf1), which is constitutively expressed, and RANKL, which is induced in response to bone resorption stimuli [50–52]. Conversely, OBs also secrete OPG, a decoy receptor that inhibits OC differentiation by preventing the interaction between RANKL and its receptor RANK on OC precursors.

Elevated ROS levels, such as H_2O_2, in OBs and BMSCs have been shown to enhance the production of RANKL mRNA and protein through the activation of signaling pathways such as ERKs and PKA-CREB [53]. This upregulation of RANKL promotes OC development and activity. This ROS-mediated increase in RANKL production and subsequent promotion of OC differentiation illustrates the complex interplay between OS and bone cell function in diabetic conditions, where ROS accelerates bone resorption by enhancing OC formation.

In conclusion, the interaction between ROS and OBs in diabetic bone regeneration significantly regulates OC formation and differentiation through both the OPG/RANK/RANKL axis. Elevated ROS levels in OBs promote RANKL expression and OC differentiation. These complex interactions contribute to the imbalance between bone formation and resorption observed in diabetes, where increased OC activity driven by OS accelerates bone loss. Understanding these mechanisms provides crucial insights into therapeutic strategies aimed at mitigating OS and restoring bone homeostasis in diabetic patients.

2.4. The central role of osteocytes in bone homeostasis and diabetic dysregulation

Osteocytes, terminally differentiated osteoblasts embedded within the mineralized bone matrix, constitute over 90 % of all bone cells and are now recognized as the primary orchestrators of bone remodeling, far beyond their role as inert placeholders [18]. They form an extensive lacunar-canalicular network, functioning as sophisticated mechanosensors and endocrine cells that critically regulate both osteoblast and osteoclast activities. The signaling molecules secreted by osteocytes, most notably sclerostin (a potent inhibitor of the Wnt/β-catenin pathway), RANKL, and OPG, are paramount for maintaining the precise balance between bone formation and resorption [54].

In diabetic conditions, osteocyte function and survival are severely compromised, constituting a central mechanism in the pathogenesis of diabetic bone disease. This dysfunction manifests in two primary, interconnected ways: 1) Aberrant Signaling: Elevated Sclerostin Expression. A hallmark of diabetic osteocyte dysfunction is the significant upregulation of sclerostin. Hyperglycemia-driven ROS overproduction, often synergizing with a pro-inflammatory milieu (e.g., elevated TNFα), is a key upstream mechanism for this pathological increase. Sclerostin acts as a powerful brake on bone formation by binding to LRP5/6 co-receptors and inhibiting the canonical Wnt/β-catenin signaling pathway, which is essential for osteoblast differentiation, function, and survival [55]. Consequently, elevated sclerostin levels directly lead to impaired osteoblastogenesis and reduced bone formation. This mechanism is particularly relevant in T2DM [56,57]. 2) Loss of Regulatory Cells: Osteocyte Apoptosis. The diabetic bone microenvironment, characterized by oxidative stress, AGEs, and potential hypoxia, imposes significant stress on osteocytes, leading to increased apoptosis [58]. The death of these master regulatory cells has a dual detrimental effect: it disrupts the vital signaling network necessary for coordinated bone remodeling, and dying osteocytes may release signals that promote osteoclast recruitment and activation, thereby further tilting the balance towards excessive bone resorption [59,60]. This aspect is crucial in T1DM, where the combined lack of insulin's anabolic action and osteocyte apoptosis leads to more severe bone loss [19].

2.5. ROS reprogramming of BMSC self-renewal and differentiation in diabetes

BMSCs are the foundational osteoprogenitors for cortical and trabecular bone. In diabetes, chronic ROS burden reduces clonogenicity, impairs self-renewal, and skews lineage fate [61]. Mechanistically, hyperglycemia/ROS suppress PI3K–Akt–mTOR and Wnt/β-catenin tone while activating p38-JNK stress arms, tipping the balance away from osteogenesis (Runx2, ALP, COL1A1) toward PPARγ-driven adipogenesis [62–64]. Mitochondrial dysfunction—via mtDNA damage, impaired OXPHOS, and diminished Sirtuin (SIRT1/SIRT3) activity—elevates FOXO3 and p16/p21 signaling, culminating in senescence and SASP release that further inhibits osteogenesis [17,65].

NRF2 shows a biphasic role: moderate activation protects stemness by maintaining glutathione (GSH) and limiting LPO, whereas chronic hyperactivation under persistent ROS may blunt osteogenic transcriptional programs [66,67]. Notch and Hedgehog pathways, both redox-sensitive, are similarly context-dependent: sustained Notch can preserve quiescence at the expense of differentiation, while Hedgehog attenuation under ROS undermines osteogenic commitment [63,68]. Autophagy/mitophagy (PINK1-PRKN) is initially adaptive but becomes insufficient with ongoing glyco-oxidative stress, accelerating BMSC attrition [69]. Functionally, diabetic BMSCs exhibit reduced mineralization, lower ALP, depressed Runx2/Osterix, and elevated PPARγ/C/EBPα, changes that correlate with trabecular rarefaction and delayed defect healing in vivo [70].

2.6. Osteoimmunology of diabetic bone: ROS-dependent immune regulation of bone cells

The diabetic marrow is a redox-inflamed niche. Macrophages polarize toward M1 (NOX2/iNOS-high)states under AGEs/RAGE and TLR–NF–κB signaling, secreting TNF-α, IL-1β, IL-6 and RANKL, which stimulate osteoclastogenesis and inhibit OB differentiation; M2 (NRF2/HO-1-associated) pro-regenerative functions are curtailed [23]. Neutrophils generate excessive ROS and NETs, which expose proteases and citrullinated histones that potentiate osteoclast precursor recruitment and osteoblast apoptosis; NET-DNA also acts as a DAMP to prime NLRP3 inflammasomes in stromal and myeloid cells [24]. Dendritic cells and B cells contribute RANKL and can be skewed by ROS toward pro-resorptive phenotypes, while B-cell OPG production is reduced, lowering the RANKL/OPG brake [71].

Within T-cell compartments, Th17 expansion (IL-17A/F) under oxidative cues enhances RANKL on stromal cells and osteocytes, whereas Tregs—which require a reduced intracellular milieu (high GSH)—are numerically and functionally impaired, diminishing anti-resorptive immune restraint [25]. Cross-talk nodes include NLRP3–Caspase-1–IL-1β, JAK/STAT3, and AGE-RAGE–NOX axes that simultaneously heighten osteoclastogenesis and blunt osteoblastogenesis [72].

2.7. Multi-mechanism inhibition of chondrocytes by ROS in diabetes

Chondrocytes are the sole cellular components of cartilage, sparsely distributed within the extracellular matrix. During bone regeneration, a soft callus consisting of new fibrous tissue and cartilage provides a scaffold for new vessel formation and accumulation of osteoprogenitors for bone formation. Once new bone formation begins, the soft callus transitions into a hard callus composed of spongy bone [73]. Recent studies have shown that in the context of ROS by reducing the regenerative potential and differentiation capacity of periosteal progenitor cells, in the early stages of fracture healing, the number of these cells differentiating into chondrocytes is reduced, significantly affecting chondrogenesis [73,74].

Diabetes increases chondrocyte apoptosis through a mechanism involving enhanced TNF-α production. TNF-α stimulates chondrocyte apoptosis and upregulates the mRNA levels of pro-apoptotic genes via activation of the pro-apoptotic transcription factor FOXO1 [20]. TNF-α also reduces angiogenesis and vascular endothelial growth factor A in endochondral bone formation, leading to diminished callus size, delayed

endochondral ossification, and reduced bone formation [75]. Additionally, ROS-induced reductions in the activity of antioxidant enzymes such as SOD2 and peroxiredoxin 3 cause mitochondrial dysfunction, which affects multiple signaling pathways. These include the activation of the catabolic MAPK pathway, inhibition of the anabolic PI3K/Akt/IGF and Smads/BMP-7 pathways, and increased degradation of the cartilage matrix [21].

3. Osteogenic pathways

3.1. RANKL pathway

The RANKL pathway is instrumental in the orchestration of OC genesis. RANKL, a cytokine of the tumor necrosis factor (TNF) family, is pivotal in mediating the generation and activation of mature OCs. The receptor activator of NF-κB on OCs and their precursors interacts with RANKL, expressed by OBs, osteocytes, stromal cells, and T cells, to initiate a series of signaling cascades [10]. This intricate signaling network, which encompasses MAPKs, nuclear factor of activated T-cells cytoplasmic 1 (NFATc1), and Ca2+ release regulators, not only promotes the differentiation and formation of OCs but also curtails their metabolic apoptosis.

Among these pathways, NFATc1 stands out as a quintessential regulator, often described as the master regulator of OC genesis. The RANKL-RANK interaction facilitates the transcription of genes essential for OC differentiation and function, including tartrate-resistant acid phosphatase (TRAP), calcitonin receptor (CTR), cathepsin K, and fusion genes, via the activation of NFATc1 [76]. Moreover, NFATc1 possesses the unique ability to auto-amplify its expression, a mechanism critical for enhancing gene transcription necessary for the fusion and maturation of OC precursors [77].

The experiment by Huang et al. [78]demonstrated that RANKL promotes osteoclast differentiation through the TAK1/MKK6 signaling pathway, leading to p65 phosphorylation and NFATc1 induction (Fig. 2). Furthermore, research by Zhong et al. [79] highlighted a critical downstream mechanism: NFATc1 mediates the upregulation of solute carrier family 7 member 11 (SLC7A11) during osteoclastogenesis. This NFATc1-driven transcriptional activation of SLC7A11 has a significant metabolic consequence. It sensitizes osteoclasts to thioredoxin reductase 1 (TXNRD1) inhibitors by promoting intracellular cystine accumulation. This accumulation induces disulfiram-like effects, leading to selective osteoclast death. Consequently, NFATc1 knockdown in pre-osteoclasts attenuates TXNRD1 inhibitor-induced cystine accumulation and reduces drug sensitivity, thereby enhancing osteoclast viability (Fig. 2).

In conclusion, the RANKL pathway is central to the formation and activation of OCs in bone regeneration, particularly under conditions of OS seen in diabetes. Through the activation of key signaling molecules like NFATc1 and the involvement of ROS as secondary messengers, the RANKL-RANK interaction drives OC differentiation and function. While this pathway is necessary for normal bone remodeling, its overactivation in diabetes due to elevated ROS levels leads to excessive bone resorption, contributing to impaired bone regeneration. Understanding the RANKL pathway's role in OC-mediated osteogenesis offers potential therapeutic targets to restore balance in bone remodeling and counteract the effects of diabetes on bone health.

3.2. NF-κB pathway

NF-κB represents a pioneering discovery in eukaryotic biology as the first transcription factor identified to be responsive to ROS and RNS [86]. The engagement of RANKL with its receptor RANK orchestrates a signaling cascade wherein the cytoplasmic domain of RANK is uniquely

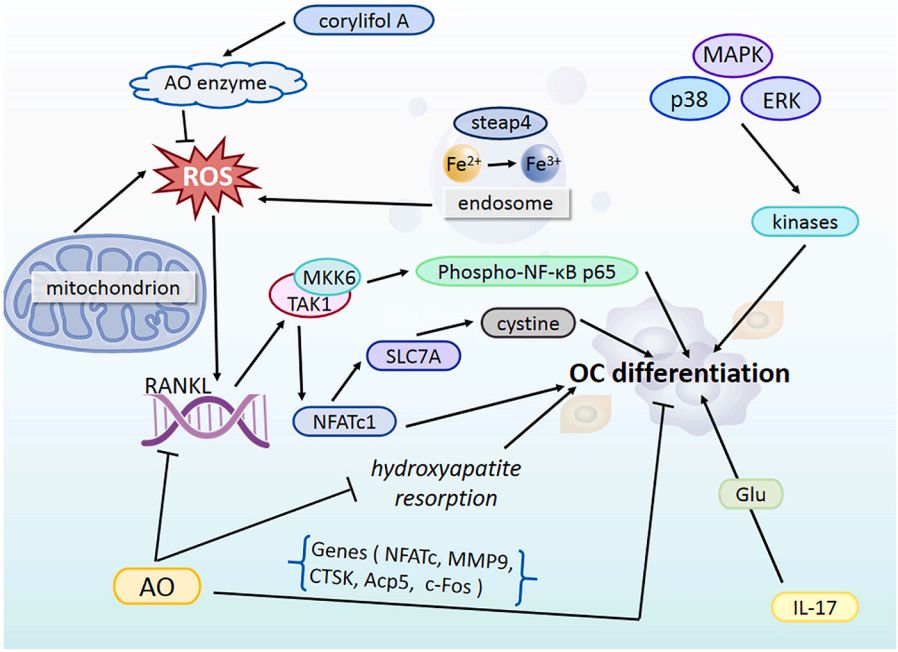

Fig. 2. RANKL promotes OC differentiation through the TAK1/MKK6 signaling pathway, leading to p65 phosphorylation and induction of NFATc1 expression. During osteoclastogenesis, NFATc1 mediates the upregulation of SLC7A11, which enhances intracellular cystine accumulation and increases OC sensitivity to TXNRD1 inhibitors, resulting in selective OC death [78,79].AOs can inhibit RANKL-induced OC differentiation, hydroxyapatite resorption activity, and the expression of key genes associated with osteoclastogenesis [80]. The p38 MAPK pathway coordinates bone resorption and remodeling by activating downstream target kinases [81]. The ERK pathway involves a ROS-mediated receptor activation mechanism, and the addition of IL-17 significantly promotes the differentiation of OC precursor cells [82]. CA prevents bone loss and inhibits osteoclastogenesis by suppressing intracellular ROS levels, while also reducing MAPK/ERK pathway activity and weakening osteoclast function [83]. Mitochondrial ROS generation is indispensable during OC formation; thus, targeting and eliminating mitochondrial ROS can suppress OC development [84]. Cellular iron homeostasis regulation and Nrf2 activity modulation control osteoclast differentiation and function, primarily involving six-transmembrane epithelial antigen of the prostate 4 (Steap4), an endosomal enzyme that reduces Fe^{3+} to Fe^{2+} [85].

linked with TNF receptor-associated factor 6 (TRAF6) [80]. This interaction prompts the activation of IKKs, including IKKα and IKKβ, which phosphorylate serine residues on the NF-κB inhibitor, IκB, facilitating the activation and nuclear translocation of NF-κB [87]. Within the nucleus, NF-κB subunits p50 and p65 upregulate the expression of critical osteoclastogenic factors such as c-fos and NFATc1 [88]. The synergistic interaction between c-fos and NFATc1 stimulates the transcription and expression of genes imperative for OC differentiation. Investigations by Kim et al. [89] demonstrated that the application of AO mitigates RANKL-induced OC formation by curtailing ROS production and subsequent NF-κB activation in OC precursors. Xiao et al. [80] further elucidated that AOs suppress RANKL-induced OC differentiation, hydroxyapatite uptake activity, and the expression of genes integral to OC genesis (e.g., NFATc1, MMP9, CTSK, Acp5, and c-Fos) in OC precursors derived from bone marrow macrophages (BMMs) and RAW264.7 cells, as well as in in vitro OVX mouse models (Fig. 2). This suppression was attributed to the inhibition of the TRAF6/ROS-dependent MAPK/NF-κB signaling pathway. Moreover, mechanistic insights have revealed that C-phycocyanin effectively impedes NF-κB activation by preventing the IκB-α on the cell membrane from degrading, thereby downregulating downstream effectors such as NFATc1 and attenuating RANKL-induced OC production and bone resorption in vitro [90]. These findings collectively underscore how significant ROS is for modulating OC differentiation via controlling NF-κB, offering novel insights into the molecular processes that underlie osteoclastogenesis and provide possible targets for treatment to reduce bone resorption in theory. The suppression of the TRAF6/ROS-dependent MAPK/NF-κB signaling pathway, as observed in various studies, further highlights the central role of ROS in modulating OC differentiation via NF-κB signaling.

In summary, the NF-κB pathway is essential for promoting OC genesis, particularly in the context of ROS-induced signaling in diabetic bone regeneration. The activation of NF-κB via the RANKL-RANK interaction and subsequent TRAF6 signaling facilitates the transcription of key osteoclastogenic factors necessary for OC differentiation and bone resorption. However, the ability of AOs and specific inhibitors to reduce ROS production and impede NF-κB activation suggests potential therapeutic targets for mitigating excessive bone resorption in diabetic conditions. Understanding the molecular mechanisms underlying NF-κB's role in osteoclastogenesis offers novel insights into the treatment of bone resorption disorders associated with diabetes.

3.3. MAPKs pathway

The MAPKs pathway, comprising a constellation of protein kinases localized within the cytoplasm, plays a pivotal role in transducing extracellular cues to elicit intracellular responses [91]. Activation of this pathway can modulate key osteogenic markers through the suppression of ALP and osteocalcin expression, thereby impeding osteogenic differentiation. The canonical MAPK pathways encompass the JNK, extracellular signal-regulated kinase (ERK1/2), and p38 pathways, each uniquely contributing to cellular dynamics [92]. In particular, the p38 MAPK pathway is closely associated with the stress response, while ERK1/2 is typically involved in cell proliferation and differentiation. JNK, on the other hand, is often activated in response to stress stimuli such as OS, which is prevalent in diabetic environments.

In diabetic bone regeneration, the dysregulation of the MAPK pathway due to increased ROS levels results in impaired OB function and inhibited osteogenic differentiation. ROS activate MAPK signaling, leading to the suppression of OB-related gene expression, such as that of ALP and osteocalcin, and thus hinder the bone formation process [93]. This modulation of MAPK signaling by OS further contributes to the imbalance between bone resorption and formation in diabetes, exacerbating the challenges of bone regeneration in diabetic conditions.

Understanding the role of the MAPK pathway in osteogenesis within the diabetic context offers valuable insights into potential therapeutic strategies aimed at modulating MAPK signaling to restore bone homeostasis and improve bone healing in diabetic patients.

3.3.1. JNK/p38 pathways

The JNK and p38 MAPK pathways are instrumental in positively regulating OC differentiation and functionality. Specifically, the JNK pathway is crucial for sustaining OC lineage commitment [94]. Under the action of RANKL, RANK activates the downstream cascade reaction through TRAF6 signaling, which ultimately leads to the formation of OCs, and JNK is a downstream molecule of TRAF6, which is phosphorylated by RANKL during the process of OCs, and JNK may regulate the osteoclastogenic effect through this pathway [95]. Meanwhile, the p38 MAPK pathway significantly influences OC formation and maturation, by activating secondary kinases that target downstream genes, thus orchestrating bone resorption and remodeling processes (Fig. 2) [81]. It is generally recognized that ROS have been documented to activate MAPK pathways, including ERKs, JNKs, and p38 MAPKs. The oxidative modification of MAPK signaling proteins, alongside the inactivation and/or degradation of MAPK phosphatases (MKPs), likely underpins the ROS-mediated activation of these pathways [92]. Typically, however, JNK and p38 MAPK pathways respond to stress stimuli, while ERK pathways are activated by growth and survival factors. Given their proclivity to induce OS within cells, ROS preferentially activate JNK and p38 MAPK pathways over the ERK pathway. On the one hand, ROS can regulate the JNK and p38 MAPK pathways by mediating apoptosis signal-regulating kinase 1 (ASK1) activity, while at the same time, activation of the JNK pathway and the p38 pathway is associated with the promotion of ROS production. The use of JNK-specific inhibitor, SP600125, to disrupt JNK signaling, diminishes the RANKL-induced anti-apoptotic influence on OCs, indicating JNK's role in mediating RANKL's anti-apoptotic effects in mature OCs [96]. Further research by Wang et al. [97] revealed that mitochondrial calcium channels (MCU) and their inhibitors could thwart p38 MAPK pathway, which would prevent RANKL-induced ROS generation and NFATc1 activation, subsequently mitigating OC generation. And within the MAPK family, ASK1 has been recognized as an ROS-responsive kinase. Activated by ROS through the oxidation of specific binding proteins, ASK1 is essential for the activation of the p38 and JNK pathways, dissociating from these binding proteins. Xu et al. [98] found that Regulates the MAPK p38 signaling pathway by blocking ASK1 phosphorylation, thereby preventing ROS-associated apoptosis.

In conclusion, the JNK and p38 MAPK pathways are vital in promoting OC differentiation and function in diabetic bone regeneration. ROS play a significant role in activating these pathways, which in turn drive the formation, survival, and activity of OCs. By modulating the effects of ROS on these signaling pathways, there is potential to control OC activity and mitigate the excessive bone resorption seen in diabetic conditions, offering therapeutic insights into improving bone health in diabetes.

3.3.2. ERK pathway

The role of ERK1/2 in OC formation and function, while generally positive in promoting OC proliferation and differentiation, has yielded inconsistent finding [99]. This discrepancy may stem from the observation that ERK inhibition does not universally suppress all components of OC differentiation; rather, it may enhance the expression of certain molecules involved in this process [100]. Notwithstanding, evidence suggests that ROS can also activate the ERK pathway in animal cells. Certain AOs, by inhibiting ROS production, concurrently inhibit ERK, suggesting a ROS-mediated activation mechanism for the ERK pathway via receptor engagement. It was found that intervention with the addition of IL-17 to BMM containing M-CSF and RANKL medium considerably improved the differentiation of OC precursor cells (Fig. 2) [82]. Xu et al. [83] found that Corylifol A (CA) prevented bone loss and suppressed osteoclastogenesis by inhibiting intracellular ROS levels, while it attenuated the MAPK/ERK pathway, but having no effect on the NF-κB signaling pathway, suggesting that inhibition of the ERK pathway also

attenuates OC activity(Fig. 2). This intricate interplay between ROS and the MAPK pathways underscores the nuanced regulatory mechanisms influencing OC differentiation and the broader implications for bone remodeling and disease.

ROS can act as upstream activators of the ERK pathway, which in turn promotes OC proliferation and differentiation. However, under certain conditions, such as AO treatment or the inhibition of ERK signaling, OC activity can be reduced, leading to decreased bone resorption [101]. This interplay between ROS and the ERK pathway is particularly relevant in the context of diabetic bone regeneration, where elevated ROS levels contribute to dysregulated bone remodeling and increased OC activity.

In conclusion, the ERK signaling pathway, while generally promoting OC formation and activity, is tightly regulated by ROS. ROS-mediated activation of ERK supports OC differentiation, but inhibiting ERK signaling can reduce OC function and mitigate bone resorption. Understanding the complex interactions between ROS, ERK, and other signaling pathways offers insights into potential therapeutic strategies for regulating OC activity and improving bone health in diabetic patients.

3.3.3. Calcium pathway

Calcium (Ca^{2+}), a versatile intracellular messenger, is critical to cellular signaling, and ROS control over it is crucial for the differentiation of OC precursors [102]. OS induces an elevation in cytosolic Ca^{2+} levels, detrimentally impacting mitochondrial membrane potential and ATP synthesis, thereby influencing OC functionality. Investigations by Kim et al. [103] elucidated that RANKL-induced Rac1 activation promotes ROS generation, which in turn stimulates phospholipase Cγ1, inducing Ca^{2+} oscillations through an increase in intracellular Ca^{2+} concentration. These sustained Ca^{2+} oscillations facilitate the Ca^{2+}/calcineurin-dependent dephosphorylation and activation of NFATc1. Intriguingly, the temporal dynamics of ROS and Ca^{2+} levels during OC precursor differentiation exhibit remarkable parallels, both peaking around the second day of differentiation concurrently with a surge in NFATc1 levels. This temporal coincidence underscores how crucial ROS are for sustaining Ca^{2+} signaling and for initiating NFATc1 amplification during OC genesis. Further research by Sun et al. [104] demonstrated that the application of AO Pteryxin (PTX) to BMMs could attenuate MAPK and Ca^{2+}-calcineurin-NFATc1 signaling pathways through diminishing ROS concentrations, thereby suppressing NFATc1 transcription and downstream OC-specific gene expression. Additionally, RNS have been shown to modulate OC differentiation and activity via Ca^{2+}-mediated alterations in cell shape and motility, with low levels of NO enhancing OC differentiation and function through actin remodeling [105,106]. Moreover, fluctuations in cytoplasmic Ca^{2+} concentrations are mirrored by changes in mitochondrial Ca^{2+} levels, which in turn affect ROS production [107]. Given the endoplasmic reticulum (ER) near proximity to mitochondria, localized spikes in cytosolic Ca^{2+} may influence mitochondrial functions, such as escalating mitochondrial ROS production and modulating OXPHOS [108]. Mitochondrial ROS generation is indispensable during OC formation; thus, the targeted scavenging of mitochondrial ROS curtails OC development (Fig. 2) [84]. Mitochondrial integrity is crucial under OS conditions, with ROS-mediated mitochondrial DNA (mtDNA) damage and lipid peroxidation (LPO) precipitating mitochondrial dysfunction. This dysfunction manifests as excessive ROS production due to inefficient electron transport and substantial alterations in mitochondrial morphology, potentially culminating in cellular demise [109]. A previous study highlighted that mitochondrial catalase(CAT) expression mitigates OC number and activity [110]. The exact mechanisms underpinning Ca^{2+} oscillations during OC formation remain elusive, which looks like a vicious cycle of ROS and Ca^{2+} crosstalk, whereby ROS can influence the location of Ca^{2+} signaling pathways, and increased Ca^{2+} levels lead to mitochondrial dysfunction, and thus OS. However, some researchers have identified the transmembrane protein 64 (Tmem64) as a significant contributor to RANKL-induced Ca^{2+} oscillations. The absence of Tmem64 markedly diminishes Ca^{2+}/IV activity and ROS generation from mitochondria, positing Tmem64 as a facilitator of Ca^{2+}-dependent signaling in OC differentiation [111].

3.4. Other pathways

Recent studies investigating the regulation of OC differentiation by ROS have uncovered the crucial roles played by cellular iron homeostasis and the modulation of Nrf2 activity in diabetic bone regeneration [112]. These pathways are integral to the complex processes governing OC differentiation and function, especially in environments characterized by OS, such as diabetes (Fig. 3).

One key pathway involves the six-transmembrane epithelial antigen of the prostate 4 (Steap4), an endosomal enzyme that reduces ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+})(Fig. 2) [85]. Specifically, it is showed that the only member of the Steap family protein that is upregulated during OC differentiation is Steap4. Conversely, the ablation of Steap4 impairs OC differentiation, concurrently diminishing ROS levels throughout cells and in mitochondria and lowering the amount of iron within OC precursors, ultimately leading to OC damage [113]. Reduced ROS generation in Steap4-deficient cells has been suggested to be caused by suppression of the CREB-PGC-1β-mitochondrial biogenesis pathway [114,115]. Zhou et al. [113] found that Lentiviruses-mediated short hairpin RNAs that stifle Steap4 expression in vitro prevent the production of OC and reduce cellular Fe^{2+} iron, ROS, and the activation of cAMP response elementbinding protein. These results demonstrate that Steap4 is an essential enzyme for the cellular uptake and utilization of iron in OCs, making it necessary for the growth and operation of OCs.

Another important pathway influencing OC differentiation is regulated by Nrf2. Nrf2, a key regulator of the cellular AO response, is identified as a negative regulator of OC differentiation. Nrf2 can activate the transcription of AO, increase the level of AO, and degrade ROS, and the inhibition of Nrf2 during OC growth can maintain the level of ROS required for OC differentiation [112]. At the same time, it has been found that excessive aggregation of Nrf2 may also increase ROS production through the activation of other regulatory factors. The effect of Nrf2 on OC differentiation may be twofold. Li et al. [116] suggested phosphorylation of Nrf2 and the nuclear translocation of Nrf2 will activate certain AO, which resist OS and reduce the differentiation of OCs. Furthermore, the differentiation of OCs under the influence of RANKL and M-CSF significantly lowers the mRNA and protein levels of Nrf2 and its downstream AO targets [117]. In an environment characterized by excessive ROS, Nrf2 is sequentially activated, accumulating in the nucleus where it engages the promoter region of Kruppel-like factor 9 (Klf9), an emergent intracellular ROS regulator [118]. This interaction enhances Klf9 transcription, potentially exacerbating ROS accumulation. The precise mechanistic underpinnings of Nrf2's involvement in OC differentiation and ROS regulation warrant further experimental scrutiny to delineate its role within this complex signaling landscape.

The Wnt/β-catenin signaling pathway plays a dual role in regulating both OB and OC activities. Wnt proteins, a family of secreted glycoproteins, stabilize β-catenin, which is crucial for OB differentiation and osteogenic potential. β-catenin accumulates in the cytoplasm and translocates to the nucleus, where it stimulates the transcription of osteogenic markers, promoting OB activity. However, Wnt signaling also plays a significant role in OC development. Wnt proteins prevent the degradation of β-catenin, which is essential for maintaining OC precursor functionality. Therefore, β-catenin signaling within OC precursors is vital for the formation of fully functinal OCs (Fig. 1B) [12,39].

ROS influences Wnt/β-catenin signaling in OBs, contributing to the regulation of OC differentiation. Specifically, under OS, Wnt16 has been shown to induce OPG expression in OBs, which inhibits OC differentiation (Fig. 1B) [40]. This suggests that the Wnt/β-catenin pathway within OBs is differentially expressed in comparison to bone marrow-derived macrophages or OCs, highlighting its complex role in

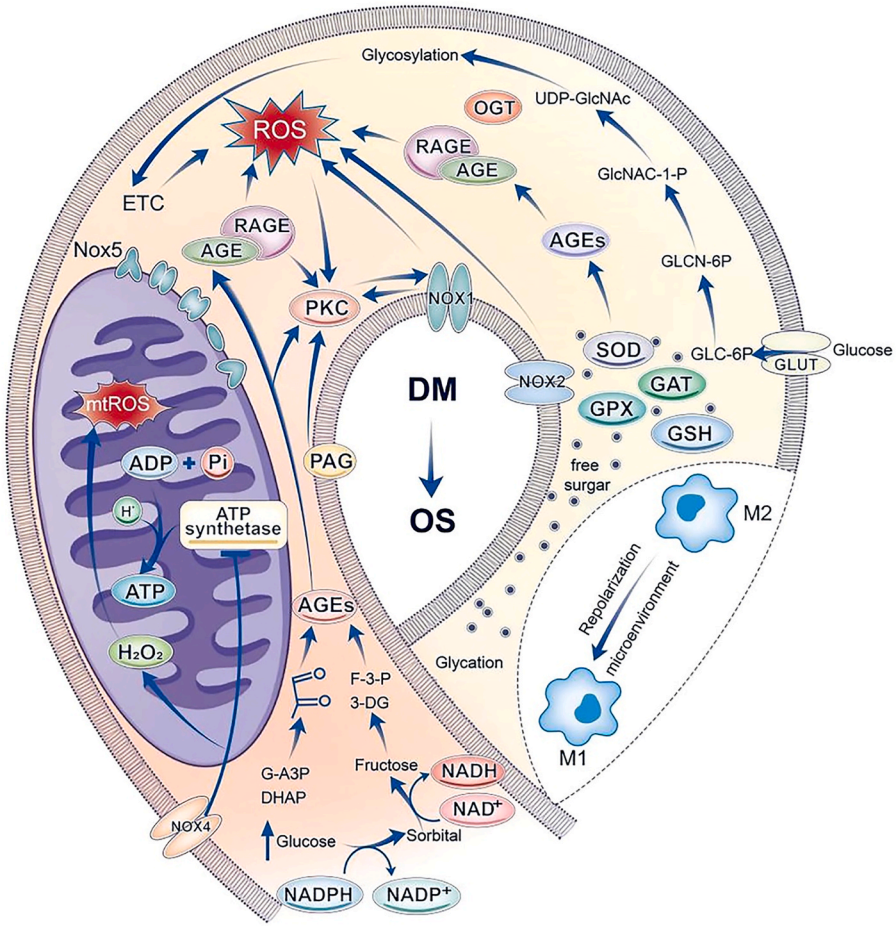

Fig. 3. Hyperglycemia-ROS feedback loop (Möbius loop, DM to OS). The diabetic microenvironment leads to uncontrolled oxidative stress, including accumulation of ROS (mediated by the mitochondrial pathway, the polyol pathway, the PKC pathway, the AGEs pathway, and the Noxs) and inhibition of AO enzyme (SOD, CAT, GPx, and GSH) activities.

balancing bone formation and resorption. Histomorphological studies in β-catenin mutant mice have shown that disruptions in β-catenin signaling impair OC differentiation, while OBs remain unaffected [119]. This further emphasizes the importance of β-catenin signaling in OC formation and functionality.

Research by You et al. [120]involving transgenic mice with deactivated Wnt signaling pathways within the OB lineage has demonstrated that Wnt signaling is critical for maintaining bone mass and regulating OC activity. In these models, the absence of Wnt signaling leads to reduced bone formation and increased bone resorption. Conversely, activating the Wnt pathway enhances bone mass and reduces resorption through the Ca2+-PKA-GFAT1 axis. Normal secretion of Wnt is essential for maintaining bone homeostasis in the human body, and Wnts in osteoblasts play a key role in enabling bone to function properly under normal load during bone anabolism [121]. Hyperglycemia-induced ROS and AGEs can inhibit the Wnt/β-catenin signaling pathway by suppressing the expression of Wnt ligands (such as Wnt1, Wnt3a, and Wnt10b) and receptors (such as LRP5/6), while increasing the expression of antagonists. This ultimately inhibits bone formation and promotes bone resorption [122].

In conclusion, both the Steap4 and Nrf2 pathways are critical in regulating OC differentiation through their impact on iron homeostasis and ROS management, and the interaction between ROS and OBs in diabetic bone regeneration significantly regulates OC formation and differentiation through the Wnt/β-catenin signaling pathway. Steap4 facilitates iron utilization and ROS production, both necessary for OC function, while Nrf2 modulates AO defenses that influence ROS levels and OC development. Wnt/β-catenin pathway plays a dual role in supporting OB activity and regulating OC formation. Understanding these pathways more fully could lead to the development of targeted therapeutic strategies to manage bone resorption disorders, particularly in the context of diabetes, where dysregulated ROS plays a central role in impaired bone regeneration.

4. Factors to inhibit osteogenesis

4.1. Apoptosis in diabetic bone regeneration

Apoptosis, commonly regarded as a mechanism of "immune silence," plays a crucial role in maintaining cellular homeostasis and defense mechanisms. This process is fundamental to balancing cell survival and death, especially in OBs, which are key players in bone formation [123]. Apoptosis can occur through two primary pathways: the intrinsic (mitochondrial) pathway and the extrinsic (death receptor-mediated) pathway. Both pathways are susceptible to modulation by ROS within OBs, particularly in the context of diabetic bone regeneration (Fig. 4) [124,129,130]. Understanding the role of ROS in modulating apoptotic pathways within OBs offers insights into potential therapeutic strategies aimed at reducing apoptosis, enhancing OB survival, and improving bone regeneration in diabetic conditions (Fig. 5).

4.1.1. Internal pathway

Endoplasmic reticulum (ER) stress and mitochondrial dysfunction are intimately linked to the intrinsic pathway of apoptosis, which plays a

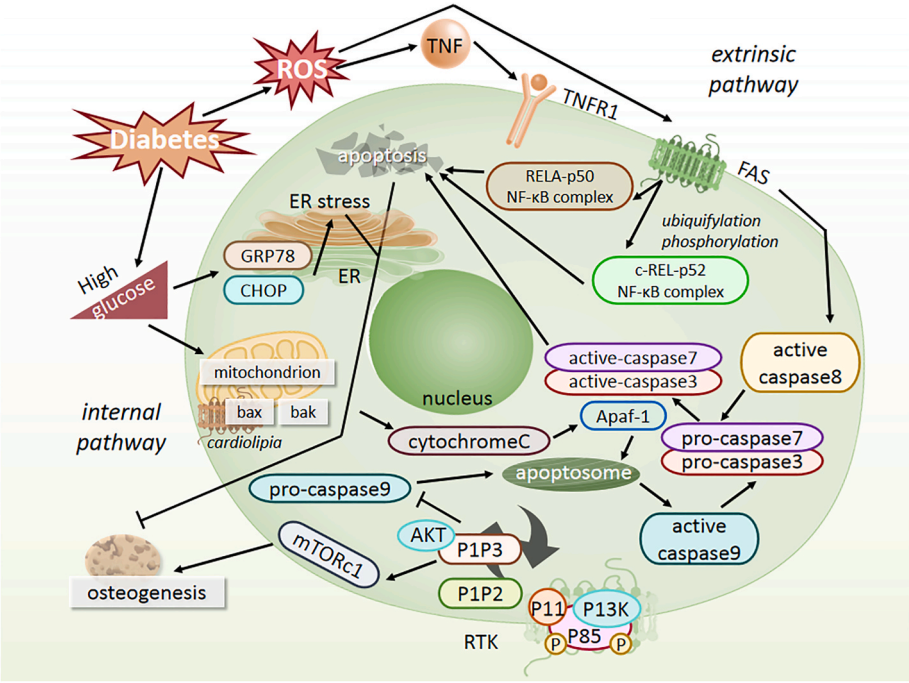

Fig. 4. Apoptosis primarily occurs through two pathways: the intrinsic (mitochondrial) pathway and the extrinsic (death receptor-mediated) pathway. In the context of diabetic bone regeneration, both pathways in OBs are modulated by ROS [124]. Endoplasmic reticulum stress and mitochondrial dysfunction in the intrinsic apoptotic pathway contribute to the inhibition of osteogenesis [125]. The oxidation of cardiolipin activates Bax/Bak channels on the OMM, increasing membrane permeability and promoting the release of cytochrome *c* and AIF [126]. The extrinsic pathway is mediated by transmembrane death receptors, including Fas, TRAILR1/2, and TNFR1, whose activation initiates a cascade of signaling events that lead to programmed cell death [127]. The PI3K/Akt pathway is also involved in regulating cells, influencing processes such as cell migration, proliferation, differentiation, and apoptosis [128].

critical role in inhibiting osteogenesis in diabetic bone regeneration (Fig. 4) [125]. ROS are key instigators in this process, as they activate signaling molecules such as p53 and c-Jun N-terminal kinase (c-JNK) [131]. This activation promotes the induction of pro-apoptotic proteins from the B-cell lymphoma-2 (Bcl-2) family, such as Bak and Bax, which are located on the outer mitochondrial membrane (OMM) [132]. These pro-apoptotic proteins act antagonistically to their anti-apoptotic counterparts, including Bcl-xL and Bcl-2, triggering a cascade of apoptotic signals.

ROS accumulation exacerbates this process by oxidizing cardiolipin, a key lipid on the inner mitochondrial membrane (IMM), which leads to mitochondrial depolarization [108]. The oxidation of cardiolipin activates Bax/Bak channels on the OMM, increasing its permeability and facilitating the release of pro-apoptotic proteins, including cytochrome *c* and apoptosis-inducing factor (AIF) (Fig. 4) [126]. The release of these proteins from the mitochondria initiates the apoptotic process, ultimately leading to cell death. In OBs, this sequence of events impairs cellular survival, limiting their ability to synthesize and mineralize the bone matrix, thereby inhibiting osteogenesis [43].

In addition to mitochondrial dysfunction, ER stress is another critical contributor to the intrinsic apoptotic pathway. Increased ROS levels can trigger the activation of ER stress-related signaling pathways, which further promote apoptosis [133]. Specifically, ROS-mediated ER stress upregulates the production of ER stress-related proteins and induces the formation of the IRE1α-TRAF2-ASK1 complex. This complex stimulates the IRE1α and c-JNK signaling pathways, both of which are closely associated with apoptosis induction [134].

The convergence of ROS-induced mitochondrial and ER stress signals results in the activation of intrinsic apoptotic pathways, significantly inhibiting OB function and contributing to the impaired bone regeneration observed in diabetic conditions. Understanding these mechanisms provides insights into potential therapeutic approaches aimed at mitigating ROS-mediated apoptosis, preserving OB viability, and enhancing bone regeneration in diabetic patients.

4.1.2. *Extrinsic pathway*

ROS also play a significant role in the activation of the extrinsic apoptosis pathway, which contributes to the inhibition of osteogenesis in diabetic bone regeneration [130]. This pathway is mediated by transmembrane death receptors, including Fas, TNF-related apoptosis-inducing ligand receptor 1/2 (TRAILR1/2), and TNF receptor 1 (TNFR1). When these death receptors are activated, they initiate a cascade of signaling events that lead to programmed cell death (Fig. 4) [127]. Additionally, certain signaling pathways, such as the PI3K/Akt pathway, are involved in regulating cell fate, influencing processes like cell migration, proliferation, differentiation, and apoptosis (Fig. 4) [128].

In the extrinsic pathway, the PI3K/Akt signaling axis plays a crucial role. Upon binding to its receptor, PI3K can alter the structure of the Akt protein, activating and phosphorylating it, which in turn modulates various downstream substrates [128]. These downstream effects can either promote or inhibit the activity of proteins involved in cellular survival or apoptosis, thus controlling OB phenotypes. For instance, the activation of Akt can stimulate IKK and engage in crosstalk with the NF-κB pathway, further regulating OB survival and apoptosis [135].

Research by Deng et al. [136]demonstrated that treatment with dexamethasone (Dex) significantly increased intracellular ROS levels, downregulated phosphorylated PI3K (p-PI3K) and Akt (*p*-Akt) expressions, and suppressed the activation of the PI3K/Akt pathway in OBs. This suppression led to an increase in the expression of glycogen synthase kinase 3β (GSK3β), a pro-apoptotic protein, ultimately resulting in apoptosis in both OBs and MC3T3-E1 cells.

While ROS are involved in both intrinsic and extrinsic apoptosis pathways, their efficiency in activating the extrinsic pathway appears to be lower compared to the intrinsic pathway [137]. Nonetheless, ROS-induced modulation of death receptor signaling and PI3K/Akt pathway inhibition still plays a significant role in OB apoptosis and the inhibition of osteogenesis in diabetic bone environments.

In summary, the involvement of ROS in the extrinsic apoptosis

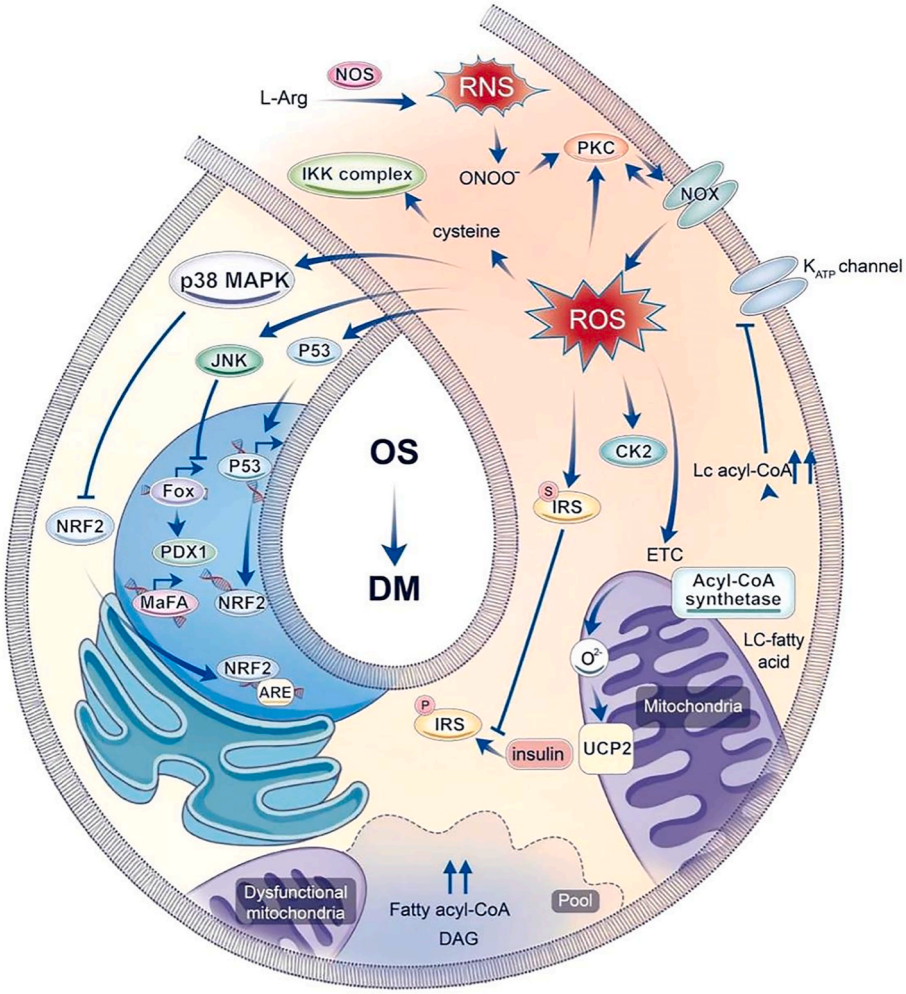

Fig. 5. Hyperglycemia-ROS feedback loop (Möbius loop, OS to DM). Oxidative stress also exacerbates the loss of control of the diabetic microenvironment, including decreasing insulin secretion, triggering insulin resistance, and decreasing insulin gene expression.

pathway highlights the complex mechanisms by which ROS influence cell fate decisions in OBs. By modulating key signaling pathways such as PI3K/Akt, ROS contribute to an intricate balance between cellular survival and death, ultimately affecting bone remodeling and homeostasis in diabetic conditions [130]. Understanding the dual roles of ROS in these pathways provides valuable insights into potential therapeutic approaches for mitigating apoptosis and enhancing osteogenesis in diabetic patients.

4.2. *Ferroptosis*

Ferroptosis represents a distinct form of cell death characterized by its dependence on iron and specific regulatory mechanisms (Fig. 6) [138]. This process is closely linked to metabolic disturbances at the molecular level, including GSH depletion, reduced activity of glutathione peroxidase 4 (GPX4), and the generation of ROS through iron (Fe^{2+})-catalyzed reactions, particularly the Fenton reaction [143]. These biochemical events lead to an accumulation of ROS and the initiation of LPO, which is a critical driver of ferroptotic cell death [144].

Ferroptosis is triggered by the buildup of ROS, which is fueled by the Fenton reaction—a process that converts endogenous H_2O_2 into hydroxyl radicals (-OH), one of the most destructive forms of ROS, via an iron-catalyzed mechanism [143]. This excessive ROS generation, in turn, damages cellular membranes and lipids, leading to OS and cell death. In the context of osteogenesis and diabetic bone regeneration, ferroptosis poses a significant barrier, as it disrupts OB function and survival, thereby inhibiting bone formation.

Contemporary research has shed light on the pivotal role of LPO in ferroptosis, emphasizing the interplay between iron metabolism and OS [145]. The intricate balance between iron homeostasis and ROS production plays a crucial role in determining cell fate, particularly in environments where oxidative damage is heightened, such as diabetic bone regeneration. The depletion of GSH and the inhibition of GPX4, which normally protect cells from oxidative damage by neutralizing lipid peroxides, further exacerbate cells' vulnerability to ferroptosis [146].

Understanding the molecular mechanisms underlying ferroptosis not only enhances our knowledge of this unique form of cell death but also highlights the potential for therapeutic interventions targeting iron metabolism and OS. By modulating these pathways, it may be possible to mitigate ferroptosis and promote osteogenesis in conditions like diabetic bone regeneration, where dysregulated iron homeostasis and oxidative damage play central roles in impaired bone healing.

4.3. *Necroptosis*

Necroptosis is a regulated form of necrosis initiated by TNF signaling, particularly through the TNFR1 complex I, which triggers the necroptotic signaling cascade (Fig. 6) [139]. This cascade culminates in the formation of necrosomes, specifically complex IIB. A key component of this process is the mixed lineage kinase domain-like protein (MLKL),

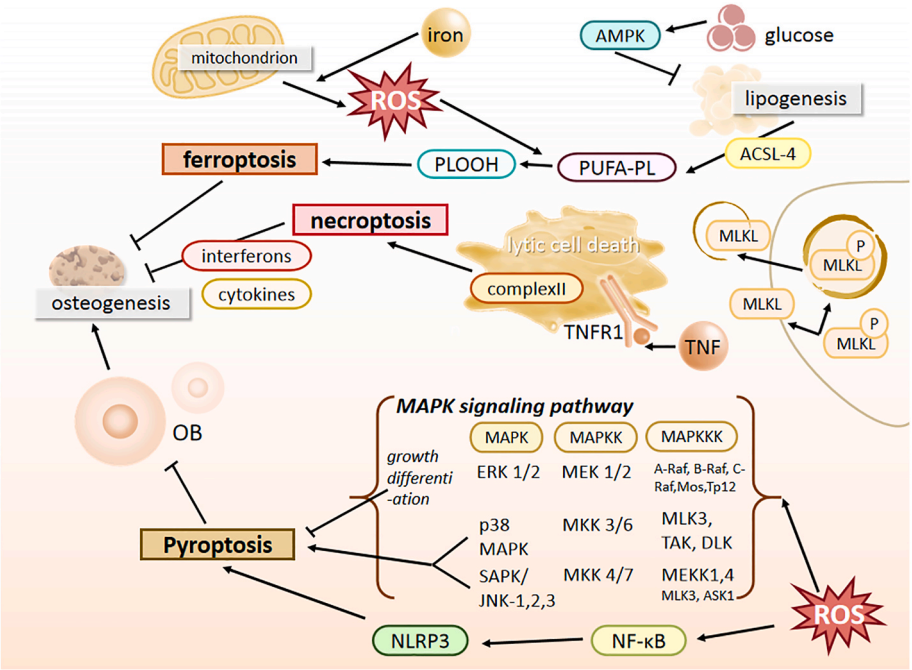

Fig. 6. Ferroptosis is a unique form of cell death dependent on iron and specific regulatory mechanisms [138]. Within the TNFR1 inflammatory signaling pathway, TNF signaling initiates and triggers the formation of necrosomes, such as complex IIB, through TNFR1 complex I [139,140]. In the context of JNK activation and ROS-regulated autophagy, these pathways not only regulate apoptosis in OCs but are also activated under elevated ROS levels, leading to the transcription of pro-apoptotic genes including caspase 3, FASL, and caspase 9 [141]. Central to this mechanism is the NLRP3 inflammasome, which plays a critical role in various inflammation-associated disorders and can be activated by ROS, thereby promoting pyroptotic cell death in OBs and further inhibiting the osteogenic process [142].

which, unlike apoptosis, is activated independently of caspase enzymes (Fig. 6) [140]. MLKL works in conjunction with receptor-interacting protein kinase 3 (RIPK3) to drive cellular death through phosphorylation and subsequent oligomerization [147]. These pore-like oligomers form on the cell membrane, disrupting ionic gradients by allowing the influx of sodium and calcium ions and the efflux of potassium, eventually leading to membrane rupture and cell death.

Mitochondrial reactive oxygen species (mtROS) play a significant role in the autophosphorylation of RIPK1, a critical component downstream of the TNFR1 signaling complex that regulates both apoptotic and necroptotic pathways [148]. The overexpression of RIPK1 leads to caspase activation and cell death, which in turn triggers necroptosis. Necroptosis also involves mitochondrial fragmentation, a process similar to the action of dynamically associated protein 1 (Drp1), which disrupts mitochondrial function and promotes cell death.

Understanding the intricate role of necroptosis in diabetic bone regeneration provides insights into potential therapeutic interventions aimed at inhibiting necroptosis and mitigating ROS-mediated damage, thereby improving osteogenesis in diabetic patients.

4.4. Pyroptosis

Central to the canonical pathway of pyroptosis is the nucleotide-binding domain and leucine-rich repeat protein-3 (NLRP3) inflammasome, a key stress sensor and inflammatory mediator within the NLR family [149]. NLRP3 is critical in various inflammation-associated disorders and is activated by ROS, particularly under conditions of OS (Fig. 6) [142]. The activation of NLRP3 inflammasomes is believed to occur through the dissociation of TR-interacting proteins from TR under oxidative conditions, which triggers the inflammasome complex and leads to pyroptosis.

OS serves as a primary catalyst for NLRP3 inflammasome activation, which results in cellular pyroptosis [150]. This process involves the strategic elimination of dysfunctional mitochondria, thereby reducing excessive mtROS production and modulating pyroptosis responses. Pyroptosis, a form of programmed cell death characterized by the inflammatory destruction of cells, is a significant factor in the regulation of bone regeneration. In diabetic conditions, where OS is heightened, pyroptosis disrupts the normal function of OBs, thereby impairing bone formation.

The induction of redox-sensitive signaling pathways, such as p38 MAPK and NF-κB, further contributes to pyroptosis under OS [151]. The MAPK pathway, which facilitates communication between OBs and OCs, includes key components such as c-JNK, ERK1/2, and p38 [152]. These pathways not only regulate apoptosis in OCs but are also activated in response to elevated ROS levels, leading to the transcription of pro-apoptotic genes like caspase 3, FAS ligand (FASL), and caspase 9. Activation of the JNK pathway, in particular, enhances the expression of these genes, promoting the pyroptotic cell death of OBs and further inhibiting osteogenesis (Fig. 6) [141].

In the context of diabetic bone regeneration, pyroptosis represents a significant obstacle to osteogenesis. The ROS-driven activation of the NLRP3 inflammasome and the subsequent induction of pyroptosis compromise the survival and function of OBs, leading to impaired bone healing. By contributing to the inflammatory destruction of bone-forming cells, pyroptosis exacerbates the challenges of bone regeneration in diabetic environments. Understanding the molecular mechanisms underlying pyroptosis offers potential therapeutic avenues for inhibiting its effects, thereby enhancing OB survival and improving bone regeneration in diabetic patients.

5. Therapy to ameliorate the hyperglycemia-ROS loop in diabetic bone regeneration

One of the major challenges in diabetic bone regeneration is transforming the hyperglycemic, inflammatory microenvironment into one that supports bone healing and regeneration [153]. The diabetic bone microenvironment is influenced by factors such as the duration of diabetes, glycemic fluctuations, and the type of diabetes, making it difficult for static therapeutic approaches to address the dynamic changes in this

environment. As a result, the development of targeted AO strategies is critical to improving the bone microenvironment and promoting osteogenesis.

The diabetic bone microenvironment is characterized by elevated levels of ROS, hyperglycemia, hyperlipidemia, and high cholesterol, all of which contribute to impaired bone healing and regeneration. These regenerative bone defects can be ameliorated by therapeutic approaches that focus on both anti-hyperglycemic and AO interventions. By reducing hyperglycemia and counteracting OS, these therapies aim to restore a more favorable environment for bone regeneration. AO strategies, in particular, have the potential to mitigate the damaging effects of ROS on bone cells and tissue, improving OB function and reducing the excessive bone resorption driven by OCs [154].

In summary, addressing the hyperglycemia-ROS loop in diabetic bone regeneration requires a combination of anti-hyperglycemic and AO therapies. These approaches can help to counterbalance the harmful effects of OS and hyperglycemia, creating a more conducive environment for bone healing and regeneration in diabetic patients.

5.1. Antihyperglycemic agents for diabetic bone regeneration

5.1.1. GSH

GSH is a crucial water-soluble tripeptide that serves as an endogenous AO responsible for maintaining cellular redox homeostasis [155]. Synthesized by glutathione synthase, GSH is utilized by enzymes such as glutathione peroxidase and glutathione lyase to detoxify free radicals, playing an essential role in neutralizing OS. Research has shown that patients with type 2 diabetes (T2D) exhibit lower erythrocyte GSH concentrations, contributing to oxidative damage within cells [156].

The therapeutic potential of GSH supplementation lies in its ability to compensate for GSH deficiency, thereby improving redox balance and potentially slowing the progression of T2D complications. For instance, oral administration of GSH in diabetic rats restored β-cell function, highlighting its capacity to ameliorate insulin secretion and attenuate oxidative damage (Fig. 7) [157]. Similar improvements have been observed in isolated cases of T2D patients, where GSH treatment reduced OS markers [162]. Sekhar et al. [158]demonstrated that dietary supplementation with GSH precursors such as cysteine and glycine increased GSH synthesis and reduced LOP in diabetic patients (Fig. 7). These findings suggest that targeting OS in pancreatic islets through GSH supplementation could be a promising strategy for diabetes management.

5.1.2. Metformin (Met)

Metformin (Met), a biguanide derived from *Galega officinalis*, is a widely used oral antidiabetic agent for managing T2D [163]. In addition to lowering blood glucose and improving insulin sensitivity, Met has been recognized for its protective effects against cardiovascular diseases. Whether used as monotherapy or in combination with other antidiabetic agents, Met's glucose-lowering efficacy has been extensively validated in large-scale clinical studies. Met acts through multiple mechanisms: inhibiting hepatic gluconeogenesis, reducing hepatic glucose output, enhancing glycogen synthesis in muscle, improving insulin sensitivity, and increasing glucose uptake in peripheral tissues. It also inhibits glucose absorption in the intestines and raises glucagon-like peptide-1 (GLP-1) levels (Fig. 7) [159]. One of Met 's key actions is the activation of adenosine 5′-monophosphate-activated protein kinase (AMPK), which enhances energy metabolism and supports cellular function.

In addition to its antihyperglycemic effects, Met has been shown to reduce ROS production and prevent early apoptosis (Fig. 7) [160]. This is thought to be related to its ability to inhibit the production of methylglyoxal (MGO), a reactive dicarbonyl metabolite produced during glycolysis. MGO acts as a precursor to AGEs, activating RAGE receptors in cardiovascular cells and contributing to cellular damage, cytotoxicity, inflammation, and apoptosis through ROS generation [164]. Wang et al. [161]found that Met prevented MGO-induced apoptosis in human umbilical vein endothelial cells (HUVECs), inhibited mitochondrial

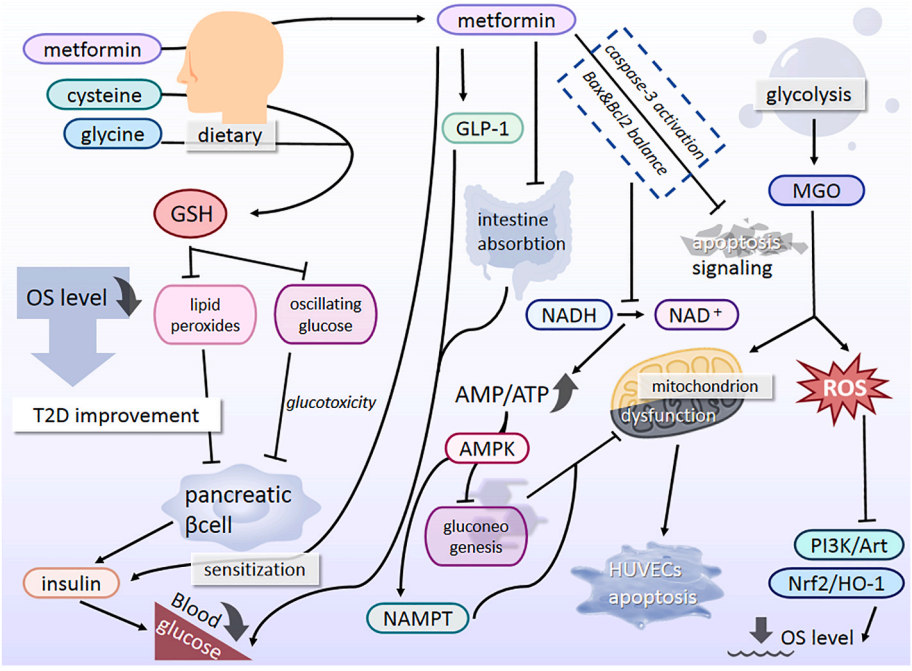

Fig. 7. Oral GSH has been shown to restore β-cell function, improve insulin secretion, and attenuate oxidative damage, which may delay the progression of complications in T2D [157]. Meanwhile, supplementation with GSH precursors similarly promotes GSH synthesis and reduces levels of lipid peroxidation products [158]. Metformin inhibits hepatic gluconeogenesis, reduces hepatic glucose output, enhances glycogen synthesis in muscle, improves insulin sensitivity, and increases GLP-1 levels [159]. It prevents MGO-induced ROS production, enhances signaling through the PI3K/Akt and Nrf2/HO-1 pathways, and boosts downstream antioxidant capacity, thereby inhibiting apoptosis. Additionally, metformin suppresses mitochondrial dysfunction and reduces apoptotic signaling by modulating the Bax/Bcl-2 ratio and inhibiting caspase-3 activation [160,161].

dysfunction, and reduced apoptotic signaling through the Bax/Bcl-2 ratio and caspase-3 activation. Met preconditioning also inhibited MGO-stimulated ROS production, increased signaling through the ROS-mediated PI3K/Akt and Nrf2/HO-1 pathways, and boosted downstream AO levels. These protective effects were observed both in vitro and in vivo, supporting Met's role in reducing OS and enhancing AO defenses (Fig. 7). Furthermore, in another study investigating the mechanism of action of Met, metformin significantly upregulated the expression of molecules related to the Nrf2 pathway in BMSCs of diabetic mice. This activation of the Nrf2-GPX7 pathway produced multiple effects: on one hand, metformin reduced ROS production and increased the levels of antioxidants such as superoxide dismutase and CAT, thereby mitigating oxidative stress; on the other hand, it enhanced ALP activity and induced the osteogenic differentiation of BMSCs [165].

Both GSH and Met offer promising therapeutic strategies for mitigating the hyperglycemia-ROS feedback loop in diabetic bone regeneration [166]. GSH supplementation addresses endogenous AO deficits and restores redox balance, while Met's multifaceted glucose-lowering and ROS-reducing effects support cellular resilience against OS. Together, these interventions highlight the potential for targeted therapies to ameliorate oxidative damage and improve bone healing outcomes in diabetic patients.

5.2. AO in diabetic bone regeneration

AO therapies represent a promising approach to ameliorating the hyperglycemia-ROS feedback loop in diabetic bone regeneration. One notable AO, interleukin-10 (IL-10), also referred to as cytokine synthesis inhibiting factor (CSIF), plays a critical role as an anti-inflammatory cytokine. It exerts its effects by inhibiting the expression of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1, which are produced by activated macrophages. In addition to its immunomodulatory function, IL-10 impacts metabolic pathways by inhibiting glucose uptake and glycolysis while promoting oxidative phosphorylation [167].

Another important AO therapy is Dex, a corticosteroid known for its strong anti-inflammatory properties and osteogenic potential. Dex has been widely used in bone regeneration due to its ability to modulate inflammatory responses (Fig. 8) [168]. Recent advances have focused on developing biomaterials that enable controlled and sustained localized release of Dex. These systems aim to enhance the therapeutic benefits of Dex while minimizing its side effects by delivering the drug in a targeted manner over a prolonged period.

In addition, thioketal (TK) linkers have gained attention as a ROS-sensitive drug delivery mechanism. TK linkers are a subclass of thioether groups that are stable in acidic and alkaline environments but cleave readily in the presence of elevated ROS levels. This property has been leveraged to create ROS-responsive drug delivery systems, where TK moieties are incorporated into polymer chains or used as linkers. Such systems enable selective drug release in response to pathological levels of ROS, providing an innovative solution to mitigate OS in diabetic bone regeneration (Fig. 8) [171].

Lastly, nanoparticles (NPs) have shown significant potential as ROS scavengers. NPs offer several advantages, including self-healing ability, water solubility, and biocompatibility, making them highly suitable for biomedical applications (Fig. 8) [172]. POM nanoclusters, formed by transition metals and oxygen atoms, have been utilized to reduce OS in bone tissues. For instance, combining POM with gelatin methacrylate (GelMA) hydrogels creates a drug delivery system that supports cell growth, differentiation, and substance exchange [173]. This system allows for the continuous release of POM at bone defect sites, effectively scavenging excess ROS and promoting bone regeneration (Table 1) [174–178].

Together, these AO therapies—IL-10, Dex, TK-Linkers, and NPs—offer innovative strategies to mitigate the oxidative damage caused by the hyperglycemia-ROS loop in diabetic bone regeneration. By targeting both inflammatory and oxidative processes, these therapies provide a comprehensive approach to improving bone healing outcomes in diabetic patients.

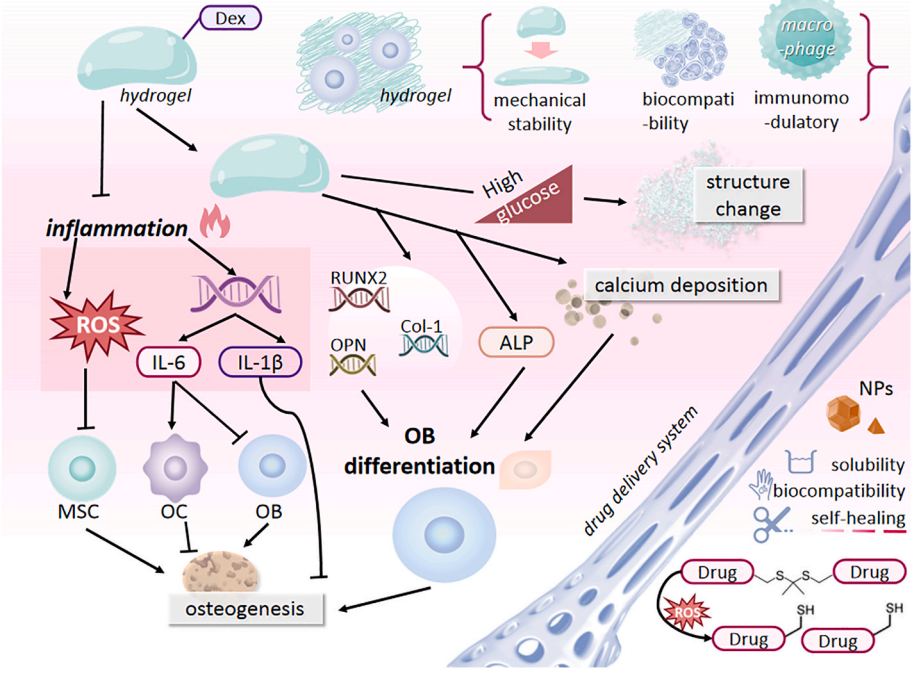

Fig. 8. Dex, with its ability to modulate inflammatory responses, is widely used in the field of bone regeneration [168]. The combined application of Dex and hydrogels not only exhibits antioxidant and anti-inflammatory activities but also allows the hydrogel to mimic the ECM, thereby minimizing immune responses. This combination also provides favorable mechanical stability, biocompatibility, and immunomodulatory effects [169]. By responding to changes in glucose levels, the hydrogel undergoes structural changes to achieve precise and controllable drug release [170]. TK bonds remain stable in both acidic and alkaline environments but readily cleave when ROS levels are elevated, enabling selective drug release under high ROS conditions [171]. NPs, serving as reactive oxygen species scavengers, possess self-healing capability, water solubility, and biocompatibility [172].

Table 1
Summary of studies on the contributing bone effects of ROS-scavenging hydrogels.

Hydrogel	AOs of hydrogels	Antihyperglycemic agent of hydrogels	signaling pathway	Response System	Mechanical Properties	Types of MSCs	Outcomes		Ref
							Effects on osteogenesis	Effects on blood glucose	
HIB (the hydrogel loaded with interleukin 10 (IL-10) and BMP-2)	IL-10	/	NLRP3	Glucose, MMP-9, or ROS	High deformability & High toughness	MC3T3-E1 cells	Higher newly formed woven bones; Higher bone union rate; Higher bone formation rate	Lower ROS, Lower M1 markers (CD86 and iNOS); Higher M2 markers CD206 and Arginine (Arg) genes	[174]
PGO-PHA-AG scaffold (polydopamine-mediated graphene oxide (PGO) & hydroxy-apatite nanoparticle (PHA) -incorporated conductive alginate/gelatin (AG) scaffold)	Functional PDA (the catechol groups on the PHA and PGO)	/	RhoA/ ROCK	/	Denser microstructures; Electrical conductivity; Higher compressive strength	BMSCs	Higher BMP-2 and TGF-β1; Higher BMD	Lower DPPH; lower iNOS and CD86; higher CD163 and CD206	[175]
A with TK(±) hydrogels(ROS-Responsive Degradable Hydrogels)	TK linkers	/	Oxidative cleavage	ROS	Fluid retention	BMSCs	Higher ALP level; higher expression of RUNX2, Col1, Opn, Ocn and Fabp4 in cells	Lower ROS	[176]
PDLLA-PEG-PDLLA-Met@MSN-SDF-1 hydrogel (mesoporous silica nanoparticle (MSN) -incorporated PDLLA (poly(dl-lactide))-PEG-PDLLA (PPP) thermosensitive hydrogel)	Met	Met	AMPK/ β-catenin	Temperature; high glucose	/	rBMSCs	ALP; Higher expression of the RUNX2 gene; Upregulated the level of β-catenin and p-β-catenin	Lower ROS	[177]
NPs-Met@ZIF-8(Met loaded zeolitic imidazolate frameworks) modified hydrogel	Met & Zn	Met	AMPK, ERK1/2, ATK, Wnt	pH	Outstanding injectability; The compression modulus of GelMA/ ZIF-8 and GelMA/ Met@ZIF-8 being almost two times enhanced	BMSCs	Higher Col1, ALP, BMP2, OSX, and OCN	Lower ROS	[178]

5.3. Drug delivery system in diabetic bone regeneration

Conventional therapies for diabetic bone defects have shown limited efficacy due to challenges such as poor solubility, instability during storage, and inadequate selectivity of traditional AOs [179]. These limitations hinder their ability to improve the bone microenvironment and promote osteogenesis effectively. A promising approach to overcome these obstacles involves the design of advanced drug delivery platforms capable of scavenging excess ROS and maintaining a reparative microenvironment at bone defect sites [180]. By controlling OS through the administration of ROS scavengers, these novel delivery systems can enhance the treatment outcomes for diabetic patients with bone defects [181]. Such systems are designed to adapt to the pathological features of bone defects, mimicking the extracellular matrix (ECM) to minimize immune responses, while providing desirable mechanical stability, biocompatibility, and immunomodulatory effects (Fig. 8) [169]. Furthermore, these platforms enable targeted inhibition of ROS production, modulation of redox-sensitive drugs, and regulation of AO enzyme activity, thereby addressing the multifaceted challenges of diabetic bone regeneration.

Recent advancements have focused on local drug delivery systems (LDDS), which offer several advantages over systemic therapies, particularly in the diabetic microenvironment. LDDS, including hydrogels, fibers, films, and NPs, provide a localized and sustained release of therapeutic agents at the site of bone defects. This approach helps retain high drug concentrations for extended periods, ensuring prolonged therapeutic effects while reducing the potential for side effects and systemic toxicity. Additionally, LDDS protect the drug from the harsh conditions often present in the diabetic bone microenvironment, such as elevated glucose and ROS levels, which can degrade traditional drugs [182]. Achieving controlled drug release based on the specific conditions of the diabetic bone microenvironment has emerged as a crucial strategy in designing effective LDDS for diabetic bone regeneration.

Furthermore, innovative “smart” hydrogels have been developed that respond to biochemical cues within the diabetic microenvironment, offering precise and timely interventions for bone healing. Unlike earlier hydrogels, which primarily focused on improving physicochemical properties such as biocompatibility and cell adhesion, these advanced hydrogels are designed to respond dynamically to the biological conditions of the tissue microenvironment. These systems possess diagnostic capabilities that enable them to detect and respond to complex pathological cues, releasing therapeutic agents in a controlled sequence

aligned with the bone healing process. This multi-dimensional orchestration supports both immunomodulation and osteogenesis, improving the effectiveness of bone regeneration treatments. Smart hydrogels can respond to stimuli from glucose levels, by undergoing changes in their structure and releasing drugs in a precise and controllable manner. Their ability to function as sensors and controlled-release mechanisms makes them particularly promising for addressing the challenges of diabetic bone regeneration (Fig. 8) [170].

5.4. *Piezocatalytic nanozyme strategy for cyclic anti-oxidative therapy*

While AO therapies and smart drug delivery systems offer promising avenues to disrupt the hyperglycemia-ROS loop, a significant limitation of conventional molecular antioxidants is their one-off, non-regenerative reaction with ROS, leading to rapid depletion and limited sustained efficacy at the defect site [183]. To address this challenge, novel piezocatalytic strategies has emerged, leveraging the unique properties of piezoelectric nanomaterials to create a continuous and cyclic anti-oxidative device [184]. The piezocatalytic strategy is an emerging approach that utilizes piezoelectric materials to convert mechanical energy (e.g., from ultrasound) into electrochemical energy for therapeutic purposes [185].

This approach centers on fabricating piezoelectric nanocomposites, such as polydopamine (PDA)-functionalized generators, which possess a built-in electric field. Under external mechanical stimulation, typically provided by non-invasive ultrasound (US) irradiation, these materials exhibit a pronounced piezocatalytic effect. The mechanical energy is converted into electrical charges that drive a continuous, regenerative redox cycle [186]. In PDA-based systems, the piezocatalytic effect enables the high-performance recycling of the catalytic reaction by providing a constant supply of electrons. This facilitates the cyclic switching of functional groups from the oxidized state (quinone) back to the reduced, active state (phenol), allowing the material to scavenge ROS repeatedly without being consumed [186].

The therapeutic benefits of this piezocatalytic strategy are multifaceted. Firstly, the substantial and sustained boost in ROS elimination directly mitigates OS, a primary driver of cellular dysfunction in the diabetic bone microenvironment. Secondly, this reversal of the oxidative status effectively downregulates pro-inflammatory cytokines and contributes to a shift in the immune landscape, promoting the M2 polarization of macrophages and establishing a pro-regenerative milieu. At the cellular level, these combined effects—reduced OS and inflammation—synergistically enhance the osteogenic differentiation capacity of BMSCs, which is typically suppressed in diabetic conditions [187].

6. Integrated redox circuits and precision therapeutic nodes in diabetic bone regeneration

The impact of ROS on bone cells exemplifies a classic ‘redox window’ phenomenon, where precise spatiotemporal regulation of specific species dictates cellular fate. This paradigm is not unique to skeletal tissue. For instance, in skeletal muscle satellite cells, NO and H_2O_2 orchestrate the transition from quiescence to activation and differentiation in a similarly precise manner. This conservation across tissues underscores the fundamental principle that ROS/RNS act as essential secondary messengers, and that diabetic bone disease may be viewed as a state of a disrupted ‘redox window’, leading to impaired OB differentiation and excessive OC activation.

Integrating the progenitor and immune tiers clarifies why anti-ROS monotherapies underperform in vivo: diabetes establishes a self-reinforcing circuit spanning BMSC senescence/adipogenic drift, osteocyte apoptosis/sclerostin upregulation, and M1/Th17/NET-dominant immunity that converges on excess RANKL, suppressed Wnt/β-catenin, and persistent NF-κB/MAPK drive [32,188]. Durable regeneration likely requires multi-node control: mitochondria-targeted redox correction in BMSCs, osteocyte-sclerostinblockade or Wnt restoration, and immunometabolic re-education (NRF2/HO-1, IL-10, selective NLRP3/NOX2 dampening) [189].

The orchestration of cellular fate by ROS is mediated through redox-sensitive TFs that decode dynamic redox signals into stage-specific transcriptional programs. This regulatory mechanism is particularly evident in skeletal muscle regeneration, where specific TFs are sequentially activated to coordinate distinct phases: 1) NRF2 orchestrates the early antioxidant defense and metabolic priming phase; 2) NF-κB transiently promotes inflammatory signaling required for recruitment but must be suppressed for differentiation; 3) FOXO1/3 maintain quiescence and stemness, regulating autophagy under mild oxidative tone. 4) HIF-1α couples redox and oxygen sensing during hypoxic remodeling [190]. This coordination parallels the interconnected actions of NRF2, NF-κB, and FOXO in bone cells, where diabetic conditions disrupt this precise regulation through sustained NF-κB activation, overwhelmed NRF2 capacity, and dysregulated FOXO signaling, collectively contributing to regenerative failure [191,192].

The Notch intracellular domain (NICD) contains critical cysteine-rich domains that are susceptible to redox modification. Evidence indicates that Hydrogen Peroxide can directly oxidize these cysteine residues, which stabilizes the NICD and enhances its transcriptional activity. This oxidation prevents the ubiquitination and proteasomal degradation of NICD, thereby prolonging Notch signaling [193]. This mechanism is crucial for maintaining SC quiescence and preventing premature differentiation. Conversely, a reducing environment can promote NICD degradation, facilitating the exit from quiescence and the initiation of differentiation.This liberation allows Dvl to activate downstream signaling, leading to the stabilization of β-Catenin and the transcription of target genes (e.g., Myf5, MyoD) that drive SC proliferation and commitment. This provides a direct molecular switch whereby ROS can potentiate Wnt signaling.The β-Catenin protein itself can be modified by ROS [192].

Post-translational modifications (PTMs)—including oxidation, S-nitrosylation (SNO), and S-glutathionylation (SSG)—offer a plausible mechanism for the direct redox-sensing capability of myogenic regulatory factors (MRFs) such as MyoD, Myf5, and Pax7. Experimental validation of these modifications is methodologically feasible, though direct in vivo evidence during regeneration remains an active pursuit [194–196]. Key cysteine residues within MRFs can be mapped using advanced techniques like liquid chromatography-tandem mass spectrometry (LC-MS/MS), often coupled with enrichment strategies such as the biotin-switch technique for labile SNO adducts. Functional validation typically involves site-directed mutagenesis (e.g., cysteine-to-serine mutants) to assess the effect of specific PTMs on MRF stability, DNA binding, protein–protein interactions, and transcriptional activity in myogenic reporter assays [197]. While current evidence supports the conceptual framework of redox-mediated MRF regulation, future studies using in vivo cross-linking and genetically encoded biosensors will be essential to capture these dynamic modifications during the spatiotemporally controlled process of muscle regeneration, thereby fully elucidating this layer of post-translational control over cell fate [198].

Furthermore, the detrimental impact of ROS extends beyond bone cells to critically dysregulate the immune microenvironment, particularly macrophage polarization. The M1-to-M2 phenotypic transition, a critical checkpoint in the inflammatory-to-regenerative shift, is fundamentally governed by dynamic redox changes. Pro-inflammatory M1 polarization is driven by high ROS/RNS flux, primarily through NOX2-mediated superoxide production and iNOS-derived NO [199]. Conversely, transitioning to the pro-regenerative M2 phenotype requires redox resolution via upregulation of antioxidant defenses, notably through NRF2-mediated expression of enzymes like HO-1. While discrete ROS/RNS concentration thresholds remain context-dependent, key molecular events serve as functional switches [200].

Beyond innate immunity, the redox landscape also critically shapes adaptive immune responses, particularly in T-cell subset differentiation and function [201]. The redox modulation of T-cell subsets represents a

crucial regulatory layer in tissue repair. Tregs and effector T cells exhibit distinct redox sensitivities that critically influence their functions. Tregs require a reduced intracellular milieu supported by high GSH levels for their stability and suppressive capacity, whereas Teffs demonstrate greater tolerance to elevated ROS, which can enhance their pro-inflammatory responses through NF-κB and mTOR signaling [202, 203].

Beyond its direct effects on bone cells and immune populations, the diabetic redox imbalance critically dictates the lineage commitment of stromal progenitors, particularly FAP (fluorogen-activating protein) [204]. The differentiation of FAPs into adipogenic or fibrogenic lineages is governed by the local redox state, acting as a pivotal fate switch. Adipogenic differentiation is favored under a relatively reduced intracellular environment, which supports the expression and transcriptional activity of the master regulator PPARγ [205]. Critically, emerging in vivo evidence supports the therapeutic potential of reprogramming this pathological FAP fate by targeting redox imbalance. This phenotypic switch, correlated with diminished tissue ROS and TGF-β/SMAD signaling, resulted in functionally improved regeneration with reduced fibrosis. Although direct evidence in the diabetic bone marrow is still evolving, these findings provide a compelling rationale that redox-targeting strategies can actively reprogram stromal cell fate to counteract the fibrotic pathology in diabetic bone regeneration [206].

Furthermore, oxidative stress directly disrupts the delicate proteolytic balance required for physiological ECM remodeling by dysregulating MMPs and their IMPs. ROS can directly activate latent MMPs via the "cysteine switch" mechanism, transcriptionally upregulate key MMPs through NF-κB and MAPK signaling, and simultaneously inactivate TIMPs through oxidation of critical methionine residues. In the context of diabetic bone repair, this dysregulation creates a chaotic ECM environment: excessive MMP activity prematurely degrades the nascent provisional matrix necessary for cell migration, while the accumulation of AGEs renders the mature matrix resistant to normal turnover. This combination—excessive degradation of regenerative scaffolds and inadequate clearance of pathologically modified ECM—severely compromises the structural and biochemical cues essential for orchestrated bone healing.

This review has delineated the core mechanisms by which ROS disrupt the osteoblast-osteoclast balance within the diabetic bone microenvironment. This paradigm of redox regulation is universal. Firstly, angiogenesis, which is indispensable for bone regeneration, is directly modulated by redox-sensitive signaling pathways; the expression of key angiogenic factors such as VEGF is regulated by ROS-sensitive pathways including NF-κB and MAPK, forming a critical link between oxidative stress, impaired vascularization, and failed bone repair in diabetes [207]. Methodologically, moving beyond conventional cell models to employ animal models that mimic diabetic complications (e.g., critical-sized calvarial defects or femoral non-union models in diabetic rodents) is paramount for uncovering redox-dependent repair mechanisms [208]. To precisely identify the most vulnerable cell populations within these models, integrating single-cell transcriptomics and redox proteomics would be highly valuable. The former can resolve the heterogeneous responses of osteoprogenitors, osteoblasts, and endothelial cells to stress, while the latter can directly map oxidative modifications on key signaling proteins like NFATc1 and Nrf2, thereby elucidating functional changes at the molecular level [209].

Methodologically, pairing single-cell atlases of diabetic defects with redox proteomics can map cell-type–specific oxidative PTMs (e.g., NFATc1, KEAP1/NRF2, FOXO3, Sirtuins) and resolve which microdomains (osteolineage vs immune vs stromal) dominate failure [210, 211]. Such resolution will guide precision redox modulation—resetting ROS into a pro-regenerative window without extinguishing essential signaling.

Regarding therapeutic strategies, future developments should move beyond traditional broad-spectrum antioxidants. More targeted genetic tools (e.g., osteoblast-specific overexpression of SOD2 or Keap1 knockdown) and pharmacological agents (e.g., mitochondrial-targeted antioxidants like MitoTEMPO and NAD^+ precursors like NMN) have shown promise in preclinical studies by improving mitochondrial function, rescuing Sirtuin activity, and mimicking physiological NO signaling to promote bone regeneration [212–214]. Ultimately, the success of any therapeutic intervention hinges on reconciling the context-dependent dual roles of ROS. In the pathological context of diabetic bone regeneration, the goal is not to eradicate ROS entirely but to achieve "precision redox modulation" through intelligent drug delivery systems [215]. This aims to "reset" pathological oxidative stress back to a "redox window" permissible for physiological bone regeneration—scavenging excessive ROS to curb cell death in the acute phase, while permitting necessary ROS signaling to drive cell differentiation and matrix remodeling during the later repair stages.

7. Conclusion and prospect

The interplay between ROS and bone cell functions in diabetic bone regeneration highlights a critical pathological cycle that impedes effective skeletal healing. Elevated ROS levels in diabetic conditions promote excessive bone resorption through increased activity of OCs while also reducing bone formation by impairing OB function, resulting in an imbalance in bone remodeling. The molecular pathways involved, including the RANKL, NF-κB, and MAPK signaling cascades, provide essential insights into the mechanisms through which OS affects bone regeneration. Moreover, ROS-induced apoptosis, ferroptosis, and necroptosis in OBs further worsen the challenges of diabetic bone healing. Despite these difficulties, emerging therapies targeting ROS, such as AO treatments and novel drug delivery systems, present promising opportunities for enhancing bone regeneration in diabetic patients. By addressing both OS and the related inflammatory microenvironment, these strategies have the potential to restore balance between bone formation and resorption, improving bone repair and the overall quality of life for individuals affected by diabetic bone disorders.

Future research should prioritize the development of precision redox-modulating therapies capable of dynamically adapting to the diabetic bone microenvironment. Integrating smart biomaterials—such as ROS-responsive hydrogels and piezoelectric nanomaterials—with real-time monitoring systems offers strong potential for achieving spatiotemporally controlled antioxidant delivery. In addition, elucidating the crosstalk among redox signaling, immunomodulation, and metabolic reprogramming within bone cell populations will be essential. Leveraging single-cell multi-omics in combination with advanced in vivo models may reveal novel cell-type-specific therapeutic targets. Ultimately, a holistic strategy that not only eliminates excessive ROS but also restores the physiological "redox window" could enable true regeneration of functional bone tissue in diabetic patients, shifting the paradigm from symptomatic relief to genuine metabolic and skeletal restoration.

While this review has focused on the direct deleterious effects of ROS on OBs and OCs, it is important to acknowledge that impaired bone regeneration in diabetes is a multifaceted process. Future investigations into the role of ROS in modulating the function of BMSCs, osteocytes, chondrocytes, and the immunomodulatory effect within the bone marrow will be critical for developing more comprehensive therapeutic strategies.

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Availability of data and materials

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CRediT authorship contribution statement

Keyue Tian: Conceptualization, Data curation, Investigation, Methodology, Visualization, Writing – original draft. **Tianchu Xiong:** Investigation, Methodology, Visualization, Writing – original draft. **Di Zeng:** Investigation, Methodology, Writing – original draft. **Ziheng Huang:** Investigation, Methodology, Writing – original draft. **Ruixi Liu:** Investigation, Methodology, Visualization. **Feng Luo:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviation

Reactive oxygen species, (ROS); oxidative stress, (OS); osteoclast, (OC); osteoblasts, (OB); antioxidant, (AO); bone mineral density, (BMD); receptor activator of nuclear factor-kappa B, (RANK); RANK ligand, (RANKL); advanced glycation end-products, (AGEs); receptor for AGEs, (RAGE); bone marrow mesenchymal stem cells, (BMSCs); nuclear factor erythroid 2-related factor 2, (Nrf2); transforming growth factor-beta, (TGF-β); mesenchymal stem cells, (MSCs); alkaline phosphatase, (ALP); ovariectomized, (OVX); osteoprotegerin, (OPG); glutathione (GSH); tumor necrosis factor, (TNF); nuclear factor of activated T-cells cytoplasmic 1, (NFATc1); tartrate-resistant acid phosphatase, (TRAP); calcitonin receptor; (CTR); solute carrier family 7 member 11, (SLC7A11); bone marrow macrophages, (BMMs); extracellular signal-regulated kinase, (ERK1/2); MAPK phosphatases, (MKPs); apoptosis signal-regulating kinase 1, (ASK1); mitochondrial calcium channels, (MCU); Corylifol A (CA); Pteryxin (PTX); mitochondrial DNA, (mtDNA); calmodulin-dependent protein kinase, (CaMK); Kruppel-like factor 9, (Klf9); Endoplasmic reticulum, (ER); c-Jun N-terminal kinase, (c-JNK); outer mitochondrial membrane (OMM); inner mitochondrial membrane, (IMM); TNF-related apoptosis-inducing ligand receptor 1/2, (TRAILR1/2); TNF receptor 1 (TNFR1); dexamethasone (Dex); phosphorylated PI3K, (p-PI3K); phosphorylated Akt, (*p*-Akt); glycogen synthase kinase 3β, (GSK3β); glutathione peroxidase 4, (GPX4); lipid peroxidation, (LPO); catalase, (CAT); hydroxyl radicals, (-OH); TNF receptor 1, (TNFR1); mixed lineage kinase domain-like protein, (MLKL); mitochondrial reactive oxygen species, (mtROS); dynamically associated protein 1, (Drp1); nucleotide-binding domain and leucine-rich repeat protein-3, (NLRP3); FAS ligand, (FASL); type 2 diabetes, (T2D); metformin, (Met); glucagon-like peptide-1, (GLP-1); adenosine 5′-monophosphate-activated protein kinase, (AMPK); methylglyoxal, (MGO); human umbilical vein endothelial cells (HUVECs); interleukin-10, (IL-10); cytokine synthesis inhibiting factor, (CSIF); thioketal, (TK); nanoparticles, (NPs); gelatin methacrylate, (GelMA); local drug delivery systems, (LDDS).

Data availability

Data will be made available on request.

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