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REVIEW

Osteoimmunology of Osteoporosis in Rheumatoid Arthritis: Emerging Mechanisms and Therapeutic Implications

Lingcai Chen, Lili Liang

Department of Rheumatology and Immunology, The People's Hospital of Yuhuan (Yuhuan People's Hospital Health Community Group), Yuhuan, 317600, People's Republic of China

Correspondence: Lili Liang, Email lianglili032@163.com

Abstract: Patients with rheumatoid arthritis (RA) exhibit a significantly higher incidence of secondary osteoporosis compared to the general population, leading to substantially increased fracture risk, compromised quality of life, and poorer prognosis. Traditional views attribute this primarily to inflammatory activity, immobilization, and glucocorticoid use. However, the emergence of osteoimmunology has revealed deeper mechanisms, demonstrating that RA-induced osteoporosis represents a classic paradigm of osteoimmune dysregulation. This review systematically synthesizes recent advances (past 5–10 years) in understanding the pathophysiology of RA-induced osteoporosis from an osteoimmunological perspective. Research indicates that within the synovial and bone marrow microenvironments of RA, activated immune cells and stromal cells secrete abundant pro-inflammatory cytokines and express signaling molecules. This process severely disrupts core regulatory pathways of bone remodeling, leading to a profound imbalance characterized by excessive bone resorption and inadequate bone formation. Key mediators of this imbalance include dysregulation of the RANKL/RANK/OPG system and upregulation of potent inhibitors of the bone-forming Wnt pathway. Complex interactions between immune cells and bone cells are critical in establishing a localized bone-destructive microenvironment. Emerging research areas, including gut microbiota dysregulation, epigenetic mechanisms, and neuro-immune interactions, provide novel insights into these mechanisms. This review emphasizes that dysregulation of the osteoimmune system constitutes the core pathophysiological basis of RA-induced osteoporosis. A deeper understanding of these mechanisms is crucial for developing targeted bone-protective therapies and guiding future clinical strategies.

Keywords: rheumatoid arthritis, RA, secondary osteoporosis, osteoimmunology, immune cells, bone metabolism regulation, bone-destructive microenvironment

Introduction

Rheumatoid Arthritis (RA) is a chronic systemic autoimmune disease characterized by persistent synovitis, progressive joint destruction, and systemic inflammation. Affecting approximately 0.5–1% of the global population, it is a leading cause of work disability and functional impairment, imposing a substantial healthcare and economic burden.[1,2] Rheumatoid arthritis imposes a substantial global burden, encompassing not only direct medical costs and significant disability-adjusted life years (DALYs) but also severe bone metabolic complications. Patients with RA frequently face the dual challenge of generalized osteoporosis and localized bony erosion, which represent a major component of this disease burden.[3] Studies demonstrate that RA patients face a 1.5–2.0-fold higher risk of osteoporotic fractures compared to age-matched healthy individuals, with vertebral and hip fractures posing particularly significant risks. These fractures further diminish quality of life and are associated with increased mortality.[4,5] The management of osteoporosis in RA presents particular therapeutic challenges, as bone loss often progresses despite conventional anti-inflammatory treatments. Notably, bone loss occurs early in the disease course, often preceding visible structural joint damage, suggesting a pathology independent of mere mechanical unloading.[6]

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Conventional perspectives attribute secondary OP in RA primarily to three factors: (1) Chronic systemic inflammation accelerating bone resorption; (2) Reduced physical activity and mechanical loading due to joint pain and dysfunction, impairing bone formation; (3) The detrimental impact of long-term glucocorticoid (GC) therapy on bone metabolism.[7] However, accumulating clinical and basic research indicates that while these factors are contributory, they inadequately explain the widespread severity and early onset of bone loss in RA patients.[8] For instance, even in patients achieving effective inflammatory control with biologic agents and avoiding GCs, bone mineral density (BMD) recovery may be delayed or incomplete. Furthermore, the intensity of bone resorption within local erosion sites far exceeds that explainable by reduced mechanical stress alone.[9,10] Current bone-protective therapies, including biologics and anti-resorptive agents like denosumab, primarily target osteoclast-mediated bone resorption but demonstrate limited efficacy in restoring osteoblast function and bone formation capacity. This points to a deeper, immune system-driven disruption of bone homeostasis.

The advent of Osteoimmunology has provided a revolutionary framework for understanding this complex pathology. This review aims to address a critical knowledge gap by systematically integrating recent osteoimmunological insights to provide a comprehensive understanding of the interconnected immune and skeletal dysregulation in RA-induced osteoporosis. This interdisciplinary field focuses on the intricate, dynamic bidirectional regulatory network between the immune and skeletal systems under both physiological and pathological conditions.[11] Under homeostasis, immune cells (eg, lymphocytes, macrophages) and bone cells (osteoclasts, osteoblasts, osteocytes) interact via cytokines, chemokines, and direct contact signals to maintain the delicate balance of bone remodeling.[12] This balance is governed by key signaling pathways that critically regulate the differentiation and activity of bone cells. In the context of chronic inflammatory RA, however, persistent and dysregulated immune activation profoundly disrupts this equilibrium. As will be detailed in subsequent sections, critical pathways such as the RANKL/RANK/OPG axis, which controls osteoclast-driven bone resorption, and the Wnt/β-catenin pathway, which is essential for osteoblast-mediated bone formation, become severely dysregulated In the context of chronic inflammatory RA, however, persistent and dysregulated immune activation profoundly disrupts this equilibrium. Substantial evidence indicates that activated immune cells infiltrating the synovium and bone marrow, along with their secreted inflammatory mediators, not only drive joint inflammation but also directly target bone cells and their precursors. This creates a "destructive bone microenvironment" that promotes osteoclastogenesis while suppressing osteoblast function.[13,14]

Based on this, we propose the central hypothesis of this review: Sustained systemic and local inflammation in RA profoundly disrupts the normal crosstalk within the osteoimmune system between immune cells and bone cells. This dysregulation leads to hyperactive osteoclast-mediated bone resorption and significantly suppressed osteoblast-mediated bone formation, forming the core pathophysiological axis driving the development of secondary OP. This mechanism operates independently of, yet amplifies, the effects of traditional risk factors like GCs and immobility.

This review aims to systematically evaluate recent advances (past 5–10 years) in understanding the pathophysiology of RA-induced OP within the osteoimmunology framework. We will critically examine: (1) The aberrant activation states and bone-destructive effects of key immune cells (T and B lymphocytes, macrophages, neutrophils, synovial fibroblasts) within the RA bone microenvironment; (2) The specific roles of core signaling pathways and molecules (including the RANKL/RANK/OPG axis, pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, IL-17, and Wnt signaling inhibitors like DKK-1 and sclerostin) in mediating excessive osteoclast activation and osteoblast suppression; (3) The contribution of complex interactions (direct contact, paracrine/autocrine signaling) between immune cells and bone cells/MSCs to bone homeostasis imbalance; (4) Novel insights from emerging research areas such as the gut microbiota-bone immune axis, epigenetic dysregulation, neuro-immune modulation, and cellular senescence. Furthermore, we will discuss the translational implications of these findings for developing targeted bone-protective therapies and outline key future research directions. By synthesizing these diverse mechanistic insights, this review seeks to bridge current knowledge gaps and provide a foundation for developing more effective therapeutic strategies that address both the inflammatory and metabolic components of RA-induced bone loss.

Clinical Features and Epidemiology of RA-Associated Osteoporosis

Patients with rheumatoid arthritis (RA) constitute a very high-risk population for osteoporosis and consequent osteoporotic fractures, which presents a significant challenge in clinical management. Large-scale epidemiological studies indicate that the prevalence of generalized osteoporosis, defined by a bone mineral density (BMD) T-score of ≤ -2.5 at

the lumbar spine or hip, ranges from 30% to 50% in RA patients. This prevalence is approximately double that observed in healthy age-matched controls. The risk demonstrates a marked increase with disease duration, effectively tripling in individuals with RA for over ten years.[15,16] The concern is even greater for fracture risk, with RA patients exhibiting hazard ratios between 1.5 and 2.5 for fragility fractures at the hip, spine, and distal radius. The most pronounced increase is observed for hip fracture risk (HR=2.0–3.1). Alarmingly, post-fracture one-year mortality is 15% to 25% higher in RA patients compared to non-RA individuals.[17,18] This risk profile is heterogeneous; while postmenopausal women are most affected, male RA patients also face a significantly elevated osteoporosis risk compared to healthy men (OR=2.2). Furthermore, seropositive patients, particularly those with high-titer anti-cyclic citrullinated peptide (anti-CCP) antibodies, experience more severe bone loss, with lumbar BMD reduction increased by 20% to 30%. These epidemiological findings underscore the profound impact of autoimmunity on bone metabolism dysregulation[19,20] and highlight the critical need for management strategies that address both joint inflammation and bone health to preserve patient quality of life and functional independence.

The bone loss associated with RA manifests a unique dual pathological pattern. The first is generalized osteoporosis, characterized by reduced BMD in both axial (eg, lumbar spine, femoral neck) and peripheral bones. This form correlates positively with systemic inflammation levels, progresses insidiously, and persists throughout the disease course. The second pattern is localized bony erosion, which often becomes evident early in the disease, occurring in approximately 30% of patients within the first year of onset. These erosions typically present as "punched-out" cortical defects at the margins of joints such as the wrists, metacarpophalangeal, and metatarsophalangeal joints, resulting from the direct invasion of subchondral bone by synovial pannus.[21] It is crucial to recognize that these two patterns are mutually reinforcing. Pro-inflammatory cytokines, including TNF-α and IL-17, released from local erosion sites can enter the systemic circulation and accelerate generalized bone resorption. Conversely, the compromised bone microarchitecture, such as trabecular fracture and cortical thinning resulting from systemic osteoporosis, weakens the joint's inherent resistance to local erosive damage, thereby creating a vicious cycle of bone destruction.

The risk of secondary osteoporosis in RA is influenced by multiple interacting factors, with chronic inflammation serving as the central driving force. Disease-related factors include high disease activity, long disease duration reflecting cumulative inflammatory damage, and impaired joint function which suppresses osteogenesis through reduced mechanical loading. Elevated serum markers of inflammation and anti-CCP antibody positivity positively correlate with the rate of bone loss, with the latter capable of directly activating osteoclast precursors.[22] Regarding treatment factors, glucocorticoids exhibit a dose-dependent dual effect. While it is important to note that non-immune factors such as mechanical unloading due to joint pain and hormonal changes contribute to the overall bone loss, the role of inflammation is predominant. This is evidenced by the fact that even in the absence of glucocorticoids, patients with highly active RA experience an annual lumbar BMD loss of 2% to 3%, a rate far exceeding the physiological loss of less than 0.5% in healthy populations.[23,24] Traditional osteoporosis risk factors, including advanced age, menopause, and low body mass index, act as a background, synergistically amplifying the risk when combined with inflammatory damage.

A significant challenge in current clinical diagnosis is that Dual-energy X-ray absorptiometry (DXA)-based BMD assessment may underestimate microstructural damage. This is highlighted by the finding that approximately 30% of RA patients experience vertebral fractures before meeting the formal diagnostic threshold for osteoporosis (T-score > −2.5), indicating that deterioration in bone quality precedes substantial bone loss.[25] Novel technologies like high-resolution peripheral quantitative computed tomography (HR-pQCT) offer solutions by enabling the early detection of microstructural alterations. Combining such imaging with the analysis of bone turnover markers provides a more sensitive reflection of bone metabolic imbalance and enhances fracture risk prediction.[26,27]

Dysregulation of Key Osteoimmune Players in RA-OP

The collapse of osteoimmune homeostasis in RA-induced osteoporosis stems from profound functional disturbances across multiple cell types, as illustrated in Figure 1, establishing a self-perpetuating cycle of hyper-resorption and hypo-formation. Among immune cells, activated T lymphocytes are central drivers of bone destruction. Synovial and bone marrow-infiltrating CD4+ T helper 17 (Th17) cells secrete IL-17A/F and TNF-α, which directly stimulate synovial fibroblasts and osteoblasts to overexpress RANKL and activate osteoclast precursors. Concurrently, the functional

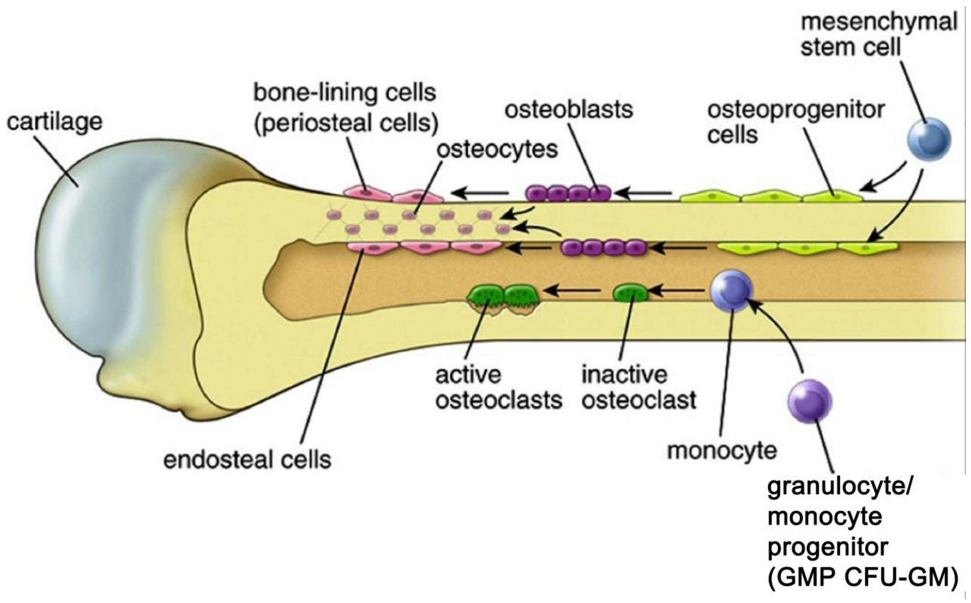

Figure 1 Cellular basis of bone remodeling imbalance in rheumatoid arthritis. This schematic illustrates the differentiation pathways of key cellular components within the bone microenvironment. Mesenchymal stem cells (MSCs) give rise to bone-forming osteoblasts and osteocytes, whereas hematopoietic stem cells differentiate into bone-resorbing osteoclasts. In rheumatoid arthritis (RA), the inflammatory milieu disrupts this dynamic balance, promoting osteoclastogenesis while suppressing osteoblast function, ultimately leading to net bone loss.

impairment of regulatory T cells diminishes their capacity to suppress osteoclast differentiation, thereby exacerbating the RANKL/OPG ratio imbalance.[28,29] Simultaneously, expanded CD8+ cytotoxic T cells at the bone interface induce osteoblast apoptosis via molecules like granzyme B, further compromising bone formation capacity.[30]

B lymphocytes exhibit a bidirectional regulatory failure in this context. Activated B cells not only produce RANKL but also generate pro-resorptive autoantibodies, such as anti-CCP antibodies, which can directly activate osteoclasts via Fcγ receptors. Their secreted immune complexes also stimulate further TNF-α release. In contrast, regulatory B cells produce insufficient amounts of protective factors like osteoprotegerin and IL-10, which destabilizes the bone regulatory network.[31,32]

Macrophages polarized to a pro-inflammatory M1 phenotype within the RA bone microenvironment exacerbate bone loss through several mechanisms. They serve as osteoclast precursors for direct differentiation into mature bone-resorbing cells, secrete abundant pro-osteolytic cytokines such as TNF-α, IL-1β, and IL-6, and overexpress matrix metalloproteinase-9, which degrades the bone matrix.[33] Neutrophils contribute uniquely through the release of neutrophil extracellular traps. Components of these traps, including citrullinated histones and the LL-37 peptide, activate Toll-like receptor signaling, promoting IL-1β release and directly stimulating osteoclast differentiation, thereby tightly coupling innate autoimmunity with bone resorption.[34]

The key bone-forming effectors, mesenchymal stromal cells and osteoblasts, suffer profound suppression within the inflammatory milieu. The osteogenic differentiation potential of bone marrow MSCs is blocked by TNF-α and IL-1β via NF-κB-mediated inhibition of key transcription factors like Runx2 and Osterix. Their immunomodulatory functions are also significantly impaired. Furthermore, inflammation-induced DNA damage promotes premature senescence in MSCs, leading to the secretion of a senescence-associated secretory phenotype, which further disrupts the microenvironment.[35–37] Mature osteoblasts face a dual insult of functional suppression, evidenced by the downregulation of osteogenic genes, and increased apoptosis, with cell mortality elevated by 40% to 60% via pathways such as Fas/FasL.[38]

Synovial fibroblasts act as pivotal "central executors" of bone destruction in RA. These cells express membrane-bound RANKL at levels 20 to 50 times higher than normal, efficiently activating osteoclasts via direct contact. They also hypersecrete the Wnt signaling inhibitors DKK-1 and sclerostin, potently inhibiting the osteoblast Wnt/β-catenin pathway. Additionally, by releasing chemokines, synovial fibroblasts continuously recruit immune cells to the bone interface, perpetuating the inflammatory cycle.[39–41]

Under excessive RANKL stimulation and CSF-1 synergy, osteoclast differentiation efficiency increases two to threefold, with upregulated integrin αvβ3 enhancing bone adhesion. Inflammatory cytokines activate pathways such as Akt/NF-κB, which inhibit caspase-3 and extend osteoclast lifespan by over 30%.[42,43] Finally, embedded osteocytes within the bone matrix also become dysfunctional. Stimulation by TNF-α and IL-1β increases their expression of SOST/sclerostin, strongly inhibiting osteogenesis. Accumulated microdamage promotes osteocyte apoptosis, releasing damage-associated molecular patterns like high-mobility group box 1 that further amplify local immune responses.[44,45]

Core Pathophysiological Mechanisms and Signaling Pathways

The severe imbalance in the RANKL/RANK/OPG signaling axis constitutes the central hub for pathological bone resorption activation in RA-induced osteoporosis. Activated T and B lymphocytes, synovial fibroblasts, and synovial macrophages are the three primary cellular sources of RANKL. Synovial fibroblasts function as "RANKL factories," expressing exceptionally high levels of membrane-bound RANKL that efficiently activate osteoclast precursors via direct contact. Th17 cells contribute by secreting soluble RANKL and potently inducing RANKL expression in synovial fibroblasts. B cells can upregulate RANKL expression via Fc receptor γ-chain signaling triggered by autoantibodies.[46,47] Concurrently, osteoprotegerin is relatively or absolutely deficient, as TNF-α and IL-1β suppress its transcription via NF-κB, and RANKL-OPG complex formation further depletes the available OPG.[48] Consequently, the serum and synovial fluid RANKL/OPG ratio in RA patients is significantly elevated, strongly correlating with bone erosion scores and BMD loss. A serum RANKL/OPG ratio greater than 2.5 has been identified as an independent predictor of vertebral fracture within two years.[49,50] The dysregulation of these core pathways and the effects of targeted interventions are summarized in Table 1.

The pro-inflammatory cytokine network profoundly amplifies this osteoimmune imbalance. TNF-α directly binds to receptors on osteoclast precursors, activating the NFATc1 pathway, and induces high RANKL and MMP expression in synovial fibroblasts while inhibiting osteoblast differentiation. IL-1β acts synergistically with RANKL, dramatically lowering the osteoclast differentiation threshold, and inhibits collagen synthesis. IL-6 promotes osteoclastogenesis via its unique trans-signaling pathway and may simultaneously induce hepcidin-mediated ferroptosis in osteoblasts. IL-17A potently stimulates RANKL expression in stromal cells and suppresses osteoblast differentiation.[55–59,62,63] However, the literature presents some contradictory findings regarding therapeutic efficacy, as not all clinical studies demonstrate consistent BMD gains with biologic therapies. This heterogeneity may reflect variations in patient populations, disease endotypes, or treatment response biomarkers, highlighting an area requiring further investigation. Other cytokines, including IL-8, IL-23, and IL-34, contribute to a synergistic destructive network.[64]

Suppression of the Wnt/β-catenin pathway is a key mechanism underlying failed bone formation. Synovial fibroblasts, osteocytes, and M1 macrophages overexpress the inhibitors DKK-1 and sclerostin. These inhibitors bind to LRP5/6 and LRP4 co-receptors, respectively, blocking Wnt ligand interactions, promoting β-catenin degradation, and inactivating key osteogenic transcription factors.[52,65] Targeted intervention studies in animal models and clinical trials confirm the potential of inhibiting these pathways to promote bone formation.[53,54]

Table 1 Dysregulation of Core Signaling Pathways in RA-OP and Effects of Targeted Interventions

Signaling Pathway	Key Dysregulated Molecules	Pathological Effects	Therapeutic Intervention	References
RANKL/RANK/OPG	RANKL↑, OPG↓	Increased osteoclast activation and bone resorption	Denosumab: ~90% reduction in new bone erosions	[49–51]
Wnt/β-catenin	DKK-1↑, Sclerostin↑	Impaired osteoblast differentiation and bone formation	Romosozumab: +9.2% lumbar spine BMD	[52–54]
Pro-inflammatory Cytokines	TNF-α, IL-6, IL-17↑	Exacerbated bone destruction and osteoblast ferroptosis	Tocilizumab: +2.1% hip BMD per year	[55–59]
Cell–Cell Contact	Membrane-bound RANKL, LFA-1	10-fold increase in osteoclast efficiency and focal bone erosion	Abatacept: Delays progression of bone erosion	[60,61]

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Direct cellular contact and overall microenvironment deterioration further amplify bone destruction. T cells activate osteoclast precursors via membrane-bound RANKL with significantly higher efficiency than soluble RANKL. Th17 cells adhere to synovial fibroblasts via adhesion molecules, forming "immunological synapses" that induce a burst-like RANKL expression.[60,61] Critically, the establishment of an "inflammatory bone marrow" microenvironment is pivotal, characterized by the abnormal accumulation of immune cells, local cytokine concentrations reaching 10 to 20 times serum levels, and hypoxic stress that induces pro-osteoclastic factors, transforming the marrow into a pathological hub for bone destruction.[66,67]

Current Therapeutic Bone Effects and Future Strategies

The intra-articular immune interaction network in RA, depicted in Figure 2, drives bone destruction and presents multiple therapeutic targets. TNF-α inhibitors suppress RANKL expression and osteoclast activation, typically leading to a modest annual increase in lumbar spine BMD and significantly slowed erosion progression. IL-6 receptor antagonists, by blocking IL-6 trans-signaling, show more pronounced effects on hip BMD and reduce vertebral fracture risk. Anti-RANKL therapy, such as denosumab, directly neutralizes RANKL activity, achieving substantial BMD gains and a pronounced reduction in new bone erosions when combined with conventional DMARDs. In contrast, glucocorticoids at sustained higher doses suppress the Wnt pathway and induce osteoblast apoptosis, causing significant bone loss.[51] A comparative analysis of these therapeutics is provided in Table 2. A critical limitation of current biologics is that while

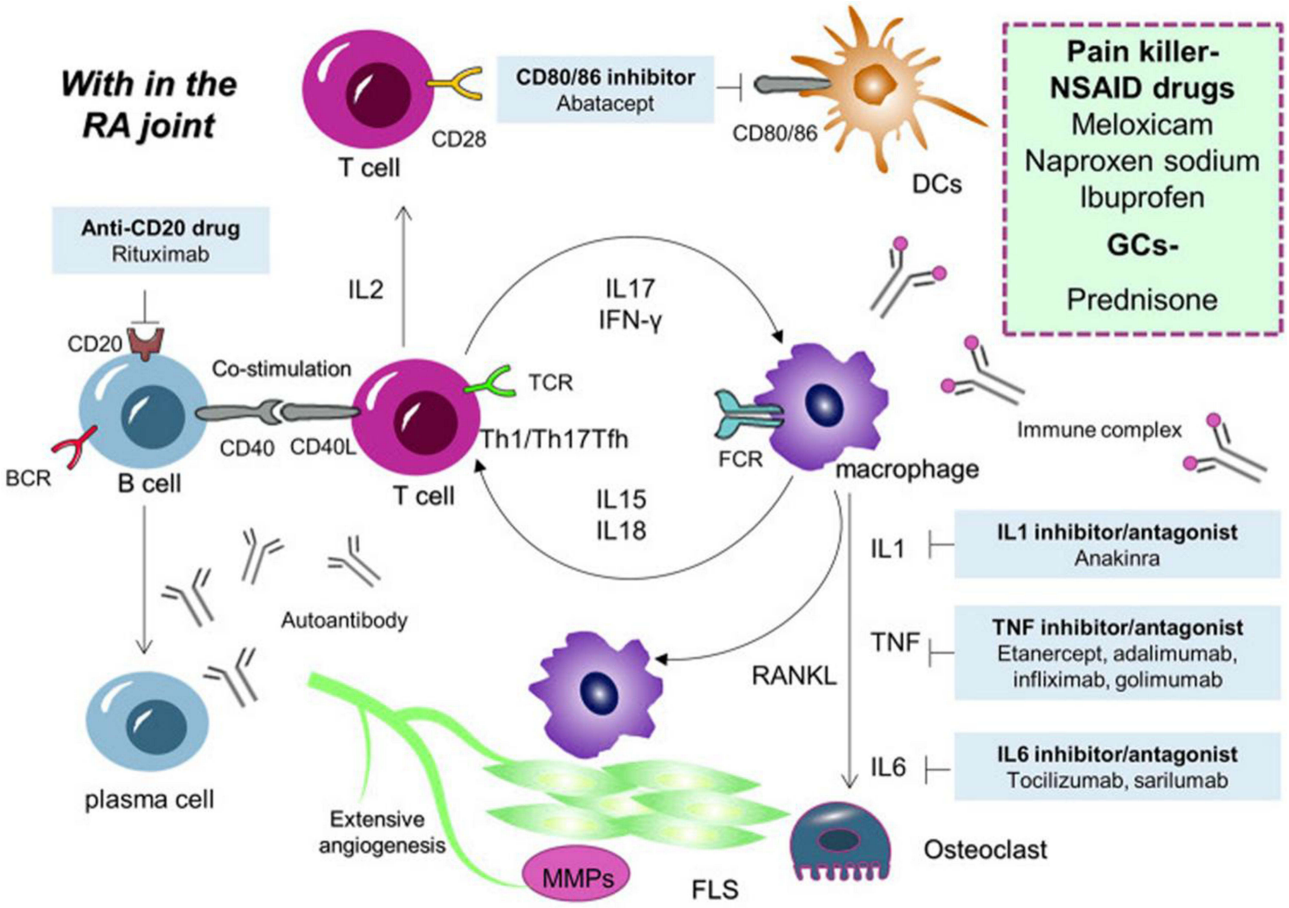

Figure 2 Osteoimmunological network and therapeutic targets in RA-associated bone loss. The diagram depicts the key immunopathogenic interactions within the RA-affected joint. Activation of B and T lymphocytes triggers a pro-inflammatory cytokine cascade (eg, TNF-α, IL-6, IL-1) that promotes osteoclast differentiation and activity, leading to bone erosion. Key therapeutic targets are highlighted in green boxes, including B-cell depletion (anti-CD20), co-stimulation blockade (CTLA4-Ig), and cytokine inhibition (TNF and IL-6R antagonists).

Table 2 Comparative Bone-Protective Effects of Current RA-OP Therapeutics

Therapy Class	Annual Lumbar BMD Change	Erosion Suppression Rate	Core Mechanism	Limitations
TNF-α Inhibitors	+0.5% to +1.5%	~70%	Inhibit RANKL, reduce osteoclast activity	Inadequate restoration of bone formation (PINP returns to baseline)
IL-6R Antagonists	+1.5% to +2.5%*	>80%	Block IL-6 trans-signaling, reverse ferroptosis	Slightly elevated infection risk
Anti-RANKL (Denosumab)	+6% to +10%	~90%	Direct neutralization of RANKL	Requires long-term subcutaneous administration
Anti-Sclerostin	+9.2% (clinical trials)	Data pending	Activates Wnt signaling to promote bone formation	Potential cardiovascular risks warrant monitoring

Note: *Hip BMD gains tend to be more pronounced; data sourced from.[51,68,69].

they effectively suppress bone resorption, they demonstrate a restricted capacity to fully restore bone formation, underscoring the unmet need for anabolic or dual-action therapies.

To address these limitations, novel therapeutic strategies targeting osteoimmune imbalance are under active development. These include agents aimed at promoting bone formation pathways, such as antibodies against DKK-1 and sclerostin, which have shown promise in early-phase trials and preclinical models.[68] Other strategies involve targeting novel mechanisms like gut microbiota modulation, epigenetic reprogramming, and neuro-immune pathways.[69,70] It is essential to maintain a balanced perspective regarding these emerging avenues. Many, particularly those involving the gut-bone axis and neuro-immunology, are primarily supported by preclinical evidence. Their translation faces challenges, including the complexity of human microbiome composition and the potential for off-target effects with systemic epigenetic modifiers, necessitating rigorous clinical validation.

One of the most promising approaches is combination therapy, particularly "dual pathway blockade" that simultaneously inhibits resorption and promotes formation, which has markedly improved bone strength in preclinical models.[71] These evolving mechanistic insights are beginning to inform clinical practice. Guidelines increasingly recommend routine osteoporosis screening in RA patients and consideration of bone-protective agents in high-risk individuals. Future precision medicine approaches may leverage biomarkers of osteoimmune dysregulation to tailor therapies more effectively.

Future research must prioritize several key directions. Mechanistic elucidation should leverage single-cell and spatial transcriptomics to map the intricate cellular crosstalk within the RA bone microenvironment. Overcoming translational barriers requires the development of bone-targeted drug delivery systems and the establishment of biomarker panels for precision medicine. Finally, clinical practice innovation should focus on prospectively validating treat-to-target strategies for osteoporosis in RA and exploring the potential of novel interventions like neuromodulation.

Conclusion

In summary, osteoporosis secondary to rheumatoid arthritis (RA) represents a quintessential disorder of osteoimmune dysregulation, demanding integrated therapeutic strategies that extend beyond conventional anti-inflammatory approaches. The pathophysiological basis of this condition centers on a severe imbalance in bone remodeling, driven by immune-mediated activation of osteoclasts through the RANKL/RANK/OPG axis and pro-inflammatory cytokines, coupled with a parallel suppression of osteoblast function via inhibition of the Wnt/β-catenin pathway. The clinical significance of these mechanisms is profound, as they underpin the high fracture risk and associated morbidity that severely impact patient quality of life.

Emerging insights into novel pathways—including gut microbiota dysbiosis, epigenetic reprogramming, and neuro-immune interactions—further illuminate the complexity of this network. Among these, the potential for targeting the gut-bone axis and employing combination therapies that simultaneously inhibit resorption and stimulate formation appears

particularly promising for achieving superior fracture prevention. Future research must leverage multi-omics technologies and interdisciplinary collaboration to fully dissect these intricate interactions.

Ultimately, the translation of these osteoimmunological insights into clinical practice is paramount. This entails the development of precise, bone-targeted therapies and the validation of treat-to-target strategies for bone health in RA. The overarching goal must be to shift the therapeutic paradigm from merely controlling inflammation to actively rebuilding bone health, thereby directly improving long-term patient outcomes and reducing the debilitating burden of fractures.

Disclosure

The authors declare no competing interests.

References

1. Hu L, Liu R, Zhang L. Advance in bone destruction participated by JAK/STAT in rheumatoid arthritis and therapeutic effect of JAK/STAT inhibitors. *Int Immunopharmacol*. 2022;111:109095. doi:10.1016/j.intimp.2022.109095
2. Fu H, Guo Y, Fang W, Wang J, Hu P, Shi J. Anti-acidification and immune regulation by nano-ceria-loaded Mg-Al layered double hydroxide for rheumatoid arthritis therapy. *Adv Sci*. 2024;11(6):e2307094. doi:10.1002/advs.202307094
3. Jurczak A, Delay L, Barbier J, et al. Antibody-induced pain-like behavior and bone erosion: links to subclinical inflammation, osteoclast activity, and acid-sensing ion channel 3-dependent sensitization. *Pain*. 2022;163(8):1542–1559. doi:10.1097/j.pain.0000000000002543
4. O'Neil LJ, Oliveira CB, Sandoval-Heglund D, et al. Anti-Carbamylated LL37 antibodies promote pathogenic bone resorption in rheumatoid arthritis. *Front Immunol*. 2021;12:715997. doi:10.3389/fimmu.2021.715997
5. Agemura T, Hasegawa T, Yari S, Kikuta J, Ishii M. Arthritis-associated osteoclastogenic macrophages (AtoMs) participate in pathological bone erosion in rheumatoid arthritis. *Immunol Med*. 2022;45(1):22–26. doi:10.1080/25785826.2021.1944547
6. Sun Y, Hong L, Gao C. The association among 14-3-3η protein, inflammation, bone remodeling and osteoporosis in patients with rheumatoid arthritis. *Pak J Med Sci*. 2020;36(5):872–876. doi:10.12669/pjms.36.5.2403
7. Zhu S, Zhou J, Xie Z. The balance between helper T 17 and regulatory T cells in osteoimmunology and relevant research progress on bone tissue engineering. *Immun Inflamm Dis*. 2024;12(9):e70011. doi:10.1002/iid3.70011
8. Gravallese EM. Bone destruction in arthritis. *Ann Rheumatic Dis*. 2002;61(Suppl 2):ii84–6. doi:10.1136/ard.61.suppl_2.ii84
9. Orsini F, Crotti C, Cincinelli G, et al. Bone involvement in rheumatoid arthritis and spondyloartritis: an updated review. *Biology*. 2023;12(10):1320. doi:10.3390/biology12101320
10. Fardellone P, Salawati E, Le Monnier L, Goëb V. Bone loss, osteoporosis, and fractures in patients with rheumatoid arthritis: a review. *J Clin Med*. 2020;9(10):3361. doi:10.3390/jcm9103361
11. Messina OD, Vidal M, Adami G, et al. Chronic arthritides and bone structure: focus on rheumatoid arthritis-an update. *Aging Clin Exp Res*. 2023;35(7):1405–1416. doi:10.1007/s40520-023-02432-9
12. Tanaka Y. Clinical immunity in bone and joints. *J Bone Miner Metab*. 2019;37(1):2–8. doi:10.1007/s00774-018-0965-5
13. Okamoto K. Crosstalk between bone and the immune system. *J Bone Miner Metab*. 2024;42(4):470–480. doi:10.1007/s00774-024-01539-x
14. Zhou A, Wu B, Yu H, et al. Current understanding of osteoimmunology in certain osteoimmune diseases. *Front Cell Develop Biol*. 2021;9:698068. doi:10.3389/fcell.2021.698068
15. Jung SM, Kim KW, Yang CW, Park SH, Ju JH. Cytokine-mediated bone destruction in rheumatoid arthritis. *J Immunol Res*. 2014;2014:263625. doi:10.1155/2014/263625
16. Oh KK, Adnan M, Cho DH. Drug investigation to dampen the comorbidity of rheumatoid arthritis and osteoporosis via molecular docking test. *Curr Issues Mol Biol*. 2022;44(3):1046–1061. doi:10.3390/cimb44030069
17. Xu H, Cai L, Li Z, et al. Dual effect of IL-7/IL-7R signalling on the osteoimmunological system: a potential therapeutic target for rheumatoid arthritis. *Immunology*. 2021;164(1):161–172. doi:10.1111/imm.13351
18. Charoenphandhu N, Chanpaisaeng K, Teerapornpuntakit J, Wongdee K. Editorial: crosstalk between bone and other cells. *Front Physiol*. 2023;14:1209053. doi:10.3389/fphys.2023.1209053
19. Okamoto K, Takayanagi H. Effect of T cells on bone. *Bone*. 2023;168:116675. doi:10.1016/j.bone.2023.116675
20. Chen TL, Chang KH, Su KY. Effects of biological/targeted therapies on bone mineral density in inflammatory arthritis. *Int J Mol Sci*. 2022;23(8):4111. doi:10.3390/ijms23084111
21. Zhao Z, Du Y, Yan K, Zhang L, Guo Q. Exercise and osteoimmunology in bone remodeling. *FASEB J*. 2024;38(7):e23554. doi:10.1096/fj.202301508RRR
22. Pascual-García S, Martínez-Peinado P, Pujalte-Satorre C, et al. Exosomal osteoclast-derived miRNA in rheumatoid arthritis: from their pathogenesis in bone erosion to new therapeutic approaches. *Int J Mol Sci*. 2024;25(3):1506. doi:10.3390/ijms25031506
23. Triguero-Martínez A, Pardines M, Montes N, et al. Genetic variants in RANK and OPG could influence disease severity and bone remodeling in patients with early arthritis. *Life*. 2024;14(9):1109. doi:10.3390/life14091109
24. Hong J, Luo F, Du X, Xian F, Li X. The immune cells in modulating osteoclast formation and bone metabolism. *Int Immunopharmacol*. 2024;133:112151. doi:10.1016/j.intimp.2024.112151
25. Komatsu N, Takayanagi H. Immune-bone interplay in the structural damage in rheumatoid arthritis. *Clin Exp Immunol*. 2018;194(1):1–8. doi:10.1111/cei.13188
26. Ahmad SS, Ahmed F, Ali R, et al. Immunology of osteoporosis: relevance of inflammatory targets for the development of novel interventions. *Immunotherapy*. 2022;14(10):815–831. doi:10.2217/imt-2021-0282
27. Maeda K, Yoshida K, Nishizawa T, et al. Inflammation and bone metabolism in rheumatoid arthritis: molecular mechanisms of joint destruction and pharmacological treatments. *Int J Mol Sci*. 2022;23(5):2871. doi:10.3390/ijms23052871

28. Chen Z, Cheng Z, Tang Z, et al. Interleukin-13 reduces bone erosion in rheumatoid arthritis by up-regulating osteoprotegerin expression in fibroblast-like synoviocytes: an in vitro and in vivo study. *Clin Exp Rheumatol*. 2023;41(11):2151–2161. doi:10.55563/clinexprheumatol/b96n1e
29. Gupta N, Kanwar N, Arora A, Khatri K, Kanwal A. The interplay of rheumatoid arthritis and osteoporosis: exploring the pathogenesis and pharmacological approaches. *Clin Rheumatol*. 2024;43(5):1421–1433. doi:10.1007/s10067-024-06932-5
30. He J, Chu Y, Li J, et al. Intestinal butyrate-metabolizing species contribute to autoantibody production and bone erosion in rheumatoid arthritis. *Sci Adv*. 2022;8(6):eabm1511. doi:10.1126/sciadv.abm1511
31. Little-Letsinger SE, Hamilton SE. Leveraging mice with diverse microbial exposures for advances in osteoimmunology. *Front Endocrinol*. 2023;14:1168552. doi:10.3389/fendo.2023.1168552
32. Su Y, Han Y, Choi HS, et al. Lipid mediators obtained from docosahexaenoic acid by soybean lipoxygenase attenuate RANKL-induced osteoclast differentiation and rheumatoid arthritis. *Biomed Pharmacother*. 2024;171:116153. doi:10.1016/j.biopha.2024.116153
33. Sapkota M, Gao M, Li L, et al. Macrolactin A protects against LPS-induced bone loss by regulation of bone remodeling. *Eur J Pharmacol*. 2020;883:173305. doi:10.1016/j.ejphar.2020.173305
34. Weivoda MM, Bradley EW. Macrophages and bone remodeling. *J Bone Miner Res*. 2023;38(3):359–369. doi:10.1002/jbmr.4773
35. Tanaka Y. Managing osteoporosis and joint damage in patients with rheumatoid arthritis: an overview. *J Clin Med*. 2021;10(6):1241. doi:10.3390/jcm10061241
36. Liu T, Zhou X, Huang C, et al. [Mechanism of Qingluo Tongbi Formula for regulating immune-bone erosion in rheumatoid arthritis]. *Nan fang yi ke da xue xue bao*. 2023;43(10):1706–1714. Sesotho. doi:10.12122/j.issn.1673-4254.2023.10.08
37. Komatsu N, Takayanagi H. Mechanisms of joint destruction in rheumatoid arthritis - immune cell-fibroblast-bone interactions. *Nat Rev Rheumatol*. 2022;18(7):415–429. doi:10.1038/s41584-022-00793-5
38. Pietschmann P, Butylina M, Kerschan-Schindl K, Sipos W. Mechanisms of systemic osteoporosis in rheumatoid arthritis. *Int J Mol Sci*. 2022;23(15):8740. doi:10.3390/ijms23158740
39. Doghish AS, Ismail A, El-Mahdy HA, et al. miRNAs insights into rheumatoid arthritis: favorable and detrimental aspects of key performers. *Life Sci*. 2023;314:121321. doi:10.1016/j.lfs.2022.121321
40. Schwendich E, Salinas Tejedor L, Schmitz G, et al. Modulation of dopamine receptors on osteoblasts as a possible therapeutic strategy for inducing bone formation in arthritis. *Cells*. 2022;11(10):1609. doi:10.3390/cells11101609
41. Matsuda K, Shiba N, Hiraoka K. New insights into the role of synovial fibroblasts leading to joint destruction in rheumatoid arthritis. *Int J Mol Sci*. 2023;24(6):5173. doi:10.3390/ijms24065173
42. Guo Y, Jiang S, Li H, et al. Obesity induces osteoimmunology imbalance: molecular mechanisms and clinical implications. *Biomed Pharmacother*. 2024;177:117139. doi:10.1016/j.biopha.2024.117139
43. Berardi S, Corrado A, Maruotti N, Cici D, Cantatore FP. Osteoblast role in the pathogenesis of rheumatoid arthritis. *Mol Biol Rep*. 2021;48(3):2843–2852. doi:10.1007/s11033-021-06288-y
44. Hu N, Wang J, Ju B, et al. Osteoimmunology research in rheumatoid arthritis: from single-cell omics approach. *Chin Med J*. 2023;136(14):1642–1652. doi:10.1097/cm9.0000000000002678
45. Huang F, Wong P, Li J, et al. Osteoimmunology: the correlation between osteoclasts and the Th17/Treg balance in osteoporosis. *J Cell Mol Med*. 2022;26(13):3591–3597. doi:10.1111/jcmm.17399
46. Yang M, Zhu L. Osteoimmunology: the CROSSTALK between T cells, B cells, and osteoclasts in rheumatoid arthritis. *Int J Mol Sci*. 2024;25(5):2688. doi:10.3390/ijms25052688
47. Srivastava RK, Sapra L, Mishra PK. Osteometabolism: metabolic alterations in bone pathologies. *Cells*. 2022;11(23):3943. doi:10.3390/cells11233943
48. Llorente I, García-Castañeda N, Valero C, González-álvaro I, Castañeda S. Osteoporosis in rheumatoid arthritis: dangerous liaisons. *Front Med*. 2020;7:601618. doi:10.3389/fmed.2020.601618
49. Li S, Liu G, Hu S. Osteoporosis: interferon-gamma-mediated bone remodeling in osteoimmunology. *Front Immunol*. 2024;15:1396122. doi:10.3389/fimmu.2024.1396122
50. Hasegawa T, Ishii M. Pathological osteoclasts and precursor macrophages in inflammatory arthritis. *Front Immunol*. 2022;13:867368. doi:10.3389/fimmu.2022.867368
51. Bruno D, Fedele AL, Tolusso B, et al. Systemic bone density at disease onset is associated with joint erosion progression in early naive to treatment rheumatoid arthritis: a prospective 12-month follow-up open-label study. *Front Med*. 2021;8:613889. doi:10.3389/fmed.2021.613889
52. Andreev D, Kachler K, Schett G, Bozec A. Rheumatoid arthritis and osteoimmunology: the adverse impact of a deregulated immune system on bone metabolism. *Bone*. 2022;162:116468. doi:10.1016/j.bone.2022.116468
53. Auréal M, Machuca-Gayet I, Coury F. Rheumatoid Arthritis in the View of Osteoimmunology. *Biomolecules*. 2020;11(1):48. doi:10.3390/biom11010048
54. Stefania S, Rotondo C, Mele A, Trotta A, Cantatore FP, Corrado A. Role of denosumab in bone erosions in rheumatoid arthritis. *Postgrad Med J*. 2023;99(1175):976–984. doi:10.1093/postmj/qgad013
55. D'Onofrio B, Di Lernia M, De Stefano L, Bugatti S, Montecucco C, Bogliolo L. Personalized therapeutic strategies in the management of osteoporosis in patients with autoantibody-positive rheumatoid arthritis. *J Clin Med*. 2022;11(9):2341. doi:10.3390/jcm11092341
56. Yadav AM, Bagade MM, Ghumnani S, et al. The phytochemical plumbagin reciprocally modulates osteoblasts and osteoclasts. *Biol Chem*. 2022;403(2):211–229. doi:10.1515/hsz-2021-0290
57. Kim Y, Kim GT. Positive effects of biologics on osteoporosis in rheumatoid arthritis. *J Rheum Dis*. 2023;30(1):3–17. doi:10.4078/jrd.22.0046
58. Lee WS, Kato M, Sugawara E, et al. Protective role of optineurin against joint destruction in rheumatoid arthritis synovial fibroblasts. *Arthritis Rheumatol*. 2020;72(9):1493–1504. doi:10.1002/art.41290
59. Tanaka S, Tanaka Y. RANKL as a therapeutic target of rheumatoid arthritis. *J Bone Miner Metab*. 2021;39(1):106–112. doi:10.1007/s00774-020-01159-1
60. Doi K, Murata K, Ito S, et al. Role of lysine-specific demethylase 1 in metabolically integrating osteoclast differentiation and inflammatory bone resorption through hypoxia-inducible factor 1α and E2F1. *Arthritis Rheumatol*. 2022;74(6):948–960. doi:10.1002/art.42074
61. Kiyoi T. Scanning electron microscopic analysis of the bone-resorption activity in mature osteoclasts. *Methods Mol Biol*. 2024;2766:263–269. doi:10.1007/978-1-0716-3682-4_27

62. Sakthiswary R, Uma Veshaaliini R, Chin KY, Das S, Sirasanagandla SR. Pathomechanisms of bone loss in rheumatoid arthritis. *Front Med*. 2022;9:962969. doi:10.3389/fmed.2022.962969
63. Kaur S, White S, Bartold M. Periodontal disease as a risk factor for rheumatoid arthritis: a systematic review. *JBI Lib Syst Rev*. 2012;10(42 Suppl):1–12. doi:10.11124/jbisrir-2012-288
64. Takeshita A, Nishida K, Yoshida A, et al. RANKL expression in chondrocytes and its promotion by lymphotoxin-α in the course of cartilage destruction during rheumatoid arthritis. *PLoS One*. 2021;16(7):e0254268. doi:10.1371/journal.pone.0254268
65. Zheng H, Liu Y, Deng Y, et al. Recent advances of NFATc1 in rheumatoid arthritis-related bone destruction: mechanisms and potential therapeutic targets. *Mol Med*. 2024;30(1):20. doi:10.1186/s10020-024-00788-w
66. Stavre Z, Kim JM, Yang YS, et al. Schnurri-3 inhibition suppresses bone and joint damage in models of rheumatoid arthritis. *Proc Natl Acad Sci USA*. 2023;120(19):e2218019120. doi:10.1073/pnas.2218019120
67. Xie G, Huang C, Jiang S, et al. Smoking and osteoimmunology: understanding the interplay between bone metabolism and immune homeostasis. *J Orthop Transl*. 2024;46:33–45. doi:10.1016/j.jot.2024.04.003
68. Sales LP, Hounkpe BW, Perez MO, et al. Transcriptomic characterization of classical monocytes highlights the involvement of immuno-inflammation in bone erosion in rheumatoid arthritis. *Front Immunol*. 2023;14:1251034. doi:10.3389/fimmu.2023.1251034
69. Tang H, Liu X, He P, et al. Lipid accumulation product is a novel index associated with osteoporosis: evidence from two independent cross-sectional chinese populations. *Clin Mol Epidemiol*. 2024;1:3. doi:10.53964/cme.2024003
70. Xia W, Wu L, Lei S. Integrative analysis identified rs907091 at the miRNA binding region of the IKZF3 gene as a potential functional variant for rheumatoid arthritis. *Clin Mol Epidemiol*. 2024;1:7. doi:10.53964/cme.2024007
71. Hasegawa T. Updating the pathophysiology of arthritic bone destruction: identifying and visualizing pathological osteoclasts in pannus. *Immunol Med*. 2021;44(4):246–251. doi:10.1080/25785826.2021.1913883