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Case Report

Oxidative Stress and Bone Remodeling: An Updated Review

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Abstract

Oxidative stress has emerged as a pivotal factor in bone remodelling, significantly influencing the balance between osteoclast-mediated resorption and osteoblast-driven formation. Reactive oxygen species (ROS), generated through various mechanisms, disrupt osteoblastic differentiation and function while enhancing osteoclastic activity, thereby promoting bone loss. This review consolidates recent findings on oxidative stress's molecular impact on bone remodelling, focusing on key signalling pathways, such as MAPKs, NF-κB, and Wnt/β-catenin. We explore the roles of glucocorticoids and inflammatory cytokines in exacerbating ROS production, leading to decreased bone mass, increased apoptosis, and altered osteoblast-osteoclast interactions. Insights into the regulatory mechanisms of osteocytes and the RANKL/OPG axis further elucidate the connection between redox imbalance and skeletal fragility. Understanding these processes underscores the therapeutic potential of antioxidants and targeted signaling pathway modulation in mitigating oxidative stress-related bone diseases. Further research into these mechanisms is crucial for developing precise interventions to improve bone health and reduce fracture risk in aging and chronic inflammation contexts.

Introduction

Bone remodelling is needed to maintain skeletal integrity, adapt to mechanical stress, and repair microdamage. Complex signaling pathways and systemic and local factors regulate this delicate balance between osteoclast resorption and osteoblast formation. Recent years have seen oxidative stress play a major role in bone remodeling and related disorders. ROS production and antioxidant defences imbalance, causing oxidative stress that damages cells and molecules. Oxidative stress has many effects on bones. It disrupts osteoblast differentiation and function and increases osteoclast activity, promoting bone loss. Glucocorticoid-induced bone loss, osteoporosis, and age-related skeletal fragility involve this imbalance. Research on oxidative stress in bone remodeling has identified key pathways, including MAPKs, NF-κB, and Wnt/β-catenin signaling. This review discusses the latest research on oxidative stress and bone remodeling molecularly, focusing on therapeutic targets to reduce its negative effects.

Oxidative stress influences osteoblastic differentiation

From embryo to adulthood, bones form and dissolve. During adult

bone remodeling, osteoblasts form and osteoclasts resorb bone. Osteoporosis decreases BMD, bone mass, and fracture risk due to osteoblastic or osteoclastic decrease [1]. Osteoporosis results from osteoblast-osteoclast differentiation. Osteoblasts are not bone marrow osteoprogenitor cells [2]. Ducy et al. [3] found Runx2 (Cbfa1) controls osteoblast differentiation. Runx2 interacts with OSE2 in osteocalcin, type I collagen, and alkaline phosphatase promoters to regulate expression [4]. BMP-Smad, MAPKs, and PI-3K differentiate osteoblasts. The signaling pathways that reduce osteoblastic differentiation in osteoporosis are unknown. Both superoxide and hydrogen peroxide damage DNA, proteins, and lipids. Due to mitochondrial electron transport or environmental factors like cytokines and UV radiation, oxidant levels harm redox equilibrium and cause oxidative stress [5]. Oxidative stress may impact cerebellar ischemia, atherosclerosis, cancer, and aging. Oxidative damage activates multiple signaling pathways that cause cell proliferation, growth or differentiation arrest, senescence, and death. The pathways are PI-3K, NF-kB, PLC-gamma 1, p53, HSF, and MAPKs (ERKs, JNK, p38 MAPK, and ERK5). Stress duration, intensity, and cell type activate pathways. Results show pathway equilibrium [6]. Oxidative stress causes osteoporosis. Increasing oxidative stress lowers older adults' BMD [7]. Plasma antioxidants plummeted in elderly osteoporotic women [8]. Antioxidants improve BMD after menopause [9]. Additionally, oxidative stress promotes osteoclast differentiation and activity [10]. We investigated the signaling mechanisms that inhibit osteoblastic differentiation in bone cells under oxidative stress after finding that H2O2-induced oxidative stress decreased rabbit primary BMSC and calvarial osteoblast ALP, type I collagen, CFU-O production, and Runx2 activation [11]. H2O2 downregulated p38 MAPK and upregulated PLC-c1, ERK1/2, and NFjB. ERK or NF-κB inhibitors can significantly improve BMSC and calvarial osteoblastic cell differentiation markers due to oxidative stress. ERK-specific inhibitors blocked H2O2-induced NF-kB activation. Research shows that oxidative stress inhibits BMSC and calvarial osteoblast growth by activating ERK and NF-κB. In vitro and rodent studies show free radicals cause osteoclastogenesis and bone loss. With H2O2, mouse calvariae resorb bone. NF-kB, an osteoclastogenesis protein, may increase bone resorption from oxidative stress [12]. The molecular regulation and effects of oxidative stress on osteoblast differentiation and function are less understood than osteoclasts. Mody et al. [13] found that H2O2 or XXO-induced oxidative stress inhibits bone cell differentiation in MC3T3-E1 preosteoblastic cells and M2-10B4 marrow stromal cells. ESW stimulation produced superoxide but not H2O2, promoting osteogenic cell proliferation and maturation, according to Wang et al. [14]. Bai's primary rabbit BMSC and calvarial osteoblast study matches Mody's, but Bai's H2O2 is 0.1 mM. Different cell types, sources, dosages, and durations of oxidative stimuli may explain these differences. The roles of ERKs and p38 MAPK in osteoblast development are disputed. Sometimes p38MAPK is required for BMP-2-induced Runx2, ALP, and osteocalcin production in mouse C2C12 cells [15], but sometimes not [16]. Fetal calf serum or pentoxifylline-induced ALP production requires p38 activation in MC3T3-E1 cells [17]. MC3T3-E1, mouse primary calvarial osteoblasts, and BMSC showed that p38 MAPK defines osteoblasts instead of ERKs [18]. P38 MAPK promotes rabbit calvarial osteoblast and BMSC differentiation, but oxidative stress inhibits them. More research is needed to confirm p38 MAPK's oxidative stress target status. ERK activates osteoblast-related gene expression via extracellular matrix-integrin receptors, BMP-2, growth factors, and mechanostensing during early osteoblast differentiation [14,19]. ERK-phosphorylated Runx2 affects osteoblast differentiation [19]. ERK inhibits osteoblast growth via BMP-2 and growth factors [20]. Bai's experiments show H2O2-induced oxidative stress activates ERK [11]. During primary rabbit calvarial osteoblast and BMSC differentiation, H2O2 reduces type I collagen, ALP activity, CFU-O formation, and nuclear Runx2 phosphorylation PD98059 inhibits ERK, reducing this. Bai discovered that ERKs may inhibit H2O2-induced osteoblast development at oxidative stress. In rat osteosarcoma ROS 17/2.8 and HeLa cells, IκB phosphorylation links NF-kB activation to ERK pathways [19]. Deformation or oxidative stress set in. NF-κB responds to various stimuli. The NF-jB knockout mice have osteopetrosis due to impaired osteoclastogenesis and function, proving its importance in bone [12]. Research shows that NF-κB inhibits osteoblast differentiation in MC3T3 cells [21] and the human osteosarcoma cell line Saos-2 [22]. Beyond NF-κB, other ERK-regulated transcription factors may be involved due to the versatility of ERK signaling. It is unclear how ERKs and NF-κB affect osteoblast growth during oxidative stress. Like CAPE, PD98059 restored osteoblast differentiation but not better. NF-jB and ERK-dependent/independent pathways may inhibit osteoblast development by H2O2. NF-kB activation phosphorylates and activates RANTES and ERK in human hepatic stellate cells [23]. The mechanisms by which NF-jB inhibits osteoblast differentiation are unknown. ERKs and NF-jB activation suppress ALP activity, type I collagen expression, and nuclear Runx2 phosphorylation in BMSC and calvarial osteoblast differentiation under oxidative stress, Bai found. In mice, Runx2 gene deletion impairs osteoblast formation, proving its importance. According to Bai's research, oxidative stress phosphorylates Runx2, an ERK and NF-kB downstream target, inhibiting rabbit BMSC and calvarial osteoblast development Franceschi and Xiao [4] say MAPK or PKA pathways phosphorylate Runx2 to activate transcription. Posttranslational modifications and protein-protein interactions control Runx2. Recent findings that Runx2 activity is negatively affected by phosphorylation of two conserved serine residues (S104 and S451) complicate its regulation [24]. Nuclear translocation and Runx2 release may affect it]. Similar to

osteoblastic differentiation markers like ALP, type I collagen, and CFU-O, nuclear Runx2 tyrosine phosphorylation activates Runx2 (Table 1).

Oxidative stress impacts osteoblastic function

The molecular mechanisms by which endogenous glucocorticoids and inflammatory cytokines decrease bone mass and strength with age are unknown. This study hypothesized that increased oxidative stress, a key insulin resistance mechanism in these two drugs, may cause skeletal issues. According to Almeida et al. [25], mice injected with prednisolone showed increased p66shc phosphorylation and mitochondrial bone H2O2 in osteoblastic cells in vitro, similar to TNFα and dexamethasone (Dex PKCβ/p66shc signaling is crucial for Dex and TNFα to produce ROS, which activates JNK and induces apoptosis. Dexamethasone (Dex) and TNFα apoptosis were reduced by ROS activating FoxO transcription factors. Drugs inhibited Wnt-induced proliferation, osteoblast differentiation, and Akt phosphorylation. The Wnt signaling inhibition was unaffected by PKCβ/p66shc. Managed by FoxOs and Akt. According to research, Dex and TNFα cause pro-apoptotic effects in osteoblastic cells by activating the PKCβ/p66shc/JNK signaling pathway via ROS Overexposure to glucocorticoids and inflammatory cytokines can worsen bone damage by inhibiting Akt and activating FoxO through Wnt/β-catenin antagonism [25]. Glucocorticoids and TNFα increase fracture risk and bone loss. Low osteoblast counts result from precursor production and early death, while glucocorticoids and TNFα increase osteoclasts [26]. The molecular mechanisms of these side effects are unknown. Age can lead to a 20-50% increase in endogenous glucocorticoids in humans and animals, as adrenocorticotropic hormone feedback inhibition decreases and bone 11β-hydroxysteroid dehydrogenase type 1 expression increases, converting in inflammatory arthritis, TNFα is crucial for skeletal damage. Increased TNFα levels with age may cause involutional osteoporosis, similar to glucocorticoids [27]. Increased osteoblast and osteocyte apoptosis, decreased osteoblast numbers, and bone formation rates decrease bone density with age [28]. ROS from adaptor protein p66shc phosphorylation cause age-related bone loss. PKCβ phosphorylation at Ser36 activates a signaling pathway involving P66shc and elevated ROS levels. Oxidative signals cause apoptosis. Phosphorylated p66shc increases mitochondrial ROS production by producing H2O2. H2O2-induced osteoblast apoptosis needs P66shc [29]. This and antioxidant delivery reducing age-related osteoblast apoptosis [30] support the oxidative stress-involutional osteoporosis hypothesis. ROS production and defense are regulated by FoxO transcription factors, which maintain bone homeostasis throughout life [31]. FoxO1–4 are expressed in mammalian bone cells. Growth hormones and insulin signal FoxO suppression via Akt [32]. Akt directly phosphorylates FoxOs at three conserved sites, suppressing FoxO-mediated transcription and retaining them in the cytoplasm. ROS nuclearly retain FoxO and activate transcription, unlike growth factors. FoxOs reduce ROS by promoting free radical-scavenging gene transcription. Increased oxidative stress enhances FoxOs-β-catenin interaction in cells, including osteoblastic cells [33]. Wnt signaling in osteoblastogenesis requires this interaction [34]. Wnt proteins activate the LRP5/6-frizzled receptor complex, preventing β-catenin degradation and inactivating GSK-3β. After nuclear translocation, β-catenin work with TCF/LEF transcription factors to regulate Wnt gene expression [35]. ROS levels in cells increase due to oxidative stress from H2O2, glucocorticoids, and TNFα. Oxidative stress from these drugs causes most insulin resistance [36]. Human osteoblasts exposed to Dex had significant oxidative stress transcript changes [37]. Additionally, TNFα induces osteoblast apoptosis via ROS-related mechanisms [38]. The mechanisms by which these drugs inhibit Wnt signaling in osteoblastic cells are unknown [39]. Almeida et al. [25] found that glucocorticoids and TNFα negatively impact osteoblastic cells by increasing reactive oxygen species. The study confirms that TNFα and GCs increase ROS via PKCβ and p66shc. Research indicates that p66shc increases ROS production in mitochondria, indicating that GCs and TNFα exposure cause ROS in osteoblasts. ROS are mostly produced by the mitochondrial electron transport chain, but NOS, xanthine oxidase, and NADPH oxidase can too. Previous research suggests that TNFα increases ROS production in cell membranes via the Nox1 pathway. Glucocorticoids activate xanthine oxidase, increasing oxidative stress. Either p66shc is the sole source of ROS in osteoblasts or enhances ROS produced outside the mitochondria within the mitochondria needs further study. Glucocorticoids and TNFα cause osteoblast and osteocyte apoptosis. Cell-autonomous bone fragility results from chronic glucocorticoid excess and osteocyte apoptosis. Reactive oxygen species boost glucocorticoids and TNFα's pro-apoptotic effects. Research suggests ROS promote TNFα-induced apoptosis in various cell types, including osteoblasts, supporting our findings [40]. The study suggests that ROS trigger a PKCβ/p66 shc/JNK signaling cascade, which mediates the pro-apoptotic effects of Dex or TNFα in osteoblasts. Research shows that GC receptors, not genes, induce osteocyte apoptosis. Cell detachment-induced apoptosis or anoikis results from rapid JNK and Pyk2 activation. High ROS levels activate Pyk2 in many cell types, suggesting ROS/p66shc signaling may activate it in osteocytes. Multiple ROS-dependent apoptotic mechanisms require JNK activation [41–43]. Research shows that ROS regulate JNK activity in osteoblasts, as NAC or p66shc deletion hinders Dex and TNFα activation of JNK. ROS inhibit phosphatase activity, sustaining JNK activation and cell death [49]. Recent research suggests that Dex and TNFα activate FoxOs in osteoblasts via ROS/JNK signaling. In response to oxidative stress, JNK directly phosphorylates FoxOs in model organisms [44]. FoxO4 moves

from cytoplasm to nucleus via JNK-phosphorylated Thr447 and Thr451 [45]. While JNK kills osteoblasts, ROS protect them with FoxOs. In vitro and in vivo studies show osteoblast FoxO3 overexpression reduces apoptosis [31]. Mouse osteoblasts that express FoxO3 have increased bone mass and quantity, reduced bone p66 shc phosphorylation, and osteoblast death. Research shows that FoxO3 overexpression, along with antioxidants NAC and ebselen, prevents TNFα and Dex-induced apoptosis, promoting osteoblast survival. Ablation of FoxO1, 3, and 4 in mice raises p66. ROS increase FoxO's interaction with β-catenin, shifting transcription from TCF to FoxO, reducing osteoblastogenesis despite FoxOs' anti-apoptotic effects [46]. How oxidative stress-induced FoxO post-translational modifications aid this interaction is unknown. According to Hoogeboom et al., β-catenin and FoxOs interact without JNK in H2O2 response, as seen in JNK1/JNK2 deficient cells [47]. The study found that FoxOs inhibit Dex and TNFα Wnt signaling without JNK involvement. Neither PKCβ activity nor ROS inhibition affected the suppressive effect of Dex and TNFα on TCF-mediated transcription. Dex and TNFα cannot solely inhibit β-catenin/TCF transcriptional activity due to increased ROS generation, as confirmed by this discovery. In bone and calvaria-derived osteoblasts and osteocytes, phosphorylation causes apoptosis, reducing bone mass and number [46]. Our research suggests that Dex and TNFα inhibit Akt activation in osteoblastic cells without ROS, which may explain the discrepancy. Increased Akt levels mitigated the negative impact of Dex and TNFα on TCF-luc activity. Serum starvation, such as Dex and TNFα, decreases Akt activity, increases β-catenin binding to FoxOs, and decreases β-catenin/TCF activity, suggesting Akt may counteract ROS in promoting FoxOs. Glucocorticoids activate FoxOs and inhibit Akt, causing skeletal muscle atrophy and decreased collagen I production [48]. To prevent muscle atrophy from Dex, use constitutively active Akt, dominant negative GSK-3β, or stable β-catenin [49]. Inhibiting β-catenin/TCF activity may intensify pathologies like involutional osteoporosis [50]. In osteoblastic cells, glucocorticoids and TNFα decrease Wnt signaling, resulting in increased DKK1 expression and decreased PI3K/Akt/GSK3β signaling [39] Data suggests that TNFα, RUNX2, and osterix inhibit BMP-induced osteoblast growth [51]. These alternative mechanisms may mitigate the effects of Dex and TNFα on osteoblastogenesis. TNFα levels in mouse bones increase with age, influenced by ROS. Previous research indicates that H2O2 increases TNFα expression in osteoblast cells in vitro [29]. Low levels of p66shc inhibit the NFkB signaling pathway, which is essential for ROS-induced TNFα in osteoblasts. Research shows that PKCβ/p66shc signaling is essential for a harmful cycle where ROS increase TNFα, worsening oxidative stress by promoting ROS production. Neels et al. [52] found that TNFα can rise in adipose tissue via PKC signaling and NF-kB, resulting in persistent TNFα levels in obesity. Additionally, glucocorticoids and TNFα can cause osteoblast and osteocyte apoptosis in aging bones Raising reactive oxygen species controls skeleton oxidative stress. Glucocorticoids (GCs) and TNFα cause ROS damage to tissues beyond bone. Adipose tissue insulin resistance, vascular endothelial dysfunction, tendon injury, heart failure, and brain development can occur [53,54]. Rheumatoid arthritis, glucocorticoid excess, and aging may reduce bone production due to excess GC and TNFα, which reduce osteoblast genesis, inhibit Wnt signaling, and increase apoptosis via ROS/PKCβ/p66 shc/JNK pathways (Table 1).

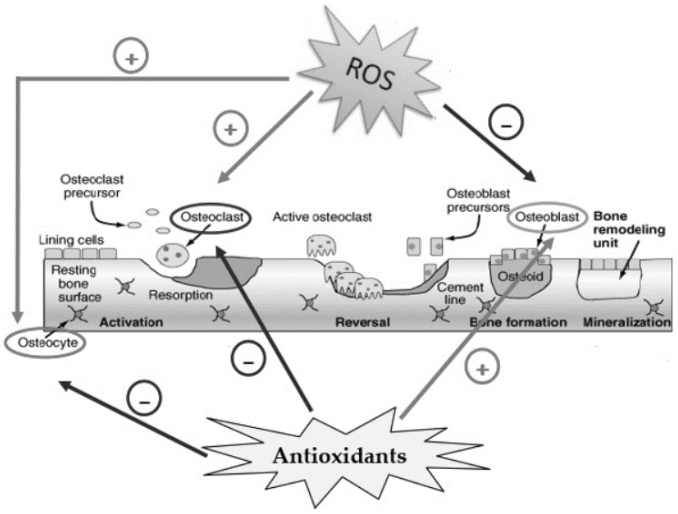

Figure 1: Effect of ROS and antioxidants on bone remodeling by osteoclasts, osteoblasts, and osteocytes. ROS promote osteoclast differentiation and apoptosis (+) while inhibiting osteoblast activity (-), causing bone resorption. Antioxidants enhance bone formation by promoting osteoblast differentiation (+). Domazetovic V, Marcucci G, Iantomasi T, Brandi ML, Vincenzini MT. Oxidative stress in bone remodeling: role of antioxidants. Clin Cases Miner Bone Metab. 2017 May-Aug;14(2):209-216. doi: 10.11138/ccmbm/2017.14.1.209. Epub 2017 Oct 25. PMID: 29263736; PMCID: PMC5726212.

Pathway	Role in Bone Remodeling	Impact of Oxidative Stress
MAPKs	Regulates osteoblast differentiation	Disrupted signaling; decreased activity
NF-κB	Promotes osteoclastogenesis	Overactivation; increased resorption
Wnt/β-catenin	Supports osteoblastogenesis	Inhibition; reduced bone formation

Table 1: Key Signaling Pathways in Oxidative Stress and Bone Remodeling.

Oxidative stress in bone remodeling processes

Redox status affects bone remodeling during continuous repair [55,56]. Osteocytes, osteoblasts, and osteoclasts renew bone throughout life. Cells remodel with hormones, growth factors, and cytokines. Osteocytes signal mechanical load, while osteoclasts replace aged or damaged bone with osteoblasts. This physiological process takes six months. Osteocytes regulate bone remodeling, affecting viability, functionality, mineralization, microdamage, and microfracture repair [57–59]. After remodeling, bone mass and mechanical integrity are protected [60]. Oxidative stress disrupts osteoclast and osteoblast activity, disrupting bone remodeling. This imbalance can cause osteoporosis and metabolic bone diseases. Bone mass and mineral density decrease with osteoporosis, increasing fracture risk. Clinical trials suggest reactive oxygen species and antioxidant systems may cause bone loss [8,61–63]. Oxidative stress increases bone resorption and preosteoclast differentiation [64,65] (Figure 1). H2O2-treated human marrow mononuclear cell cultures had more osteoclasts, activity, and tartrate-resistant acid phosphatase [61]. ROS activate multiple signaling pathways that cause cell proliferation, growth, differentiation arrest, and death [46,57,58,66,67]. JNK, ERK1/2, and p38 MAPK kill osteoblasts and osteocytes. High reactive oxygen species prevent osteoblast differentiation, mineralization, and osteogenesis [11,68,69]. These events reduce bone mass and remodel bone. Antioxidants boost osteoblast activity and osteogenesis and inhibit osteoclast differentiation and activity in osteocytes. Osteocytes and osteoblasts produce most bone remodeling factors that control osteoclast and osteoblast activity. The most important proteins are OPG and RANKL. Oxidative stress upregulates RANKL and downregulates OPG via ERK1/2, JNK, and other transcription factors [56,68,70]. It impacts expression. RANKL enhances osteoclast differentiation and function via preosteoclast receptors, promoting osteoclastogenesis and bone resorption. The Wnt/β-catenin pathway produces OPG, a soluble receptor that binds RANKL to inhibit osteoclast activity. RANKL differentiates and activates osteoclasts, while oxidative stress inhibits osteoblast activation and OPG synthesis. High RANKL/OPG ratios indicate bone resorption and remodeling [71,72]. Balanced bone formation and resorption require RANKL/OPG. Low bone formation and high resorption cause osteoporosis and inflammation-related bone diseases [58,59,72]. Higher ratios increase bone remodeling turnover. Bone formation and remodeling require osteoblast and osteocyte death, but hormones and cytokines regulate RANKL and OPG production. Experiments show that oxidative stress increases osteoblast death and osteoclastogenesis. Few molecular mechanisms are known, but many studies are studying osteocyte regulation. These matrix-embedded cells make up 90% of bone. They communicate with bone cells, blood capillaries, and nerve endings via their central body and dendritic extensions, like neurons. These cells detect mechanos [57,66]. Microdamage, physical and hormonal signals, and estrogen deficiency can cause mature osteocyte apoptosis from oxidative stress [67,73,74]. Bone lining cells released by apoptotic osteocytes allow RANKL to recruit and activate mature osteoclasts. High levels of sclerostin and DKK1 inhibit OPG synthesis and secretion in osteoblasts and osteocytes via the Wnt/β-catenin pathway [57,59,67]. A higher RANKL/OPG ratio increases osteoclast activity, osteoblast apoptosis, and bone resorption. Microfractures disrupt cell-blood vessel connections by breaking dendritic filaments. Remodeling, bone resorption, metabolic changes, oxidative stress, and osteocyte death result from unabsorbed O2, nutrients, hormones, and viability factors [66,67,75–77]. In healthy bone resorption from bone matrix substances, osteoblast precursors become bone-synthesizing cells. Because of excessive oxidative stress, osteoblast apoptosis hinders bone formation and remodeling. This occurs with aging, glucocorticoid treatment, osteoporosis, and other oxidative stress-related bone diseases. Important osteocytes increase OPG, which boosts osteoblast differentiation and mineralization [59,73].

Conclusion

Osteoporosis and age-related bone loss result from oxidative stress disrupting bone remodeling. Oxidative stress activates ROS-mediated signaling pathways, inhibiting osteoblast differentiation and promoting osteoclast activity. New therapeutic approaches have emerged from research on molecular mechanisms like MAPKs, NF-κB, and Wnt/β-catenin signaling pathways. Lifestyle changes, antioxidant therapies, and signaling pathway modulation can slow bone disease progression. More research is needed to understand the complex interactions between oxidative stress and bone cells, especially in aging and chronic inflammation. The findings will help develop precise and effective strategies to counteract oxidative stress's skeleton damage, improving bone fragility and fracture outcomes.

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