Mechanisms of monosodium urate crystal-induced bone destruction in gouty arthritis (Review)

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Abstract. The deformities and disabilities resulting from bone destruction in gouty arthritis impose substantial physical and psychological burdens on patients, underscoring the urgent need to elucidate the mechanisms underlying gout-induced osteolysis. Monosodium urate (MSU) crystals play a central role in the pathogenesis of bone destruction in gouty arthritis, significantly disrupting the activity and function of bone-related cells. Mechanistically, MSU induces bone loss by triggering oxidative stress, amplifying inflammatory cascades, and dysregulating bone remodeling pathways. Understanding these pathological mechanisms is essential for early clinical intervention and the development of targeted therapies to prevent disease progression. The present review systematically examines the multifaceted impact of MSU on bone homeostasis and its molecular interactions in gouty arthritis-associated bone destruction, providing insights to refine diagnostic strategies and advance novel therapeutic approaches.

Contents

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1. Introduction

Prolonged untreated gouty arthritis leads to extensive deposition of serum-free monosodium urate (MSU) crystals in peripheral joints, leading to inflammatory fibrous tissue hyperplasia and tophus formation. Over time, this process causes irreversible damage to the articular cartilage and synovium. In advanced cases, the disease extends into bone tissue, producing joint deformities and gout-related fractures. Current clinical management strategies are insufficient to effectively address gout-associated bone destruction. Conventional non-surgical therapies fail to reverse the pathological progression of tophi (1). Surgery carries risks such as post-operative infection and a high risk of recurrence, and numerous patients require additional operations (2). Therefore, an in-depth exploration of the mechanisms underlying gout-induced bone destruction is imperative.

A defining feature of bone destruction in gouty arthritis is abnormal bone metabolism. MSU crystals impair bone remodeling through direct and indirect mechanisms. Chhana *et al* (3) reported a marked reduction in osteoblast numbers adjacent to tophi in skeletal samples from patients with gout. Dual-energy computed tomography further revealed that MSU crystals drive bone erosion via an 'outside-in' mechanism, as MSU crystals are absent from the bone marrow unless cortical fractures are present (4). Studies have indicated elevated serum levels of receptor activator of NF-κB ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) in patients with severe erosive gout. Serum RANKL concentrations showed a strong correlation with radiographic erosion scores, while M-CSF levels were closely associated with tophus burden (5,6). *In vitro* experiments in which MSU crystals were added to ivory slices for 14 days demonstrated no direct physicochemical erosion of bone by MSU (6). Nevertheless, the pathological processes of gouty arthritis have been shown to clearly lead to severe joint destruction, with MSU crystal-induced imbalance in bone metabolism playing a pivotal role.

2. Direct effects of MSU crystals on bone tissue cells

Clinically, the accumulation of MSU crystals is associated with the severity of cartilage and bone destruction. Patients with severe erosive gout exhibit elevated circulating levels

of RANKL and M-CSF. However, whether MSU crystals directly cause chondrocyte damage or disrupt the balance between osteoblast and osteoclast remains debated. Extensive *in vitro* studies indicate that MSU crystals indirectly inhibit the activity of osteoblasts, osteocytes, and chondrocytes by inducing the production of inflammatory mediators in fibroblast-like synoviocytes, neutrophils, macrophages, and human monocytes. This process promotes osteoclast activation and disrupts the osteoprotegerin (OPG)/RANKL balance (7-11).

Chondrocytes. Under optical microscopy, cartilage adjacent to MSU crystals exhibits a disorganized architecture, compromised hyaline cartilage integrity, surface discontinuities, and altered chondrocyte lacunae. Some researchers have proposed that MSU crystals may induce chondrocyte death by disrupting nutrient supply and enhancing cartilage matrix catabolism, although this hypothesis remains unverified (12). *In vitro*, however, MSU crystals have been demonstrated to directly and rapidly reduce chondrocyte viability in a dose-dependent manner, promote apoptosis, and suppress the mRNA expression of type II collagen, aggrecan, and cytoplasmic proteins. Notably, this inhibitory effect is independent of MSU crystal length. Additionally, type II collagen in the chondrocyte extracellular matrix forms complexes with MSU crystals. These complexes alter the morphology and density of MSU crystals, promote their uptake by macrophage phagocytosis, and amplify the release of pro-inflammatory cytokines. As a result, they enhance the recruitment of neutrophils and macrophages and intensify MSU-driven inflammatory response (12). Furthermore, another *in vitro* study indicated that MSU directly stimulates chondrocytes to upregulate inflammatory mediators associated with the NF-κB signaling pathway. Notably, MSU has been found to enhance the synthesis of hydroxyproline and glycosaminoglycans in chondrocytes, suggesting concurrent cartilage damage and remodeling following MSU exposure (13). A previous study suggested that MSU-induced chondrocyte death occurs primarily through autophagy rather than apoptosis or endoplasmic reticulum stress (14).

Osteoblasts. *In vitro* investigations on osteoblasts have revealed that MSU crystals inhibit osteocyte proliferation and osteoblast activity. This effect is achieved by downregulating the expression of osteogenic transcription factors, such as runt-related transcription factor 2 (Runx2) and transcription factor Sp7 (Sp7), and by inhibiting the synthesis of integrin-binding sialoprotein (Ibsp) and bone bone γ-carboxyglutamic acid-containing protein (Bglap) (3,10,15). Furthermore, MSU has been shown to decrease alkaline phosphatase (ALP) levels, thereby impairing bone matrix formation and mineralization. By disrupting the OPG/RANKL balance, MSU has been demonstrated to exacerbate the dysregulation of bone metabolism, particularly in the presence of immune cells (7,9,16).

Osteoclasts. There is currently no consensus regarding the direct role of MSU in promoting *in vitro* osteoclast differentiation (6,17). Nonetheless, the involvement of neutrophil extracellular traps (NETs), which are composed of neutrophil antimicrobial proteins, was shown to enable MSU to effectively induce osteoclast differentiation. This induction was accompanied by the increased secretion of tartrate-resistant acid phosphatase (TRAP), RANK, and cathepsin K (Ctsk), thereby enhancing the bone resorption capacity of osteoclasts (9,18). Further evidence revealed that MSU significantly promotes osteoclast differentiation in the presence of RANKL and enhances bone resorption through activation of the calcineurin-nuclear factor of activated T-cells, cytoplasmic 1 (NFATc1) and c-Jun N-terminal kinase (JNK) pathways (19).

In vitro experiments have also demonstrated that MSU does not directly affect the expression of bone-related or inflammatory genes in osteocytes; however, these effects can be mediated by monocytes (11). Additionally, MSU has been found to inhibit OPG expression in bone marrow stromal cells (6). Notably, the limited experimental evidence suggests that direct stimulation of synovial mesenchymal stem cells by MSU crystals leads to a marked increase in Runx2 protein expression (20). The effects of MSU crystals on bone-related cells are summarized in Table I.

3. Oxidative stress-driven bone destruction by MSU crystals

During purine metabolism, the formation of MSU is accompanied by redox reactions that lead to excessive production of reactive oxygen species (ROS). Concurrently, MSU activates immune cells to generate ROS, which interferes with bone remodeling by impairing osteogenesis and promoting bone resorption, ultimately resulting in joint destruction (21).

ROS generation. MSU is the primary end product of purine metabolism, whereas ROS are byproducts generated during the catalytic activity of xanthine oxidase (XO) in this pathway. XO facilitates the breakdown of purine nucleotides by oxidizing hypoxanthine to xanthine and subsequently producing uric acid. During this process, oxygen molecules involved in metabolism are reduced to form superoxide anion radicals and hydrogen peroxide (22). When serum uric acid levels reach saturation, urate crystals precipitate in the joints, where they combine with surrounding Na^+ to form MSU. These crystals subsequently deposit within the joints, leading to the formation of gouty tophi. *In vivo*, MSU has been shown to impair nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated antioxidant signaling and enhance ROS production (23). Upon MSU stimulation, inflamed and infiltrating macrophages were shown to release substantial amounts of IL-33, which promotes neutrophil influx into the joints and initiates neutrophil-dependent ROS production during gout attacks (24). López-Reyes *et al* (8) suggested that during gout attacks, in addition to activating the NOD-like receptor thermal protein domain-associated protein 3 (NLRP3) inflammasome in monocytes, MSU crystals also induce the release of significant quantities of ROS, including superoxide anions.

Effects of ROS on bone metabolism. In the pathological process of gouty arthritis, elevated levels of ROS have been found to reduce the osteogenic differentiation potential of bone mesenchymal stem cells (BMSCs) (25), induce apoptosis in osteoblasts, and enhance osteoclast-mediated bone resorption (26,27). However, the effect of ROS on chondrogenic differentiation remains poorly understood. *In vitro* studies have

Table I. Direct intervention effects of MSU on the metabolism of bone-related cells.

Cell Type	Intervention	Results	(Refs.)
HC	MSU	Reduced cell viability, decreased mRNA expression of Type II collagen, cartilage matrix protein-aggregating protein and cytoplasmic proteins	(12)
Rat chondrocytes	MSU	Significant reduction in cell activity, increased expression of IL-1, IL-6, TNF-α, hydroxyproline and glycosaminoglycans	(13)
HC	MSU	Decreased cell viability, elevated expression of autophagy-related protein LC3-II.	(14)
	MSU	Increased expression of IL-6 and IL-8	
HC	MSU-stimulated synovial cell medium	Significant increase in IL-6, IL-8, ROS and RNS expression	(8)
hFOB	MSU-stimulated neutrophil-derived NETs	Reduced cell viability, decreased ALP and OPG expression, increased RANKL expression.	(9)
hFOB	MSU-stimulated neutrophil-derived exosomes	Reduced cell viability, decreased OPG and ALP expression, increased RANKL expression.	(7)
Mouse pre-osteoblasts (MC3T3-E1)	MSU	Reduced cell viability, decreased expression of Runx2, Sp7, Ibsp and Bglap	(3)
Mouse pre-osteoblasts (MC3T3-E1)	MSU-stimulated RAW264.7 cell medium	Normal cell viability, inhibited osteogenic differentiation, suppressed expression of Type I collagen α1 chain, Runx2, Sp7, Bglap, Ibsp and Dmp1, no detectable RANKL expression	(10)
Human osteoblasts	MSU-stimulated THP-1 cell medium	Type I collagen α1 chain and Ibsp expression similar to control, reduced Bglap expression, transient increase in OPG, RANKL first inhibited then elevated, significant increase in IL-1β, IL-6 and PTGS2	
SD rat-derived osteoblasts	MSU	Reduced cell viability, decreased expression of Runx2,Sp7, Ibsp, Bglap and Dmp1	(15)
Human osteosarcoma cells (Saos-2)	MSU	Reduced cell count and activity, decreased ALP expression	(16)
THP-1 cells	MSU-stimulated NETs treated with osteoblast medium	Induced osteoclast differentiation, significant increase in TRAP, RANK and Ctsk expression	(9)
RAW 264.7 cells	MSU	No direct promotion of osteoclast formation, no change in RANKL expression	(6)
Peripheral blood mononuclear cells	MSU	Promoted osteoclast differentiation, increased RANKL mRNA expression, suppressed OPG expression	(17)
Osteoclast precursors	MSU	Increased number of $TRAP^+$ multinucleated cells	(18)
Mouse osteocyte line (MLO-Y4)	MSU	Reduced cell viability, no difference in bone-related or inflammatory gene expression	(11)
RAW264.7 cell medium	MSU-stimulated RAW264.7 cell medium	Normal cell viability, increased the expression of RANKL, decreased OPG expression	
Synovial mesenchymal stem cells	MSU	Significant increased the expression of Runx2, enhanced osteogenic differentiation	(20)
Bone marrow stromal cells (ST2)	MSU	Decreased the expression of OPG	(6)

HC, human chondrocytes; hFOB, human fetal osteoblasts; IL-, interleukin; TNF-α, tumor necrosis factor-α; LC3-II, microtubule-associated protein 1 light chain 3 II; ROS, reactive oxygen species; RNS, reactive nitrogen species; NETs, neutrophil extracellular traps; ALP, alkaline phosphatase; OPG, osteoprotegerin; RANKL, receptor activator of NF-κB ligand; Runx2, runt-related transcription factor 2; Sp7, specificity protein 7; Ibsp, integrin-binding sialoprotein; Bglap, bone γ-carboxyglutamic acid-containing protein; Dmp1, dentin matrix acidic phosphoprotein 1; PTGS2, prostaglandin-endoperoxide synthase 2; TRAP, tartrate-resistant acid phosphatase; Ctsk, cathepsin K.

revealed that hydrogen peroxide (H_2O_2) induces methylation of Kruppel-like factor 5 (KLF5), leading to decreased β-catenin expression and impaired osteogenic differentiation of BMSCs (28). Additionally, H_2O_2 and hydroxyl radicals (OH-) were shown to compete for binding to the transcription factor Nrf2, thereby attenuating WNT/β-catenin signaling. This classical pathway is essential for ALP expression and mineralization, and its inhibition was demonstrated to disrupt the osteogenic differentiation of BMSCs (29).

Additionally, research has shown that ROS can stimulate NFATc1 expression through activation of NF-κB or via calmodulin recruitment mediated by changes in membrane potential. NFATc1, in turn, was revealed to regulate osteoclastogenesis and the expression of bone resorption markers, such as TRAP and Ctsk (30). Experimental evidence indicates that NADPH oxidase 2, a key member of the NADPH oxidase family, activates extracellular signal-regulated kinase 1/2 in osteoclast precursors (31). Moreover, ROS have been reported to upregulate tumor necrosis factor receptor-associated factor 6 (TRAF6), which interacts with RANKL and its receptor (RANK) to promote osteoclastogenesis (32). Inhibition of TRAF6/ROS-dependent activation of the mitogen-activated protein kinase (MAPK) and NF-κB pathways was shown to effectively suppress osteoclast formation (33). Oxidative stress also impaired phosphorylation of phosphatidylinositol 3-kinase (PI3K) and protein kinase B (PKB), thereby disrupting PKB signaling. Zoledronic acid exhibited anti-osteoclastic effects by modulating the ROS-PI3K/PKB signaling pathway (34).

Research indicates a bidirectional relationship between oxidative stress and inflammation: Inflammation can increase ROS production, while ROS, in turn, can amplify inflammatory responses. Experimental evidence revealed that ROS directly activate the NF-κB pathway, promoting the production of pro-inflammatory cytokines (35). By activating the MAPK pathway, ROS was shown to upregulate NF-κB and the NLRP3 inflammasome, thereby enhancing osteoclast-mediated bone resorption *in vitro* (36). Additionally, it has been reported that RANKL acts as an upstream signal that triggers the ROS/MAPK/NF-κB/NLRP axis (37) (Fig. 1).

4. MSU stimulates inflammatory bone destruction

The central mechanism of gout-induced bone destruction involves the interplay between MSU crystals, which trigger inflammatory cascades and bone metabolism. MSU influences bone metabolism through dual-signal activation of the NLRP3 inflammasome, promotion of NET release, and regulation of macrophage polarization (38).

NLRP3 inflammasome and bone metabolism. Research indicates that a key step in gouty arthritis flare-ups is the activation of leukocytes by MSU crystals, which act as a danger signal to initiate inflammatory cascades. As a damage-associated molecular pattern (DAMP), MSU has been shown to activate the innate immune system. Evidence has revealed that activation of the NLRP3 inflammasome in macrophages and monocytes occurs through a dual-signal mechanism. The first signal involves Toll-like receptor (TLR)4, TLR2, and transient receptor potential vanilloid 4 (TRPV4) receptors activating the NF-κB pathway, leading to the synthesis of pro-IL-1β, pro-IL-18, and NLRP3 protein (39). MSU crystals serve as the second signal, inducing NLRP3 oligomerization, recruitment of apoptosis-associated speck-like protein containing a CARD, and activation of caspase-1. This process has been shown to catalyze the cleavage of pro-IL-1β and pro-IL-18 into their mature forms (40). IL-1β and IL-18 then bind to their receptors to trigger downstream signaling cascades, activating pro-inflammatory cytokines and chemokines, and promoting the recruitment of immune cells, including neutrophils and macrophages, to sites of crystal deposition (41).

Research has demonstrated that the NLRP3 inflammasome, a key inflammatory mediator in gouty arthritis, exacerbates bone resorption under conditions of estrogen deficiency or prolonged parathyroid hormone exposure. Notably, NLRP3 deletion has been reported to mitigate bone loss in models with high bone turnover (42). Experimental evidence suggests that the NLRP3 inflammasome impairs osteogenic differentiation by inhibiting deacetylase 1, thereby promoting adipogenesis in BMSCs, a process activated by lipopolysaccharides and palmitic acid (43). Furthermore, studies indicate that the downstream NF-κB and MAPK signaling pathways, activated by the NLRP3 inflammasome and IL-1β, upregulate RANKL and M-CSF production. This cascade has been reported to induce osteoclastogenesis, reduce OPG expression in osteoblasts, and disrupt bone remodeling (44,45). IL-1β, a major inflammatory cytokine, has been shown to facilitate the sustained secretion of matrix-degrading enzymes, contributing to cartilage and bone degradation (46). Mature IL-1β was demonstrated to enhance the expression of RANKL in osteoblasts and BMSCs, promoting osteoclastogenesis (47). It can also act on T cells, B cells, and macrophages to increase RANKL production (48), enhance osteoclastogenesis through insulin-like growth factors and chemokines in non-osteoclast cells (49), and inhibit TGF-β signaling and Runx2 activation, thereby blocking osteogenesis (50). IL-18, a downstream mediator in MSU-induced inflammatory processes, has been reported to play a critical role in stimulating Th17 cells to secrete IL-17, which subsequently upregulates RANKL. IL-18 inhibition was shown to reduce the Th17/Treg ratio *in vitro*, contributing to the restoration of trabecular bone microarchitecture (51). Targeting the NLRP3/caspase-1/IL-1β/IL-18 signaling axis can also ameliorate estrogen deficiency-induced osteoporosis (52). Additionally, a Mendelian randomization analysis using genome-wide data has identified a correlation between IL-18 levels and osteoporosis risk (53).

NETs and bone metabolism. Research has shown that following their recruitment to sites of inflammation, neutrophils release cytokines such as IL-1, IL-6, and TNF-α, along with other mediators, including matrix metalloproteinases (MMPs), prostaglandins, leukotrienes, ROS, and lysosomal enzymes (54). These substances have been reported to further promote the accumulation of mononuclear phagocytes, neutrophils, and other immune cells at inflammatory sites, initiating inflammatory cascades. Additionally, neutrophils can release DNA, histones, and NETs through exocytosis. The formation of large amounts of NETs has been shown to lead to the development of aggregated NETs (aggNETs), which trap and encapsulate MSU crystals, thereby preventing their accumulation and limiting inflammation (55).

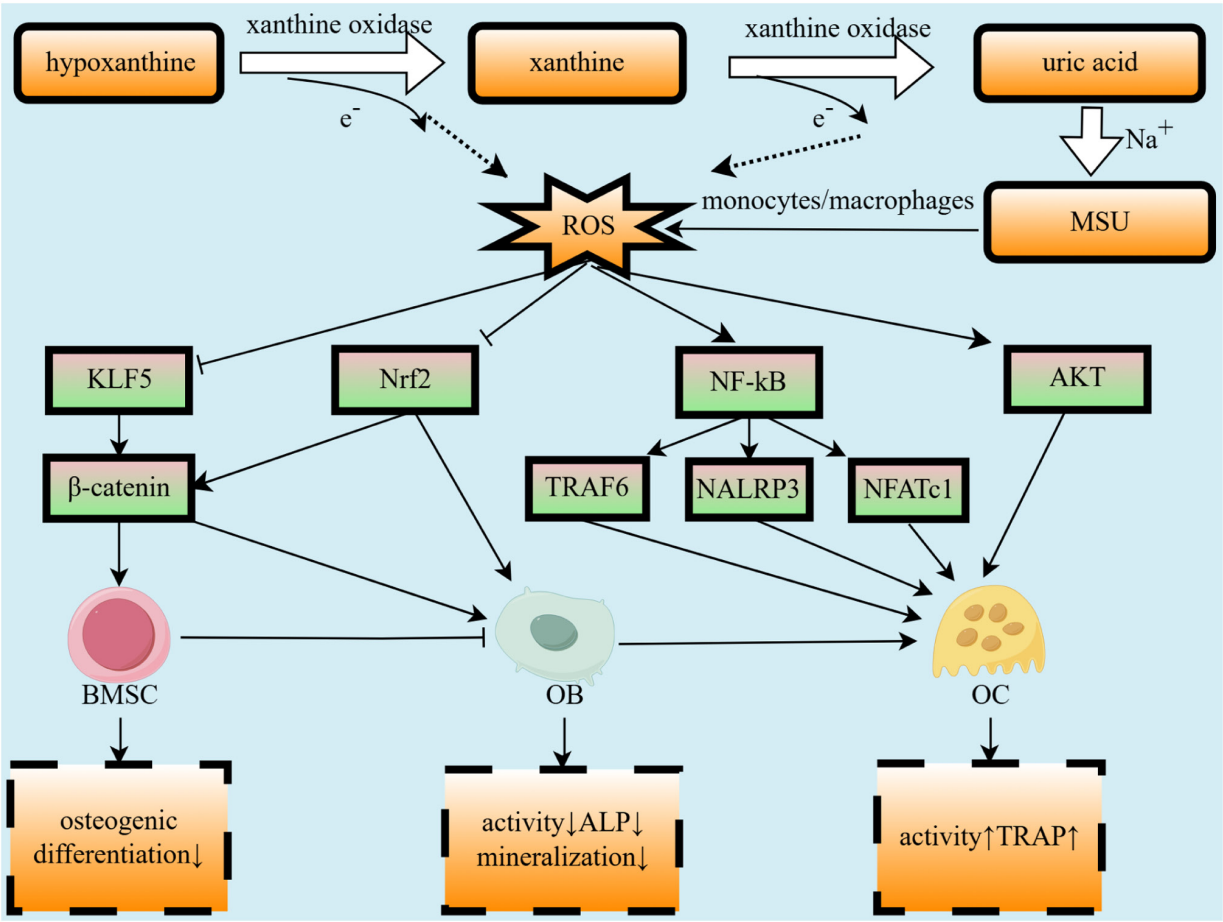

Figure 1. Impact of oxidative stress during MSU formation on bone metabolism. MSU, monosodium urate; ROS, reactive oxygen species; KLF5, Kruppel-like factor 5; Nrf2, nuclear factor erythroid 2-related factor 2; TRAF6, tumor necrosis factor receptor-associated factor 6; NLRP3, NOD-like receptor family, pyrin domain containing 3; NFATc1, nuclear factor of activated T-cells, cytoplasmic 1; BMSC, bone mesenchymal stem cell; OB, osteoblast, OC, osteoclast; ALP, alkaline phosphatase; TRAP, tartrate-resistant acid phosphatase.

Research has shown that NETs are secreted by activated neutrophils to capture and eliminate extracellular pathogens, a process that relies on ROS. However, the structure and function of NETs are nonspecific, with DAMPs serving as the primary triggers for NET formation. Activation of NETs can lead to uncontrolled inflammation. NETs induced by MSU crystals have been found to contribute to the degradation and remodeling of local cartilage and peripheral tissues and play a significant role in bone erosion. NETs have been reported to inhibit the expression of ALP and OPG in chondrocytes while promoting increased expression of RANKL (9). Concurrently, NETs have been shown to reduce osteoblast viability and stimulate RANKL release from osteoblasts, thereby enhancing osteoclast activity and inhibiting OPG formation (9,56). Furthermore, NETs have been reported to facilitate osteoclastogenesis through mechanisms involving the activation of TLR4, histones, and neutrophil elastase, with carbamylated NETs accelerating this process (57). Cytokines such as IL-1β, IL-6, and TNF-α have been demonstrated to directly promote osteoclastogenesis and bone resorption, while also stimulating osteoblasts to produce RANKL and acting synergistically with RANKL (58). IL-6 has been shown to inhibit WNT/β-catenin signaling by upregulating TNF-α in osteoblasts; suppression of IL-6 enhances the osteogenic capacity of BMSCs and increases the expression of Runx2, ALP, osteopontin, and Bglap (59). Notably, low levels of TNF-α were demonstrated to promote osteoblast proliferation, whereas high levels inhibited it (60).

Macrophage polarization and bone metabolism. The interplay between macrophage polarization and bone metabolism has been the focus of extensive research in recent years. Macrophages, a phagocytic subset of leukocytes, are integral to the innate immune system. Their polarization state is considered 'dynamic' rather than 'fixed', allowing rapid shifts between M1 and M2 phenotypes in response to changes in the microenvironment. Research indicates that macrophages in patients with acute gout initially polarize towards the M1 phenotype and subsequently transition to the M2 phenotype in later stages, whereas macrophages in patients with chronic gout predominantly exhibit M2 polarization (61). Nevertheless, an elevated M1/M2 macrophage ratio may represent a critical phenotype contributing to bone destruction in the context of prolonged chronic inflammation, partially contradicting previous findings. In MSU-induced gouty arthritis, research has shown that neutrophils release TNF-α to promote M1 macrophage polarization, and these macrophages in turn produce endogenous TNF-α (62). Furthermore, it has been demonstrated that MSU facilitates M1 polarization through

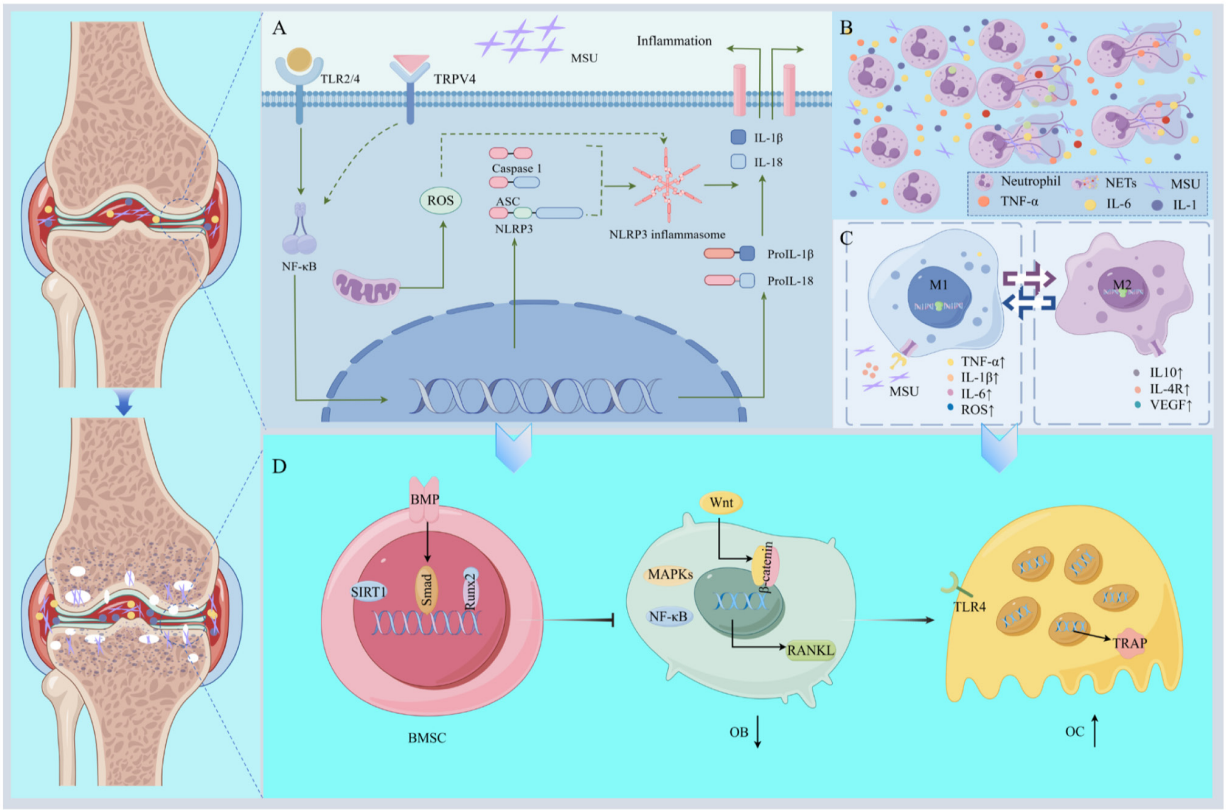

Figure 2. Mechanisms of bone destruction caused by MSU-induced inflammation. (A) MSU-induced activation of the NLRP3 inflammasome. (B) MSU-induced NETosis in neutrophils. (C) MSU-induced macrophage polarization. (D) Inflammatory cytokine-mediated modulation of BMSCs, osteoblasts and osteoclasts in gouty arthritis-associated bone erosion. MSU, monosodium urate; NLRP3, NOD-like receptor thermal protein domain-associated protein 3; BMSCs, bone mesenchymal stem cells; TRL, Toll-like receptor; TRPV4, transient receptor potential vanilloid 4; ASC, apoptosis-associated speck-like protein containing a CARD; ROS, reactive oxygen species; Il-, interleukin; TNF-α, tumor necrosis factor-α; NETs, neutrophil extracellular traps; VEGF, vascular endothelial growth factor; BMPs, bone morphogenic proteins; SIRT1, sirtuin 1; MAPK, mitogen-activated protein kinase; Runx2, runt-related transcription factor 2; RANKL, receptor activator of NF-κB ligand; TRAP, tartrate-resistant acid phosphatase; OB, osteoblasts; OC, osteoclasts.

the miR-449a/NLRP3 axis and the STAT3/NF-κB signaling pathways, thereby disrupting the M1/M2 balance (63). Such an imbalance in M1/M2 ratios may result in bone metabolic disorders. Experimental evidence indicates that activated M1 macrophages produce substantial amounts of pro-inflammatory cytokines and ROS, and can even transfer mitochondria to BMSCs, thereby inhibiting their osteogenic differentiation (64). By contrast, M2 macrophages have been reported to secrete significantly higher levels of bone morphogenetic protein-2 than M0 and M1 macrophages, thereby promoting the osteogenic differentiation of BMSCs (Fig. 2) (65).

5. Other influencing factors (vitamin D and estrogen)

An observational study involving Han Chinese women found a significant correlation between hyperuricemia and reduced vitamin D levels, particularly among patients with chronic kidney disease (66). MSU crystals have been found to suppress 1α-hydroxylase protein and mRNA expression in proximal renal tubular cells, thereby impairing the conversion of 25-hydroxyvitamin D (25(OH)D) to its active form, 1,25-dihydroxyvitamin D (1,25(OH)2D), and ultimately decreasing the levels of 1,25(OH)2D. Treatment with the urate-lowering agent allopurinol has been observed to increase vitamin D levels in affected patients (67). Vitamin D is critical for regulating osteoblast function, extracellular matrix mineralization, and osteoclast differentiation through the induction of RANKL expression in osteoblasts. Notably, physiological doses of 1,25-dihydroxyvitamin D3 have been shown to enhance osteoblast activity and number, whereas supraphysiological doses tend to increase osteoclast activity (68). Consequently, uric acid may influence bone resorption and formation by inhibiting vitamin D activation. Furthermore, the interaction between serum uric acid and vitamin D warrants further investigation (69,70).

Epidemiological studies have revealed that gout is 3-10 times more prevalent in males than in females and is strongly linked to estrogen levels (71). A nationwide Chinese health survey identified significant differences in the prevalence of hyperuricemia and gout between pre- and post-menopausal women (72). Another cross-sectional study found that endogenous estrogen exposure reduces the risk of gout, whereas exogenous hormone exposure increases it (73), likely due to the role of estrogen in promoting renal urate excretion. However, no evidence suggests that uric acid or MSU inversely regulates estrogen. Clinical evidence indicates that combining estrogen-progestogen therapy with antihypertensive treatment in post-menopausal women prevents hyperuricemia (74).

6. Conclusion

Oxidative stress is widely acknowledged as an independent risk factor for osteoporosis. Although MSU exists in ionic

form (Na^+ and urate ions) dissolved in body fluids and exhibits antioxidant properties at low serum uric acid concentration, long-term elevation of serum uric acid causes soluble MSU to promote oxidative stress and precipitate as solid crystals that deposit in joints. Meanwhile, ROS generated during uric acid production plays a pivotal role in local bone destruction associated with gouty arthritis. Notably, the influence of inflammation on bone metabolism varies across diseases. For example, local inflammatory responses during fracture repair facilitate angiogenesis and stimulate the proliferation and differentiation of BMSCs and osteoprogenitor cells (75). In heterotopic ossification, inflammatory mediators such as TNF-α and IL-17 induce aberrant expression of bone morphogenic proteins (76). Clinically, tophi contribute not only to joint erosion but also affect tendons, skin, and even the spinal cord (77-79), likely due to MSU-induced inflammatory infiltration and MMP-mediated matrix degradation (80), underscoring the widespread nature of inflammatory damage triggered by MSU.

MSU crystals significantly disrupt the function of bone-related cells. In chondrocytes, MSU reduces cell viability in a dose-dependent manner, triggers autophagic cell death, and suppresses the production of type II collagen and other cartilage matrix proteins, resulting in structural disorganization. MSU also forms complexes with type II collagen, which enhances macrophage phagocytosis and further amplifies inflammatory responses. In osteoblasts, MSU directly suppresses key transcription factors (Runx2 and Sp7) as well as osteogenic markers such as Ibsp, Bglap, while reducing ALP activity, thereby impairing bone matrix mineralization. Additionally, MSU disrupts the OPG/RANKL balance, indirectly favoring osteoclast differentiation. Although the direct role of MSU in osteoclastogenesis remains controversial, its pro-osteoclastic effects are markedly enhanced in inflammatory microenvironments, such as those involving neutrophil extracellular traps. This is reflected by increased secretion of TRAP and Ctsk, and along with heightened bone resorption mediated through the calcineurin-NFATc1 and JNK signaling pathways.

MSU crystals generate substantial amounts of ROS during purine metabolism and inhibit Nrf2-mediated antioxidant pathways, creating a pro-oxidative milieu. Elevated ROS levels impair BMSC osteogenic differentiation by disrupting WNT/β-catenin signaling (for instance, KLF5 methylation and Nrf2 competitive binding) and activate NF-κB and MAPK pathways to upregulate RANKL expression, thereby further driving osteoclastogenesis. MSU activates the NLRP3 inflammasome through a dual-signal mechanism: TLR/TRPV4-mediated NF-κB signaling initiates the synthesis of pro-inflammatory cytokines (IL-1β and IL-18), while crystal deposition triggers NLRP3 oligomerization, caspase-1 activation, and cytokine maturation. IL-1β and IL-18 exacerbate bone remodeling imbalance by stimulating RANKL production, suppressing TGF-β/Runx2 pathways, and promoting osteoclast activity. NETs encapsulate MSU crystals to form aggNETs, which suppress osteoblast OPG expression and enhance osteoclast function. Macrophage polarization, characterized by an M1/M2 imbalance, further aggravates bone destruction through the release of TNF-α, IL-6, and ROS.

In this review, the mechanisms by which MSU crystals contribute to bone destruction were elucidated, highlighting both their direct effects on bone cell metabolism and indirect pathways involving oxidative stress and inflammatory responses. An overview of the clinical implications of bone damage associated with gouty arthritis was first provided, emphasizing the strong epidemiological and radiological associations between MSU deposition and osteolysis. Experimental evidence that demonstrates the direct inhibitory effects of MSU on bone-related cells *in vitro* was then synthesized. Subsequently, the molecular mechanisms by which oxidative stress and inflammation, arising during MSU formation and metabolism, disrupt bone homeostasis were analyzed, while their interactions with vitamin D and estrogen were also considered. Overall, the mechanisms underlying MSU-induced bone destruction are complex and multifaceted, occasionally exhibiting bidirectional regulatory effects.

With the improvement in living standards and changes in lifestyle habits, the incidence of gouty arthritis is likely to continue rising and remain associated with a high burden of disability. Currently, specific clinical therapies targeting bone destruction are lacking. Consequently, an in-depth understanding of the mechanisms underlying MSU-induced bone destruction is essential. Exploring therapeutic strategies that target ROS, NLRP3, NETs, or macrophage polarization may provide valuable guidance for future clinical drug development.

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Authors' contributions

LH and HuaL conceived and designed the review. LH and HuiL wrote major sections of the manuscript. HX, WS and QY performed literature searches. HuaL provided funding. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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