E-ISSN: 2147-2653

TURKISH JOURNAL OF OSTEOPOROSIS

Cilt / Vol.: 32 Sayı / Issue: Suppl 1 Eylül / September 2026

www.turkosteoporozdergisi.org

TÜRKİYE OSTEOPOROZ DERNEĞİ
1998
www.osteoporoz.org.tr

TURKISH JOURNAL OF
OSTEOPOROSIS
TÜRK OSTEOPOROZ DERGİSİ

TURKISH JOURNAL OF
OSTEOPOROSIS
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Türkiye Osteoporoz Derneği "International Osteoporosis Foundation" Üyesidir.
"Web tabanlı danışma kurulu ve hakem listesi www.turkosteoporozdergisi.com adresinde yer almaktadır"
Derginin eski adı "Osteoporoz Dünyasından Dergisi"dir.

Yayınevi İletişim/Publisher Contact
Adres/Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 Fındıkzade-İstanbul-Türkiye
Telefon/Phone: +90 (530) 177 30 97
E-posta/E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr
Yayıncı Sertifika No/Publisher Certificate Number: 14521

Online Yayınlanma Tarihi/Online Publishing Date: Eylül 2026/September 2026
E-ISSN: 2147-2653
Yılda üç kez yayımlanan süreli yayındır.
International periodical journal published three times in a year.

TURKISH JOURNAL OF
OSTEOPOROSIS
TÜRK OSTEOPOROZ DERGİSİ

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Sahibi: Türkiye Osteoporoz Derneği

Sorumlu Yönetici: Yeşim Kirazlı

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The journal is published online.

Owner: Turkish Osteoporosis Society

Responsible Manager: Yeşim Kirazlı

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OSTEOPOROSIS
TÜRK OSTEOPOROZ DERGİSİ

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Siz değerli meslektaşlarımızın ulusal kongremize katılarak katkı sunmasını dileyerek, sevgi ve saygılarımı sunarım.

Editör
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DOI: 10.4274/tod.galenos.2025.32656
Turk J Osteoporos 2026;32(Suppl 1):1-7

The Roles Played by Pathogen Recognition Receptors in Pathophysiology of Osteoporosis

Osteoporoz Patofizyolojisinde Patojen Tanıma Reseptörlerinin Oynadığı Roller

Tayebeh Sadeghi[1], Seyedeh Zahra Mousavi Masouleh[2], Hossein Mokhtari[2]

[1]Faculty of Medicine, K.C., Islamic Azad University, Kerman, Iran
[2]Islamic Azad University Faculty of Science, Department of Science and Technology, Tehran, Iran

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

Corresponding Author/Sorumlu Yazar: Tayebeh Sadeghi, MD, Faculty of Medicine, K.C., Islamic Azad University, Kerman, Iran
E-mail: t.sadeghi.g@gmail.com **ORCID ID:** orcid.org/0000-0001-5656-0283
Received/Geliş Tarihi: 26.08.2025 **Accepted/Kabul Tarihi:** 04.11.2025 **Publication Date/Yayınlanma Tarihi:** 01.09.2026

Cite this article as/Atıf: Sadeghi T, Masouleh SZM, Mokhtari H. The roles played by pathogen recognition receptors in pathophysiology of osteoporosis. Turk J Osteoporos. 2026;32(Suppl 1):1-7

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.

Acknowledgments

Authors have an opportunity to thank the staff of Islamic Azad University, Kerman Branch, for their warm corporations. Authors have an opportunity to thanks the staff of Immunology of Infectious Diseases Research Center for their warmly corporations.

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.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/tod.galenos.2026.56873
Turk J Osteoporos 2026;32(Suppl 1):8-13

When Vitamin D Improves but Bone Density Does Not: A Comparative Study of Treated and Newly Diagnosed Osteoporosis Patients

Osteoporotik Kırık Hastalarında D Vitamini Düzeyleri ile Kemik Mineral Yoğunluğu Arasındaki İlişki: Tedavi Alan ve Yeni Tanı Almış Hastaların Karşılaştırılması

Benil Nesli Ata[1], Buğra İnce[2]

[1]İzmir City Hospital, Department of Physical Medicine and Rehabilitation, İzmir, Türkiye
[2]University of Health Sciences Türkiye Faculty of Medicine, İzmir City Hospital, Department of Physical Medicine and Rehabilitation, İzmir, Türkiye

Abstract

Objective: Although osteoporosis treatment improves biochemical parameters, particularly vitamin D status, evidence regarding its relationship with actual changes in bone mineral density (BMD) remains inconsistent. Given these conflicting findings, this study aimed to compare biochemical parameters and dual-energy X-ray absorptiometry (DXA)-derived BMD between newly diagnosed osteoporotic fracture patients and those receiving osteoporosis treatment for at least one year.

Materials and Methods: This retrospective study included 100 patients with osteoporotic fragility fractures and complete DXA and laboratory data; 53 were newly diagnosed and 47 had been receiving osteoporosis treatment. Lumbar and femoral BMD and corresponding T-scores were evaluated. Serum 25-hydroxyvitamin D, calcium, phosphorus, renal function parameters, and body mass index (BMI) were recorded. Between-group comparisons used an independent samples t-test or Mann-Whitney U test. Correlations were analyzed using Pearson or Spearman tests.

Results: In the treated group, serum vitamin D levels showed a significant negative correlation with both lumbar and femoral BMD and corresponding T-scores, representing the most striking finding ($p<0.01$). In contrast, no significant association was observed in the newly diagnosed group. Serum 25-hydroxyvitamin D levels were higher in treated patients ($p<0.05$); however, lumbar and femoral BMD values, T-scores, renal function parameters, BMI, and serum calcium and phosphorus levels did not differ between groups (all $p>0.05$). Additionally, BMI showed a positive correlation with femoral BMD in the treated group ($p<0.01$).

Conclusion: In osteoporotic fracture patients, at least one year of osteoporosis treatment is associated with higher serum vitamin D levels but not with gains in DXA-derived BMD. The negative correlation between vitamin D levels and BMD in treated patients suggests that biochemical improvement may reflect supplementation rather than true skeletal recovery. These findings highlight a dissociation between biochemical response and structural bone adaptation and emphasize that follow-up should rely primarily on densitometric assessment and fracture risk rather than vitamin D levels alone.

Keywords: Osteoporosis, fragility fracture, vitamin D, bone mineral density, dual-energy X-ray absorptiometry, body mass index

Öz

Amaç: Osteoporoz tedavisinin özellikle D vitamini başta olmak üzere bazı biyokimyasal parametrelerde düzelme sağladığı bilinmekle birlikte, bu iyileşmenin çift enerjili X-ışını absorbsiyometrisi (DXA) ile ölçülen kemik mineral yoğunluğu (KMY) üzerindeki etkileri konusunda literatürde çelişkili bulgular bulunmaktadır. Bu çalışmanın amacı, yeni tanı almış osteoporotik kırık hastaları ile en az bir yıldır osteoporoz tedavisi alan hastalarda biyokimyasal parametreler ve DXA ile ölçülen KMY değerlerini karşılaştırmaktır.

Gereç ve Yöntem: Çalışmaya, osteoporotik frajilite kırığı bulunan ve DXA ile laboratuvar verileri tam olan 100 hasta dahil edildi; 53'ü yeni tanı almış, 47'si ise en az 12 aydır osteoporoz tedavisi almaktaydı. Lomber ve femoral KMY ile buna ait T-skorları değerlendirildi. Serum 25-hidroksivitamin D, kalsiyum, fosfor, renal fonksiyon parametreleri ve vücut kitle indeksi (VKİ) kaydedildi. Gruplar arası karşılaştırmalar t-testi veya Mann-Whitney U testi ile yapıldı. Biyokimyasal parametreler ile dansitometrik ölçümler arasındaki ilişkiler Pearson veya Spearman korelasyon analizleri ile değerlendirildi.

Corresponding Author/Sorumlu Yazar: Benil Nesli Ata, MD, İzmir City Hospital, Department of Physical Medicine and Rehabilitation, İzmir, Türkiye
E-mail: drbenilnesli@gmail.com **ORCID ID:** orcid.org/0000-0003-0900-0069
Received/Geliş Tarihi: 10.12.2025 **Accepted/Kabul Tarihi:** 26.01.2026 **Epub:** 23.02.2026 **Publication Date/Yayınlanma Tarihi:** 01.09.2026

Cite this article as/Atıf: Ata BN, İnce B. When vitamin D improves but bone density does not: a comparative study of treated and newly diagnosed osteoporosis patients. Turk J Osteoporos. 2026;32(Suppl 1):8-13

Bulgular: Tedavi alan grupta serum D vitamini düzeyleri ile hem lomber hem de femoral KMY ve buna ait T-skorları arasında anlamlı negatif korelasyon saptandı ve bu bulgu çalışmanın en önemli sonucu olarak değerlendirildi (p<0,01). Buna karşılık yeni tanı grubunda D vitamini ile dansitometrik ölçümler arasında ilişki saptanmadı. Serum 25-hidroksivitamin D düzeyleri tedavi alan hastalarda daha yüksek bulunurken (p<0,05), lomber ve femoral KMY, T-skorları, renal fonksiyon parametreleri, VKİ, kalsiyum ve fosfor açısından gruplar arasında fark izlenmedi (tümü için p>0,05). Ayrıca tedavi grubunda VKİ ile femoral KMY arasında pozitif korelasyon saptandı (p<0,01).

Sonuç: Kırıklı hastalarda en az bir yıllık osteoporoz tedavisi, serum D vitamini düzeylerinde artış ile ilişkili olmakla birlikte DXA ile ölçülen KMY'de artış sağlamamaktadır. Tedavi grubunda saptanan negatif korelasyon, biyokimyasal düzelmenin her zaman gerçek iskelet iyileşmesini yansıtmadığını düşündürmektedir. Bu bulgular, biyokimyasal yanıt ile yapısal kemik adaptasyonu arasında bir ayrışma olduğunu ve osteoporoz takibinde yalnızca D vitamini düzeylerine değil, dansitometri ve klinik kırık riskine birlikte odaklanılması gerektiğini göstermektedir.

Anahtar kelimeler: Osteoporoz, frajilite kırığı, D vitamini, kemik mineral yoğunluğu, çift enerjili X-ışını absorbsiyometrisi, vücut kitle indeksi

Introduction

Osteoporosis is a systemic skeletal disorder characterized by reduced bone mass and deterioration of bone microarchitecture, leading to increased bone fragility and susceptibility to fractures. It represents a major global public health problem and affects more than 200 million individuals worldwide, particularly postmenopausal women and elderly populations. Osteoporotic fractures are associated with substantial morbidity, mortality, loss of independence, and a significant socioeconomic burden. Vertebral, hip, and distal radius fractures are the most common clinical manifestations, while hip fractures carry the highest risk of mortality and long-term disability (1).

Bone mineral density (BMD), assessed by dual-energy X-ray absorptiometry (DXA), remains the most reliable and widely accepted structural predictor of osteoporotic fracture risk. Lumbar spine and femoral neck BMD measurements are essential for diagnostic classification, therapeutic decision-making, and longitudinal monitoring. It is well established that each standard deviation (SD) decrease in BMD is associated with an approximately two-fold increase in fracture risk. Accordingly, preservation or improvement of BMD constitutes the primary structural goal of osteoporosis therapy (2).

Vitamin D plays a pivotal role in calcium and phosphate homeostasis, intestinal calcium absorption, bone mineralization, and skeletal muscle function. Vitamin D deficiency is highly prevalent among patients with osteoporosis and has been consistently linked to reduced BMD, impaired bone quality, increased fall risk, and higher fracture incidence. Multiple clinical studies have demonstrated significant associations between serum 25-hydroxyvitamin D levels and both lumbar and femoral BMD values, emphasizing the direct contribution of vitamin D status to skeletal integrity (3).

Current expert consensus statements highlight that achieving and maintaining sufficient vitamin D levels is a fundamental component of osteoporosis prevention and treatment. Adequate vitamin D supplementation enhances intestinal calcium absorption, improves the anti-fracture efficacy of antiresorptive and anabolic agents, and contributes to neuromuscular function and fall prevention. However, despite ongoing pharmacological therapy, a substantial proportion of patients fail to reach or maintain optimal vitamin D concentrations, potentially limiting structural bone recovery and delaying fracture risk reduction (4).

Although the role of vitamin D in skeletal health and bone metabolism is well established, the temporal relationship between biochemical improvement and structural bone response remains incompletely understood. While serum vitamin D levels may normalize relatively rapidly with supplementation, bone remodeling is inherently slow, and measurable increases in BMD often require prolonged treatment durations. Consequently, biochemical normalization does not necessarily translate into parallel structural improvement of bone tissue. Moreover, data directly comparing newly diagnosed osteoporosis patients with those undergoing long-term treatment in terms of vitamin D status, fracture characteristics, renal function, body composition, and site-specific BMD parameters remain limited in the current literature (2-4).

Although the biochemical effects of osteoporosis treatment—particularly on vitamin D and mineral metabolism—are well established, real-world data directly comparing biochemical and DXA-derived densitometric profiles of newly diagnosed osteoporotic fracture patients with those receiving long-term treatment remain limited and inconsistent (4,5). Moreover, the extent to which treatment-related biochemical changes translate into structural skeletal improvement assessed by DXA is still incompletely understood (6,7). Therefore, this study aimed to compare biochemical parameters and DXA-derived BMD between newly diagnosed osteoporotic fracture patients and those receiving osteoporosis treatment for at least one year.

Materials and Methods

This study was designed as a single-center, retrospective observational study. Medical records of patients who attended a tertiary care outpatient clinic for the evaluation of osteoporotic fragility fractures between January 2025 and October 2025 were reviewed retrospectively. Patients were identified through the hospital electronic medical record system using diagnostic codes related to osteoporotic fragility fractures. Only patients with complete DXA measurements, radiologically confirmed osteoporotic fractures, and complete laboratory data were included in the study. Patients with secondary causes of osteoporosis, active malignancy, chronic inflammatory disease, long-term systemic corticosteroid use, or advanced chronic kidney disease were excluded.

Eligible patients were divided into two groups according to their osteoporosis treatment status. The newly diagnosed group consisted of patients who were diagnosed with osteoporosis for the first time during the screening period and had not received any prior anti-osteoporotic treatment. The treated group consisted of patients who had been receiving regular anti-osteoporotic therapy for at least 12 months before the evaluation. All analyses were performed based on this two-group classification.

Demographic data including age, height, weight, and body mass index (BMI) were recorded. Clinical data regarding fracture number, fracture localization, and fracture duration were obtained from patient files and imaging records. Fracture duration was defined as the time interval between the first radiologically confirmed osteoporotic fracture and the index outpatient clinic visit.

Laboratory parameters obtained at the time of DXA assessment included serum calcium, serum phosphorus, serum 25-hydroxyvitamin D, serum creatinine, and estimated glomerular filtration rate (eGFR). All biochemical analyses were performed in the central hospital laboratory using standardized automated techniques. eGFR values were calculated using the CKD-EPI equation.

BMD measurements were performed using DXA with a Lunar Prodigy Advance system (GE Healthcare, Madison, WI, USA; model number 513540) at the lumbar spine (L1-L4), femoral neck, and total femur regions. For all skeletal sites, both BMD values expressed in g/cm² and corresponding T-scores were recorded. Vertebrae affected by compression fractures or severe degenerative changes were excluded from lumbar spine analysis. Lumbar BMD measurements were calculated using at least two evaluable vertebrae in accordance with international DXA guidelines. All DXA measurements were obtained using the same device to ensure technical consistency.

Ethical approval for the study was obtained from a Local Non-Interventional Clinical Research Ethics Committee of University of Health Sciences Türkiye, İzmir City Hospital (decision no: 2025/548; date: 16 October 2025). Due to the retrospective study design, the requirement for informed consent was waived. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed continuous variables were expressed as mean ± SD, whereas non-normally distributed variables were presented as median and interquartile range.

Between-group comparisons between newly diagnosed and treated patients were conducted using the independent-samples t-test for normally distributed continuous variables. The Mann-Whitney U test was used for non-normally distributed variables, including fracture duration, and serum 25-hydroxyvitamin D levels.

Within each group, the associations between continuous clinical, biochemical, and densitometric variables were analyzed using Pearson correlation analysis. Correlation strength was interpreted based on the absolute value of the correlation coefficient (r).

All statistical tests were performed as two-tailed analyses, and a p-value <0.05 was considered statistically significant.

Results

A total of 100 osteoporotic patients with fragility fractures were included in the study, of whom 53 were newly diagnosed and 47 were receiving long-term osteoporosis treatment. The between-group comparisons of parametric variables are presented in Table 1, while non-parametric variables are summarized in Table 2.

Table 1. Comparison of parametric variables between newly diagnosed and treated patients

Variable	Newly diagnosed (mean ± SD) (n=53)	Treated (mean ± SD) (n=47)	p-value
Serum calcium (mg/dL)	9.49±0.57	9.52±0.46	>0.05
Serum phosphorus (mg/dL)	3.52±0.45	3.46±0.53	>0.05
eGFR (mL/min/1.73 m²)	81.91±15.22	85.31±17.02	>0.05
Lumbar BMD (g/cm²)	0.941±0.143	0.953±0.105	>0.05
Femoral neck BMD (g/cm²)	0.760±0.118	0.776±0.091	>0.05
Total femur BMD (g/cm²)	0.789±0.123	0.811±0.105	>0.05
Lumbar T-score	-2.06±1.16	-1.90±0.86	>0.05
Femoral neck T-score	-2.01±0.85	-1.88±0.65	>0.05
Total femur T-score	-1.77±0.97	-1.56±0.84	>0.05
BMI (kg/m²)	28.02±5.03	26.91±4.27	>0.05
Age (years)	68.83±9.17	66.85±9.09	>0.05

Between-group comparisons were performed using the independent samples t-test. Statistical significance was defined as p<0.05, SD: Standard deviation, BMD: Bone mineral density, BMI: Body mass index, eGFR: Estimated glomerular filtration rate

Table 2. Comparison of newly diagnosed and treated patients (non-parametric variables)			
Variable	**Newly diagnosed (n=53)**	**Treated (n=47)**	**p-value**
Fracture duration (months)	3 (5)	12 (38)	<0.05
Vitamin D (ng/mL)	23.4 (20.4)	38.9 (27.9)	<0.05
Note: Data are presented as median (interquartile range). Between-group comparisons were performed using the Mann-Whitney U test. Statistical significance was defined as p<0.05			

Patients in the treated group exhibited a significantly longer fracture duration and higher serum vitamin D levels compared to newly diagnosed patients (p<0.05 for both; Table 2). No significant differences were observed between the groups with respect to age, BMI, renal function, serum calcium and phosphorus levels, or lumbar, femoral neck, and total femur BMD and T-score parameters (all p>0.05; Table 1).

Correlation analyses performed within the treated group revealed several clinically meaningful associations (Table 3). Serum vitamin D levels showed significant negative correlations with lumbar and femoral BMD and corresponding T-scores (r=-0.306 to -0.437, p=0.002-0.041). Advancing age was significantly associated with lower eGFR and reduced femoral neck and total femur bone density and T-scores (r=-0.292 to -0.385, p=0.005-0.037). In contrast, BMI demonstrated significant positive correlations with femoral neck and total femur BMD and T-scores (r=+0.402 to +0.484, p=0.001-0.003).

No clinically meaningful correlations were observed between vitamin D, age, BMI, and site-specific BMD parameters in the newly diagnosed group (all p>0.05).

Discussion

In this study, we found that patients receiving long-term osteoporosis treatment exhibited significantly higher serum 25-hydroxyvitamin D levels and longer fracture duration compared with newly diagnosed patients, whereas lumbar and femoral BMD values and corresponding T-scores were broadly comparable between the two groups. This dissociation between biochemical improvement and structural skeletal response indicates that correction of vitamin D deficiency does not necessarily translate into measurable gains in BMD in patients with established fragility fractures. These findings are consistent with previous randomized controlled trials and large population-based studies demonstrating that vitamin D supplementation leads to substantial increases in circulating 25-hydroxyvitamin D levels but only minimal or no clinically meaningful changes in spine or hip BMD (6-8). Furthermore, recent observational data have emphasized that improvement in vitamin D status may coexist with persistently low BMD in high-risk fracture populations (9). Collectively, our results emphasize that biochemical normalization alone should not be interpreted as evidence of structural bone recovery.

In the present study, a significant negative correlation was observed between serum 25-hydroxyvitamin D levels and both BMD values and corresponding T-scores in the treated group. Although vitamin D deficiency is traditionally associated with low BMD and increased fracture risk, recent large-scale randomized trials and meta-analyses have shown that vitamin

Table 3. Significant correlations between clinical variables and bone density parameters in the treated group			
Clinical variable	**Bone parameter**	**r**	**p-value**
Vitamin D (ng/mL)	Lumbar spine BMD (g/cm²)	-0.361	0.015
Vitamin D (ng/mL)	Femoral neck BMD (g/cm²)	-0.437	0.002
Vitamin D (ng/mL)	Total femur BMD (g/cm²)	-0.313	0.034
Vitamin D (ng/mL)	Lumbar spine T-score	-0.360	0.015
Vitamin D (ng/mL)	Femoral neck T-score	-0.435	0.003
Vitamin D (ng/mL)	Total femur T-score	-0.306	0.041
Age (years)	Femoral neck BMD (g/cm²)	-0.294	0.036
Age (years)	Total femur BMD (g/cm²)	-0.385	0.005
Age (years)	Femoral neck T-score	-0.292	0.037
Age (years)	eGFR (mL/min/1.73 m²)	-0.369	0.011
Body mass index (kg/m²)	Femoral neck BMD (g/cm²)	+0.402	0.003
Body mass index (kg/m²)	Total femur BMD (g/cm²)	+0.484	<0.001
Body mass index (kg/m²)	Femoral neck T-score	+0.402	0.003
Body mass index (kg/m²)	Total femur T-score	+0.402	0.003
Pearson correlation analysis was used. Only statistically significant correlations (p<0.05) are shown. BMD: Bone mineral density, eGFR: Estimated glomerular filtration rate			

D supplementation, despite effectively increasing serum levels, confers only modest or even negligible benefits on lumbar and femoral BMD (6). Moreover, studies in fracture populations indicate marked interindividual variability in skeletal response following vitamin D repletion, reflecting heterogeneous post-fracture bone remodeling (10).

Population-based data further suggest that the association between vitamin D and BMD is weak, site-dependent, and strongly influenced by age, adiposity, and hormonal factors (11). In addition, Mendelian randomization analyses have failed to demonstrate a causal relationship between genetically determined vitamin D levels and BMD, supporting the role of confounding and reverse causality (12). This finding also underscores that higher vitamin D levels in treated patients may reflect pharmacological supplementation rather than true skeletal response. Accordingly, the inverse association observed in our cohort is most plausibly explained by disease severity bias and temporal dissociation. Patients with more advanced bone loss and longer fracture histories are more likely to receive intensive vitamin D supplementation, while structural bone recovery remains limited due to the slow dynamics of bone remodeling.

In our cohort, fracture duration was substantially longer in the treated group, whereas lumbar and femoral BMD values and corresponding T-scores were comparable to those of newly diagnosed patients. This finding supports the concept that once a fragility fracture has occurred, the skeleton may remain chronically fragile even when areal BMD appears relatively stable. Large population-based studies and meta-analyses have consistently demonstrated that a prior low-trauma fracture is among the strongest independent predictors of subsequent fractures, with a markedly increased risk in the early post-fracture period and a persistently elevated risk over longer follow-up, irrespective of baseline BMD (13-16). Accordingly, the similar BMD profiles observed in patients with longer fracture duration in our study likely reflect irreversible or only partially reversible microarchitectural damage, as well as the contribution of non–BMD determinants of bone strength—such as fall risk, comorbidities, and bone material properties—that are not captured by DXA measurements. Clinically, these findings underscore that fracture history and fracture duration should be considered alongside BMD and vitamin D status when assessing residual skeletal fragility in treated osteoporosis patients.

In our cohort, BMI showed a significant positive correlation with femoral neck and total femur BMD values ($r=0.402$-0.484, $p<0.01$), suggesting a protective mechanical effect of higher body weight on hip bone mineral content in osteoporotic patients. This finding is consistent with previous studies demonstrating that individuals with higher BMI tend to have greater proximal femur BMD and more favorable hip geometry, which may reduce the risk of hip fractures (17,18). In addition, meta-analytic data confirm that low BMI is a strong and consistent risk factor for hip and other fragility fractures, whereas moderate overweight may confer relative skeletal protection (19).

From a mechanistic perspective, increased mechanical loading stimulates bone formation through adaptive remodeling, while adipose tissue–derived endocrine factors, such as peripheral estrogen production and leptin signaling, may further contribute to bone mass accrual (18,20). Nevertheless, the apparent protective effect of high BMI should be interpreted with caution, as excess adiposity is also associated with impaired bone quality, altered microarchitecture, and increased fall risk, particularly in elderly individuals (19,20). Clinically, our findings indicate that although higher BMI may provide a modest biomechanical advantage at the femur in treated osteoporosis patients, it should not be regarded as a substitute for pharmacologic bone-strengthening therapy.

From a clinical standpoint, the present findings indicate that normalization of serum vitamin D levels should not be interpreted as a surrogate marker of skeletal recovery in patients with established osteoporotic fractures. The coexistence of improved biochemical parameters with persistently low lumbar and femoral BMD underscores the need for fracture risk assessment based not only on laboratory indices, but also on fracture history, fracture duration, and site-specific BMD measurements. Furthermore, although higher BMI was positively associated with proximal femoral BMD in our cohort, this mechanical advantage appears insufficient to offset the underlying skeletal fragility in high-risk osteoporotic patients. Collectively, these results highlight that assessment and follow-up of treated osteoporosis should integrate biochemical markers with densitometric findings and fracture-related clinical characteristics rather than relying on vitamin D status alone.

Study Limitations

Several limitations of this study should be acknowledged. First, the retrospective and single-center design limits causal inference and may reduce the generalizability of the findings. Second, detailed data regarding the type, dose, and duration of specific anti-osteoporotic medications were not available, which precluded treatment-based subgroup analyses. Third, skeletal strength was assessed using areal BMD derived from DXA, which does not reflect bone microarchitecture or material properties that also contribute to fracture resistance. In addition, important potential confounders, including physical activity level, fall frequency, frailty status, and parathyroid hormone levels, could not be evaluated. Nevertheless, despite these limitations, the present study provides valuable real-world data from a fracture-based osteoporotic population and offers clinically meaningful insight into the dissociation between biochemical improvement and structural skeletal recovery in treated patients. In addition, bone turnover markers were not available, which limits the interpretation of dynamic skeletal remodeling.

Conclusion

In patients with osteoporotic fractures, long-term treatment was associated with significantly higher serum vitamin D levels and longer fracture duration, but not with improvement

in lumbar BMD or corresponding T-scores. These findings indicate that biochemical correction of vitamin D deficiency does not necessarily translate into structural skeletal recovery in patients with established fragility fractures. The observed inverse association between vitamin D and BMD parameters in the treated group further supports the presence of disease severity bias and temporal dissociation between biochemical and densitometric responses. In addition, the positive relationship between BMI and proximal femoral BMD suggests a limited mechanical advantage, which appears insufficient to offset underlying osteoporotic fragility. Collectively, our results emphasize that fracture history, fracture duration, and site-specific BMD should remain central components of fracture risk assessment in treated osteoporosis patients, beyond biochemical parameters alone.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from a Local Non-Interventional Clinical Research Ethics Committee of University of Health Sciences Türkiye, İzmir City Hospital (decision no: 2025/548; date: 16 October 2025).

Informed Consent: Due to the retrospective study design, the requirement for informed consent was waived.

Footnotes

Authorship Contributions

Concept: B.N.A., Design: B.N.A., B.İ., Data Collection or Processing: B.N.A., Analysis or Interpretation: B.N.A., B.İ., Literature Search: B.N.A., B.İ., Writing: B.N.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/tod.galenos.2026.48295
Turk J Osteoporos 2026;32(Suppl 1):14-19

From Neurorehabilitation to Robotics and Artificial Intelligence: A Decade of Global Public Interest Assessed by Google Trends

Nörorehabilitasyondan Robotik ve Yapay Zekaya: Google Trends ile Değerlendirilen Küresel Kamu İlginin On Yıllık Analizi

Muhsin Doran

Liv Hospital Vadistanbul, Clinic of Physical Medicine and Rehabilitation, İstanbul, Türkiye

Abstract

Objective: Rapid advances in digital health technologies have increased public interest in robotic and technology-assisted rehabilitation approaches. Internet search engines reflect individuals' health-related information-seeking behaviors and enable the assessment of this interest. The aim of this study was to evaluate global public interest in key terms related to neurological, robotic, and technology-assisted rehabilitation over the past decade using Google trends data and to compare interest levels between two consecutive five-year periods.

Materials and Methods: In this retrospective, observational infodemiology study, relative search volume data from January 1, 2016 to December 31, 2025 were analyzed. The study period was divided into two equal intervals: 2016-2020 and 2021-2025. Keywords were selected in accordance with the priorities of the World Federation for NeuroRehabilitation and the European Federation of NeuroRehabilitation Societies. Inter-period comparisons were performed using the Mann-Whitney U test.

Results: A significant increase in public interest was observed for the majority of the analyzed keywords during the 2021-2025 period ($p<0.001$ for most terms). Notable increases were identified for the terms robotic rehabilitation, robotic gait training, exoskeleton rehabilitation, stroke robotic rehabilitation, artificial intelligence rehabilitation, and virtual reality rehabilitation. In contrast, no significant difference was observed for the term neurorehabilitation, while the brand-specific term Lokomat demonstrated a high but stable level of public interest.

Conclusion: Global public interest in robotic and technology-assisted neurological rehabilitation has increased markedly over the past decade. This trend indicates growing societal awareness of the digital transformation within the field of rehabilitation.

Keywords: Neurorehabilitation, robotic rehabilitation, technology-assisted rehabilitation, Google trends

Öz

Amaç: Dijital sağlık teknolojilerindeki hızlı gelişmeler, robotik ve teknoloji destekli rehabilitasyon yaklaşımlarına yönelik kamu ilgisini artırmaktadır. İnternet arama motorları, bireylerin sağlıkla ilgili bilgi arama davranışlarını yansıtarak bu ilginin değerlendirilmesine olanak sağlar. Bu çalışmanın amacı, Google trends verileri kullanılarak son on yılda nörolojik, robotik ve teknoloji destekli rehabilitasyonla ilişkili anahtar terimlere yönelik küresel kamu ilgisini değerlendirmek ve iki ardışık beş yıllık dönem arasında karşılaştırmaktır.

Gereç ve Yöntem: Bu retrospektif gözlemsel infodemiyoloji çalışmasında, 1 Ocak 2016-31 Aralık 2025 dönemine ait göreceli arama hacmi verileri analiz edilmiştir. Çalışma dönemi 2016-2020 ve 2021-2025 olmak üzere iki eşit periyoda ayrılmıştır. Anahtar terimler, World Federation for NeuroRehabilitation ve European Federation of NeuroRehabilitation Societies öncelikleri doğrultusunda seçilmiştir. Dönemler arası karşılaştırmalar Mann-Whitney U testi ile yapılmıştır.

Bulgular: Anahtar kelimelerin büyük çoğunluğunda 2021-2025 döneminde kamu ilgisinin anlamlı düzeyde arttığı saptanmıştır (çoğu terim için $p<0,001$). Robotic rehabilitation, robotic gait training, exoskeleton rehabilitation, stroke robotic rehabilitation, AI rehabilitation ve virtual reality rehabilitation terimleri belirgin artış göstermiştir. Neurorehabilitation teriminde anlamlı fark izlenmezken, Lokomat yüksek ancak stabil bir ilgi düzeyi sergilemiştir.

Corresponding Author/Sorumlu Yazar: Muhsin Doran, MD, Liv Hospital Vadistanbul, Clinic of Physical Medicine and Rehabilitation, İstanbul, Türkiye
E-mail: muhsin-doran@hotmail.com **ORCID ID:** orcid.org/0000-0002-6314-1981
Received/Geliş Tarihi: 13.01.2026 **Accepted/Kabul Tarihi:** 18.03.2026 **Epub:** 29.04.2026 **Publication Date/Yayınlanma Tarihi:** 01.09.2026

Cite this article as/Atıf: Doran M. From neurorehabilitation to robotics and artificial intelligence: a decade of global public interest assessed by Google trends. Turk J Osteoporos. 2026;32(Suppl 1):14-19

Sonuç: Son on yılda robotik ve teknoloji destekli nörolojik rehabilitasyona yönelik küresel kamu ilgisi belirgin biçimde artmıştır. Bu eğilim, rehabilitasyon alanındaki dijital dönüşüme yönelik toplumsal farkındalığın güçlendiğini göstermektedir.
Anahtar kelimeler: Nörorehabilitasyon, robotik rehabilitasyon, teknoloji destekli rehabilitasyon, Google trends

Introduction

Health-related information seeking has increasingly shifted to online environments in recent years, with search engines becoming one of the primary sources for patients and their caregivers to obtain information about symptoms, diagnoses, and treatment options. Indeed, analyses based on European data report that approximately half of individuals searched the internet for health-related information and symptoms in 2022, and that this trend continues to increase (1). This behavioral shift enhances the value of "digital traces" for understanding societal awareness and expectations regarding specific diseases and therapeutic approaches.

In this context, infodemiology/infoveillance has been defined as an approach aimed at examining the distribution and determinants of information in online environments and generating insights for the health domain based on these data (2). The analysis of digital traces such as internet search queries allows the investigation of which clinical topics attract public interest and how this interest changes over time. Google trends (GT) is one of the most widely used open-access tools for measuring public interest in a time-series format by providing relative search volume (RSV) data for specific keywords.

The use of GT in health research has increased steadily, and methodological evaluations and reviews have shown that GT has been applied in various ways to characterize, monitor, and, in some scenarios, predict online interest in health-related phenomena (3). However, it is emphasized that GT data do not directly represent clinical prevalence or actual healthcare utilization; rather, they primarily reflect information-seeking behavior and public interest (3). Accordingly, GT-based studies are particularly valuable for tracking changes in societal awareness, curiosity, and perceptions rather than clinical outcomes.

Research on rehabilitation robotics has gained substantial momentum since the 1990s, a period that has been identified as a turning point during which the field began to develop in a systematic manner (4). Within the rehabilitation domain, robotic and advanced technologies—such as exoskeletons, robotic gait training systems, virtual reality applications, and artificial intelligence (AI)–based approaches—have attracted increasing attention due to the long-term and intensive rehabilitation requirements characteristic of neurological disorders. Scientific output related to these technologies has likewise increased, with bibliometric analyses covering the 2010-2020 period reporting steady growth in the rehabilitation robotics literature and a progressive concentration of research focus on themes such as exoskeletons, virtual reality, brain-computer interfaces, and intelligent control systems (5).

Despite this expansion in the scientific literature, infodemiological studies evaluating how these developments are reflected at the societal level—specifically, the temporal evolution of global public interest in robotic and technology-assisted rehabilitation approaches—remain relatively limited.

The aim of this study was to examine changes in global public interest in selected keywords related to neurological, robotic, and technology-assisted rehabilitation during the 2016-2025 period using GT data, and to compare RSV levels between two consecutive five-year intervals (2016-2020 and 2021-2025). By doing so, the study sought to provide a data-driven framework illustrating how technology-oriented transformations within the rehabilitation ecosystem are reflected in societal information-seeking behavior.

Materials and Methods

Study Design

This study was designed as a retrospective, observational infodemiology study based on GT data. Global public interest was assessed using online search behaviors related to neurological and technology-assisted rehabilitation.

Data Source and Search Strategy

Data were obtained from the GT platform (https://trends.google.com). Searches were conducted using the web search option, across all categories, and on a worldwide scale. The study period was defined as January 1, 2016 to December 31, 2025, and monthly RSV data provided by GT were used for the analyses.

Selection of Keywords

Keywords were determined by a physical medicine and rehabilitation specialist with clinical experience in neurological rehabilitation, robotic rehabilitation, and technology-assisted rehabilitation. During the selection process, the research and clinical priorities of international neurorehabilitation organizations—the World Federation for NeuroRehabilitation and the European Federation of NeuroRehabilitation Societies—were taken into consideration. To ensure suitability for GT analysis, commonly used, concise, and English-language terms were selected.

The keywords included in the analysis were as follows:

- Neurorehabilitation
- Stroke rehabilitation
- Robotic rehabilitation
- Robotic therapy
- Robotic gait training
- Exoskeleton rehabilitation

- Lokomat
- Stroke robotic rehabilitation
- Spinal cord injury robot therapy
- AI rehabilitation
- Virtual reality rehabilitation
- Rehabilitation technology
- Rehabilitation technologies
- Technology-based rehabilitation.

Definition of Study Periods

The ten-year study duration was divided into two equal five-year periods:

- **Period 1 (P1):** January 1, 2016-December 31, 2020
- **Period 2 (P2):** January 1, 2021-December 31, 2025.

This division was applied to evaluate changes in interest in digital and robotic health technologies during the post-pandemic period.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics software (version 29.0; IBM Corp., Armonk, NY, USA). RSV data obtained from the GT platform were analyzed on a monthly basis. Descriptive statistics were presented as mean, median, standard deviation, and minimum-maximum values for each keyword and study period.

As the RSV data did not meet the assumption of normal distribution, as confirmed by the Shapiro-Wilk test and visual inspection of distribution plots, non-parametric Mann-Whitney U tests were used to compare the two periods (2016-2020 and 2021-2025). Analyses were conducted separately for each keyword to evaluate inter-period differences.

All statistical tests were two-sided, and a p-value of <0.05 was considered statistically significant.

In addition to period-based comparisons, annual mean RSV values were calculated to visualize temporal trends between 2016 and 2025, and line graphs were generated to illustrate longitudinal changes.

Results

For all keywords included in the GT analysis, notable changes in global public interest were observed between the 2016-2020 and 2021-2025 periods. For the majority of terms related to robotic and technology-assisted rehabilitation, RSV increased significantly during the second five-year period (Table 1).

Annual trend analysis demonstrated a gradual increase beginning in 2019, followed by a steeper acceleration after 2021 for several technology-oriented keywords (Figure 1).

In particular, public interest in the terms robotic rehabilitation, robotic therapy, robotic gait training, exoskeleton rehabilitation, stroke robotic rehabilitation, AI rehabilitation, and virtual reality rehabilitation was significantly higher in the 2021-2025 period compared with the 2016-2020 period (all p<0.001). For most of these terms, low or near-zero search volumes were observed during the first period, followed by sharp increases in the second period.

Table 1. Comparison of global public interest in neurological and technology-assisted rehabilitation terms according to Google trends (2016-2020 vs. 2021-2025)

Keyword	P1 Mean ± SD	P1 Median	P1 Min-max	P2 Mean ± SD	P2 Median	P2 Min-max	p-value
Robotic rehabilitation	9.30±1.67	9.0	5-13	23.48±22.04	18.0	4-100	**<0.001**
Robotic therapy	7.70±1.81	8.0	4-12	17.82±22.23	10.0	3-100	**<0.001**
Robotic gait training	0.00±0.00	0.0	0-0	10.10±23.84	0.0	0-100	**<0.001**
Exoskeleton rehabilitation	3.03±2.84	4.0	0-8	13.30±22.30	7.0	0-100	**<0.001**
Lokomat	35.28±5.97	36.0	22-55	33.93±14.52	30.5	23-100	**<0.001**
Neurorehabilitation	27.42±3.39	27.0	19-34	33.05±18.64	28.0	17-100	0.61
Stroke rehabilitation	17.37±1.55	17.0	15-21	25.27±17.40	20.0	15-100	**<0.001**
Stroke robotic rehabilitation	0.38±2.97	0.0	0-23	12.50±22.27	0.0	0-100	**<0.001**
Spinal cord injury robot therapy	0.00±0.00	0.0	0-0	1.67±12.91	0.0	0-100	0.33
AI rehabilitation	0.00±0.00	0.0	0-0	9.82±24.62	1.0	0-100	**<0.001**
Virtual reality rehabilitation	8.08±2.92	8.0	0-18	17.45±21.40	10.5	5-100	**<0.001**
Rehabilitation technology	7.45±0.93	7.0	6-10	16.25±21.18	10.0	5-100	**<0.001**
Rehabilitation technologies	6.63±1.83	6.0	0-12	15.75±21.53	9.0	0-100	**<0.001**
Technology-based rehabilitation	0.00±0.00	0.0	0-0	11.72±22.44	0.0	0-100	**<0.001**

P1: 01.01.2016-31.12.2020. P2: 01.01.2021-31.12.2025, RSV: Relative search volume, SD: Standard deviation, Mann-Whitney U test, AI: Artificial intelligence

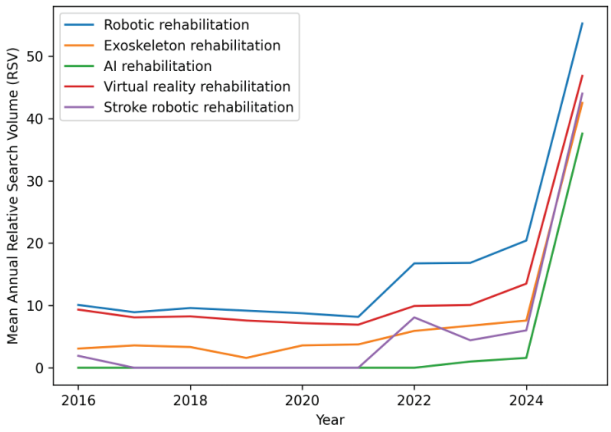

Figure 1. Annual mean relative search volume trends for selected technology-oriented rehabilitation keywords between 2016 and 2025
AI: Artificial intelligence

In contrast, no statistically significant difference was observed between the two periods for the more general term neurorehabilitation (p=0.61). Similarly, although an upward trend was noted for the term spinal cord injury robot therapy during the second period, this difference did not reach statistical significance (p=0.33).

The brand-specific keyword Lokomat exhibited a relatively high level of public interest across both periods but did not demonstrate a significant increase between periods. Collectively, these findings indicate that public interest has shifted particularly toward emerging robotic and digital rehabilitation technologies, while more established and general concepts have remained relatively stable.

Discussion

This study examined changes in global public interest in neurological, robotic, and technology-assisted rehabilitation approaches over the past decade using GT data and revealed a marked increase, particularly during the 2021-2025 period. The findings indicate that society's health information–seeking behavior in the field of rehabilitation has evolved over time, with a pronounced shift toward innovative, technology-based, and practice-oriented rehabilitation approaches.

The acceleration observed during the 2021-2025 period may also be interpreted within the broader context of the global digital health transformation that intensified following the coronavirus disease-2019 (COVID-19) pandemic. The pandemic substantially accelerated the integration of telemedicine, remote assessment tools, and technology-enhanced therapeutic platforms into routine healthcare delivery. In rehabilitation medicine, this digital momentum likely increased both professional and public awareness of robotic, AI-supported, and virtual reality-based interventions, which align with emerging trends toward data-driven, intensive, and technology-integrated therapy models.

Within rehabilitation sciences, the rapid expansion of digital health technologies likely increased scientific output, media visibility, and professional discourse surrounding robotic, AI-assisted, and immersive rehabilitation systems, thereby contributing to heightened societal awareness.

Robotic and technology-assisted rehabilitation approaches have attracted growing research and clinical interest because they move beyond classical rehabilitation paradigms by offering intensive, repeatable, and quantifiable exercise capacity. Systematic reviews have demonstrated that robotic motor rehabilitation systems have the potential to improve both upper and lower extremity function and that these technologies may also reduce therapist workload while making rehabilitation interventions more standardized and reproducible (6).

Some neurological diseases are characterized by the need for long-term rehabilitation and slow, gradual recovery processes (7,8). This situation creates a trajectory shaped not only by the experiences of patients but also by those of their families and caregivers, involving uncertainty, expectations, and a continual search for hope (9). In this context, the increasing public interest in robotic and technology-assisted rehabilitation approaches may be associated not only with the availability of technological advances but also with societal expectations that these methods can accelerate recovery, enhance functional outcomes, and render the rehabilitation process more predictable (10).

The pronounced increase observed in terms such as robotic rehabilitation, exoskeleton rehabilitation, stroke robotic rehabilitation, and robotic gait training suggests that public interest has shifted away from abstract technological concepts toward applications directly associated with functional recovery and perceived tangible clinical benefits. Given the time-consuming nature of conventional rehabilitation approaches in neurological disorders, the intensive, repeatable, and quantifiable treatment characteristics offered by robotic systems are likely perceived by patients and their families as an attractive alternative. Furthermore, the increasing integration of these technologies into routine clinical practice across a growing number of centers, along with their greater visibility in patient education and informational materials, may have contributed to the perception of robotic rehabilitation as an accessible and viable option within the community.

The observed increase in technology-oriented search terms may reflect broader structural transformations within the rehabilitation ecosystem, as reflected in patterns of public information-seeking behavior. The shift in search trends from broader umbrella terms such as robotic rehabilitation toward more specific, application-oriented terms—including exoskeleton rehabilitation, stroke robotic rehabilitation, virtual reality rehabilitation, and AI rehabilitation—indicates that public interest has moved from general concepts to concrete technologies and interventions. The fact that several technology-based keywords exhibited very low or near-zero search volumes during the first

period but demonstrated substantial growth in the second period suggests that these concepts have only relatively recently entered the public lexicon, with meaningful search activity emerging predominantly in recent years. However, as GT provides normalized relative search volumes rather than absolute counts, these findings should be interpreted as indicative of proportional changes in interest rather than exact magnitudes of public engagement. Conversely, the consistently high yet relatively stable interest observed for brand-specific terms such as Lokomat implies that public attention may be influenced not only by technological innovation but also by factors such as brand recognition and institutional visibility.

The increase in public interest identified in this study is also consistent with research trends reported in the scientific literature. Bibliometric analyses in the field of rehabilitation robotics have demonstrated a steady rise in scientific output over the past decade, with a progressive shift in research focus toward more sophisticated and technology-intensive topics (5,11). In particular, the emergence of exoskeletons, virtual reality, brain-computer interfaces, and AI-driven control systems as prominent research themes suggests that these technologies have gained visibility not only within academic communities but also within a broader societal context. When bibliometric findings are considered alongside GT data, the results indicate that growth in the field of robotic rehabilitation encompasses not only scientific production but also increasing societal awareness and expectations over time.

Recent analyses have highlighted the exponential growth of AI applications in healthcare, particularly in rehabilitation engineering, predictive analytics, and adaptive therapy systems (12-14). The integration of machine learning algorithms into robotic rehabilitation devices has enabled adaptive and personalized treatment modulation based on patient performance metrics. This technological evolution may have contributed not only to scientific expansion but also to increased media visibility, thereby influencing public search behavior.

These findings suggest that the future development of robotic and technology-assisted rehabilitation will be shaped not only by technical advancements but also by the expectations and perceptions of patients, caregivers, and clinical stakeholders. Accordingly, this shift in public interest indicates an increasing societal awareness of technology-based approaches within the field of rehabilitation.

From a clinical perspective, the increasing public interest in robotic and technology-assisted rehabilitation underscores the necessity for clinicians to be adequately informed about these modalities. As patients increasingly seek information about robotic systems, AI-based rehabilitation platforms, and virtual reality interventions, healthcare providers may encounter higher expectations regarding availability, accessibility, and outcomes of such technologies. This trend highlights the importance of evidence-based communication and realistic expectation management in clinical practice.

Study Limitations

This study has several limitations. First, GT data provide normalized RSV rather than absolute search counts. Consequently, the findings do not directly reflect the actual clinical utilization of rehabilitation technologies, disease prevalence, or healthcare demand; instead, they primarily represent public information-seeking behavior and levels of awareness.

Second, GT data are derived from the search behavior of users with internet access. Regions with limited internet availability or populations with lower socioeconomic status may therefore be underrepresented. This limitation may restrict the interpretation of the geographic distribution of global public interest.

Third, the keywords used in the analysis were selected in English. Searches conducted in languages other than English were not included, which may have resulted in an underrepresentation of search behaviors in non-English-speaking countries.

Finally, GT analyses do not establish causality. It is not possible to determine with certainty whether observed increases in public interest during specific periods are attributable to technological advancements, scientific publications, media influence, or external factors such as the COVID-19 pandemic. Accordingly, the results should be interpreted in terms of temporal trends and changes in awareness rather than causal relationships.

Conclusion

This study demonstrates a significant increase in global public interest in robotic and technology-assisted neurological rehabilitation approaches over the past decade, based on analyses of GT data. In particular, the marked rise in search trends related to robotic rehabilitation, exoskeleton systems, AI, and virtual reality–based rehabilitation applications during the 2021-2025 period highlights growing societal awareness of the technological transformation within the field of rehabilitation.

These findings may help inform future clinical, educational, and research priorities related to digital and robotic rehabilitation applications.

Ethics

Ethics Committee Approval: This study did not require ethics committee approval as it was based on publicly available data.

Informed Consent: Informed consent was not required for this study as it did not involve human participants or private medical information.

Footnotes

Financial Disclosure: The author declared that this study received no financial support.

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DOI: 10.4274/tod.galenos.2026.76069
Turk J Osteoporos 2026;32(Suppl 1):20-27

The Relationship Between Rheumatoid Arthritis and Osteoporosis and Factors Contributing to This Connection

Romatoid Artrit ile Osteoporoz Arasındaki İlişki ve Bu Bağlantıya Katkıda Bulunan Faktörler

Eman Mohammed Ibrahem, Mostafa Abdullah Mohamed Ahmad Haridi, Felopateer Talaat Sedhom Ebrahim

Assiut University Faculty of Medicine, Department of Internal Medicine, Rheumatology and Clinical Immunology Unit, Assiut, Egypt

Abstract

Objective: Rheumatoid arthritis (RA) is a chronic autoimmune condition marked by ongoing synovial inflammation and associated with multiple extra-articular manifestations, including osteoporosis (OP). Loss of bone mineral density (BMD) in RA arises from ongoing inflammation, glucocorticoid therapy, reduced mobility, and several metabolic influences. This study sought to ascertain the prevalence and pattern of OP among RA patients and to identify clinical, biochemical, and disease-related factors linked to reduced BMD.

Materials and Methods: This prospective cross-sectional research (January 2024-January 2025) included 120 adults diagnosed with RA. Clinical evaluation comprised the disease activity score-28 (DAS-28) in addition to the health assessment questionnaire disability index. Laboratory investigations involved measuring vitamin D, calcium, parathyroid hormone, thyroid function, and inflammatory indicators. Dual-energy X-ray absorptiometry was employed for estimating BMD and it was categorized in accordance with World Health Organization standards.

Results: Of the 120 participants (mean age 41.5 years; 90% women), 33.3% exhibited reduced BMD, with 29.1% meeting criteria for OP. Individuals with decreased BMD tended to be older, had lower body mass index, longer RA duration, elevated thyroid-stimulating hormone, more frequent subclinical hypothyroidism (25% vs. 10%), and reduced vitamin D. They also showed higher disease activity (DAS-28: 4.9 vs. 2.6, $p<0.001$). Independent predictors of decreased BMD were advanced age, female sex, prolonged disease duration, subclinical hypothyroidism, vitamin D deficiency, and elevated DAS-28.

Conclusion: OP is prevalent and multifactorial in RA. Routine evaluation of thyroid function, vitamin D status, and strict disease activity control are vital to mitigate bone loss.

Keywords: Osteoporosis, rheumatoid arthritis, bone mineral density, vitamin D

Öz

Amaç: Romatoid artrit (RA), eklem iltihabı ve yıkımının yanı sıra osteoporoz (OP) gibi belirgin ekstra-artiküler komplikasyonlarla seyreden kronik sistemik otoimmün bir hastalıktır. RA'da kemik mineral yoğunluğu (KMY) kaybı, kronik enflamasyon, glukokortikoid kullanımı, immobilite ve metabolik faktörlerin birleşik etkisiyle gelişir. Bu çalışma, RA hastalarında OP prevalansını belirlemeyi ve düşük KMY ile ilişkili klinik, biyokimyasal ve hastalıkla ilişkili belirteçleri tanımlamayı amaçladı.

Gereç ve Yöntem: Ocak 2024-Ocak 2025 tarihleri arasında yapılan bu prospektif kesitsel çalışmaya 120 erişkin RA hastası dahil edildi. Klinik değerlendirmede sağlık değerlendirme anketi engellilik indeksi ve hastalık aktivite skoru-28 (DAS-28) kullanıldı. Laboratuvar incelemelerinde tiroid fonksiyon testleri, D vitamini, kalsiyum, paratiroid hormonu ve enflamatuvar belirteçler değerlendirildi. KMY, çift enerjili X-ışını absorbsiyometri yöntemiyle ölçülerek Dünya Sağlık Örgütü kriterlerine göre sınıflandırıldı.

Bulgular: Ortalama yaşı 41,5 olan 120 hastanın (%90'ı kadın) %33,3'ünde anormal KMY, %29,1'inde ise OP saptandı. Anormal KMY'ye sahip hastalar daha ileri yaşta, daha düşük beden kütle indeksine sahip, daha uzun hastalık süresine, yüksek tiroid uyarıcı hormon düzeylerine,

Corresponding Author/Sorumlu Yazar: Eman Mohammed Ibrahem, MD, Assiut University Faculty of Medicine, Department of Internal Medicine, Rheumatology and Clinical Immunology Unit, Assiut, Egypt
E-mail: emanmibrahem@gmail.com **ORCID ID:** orcid.org/0000-0003-0672-6630
Received/Geliş Tarihi: 28.11.2025 **Accepted/Kabul Tarihi:** 23.04.2026 **Epub:** 05.05.2026 **Publication Date/Yayınlanma Tarihi:** 01.09.2026

Cite this article as/Atıf: Ibrahem EM, Haridi MAMA, Ebrahim FTS. The relationship between rheumatoid arthritis and osteoporosis and factors contributing to this connection. Turk J Osteoporos. 2026;32(Suppl 1):20-27

daha sık subklinik hipotiroidiye (%25'e karşı %10) ve daha düşük D vitamini düzeylerine sahipti. Ayrıca bu hastalarda hastalık aktivitesi daha yüksekti (DAS-28: 4,9'a karşı 2,6; p<0,001). Düşük KMY'nin bağımsız belirteçleri ileri yaş, kadın cinsiyet, uzun RA süresi, subklinik hipotiroidi, D vitamini yetersizliği ve yüksek DAS-28 olarak belirlendi.

Sonuç: OP, RA hastalarında yaygın ve çok faktörlü bir komplikasyondur. Tiroid fonksiyonlarının ve D vitamini düzeylerinin rutin değerlendirilmesi ile hastalık aktivitesinin etkin kontrolü, kemik kaybını önlemede kritik öneme sahiptir. Elde edilen bulguların desteklenmesi amacıyla ek araştırmalar yapılması gerekmektedir.

Anahtar kelimeler: Osteoporoz, romatoid artrit, kemik mineral yoğunluğu, D vitamini

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder marked by constant synovial inflammation, cumulative joint damage, and a spectrum of extra-articular manifestations. In addition to its prominent effects on the musculoskeletal system, RA is now recognized as a multisystem disorder linked to several systemic complications, including cardiovascular morbidity, hematologic abnormalities, and importantly, osteoporosis (1,2).

Osteoporosis—defined by diminished bone mineral density (BMD) and degradation of bone microarchitecture—represents an integral source of patient morbidity in RA because it markedly heightens the risk of fragility fractures (3,4). Chronic inflammation, long-standing corticosteroid use, immobility, and nutritional deficiencies collectively contribute to accelerated bone loss in this population (5).

Chronic inflammatory conditions such as RA promote excessive release of pro-inflammatory cytokines, which disturb the normal equilibrium between bone formation and resorption. This cytokine-driven imbalance alters bone composition and plays a leading role in the evolution of osteoporosis among individuals with RA (6).

In the current study our objective was to explore the association between RA and osteoporosis and focusing on the key factors that may cause or affect osteoporosis progress in patients with RA.

Materials and Methods

Study Setting and Design

The present study was structured as a hospital-based cross-sectional prospective study and implemented in outpatient clinics and rheumatology unit in the department of internal medicine. It was performed in the period between January 2024 and January 2025. The present study was registered at clinicaltrials.gov with NCT06038292.

Selection Criteria

Adults with a confirmed diagnosis of RA, verified according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria (7), aged at least 18 years or older were included in the study.

Participants were ruled out if they had any condition that could independently affect bone metabolism, including pregnancy, lactation, hyperthyroidism, primary hyperparathyroidism, Cushing's syndrome, prolonged immobility, osteomalacia, malabsorption disorders, malignancy, or if they were receiving antiresorptive or anabolic therapy for osteoporosis.

Sample Size Calculation

The sample size was anticipated via G*Power version 3.1.9.4, with parameters set at a 5% alpha level, 80% statistical power, and a 95% confidence interval. Considering that the prevalence of osteoporosis among individuals with RA is approximately 20% (up to 50% in postmenopausal women) and nearly double that of the general population (8), the calculated sample size was 106 participants. To compensate for potential attrition, 120 patients were ultimately enrolled.

Ethical Approval

The research was carried out in full adherence to the ethical rules of the Declaration of Helsinki. Approval was acquired from the Assiut Faculty of Medicine's Ethics Committee (IRB: 04-2024-200741, date: 04.03.2024). Each participant was thoroughly informed about the study objectives and procedures. Prior to enrollment, signed informed consent was acquired.

Data Collection

History taking and clinical evaluation

All participants were evaluated through a thorough medical history review, accompanied by complete general and musculoskeletal examinations. A focused rheumatologic assessment was carried out for each patient, which included clinical evaluation of functional status using the Health Assessment Questionnaire Disability Index (9). Disease activity was estimated using the disease activity score-28 (DAS-28) (10).

Laboratory data

Laboratory investigations included:

- Complete blood count: Determined using an automated hematology analyzer (e.g., Sysmex XN-Series).
- Liver function tests: Involved serum alanine aminotransferase, aspartate aminotransferase, serum albumin, and alkaline phosphatase all measured using enzymatic colorimetric methods on an automated chemistry analyzer (Cobas Integra 400 Plus, Roche Diagnostics, Germany) with commercially available reagent kits supplied by the manufacturer.
- Kidney function tests: Included serum urea and creatinine, analyzed by enzymatic and ion-selective electrode methods using the same automated analyzer (Cobas Integra 400 Plus, Roche Diagnostics) and reagent kits from Roche Diagnostics.

- Erythrocyte sedimentation rate (ESR): Specified by the Westergren method.
- C-reactive protein (CRP): Measured by immunoturbidimetric assay (Roche Diagnostics).
- Serum uric acid, lipid profile (total cholesterol, high density lipoproteins, low density lipoproteins, and triglycerides), random blood glucose, and hemoglobin A1c were also analyzed with Roche reagent kits on the same platform.
- Rheumatoid factor plus anti-cyclic citrullinated peptide antibodies: Identified by indirect immunofluorescence using the Kallestad kit (Bio-Rad Laboratories, USA), as directed by the manufacturer.
- Serum calcium was done by HumaStar 200 automated analyzer (Human Diagnostics Worldwide, Wiesbaden, Germany) utilizing an enzymatic colorimetric method.
- Thyroid function assessment: A chemiluminescence-based analyzer (Dimension VISTA, Siemens Healthcare Diagnostics, Deerfield, IL, USA) was used to detect serum levels of thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) in order to evaluate thyroid function. The reference values adopted were TSH (0.49-3.29 mU/L), FT4 (9.8-18.8 pmol/L), and FT3 (3.3-6.1 pmol/L), according to the manufacturer's directions.
- Serum parathyroid hormone (PTH) concentrations: Quantified via a chemiluminescent immunoassay using the Immulite 2000 analyzer (Diagnostic Products Corporation, Los Angeles, CA, USA).
- Vitamin D assessment: Measured using vitamin D ELISA Kit (catalogue no: 201-12-8108, China). vitamin D level was recognized as sufficient [25(OH)D ≥75 nmol/L], insufficient [25(OH)D 50-74 nmol/L], and deficient [25(OH)D <50 nmol/L] according to the Endocrine Society guidelines (11).

Bone mineral densitometry (BMD)

Dual-energy X-ray absorptiometry (DEXA) was used to estimate BMD, performed with a GE Lunar densitometer (Madison, WI 53717-1915, USA). Scans were conducted at the lumbar spine (L2-L4), femoral neck, and distal radius in accordance with standardized operating procedures, with values adjusted for age, sex, body weight, and ethnicity.

Based on the World Health Organization criteria, DEXA-derived T-scores were interpreted as follows: normal BMD (≥-1.0), osteopenia (between -1.0 and -2.5), osteoporosis (≤-2.5), and severe or established osteoporosis (≤-2.5 accompanied by one or more fragility fractures) (12).

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics version 24.0 (IBM Corp., Chicago, IL, USA). Continuous variables were pointed out as mean ± standard deviation or as median (range), while categorical variables were displayed as frequencies and percentages. Comparisons between groups were performed using the chi-square test and independent t-tests. Associations between continuous variables were examined with Pearson's correlation, whereas multivariate regression modeling was utilized to determine independent predictors of reduced (BMD in RA patients. Statistical significance was set at $p<0.05$.

Results

Baseline clinical and demographic data of enrolled patients (Table 1)

The study population had a mean age of 41.54 years, and women constituted the majority of participants (90%). Most individuals were from rural areas (66.7%). The average duration of RA was 6.18 years. Regarding disease activity, 18 patients (15%) were in remission, whereas 39 patients (32.5%) each had mild and moderate activity, and 24 patients (20%) exhibited high activity. Full descriptive characteristics are presented in Table 1.

Laboratory data in enrolled patients (Table 2)

A total of 18 patients (15%) demonstrated thyroid function results compatible with subclinical hypothyroidism. The mean vitamin D level was 62.82 nmol/L, with 90 patients (75%) having sufficient levels and 30 patients (25%) exhibiting vitamin D insufficiency. The average serum calcium concentration was

Table 1. Initial data of the study participants

	n=120
Age (years)	41.54±11.27
Sex	
Male Female	12 (10%) 108 (90%)
Body mass index (kg/m^2)	27.87±3.77
Smoking	15 (12.5%)
Diabetes mellitus	35 (29.2%)
Hypertension	19 (15.8%)
Family history of rheumatoid arthritis	25 (20.8%)
Duration of the disease (years)	6.18±2.19
Lines of therapy	
Corticosteroids Duration (years) Doses (mg)	40 (33.3%) 1.07±0.50 7.50±2.45
Hydroxychloroquine Methotrexate Leflunomide Sulphasalazine Biological agents	102 (85%) 69 (57.5%) 56 (46.7%) 11 (9.2%) 7 (5.8%)
HAQ-DI	1.02±0.06
DAS-28 score	4.78±1.65
Classes of disease activity	
Remission Mild Moderate High	18 (15%) 39 (32.5%) 39 (32.5%) 24 (20%)

Data expressed as mean (standard deviation), frequency (percentage).
HAQ-DI: Health assessment questionnaire-disability index, DAS-28: Disease activity score-28

8.04 g/dL, and the mean PTH level was 36.27 ng/mL. These findings are summarized in Table 2.

DEXA scan and its category among the studied patients (n=120)

Mean BMD was -0.63 (gm/cm^2). Category of patients based on BMD was normal (66.7%), osteopenia (4.2%) and osteoporosis (29.1%). A total of 12 (10%) patients had severe osteoporosis.

Baseline data of studied patients based on DEXA scan (Table 3)

Patients with abnormal BMD were older, had a lower body mass index, and exhibited a significantly longer duration of RA (8.56±3.01 vs. 2.18±0.76 years; p<0.001). This group also demonstrated markedly higher disease activity, as reflected by elevated DAS-28 scores (4.90±1.23 vs. 2.60±1.11; p<0.001). All individuals with reduced BMD had either moderate (40%) or high (60%) disease activity, with none achieving remission or displaying mild activity. Additional details are provided in Table 3.

Table 2. Baseline laboratory data in enrolled patients

	n=120
Hemoglobin (g/dL)	11.52±2.82
Platelets (10^3/uL)	292.37±114.01
Leucocytes (10^3/uL)	7.10±1.67
Urea (mg/dL)	6.25±2.67
Creatinine (mg/dL)	1.08±0.17
Albumin (g/dL)	37.14±5.62
AST (u/L)	29.40±7.34
ALT (u/L)	23.91±8.50
RBG (mg/dL)	135.96±21.89
HbA1C	5.61±0.46
CRP (mg/dL)	11.21±4.44
ESR (mm/hr)	25.67±7.87
LDL (mg/dL)	126.82±39.33
HDL (mg/dL)	42.05±8.63
Triglycerides (TGs) (mg/dL)	157.11±50.80
Cholesterol (mg/dL)	213.19±48
TSH (mu/L)	3.05±1.12
SCH	18 (15%)
Vitamin D (nmol/L)	62.82±18.78
Class of vit. D	
Sufficient Insufficient	90 (75%) 30 (25%)
Calcium (mg/dL)	8.04±2.22
Parathyroid hormone (PTH) (ng/mL)	36.27±13.14

Data represented as frequency (percentage), mean (standard deviation).
AST: Aspartate transaminase, ALT: Alanine transaminase, RBG: Random blood glucose, HbA1C: Glycosylated haemoglobin, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LDL: Low density lipoprotein, HDL: High density lipoprotein, TSH: Thyroid stimulating hormone, SCH: Subclinical hypothyroidism

Laboratory data of patients based on DEXA scan (Table 4)

Patients with low BMD exhibited significantly higher TSH levels (4.05±1.29 vs. 2.05±1.10 µU/L; p<0.001) and a greater prevalence of subclinical hypothyroidism (SCH) compared to those with normal BMD (25% vs. 10%; p=0.03). Additionally, vitamin D levels were notably lower in patients with abnormal BMD (55.03±23.92 vs. 66.71±14.24 nmol/L; p=0.001). Table 4 summarizes the laboratory results comparing the two groups.

Correlation between BMD with other variables (Table 5)

There are negative significant correlations between BMD with age, duration of disease, ESR, CRP and TSH and DAS-28. Meanwhile, there are significant positive correlations between BMD with vitamin D and serum calcium. These results are demonstrated in Table 5.

Table 3. Baseline data of studied patients according to DEXA scan

	Abnormal BMD (n=40)	Normal BMD (n=80)	p-value
Age (years)	49.20±13.23	40.21±9.99	**<0.001**
Sex			
Male Female	5 (12.5%) 35 (87.5%)	7 (8.8%) 73 (91.3%)	0.36
BMI (kg/m^2)	23.90±3.97	28.09±2.14	**0.01**
Smoking	10 (25%)	5 (6.3%)	0.005
Diabetes mellitus	11 (27.5%)	24 (56%)	0.47
Hypertension	6 (15%)	13 (16.3%)	0.54
Family history of RA	8 (20%)	17 (21.3%)	0.53
Duration (years)	8.56±3.01	2.18±0.76	**<0.001**
Lines of therapy			
Steroid Duration (years) Doses (mg)	10 (25%) 1.06±0.50 7.56±1.98	30 (37.5%) 1.08±0.45 6.89±2.71	0.90 0.56 0.87
Hydroxychloroquine Methotrexate Leflunomide Sulphasalazine Biological agents	37 (92.5%) 22 (55%) 18 (45%) 3 (7.5%) 4 (10%)	65 (81.3%) 47 (58.8%) 38 (47.5%) 8 (10%) 3 (3.8%)	0.08 0.42 0.47 0.48 0.16
HAQ-DI	1.03±0.04	1.01±0.05	0.55
DAS-28 score	4.90±2.60	2.60±1.11	**<0.001**
Classes of activity			
Remission Mild Moderate High	0 0 16 (40%) 24 (60%)	18 (22.5%) 39 (48.8%) 23 (28.7%) 0	**<0.001**

Data provided as mean (standard deviation), frequency (percentage).
BMD: Bone mineral density, BMI: Body mass index, RA: Rheumatoid arthritis, HAQ-DI; Health assessment questionnaire-disability index, DAS: Disease activity score, DEXA: Dual-energy X-ray absorptiometry

Predictors of abnormal BMD in RA (Table 6)

To find independent determinants of low BMD in RA patients, a multivariate logistic regression analysis was carried out. Results were demonstrated as odds ratios with 95% confidence intervals and corresponding p-values. The analysis demonstrated that older age, female sex, longer disease duration, SCH, vitamin D insufficiency, and higher DAS-28 scores were all significant independent predictors of abnormal BMD in RA patients ($p<0.001$ for each). Detailed results are provided in Table 6.

Discussion

Despite significant progress in elucidating the pathogenic mechanisms of RA and the availability of effective pharmacologic therapies, RA-related complications remain a major clinical concern. Osteoporosis is among the most common and debilitating extra-articular manifestations, which leads to increased morbidity and reduced life quality. The chronic inflammatory environment in RA, characterized by heightened levels of cytokines like tumor necrosis factor-α, interleukin-1, and interleukin-6, promotes osteoclast-mediated bone resorption while inhibiting osteoblast function, resulting in progressive and generalized bone loss (1,2).

Therefore, implementing systematic screening for osteoporosis and promptly identifying patients at high risk is crucial. Early detection enables timely preventive and therapeutic strategies, which can reduce fracture incidence and enhance overall musculoskeletal health in subjects with RA.

In this study, 120 patients with confirmed RA were evaluated to determine the prevalence of osteoporosis. Reduced BMD was observed in 40 patients (33.3%), aligning with prior studies that reported similar rates of osteoporosis among RA populations, such as a previous report indicating a prevalence of 27.6% (5), whereas an Egyptian study conducted by Hassan et al. (13) observed that 34% of RA patients had osteoporosis, with 4% experiencing severe forms complicated by fractures.

These findings underscore that individuals with RA face a substantially higher risk of developing osteoporosis in

Table 4. Laboratory data of patients given the DEXA scan

	Abnormal BMD* (n=40)	Normal BMD (n=80)	p-value
Hemoglobin (g/dL)	11.08±2.45	11.98±2.44	0.43
Platelets (10^3/uL)	299±56.87	289.37±108.77	0.08
Leucocytes (10^3/uL)	7.22±1.51	7.09±1.33	0.17
Urea (mg/dL)	6.70±2.09	6.05±2.01	0.29
Creatinine (mg/dL)	1.09±0.23	1.08±0.11	0.11
Albumin (g/dL)	38.14±3.44	37.14±5.06	0.07
AST (u/L)	30±7.21	29.20±7.21	0.22
ALT (u/L)	24.44±8.11	23.01±8.76	0.32
RBS (mg/dL)	136.78±21.21	135.16±21.44	0.48
HbA1C	5.62±0.49	5.59±0.89	0.07
CRP (mg/dL)	18±4.10	5.81±2.01	**0.03**
ESR (mm/hr)	29.89±7.17	11.67±2.34	**0.01**
LDL (mg/dL)	127.91±39.98	123.80±30.11	0.11
HDL (mg/dL)	44.57±8.20	41.15±8.20	0.67
TGs (mg/dL)	160±50.80	156.21±50.77	0.15
Cholesterol (mg/dL)	217.17±34.91	212.89±56.09	0.78
Calcium (mg/dL)	8.02±2.98	8.37±3.09	0.18
PTH (ng/mL)	37.89±13.12	35.67±12.54	0.11
TSH (mu/L)	4.05±1.29	2.05±1.10	**<0.001**
SCH	10 (25%)	8 (10%)	**0.10**
Vitamin D (nmol/L)	55.03±23.92	66.71±14.24	**0.001**
Class of vit. D			**0.002**
Sufficient Insufficient	23 (57.5%) 17 (42.5%)	67 (83.3%) 13 (16.3%)	

Data stated as frequency (percentage), mean (standard deviation).
AST: Aspartate transaminase, ALT: Alanine transaminase, RBS: Random blood sugar, HbA1C: Glycosylated haemoglobin, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LDL: Low density lipoprotein, HDL: High density lipoprotein, TGs: Triglycerides, TSH: Thyroid stimulating hormone, SCH: Subclinical hypothyroidism, BMD: Bone mineral density, *: This included those with osteoporosis and osteopenia, DEXA: Dual-energy X-ray absorptiometry, PTH: Parathormone

Table 5. Correlation between bone mineral density with other variables

	r value (p-value)
Age (years)	**-0.36 (0.03)**
Body mass index (kg/m^2)	0.12 (0.18)
Duration (years)	**-0.41 (0.02)**
Laboratory data	
Hemoglobin (g/dL)	-0.21 (0.06)
Platelets (10^3/uL)	-0.06 (0.91)
Leucocytes (10^3/uL)	-0.10 (0.11)
Urea (mg/dL)	0.11 (0.21)
Creatinine (mg/dL)	0.12 (0.58)
Albumin (g/dL)	0.08 (0.07)
AST (u/L)	0.18 (0.21)
ALT (u/L)	-0.10 (0.21)
RBG (mg/dL)	0.04 (0.41)
HbA1C	0.19 (0.08)
CRP (mg/dL)	**-0.50 (0.001)**
ESR (mm/hr)	**-0.53 (0.001)**
LDL (mg/dL)	0.10 (0.08)
Cholesterol (mg/dL)	0.10 (0.18)
HDL (mg/dL)	0.11 (0.40)
TGs (mg/dL)	0.19 (0.39)
TSH (mu/L)	**-0.55 (0.001)**
Vitamin D (nmol/L)	**0.76 (0.001)**
Calcium (mg/dL)	**0.20 (0.04)**
PTH (ng/mL)	0.10 (0.31)
HAQ-DI	0.18 (0.87)
DAS-28 score	**-0.60 (<0.001)**

AST: Aspartate transaminase, ALT: Alanine transaminase, RBG: Random blood glucose, HbA1C: Glycosylated haemoglobin, LDL: Low density lipoprotein, HDL: High density lipoprotein, TGs: Triglycerides, TSH: Thyroid stimulating hormone, PTH: Parathormone, HAQ-DI: Health assessment questionnaire-disability index, DAS: Disease activity score

comparison with the general population. The elevated risk is multifactorial, involving persistent systemic inflammation, long-term glucocorticoid use, decreased physical activity, hormonal changes, and the direct effects of proinflammatory cytokines on bone turnover (3,4).

In the present study, patients with reduced BMD were older and had lower body mass index compared to those with normal BMD. This aligns with earlier studies that have highlighted advanced age and lower BMI as significant risk factors for osteoporosis in individuals with RA (13-16).

Furthermore, our analysis demonstrated that patients with low BMD were more likely to be smokers. This result is consistent with prior research showing that smoking independently contributes to decreased bone density and an elevated risk of osteoporosis in individuals with RA (17,18).

Table 6. Predictors of abnormal BMD in patients with rheumatoid arthritis

Variables	Odds ratio	95% confidence interval	p-value
Age (years)	1.68	1.22-2.40	**<0.001**
Female sex	3.95	1.22-7.90	**<0.001**
Durtaion of disease (years)	2.09	1.41-5.18	**<0.001**
Smoking	0.89	0.23-1.90	0.19
Steroid therapy	1.32	0.55-2.12	0.57
Albumin (g/dL)	0.78	0.33-1.80	0.09
CRP (mg/dL)	1.24	0.44-2.17	0.21
ESR (mm/h)	1.20	0.78-2.67	0.08
SCH	5.09	3.58-14.78	**<0.001**
Insufficient vitamin D	3.45	2.19-8.10	**<0.001**
DAS-28 score	7.56	4.11-11.98	**<0.001**

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, SCH: Subclinical hypothyrodism, DAS-28: Disease activity score-28, BMD: Bone mineral density

Another key observation from our study was that patients with abnormal BMD had a significantly longer duration of RA compared to those with normal BMD. This finding corroborates previous research highlighting that extended disease duration, which reflects the cumulative inflammatory burden, is a critical factor contributing to bone loss and the increased incidence of osteoporosis in RA patients (19,20).

In addition to demographic and lifestyle factors, disease-related variables significantly influence bone health in patients with RA. Our study demonstrated that patients with abnormal BMD had notably higher disease activity, as reflected by elevated DAS28 scores, compared to those with normal BMD. This finding aligns with prior evidence suggesting that increased disease activity exacerbates bone resorption and heightens the hazard of osteoporosis and structural joint damage (13,21).

Similarly, Ismail (22) reported that fracture risk was positively correlated with DAS28-ESR, further highlighting the detrimental impact of uncontrolled inflammation on bone metabolism in patients with RA.

Consistent with the role of inflammation in bone loss, our research spotted that patients with abnormal BMD had significantly greater levels of inflammatory markers, particularly CRP and erythrocyte ESR. Elevated CRP and ESR correlated with greater reductions in BMD, underscoring the detrimental effects of ongoing systemic inflammation on skeletal integrity. These results suggest that monitoring acute-phase reactants may help identify RA patients at heightened risk for osteoporosis.

In this study, glucocorticoid therapy, despite being a recognized risk factor for osteoporosis, revealed no discernible difference between patients with normal and abnormal BMD. Both groups received comparable mean doses and treatment durations. This lack of association may be attributable to the relatively low doses and short-term use of steroids among participants, or to the

influence of other confounding factors, including disease activity, vitamin D insufficiency, and coexisting thyroid dysfunction.

This finding may be explained by the modulatory role of low-dose glucocorticoids on bone metabolism. At low doses, glucocorticoids can mitigate inflammation-driven bone loss during active polyarthritis flares by suppressing pro-inflammatory cytokines, thereby reducing osteoclast activation and limiting bone resorption (23). This anti-inflammatory benefit may, to some extent, offset the direct deleterious effects of GCs on bone metabolism, potentially resulting in a neutral or even favorable net skeletal balance.

Vitamin D is crucial for bone metabolism, calcium homeostasis, and immune system regulation. In our study, patients with abnormal BMD exhibited significantly lesser levels of vitamin D and a greater frequency of vitamin D insufficiency. These results align with prior research demonstrating an inverted relation between status of vitamin D and bone loss in autoimmune conditions, including RA. Additionally, vitamin D deficiency may compromise immune regulation, thereby sustaining systemic inflammation and contributing to RA progression. Although some debate exists, the vast majority of evidence supports the link between lower vitamin D levels and more severe disease manifestations in RA (24,25).

Furthermore, reduced 25(OH)D levels have been linked with sarcopenia and diminished muscle strength, which can exacerbate skeletal fragility in patients with RA. Taken together, these findings highlight the multifaceted role of vitamin D deficiency, affecting both bone density and muscle function, and underscore its contribution to increased fracture risk and overall musculoskeletal vulnerability in RA (26).

Despite that serum calcium and PTH levels did not significantly differ between groups, patients with abnormal BMD exhibited calcium levels at the lower end of normal and a slight elevation in PTH. This pattern likely represents secondary hyperparathyroidism induced by chronic vitamin D deficiency, a recognized contributor to enhanced bone resorption and diminished bone density in RA.

In the present study, thyroid dysfunction, specifically SCH, was significantly more common in patients with low BMD, accompanied by elevated TSH levels. SCH was found to be an independent predictor of abnormal BMD, and the negative correlation between TSH and BMD reinforces this relationship. These results are clinically important, as thyroid hormones are critical regulators of bone turnover, and even mild thyroid dysfunction can favor bone resorption. Prior research has reported thyroid abnormalities in 6-34% of patients with RA (27-29) and suggested that subclinical thyroid abnormalities and variations in TSH levels are associated with altered BMD and a greater fracture risk (30-32).

The principal finding of this study was that multivariate logistic regression identified several independent predictors of abnormal BMD in RA patients: Older age, female sex, longer disease duration, subclinical hypothyroidism, vitamin D insufficiency, and higher DAS-28 scores. These results highlight the multifactorial etiology of bone loss in RA, demonstrating the interplay of inflammatory, endocrine, nutritional, and demographic factors in determining bone health.

Study Limitations

This study acknowledges some limitations. As this is a single-center study included a relatively small number of participants, the extent to which our findings can be applied to larger or more diverse populations may be limited. Longitudinal studies applying larger, more diverse cohorts are warranted to evaluate temporal changes in BMD and the long-term effects of therapeutic interventions.

Nonetheless, the prospective design and standardized data collection over a full year enhance the reliability and internal validity of the observed associations between RA-related variables and BMD.

Conclusion

Osteoporosis is a prevalent and clinically important comorbidity in patients with RA, driven by the combined effects of chronic inflammation, hormonal imbalances, nutritional deficiencies, and disease-specific factors. Key predictors identified in this study—including older age, female sex, longer disease duration, high disease activity, vitamin D insufficiency, and subclinical hypothyroidism—offer valuable guidance for risk stratification. These findings reinforce the importance of routine BMD assessment and metabolic evaluation in RA management. Early identification, effective disease control, correction of modifiable risk factors, and judicious use of bone-protective therapies are critical to reducing fracture risk and improving long-term outcomes in this patient population.

Ethics

Ethics Committee Approval: Approval was acquired from the Assiut Faculty of Medicine's Ethics Committee (IRB: 04-2024-200741, date: 04.03.2024).

Informed Consent: Prior to enrollment, signed informed consent was acquired.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.M.I., M.A.M.A.H., F.T.S.E., Concept: E.M.I., M.A.M.A.H., Design: M.A.M.A.H., Data Collection or Processing: F.T.S.E., Analysis or Interpretation: F.T.S.E., Literature Search: E.M.I., F.T.S.E., Writing: E.M.I., F.T.S.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/tod.galenos.2026.27880
Turk J Osteoporos 2026;32(Suppl 1):28-35

Sarcopenia in Postmenopausal Women: Associations with Age at Menopause and Osteoporosis

Postmenopozal Kadınlarda Sarkopeni: Menopoz Yaşı ve Osteoporoz ile İlişkisi

Esra Metko[1], Neşe Ölmez Sarıkaya[2], İlker Şengül[2], Ayhan Aşkın[2]

[1]Yeşilyurt Physical Therapy and Rehabilitation Center, İzmir, Türkiye
[2]İzmir Katip Çelebi University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, İzmir Türkiye

Abstract

Objective: To investigate the relationship between age at menopause, osteoporosis, and sarcopenia in postmenopausal women.

Materials and Methods: This cross-sectional study included 128 postmenopausal women. While sarcopenia was defined according to European working group on sarcopenia in older people criteria, osteoporosis was diagnosed by dual-energy X-ray absorptiometry. Associations between sarcopenia, age at menopause, and osteoporosis were examined using chi-square tests, One-Way ANOVA, and standard/penalized binary logistic regression.

Results: Probable sarcopenia was identified in 19.5% of participants (n=25), and sarcopenia in 21.1% (n=27). The frequency of osteoporosis was 19.7% in those without sarcopenia, 48.0% in those with probable sarcopenia, and 82.0% in those with sarcopenia. Mean age at menopause was significantly lower in individuals with sarcopenia compared with those with probable sarcopenia and those without sarcopenia (41.4 vs. 45.0 vs. 46.0 years, respectively; p<0.001). In the penalized multivariable binary logistic regression analysis, after adjusting for chronological age and body mass index, osteoporosis demonstrated a borderline non-significant association with sarcopenia [odds ratio (OR), 3.59; 95% confidence interval (CI), 0.96-14.76; p=0.058]. On the other hand, a statistically significant independent association was found between earlier age at menopause and sarcopenia (OR, 0.89; 95% CI, 0.78-0.99; p=0.041).

Conclusion: While earlier age at menopause was independently associated with sarcopenia in postmenopausal women, robust studies with large sample sizes are needed to more clearly establish the statistical and clinical significance of the association between osteoporosis and sarcopenia.

Keywords: Age at menopause, osteoporosis, postmenopausal women, sarcopenia

Öz

Amaç: Postmenopozal kadınlarda menopoz yaşı, osteoproz ve sarkopeni arasındaki ilişkiyi incelemektir.

Gereç ve Yöntem: Bu kesitsel çalışmaya 128 postmenopozal kadın dahil edildi. Sarkopeni tanısı yaşlılarda sarkopeni üzerine Avrupa çalışma grubu kriterlerine göre konarken osteoporoz tanısı çift enerjili X-ışını absorpsiyometri ile kondu. Sarkopeni, menopoz yaşı ve osteoporoz arasındaki ilişkiler ki-kare testleri, tek yönlü ANOVA ve standart/kısıtlanmış ikili lojistik regresyon kullanılarak incelendi.

Bulgular: Katılımcıların %19,5'inde (n=25) muhtemel sarkopeni saptanırken, %21,1'inde (n=27) ise sarkopeni tespit edildi. Osteoporoz sıklığı, sarkopeni olmayanlarda (%19,7), muhtemel sarkopeni olanlarda (%48,0) ve sarkopeni olanlarda (%82,0) idi. Menopoz yaşı ortalaması, sarkopeni olan bireylerde muhtemel sarkopeni olan ve sarkopeni olmayan bireylere kıyasla anlamlı olarak daha düşüktü (sırasıyla 41,4, 45,0 ve 46,0 yıl; p<0,001). Kısıtlanmış çok değişkenli ikili lojistik regresyon analizinde, kronolojik yaş ve vücut kitle indeksi kontrol altına alındığında, osteoporoz sarkopeni ile istatistiksel olarak anlamlı olmayan sınırda bir ilişki gösterdi [olasılık oranı (OR): 3,59; %95 güven aralığı (GA): 0,96-14,76; p=0,058]. Diğer yandan, erken menopoz yaşı ile sarkopeni arasında ise istatistiksel olarak anlamlı bağımsız bir ilişki bulundu [OR (%95 GA): 0,89 (0,78-0,99), p=0,041].

Sonuç: Postmenopozal kadınlarda erken menopoz yaşı ile sarkopeni arasında bağımsız bir ilişki saptanırken, osteoporoz ve sarkopeni arasındaki ilişkinin istatistiksel ve klinik önemini daha net ortaya koymak için büyük örneklemli sağlam çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Menopoz yaşı, osteoporoz, postmenopozal kadın, sarkopeni

Corresponding Author/Sorumlu Yazar: Prof. MD, Neşe Ölmez Sarıkaya, İzmir Katip Çelebi University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, İzmir Türkiye
E-mail: neseo@hotmail.com **ORCID ID:** orcid.org/0000-0002-9755-5875
Received/Geliş Tarihi: 16.01.2026 **Accepted/Kabul Tarihi:** 01.06.2026 **Epub:** 08.06.2026 **Publication Date/Yayınlanma Tarihi:** 01.09.2026

Cite this article as/Atıf: Metko E, Ölmez Sarıkaya N, Şengül İ, Aşkın A. Sarcopenia in postmenopausal women: associations with age at menopause and osteoporosis. Turk J Osteoporos. 2026;32(Suppl 1):28-35

Introduction

Sarcopenia is a progressive, generalized disorder of the skeletal muscles associated with an increased risk of adverse outcomes, such as falls, fractures, physical disability and death (1-3). The prevalence of sarcopenia in the elderly population ranges between 12% and 27%, depending on the classification method used (4). The prevalence also varies according to sex. Although this is a controversial topic, the prevalence of sarcopenia in older women is generally higher than in older men, depending on the classification used (4).

One of the main factors for the sex difference in the prevalence of sarcopenia is attributed to menopause that women experience (5). The menopausal period is characterized by a dramatic decrease in cessation of ovarian follicular activity (6), which not only affect productivity but also affect a woman's metabolism, bone health and muscle function (7-10). Along with the decline in estrogen levels, numerous metabolic pathways, including those related to muscle and bone physiology, are affected. Changes in the metabolism of proteins, carbohydrates and fats result in a decrease in muscle and bone mass (11), which has direct and indirect effects on functionality. Beyond aging and alongside it, the menopausal state has been identified as risk factor for sarcopenia development in women (9). Conceptually, the relationship between sarcopenia and menopause is not only confined to the menopausal period (i.e., the physiological changes that occur during this time). Both premature menopause and the length of the postmenopausal period are also risk factors for developing sarcopenia (12,13). Age at menopause is another factor that may be associated with sarcopenia, in addition to premature/early menopause and the length of the postmenopausal period (14,15). Although the premature/early menopause, the age at menopause, and the length of the postmenopausal period are interrelated, they are not exactly the same concepts. The age at menopause addresses the transition process more gradually, rather than classifying women as experiencing premature/early menopause or entering menopause at the normal expected age. Under this approach, a woman who enters menopause at 44 is not distinguished sharply from one who enters menopause at 45. This approach also mitigates the limitations of placing women who enter menopause at ages 45 and 55 in the same category. In addition, the relationship between the duration of the postmenopausal period and chronological age is likely stronger than that between the other two factors. This may complicate the relationship between sarcopenia and the duration of the postmenopausal period, making it difficult to reach a definitive conclusion.

Starting from the onset of menopause the combination of reduced bone mass and muscle mass/function during the postmenopausal period may lead to increase in fracture risk (16). Accordingly, to focus on both sarcopenia and osteoporosis simultaneously in terms of preventing fractures during the postmenopausal process is of importance. In this respect, this study aimed to investigate whether age at menopause and osteoporosis are associated with sarcopenia in postmenopausal women. Despite certain limitations (such as the possibility that the relationship between age at menopause and sarcopenia may not be linear), this study focused on the relationship between age at menopause and sarcopenia for the reasons explained above. The hypothesis was that age at menopause and existence of osteoporosis are independently associated with sarcopenia after adjustment for confounding factors.

Materials and Methods

Approval for this cross-sectional observational study was obtained from the Local Ethics Committee of İzmir Katip Çelebi University (decision no: 0167, dated: 03/21/24), and the study was conducted in accordance with the relevant guidelines and regulations of the Declaration of Helsinki. Participants were informed about the study and their written consent was obtained. After obtaining the ethics committee approval, the participants were evaluated between March 22, 2024, and December 31, 2024.

Participants

This study included postmenopausal women aged 50-80 who attended the physical medicine and rehabilitation clinic at a tertiary care hospital and who had dual-energy X-ray absorptiometry (DXA) results taken within the last year. The following individuals were excluded from the study: Participants with impaired cognitive function; those with serious medical conditions, including stroke, severe cardiovascular disease, or a history of severe pulmonary disease; those with rheumatic disorders; those with prostheses or implants in the lower extremities; those with spinal cord injury; those with a history of spinal surgery; those receiving glucocorticoid therapy; and those with a diagnosis of cancer. Participants were included in the study on a consecutive basis.

Diagnosis of Sarcopenia

The diagnosis of sarcopenia was based on the European working group on sarcopenia in the elderly (EWGSOP2) criteria (1). Accordingly, the evaluation was based on muscle strength assessment, appendicular skeletal muscle measurement, and physical performance.

Muscle strength was assessed using a hand-grip strength test with a dynamometer (Jamar Hydraulic Hand Dynamometer, Patterson Medical, Warrenville, IL, USA). Patients were seated in a standard chair with their forearms resting on the armrests. They were then asked to grip the dynamometer as tightly as possible. A total of six measurements were taken, three for each arm. Ideally, patients were encouraged to squeeze with maximum force for three to five seconds during each trial. The highest value obtained from the six measurements was reported (17). Muscle strength was considered low if measured ≤16 kg for women (1).

Appendicular muscle mass measurement was assessed using bioelectrical impedance analysis (BIA) with the Tanita BC-601 body composition monitor (Tanita, Tokyo, Japan). A height-adjusted appendicular skeletal muscle mass of <5.5 kg/m² in women was considered low muscle mass (1). The BIA is a non-invasive method that can be used as an alternative to techniques such as DXA, computed tomography and magnetic resonance imaging. Rather than measuring muscle mass directly, BIA estimates it using a regression equation. To the best of our knowledge, although the regression equation for this device has not been disclosed, it includes variables such as impedance, gender, age and height (18,19). BIA demonstrates strong criterion validity, showing high correlation with DXA-derived measurements for fat-free mass (FFM) (19,20). BIA systems often prioritized over DXA due to their cost-effectiveness, portability, ease of operation. Furthermore, BIA offers a non-ionizing alternative to DXA. In this study a device that performs BIA measurements was used due to its availability and the fact that it does not emit radiation.

Physical performance was assessed using the short physical performance battery (SPPB) (21). The SPPB is a composite test combining walking speed, chair rise and balance results. Scores range from 0 (worst performance) to 12 (best performance). The maximum possible score is 12. A score of ≤8 indicates poor physical performance (21).

According to these assessments, individuals with no loss in muscle strength, muscle mass, or physical performance were classified as not having sarcopenia; those with only muscle strength loss were classified as having probable sarcopenia; and those with muscle strength and mass loss were classified as having sarcopenia (1). Individuals with severe sarcopenia in whom all three components were impaired were merged into the sarcopenia group for the analysis.

All sarcopenia components (muscle strength, mass, and physical performance) were assessed by the same trained clinician using calibrated equipment (JAMAR dynamometer and Tanita BC-601 body composition monitor) according to a pre-defined EWGSOP2 protocol.

Diagnosis of Osteoporosis

Osteoporosis was diagnosed based on bone mineral density (BMD) measurements obtained using DXA. Participants were classified as having normal BMD if the T-score was >-1.0, osteopenia if the T-score ranged from -1.0 to -2.49, and osteoporosis if the T-score was ≤-2.5, or ≤-1.0 in the presence of a history of at least one fragility fracture (22). Diagnostic criteria for osteoporosis were consistently applied based on DXA scores and fracture history to ensure categorical accuracy.

Assessment of Balance

Balance, a clinically important factor associated with sarcopenia and osteoporosis as well as fall risk and subsequent fracture development, was also assessed. Balance was assessed using the Berg balance scale (BBS) (23,24) by the same trained clinician. The scale contains 14 items, and for each item, the patient's performance is observed and scored on a scale of 0 to 4. If the patient is unable to perform the activity at all, a score of 0 is given; if the patient completes the activity independently, a score of 4 is given. The maximum score is 56, with 0-20 points indicating balance impairment, 21-40 points indicating acceptable balance, and 41-56 points indicating good balance (23). The reliability and validity of this scale in Turkish have been established by Sahin et al. (24)

Sample Size

The sample size was determined using G*Power software (version 3.1.9.6, Universität Kiel, Germany). Based on the reported prevalence of sarcopenia in the general population (20% among non-Asian women) versus that of postmenopausal women in Türkiye (44%), an a priori sample size calculation was performed (25,26). Using the Exact test family for proportions (difference from constant/binomial test), a minimum requirement of 40 participants was indicated, assuming a power of 0.90, a two tailed significance level of 0.05, and an effect size (g) of 0.24 (large effect size). Given that the 44% rate also included individuals with probable sarcopenia, and to accommodate subgroup analyses while ensuring robust parameter estimation in multivariate logistic regression models, the target sample size was increased to at least 100 participants.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). Categorical variables are presented as frequencies and percentages, and continuous variables as mean ± standard deviation. The normality of continuous variables was assessed using the Shapiro-Wilk test. Comparisons among groups defined by sarcopenia status (no sarcopenia, probable sarcopenia, and sarcopenia) were conducted using One-Way Analysis of Variance for normally distributed continuous variables. In post-hoc analyses, the Tukey test was applied when the assumption of homogeneity of variances was met, whereas the Dunnett T3 test was used when this assumption was violated. Categorical variables were compared using the chi-square test or exact test, as appropriate. For ordinal categorical variables chi-squared tend test was also performed. Standard multivariable binary logistic regression analyses was performed to examine the associations of sarcopenia (dependent variable) with age at menopause and osteoporosis (independent variables) (Model 1). Chronological age and body mass index (BMI) were included in the regression models as potential confounding variables (Model 2 and 3). A binary logistic regression analysis with Firth's penalized likelihood approach was also performed to examine the association between sarcopenia (dependent variable) and osteoporosis, age at menopause, chronological age, and BMI (independent variables). The Firth's method was preferred due to the relatively small sample size and low number of events, in order to reduce small-sample bias and to address potential issues of separation. All variables were entered simultaneously into the model based on their clinical relevance. Internal validation and parameter

stability of Model 3 were rigorously verified through a 1.000-fold bootstrapping procedure, ensuring the robustness of the estimates. The model's calibration was measured by the mean absolute error (MAE), and the consistency of its discrimination was assessed using the optimism-corrected C-index. Penalized regression and model validation analyses were carried out using R software (R: A Language and Environment for Statistical Computing, R Core Team, R Foundation for Statistical Computing, Vienna, Austria, 2024, https://www.R-project.org), specifically employing the logistf and rms packages, respectively. A p-value ≤0.05 was considered statistically significant.

Results

A total of 128 postmenopausal women were included in the study, with a mean age [standard deviation (SD)]) of 63.7 (7.6) years. The mean age at menopause was 44.8 (5.7) years, and the mean BMI fell within the overweight range. The most frequently observed comorbid conditions were hypertension and diabetes mellitus. The demographic and clinical characteristics of the participants are presented in Table 1.

According to the EWGSOP2 criteria, 25 participants (19.5%) were classified as having probable sarcopenia, while 27 participants (21.1%) were classified as having sarcopenia. Comparisons of demographic and clinical characteristics according to sarcopenia status are presented in Table 2. Sarcopenia was significantly associated with older age, the presence of osteoporosis, a history of falls, fragility fractures, and lower balance scores (all p<0.05). In addition, sarcopenia showed a significant linear association with age (χ^2_{trend} =20.569, total χ^2 =29.180, p<0.001). A similar linear association was observed between sarcopenia and osteoporosis (χ^2_{trend} =33.073, total χ^2=33.389, p<0.001). Furthermore, age was significantly linearly associated with osteoporosis (χ^2_{trend} =5.696, total χ^2=6.015, p=0.017). Mean age at menopause differed significantly across the groups, with the lowest values observed in the sarcopenia group (p<0.001). The BBS score was significantly higher in participants without sarcopenia than in those with probable or definite sarcopenia (p<0.001).

Table 1. Demographic, lifestyle and clinical characteristics of the study sample, n=128

Age, year, mean (SD)	63.7 (7.6)
BMI, kg/m^2, mean (SD)	28.6 (6.3)
Age at menopause, year, mean (SD)	44.8 (5.7)
Smoking, n (%)	16 (12.5)
Alcohol consumption, n (%)	9 (7)
Hypertension, n (%)	67 (52.3)
Diabetes mellitus, n (%)	40 (31.3)
Hypothyroidia, n (%)	26 (20.3)
Knee osteoarthritis, n (%)	21 (16.4)
Cardiovascular disease, n (%)	8 (6.3)
Regular exercise, n (%)	13 (10.2)
Fragility fracture, n (%)	12 (9.4)
Fall, n (%)	48 (37.5)

BMI: Body mass index, SD: Standard deviation

Standard and penalized multivariable binary logistic regression analysis demonstrated that age at menopause significantly associated with sarcopenia after adjustment for chronological age and BMI [odds ratio (OR) =0.89, 95% confidence interval (CI): (0.78 to 0.99), p=0.041] (Table 3). The association between osteoporosis and sarcopenia remained at the threshold of statistical significance after adjustment for age and BMI (OR =3.59, 95% CI: 0.96 to14.76, p=0.058) (Table 3). Standard full model (Model 3) explained 69.9% (Nagelkerke R^2, from the Model 3) of the total variance, indicating a strong explanatory power for the identified associations and large data representativeness (MAE =0.008). Validation results revealed a Somers' Dxy of 0.916 and a remarkably low optimism index of 0.018. The corrected Dxy was 0.898, corresponding to an optimism-corrected C-statistic (area under the curve) of 0.949.

Discussion

The present study investigated sarcopenia and its association with age at menopause and osteoporosis. The main findings indicated that earlier age at menopause was significantly and independently associated with sarcopenia. While the association between the osteoporosis and sarcopenia did not reach statistical significance, the magnitude of the effect (OR) suggests a potential clinical relevance despite the statistical uncertainty reflected by the wide confidence interval.

The multivariate analysis revealed that age at menopause was more strongly and independently associated with sarcopenia than osteoporosis. This finding is supported by recent molecular evidence indicating that estrogen withdrawal impacts skeletal muscle through pathways distinct from bone mineral loss. Specifically, the loss of ERα-mediated satellite cell proliferation (27) and the acceleration of mitochondrial dysfunction (28) suggest that muscle tissue may be more sensitive to the duration of estrogen deficiency than the bone matrix is to mineral resorption during the early menopausal transition. While osteoporosis and sarcopenia often coexist as osteosarcopenia, the earlier onset of estrogen deficiency may trigger a more immediate catabolic state in muscle through the upregulation of pro-inflammatory cytokines and alterations in myosin heavy chain proteomes, independent of the slower bone remodeling cycle (9,29).

Reduced muscle strength can result in functional impairments, including difficulty rising from a chair, decreased walking speed, challenges in stair climbing, and impaired balance (30-32). Women typically experience a marked decline in muscle mass and strength between the ages of 50 and 60 years (33-36). Evidence regarding the role of estrogen replacement therapy in mitigating this loss remains inconsistent; while some meta-analyses report modest strength improvements (37), other longitudinal studies

Table 2. Comparison of participants' demographic and clinical characteristics according to the sarcopenia status

	No sarcopenia (n=76)	Probable sarcopenia (n=25)	Sarcopenia (n=27)	p-value
Age, years, mean (SD)	60.8	67.7 (6.3)[a]	68.0 (7.2)[a]	< 0.001
Age categoria, n (%) 50-59 years 60-69 years ≥70 years	 38 (50) 27 (36) 11 (14)	 01 (4) 14 (56) 10 (40)	 02 (07) 15 (56) 10 (37)	< 0.001
Osteoporosis, n (%) Osteoporosis	 15 (20)	 12 (48)	 22 (82)	<0.001
Age at menopause, years, mean (SD)	46.0 (5.1)	45.0 (6.3)	41.4 (5.2)[b,c]	<0.001
Regular exercise, n (%)	9 (12)	1 (4)	3 (11)	0.530
BMI, kg/m², mean (SD)	29.3 (5.1)[d]	31.9 (5.8)[d]	21.8 (3.4)	<0.001
BMI category Normal Overweight Obesite	 13 (17) 32 (42) 31 (41)	 2 (8) 8 (32) 15 (60)	 19 (70) 8 (30) 0 (0)	<0.001
Fall, n (%)	18 (24)	15 (60)	15 (56)	0.001
Fragility fracture, n (%)	1 (1)	6 (24)	5 (19)	<0.001
Smoking, n (%)	12 (16)	2 (8)	2 (7)	0.407
Alcohol, n (%)	4 (5)	2 (8)	3 (11)	0.704
Comorbid disease, n (%)	65 (86)	25 (100)	25 (93)	0.057
BBS, mean (SD)	52.2 (5.2)	43.0 (7.4)[e]	42.7 (12.2)[f]	<0.001

BBS: Berg balance scale, BMI: Body mass index, SD: Standard deviation, [a]: Post-hoc comparison, different from no sarcopenia (adjusted p<0.001), [b]: Post-hoc comparison, different from no sarcopenia (adjusted p=0.001), [c]: Post-hoc comparison, different from probable sarcopenia (p=0.046), [d]: Post-hoc comparison, different from sarcopenia (adjusted p<0.001), [e]: Post-hoc comparison, different from no sarcopenia (adjusted p<0.001), [f]: Post-hoc comparison, different from no sarcopenia (adjusted p=0.001)

(38,39) found no significant differences across various hormonal states. Our results suggest that the timing of hormonal loss (age at menopause) may be a more critical factor for muscle health than the simple presence of a postmenopausal state.

The coexistence of osteoporosis and sarcopenia markedly compromises quality of life by substantially increasing fracture risk, physical frailty, and mortality (40-42). The present study suggests a potentially clinically relevant association between osteoporosis and sarcopenia, consistent with current conceptualizations of the muscle-bone axis (43-45). However, our multivariable logistic regression indicates that age and BMI acts as a powerful confounders. Nevertheless, in terms of osteoporosis, the stabilization of coefficients via Firth's method and the notably low optimism index obtained from bootstrap validation suggest that this association represents a stable clinical trend rather than a chance fluctuation. Despite these strengths, the study might have been constrained by a limited number of events per variable. This constraint is reflected in the wide confidence intervals, suggesting that while the internal consistency metrics are encouraging, the magnitude of this association should be interpreted with caution. The lack of nominal significance is likely attributable to the limited sample size rather than a lack of biological relationship, necessitating confirmation in larger study populations.

Regarding body composition, we observed an inverse association between BMI and sarcopenia. However, it is critical to acknowledge that an elevated body fat percentage can mask the underlying depletion of muscle mass, a condition increasingly recognized as sarcopenic obesity. In our cohort, individuals with probable sarcopenia often exceeded the threshold for obesity. For such populations, traditional screening metrics may lack sensitivity; therefore, diagnostic approaches that directly quantify skeletal muscle mass—independent of adiposity—are essential for an accurate assessment.

As balance plays a critical role in daily functioning, persistent balance impairments in individuals with sarcopenia can substantially hinder the performance of everyday activities. The present study demonstrates a progressive deterioration in balance as muscle strength and functional capacity decline from normal levels to those characteristic of sarcopenia. However, it should be acknowledged that balance impairment may also be influenced by factors other than sarcopenia. The coexistence of sarcopenia, osteoporosis, and balance impairment—together with the effects of ageing—may synergistically contribute to an increased risk of fractures.

Study Limitations

This study has several limitations. First, the cross-sectional design precludes causal inferences. Second, compared to DXA — the gold standard technique for measuring body composition — it has been reported that BIA overestimates FFM

Table 3. Association between sarcopenia and age at menopause with osteoporosis: Results of univariate, standard multivariate and penalized multivariate binary logistic regression analyses

	Univariate		Multivariate model		
	b (se)	p-value	b (se)	p-value	OR (95% CI)
Age at menopause, years	0.14	0.001			
Osteoporosis, yes	2.49	<0.001			
Chronological age	0.10	0.001			
BMI, kg/m^2	0.46	<0.001			
			Model 1		
Age at menopause, years			-0.013 (0.05)	0.004	0.88 (0.80 to 0.95)
Osteoporosis, yes			2.44 (0.57)	<0.001	11.5 (3.80 to 34.98)
			Model 2		
Age at menopause, years			-0.13 (0.05)	0.006	0.88 (0.80 to 0.96)
Osteoporosis, yes			2.27 (0.58)	<0.001	9.64 (3.11 to 29.86)
Chronological age, years			0.08 (0.04)	0.034	1.08 (1.0 to 1.16)
			Model 3		
Age at menopause, years			-0.13 (0.07)	0.045	0.88 (0.77 to 0.99)
Osteoporosis, yes			1.42 (0.74)	0.055	4.12 (0.07 to 17.49)
Chronological age, years			0.12 (0.05)	0.016	1.13 (1.02 to 1.24)
BMI, kg/m^2			-0.46 (0.11)	<0.001	0.63 (0.51 to 0.78)
			Penalized model		
Age at menopause, years			-0.12 (0.06)	0.041	0.89 (0.78 to 0.99)
Osteoporosis, yes			1.28 (0.66)	0.058	3.59 (0.96 to 14.76)
Chronological age, years			0.11 (0.04)	0.012	1.11 (1.02 to 1.22)
BMI, kg/m^2			-0.41(0.09)	<0.001	0.66 (0.54 to 0.79)

AIC: Akaike information criterion, BMI: Body mass index, CI: Confidence interval, df: Degrees of freedom, OR: Odds ratio, se: Standard error
Model 1: X^2 =36.50, df =2, p<0.001; Hosmer-Lemeshow test: X^2 =9.68, df =8, p=0.288, Cox-Snell R^2 =0.248, Nagelkerke R^2 =0.386, AIC =101.4
Model 2: X^2 =41.35, df =3, p<0.001; Hosmer-Lemeshow test: X^2 =6.69, df =8, p=0.571, Cox-Snell R^2 =0.276, Nagelkerke R^2 =0.429, AIC =98.5
Model 3: X^2 =6.46, df =4, p<0.001; Hosmer-Lemeshow test: X^2 =1.20, df =8, p=0.997, Cox-Snell R^2 =0.450, Nagelkerke R^2 =0.699, AIC =65.4
Model 1 vs. Model 2: X^2 =4.81, df =1, p=0.028
Model 2 vs. Model 3: X^2 =35.11, df =1, p<0.001
Penalized model: Likelihood ratio test =70.88, df =4, p<0.001, AIC =65.8

at the individual level (19,20). This may have resulted in a lower frequency of diagnosing sarcopenia than is actually the case. Third, the presence of wide confidence intervals for certain ORs indicates a lack of statistical precision, likely attributable to an insufficient sample size. Fourth, the absence of a male control group limits the ability to disentangle the relative contributions of menopause versus chronological ageing. Finally, while age and BMI were identified as major confounders, other factors such as physical activity levels and nutritional status were not fully controlled for. It should be noted, however, evaluating the association between dynamic parameters (e.g., nutritional status and vitamin levels) and sarcopenia is better suited to prospective cohort studies than cross-sectional designs. Nevertheless, a more comprehensive analysis could be achieved by incorporating additional risk factors, such as physical activity and nutritional status, alongside a larger sample size to enhance the power of study.

Conclusion

In conclusion, this study demonstrates an independent association between sarcopenia and age at menopause along with chronological age and BMI. Although no statistically significant association was found between osteoporosis and sarcopenia, the findings suggest that there may be a potential clinical association. The coexistence of sarcopenia, osteoporosis, and balance impairment represents a high-risk phenotype for fractures in postmenopausal women. Early identification and integrated management strategies targeting both muscle strength and bone health are essential to improve functional outcomes in this population.

Ethics

Ethics Committee Approval: Approval for this cross-sectional observational study was obtained from the Local Ethics Committee of İzmir Katip Çelebi University (decision no: 0167, dated: 03/21/24), and the study was conducted in accordance

with the relevant guidelines and regulations of the Declaration of Helsinki.

Informed Consent: Participants were informed about the study and their written consent was obtained.

Footnotes

Authorship Contributions

Concept: E.M., N.Ö.S., İ.Ş., A.A., Design: E.M., N.Ö.S., İ.Ş., A.A., Data Collection or Processing: E.M., N.Ö.S., Analysis or Interpretation: E.M., N.Ö.S., İ.Ş., A.A., Literature Search: E.M., N.Ö.S., İ.Ş., A.A., Writing: E.M., N.Ö.S., İ.Ş., A.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/tod.galenos.2025.79027
Turk J Osteoporos 2026;32(Suppl 1):36-37

Sacral Insufficiency Fracture: A Frequently Overlooked Musculoskeletal Mimic of Lumbosacral Radiculopathy

Lumbosakral Radikülopatiyi Taklit Eden, Sıklıkla Gözden Kaçan Bir Kas-iskelet Sistemi Nedeni: Sakral Yetersizlik Kırığı

İlhami Ata, Alper Uysal

Mersin City Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, Mersin, Türkiye

Keywords: Sacral insufficiency fracture, imaging protocols, osteoporosis
Anahtar kelimeler: Sakral yetersizlik kırığı, görüntüleme protokolleri, osteoporoz

Dear Editor,

A 73-year-old female patient presented with persistent lower back, hip, and thigh pain for three months, without any history of trauma. She reported a history of previous episodes of low back pain, which had resolved either spontaneously or with medical treatment. At presentation, she arrived in a wheelchair due to severe pain, which was exacerbated by standing and walking. She exhibited an antalgic gait pattern.

On physical examination, hip range of motion was painful and limited, especially on the left side. The sacroiliac joint was also markedly tender bilaterally, especially on the left. Muscle strength in the lower extremities was reduced, particularly in the proximal muscles (4/5 on the right, 3/5 on the left). Sensory examination was normal, and no abnormal reflexes were detected.

Direct radiographs did not reveal any significant pathology to explain the patient's symptoms. Lumbar spine magnetic resonance imaging (MRI) showed only moderate disc degenerations, failing to explain the severity of her symptoms. Given the clinical suspicion, further imaging was pursued. Pelvic computed tomography (CT) revealed a sacral fracture, and subsequent sacroiliac MRI confirmed hypointense changes on T1-weighted images and hyperintense changes on T2-weighted images, characteristic of sacral insufficiency fractures (SIF) (Figure 1). Whole-body positron emission tomography ruled out malignancy, and DEXA confirmed osteoporosis (L1-L4: -2.1; femoral neck: -3.3; total hip: -2.9). The patient was diagnosed with an osteoporotic SIF and opted for conservative management involving bed rest, analgesics, and osteoporosis treatment, despite recommendations for surgical intervention.

SIFs are stress fractures of the sacrum, frequently associated with osteoporosis and often seen in postmenopausal women. Additional risk factors include prior fragility fractures, metabolic bone diseases, malignancy, local radiotherapy, and multi-segment spinal fusion (1). SIF can present with non-specific lower back and hip pain and often mimics lumbar spine pathology (2). In some cases, patients may also experience radiating pain or possibly neurological disorders (3). Importantly, CT can detect sclerosis or fracture lines, but MRI remains the most sensitive modality and reveals low T1 and high T2/STIR signal intensities (1). For example, in a study involving 50 patients diagnosed with SIF, MRI successfully confirmed the diagnosis in 74% of cases, whereas CT and X-ray each identified only 12% of cases accurately (4).

A significant limitation of standard lumbar MRI protocols is the exclusion of the sacral region, which complicates the identification of SIF in patients with chronic low back pain. In a study analyzing lumbar MRI scans, sacroiliac joint screening was absent in 40% of cases, and essential sequences such as T1-weighted axial or sagittal views were also frequently omitted (5). These findings highlight the need for comprehensive imaging protocols that include sacral evaluation to differentiate musculoskeletal conditions that may mimic radiculopathy.

This case highlights the need for standardized lumbar MRI protocols that routinely include sacroiliac joint and sacral bone

Corresponding Author/Sorumlu Yazar: Alper Uysal MD, Mersin City Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, Mersin, Türkiye
E-mail: alperuysal82@gmail.com **ORCID ID:** orcid.org/0000-0002-4114-1649
Received/Geliş Tarihi: 06.04.2025 **Accepted/Kabul Tarihi:** 03.06.2025 **Epub:** 07.08.2025 **Publication Date/Yayınlanma Tarihi:** 01.09.2026

Cite this article as/Atıf: Ata İ, Uysal A. Sacral insufficiency fracture: a frequently overlooked musculoskeletal mimic of lumbosacral radiculopathy. Turk J Osteoporos. 2026;32(Suppl 1):36-37

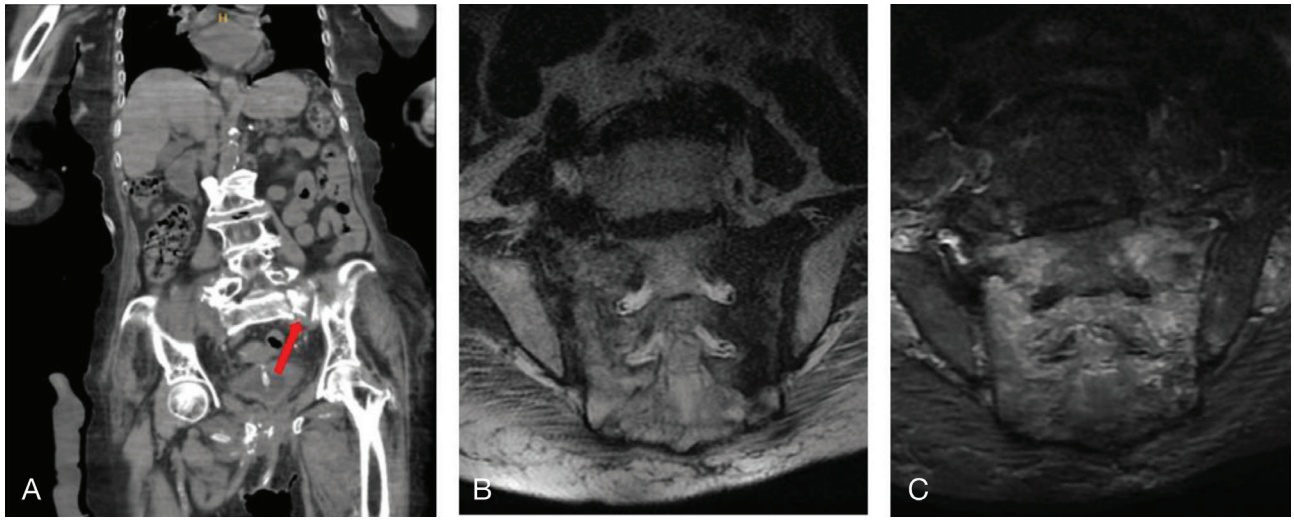

Figure 1. (A) The red arrow indicates a fracture line in the left sacrum in the coronal plane on CT. **(B)** T1-weighted MRI shows hypointense changes in the sacrum. **(C)** T2-weighted MRI shows hyperintense changes in the sacrum

MRI: Magnetic resonance imaging, CT: Computed tomography

imaging in patients presenting with chronic low back pain. Increased clinical awareness and revised imaging guidelines are essential for the timely diagnosis and effective management of SIFs.

Yours sincerely,

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DOI: 10.4274/tod.galenos.2025.34651
Turk J Osteoporos 2026;32(Suppl 1):38-39

Harnessing Climate Intelligence for Bone Health: A New Era in Osteoporosis Prevention

Kemik Sağlığı için İklim Zekasından Yararlanmak: Osteoporozun Önlenmesinde Yeni Bir Dönem

Beyza Öztürk[1], Rümeysa Çalışkan[2], Fatih Bağcıer[2], Burcu Hazer[2]

[1]University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital, Department of Physical Medicine and Rehabilitation, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Department of Physical Medicine and Rehabilitation, İstanbul, Türkiye

Keywords: Osteoporosis, bone health, climate intelligence, vitamin D, environmental factors, sunlight exposure, physical activity, artificial intelligence, risk mapping, public health, preventive care
Anahtar kelimeler: Osteoporoz, kemik sağlığı, iklim zekası, D vitamini, çevresel faktörler, güneş ışığı, fiziksel aktivite, yapay zeka, risk haritalama, halk sağlığı, koruyucu sağlık

Dear Editor,

Osteoporosis affects millions of people around the world and affects the increase as the global population grows and sedentent habits become more widespread (1). Although genetic, hormonal changes and lifestyle factors such as diet and exercise have been considered the main causes for a long time, it is becoming clear that environmental factors also play an important role in bone health. Bone metabolism and osteoporosis' can influence the risk in many ways, which we only started to understand.

Recently, Nvidia introduced an artificial intelligence-supported climate modeling system called "Climate in a Bottle", which is designed to predict environmental changes with extraordinary accuracy. This system integrates real-time climate data and uses machine learning algorithms to simulate variables such as ultraviole radiation, pollution levels, and temperature with high resolution. In this letter we would like to emphasize how such climate models can identify environmental conditions that may be involved in osteoporosis, opening new doors for preventive health strategy.

The production of vitamin D in the human body, which is essential for maintaining healthy bones and regulating calcium levels, mainly depends on exposure to sunlight, specifically ultraviolet B (UVB) radiation. However, environmental factors such as seasonal variations, geographic location, increasing air pollution, and urban living often limit how much UVB people receive (2). In regions in which cloudy weather or air pollution blocks daylight for a long-term, vitamin D deficiency frequently turns into general, that's the cause of osteoporsis danger. With the help of advanced weather versions consisting of "Climate in a Bottle", it is possible to assume changes in sunlight and air pleasant. Such projections could support public health planning by indicating when and where vitamin D supplementation or safe sun exposure is needed most. This can provide fitness officials a strategy to develop a good deal higher for vitamin D fashion and show people when and how to safely receive solar radiation (3).

Weather conditions also play an important role in how active people are, especially older adults who are more likely to develop osteoporosis. When the weather is too cold or too hot, people tend to stay indoors and move less, which means they miss out on activities that help keep their bones strong. Research from a rural community in Thailand showed that people who stayed physically active and consumed enough calcium had better bone density and a lower risk of osteoporosis (1). If we can use weather forecasts to plan physical activity, we may be able to reduce the research risk group of osteoporosis.

Furthermore, emerging research has linked air pollution, particularly fine particulate matter (PM2.5), to reduced bone mineral density and increased fracture risk through systemic

Corresponding Author/Sorumlu Yazar: Asst. Rümeysa Çalışkan, University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Department of Physical Medicine and Rehabilitation, İstanbul, Türkiye
E-mail: rumeysa98clskn@hotmail.com **ORCID ID:** orcid.org/0009-0001-7035-7000
Received/Geliş Tarihi: 09.07.2025 **Accepted/Kabul Tarihi:** 19.07.2025 **Publication Date/Yayınlanma Tarihi:** 01.09.2026
Cite this article as/Atıf: Öztürk B, Çalışkan R, Bağcıer F, Hazer B. Harnessing climate intelligence for bone health: a new era in osteoporosis prevention. Turk J Osteoporos. 2026;32(Suppl 1):38-39

inflammation and oxidative stress (4). Predictive climate and pollution models can help identify high-risk regions and populations, enabling tailored prevention strategies.

Beyond environmental exposures, recent machine learning research has highlighted the importance of both individual-level (psychological, behavioral) and nation-level (economic, cultural) factors in shaping climate-relevant beliefs and behaviors (5). Integrating these behavioral insights with climate-based bone health data could help develop personalized osteoporosis prevention strategies, such as predicting individuals' sun exposure patterns or activity levels. This approach could be extended to osteoporosis research by integrating personal health data with environmental forecasts to create individualized bone health risk profiles.

In conclusion, osteoporosis prevention must evolve beyond static risk factor assessments to dynamic, predictive models that incorporate environmental changes. Tools like "Climate in a Bottle" provide new opportunities to anticipate and mitigate environmental risk factors for osteoporosis on both an individual and population scale. Collaborative efforts between climate scientists, bone health specialists, and public health policymakers are needed to translate these climate models into actionable health interventions.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.Ö., B.H., Concept: B.Ö., Design: R.Ç., Data Collection or Processing: F.B., B.H., Analysis or Interpretation: R.Ç., Literature Search: B.Ö., Writing: R.Ç., B.H.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/tod.galenos.2025.95776
Turk J Osteoporos 2026;32(Suppl 1):40-41

Artificial Intelligence and the Proposed Phenomenon of Emerging Psychosis: A Hidden Challenge for Rehabilitation Physicians

Yapay Zeka ve Ortaya Çıkan Psikoz Olgusu: Rehabilitasyon Hekimleri için Gizli Bir Zorluk

Serkan Polat[1], Bülent Alyanak[2], Burak Tayyip Dede[3], Mustafa Hüseyin Temel[4], Mustafa Turgut Yıldızgören[5], Fatih Bağcıer[6]

[1]Sivas State Hospital, Clinic of Physical Medicine and Rehabilitation, Sivas, Türkiye
[2]Gölcük Necati Çelik State Hospital, Clinic of Physical Medicine and Rehabilitation, Kocaeli, Türkiye
[3]University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital, Department of Physical Medicine and Rehabilitation, İstanbul, Türkiye
[4]Üsküdar State Hospital, Clinic of Physical Medicine and Rehabilitation, İstanbul, Türkiye
[5]Necmettin Erbakan University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Konya, Türkiye
[6]University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Department of Physical Medicine and Rehabilitation, İstanbul, Türkiye

Keywords: Generative artificial intelligence, rehabilitation, psychotic disorders
Anahtar kelimeler: Üretken yapay zeka, rehabilitasyon, psikotik bozukluklar

Dear Editor,

The increasing presence of artificial intelligence (AI) in daily life has created new challenges for clinicians across disciplines. Recently, the term "AI psychosis" has been proposed as a preliminary concept, rather than an established diagnosis, to describe cases where vulnerable individuals may develop psychotic symptoms after prolonged and maladaptive use of AI chatbots (1). As Dr. Keith Sakata, a psychiatrist at University of California San Francisco, noted in a recent report, he has already treated multiple young patients hospitalized with such presentations in 2025. While this phenomenon has been described primarily in psychiatric settings, its implications extend beyond psychiatry and warrant careful consideration by rehabilitation physicians.

Physical medicine and rehabilitation (PM&R) specialists frequently manage patients with complex biopsychosocial profiles, including chronic pain, stroke, spinal cord injury, traumatic brain injury, and musculoskeletal disorders. These populations are already at elevated risk for mood disturbances, social withdrawal, and impaired coping mechanisms (2). For example, a stroke survivor with post-stroke depression may become increasingly dependent on AI-based interactions, withdrawing from social and therapeutic activities; similarly, a patient with chronic pain who is prone to catastrophizing may adopt maladaptive beliefs reinforced by AI dialogue systems. In such contexts, maladaptive engagement with AI could emerge as a barrier to rehabilitation, amplifying existing vulnerabilities.

From a PM&R perspective, the concern is not the technology itself but its potential to interfere with functional recovery and therapeutic adherence. Patients who spend excessive time in isolated interaction with AI systems may disengage from structured rehabilitation activities, neglect prescribed exercise regimens, or develop distorted beliefs about their condition. Early recognition of such behavioral shifts is essential for maintaining rehabilitation progress.

Red flags for rehabilitation physicians may include unexplained withdrawal from therapy sessions, diminished motivation for functional training, or the adoption of unscientific beliefs regarding treatment (3). Unlike psychiatry, where delusional thought content may dominate clinical encounters, PM&R settings often reveal subtler manifestations: Loss of therapeutic engagement, reduced participation, and impaired progress without a clear medical explanation.

The multidisciplinary nature of PM&R uniquely positions rehabilitation physicians to detect and intervene in these situations. Collaboration with psychiatry and psychology is

Corresponding Author/Sorumlu Yazar: Serkan Polat MD, Sivas State Hospital, Clinic of Physical Medicine and Rehabilitation, Sivas, Türkiye
E-mail: dr.serkan.0505@gmail.com **ORCID ID:** orcid.org/0009-0000-8386-2842
Received/Geliş Tarihi: 05.09.2025 **Accepted/Kabul Tarihi:** 11.09.2025 **Epub:** 22.09.2025 **Publication Date/Yayınlanma Tarihi:** 01.09.2026

Cite this article as/Atıf: Polat S, Alyanak B, Dede BT, Temel MH, Yıldızgören MT, Bağcıer F. Artificial intelligence and the proposed phenomenon of emerging psychosis: a hidden challenge for rehabilitation physicians. Turk J Osteoporos. 2026;32(Suppl 1):40-41

crucial, but equally important is the incorporation of socially interactive rehabilitation modalities-not only general approaches such as group exercise or caregiver involvement, but also PM&R-specific strategies including the careful monitoring of AI use in virtual rehabilitation programs and the establishment of structured patient–robot interaction protocols—to counteract isolation and maintain patient connection with reality. Patient and family education on the safe, structured use of AI tools should also become part of broader counseling strategies in rehabilitation clinics.

Looking ahead, PM&R research should not only document risks but also explore constructive ways in which AI might serve rehabilitation: structured journaling for chronic pain, motivational dialogue for adherence, or cognitive training in neurological recovery (4,5). Clear guidelines are needed to ensure AI augments, rather than undermines, rehabilitation outcomes. Future studies should aim to define clear, field-specific guidelines to ensure that AI augments-rather than undermines-rehabilitation outcomes.

In conclusion, the emergence of AI-related psychotic symptoms, still at the level of preliminary observations, serves as a reminder that novel technologies can have unintended consequences in vulnerable populations (6). Rehabilitation physicians must remain vigilant, integrating awareness of these risks into daily practice, and ensuring that AI, when present in patients' lives, is harnessed to support - not derail - functional recovery.

Footnotes

Authorship Contributions

Concept: B.A., M.H.T, M.T.Y., Design: S.P., B.T.D., Data Collection or Processing: M.H.T., F.B., Analysis or Interpretation: S.P., B.T.D., Literature Search: B.A., M.T.Y., Writing: S.P., F.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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DOI: 10.4274/tod.galenos.2025.76258
Turk J Osteoporos 2026;32(Suppl 1):42-43

Early Osteoporosis Evaluation in Pituitary Adenomas Through Opportunistic CT-based Radiomics

BT Radyomik Analizi ile Pitüiter Adenom Hastalarında Erken Osteoporoz Değerlendirme Potansiyeli

Taner Dandinoğlu

University of Health Sciences Türkiye, Bursa City Hospital, Department of Physical Medicine and Rehabilitation, Bursa, Türkiye

Keywords: Osteoporosis, radiomics, pituitary neoplasms
Anahtar kelimeler: Osteoporoz, radyomik, hipofiz neoplazmları

Dear Editor,

I would like to congratulate the authors for their valuable contribution to the literature with this innovative and elegantly designed study. The work by Güngör et al. (1), which explores the opportunistic prediction of osteoporosis using clivus-based radiomic features derived from routine cranial computed tomography (CT) imaging, represents a remarkable step forward in integrating radiomics and musculoskeletal assessment within daily clinical practice. I sincerely thank the authors for presenting a method that has the potential to enhance early osteoporosis detection using imaging data already available for other clinical purposes. Their study provides both scientific insight and practical applicability, and I believe it will stimulate further research in this promising field (1).

The valuable insights provided by this study have encouraged us to consider that the radiomic approach described by the authors may hold additional clinical utility in another important context. The successful extraction of bone-related information from cranial CT images suggests that this method could be extended to certain endocrine disorders in which osteoporosis is both common and frequently under-recognized. In particular, patients with pituitary adenomas—especially prolactinomas, adrenocorticotropic hormone (ACTH)-secreting adenomas, and select growth hormone-producing tumors—often present with significant bone loss at the time of diagnosis (2,3).

Despite the limited diagnostic role of CT in pituitary adenomas, a subset of patients arrive at the stage of definitive diagnosis with a previously performed cranial CT scan. This often occurs for reasons such as the evaluation of acute or chronic headache before the pituitary lesion is suspected, exclusion of alternative neurological conditions, or in situations where magnetic resonance imaging is contraindicated or temporarily unavailable. Therefore, in patients with prolactinoma along with other pituitary adenomas known to increase fracture risk such as ACTH-producing adenomas (Cushing disease) and, to a lesser extent, growth hormone–secreting adenomas opportunistic assessment of bone health using clivus-based radiomic features from these existing CT examinations may provide significant clinical advantage (2,3). Such an approach would allow early detection of osteoporosis at the moment the pituitary disease is first recognized, eliminating the immediate need for additional imaging dedicated to bone evaluation.

This strategy may be particularly valuable because prolactinoma is strongly associated with secondary osteoporosis and vertebral fragility fractures, especially in male patients in whom hypogonadism is frequently under-recognized (4). The ability to derive bone quality information from CT images already available in the patient's diagnostic workflow represents a practical, cost-effective, and innovative method for improving the early identification and management of osteoporosis (5,6).

I believe that this concept not only aligns with the opportunistic CT-based framework proposed in the study but may also guide future research exploring the integration of radiomic bone analysis into the routine evaluation of pituitary disorders.

Corresponding Author/Sorumlu Yazar: Taner Dandinoğlu, MD, University of Health Sciences Türkiye, Bursa City Hospital, Department of Physical Medicine and Rehabilitation, Bursa, Türkiye
E-mail: dandinoglu@gmail.com **ORCID ID:** orcid.org/0000-0002-6010-7315
Received/Geliş Tarihi: 24.11.2025 **Accepted/Kabul Tarihi:** 16.12.2025 **Epub:** 20.02.2026 **Publication Date/Yayınlanma Tarihi:** 01.09.2026
Cite this article as/Atıf: Dandinoğlu T. Early osteoporosis evaluation in pituitary adenomas through opportunistic CT-based radiomics. Turk J Osteoporos. 2026;32(Suppl 1):42-43

Footnotes

Financial Disclosure: The author declared that this study received no financial support.

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