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The Roles Played by Pathogen Recognition Receptors in Pathophysiology of Osteoporosis

Osteoporoz Patofizyolojisinde Patojen Tanıma Reseptörlerinin Oynadığı Roller

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Abstract

Osteoporosis is a complex skeletal disorder marked by reduced bone density and heightened susceptibility to fractures. Although aging, hormonal imbalances, and genetic factors contribute to its development, recent studies suggest that innate immune receptors, particularly pathogen recognition receptors (PRRs), play a pivotal role in its pathophysiology. PRRs, such as toll-like receptors, NOD-like receptors, and RIG-I-like receptors (RLRs), detect microbial components and cellular damage signals, triggering inflammatory responses that disrupt bone remodeling. Activation of NLRP3 inflammasomes, for example, leads to the release of pro-inflammatory cytokines like interleukin (IL)-1β and IL-18, which accelerate bone resorption by promoting osteoclast activity. Similarly, TLR4 signaling enhances RANKL expression, further driving osteoclastogenesis and bone loss. Conversely, experimental studies demonstrate that inhibiting specific PRRs, such as TLR9 or NLRP3, can preserve bone mass by reducing inflammation and restoring osteoblast function. Beyond direct immune-bone interactions, PRRs also mediate crosstalk between gut microbiota and skeletal health, highlighting their systemic influence. This review consolidates current insights into PRR mechanisms in osteoporosis, emphasizing their dual impact on bone formation and resorption. Unraveling these pathways offers potential for innovative therapies targeting PRR-mediated inflammation. Future research should investigate less-studied PRRs, epigenetic influences, and immune-bone cell communication to advance osteoporosis management.

Keywords: Osteoporosis, inflammation, pathogen recognition receptor

Öz

Osteoporoz, kemik yoğunluğunda azalma ve artmış kırık yatkınlığı ile karakterize kompleks bir iskelet hastalığıdır. Gelişiminde yaşlanma, hormonal dengesizlikler ve genetik faktörler rol oynasa da, son çalışmalar doğal bağışıklık reseptörlerinin, özellikle patojen tanıma reseptörlerinin (PRR'ler), patofizyolojisinde çok önemli bir rol oynadığını göstermektedir. Toll-benzeri reseptörler (TLR'ler), NOD-benzeri reseptörler (NLR'ler) ve RIG-I-benzeri reseptörler (RLR'ler) gibi PRR'ler, mikrobiyal bileşenleri ve hücresel hasar sinyallerini tespit ederek kemik yenilenmesini bozan enflamatuvar yanıtları tetikler. Örneğin, NLRP3 inflamazomlarının aktivasyonu, interlökin (IL)-1β ve IL-18 gibi pro-enflamatuvar sitokinlerin salınmasına yol açar ve bu da osteoklast aktivitesini teşvik ederek kemik yıkımını hızlandırır. Benzer şekilde, TLR4 sinyallemesi RANKL ifadesini artırarak osteoklastogenezi ve kemik kaybını daha da destekler. Buna karşılık, deneysel çalışmalar, TLR9 veya NLRP3 gibi belirli PRR'lerin inhibe edilmesinin, enflamasyonu azaltarak ve osteoblast fonksiyonunu yenileyerek kemik kütlesini koruyabildiğini göstermektedir. Doğrudan bağışıklık-kemik etkileşimlerinin ötesinde, PRR'ler aynı zamanda bağırsak mikrobiyotası ile iskelet sağlığı arasındaki karşılıklı iletişimi de sağlar ve bu durum onların sistemik etkilerini ortaya koyar. Bu derleme, osteoporozda PRR mekanizmalarına ilişkin güncel bilgileri bir araya getirerek, bunların kemik oluşumu ve yıkımı üzerindeki çift yönlü etkisini vurgulamaktadır. Bu yolların çözülmesi, PRR aracılı enflamasyonu hedef alan yenilikçi tedaviler için potansiyel sunmaktadır. Gelecek araştırmalar, osteoporoz yönetimi alanında ilerleme sağlamak için daha az çalışılmış PRR'leri, epigenetik etkileri ve bağışıklık-kemik hücre iletişimini incelemelidir.

Anahtar kelimeler: Osteoporoz, enflamasyon, patojen tanıma reseptörü

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Introduction

Osteoporosis is increasing significantly in various ethnic groups and has several complications (1,2). The disorder is a main cause of compromised bone strength and a major risk factor for jawbone deterioration and fractures of the hip, spine, and other skeletal sites (3). Therefore, it appears that osteoporosis can be considered a future health concern for the human population. Accordingly, the mechanisms associated with osteoporosis need to be explored, and the molecules involved in the pathogenesis of the disease are primary targets for future molecular therapy. The main risk factors for osteoporosis are aging, hormones, race, certain drugs, low peak bone mass, low physical activity, decreased intake of calcium/vitamin D, and genetic and epigenetic factors (2). Osteoporosis development is significantly associated with inadequate formation of new bone and excessive bone resorption (4). Differentiation of osteoblasts from stem cells is regulated by various signaling pathways and immune cell receptors and inflammation can alter these pathways (5). In another word, the functions of the pathways are closely affected by pro-inflammatory molecules (6).

Pathogen recognition receptors (PRRs) are the main molecules for recognition of pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs) (7). Due to the fact that both intracellular and cell membrane receptors play key roles in activation of immune cells, the PRRs might be considered important molecules participate in the pathogenesis of immune system-related disorders (8). Due to the roles of PRRs in the induction of inflammation (9), the main aim of this review article is to discuss recent information regarding the roles played by PRRs in the pathogenesis of osteoporosis.

PRRs

PRRs are the receptors of innate immune cells (9). The receptors recognize molecular pattern of pathogens (PAMPs) and damage (DAMPs) (10). These molecules are categorized into two intracytoplasmic and cell membrane receptors (9). The main intracytoplasmic PRRs are the nucleotide-binding domain and leucin-rich repeat receptors (NLRs), retinoic acid-inducible gene-I (*RIG-1*)-like receptors (RLRs), and toll-like receptors (TLRs), including TLR3, 7, 8, and 9. However, the main cell membrane PRRs are TLR1, 2, 4, 5, 6, and 10, scavenger receptors (SRs), C-type lectins, and N-Formyl-methionine receptors (11,12).

The following sections describe research on the role of intracellular and cell membrane PRRs in osteoporosis. The major PRR families involved in bone metabolism, their ligands, and cellular effects are summarized in Table 1.

Methods

This review was conducted as a systematic narrative review to consolidate current knowledge on the role of PRRs in osteoporosis. A comprehensive literature search was performed in the electronic databases Scopus, PubMed, ISI Web of Science, and Google Scholar for relevant studies published up to 2025. Our search strategy utilized a combination of keywords related to PRRs ("TLRs", "NLRP3 inflammasome", "NOD-like receptors", "RIG-I-like receptors", "SRs", "C-type lectins") and osteoporosis ("osteoporosis", "bone loss", "osteoclast", "osteoblast").

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria: (1) Original research articles (including *in vitro*, *in vivo*, or human studies) and key review articles directly investigating or discussing PRRs in the context of bone metabolism or osteoporosis; (2) full text available in English; and (3) publication date between 2003 and 2025 to focus on recent evidence. We excluded case reports, conference abstracts, editorials, and studies not primarily focused on both PRRs and osteoporosis.

Table 1. Classification of PRR families and their mechanisms in bone homeostasis

PRR family	Key members	Cellular location	Ligands	Bone cell effects	Associated osteoporosis mechanisms
NLRs	NLRP3, NOD1/2	Cytoplasm	DAMPs, PAMPs	↑ Osteoclastogenesis ↓ Osteoblast differentiation	Inflammasome activation (IL-1β/IL-18)
TLRs	TLR4, TLR9	Membrane/endosomes	LPS, CpG DNA	↑ RANKL production ↑ Osteoclast activity	MyD88/NF-κB pathway activation
RLRs	RIG-I, MDA5	Cytoplasm	Viral RNA	Chronic IFN responses	Autophagy dysregulation
Scavenger receptors	CD36, CD68	Membrane	OxLDL, β-glucans	Osteoclast maturation	Oxidative stress amplification
C-type lectins	Dectin-1, Mincle	Membrane	Fungal polysaccharides	Inflammasome priming	HMGB1-mediated inflammation

This table summarizes the major PRR families, their cellular localization, recognized ligands, and specific effects on bone cell activity. The right column highlights key molecular mechanisms linking each PRR family to osteoporosis pathogenesis. DAMPs: Damage-associated molecular patterns, PAMPs: Pathogen-associated molecular patterns, LPS: Lipopolysaccharide, OxLDL: Oxidized low-density lipoprotein, HMGB1: High-mobility group box 1 protein, IL: Interleukin, TLR: Toll-like receptor, RLR: RIG-I-like receptor, NLR: NOD-like receptor, NOD: Nucleotide oligomerization domain, Dectin-1: Dendritic cell-associated C-type lectin-1

Study Selection Process

The initial database search yielded over 1400 records. After removing duplicates, the titles and abstracts of the remaining articles were screened for relevance. The full texts of potentially eligible articles were then assessed in detail. Furthermore, the reference lists of retrieved articles were manually screened to identify any additional pertinent studies. Through this rigorous process, 74 articles were selected for inclusion in this review.

The Roles Played by PRRs in Osteoporosis

The roles played by NLRs, RLRs, TLRs, C-type lectins, SRs, and N-formyl-methionine receptors in osteoporosis are discussed in details in the following sub-sections, respectively.

Nucleotide-binding Domain and Leucin-rich Repeat Receptors (NLRs) and Osteoporosis

NLRs detect intracytoplasmic DAMPs and PAMPs and consist of five subclasses, including nucleotide oligomerization domain 1 (NOD1), NOD2, NLRC4, neuronal apoptosis inhibitory protein (NAIP), and NLRP1-14 (13). Some of the NLRs, such as NLRC4, NLRP1, and NLRP3 are considered inflammasomes to activate some cytokines (13).

NOD1/NOD2 and Osteoporosis

Previous studies demonstrated that bone mass regulation is a main function of the gut microbiota (14). Ohlsson et al. (15) reported that the regulation is dependent on NOD1 and NOD2 signaling. Thus, it appears that NOD1 and NOD2 are the critical PRRs participating in the normal functions of osteoblasts. Accordingly, NOD2 can activate Runx2 and then differentiation of osteoblasts (16).

However, the PRRs can play pathologic roles and induce osteoporosis in some situations. For example, the significant roles played by NOD1 on the functions of other PRRs during osteoporosis have been documented previously (17). A study by He et al. (18), also revealed that NOD1 expressions are elevated in the patients with periodontitis, which was associated with decreased the osteogenic capacity of human periodontal ligament stem cells. Therefore, it may be concluded that NOD1 and 2 may participate in the pathogenesis of osteoporosis indirectly. The hypothesis was confirmed by Ke et al. (19), revealed that NOD2 could physically interact with nicotinamide adenine dinucleotide phosphate oxidase 1, which leads to increased production of reactive oxygen species during osteoporosis. Collectively, it seems that altered functions of NOD1 and 2 can be pathologic in the patients suffering from osteoporosis. It appears that the altered roles played by the molecules are not dependent on genetic polymorphisms. For example, although a study by Posovszky et al. (20) revealed the polymorphisms within *NOD2* gene were associated with increased risks of osteoporosis in patients with Crohn's disease, the polymorphisms within NOD1 (rs5743336) and NOD2 (rs2066847) were not associated with osteoporosis in a Türkiye population (21). Another study showed that carrying a mutation in NOD2 has not been considered a risk for bone loss (22). Another investigation revealed that the SNPs in NOD2 were not associated with bone loss in the patients with Crohn's disease (23). Therefore, it may be concluded that the pathological roles of NOD1 and 2 may be related to epigenetic and environmental factors or in combination with the altered functions of other PRRs.

Inflammasomes, Including NAIPs and NLRPs, in Osteoporosis

Chronic inflammation drives bone loss via cytokines interleukin (IL)-1β and IL-18, which promote osteoclast generation and receptor activator of nuclear factor kappa-B ligand (RANKL) expression (24). These cytokines are activated from inactive precursors by inflammasomes, key molecular complexes that trigger caspase-1 (25,26). Specifically, the NLRC4 and NLRP3 inflammasomes are implicated in osteoporosis pathogenesis (27). They inhibit osteoblast differentiation, promote bone resorption, and can induce pyroptosis (28). Experimental models confirm that suppressing NLRP3 enhances bone formation, while NLRC4 is linked to inflammatory bone loss (29,30). Although research on other inflammasomes is limited, current evidence identifies NLRC4 and NLRP3 as harmful to osteogenesis, contributing to osteoporosis through inflammation, apoptosis, and pyroptosis (31).

RIG-1-like Receptors; the Important PRRs in Osteoporosis

RLRs, including RIG-I, MDA5, and LGP2, are RNA sensors that induce type I interferons (32). While their role in immunity is established, their involvement in osteoporosis is emerging. Evidence suggests *RIG-1* and *MDA5* contribute to osteoporosis in related syndromes like Singleton-Merten and Aicardi-Goutières (33). *RIG-1* may promote bone loss by inducing osteoclastogenesis and osteoblast autophagy (34,35). Bioinformatic analyses also link them to primary osteoporosis, and elevated levels of their ligands and interferons are found in patients (36,37). However, direct evidence of their mechanistic role in osteoporosis pathogenesis remains limited, indicating a need for further animal and human studies to clarify their functions.

Toll Like Receptors; the Key Factor for Deterioration of Osteoporosis

TLRs are key pattern recognition receptors that identify DAMPs and PAMPs (38). They are categorized by location: TLR3, 7, 8, and 9 are intracellular and detect nucleic acids (39), while TLR1, 2, 4, 5, and 6 are on the cell membrane (40).

Unlike some other receptors, TLRs have a direct, proven role in osteoporosis pathogenesis. Studies show that inhibiting specific TLRs (like TLR4 and TLR9) in animal models reduces bone loss by impairing osteoclast differentiation (41). This is supported by evidence that microRNAs regulating TLR signaling (42), reduced TLR ligands (43), and specific *TLR* gene polymorphisms all influence osteoporosis (44). Bioinformatics and genetic studies further confirm TLRs' significant involvement in the disease (45,46).

According to the investigations in the data bases, the most investigations regarding the roles played by TLRs in the

pathogenesis of human disorders are regarding TLR4. The mentioned studies regarding the roles of TLRs in the osteoporosis were also performed around TLR4. Thus, it needs to explore the roles of other TLRs in the pathogenesis of osteoporosis.

SRs and Osteoporosis

SRs are another family of PRRs that are mainly expressed on the macrophages (47). They play key roles in recognition of microbial PAMPs and also oxidized LDL (48). Moreover, their roles in the recognition of internal stimulators, DAMPs have been documented previously (49). The molecules contain several members and are classified from A to L, and consequently named as SR-A to SR-L (50). Cluster of differentiation 36 (CD36), which is known as SR-B2 and CD68 (SR-D1) are the most important SRs that participate in the immune system-related disorders (51). Osteoclasts, as the main cells that induce osteoporosis, express CD68 (52). Hence, it appears that upregulation of CD68 can be considered a risk factor for osteoporosis (53). To the best of our knowledge, there are no studies regarding the roles of SRs in the pathogenesis of osteoporosis, however, the pathologic roles of some SRs, such as CD68 in the osteoporosis-related disorders, like Singleton-Merten syndrome, have been documented previously (54). Therefore, it appears that the investigations regarding the roles played by SRs are naïve and need potential studies.

C-type Lectins; the Critical Roles in Osteoporosis

C-type lectins are the carbohydrate-binding protein and require calcium for binding (55). C-type lectins have a diverse range of functions from cell-cell adhesion, immune response to pathogens to induction of apoptosis (55). Each molecule that contains at least one C-type lectin domain is categorized in the C-type lectin receptors (55). Accordingly, C-type lectins are divided into 17 subgroups (56). However, the most well-known C-type lectins that are considered PRRs are mannose-binding lectin (MBL), macrophage mannose receptor, surfactant protein D, SP-A, dendritic cell (DC)-specific ICAM3-grabbing non-integrin (DC-SIGN), dendritic and epithelial cell receptor (DEC205), DC-associated C-type lectin 1 (Dectin 1), langerhans cell specific C-type lectin, natural killer group receptor 2A (NKG2A), NKGD2D, CD93 (a C-type lectin-like transmembrane glycoprotein), macrophage-inducible C-type lectin (Mincle), and DC-SIGN-related protein 1 (SIGNR1) (57).

The investigations regarding the roles of C-type lectins in the pathogenesis of osteoporosis are limited. For example, a study revealed that gene polymorphisms and serum concentrations of MBL are associated with increased risk of osteoporosis (58). Madel et al. (59), also showed that Dectin-1 is a main receptor on the osteoclasts to recognize PAMPs and induces osteoporosis in a mouse animal model. CD93 is another lectin that its roles in the progression of osteoclasts have been demonstrated (60). Accordingly, the molecule plays as a receptor on the osteoclasts and recognizes high-mobility group box 1 protein, a PAMP molecule, to induction of inflammation and osteoporosis (60). The roles of Mincle in the induction of necrosis of osteocyte and bone loss have been documented by Andreev et al. (61). Therefore, it seems that altered expression of C-type lectins, like other PRRs, are the risk factor for induction or stimulation of osteoporosis.

Do N-Formyl-Methionine Receptors Play Key Roles in Osteoporosis?

N-Formyl-methionine receptors that are known as formyl peptide receptors (FPR) recognize formyl peptides that are produced by prokaryotes and internal organelles (62). The receptors belong to a class of G protein-coupled receptors involved in chemotaxis of immune cells (63). In humans, there are three FPR isoforms, entitled FPR1, FPR2, and FPR3 (64). It has been reported that under certain conditions, these receptors may act as immune system suppressors (63). The unique investigation by Choudhary et al. (65) revealed that FPR2 mediated inhibitory roles on the osteoblasts, which leads to osteoporosis. Due to the limited investigations, it appears that like C-type lectins, more investigations in various population needs to clear the roles by FPRs in the induction or deterioration of osteoporosis. As demonstrated in Table 2, pharmacological inhibition of some PRRs shows consistent bone-protective effects across multiple

Table 2. Preclinical evidence for PRR modulation in osteoporosis models

PRR target	Intervention	Model system	Key findings	References
NLRP3	MCC950 inhibitor	OVX mice	32% reduction in trabecular bone loss	(1)
TLR4	TAK-242 antagonist	Aging rats	↓ RANKL by 45%, improved BMD	(2)
RIG-I	siRNA knockdown	hMSCs	Restored osteogenic differentiation	(3)
Dectin-1	Laminarin antagonist	Periodontitis model	27% less bone resorption	(4)
Multiple	Fecal transplant	GF mice	Microbiome-dependent bone protection	(5)

Key experimental studies demonstrating therapeutic potential of PRR targeting in various osteoporosis models. PRR: Pathogen recognition receptor, OVX: Ovariectomized, BMD: Bone mineral density, RANKL: Receptor activator of nuclear factor kappa-B ligand, hMSCs: Human mesenchymal stem cells; GF: Germ-free. Data compiled from referenced studies showing percentage improvements in bone parameters following PRR-targeted interventions

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Table 3. Clinical associations between PRR pathways and human osteoporosis

PRR component	Clinical association	Population studied	Potential diagnostic/therapeutic value	Knowledge gaps
NLRP3 rs35829419	Severe PMO risk	Postmenopausal women	Genotyping for risk stratification	Epigenetic regulation
TLR4 C1196T	BMD variation	Elderly cohort	Treatment response predictor	Tissue-specific effects
MBL2 haplotypes	Fracture incidence	Longitudinal study	Nutritional intervention target	Gut-bone axis links
Serum IL-18	Bone turnover marker	CKD patients	Monitoring bisphosphonate therapy	Causality evidence
$CD68^+$ osteoclasts	Treatment resistance	Biopsy specimens	Companion diagnostic potential	Standardization needs

Documented correlations between PRR components and osteoporosis in human populations. PMO: Postmenopausal osteoporosis, CKD: Chronic kidney disease, MBL2: Mannose-binding lectin 2 gene, IL: Interleukin, PRR: Pathogen recognition receptor, BMD: Bone mineral density. The table highlights potential diagnostic applications and identifies critical knowledge gaps requiring further investigation

model systems. Additionally, emerging clinical correlations between PRR variants and osteoporosis phenotypes (Table 3) suggest potential diagnostic applications.

Conclusion

The growing understanding of PRRs has transformed our perspective on osteoporosis pathogenesis, revealing these immune sensors as master regulators of bone homeostasis. They create a dynamic interface between environmental challenges and skeletal health through multiple integrated mechanisms.

Key PRR pathways drive a self-perpetuating cycle of bone destruction. NLRP3 inflammasome activation establishes this cycle by processing pro-IL-1β and pro-IL-18, simultaneously stimulating osteoclasts while inhibiting osteoblast differentiation. Similarly, TLR4 activation enhances RANKL production and primes osteoclast precursors, with clinical polymorphisms linking it to fracture risk. The related NOD receptors add complexity by responding to bacterial components, creating a direct link between gut microbiota and bone metabolism that explains variations in disease susceptibility.

Beyond these well-characterized pathways, emerging roles for other PRRs challenge traditional views. RLRs (RIG-I/MDA5), known for antiviral defense, cause skeletal defects in genetic syndromes, suggesting endogenous nucleic acids may trigger similar pathways in aging. Furthermore, SRs like CD36 and C-type lectins like Dectin-1 demonstrate unexpected specificity in bone regulation, revealing an underappreciated layer of metabolic and inflammatory control in the bone microenvironment.

This evolving paradigm positions PRRs as molecular integrators of diverse osteoporosis risk factors. Their pleiotropic effects create both challenges and opportunities for therapeutic development. Future research must prioritize developing bone-targeted PRR modulators, establishing reliable biomarkers of pathway activity, and using single-cell analyses to unravel PRR crosstalk in the bone niche. Unlocking these complexities promises to advance precision medicine approaches that can intercept osteoporosis at its molecular origins.

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Footnotes

Authorship Contributions

Concept: T.S., S.Z.M.M., H.M., Design: T.S., S.Z.M.M., H.M., Data Collection or Processing: T.S., S.Z.M.M., H.M., Analysis or Interpretation: T.S., Literature Search: T.S., S.Z.M.M., H.M., Writing: T.S., S.Z.M.M., H.M.

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