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# Decoding immunoporosis-novel insights into immune system dysregulation in bone health and disease

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## Abstract

Immunoporosis represents a novel field that investigates the crucial role of immune system dysregulation in bone health and disease, particularly in conditions like osteoporosis. Traditionally, osteoporosis has been viewed primarily as a bone remodeling disorder influenced by factors such as estrogen deficiency or aging. However, recent advancements in osteoimmunology have highlighted the extensive communication between bone and the immune system in maintaining skeletal homeostasis. The term immunoporosis emphasizes on the significant impact of immune cells and inflammatory factors on the pathophysiology of osteoporosis. This paradigm shift recognizes osteoporosis as a chronic immune-mediated disease. The immune system influences bone remodeling and regulates bone mass through the production of various cytokines, chemokines, and growth factors. Inflammatory bone conditions, including osteoporosis, often arise from a dysregulation in the intricate balance between the bone and immune systems. Both innate and adaptive immune cells and their secretory cytokines are crucial players in skeletal homeostasis. For instance, immune cells can directly influence bone health, and the dysregulation of immune function can lead to abnormal bone conditions. The interplay between these systems offers promising avenues for developing immunomodulatory treatments for osteoporosis and other bone pathologies.

**Keywords:** Osteoimmunology, Osteoporosis, Bone, Vitamin D, Immunoporosis, Cytokines

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## Introduction

Osteoporosis, traditionally viewed as a metabolic bone disorder characterized by reduced bone mass and deterioration of bone microarchitecture, has increasingly been recognized as a condition with significant immunological underpinnings (1). Though the classical understanding of osteoporosis centers on the imbalance between bone resorption and bone formation primarily driven by osteoclasts and osteoblasts, respectively; however, recent advances in immunology and bone biology have illuminated the intricate crosstalk between the immune system and skeletal homeostasis. This emerging field, often termed osteoimmunology, accentuates how immune cells, cytokines, and inflammatory mediators profoundly influence bone remodeling processes and contribute to

the pathogenesis of osteoporosis (2). The immunological features of osteoporosis are multifaceted, involving both innate and adaptive immune responses, chronic low-grade inflammation also known as inflammaging, and dysregulation of immune-bone signaling pathways (3). At the core of osteoimmunology lies, the recognition that bone and immune cells share a common microenvironment, addressed overlapping molecular signaling networks (4). Hematopoietic stem cells in the bone marrow give rise to both immune cells and osteoclast precursors, establishing a developmental and functional link between the immune and skeletal systems (5). The goal of this narrative review is to talk on novel insights in immunoporosis and considering immune system dysregulation in bone health and disease.

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### ■ Implication for health policy/practice/research/medical education

Osteoporosis is a skeletal disorder characterized by reduced bone mass and deterioration of bone microarchitecture, leading to increased fracture risk. Traditionally viewed as a result of hormonal, metabolic, and mechanical causes, recent advances reveal that the immune system plays an integral role in osteoporosis pathogenesis through complex interactions influencing bone remodeling. This emerging perspective, termed immunoporosis, highlights the role of immune cells and inflammatory mediators in altering bone resorption and formation.

### Search strategy

To identify relevant literature for this narrative review, a systematic and comprehensive search was conducted across multiple electronic databases, including PubMed/MEDLINE, Scopus, Embase, Web of Science, EBSCO, the Directory of Open Access Journals (DOAJ), and Google Scholar. The search was performed without restriction on publication date in order to capture the full breadth of available evidence, and was limited to articles published in the English language. The following Medical Subject Headings (MeSH) terms and free-text keywords were employed, both individually and in combination using Boolean operators (AND, OR): “osteimmunology,” “osteoporosis,” “bone metabolism,” “bone remodeling,” “vitamin D,” “vitamin D deficiency,” “immunoporosis,” “cytokines,” “inflammatory mediators,” “immune cells,” “osteoclast,” “osteoblast,” and “bone-immune system interaction.” Titles and abstracts of retrieved records were independently screened for relevance by the authors, and full texts of potentially eligible articles were subsequently reviewed in detail. Additional relevant references were identified through manual screening of the reference lists of included studies and pertinent review articles. Studies were included if they addressed the immunological mechanisms underlying bone loss, the role of vitamin D in immune-mediated bone regulation, or the contribution of cytokines and immune cells to the pathogenesis of osteoporosis.

### Immunological features of osteoporosis

Bone remodeling maintains skeletal integrity by a balanced process of osteoclast-mediated bone resorption and osteoblast-driven bone formation. This balance is finely regulated by a dynamic crosstalk between bone cells and immune cells within the bone microenvironment (6). Immune cells, including macrophages, dendritic cells, neutrophils, T lymphocytes, and B-lymphocytes, secrete cytokines, chemokines, and growth factors that modulate osteoclastogenesis and osteoblast activity (7). Conversely, bone cells influence immune cell development and function, establishing an intricate network that determines bone homeostasis. Meanwhile, macrophages, derived from monocytes, exhibit plasticity in bone physiology (8). The pro-inflammatory M1 macrophages promote osteoclast differentiation and activity through secretion of tumor

necrosis factor-alpha (TNF- $\alpha$ ), interleukins IL-1 $\beta$  and IL-6, and reactive oxygen species. This condition contributes to enhanced bone resorption. In contrast, anti-inflammatory M2 macrophages support osteoblast differentiation and bone formation by producing transforming growth factor-beta (TGF- $\beta$ ) and insulin-like growth factor-1 (9). Alterations in the M1/M2 balance, such as increased M1 polarization in estrogen deficiency or aging, shift bone remodeling toward net bone loss (3). Similarly, dendritic cells (DCs), key antigen-presenting cells, can promote osteoclastogenesis by expressing receptor activator of NF- $\kappa$ B ligand (RANKL) and producing pro-inflammatory cytokines, thus directly contributing to bone resorption (10). Intriguingly, DCs can transdifferentiate into osteoclast-like cells, amplifying bone destruction in inflammatory states. In addition, neutrophils, although critical for pathogen clearance, also influence bone remodeling (10). Activated neutrophils secrete RANKL and pro-osteoclastogenic cytokines like IL-17, supporting osteoclast formation, while also producing growth factors that may promote osteogenesis. Their net effect depends on the local environment, with hyper-activation favoring inflammatory bone loss (11). Preliminary studies detected that, adaptive immune cells, particularly T lymphocytes, are crucial drivers of osteoporosis-related inflammation (3). In fact, CD4+ T helper cell subsets exhibit diverse roles; Th17 cells produce IL-17, IL-22, and TNF- $\alpha$ , stimulating osteoclast differentiation and activity, whereas regulatory T cells (Tregs) inhibit osteoclastogenesis by anti-inflammatory cytokines like IL-10 and TGF- $\beta$  (12). An imbalance favoring Th17 over Treg cells is implicated in increased bone resorption in osteoporosis (13). Besides, CD8+ cytotoxic T cells may exert protective effects by secreting osteoprotegerin (OPG), a decoy receptor for RANKL, thereby inhibiting osteoclastogenesis (14). Other studies detected that, B-lymphocytes contribute to osteoporosis through production of RANKL, promoting osteoclast differentiation. They also secrete OPG, underscoring a dual regulatory role (15). Estrogen deficiency increases osteoclastogenic B cell precursors in bone marrow, facilitating bone loss (16). Additionally, B cells can inhibit osteoblast differentiation by activation of signaling pathways such as ERK and NF- $\kappa$ B, further impairing bone formation (17). Likewise, estrogen deficiency, characteristic of postmenopausal osteoporosis, triggers immune dysregulation that accelerates bone loss. Estrogen loss enhances M1 macrophage polarization and pro-inflammatory cytokine production (TNF- $\alpha$ , IL-1 $\beta$ ), promotes increased survival and activity of dendritic cells, and favors expansion of osteoclastogenic Th17 cells while reducing regulatory T cells (3). Accordingly, B cell numbers and RANKL expression also increase under estrogen deficiency, collectively shifting bone remodeling toward resorption (18). At the molecular level, pro-inflammatory cytokines such as IL-1, IL-6, and TNF- $\alpha$  are central mediators linking inflammation and

bone remodeling. These cytokines increase osteoclast differentiation, survival, and resorptive activity primarily by upregulating RANKL expression on osteoblasts and immune cells. The RANKL-RANK signaling axis is critical for osteoclastogenesis (19). OPG acts as a soluble decoy receptor that neutralizes RANKL, thus inhibiting osteoclast formation. Dysregulation of the RANKL/OPG ratio under inflammatory conditions dictates increased bone resorption seen in osteoporosis (20). Additionally, inflammatory mediators induce osteoblast apoptosis and inhibit matrix synthesis, further impairing bone formation. Nitric oxide synthesized by inducible nitric oxide synthase (iNOS) in response to inflammatory cytokines inhibits osteoblast function and promotes apoptosis, contributing to bone loss (21). Reactive oxygen species generated during inflammation exacerbate osteoclast differentiation and activity, and inhibit osteoblast differentiation through oxidative stress pathways (22).

### The concept of osteoimmunology

Osteoimmunology, the interdisciplinary field that studies bone-immune system interactions, has revealed that bone and immune cells share common progenitors and signaling pathways. This cross-talk is bidirectional, with immune cells regulating bone remodeling and bone cells influencing immune cell development and function (23). Key signaling molecules such as tumor necrosis factor receptor-associated factor 6 integrate signals from both immune and bone cells, underscoring the interconnectedness of these systems (6). Genetic polymorphisms in cytokine genes including IL-6 and IL-1 $\beta$  influence individual susceptibility to osteoporosis, highlighting genetic contributions to immunoregulatory aspects of bone remodeling (7). Furthermore, sex hormones modulate immune responses; estrogen suppresses IL-6 and TNF- $\alpha$  production, thus exerting protective effects on bone (24). The decline of estrogen with aging disrupts this inhibition, facilitating inflammatory bone loss (25).

### Focus on senile osteoporosis

Senile osteoporosis, prevalent in older adults, involves chronic low-grade inflammation termed inflammaging, characterized by persistent elevation of pro-inflammatory cytokines such as IL-6 and TNF- $\alpha$  (26). Aging immune cells become senescent, with altered macrophage, neutrophil and dendritic cell function that supports inflammation-induced bone resorption (27). Then, T cell function declines, reducing immune regulation and perpetuating chronic inflammation, while B cell populations and their antibody responses dwindle. This pro-inflammatory environment disrupts bone remodeling balance, decreasing osteoblast activity and enhancing osteoclastogenesis (28).

### Focus on diabetic osteoporosis

Diabetic osteoporosis, a secondary form associated with

diabetes mellitus, arises partly due to altered immune responses triggered by hyperglycemia (29). High glucose levels induce M1 macrophage polarization and inhibit M2 phenotype, increase reactive oxygen species production, and alter signaling pathways that enhance inflammation and bone resorption (30). Hyperglycemia also impairs neutrophil and dendritic cell function, contributing to chronic inflammation (31). Adaptive immunity is affected with increased pro-inflammatory Th1 and Th17 cells and reduced regulatory T cells, promoting osteoclast activity and bone loss (32).

### A short look at the gut-bone axis

The gut-bone axis represents another immunological dimension of osteoporosis. The gut microbiota plays a crucial role in shaping systemic immunity, and dysbiosis as an imbalance in microbial composition has been linked to both inflammation and bone loss (33). Germ-free mice exhibit higher bone mass, while colonization with certain pathobionts can induce osteoporosis (34). Mechanistically, gut dysbiosis increases intestinal permeability, known as leaky gut, allowing bacterial products like lipopolysaccharide to enter systemic circulation (35). Lipopolysaccharide activates Toll-like receptors (TLRs), particularly TLR4, on immune and bone cells, triggering NF- $\kappa$ B signaling and the production of pro-inflammatory cytokines that drive osteoclastogenesis (36). Short-chain fatty acids, produced by beneficial gut bacteria through fermentation of dietary fiber, exert anti-inflammatory effects and promote Treg differentiation, thereby protecting against bone loss. Thus, modulation of the gut microbiome represents a potential immunomodulatory strategy for osteoporosis prevention and treatment (37).

### Biomarkers of inflammation

In clinical practice, recognizing the immunological features of osteoporosis can inform risk stratification and personalized treatment (38). Biomarkers of inflammation such as high-sensitivity CRP, IL-6 and TNF- $\alpha$  may help identify individuals with inflammatory osteoporosis who could benefit from targeted immunomodulatory interventions (26). Patients with autoimmune diseases, chronic infections, or a history of prolonged glucocorticoid use warrant vigilant bone health monitoring (39). Furthermore, the presence of comorbidities like obesity, type 2 diabetes, and cardiovascular disease, which are themselves associated with chronic inflammation should raise suspicion for immune-mediated bone loss (40). Animal models have been instrumental in elucidating the immunological mechanisms of osteoporosis. Ovariectomized mice, the standard model for postmenopausal osteoporosis, exhibit T cell activation, increased TNF- $\alpha$  production, and elevated RANKL expression, mirroring human pathophysiology (41). Studies using T cell-deficient or cytokine-knockout mice have confirmed the causal role of specific immune

components in bone loss (42). Recent studies found that, TNF receptor-deficient mice are protected from ovariectomized-induced osteoporosis, and IL-17 blockade attenuates bone resorption in inflammatory models. These preclinical findings provide a foundation for translating immunological insights into clinical applications (26).

### A short look at sex disparities

Sex differences in immune responses also influence osteoporosis risk. Women are more susceptible to postmenopausal osteoporosis due to the abrupt loss of estrogen's immunomodulatory effects, whereas men experience a more gradual decline in sex hormones with aging (43). However, men with hypogonadism or chronic inflammatory conditions are also at significant risk (44). The X chromosome contains numerous immune-related genes, and X-chromosome inactivation patterns may contribute to sex-specific immune responses that affect bone (45). Moreover, pregnancy and lactation involve dynamic immune adaptations that temporarily alter bone metabolism, underscoring the lifelong interplay between immunity and skeletal health (46).

### Secondary osteoporosis

Autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondylitis are frequently associated with secondary osteoporosis, highlighting the direct impact of immune dysregulation on bone health (47). In rheumatoid arthritis, for example, synovial inflammation leads to local and systemic bone loss through the overproduction of TNF- $\alpha$ , IL-1, IL-6, and RANKL by infiltrating immune cells (48). Similarly, in systemic lupus erythematosus, autoantibodies, immune complex deposition, and chronic interferon signaling contribute to accelerated bone resorption (48). Glucocorticoid therapy, commonly used to treat autoimmune conditions, further exacerbates bone loss by suppressing osteoblast function, promoting osteocyte apoptosis, and enhancing osteoclast survival (49). The interplay between autoimmune inflammation and pharmacological immunosuppression creates a complex scenario in which immunological features dominate the osteoporotic process (3).

### Therapeutic modalities

The therapeutic implications of the immunological features of osteoporosis are profound. Denosumab, a monoclonal antibody against RANKL, directly targets the immune-bone axis by inhibiting osteoclast formation and is highly effective in reducing fracture risk (50). Biologic agents used in autoimmune diseases, such as TNF inhibitors (e.g., infliximab, adalimumab) and IL-6 receptor blockers (e.g., tocilizumab), have been shown to improve bone mineral density in patients with inflammatory arthritis, further validating the role of cytokines in bone loss (51). Recent therapies aim to modulate specific immune cell

populations to restore immune-bone homeostasis (52). Senolytic drugs that selectively eliminate senescent cells are being investigated for their potential to reduce SASP-driven inflammation and preserve bone mass in aging (53). Additionally, probiotics and prebiotics that restore gut microbial balance may offer a non-pharmacological approach to mitigate inflammation and support skeletal health. Nutritional and lifestyle factors intersect with immunological mechanisms in osteoporosis (54). Vitamin D, beyond its classical role in calcium homeostasis, is a potent immunomodulator that promotes Treg differentiation and suppresses Th17 responses. Vitamin D deficiency, common in older adults, is associated with increased inflammation and higher fracture risk (55). Omega-3 fatty acids possess anti-inflammatory properties and may reduce the production of pro-osteoclastogenic cytokines (56). Conversely, diets high in saturated fats and refined sugars promote gut dysbiosis and systemic inflammation, potentially accelerating bone loss (57). Physical activity exerts anti-inflammatory effects and enhances bone formation, while sedentary behavior and chronic psychological stress elevate cortisol and pro-inflammatory cytokines, contributing to osteoporosis (58).

### Conclusion

Immunoporosis, highlights the critical role of the immune system in the pathophysiology of osteoporosis, an inflammatory bone anomaly affecting over 500 million people globally. This novel concept emerged from discoveries emphasizing the extensive communication between bone and the immune system in maintaining skeletal homeostasis. Osteoporosis, traditionally viewed as a bone remodeling disorder primarily driven by estrogen deficiency or aging, is now understood to involve significant immune system modulation of inflammatory bone loss. The interconnectedness of bone and the immune system, termed osteoimmunology, has been a focus of research for the past two decades. Immune cells and their secreted cytokines are pivotal in skeletal homeostasis. Dysregulation within the immune system is a key factor in inflammatory bone conditions like rheumatoid arthritis, osteoarthritis, and osteoporosis. This dysregulation can lead to an imbalance in bone remodeling, characterized by reduced bone mineral density and mechanical strength, increasing fracture risk. Recent advancements have revealed that commonly used osteoporosis therapies, such as bisphosphonates and denosumab, modulate immune mediators, further underscoring the immune system's impact on bone health. Understanding the specific roles of various innate and adaptive immune cells and their plasticity is crucial for identifying new therapeutic opportunities in clinical interventions for osteoporosis. Therefore, focusing on immune pathways offers a promising avenue for developing immunomodulatory treatments for this debilitating disease.

**Authors' contribution****Conceptualization:** Aysuliu Sharopova and Maftuna Aliyeva.**Data curation:** Zulfiya Davlyatova and Iroda Tishabayeva.**Investigation:** Tulkin Elmurodov, Aysuliu Sharopova, and Munira Payziyeva.**Supervision:** All authors.**Validation:** Nodira Shukurova and Gulshod Usmonova.**Visualization:** Fayzulla Yuldashov and Adkhambek Nurboboyev.**Writing—original draft:** All authors.**Writing—review and editing:** All authors.**Conflicts of interest**

The authors declare that they have no competing interests.

**Declaration of generative AI and AI-assisted technologies in the writing process**During the preparation of this work, the authors utilized *Perplexity* to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.**Ethical issues**

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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