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The Dynamic Osteocyte: Master Signaling Cell Integrating Bone Biology and Systemic Physiology

Dinamik Osteosit: Kemik Biyolojisi ile Sistemik Fizyolojiyi Bütünleştiren Ana Sinyal Hücresi

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Abstract

Osteocytes, long considered passive residents of bone, are now recognized as master regulators of skeletal remodeling and systemic metabolism. This review synthesizes current knowledge on osteocyte signaling, evaluates mechanotransduction mechanisms, and identifies key knowledge gaps to guide future research. A narrative review was conducted using MEDLINE, PubMed, Embase, Cochrane CENTRAL, and Google Scholar for studies published between January 2016 and December 2024. Keywords included "osteocyte signaling," "bone homeostasis," and "mechanotransduction." Included studies encompassed experimental, preclinical, translational, and clinical research. Osteocytes coordinate bone formation and resorption through paracrine and endocrine mediators, including sclerostin, receptor activator of nuclear factor-κB ligand, wingless-related integration site ligands, and fibroblast growth factor 23. Their extensive lacuno-canalicular network facilitates mechanosensation via fluid shear stress, ion channels (e.g., Piezo1), and cytoskeletal remodeling. Osteocytes also influence mineral metabolism, immune responses, energy homeostasis, and aging. Emerging evidence highlights their heterogeneity and context-dependent signaling, though debates persist regarding primary mechanosensors, signal hierarchy, and spatial regulation of outputs. Osteocytes act as central integrators of mechanical and biochemical cues, orchestrating skeletal and systemic physiology. Advancing *in vivo* models, spatial transcriptomics, and mechanistic studies will deepen understanding of osteocyte signaling, offering promising therapeutic avenues for osteoporosis, metabolic bone disorders, and chronic inflammation.

Keywords: Osteocyte, mechanotransduction, bone remodeling, sclerostin, RANKL, Wnt pathway, FGF23

Öz

Uzun süre kemiğin pasif yerleşik hücreleri olarak kabul edilen osteositlerin, günümüzde iskelet yeniden yapılanmasının ve sistemik metabolizmanın temel düzenleyicileri olduğu anlaşılmıştır. Bu derlemede, osteosit sinyallemesine ilişkin güncel bilgilerin sentezlenmesi, mekanotransdüksiyon mekanizmalarının değerlendirilmesi ve gelecekteki araştırmalara yön verecek temel bilgi boşluklarının belirlenmesi amaçlanmıştır. Ocak 2016 ile Aralık 2024 arasında yayımlanan çalışmalar MEDLINE, PubMed, Embase, Cochrane CENTRAL ve Google Scholar veri tabanlarında taranarak anlatısal bir derleme gerçekleştirilmiştir. Aramada "osteosit sinyallemesi", "kemik homeostazı" ve "mekanotransdüksiyon" anahtar kelimeleri kullanılmıştır. Deneysel, preklinik, translasyonel ve klinik araştırmalar derlemeye dahil edilmiştir. Osteositler; sklerostin, nükleer faktör-κB ligand reseptör aktivatörü, Wingless ile ilişkili entegrasyon bölgesi ligandları ve fibroblast büyüme faktörü 23 dâhil olmak üzere parakrin ve endokrin mediyatörler aracılığıyla kemik oluşumu ve rezorpsiyonunu koordine eder. Osteositlerin geniş laküno-kanaliküler ağı; sıvı kayma gerilimi, iyon kanalları (örneğin, Piezo1) ve hücre iskeletinin yeniden düzenlenmesi yoluyla mekanik uyaranların algılanmasını sağlar. Osteositler ayrıca mineral metabolizmasını, bağışıklık yanıtlarını, enerji homeostazını ve yaşlanmayı da etkiler. Güncel bulgular, osteositlerin heterojenliğini ve bağlama bağlı sinyal özelliklerini ortaya koymakla birlikte, birincil mekanik algılayıcılar, sinyal hiyerarşisi ve hücresel çıktıların uzamsal düzenlenmesine ilişkin tartışmalar devam etmektedir. Osteositler, mekanik ve biyokimyasal uyaranları bütünleştiren merkezi düzenleyiciler olarak iskelet ve sistemik fizyolojiyi yönlendirir. *İn vivo* modellerin, uzamsal transkriptomik yöntemlerin ve mekanistik çalışmaların geliştirilmesi, osteosit sinyallemesinin daha iyi anlaşılmasını sağlayarak osteoporoz, metabolik kemik hastalıkları ve kronik enflamasyon için umut verici tedavi olanakları sunabilir.

Anahtar kelimeler: Osteosit, mekanotransdüksiyon, kemik yeniden yapılanması, sklerostin, RANKL, Wnt yolağı, FGF23

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Introduction

For decades, bone biology was dominated by the interplay between osteoblasts, which form bone, and osteoclasts, which resorb it. Osteocytes—making up over 90% of all bone cells—were long considered passive, terminally embedded cells with minimal functional significance (1). This perspective has shifted dramatically. Landmark studies over the past two decades have established osteocytes as central regulators of skeletal homeostasis and sophisticated signaling hubs capable of integrating mechanical, biochemical, and endocrine cues (2).

Osteocytes influence both local and systemic physiology. Through the secretion of sclerostin, they inhibit osteoblast activity, whereas receptor activator of nuclear factor-κB ligand (RANKL) production drives osteoclastogenesis, directly coordinating bone remodeling (3). Endocrine roles have also emerged, exemplified by fibroblast growth factor 23 (FGF23) in phosphate homeostasis (4). Furthermore, osteocyte apoptosis is a critical initiator of targeted bone resorption during microdamage repair or glucocorticoid-induced bone loss (5). These findings underscore that understanding osteocyte signaling is not purely academic but central to developing novel diagnostics and therapies for skeletal diseases.

Despite these advances, significant gaps remain. A major controversy concerns the primary mechanosensor within osteocytes: is it the deflection of primary cilia, integrin-based focal adhesion complexes, or fluid shear stress–gated ion channels? The spatial logic of osteocyte signaling is also unclear: how do cortical versus trabecular osteocytes coordinate responses, and how is mechanical load translated into differential formation versus resorption (6)?

This narrative review aims to provide a comprehensive synthesis of osteocyte biology as a signaling cell. Its objectives are to: 1) delineate mechanotransduction and signal transduction mechanisms; 2) critically evaluate osteocyte communication with osteoblasts, osteoclasts, and bone-lining cells; 3) analyze endocrine contributions to mineral metabolism; and 4) identify knowledge gaps and propose actionable future research directions to resolve current controversies.

Materials and Methods

This study was conducted as a narrative review to provide a comprehensive and critical synthesis of contemporary literature on osteocyte signaling. The narrative design enabled integration of mechanistic, preclinical, and clinical evidence while emphasizing areas of a structured search was performed in MEDLINE via Ovid, PubMed, Embase, Cochrane CENTRAL, and Google Scholar. The timeframe was restricted to January 2016 through December 2024 to capture recent advances in osteocyte biology. Search terms included combinations of "osteocyte" with "signaling," "mechanotransduction," "communication," "RANKL," "sclerostin," and "FGF23," linked to "bone remodeling," "bone metabolism," or "osteoporosis." Search strategies were adapted for each database, and additional studies were identified through manual screening of reference lists.

Eligible studies included *in vitro* and *in vivo* preclinical investigations elucidating osteocyte signaling mechanisms, longitudinal cohort studies and randomized controlled trials evaluating therapeutics targeting osteocyte pathways (such as anti-sclerostin antibodies), and relevant systematic reviews or meta-analyses. Non-English articles, non-peer-reviewed publications, and reports not directly addressing osteocyte signaling or bone physiology were excluded.

Titles and abstracts were screened for relevance, followed by full-text evaluation of selected articles. Data extraction focused on signaling pathways, experimental models, and principal findings, which were synthesized thematically to generate an integrated conceptual framework.

As a narrative review, formal methodological quality assessment and risk-of-bias appraisal were not performed, introducing potential selection bias. The predominance of murine and *in vitro* models may limit direct translational applicability to human physiology. Furthermore, *in vitro* systems may not fully replicate the mechanical and biochemical complexity of the osteocyte lacuno-canalicular network. These limitations are acknowledged in the interpretation of findings.

Molecular and Cellular Mechanisms of Osteocyte Signaling

This section defines the molecular and cellular machinery that enables osteocytes to function as mechanosensory and signaling hubs. Emphasis is placed on structural organization, sensor systems, intracellular transduction pathways, effector outputs, and cell fate decisions. Integration at the tissue and systemic levels is addressed in subsequent sections.

The Lacunar-Canalicular Network: Structural Basis for Communication

Osteocytes reside within lacunae and extend 50-100 dendritic processes through micron-sized canaliculi, forming a dense, interconnected syncytium throughout mineralized bone (7). This lacunar–canalicular network (LCN) serves as a three-dimensional communication system in which interstitial fluid flow generates shear stress that is converted into biochemical signals, establishing osteocytes as widely regarded as dominant mechanosensors of the skeleton (8).

The structural integrity of this network depends on an actin-rich cytoskeleton that stabilizes dendritic projections (9). Gap junctions composed largely of connexin 43 (Cx43) permit direct intercellular communication and rapid signal propagation (10). Cx43 also forms hemichannels that connect osteocytes to the extracellular space and regulate paracrine factor release (11). Osteocyte-specific deletion of Cx43 increases apoptosis, produces empty lacunae in cortical bone, and blunts anabolic responses to mechanical loading (12) (Table 1).

Cx43 interacts with integrins at dendritic attachment sites, suggesting an integrated mechanotransduction complex (13). Super-resolution imaging demonstrates colocalization of β3 integrin with pannexin 1, purinergic receptor P2X7, and

calcium voltage-gated channel subunit alpha1 H (CaV3.2) along dendritic processes—structures absent from the cell body (14). Mechanical stimulation of dendrites triggers directional calcium influx through integrin alpha-V beta-3 (αVβ3) integrin-dependent mechanisms (9), supporting the view that dendritic processes function as specialized mechanosensory domains.

Molecular Mechanosensors: Primary Cilia, Integrins, and Ion Channels

Osteocytes transduce fluid shear stress through multiple mechanosensitive systems operating in parallel, including primary cilia, integrin-based adhesions, ion channels, and select G protein–coupled receptors. The primary cilium, a microtubule-based projection from the cell body, deflects under fluid flow and activates signaling pathways involving polycystin-1 (PC1) (15).

Integrins anchor osteocytes to the canalicular matrix. Integrin β1 is enriched at the cell body, whereas integrin β3 localizes predominantly to dendritic puncta (14), reflecting spatial specialization. Among mechanosensitive ion channels, PIEZO1 mediates mechanically induced calcium entry in osteocytes (16). Pharmacological activation of PIEZO1 reproduces load-induced calcium responses and suppresses sclerostin expression, whereas knockdown attenuates fluid flow–induced signaling (17). Conditional Piezo1 deletion leads to marked reductions in cancellous bone mass and cortical thickness, with severely impaired anabolic responses to mechanical loading (18).

Transient receptor potential vanilloid 4 (TRPV4) localizes to discrete sites along osteocyte processes in proximity to αVβ3 integrin attachments (14). The balance between depolarizing cation influx and hyperpolarizing potassium efflux likely determines activation thresholds (19). Certain G protein-coupled receptors also act as direct mechanosensors; fluid shear stress induces conformational changes in the parathyroid hormone type 1 receptor (PTH1R) independent of ligand binding (20) (Table 1).

Together, these pathways indicate a distributed and context-dependent mechanosensory apparatus rather than a single dominant sensor.

Intracellular Signal Transduction: From Membrane to Nucleus

Mechanical stimulation rapidly activates second messenger systems. Nitric oxide (NO) production increases within minutes via endothelial NO synthase activation and is required for subsequent prostaglandin E_2 synthesis and sclerostin downregulation (21).

Mechanical cues further regulate nuclear responses through yes-associated protein/transcriptional coactivator with PDZ-binding motif (TAZ), which shuttle between cytoplasm and nucleus.

Table 1. Major osteocyte-derived signaling molecules and actions

Molecule	Primary action	Target cells	Key references	Physiological context	Disease relevance
Sclerostin	Inhibits Wnt/β-catenin signaling	Osteoblasts	(3,22)	Mechanical unloading, aging	Osteoporosis (target of romosozumab)
RANKL	Promotes osteoclast differentiation	Osteoclast precursors	(1,39,40)	Targeted remodeling, microdamage	Osteoporosis, inflammatory bone loss
FGF23	Regulates phosphate homeostasis	Kidney (proximal tubule)	(4,28,29)	Phosphate/vitamin D balance	CKD-MBD, hypophosphatemic rickets
PGE_2	Promotes bone formation	Osteoblasts	(21)	Mechanical loading response	Mechanotransduction
Wnt ligands	Promotes bone formation, cell survival	Osteoblasts	(22,70)	Coupling, anabolic windows	Bone formation
OPG	Decoy receptor for RANKL	Osteoclast precursors	(39)	RANKL buffering	Osteoprotection
DKK1	Wnt antagonist	Osteoblasts	(35)	Formation inhibition	Diabetes, myeloma
EVs	Interorgan communication, miRNA transfer	Multiple distant tissues	(26,27)	Systemic signaling	Alzheimer's, osteoarthritis
NO	Vasodilation, signaling mediator	Endothelium, osteoblasts	(21)	Acute load response	Mechanotransduction
TGF-β	Coupling factor	Osteoblasts	(47)	Matrix release signals	Remodeling balance
PTHrP	Local calcium regulation	Osteocytes, osteoblasts	(20,43)	Perilacunar remodeling	Lactation, calcium demand

RANKL: Receptor activator of nuclear factor-κB ligand, FGF23: Fibroblast growth factor 23, PGE_2: Prostaglandin E_2, OPG: Osteoprotegerin, DKK1: Dickkopf-related protein 1, EVs: Extracellular vesicles, NO: Nitric oxide, TGF-β: Transforming growth factor-beta, PTHrP: Parathyroid hormone-related protein, CKD-MBD: Chronic kidney disease–mineral bone disorder

Osteocyte-specific deletion leads to low bone mass, impaired mechanical properties, disorganized collagen architecture, and reduced mechanoresponsiveness (23). The LINC complex couples the actin cytoskeleton to the nuclear lamina, enabling direct transmission of force to the nucleus (24).

Mechanotransduction is closely linked to metabolic state. Osteocytes reside in a relatively hypoxic microenvironment and rely largely on glycolytic metabolism (25). Their secretome includes soluble mediators and extracellular vesicles (EVs) capable of traversing the LCN and entering systemic circulation. EVs from young mice improve cognitive function in Alzheimer's disease models and mediate bone–cartilage communication in osteoarthritis (26). In addition, osteolineage cells can transfer functional mitochondria to myeloid cells through tunneling nanotubes and EVs, revealing an additional mechanism of intercellular coordination (27) (Table 1).

Effector Outputs: Sclerostin, RANKL, and Other Signaling Molecules

Sclerostin, encoded by *SOST* gene and secreted primarily by mature osteocytes, inhibits bone formation by antagonizing Wnt/β-catenin signaling. Mechanical loading suppresses sclerostin expression, permitting anabolic activity (22). Brief axial loading induces localized and transient loss of sclerostin in osteocytes located within high-strain regions (3).

Osteocytes are the principal source of RANKL, the cytokine essential for osteoclast differentiation. Osteocyte-specific RANKL deletion results in severe osteopetrosis, failed tooth eruption, and absence of cancellous osteoclasts (39). Following fatigue-induced microdamage, surviving osteocytes surrounding apoptotic cells upregulate RANKL and related mediators to recruit osteoclasts precisely to damaged sites (40).

Osteocytes produce additional signaling molecules that modulate bone remodeling, including Wnt ligands that promote formation and osteoprotegerin (OPG) that buffers RANKL activity. The balance between these effectors determines net remodeling outcomes (Table 1).

Cell Fate Decisions: Apoptosis and Senescence as Signaling Events

Osteocyte apoptosis initiates bone loss in settings such as disuse, microdamage, glucocorticoid excess, sex steroid deficiency, and aging (3). Mechanical stimulation promotes survival through integrin-, steroid receptor coactivator/sarcoma kinase (Src)-, focal adhesion kinase (FAK)-, and extracellular signal-regulated kinase (ERK)-dependent pathways (30). Sex steroids preserve osteocyte viability via rapid activation of inducible phosphoinositide 3-kinase and Src/Shc/ERK signaling through non-genotropic mechanisms (31). Bisphosphonates enhance survival through ERK activation and Cx43-dependent signaling independent of gap junction formation (5). In contrast, glucocorticoid-induced apoptosis involves proline-rich tyrosine kinase 2 (PYK2) activation and disruption of FAK–mediated survival signaling (32).

The penumbra model clarifies targeted remodeling: apoptotic osteocytes mark the site of damage, while adjacent viable cells upregulate RANKL to execute localized resorption (23,39). This spatial organization ensures that resorption is confined to damaged bone while preserving healthy tissue.

Cellular senescence represents a distinct fate characterized by irreversible cell cycle arrest and acquisition of a senescence-associated secretory phenotype (SASP) composed of inflammatory cytokines, proteases, and growth factors (33,49). Pharmacologic elimination of senescent cells or suppression of their secretory activity prevents age-related bone loss and attenuates radiation-induced skeletal damage in mice (28,49). Unlike apoptosis, which provides a spatially targeted signal for remodeling, senescence exerts broader, chronic effects on the bone microenvironment through sustained SASP factor release.

Osteocytes as Systemic Regulators

While the preceding section focused on the molecular machinery within individual osteocytes, osteocyte functions extend far beyond the bone microenvironment. This section examines how osteocyte-derived signals reach distant organs and contribute to whole-body physiology and disease.

Endocrine Functions: FGF23 and Mineral Metabolism

Osteocytes function as endocrine regulators beyond the bone microenvironment. They produce FGF23, a hormone controlling phosphate balance and vitamin D metabolism (29). Excess FGF23 causes hereditary hypophosphatemic rickets and tumor-induced osteomalacia, whereas deficiency results in hyperphosphatemia and ectopic calcifications (30). In chronic kidney disease, sustained FGF23 elevation contributes to mineral bone disorder and increased cardiovascular mortality (35,36) (Table 1).

Interorgan Communication: Extracellular Vesicles and Beyond

Osteocyte-derived sclerostin also influences systemic metabolism, affecting adipose tissue and glucose homeostasis (31). Osteocytic peroxisome proliferator-activated receptor gamma (PPARγ) signaling regulates sclerostin expression and mediates bone deterioration associated with diabetes (32).

Bone–muscle crosstalk is bidirectional: conditioned media from osteocyte-like cells accelerates myogenesis, while exercise-induced muscle factors protect osteocytes from apoptosis (33). Circulating osteocyte-derived EVs further extend this influence to distant organs, including the brain, where EVs from young mice enhance cognitive function in Alzheimer's disease models (26). These findings position osteocytes as nodes in a broader interorgan communication network.

Osteocyte Signaling in Disease States

Dysregulation of osteocyte signaling pathways contributes directly to skeletal and systemic disease states, illustrating the physiological importance of the mechanisms described above.

Osteoporosis and Estrogen Deficiency: Estrogen deficiency increases sclerostin expression, epigenetic alterations reduce osteogenic activity, FGF23 rises, and RANKL expression escalates, collectively favoring bone resorption over formation (29) (Table

1). Romosozumab, a monoclonal antibody targeting sclerostin, represents the first therapy to directly exploit osteocyte biology and has proven effective in treating postmenopausal osteoporosis (34,51).

Chronic Kidney Disease–Mineral Bone Disorder (CKD-MBD): CKD-MBD illustrates the systemic consequences of dysregulated osteocyte signaling, as phosphate retention drives sustained FGF23 secretion that becomes maladaptive, contributing to cardiovascular mortality (34,36).

Diabetes and Skeletal Fragility: In diabetes, hyperglycemia and advanced glycation end-products impair osteocyte function and increase sclerostin and Dickkopf-related protein 1 expression, contributing to skeletal fragility (35). Osteocytic PPARγ signaling mediates some of these effects (32).

Local Inflammation: Periodontal Disease: Periodontal disease provides another example: bacterial infection activates the toll-like receptor/myeloid differentiation primary response 88 pathway in alveolar osteocytes, leading to RANKL upregulation and localized bone resorption (36) (Table 2).

Having established the molecular toolkit osteocytes use to sense and transmit signals (section 3) and their systemic reach (section 4), we now examine how these individual pathways are orchestrated at the tissue level to coordinate bone remodeling—the process by which the skeleton maintains its integrity and adapts to physiological demands.

Osteocyte Coordination of Bone Remodeling

The molecular mechanisms detailed in section 3 operate within individual osteocytes, but skeletal homeostasis requires the coordinated activity of thousands of these cells across the bone matrix. This section examines how osteocyte networks integrate local and systemic signals to produce coherent remodeling responses that align skeletal adaptation with physiological demands.

The Remodeling Cycle: Osteocytes as Conductors

Bone remodeling replaces old or damaged bone through tightly coupled osteoclast-mediated resorption followed by osteoblast-driven formation. Osteocytes direct this sequence with spatial and temporal precision (37). In cortical bone, remodeling proceeds within basic multicellular units (BMUs); on cancellous surfaces, it occurs in coordinated cellular packets. The LCN provides the structural framework that allows osteocytes to target remodeling to specific regions of need (38).

Spatial Organization of Targeted Remodeling

As detailed in section 3.5, osteocyte apoptosis provides a spatially precise signal for remodeling initiation. The "penumbra" model clarifies this process: apoptotic osteocytes mark the site of damage, while adjacent viable cells upregulate RANKL and chemotactic factors that recruit osteoclasts selectively to compromised matrix (5,40,44). Resorption is thus confined to damaged bone and followed by coupled formation to restore structure (46).

This spatial precision depends on the LCN architecture described in section 3.1, which enables rapid communication between apoptotic cells and their neighbors while limiting signal diffusion to healthy regions.

Mechanical Integration at the Tissue Level

Building on the mechanotransduction pathways detailed in sections 3.2–3.3, mechanical loading suppresses resorption and stimulates formation through osteocyte-dependent mechanisms at the tissue level. Osteocytes discriminate between loading and unloading, dynamic and static forces, and differences in strain magnitude (41). Brief loading episodes suppress sclerostin for hours, creating transient anabolic windows, whereas sustained unloading increases sclerostin and RANKL expression, driving disuse-associated bone loss (34).

In vivo imaging studies reveal that osteocyte calcium responses encode strain magnitude by increasing the proportion of activated cells rather than signal amplitude, supporting a binary recruitment model (59). This population-level response transforms individual cell mechanosensitivity into graded tissue-level adaptation.

The multiscale integration of osteocyte signaling—from molecular sensors to systemic effects—is illustrated in Figure 1, which serves as a roadmap for the sections that follow.

Hormonal Integration: Parathyroid Hormone, Estrogen, and Glucocorticoids

Osteocytes integrate endocrine signals with mechanical input to fine-tune remodeling. Parathyroid hormone (PTH) exerts context-dependent effects: intermittent exposure is anabolic, while sustained elevation is catabolic (42). These effects are mediated through PTH1R signaling in osteocytes, which regulates both sclerostin and RANKL expression. Intermittent PTH suppresses sclerostin and promotes formation, whereas continuous PTH increases RANKL and enhances resorption (43).

Estrogen preserves bone mass partly by maintaining osteocyte viability (section 3.5) and restraining RANKL expression (39). In contrast, glucocorticoids induce osteocyte apoptosis, elevate sclerostin and RANKL, and suppress perilacunar remodeling, contributing to glucocorticoid-induced osteoporosis (44).

Perilacunar Remodeling: A Specialized Osteocyte Function

Beyond directing surface remodeling, osteocytes remodel the matrix immediately surrounding their lacunae—a process termed perilacunar remodeling or osteocytic osteolysis (45). This involves expression of matrix-degrading enzymes such as cathepsin K, MMP13, and MMP14 and is regulated by PTH, PTHrP, and mechanical unloading (43). During lactation, osteocytic osteolysis mobilizes calcium for milk production; unloading similarly expands the lacunar–canalicular system through local resorption (45). This mechanism enables rapid mineral mobilization independent of classical BMU activity.

Coupling Formation to Resorption

The net skeletal outcome depends on coupling between resorption and formation. Osteocytes influence this balance through both matrix-derived and cell-derived signals. Growth factors released from resorbed bone matrix—including TGF-β, insulin-like growth factor-1, and bone morphogenetic proteins—promote osteoblast recruitment and differentiation (47). Osteocytes further contribute by producing canonical coupling factors such as Wnts and cardiotrophin-1, supporting osteoblast activity at remodeling sites (48).

Age-Related Remodeling Dysregulation

Aging disrupts osteocyte-mediated coordination through two distinct but related cell fates introduced in section 3.5: apoptosis and senescence. Apoptosis provides targeted signals for focal remodeling, but excessive apoptosis with age depletes the osteocyte network. Simultaneously, the accumulation of senescent osteocytes creates broader dysfunction through SASP factors that favor resorption and suppress formation (33,49). This, combined with structural deterioration of the LCN and increased empty lacunae, shifts the remodeling balance toward net bone loss with age (50).

Future Directions: Toward an Integrated Osteocyte Biology

Osteocyte research is transitioning from descriptive cell biology toward integrated systems-level investigation. Having examined molecular mechanisms (section 3), systemic regulation (section 4), and tissue-level remodeling (section 5), this final section considers how emerging technologies and conceptual frameworks can unify these layers into a coherent model of skeletal and systemic regulation.

New technologies now permit interrogation of osteocytes at molecular resolution while preserving their anatomical context. The central challenge is to connect gene programs, mechanotransduction, metabolism, and endocrine signaling into a coherent physiological framework that explains skeletal adaptation and systemic disease.

Technological Frontiers

Transcriptomic Mapping: Single-Cell and Spatial Approaches

Comprehensive transcriptomic profiling has revealed more than 1,000 genes differentially expressed in osteocytes compared with other bone cells, the majority with unknown skeletal function. Importantly, human homologs of several of these genes are linked to monogenic skeletal disorders and complex traits, highlighting the translational relevance of osteocyte-specific gene networks (54).

Single-cell RNA sequencing is beginning to resolve osteocyte heterogeneity across maturation states and disease contexts (55). Early osteocytes near bone surfaces express higher levels of osteocalcin, RANKL, and PTHrP, whereas deeply embedded

Table 2. Osteocyte signaling alterations in bone diseases

Disease state	Key osteocyte changes	Molecular mediators	Key references	Therapeutic implications
Postmenopausal osteoporosis	↑ Sclerostin, ↑ RANKL, ↑ apoptosis	Estrogen deficiency, ↑ RANKL/OPG ratio	(1,29,33)	Anti-sclerostin antibodies (romosozumab)
CKD-MBD	↑ FGF23 (maladaptive), ↓ Klotho	Phosphate retention, ↑ FGF23	(4,28,36)	FGF23 blockade (investigational)
Type 2 diabetes	↑ Sclerostin, ↑ DKK1, ↓ viability	Hyperglycemia, AGEs, PPARγ signaling	(31,32,35)	PPARγ modulation, anti-sclerostin
Glucocorticoid-induced	↑ Apoptosis, ↑ RANKL, ↓ Cx43	PYK2 activation, ↓ survival signaling	(5,44,55)	PYK2 inhibition (preclinical)
Aging	Senescence, SASP, network deterioration	p16/p21, JAK-STAT, ↓ autophagy	(48,49,52)	Senolytics (dasatinib+quercetin), senomorphics
Periodontal disease	↑ RANKL, TLR/MYD88 activation	Bacterial LPS, local inflammation	(35)	Local anti-RANKL strategies
Disuse/osteoporosis	↑ Sclerostin, ↑ RANKL, ↑ apoptosis	Mechanical unloading, ↓ NO/PGE_2	(3,21,41)	Mechanical loading mimetics
Cancer-associated	↑ Sclerostin, ↑ RANKL/OPG ratio	Tumor-derived factors, microenvironment	(22,46)	Anti-sclerostin, bone-targeted agents
Osteogenesis imperfecta	Altered LCN, abnormal signaling	Collagen mutations, secondary effects	(7,8)	Unclear—needs investigation
Lactation	↑ Perilacunar remodeling	↑ PTHrP, ↑ calcium demand	(43,45)	Targets for calcium mobilization

CKD-MBD: Chronic kidney disease–mineral bone disorder, AGEs: Advanced glycation end-products, PPARγ: Peroxisome proliferator-activated receptor gamma, Cx43: Connexin 43, SASP: Senescence-associated secretory phenotype, TLR: Toll-like receptor, MYD88: Myeloid differentiation primary response 88, LPS: Lipopolysaccharide, NO: Nitric oxide, PGE_2: Prostaglandin E_2, LCN: Lacunar-canalicular network, PTHrP: Parathyroid hormone-related protein

cells preferentially express sclerostin (56). Serial collagenase/ethylenediaminetetraacetic acid digestion combined with fluorescence-activated cell sorting has enabled isolation of viable osteocytes suitable for transcriptomic analysis, overcoming long-standing technical barriers imposed by the mineralized matrix (57). Integration of single-cell sequencing with spatial transcriptomics and computational modeling is further refining maps of osteocyte diversity and lacunar–canalicular organization (58).

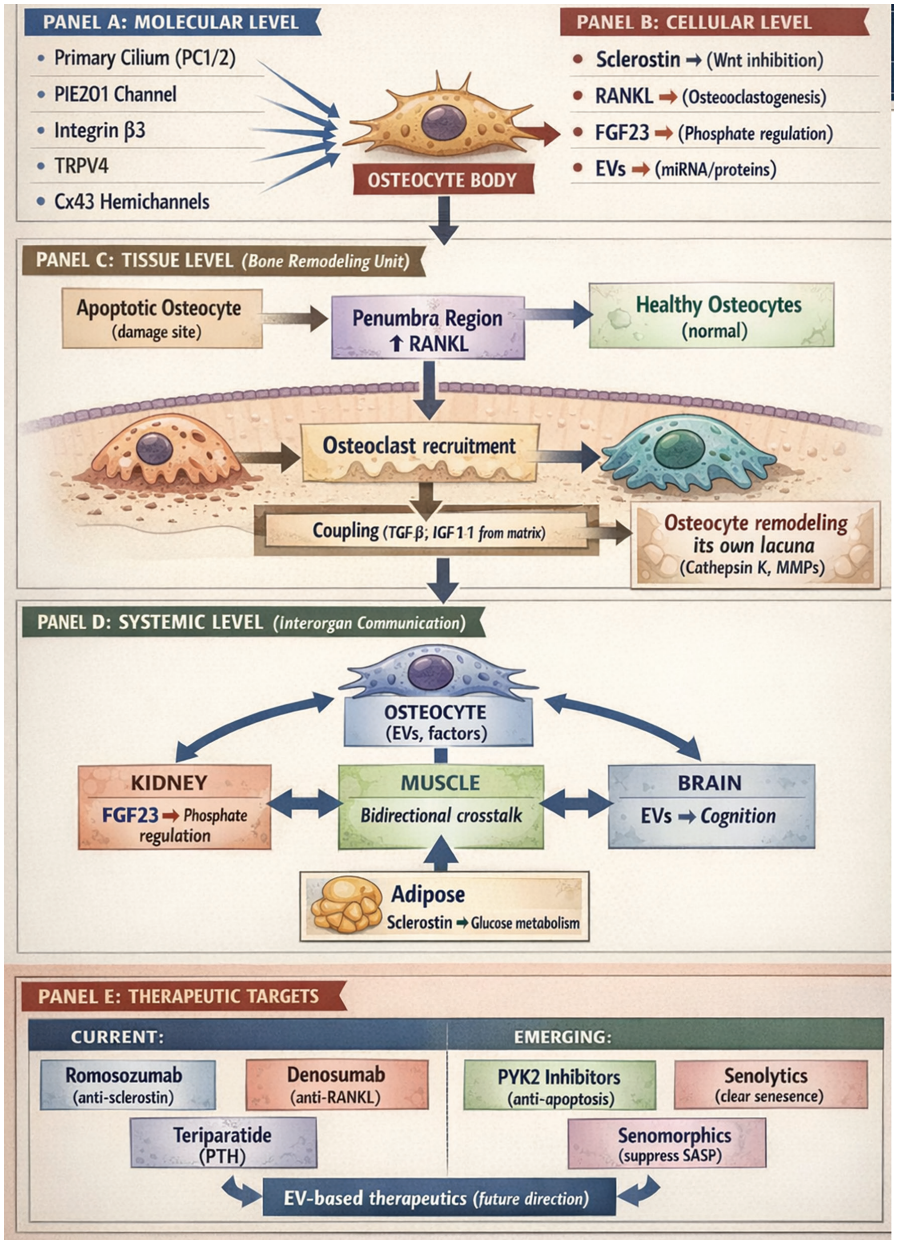

Figure 1. The osteocyte as a multiscale signaling Hub
Osteocytes integrate mechanical and biochemical signals across multiple organizational levels. Panel A depicts molecular mechanosensors including the primary cilium, PIEZO1 ion channels, integrin β3 attachments, TRPV4 channels, and connexin 43 hemichannels. Panel B shows cellular effector outputs: sclerostin (inhibiting Wnt signaling), RANKL (promoting osteoclastogenesis), FGF23 (regulating phosphate metabolism), and extracellular vesicles (EVs) carrying bioactive cargo. Panel C illustrates tissue-level coordination of bone remodeling: apoptotic osteocytes mark damage sites, adjacent cells in the "penumbra" upregulate RANKL to recruit osteoclasts, and coupling factors from resorbed matrix recruit osteoblasts for formation. The inset shows perilacunar remodeling, where osteocytes locally degrade and replace surrounding matrix. Panel D depicts systemic interorgan communication via FGF23 (kidney), EVs (brain), and sclerostin (adipose, muscle). Panel E summarizes current and emerging therapeutic strategies targeting osteocyte pathways. Together, these scales illustrate the osteocyte's role as the central integrator of skeletal and systemic physiology
Cx43: Connexin 43, RANKL: Receptor activator of nuclear factor-κB ligand, FGF23: Fibroblast growth factor 23, MMPs: Matrix metalloproteinases, PTH: Parathyroid hormone, SASP: Senescence-associated secretory phenotype

Epigenetic regulation remains poorly defined. Deoxyribonucleic acid methylation, histone modifications, and chromatin accessibility likely shape osteocyte differentiation and functional plasticity, yet systematic profiling is limited (55). Clarifying these mechanisms will be essential for understanding age-related transcriptional drift and disease susceptibility.

Advanced Imaging: Visualizing Osteocytes in Action

Advances in multiphoton microscopy, tissue clearing, and reporter systems now permit high-resolution imaging of osteocytes within intact bone (55). A major step forward has been the development of *in vivo* loading devices compatible with real-time imaging. Using such systems, osteocyte calcium responses were shown to encode strain magnitude by increasing the proportion of activated cells rather than signal amplitude, supporting a binary recruitment model (59). These approaches bridge *in vitro* mechanotransduction studies and whole-bone physiology, allowing direct observation of network behavior under defined strain conditions.

Technical hurdles remain. Osteocyte isolation still requires careful validation to preserve native transcriptional states (60). Imaging fragile structures such as the primary cilium within mineralized tissue remains challenging, and improved fixation and imaging protocols are needed to determine its orientation and functional relevance *in vivo* (61).

Organ-on-Chip and *Ex Vivo* Models

Organ-on-a-chip platforms and live imaging strategies further enable analysis of osteocyte–osteoblast–osteoclast interactions under mechanical load (47). Future refinements may clarify the temporal sequence of cellular recruitment during remodeling and how aging or pharmacologic interventions shift activation thresholds.

Fundamental Unresolved Questions

The Mechanosensation Hierarchy: Despite substantial progress, fundamental integrative questions remain. At the cellular level, whether osteocytes function as the dominant mechanosensors *in vivo* or operate in concert with other osteolineage cells remains unsettled (62). The relative contributions of fluid shear, matrix deformation, and substrate strain—and how distinct sensors integrate these cues—are incompletely understood (63). The molecular basis of primary cilium–mediated sensing, including potential activation of PC1/2 or TRPV4 channels, requires confirmation under physiological loading conditions (15). Advances in cell type–specific genetic tools should clarify these mechanisms (62).

Metabolic Regulation of Osteocyte Function: Osteocytes rely on tightly regulated glucose and amino acid metabolism to sustain survival within a hypoxic niche (55). Inhibition of glucose transporter 1 reduces RANKL and osteocalcin expression, linking cellular energetics to remodeling capacity (64). Disruption of von Hippel–Lindau protein enhances hypoxia-inducible factor-1α signaling and increases bone mass, underscoring coupling between oxygen sensing and skeletal homeostasis (65). Taurine production has emerged as a modulator of sclerostin and Wnt signaling (66). Age-associated energy deficits and circadian disruption further compromise osteocyte function (67). Defining how metabolic decline drives skeletal fragility remains a priority.

The Senescence-Apoptosis Continuum: The temporal relationship between osteocyte senescence and apoptosis is unclear (55,49). Transcriptomic data from aged bone reveal upregulation of innate immune and inflammatory pathways, including Janus kinase/signal transducer and activator of transcription signaling (68). Whether these changes initiate senescence or arise secondarily remains unresolved. Autocrine feedback loops may modulate osteocyte responsiveness, yet this area remains underexplored (55). Aging is associated with reduced expression of PTH1r, vitamin D receptor), and FGFRs in cortical bone, potentially blunting hormonal responsiveness (50). Mechanisms governing receptor regulation and sensitivity warrant deeper investigation.

Osteocyte Heterogeneity and Spatial Logic: The functional significance of osteocyte heterogeneity across skeletal sites (cortical vs. trabecular) and depth from bone surface remains poorly understood. How spatial position determines signaling outputs and how this organization is established and maintained are critical unanswered questions.

Translational Horizons

Targeting Osteocyte Signaling: Current and Emerging Strategies

Improved genetic tools are needed to validate osteocyte-specific targets without off-target expression (55). PYK2 inhibition shows promise in preventing glucocorticoid-induced bone loss in preclinical models (53). Bone-targeted modulation of pathways such as Notch may achieve skeletal specificity while limiting systemic toxicity (55).

The therapeutic success of agents targeting osteocyte-derived signals underscores their central role in remodeling. Romosozumab demonstrates that inhibiting an osteocyte-specific signal can simultaneously increase formation and decrease resorption (51). Denosumab, while effectively inhibiting RANKL-driven resorption, does not distinguish between RANKL's cellular sources; whether a strategy selectively targeting osteocyte-derived RANKL could offer advantages in preserving bone formation remains an open question (51). Teriparatide promotes bone formation in part by suppressing osteocyte sclerostin expression, illustrating how even established therapies work through these master regulators (52).

Senolytics and Senomorphics: Senolytic therapies, which clear senescent cells, and senomorphic agents, which suppress the SASP, have prevented age-related and radiation-induced bone loss in mice (49), though the degree to which these approaches selectively target osteocytes remains uncertain (69).

Cancer and the Osteocyte Niche: In oncology, tumor–osteocyte interactions increase sclerostin and shift the RANKL/OPG ratio toward resorption (22). Anti-sclerostin therapy may interrupt this cycle, but whether benefits arise solely from microenvironmental modulation requires clarification.

Osteocytes as Endocrine Therapeutic Targets: Defining causal links between osteocyte-derived factors such as FGF23 and sclerostin and systemic metabolic disease demands interventional human studies (55). Emerging evidence of osteocyte-derived EVs influencing distant organs underscores the need to understand bone as an endocrine regulator of whole-body homeostasis (47). Pathways governing perilacunar remodeling are being explored as targets for conditions requiring rapid calcium mobilization, and the recognition that osteocytes communicate via EVs opens speculative but exciting possibilities for delivering therapeutics directly to the osteocyte syncytium (26).

Toward a Quantitative Systems Framework

Amplified Wnt/β-catenin signaling in osteocytes increases mineral apposition in craniofacial bone, whereas excessive activation promotes lacunar mineralization, illustrating how signaling amplitude dictates divergent outcomes (70).

Future progress will require quantitative frameworks that integrate mechanotransduction, gene regulation, metabolism, and endocrine signaling across skeletal sites. The next phase of osteocyte research must combine single-cell and spatial technologies with functional validation in genetic models and human tissue. Only through this integration will osteocyte-directed therapies move from experimental promise to clinical reality.

Conclusion

Osteocytes have emerged from obscurity to take their rightful place as master regulators of the skeleton, but this review reveals that their influence extends far beyond bone remodeling. Three organizing principles emerge from the current literature:

First, osteocyte signaling operates across multiple scales—from the nanoscale organization of mechanosensors along dendritic processes (section 3), through the tissue-level coordination of remodeling units (section 5), to systemic endocrine effects on mineral metabolism and distant organs (section 4).

Second, osteocyte functions are context-dependent and heterogeneous. The same cell that suppresses bone formation through sclerostin under unloading conditions can promote formation when mechanically stimulated, while neighboring osteocytes may simultaneously execute apoptosis or senescence programs that shape the local remodeling environment. This heterogeneity, revealed by emerging transcriptomic technologies (section 6), challenges us to move beyond viewing osteocytes as a uniform population.

Third, therapeutic targeting of osteocyte pathways has already proven transformative, but realizing the full potential of these cells requires moving beyond single-molecule approaches. Romosozumab's success demonstrates that modulating osteocyte signals can uncouple formation from resorption in ways previously thought impossible—yet this likely represents the first generation of osteocyte-directed therapies.

The next decade will determine whether we can translate our growing understanding of osteocyte heterogeneity, mechanotransduction hierarchies, and systemic communication into therapies that prevent age-related bone loss, mitigate cancer treatment-induced skeletal damage, and harness osteocyte-derived EVs for targeted drug delivery. Meeting this challenge requires the integrated, multiscale approach outlined in this review—one that respects the osteocyte not as an isolated cell, but as the central node in a dynamic network connecting the skeleton to the entire organism.

Footnotes

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Digital Rehabilitation in Parkinson's Disease: The Role of Artificial Intelligence-Assisted Exercise Training

Parkinson Hastalığında Dijital Rehabilitasyon: Yapay Zeka Destekli Egzersiz Eğitiminin Rolü

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Abstract

Objective: The aim of this study is to evaluate the content quality, readability, reliability, understandability and applicability of ChatGPT-4o exercise recommendations for Parkinson's patients.

Materials and Methods: Questions about balance and coordination exercises for Parkinson's patients were directed to ChatGPT-4o with the literature and the experiences of physical medicine specialists. Readability was examined with simple measure of gobbledygook and the other most popular readability formula tests, understandability and applicability were examined with 5-point Likert. Content quality was evaluated with ensuring quality information for patients (EQIP), and global quality score (GQS), and reliability was evaluated with modified DISCERN (mDISCERN) and JAMA score.

Results: It was determined that all readability scores were above the 6th grade reading level ($p<0.001$). The understandability score was 3.80±1.01 and the applicability score was 3.73±0.96. In reliability and quality assessment, EQIP mean was determined as 50.86±3.83, GQS as 2.66±1.17, mDISCERN as 1.86±0.51. JAMA scores were 1.

Conclusion: ChatGPT-4o exercise information for Parkinson's disease patients was found to be understandable and applicable. However, the high readability level (average Flesch reading ease score of 38, equivalent to 11 years of education) limits accessibility for individuals with low health literacy, and the lack of reliability restricts safe clinical use. These limitations should be carefully considered before clinical implementation, and future improvements are required to enhance the accuracy and accessibility of AI-based health guidance.

Keywords: Artificial intelligence, ChatGPT, exercise, Parkinson's disease, quality assessment, readability

Öz

Amaç: Bu çalışmanın amacı, ChatGPT-4o tarafından Parkinson hastaları için önerilen egzersizlerin içerik kalitesini, okunabilirliğini, güvenilirliğini, anlaşılabilirliğini ve uygulanabilirliğini değerlendirmektir.

Gereç ve Yöntem: Parkinson hastalarına yönelik denge ve koordinasyon egzersizleri hakkında, literatür ve fiziksel tıp uzmanlarının klinik deneyimleri doğrultusunda oluşturulan sorular ChatGPT-4o'ya yöneltilmiştir. Okunabilirlik; anlaşılmazlığın basit ölçüsü ve diğer yaygın okunabilirlik formülleriyle değerlendirilmiştir. Anlaşılabilirlik ve uygulanabilirlik 5'li Likert ölçeğiyle değerlendirilmiştir. İçerik kalitesi; hastalar için bilgi kalitesinin sağlanması (EQIP) ve global kalite skoru (GQS) ile, güvenilirlik ise modifiye DISCERN (mDISCERN) ve JAMA skoru ile değerlendirilmiştir.

Bulgular: Tüm okunabilirlik skorlarının 6. sınıf okuma seviyesinin üzerinde olduğu belirlenmiştir ($p<0,001$). Anlaşılabilirlik skoru 3,80±1,01, uygulanabilirlik skoru 3,73±0,96 olarak saptanmıştır. Güvenilirlik ve kalite değerlendirmesinde EQIP ortalaması 50,86±3,83, GQS 2,66±1,17, mDISCERN 1,86±0,51 olarak bulunmuştur. JAMA skoru ise 1'dir.

Sonuç: ChatGPT-4o tarafından Parkinson hastaları için sağlanan egzersiz bilgileri anlaşılır ve uygulanabilir bulunmuştur. Ancak, yüksek okuma düzeyi (ortalama Flesch okuma kolaylığı skoru 38, yaklaşık 11 yıllık eğitim seviyesine eşdeğer) düşük sağlık okuryazarlığına sahip bireyler için

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erişilebilirliği sınırlamakta ve güvenilirliğin olmaması güvenli klinik kullanımını kısıtlamaktadır. Bu sınırlamalar, klinik uygulamaya konmadan önce dikkatle değerlendirilmelidir ve yapay zeka tabanlı sağlık rehberliğinin doğruluğunu ve erişilebilirliğini artırmak için gelecekte iyileştirmeler yapılması gerekmektedir.

Anahtar kelimeler: Yapay zeka, ChatGPT, egzersiz, Parkinson hastalığı, kalite değerlendirmesi, okunabilirlik

Introduction

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder characterized by motor symptoms such as tremor, rigidity, bradykinesia, and postural instability, which significantly impair patients' functional independence and quality of life (1,2). Although pharmacological treatments are the cornerstone of symptom management, they are often insufficient in addressing motor impairments. For this reason, rehabilitation programs—including balance and coordination exercises—have emerged as essential components of PD management, aiming to maintain mobility, reduce fall risk, and improve daily living activities (3,4).

Despite the proven benefits of exercise, many PD patients encounter substantial barriers to implementing rehabilitation protocols. These include motor and cognitive challenges, limited access to specialized care, and insufficient guidance on proper exercise execution (5). Traditional rehabilitation services are often limited by workforce capacity, geographic disparities, and scheduling difficulties. Consequently, digital health technologies have gained increasing attention as tools to improve accessibility and adherence to exercise programs.

Artificial intelligence (AI), particularly large language models such as ChatGPT, has recently emerged as a novel approach to address such gaps in health education. These tools have the potential to deliver personalized, on-demand exercise recommendations, bridging the divide between clinical expertise and patient access. Recent studies have demonstrated that AI-based chatbots can assist patients with various chronic diseases—including fibromyalgia, low back pain, and spinal cord injury—by providing general information and exercise guidance with varying degrees of quality and reliability (6-12). However, limited research has focused specifically on their utility in Parkinson's rehabilitation.

Furthermore, while AI systems such as ChatGPT-4o have shown promise in improving patient engagement and understanding, concerns persist regarding the readability, reliability, and quality of the information they provide. For individuals with low health literacy, the complexity of AI-generated responses can hinder effective use. Additionally, the absence of references, author attribution, and evidence-based justification in chatbot outputs raises questions about their role as reliable health communication tools (13-15). Therefore, assessing these tools using validated readability, quality, and reliability metrics is essential before integrating them into clinical care.

This study aims to evaluate the content quality, readability, reliability, understandability, and applicability of ChatGPT-4o's exercise recommendations for patients with PD. By benchmarking the outputs against established standards and comparing them to the needs and limitations of PD patients, this study seeks to determine whether AI-assisted exercise guidance can serve as a viable complement to traditional rehabilitation methods.

Materials and Methods

Ethics Comittee Permission

This study was conducted at the University of Health Sciences Türkiye, Derince Training and Research Hospital, on April 24, 2025. The planning, execution and data collection processes of this cross-sectional study were carried out in accordance with the approval of the relevant ethics committee (Sivas Cumhuriyet University's Ethics Committee, ethics committee no: 2025-04/67, date: 24.04.2025).

Data Collection

This study evaluated the potential of ChatGPT-4o, an AI-supported language model, in delivering exercise training recommendations for patients with PD. To generate relevant queries, a pool of questions was created based on established clinical guidelines and recent meta-analyses focusing on balance and coordination exercises commonly prescribed in PD rehabilitation. The inclusion criteria prioritized clinical relevance, linguistic clarity, and alignment with functional goals such as fall prevention, mobility improvement, and postural control. Ambiguous, overly technical, or redundant questions were excluded. Two physical medicine and rehabilitation specialists (ICO and EO) independently reviewed the question set to ensure face and content validity (Table 1) (16-18).

To standardize the data collection process and reduce variability, all questions were entered using consistent phrasing and submitted in separate chat sessions to minimize contextual bias between responses. A dedicated ChatGPT-4o account was created for the study, and all interactions were conducted using the April 2025 version. The AI-generated responses were systematically documented and later evaluated in terms of quality, comprehensiveness, readability, and scientific accuracy (https://archive.org/details/chatgpt-parkinson-answers).

Readability Assessment

Readability assessment of the response texts was performed using two different web-based readability calculators: http://readabilityformulas.com/, https://www.online-utility.org/.

During the readability evaluation of the AI-generated texts, each calculator was evaluated separately, and their arithmetic averages were taken to record the final readability median (minimum-maximum) values.

Commonly used formulas were used to measure the readability of texts:

- Simple measure of gobbledygook (SMOG)
- Automated readability index (ARI)
- Gunning fog readability (GFOG)
- Flesch-Kincaid grade level (FKGL)

- Coleman-Liau readability index (CLI)
- The Flesch reading ease score (FRES).

Formulas and data for calculating the readability score are given in Table 2.

According to the standards set by the National Institutes of Health (NIH) and the American Medical Association (AMA), patient education materials must have a readability grade of six or below for the average individual to read. Therefore, the final readability scores we obtained were analyzed based on the sixth-grade readability level recommended by the institutions mentioned above. Accordingly, while the accepted average readability level is 6 for the other 6 formulas, 80.0 points are accepted for FRES (19,20).

Reliability Assessment

The reliability of the response texts was examined using two different scales:

1. JAMA Benchmark: Four basic criteria (transparency, authorship, timeliness and reference) were taken into account and the presence of each criterion was evaluated with 1 point and its absence with 0 points (21).

2. Modified DISCERN: Based on five basic criteria (whether the content included discussions, clarity, up-to-dateness of sources, impartiality and listing of additional sources), each criterion was evaluated out of 1 point (22).

Table 1. Questions asked to ChatGPT-4o for exercise training for Parkinson's disease patients

What is balance and which systems in the body provide balance?
What is the definition of coordination and which muscle groups is it related to?
Why does balance disorder occur in elderly people and how can it be prevented?
What are beginner level balance exercises?
How should balance exercises be performed with eyes closed?
What is the recommended duration for daily balance and coordination exercises?
How to do one-leg stand exercise and what are the benefits?
What are the appropriate coordination exercises for individuals with balance disorders?
What is the role of the vestibular system on balance?
What is proprioception and how can it be improved with balance exercises?
What are the common mistakes in balance exercises?
How can we improve the activities of daily living of patients with balance disorders?
What are the simple balance exercises we can apply at home?
How does artificial intelligence contribute to learning balance and coordination exercises?
How can health professionals use ChatGPT in balance exercises training?

Quality Assessment

The quality assessment of the response texts was carried out using two different methods:

1. Global quality score (GQS): This scale is scored from 1 to 5, with 1 point being considered "low quality" and 5 points being considered "very high quality" (23).

2. Ensuring quality information for patients (EQIP): In this 20-question assessment tool, "yes" was calculated as 1 point, "partially" as 0.5 points and "no" as 0 points. The results were interpreted on a scale of 0-100 (24).

Each text was independently assessed by two physical medicine and rehabilitation experts (ICO and EO) in different settings to reduce bias. In case of any differences, the assessment was re-performed and solutions were found by consensus among the experts.

In addition, the scientific accuracy of the responses was examined by two expert physicians (ICO and EO) in terms of compliance with the literature, and the criteria for understandability and applicability in terms of patient education were evaluated using a 5-point Likert scale (1: Very incomprehensible, 5: Very understandable) (25).

Statistical Analysis

Statistical analyses were conducted using SPSS software, version 24.0 for Windows (SPSS Inc., USA). Categorical data were expressed as frequencies and percentages, whereas continuous data were reported as both means with standard deviations and medians with their corresponding minimum and maximum values. Comparisons between categorical variables were carried out using Fisher's exact test and the chi-square test. For continuous variables, the Mann-Whitney U test and Wilcoxon signed-rank test were employed. To assess the level of agreement between the two readability calculators used in the study, intraclass correlation coefficients (ICC) were calculated. A two-way mixed-effects model with absolute agreement and average measures was applied, as the same two fixed tools were used to rate all items. The ICC values were computed for each readability formula (SMOG, ARI, GFOG, FKGL, CLI, FRES). A p-value of less than 0.05 was considered indicative of statistical significance.

Results

Table 3 presents the mean, standard deviation, minimum and maximum values of SMOG, ARI, GFOG, FKGL, CLI and FRES scores. SMOG score ranged from 8.58 to 15.18, with a mean of 12.35±2.43. ARI score ranged from 4.74 to 14.48, with a mean value of 10.17±3.57. GFOG scores ranged from 7.91 to 16.12, with a mean of 12.66±3.33. The scores obtained for FKGL ranged from 5.70 to 15.00, with a mean value of 11.12±3.40. CLI score ranged from 6.06 to 17.32, with a mean of 13.11±3.81. The FRES score was observed between 13.05 and 76.09 and the mean was determined as 38.81±21.84.

Table 3 includes the comparison of SMOG, ARI, GFOG, FKGL, CLI and FRES scores according to the 6th grade reading level median.

Table 2. Readability formulas

Readability index	Description	Formula
Flesch reading ease score	It was developed to evaluate the readability of newspapers. It is best suited for evaluating school textbooks and technical manuals. The standardized test used by many US government agencies. Scores range from 0 to 100, with higher scores indicating easier readability.	I = (206.835 - (84.6 X (B/W)) - (1.015 X (W/S)))
Flesch-Kincaid grade level	Part of the Kincaid navy personnel test collection. Designed for technical documentation and suitable for a wide range of disciplines.	G = (11.8 X (B/W)) + (0.39 X (W/S)) −15.59
Simple measure of gobbledygook	It is generally suitable for middle-aged (4^{th} grade to college level) readers. While testing 100% comprehension, most formulas test about 50-75% comprehension. Most accurate when applied to documents ≥30 sentences long.	G = 1.0430 X √C + 3.1291
Gunning FOG	It was developed to help American businesses improve the readability of their writing. Applicable to many disciplines.	G = 0.4 X (W/S+((C∗/W) X 100))
Coleman-Liau index	It is designed for middle-aged (4^{th} grade to college level) readers. The formula is based on text in the grade level range of 0.4 to 16.3. It applies to many industries.	G = (−27.4004 X (E/100)) + 23.06395
Automated readability index (ARI)	ARI has been used by the military in writing technical manuals, and its calculation returns a grade level necessary for understanding.	ARI = 4.71 X l + 0.5*ASL - 21.43

W: Number of words, S: Number of sentences, B: Number of syllables, C: Number of polysyllabic words (≥3 syllables), l: Average number of letters per word, ASL: Average sentence length (number of words), E: Average number of letters per 100 words, US: Ultrasound, FOG: Fog readability

The p-values obtained for all scores were <0.001, indicating a statistically significant difference.

Table 4 shows the distribution of understandability and applicability scores. The understandability score ranged from 2 to 5, with an average of 3.80±1.01. Similarly, the applicability score ranged from 2 to 5, with an average of 3.73±0.96.

Table 5 provides a summary of reliability and quality scores. The EQIP score ranged from 42.30 to 66.60, with a mean of 50.86±3.83. The GQS score ranged from 1 to 4, with a mean of 2.66±1.17. The JAMA score was set to 1 in all data. The mDISCERN score ranged from 1 to 3, with a mean of 1.86±0.51. The ICC calculated in the study were as follows: 0.915 for JAMA Benchmark, 0.892 for Modified DISCERN, 0.938 for GQS, 0.927 for EQIP, 0.879 for SMOG, 0.862 for ARI, 0.895 for GFOG, 0.912 for FKGL, 0.921 for CLI and 0.934 for FRES. The ICC value for understandability score was calculated as 0.902, and the ICC value for applicability score was calculated as 0.918.

Discussion

In this study, the information provided by ChatGPT-4o on exercise training for PD patients was evaluated in terms of readability, quality, and reliability. Our analysis showed that the AI-generated texts exceeded the 6^{th}-grade readability level recommended by the NIH and AMA, with a mean FRES score of 38, suggesting a complexity equivalent to approximately 11 years of education.

While the responses were rated as generally understandable and applicable, they displayed limitations in reliability and technical depth. The EQIP and GQS scores reflected moderate content quality, whereas the JAMA and mDISCERN scores highlighted a lack of transparency and evidence-based references. These findings align with previous studies examining AI-based health information tools for other conditions, such as fibromyalgia, low back pain, and spinal cord injury, which similarly noted issues with readability and content reliability (9-12).

The need for accessible and reliable health information for PD patients is well-documented. A recent study evaluating 60 PD websites found that only a small proportion provided clear, comprehensive, and useful information, indicating that the availability of adequate online resources remains limited (26). Similarly, studies evaluating online videos about PD, such as those by Kim et al. (27) and Al-Busaidi et al. (28), revealed that the majority of content was of mediocre quality and often lacked scientific rigor. Our findings are consistent with these observations, suggesting that even advanced AI systems

like ChatGPT-4o struggle to meet the readability and reliability standards necessary for patient education.

Beyond PD, AI chatbots have been evaluated in other medical contexts. Zaleski et al. (9) reported that ChatGPT's exercise recommendations for fibromyalgia patients often lacked sufficient clarity and referenced sources, limiting their usefulness. Scaff et al. (10) also highlighted readability challenges in ChatGPT responses to common low back pain questions, describing the text as "moderately difficult". Fahy et al. (11) demonstrated similar concerns in the context of anterior cruciate ligament injuries, finding that response readability frequently exceeded the recommended level for patient materials. In a study of spinal cord injury information, Temel et al. (12) noted that AI responses lacked sufficient detail for practical application, echoing our findings for Parkinson's rehabilitation. These consistent patterns across multiple studies suggest that large language models, despite their potential, require further refinement for effective patient education.

One distinctive aspect of our study is its focus on PD-specific rehabilitation exercises. While prior research largely addressed general health information or diagnosis-related content, we specifically assessed balance and coordination exercise guidance, which are critical components of PD management (3,4). The ability of ChatGPT-4o to provide clear, structured exercise descriptions, with appropriate safety warnings and emphasis on consulting healthcare professionals, highlights its potential utility. However, the absence of detailed, step-by-step instructions and supporting references diminishes its applicability in clinical settings.

The strengths of our study include a comprehensive evaluation using multiple validated metrics and independent assessments by two rehabilitation specialists. To our knowledge, this is the first study to evaluate the readability, quality, and reliability of AI-generated content specifically for PD exercise training, providing a valuable foundation for future research.

Study Limitations

However, some limitations should be acknowledged. The scope was restricted to responses generated for predefined questions, which may not fully represent real-world patient queries. Additionally, the study did not assess the variability of ChatGPT-4o's responses over time, nor did it examine language adaptability for patients with low health literacy.

Future research should explore ways to enhance the clarity and personalization of AI-generated health information. Simplifying language, incorporating references, and providing more detailed exercise instructions could improve applicability. Moreover, integrating AI tools into supervised rehabilitation programs may increase patient adherence and safety. In addition, it may be valuable to investigate whether prompting ChatGPT to generate

Table 3. Readability scores and comparison with 6th grade reading level median

	Minimum	Maximum	Median	Mean	SD	p
SMOG	8.58	15.18	13.41	12.35	2.43	<0.001
ARI	4.74	14.48	11.94	10.17	3.57	<0.001
GFOG	7.91	16.12	14.08	12.66	3.33	<0.001
FKGL	5.70	15.00	12.72	11.12	3.40	<0.001
CLI	6.06	17.32	14.99	13.11	3.81	<0.001
FRES	13.05	76.09	30.58	38.81	21.84	<0.001

SMOG: Simple measure of gobbledygook, ARI: Automated readability index, GFOG: Gunning fog readability, FKGL: Flesch-Kincaid grade level, CLI: Coleman-Liau index, FRES: The Flesch reading ease score, SD: Standard deviation

Table 4. Statistics of understandability and applicability scores

	Minimum	Maximum	Median	Mean	SD
Understandability (Likert)	2	5	4	3.80	1.01
Applicability (Likert)	2	5	4	3.73	0.96

SD: Standard deviation

Table 5. Statistics of reliability and quality scoress

	Minimum	Maximum	Median	Mean	SD
EQIP	42.30	66.60	50	50.86	3.83
GQS	1	4	3	2.66	1.17
JAMA	1	1	1	1	0
mDISCERN	1	3	2	1.86	0.51

JAMA: The Journal of the American Medical Association, GQS: Global quality score, EQIP: The Ensuring quality information for patients, SD: Standard deviation, mDISCERN: Modified DISCERN

responses at a lower readability level (e.g., sixth grade or below, as recommended by the NIH and AMA) improves accessibility and comprehension among Parkinson's patients. Comparative studies evaluating this approach could provide meaningful insights for optimizing AI-based patient education tools.

Conclusion

ChatGPT-4o demonstrates potential as a supplementary tool for delivering exercise guidance to patients with PD. Nevertheless, our analysis revealed that its readability exceeds the NIH and AMA's recommended 6th-grade level, with an average FRES score of 38—corresponding to approximately 11 years of education. This significantly limits accessibility for patients with lower health literacy. Furthermore, the lack of reliability reduces its suitability for direct clinical application. Addressing these shortcomings through model refinement, health-literacy–oriented design, and rigorous validation studies will be essential for transforming such AI systems into reliable and equitable aids for patient education and rehabilitation.

Ethics

Ethics Committee Approval: The planning, execution and data collection processes of this cross-sectional study were carried out in accordance with the approval of the relevant ethics committee (Sivas Cumhuriyet University's Ethics Committee, ethics committee no: 2025-04/67, date: 24.04.2025).

Informed Consent: Not applicable.

Footnotes

Authorship Contributions

Concept: İ.C.Ö., E.Ö., Design: İ.C.Ö., E.Ö., Data Collection or Processing: İ.C.Ö., E.Ö., Analysis or Interpretation: İ.C.Ö., E.Ö., Literature Search: İ.C.Ö., E.Ö., Writing: İ.C.Ö., E.Ö.

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Serotonin Transporter Gene Polymorphisms and Bone Mineral Density in North Indian Postmenopausal Women

Kuzey Hindistan'daki Menopoz Sonrası Kadınlarda Serotonin Taşıyıcı Gen Polimorfizmlerinin Dolaşım Seviyesi ve Kemik Mineral Yoğunluğu ile İlişkisi

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Abstract

Objective: Osteoporosis is a serious metabolic bone disease worldwide, with genetic factors contributing significantly. We investigated the 5-HTT variable number tandem repeats (5HTTVNTR) & serotonin transporter gene 5-hydroxy tryptamine transporter linked polymorphic region or serotonin-transporter-linked promoter region (5HTTLPR) polymorphisms their serum levels & bone mineral density (BMD) in osteoporotic postmenopausal & healthy postmenopausal North Indian women.

Materials and Methods: In the present study, we included 165 post-menopausal osteoporotic (age 54.44±6.00) & 165 post-menopausal healthy North Indian women (age 54.47±6.46). BMD of different skeletal sites were analyzed using dual-energy X-ray absorptiometry. Serotonin serum level was assessed using enzyme linked immunosorbent assay & genotyping was done using polymerase chain reaction method.

Results: The current research demonstrated that in the patient group, subjects with the homozygous mutant 12/12 genotype of the 5HTTVNTR polymorphism exhibited significantly reduced BMD in the femoral neck region, accompanied by reduced serotonin levels. Similarly, subjects carrying the LL genotype of the 5HTTLPR variant showed significantly reduced BMD at both the lumbar spine & femoral neck, along with lower serotonin levels. In the controls, serum levels of both polymorphisms were found to be significantly lower. No significantly low BMD was found with homozygous mutant 12/12 genotype of 5HTTVNTR while LL genotype of 5HTTLPR showed significant decrease BMD at femoral neck. Furthermore, no significant variation was observed in serotonin genotype or allele frequencies among patients compared to controls.

Conclusion: This study indicates that serotonin gene polymorphisms may be linked with variations in BMD and involved in the development of osteoporosis in postmenopausal women from North India.

Keywords: Osteoporosis, serotonin transporter gene, postmenopausal women, BMD, genotype

Öz

Amaç: Osteoporoz, dünya çapında genetik faktörlerin önemli ölçüde katkıda bulunduğu ciddi bir metabolik kemik hastalığıdır. Menopoz sonrası osteoporotik ve menopoz sonrası sağlıklı Kuzey Hindistanlı kadınlarda 5-HTT değişken sayılı tandem tekrarları (5HTTVNTR) ve serotonin taşıyıcı geni 5-hidroksi triptamin taşıyıcı bağlantılı polimorfik bölge veya serotonin taşıyıcı bağlantılı promotör bölgesi (5HTTLPR) polimorfizmlerini, serum seviyelerini ve kemik mineral yoğunluğunu (KMY) araştırdık.

Gereç ve Yöntem: Bu çalışmaya 165 menopoz sonrası osteoporotik (yaş 54,44±6,00) ve 165 menopoz sonrası sağlıklı Kuzey Hindistanlı kadın (yaş 54,47±6,46) dahil edildi. Farklı iskelet bölgelerinin KMY'leri çift enerjili X-ışını absorpsiyometrisi ile ölçüldü. Serotonin serum seviyesi enzim bağlantılı immünosorbent testi ile değerlendirildi ve genotipleme polimeraz zincir reaksiyonu yöntemi kullanılarak yapıldı.

Bulgular: Bu çalışma, hasta grubunda, 5HTTVNTR polimorfizminin homozigot mutant 12/12 genotipine sahip deneklerin femur boynunda anlamlı derecede daha düşük KMY ve buna eşlik eden serotonin seviyelerinin azaldığını göstermiştir. Benzer şekilde, 5HTTLPR varyantının LL genotipine sahip deneklerde, hem lomber omurgada hem de femur boynunda anlamlı derecede düşük KMY ve daha düşük serotonin seviyeleri gözlenmiştir. Kontrol grubunda, her iki polimorfizmin serum seviyelerinin anlamlı derecede düşük olduğu bulunmuştur. Homozigot

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mutant 12/12 5HTTVNTR genotipinde anlamlı derecede düşük KMY bulunmazken, 5HTTLPR LL genotipinde femur boynunda anlamlı KMY düşüşü gözlenmiştir. Ayrıca, hastalar ve kontroller arasında serotonin genotipleri ve alellerinin sıklığında anlamlı bir fark gözlenmemiştir.

Sonuç: Bu bulgular, serotonin gen polimorfizmlerinin BMD'deki varyasyonlarla ilişkili olabileceğini ve Kuzey Hindistan'daki postmenopozal kadınlarda osteoporoz gelişimine katkıda bulunabileceğini düşündürmektedir.

Anahtar kelimeler: Osteoporoz, serotonin taşıyıcı gen, postmenopozal kadın, BMD, genotip

Introduction

Osteoporosis is a prevalent public health concern, defined by reduced bone strength and an elevated risk of fractures. Bone mineral density (BMD) and bone quality both play an important role in determining bone strength (1). BMD contributes to approximately 70% of the variability in bone strength, & findings from family and twin studies suggest that between 50% and 85% of BMD variability are influenced by genetic determinants (2-4). Since low BMD is a key contributor to the development of osteoporosis, it plays a critical role in disease prediction and prevention. Globally, osteoporosis affects an estimated 200 million women (5). In India about 50 million individuals were affected by either osteoporosis or osteopenia in 2013 (6).

Serotonin, referred as 5-hydroxytryptamine (5-HT), is a neurotransmitter whose transporter gene (*SLC6A4*) is approximately 31 kb in length, located on the 17p11.2 region of chromosome 17, and comprises 14 exons (7). It is expressed throughout various bone cell types, including osteoclasts, osteoblasts, osteocytes, and osteoblast precursor cells, & is considered to play a significant role in regulating bone mass formation. Two polymorphic regions have been observed in the *SLC6A4* gene. The first referred to as 5-HTT variable number tandem repeats (5-HTTVNTR), is situated in intron 2 and consists of a variable number of tandem repeats (VNTR), with alleles carrying 9, 10, or 12 copies of a 17-base pair sequence. The second polymorphism is a 44 bp insertion/deletion (indel) polymorphism situated in the promoter region, known as 5-hydroxy tryptamine transporter linked polymorphic region or serotonin-transporter-linked promoter region (5HTTLPR), which results in two alleles: the short (S) allele containing 14 repeats & the long (L) allele carrying 16 repeats (8-11).

Recent advances in bone biology have revealed a role for the serotonergic system traditionally studied in the context of neuropsychiatric function in the regulation of bone homeostasis in peripheral tissues. Ferreira et al. (12), 2011 demonstrated that the 5-HTTVNTR polymorphism has been significantly linked with an increased risk of osteoporosis. Previous studies have revealed that the long (L) allele results in normal transcription, whereas the short (S) variant is less effective (13-15). Additionally, some studies have found that the S allele of 5-HTTLPR is significantly associated with decreased BMD, while the L allele shows no such association (16,17).

Several studies have been conducted on serotonin gene polymorphism, but a comprehensive study on the effect of serotonin gene polymorphism on BMD and serotonin levels has not been done in this ethnic group so in a current study, we have explored the association between serotonin transporter gene (*5HTTVNTR* & *5HTTLPR*) polymorphisms with their circulatory levels & BMD in North Indian postmenopausal women.

Materials and Methods

Subjects

In this case control study we enrolled 165 postmenopausal osteoporotic women (patients) (mean age 54.44±6.00) and 165 postmenopausal healthy women (controls) (mean age 54.47±6.46) who visited OPD at the Department of Orthopedics, King George Medical University, Lucknow, India between December 2018 and April 2021. For at least one year, all the women did not experienced menstruation. Before participating in this study, we obtained a questionnaire from each participant's current health status and medical history with informed consent. The study received ethical approval from the Institutional Ethics Committee of King George's Medical University, Lucknow, India (approval number: 1094, dated: 29.07.2019). Dual-energy X-ray absorptiometry (DEXA) was used for the assessment of each individual's BMD at different skeletal sites. According to the World Health Organization (WHO) criteria of osteoporosis, the individuals were categorized as osteoporotic or normal based on the T-score of DEXA, and after that sample was taken from all recruited subjects.

BMD Measurements

At the skeletal site of the hip, forearm, femoral neck & lumbar spine L1-L4, the BMD (g/cm^2) was evaluated by DEXA. The range of variance percent coefficient was 0.5% to 1.1% based on the measurement site. The peak bone density (T-score) of a healthy young adult of the same sex is defined by the WHO as BMD values at or above -1 standard deviation (S.D.). Osteoporotic BMD was defined as a measurement at or below -2.5 S.D.

DNA Isolation and Genotyping

For serotonin transporter gene genotyping, 5 mL of venous blood was collected from each subject. Of this, 2 mL was collected into ethylene diamine tetra acetic acid vials for DNA isolation using the salting-out method, to study genetic polymorphisms. The serum was extracted from 3 mL of blood collected in the plain vial by centrifuging at 3000 rpm for 5 minutes. The resulting serum was then stored at -20 °C for enzyme linked immunosorbent assay analysis. The extracted DNA was utilized to genotype *5-HTTVNTR* and *5-HTTLPR* gene polymorphisms using the polymerase chain reaction (PCR) method. Both polymorphisms produced distinct amplicons, as identified through 3% agarose gel electrophoresis.

Detection of Serotonin Transporter Gene 5HTTVNTR Polymorphism

PCR was conducted to identify the 5-HTTVNTR polymorphism in the serotonin transporter gene, using the primers F-5′ GTCAGTATCACAGGCTGCGAG 3′ and R-5′ TGTTCCTA GTCTTACGCCAGTG 3′. The PCR reaction mixture was prepared in a final volume of 25 µL containing 2x PCR master mix, 150-200 ng genomic DNA, 10pmol of each primer (forward & reverse). PCR amplification was performed for 5 min at 94 °C followed by 30 cycles of 94 °C/40 sec, 57 °C/40 sec, extension at 72 °C/40 sec & final extension for 5 minutes at 72 °C. All the PCR reactions were performed using an automated thermal cycler (BIO-RAD T100). In 5-HTTVNTR polymorphism PCR product was separated by 3% agarose gel electrophoresis containing ethidium bromide to enable the detection of 267 bp (10/10), 267 bp, 299 bp (10/12) and 299 bp (12/12) genotypes.

Detection of Serotonin Transporter Gene 5HTTLPR Polymorphism

PCR was conducted to identify the 5-HTTLPR polymorphism in the serotonin transporter gene, using the primers F-5′-ATGCCAGCACCTAACCCCTAATGT-3′ & R-5′-GGACCGCAA GGTGGGCGGGA-3′. The PCR reaction mixture was prepared in a final volume of 25 µL containing 2x PCR master mix, 150-200ng genomic DNA, 10 pmol of each primer (forward & reverse). PCR amplification was performed for 5 min at 95 °C followed by 35 cycles of 95 °C/30 sec, 66 °C/40 sec, extension at 72 °C/40 sec & final extension for 5 minutes at 72 °C. All the PCR reaction were performed using an automated thermal cycler (BIO-RAD T100). In 5-HTTLPR polymorphism PCR product was separated by 3% agarose gel electrophoresis containing ethidium bromide to enable the detection of 375 bp (S/S), 375 bp, 419 bp (S/L) and 419 bp (L/L) genotypes.

Statistical Analysis

The statistical analysis was conducted using INSTAT version 3.05 (Graph Pad Software, San Diego, CA, USA). All categorical variables were summarized as percentages. The study had a statistical power of 90%, determined from the odds ratio (OR) of the study genotype under both the null and research hypotheses. Numerical data were expressed as mean values with S.Ds. Genotype frequencies were consistent with Hardy-Weinberg equilibrium. Comparisons of genotype & allele distributions between patients & controls were performed using the chi-square test. The independent samples t-test was employed to compare mean values between the case & control groups, while One-Way ANOVA was comparisons involving more than two groups. Adjusted ORs with 95% confidence intervals were used to analyze the associations of genetic, demographic, and anthropometric factors with the osteoporosis. Logistic regression analysis was used to calculate adjusted OR and 95% confidence interval for the genotypes. Adjustments were made for age, body mass index (BMI), and years since menopause. A p-value of ≤0.05 was considered statistically significant.

Results

The baseline characteristics of the patients & controls are presented in Table 1. BMD across various skeletal regions was found to be significantly low in the patients in comparison to the controls (p≤0.0001*****). Height is also significantly decreased in patients as controls (p=0.035*). Additionally, BMI & serum serotonin levels were significantly higher among patients than among controls (p=0.046*; p<0.0001*).

Figure 1 illustrates the comparison of BMD across different skeletal sites & serotonin levels among patients, categorized by the various genotypes of 5HTTVNTR and 5HTTLPR. The present investigation revealed that individuals carrying the homozygous mutant 12/12 genotype of 5HTTVNTR had significantly reduced BMD at the femoral neck, along with lower serotonin levels, compared to those with the 10/10 and 10/12 genotypes. Additionally, for 5HTTLPR, individuals with the homozygous mutant LL genotype exhibited significantly reduced BMD at the femoral neck & lumbar spine along with lower serotonin levels, in comparison to those with the LS and SS genotypes.

Table 1. Biochemical and anthropometric characteristics of patients and controls

S.no.	Variables	Postmenopausal women with osteoporosis (n=165)	Postmenopausal women without osteoporosis (n=165)	p-value
1.	Age	54.44±6.00	54.47±6.46	0.959
2.	Weight	57.67±10.06	56.78±7.03	0.355
3.	Height	152.07±6.48	153.64±6.98	0.035*
4	BMI	24.86±3.98	24.07±3.02	0.046*
5.	YSM	9.33±5.92	9.53±6.50	0.770
6.	BMD L_1-L_4 lumbar spine (g/cm^2)	0.69±0.12	0.89±0.12	<0.0001*****
7.	BMD hip (g/cm^2)	0.54±0.13	0.84±0.11	<0.0001*****
8.	BMD forearm (g/cm^2)	0.58±0.13	0.81±0.11	<0.0001*****
9.	BMD femoral neck (g/cm^2)	0.66±0.11	0.78±0.09	<0.0001*****
10.	Serotonin (ng/mL)	103.80±19.96	122.10±36.51	<0.0001*

All data are shown as mean ± standard deviation, p<0.05 is considered statistically significant, BMI: Body mass index, YSM: Year since menopause, BMD: Bone mineral density, kg: Kilogram, cm: Centimetre, kg/m^2: Kilogram per square metre, kg: Kilogram, g/cm^2: Gram per square centimetre, ng/mL: Nanograms per millilitre

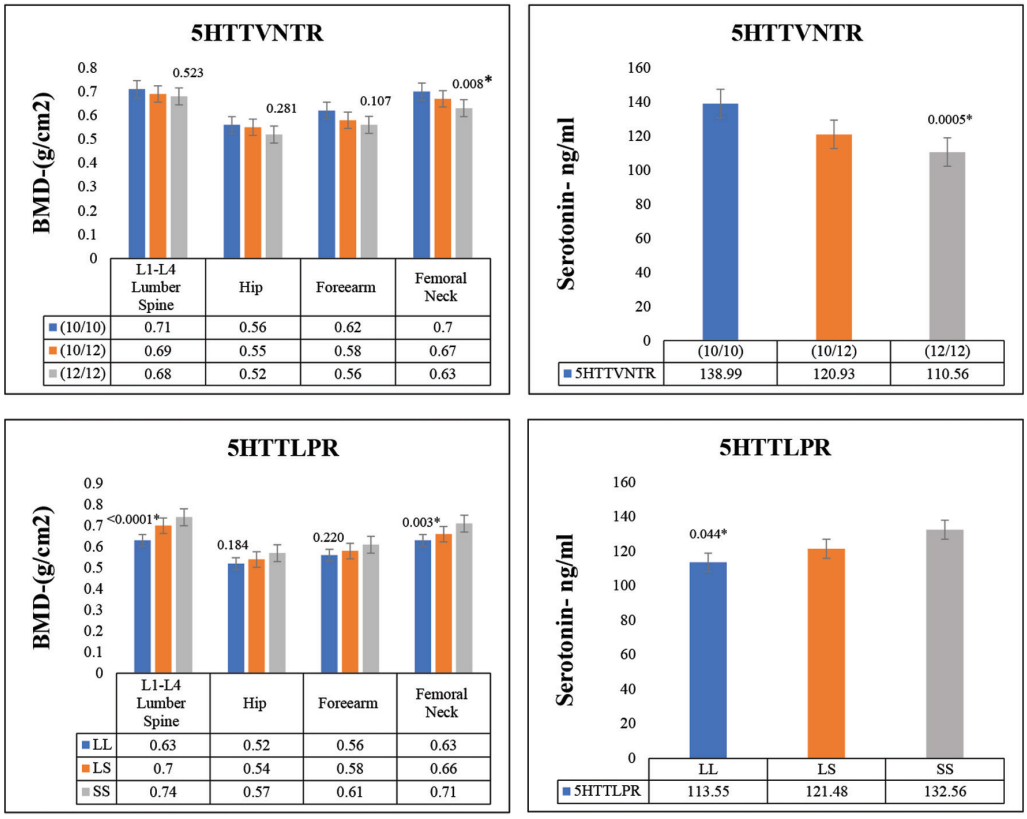

Figure 1. The comparison of BMD at different skeletal sites and serotonin among patients according to different genotypes of serotonin – *5HTTVNTR* and *5HTTLPR* gene polymorphism
BMD: Bone mineral density, 5HTTVNTR: 5-HTT variable number tandem repeats, 5HTTLPR: 5-hydroxy tryptamine transporter linked polymorphic region or serotonin-transporter-linked promoter region

Figure 2 illustrates the comparison of BMD at various skeletal locations & serotonin levels in the control group, categorized by different genotypes of 5HTTVNTR and 5HTTLPR. Current study revealed that participants carrying homozygous mutant 12/12 genotype of 5HTTVNTR showed low BMD at various skeletal locations & low serotonin level as compared to 10/10 & 10/12 genotypes. For 5HTTLPR, individuals with the homozygous mutant LL genotype exhibited decreased BMD at various skeletal regions & significantly reduced BMD at the femoral neck along with low serotonin levels, in comparison to those with the LS and SS genotypes.

A comparison of frequency distribution of serotonin genotypes & alleles (5HTTVNTR and 5HTTLPR) between the patient & control groups, followed by univariate analysis is illustrated in Table 2. In case of 5HTTVNTR, the genotype frequencies of 10/10, 10/12 and 12/12 in patients were 25.45%, 41.21% and 33.33% as compared to 27.27%, 43.64% and 29.10% in controls, respectively. The difference between the groups was not statistically significant (p=0.707). Similarly, the distribution of the 10 and 12 alleles at 5HTTVNTR did not differ significantly between patients and controls (p=0.483). For 5HTTLPR, the genotype frequencies of the LL, LS, and SS genotypes among patient group were 29.10%, 44.85%, and 26.10%, compared to the frequencies 26.10%, 49.10%, and 24.85 in controls. No statistically significant difference was observed in the genotype distribution between patients & controls (p=0.727). Additionally, the allele frequencies (L and S) at 5HTTLPR also showed no significant difference between patients and controls (p=0.876). The genotype frequency distribution among both groups (patients & controls) adhered to Hardy-Weinberg equilibrium. For 5HTTVNTR, the p-values were 0.06 in patient group & 0.10 in control group, while for 5HTTLPR; the p-values were 0.08 in patient group & 0.60 in control group.

Logistic regression analysis for 5HTTVNTR and 5HTTLPR indicated that there were no significant distinctions between the patient & controls, as presented in Tables 3 and 4.

Discussion

A neuropeptide serotonin (5-hydroxytryptamine, 5-HT) has attracted significant interest in recent years because of its possible involvement in bone metabolism (18,19). The serotonin gene polymorphisms have been widely studied across various populations. Current study demonstrated that participants with homozygous mutant 12/12 genotype of 5HTTVNTR & LL genotypes of 5HTTLPR exhibited low BMD at various skeletal sites along with lower serotonin levels. Study by Gustafsson et al. (20), says that serotonin stimulated osteoblasts to secrete more osteoprotegerin while reducing the release of receptor

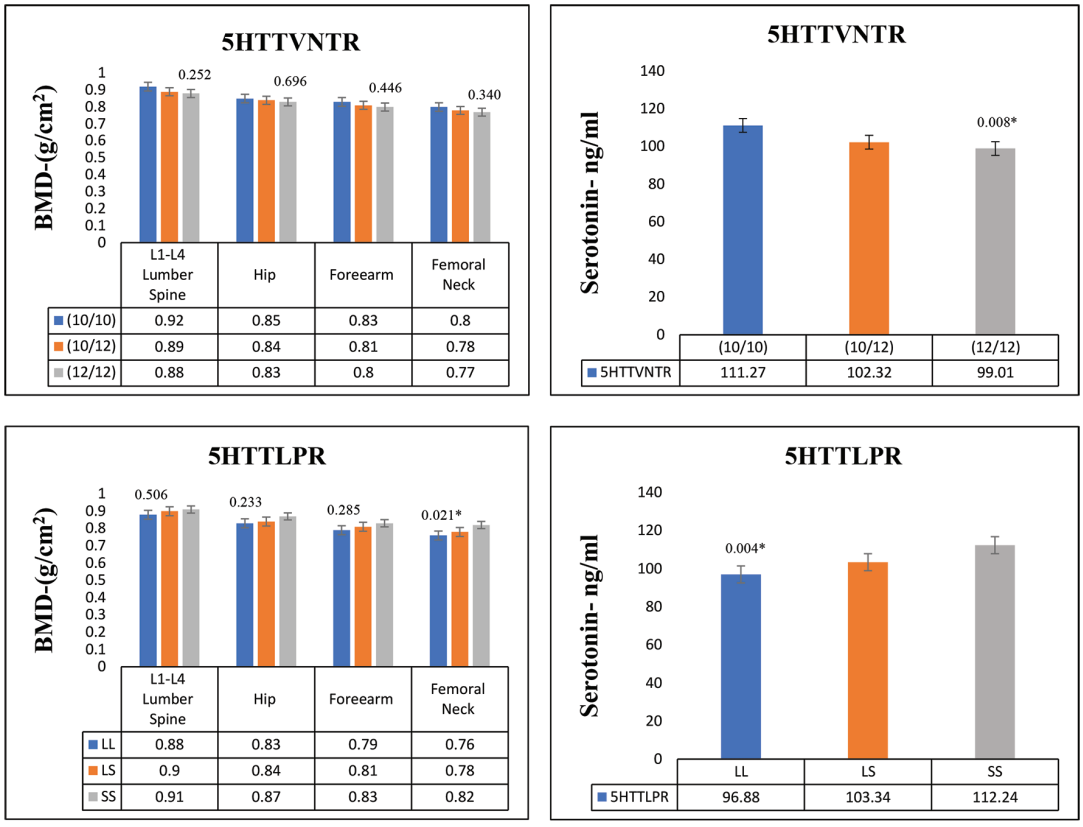

Figure 2. The comparison of BMD at different skeletal sites and serotonin among controls according to different genotypes of serotonin – *5HTTVNTR* and *5HTTLPR* gene polymorphism
BMD: Bone mineral density, 5HTTVNTR: 5-HTT variable number tandem repeats, 5HTTLPR: 5-hydroxy tryptamine transporter linked polymorphic region or serotonin-transporter-linked promoter region

Table 2. Frequency distribution of genotypes and alleles of 5HTTVNTR and 5HTTLPR among patients and healthy controls by univariate analysis

	5HTTVNTR		
Genotypes	**Patients (165)**	**Controls (165)**	**p-value**
10/10 10/12 12/12	42 (25.45%) 68 (41.21%) 55 (33.33%)	45 (27.27%) 72 (43.64%) 48 (29.10%)	0.707
Alleles			
10 12	152 (46.10%) 178 (53.94%)	162 (49.10%) 168 (50.90%)	0.483
	5HTTLPR		
Genotypes	**Patients (165)**	**Controls (165)**	**p-value**
LL SL SS	48 (29.10%) 74 (44.85%) 43 (26.10%)	43 (26.10%) 81 (49.10%) 41 (24.85%)	0.727
Alleles			
L S	170 (51.52%) 160 (48.48%)	167 (50.61%) 163 (49.39%)	0.876

p<0.05 is considered statistically significant, data is presented in number and percentage, 5HTTVNTR: 5-HTT variable number tandem repeats, 5HTTLPR: 5-hydroxy tryptamine transporter linked polymorphic region or serotonin-transporter-linked promoter region

activator of NF-κB ligand, indicating its involvement in osteoblast-driven suppression of osteoclast differentiation. Administering serotonin led to a notable increase in BMD suggesting that serotonin positively influences bone formation in rat (20). The research carried out by Wang et al. (21) in postmenopausal women showed that lower serum serotonin level is associated with reduced BMD of femoral neck which is consistent with our findings. Moreover Wei et al. (22), 2017 demonstrated that low serum serotonin levels are linked with low BMD at lumbar spine & femoral neck in postmenopausal women which implies its positive correlation with BMD.

Mödder et al. (23), 2010 observed a tendency for an inverse correlation with serum serotonin levels & lumbar spine BMD in postmenopausal women. As presented Kim et al. (24) investigation that elevated serum serotonin levels were linked specifically to reduce BMD in the lumbar spine. Zhang and Drake (25) reported that higher level of 5-HTT is also linked with lower BMD which is responsible for reduced bone formation activity. The S allele was linked to a greater risk of decreased BMD in the lumbar spine & radial sites (26). Our observation is contradictory with above findings.

According to Ferreira et al. (12) the genotypic frequencies of 10/12 and 12/12 were higher in patients then in controls which are in concordance with our results. Reduced bone formation has been linked to the L allele of the low-expressing serotonin receptor (HTR1B) (26).

Table 3. Comparison of frequency distribution of 5HTTVNTR genotypes among patients and controls after adjusting for age, YSM & BMI

	5HTTVNTR				
Genotype	**Patients (n=165)**	**Control (n=165)**	**p**	**OR**	**95% CI**
Codominant model					
10/10	42 (25.45%)	45 (27.27%)	Ref.	Ref.	Ref.
10/12	68 (41.21%)	72 (43.64%)	0.965	1.012	(0.592-1.729)
12/12	55 (33.33%)	48 (29.10%)	0.482	1.228	(0.693-2.174)
Dominant model					
10/10	42 (25.45%)	45 (27.27%)	Ref.	Ref.	Ref.
10/12+12/12	123 (74.55%)	120 (72.73%)	0.708	1.098	(0.673-1.793)
Recessive model					
10/10+10/12	110 (66.67%)	117 (70.91%)	Ref.	Ref.	Ref.
12/12	55 (33.33%)	48 (29.10%)	0.265	1.302	(0.818-2.071)

p<0.05 is considered statistically significant, data is expressed in number and percentage, 5HTTVNTR: 5-HTT variable number tandem repeats, BMI: Body mass index, YSM: Year since menopause, OR: Odds ratio, CI: Confidence interval

Table 4. Comparison of frequency distribution of 5HTTLPR genotypes among patients and controls after adjusting for age, YSM & BMI

	5HTTLPR				
Genotype	**Patients (n=165)**	**Controls (n=165)**	**p**	**OR**	**95% CI**
Codominant model					
LL	48 (29.10%)	43 (26.10%)	Ref.	Ref.	Ref.
SL	74 (44.85%)	81 (49.10%)	1.551	0.818	(0.487-1.374)
SS	43 (26.10%)	41 (24.85%)	1.163	0.940	(0.519-1.701)
Dominant model					
LL	48 (29.10%)	43 (26.10%)	Ref.	Ref.	Ref.
SL+SS	117 (70.91%)	122 (73.94%)	1.462	0.859	(0.530-1.393)
Recessive model					
LL+SL	122 (73.94%)	124 (75.15%)	Ref.	Ref.	Ref.
SS	43 (26.10%)	41 (24.85%)	0.800	1.066	(0.649-1.750)

p<0.05 is considered statistically significant, data is expressed in number and percentage, 5HTTLPR: 5-hydroxy tryptamine transporter linked polymorphic region or serotonin-transporter-linked promoter region, BMI: Body mass index, YSM: Year since menopause, OR: Odds ratio, CI: Confidence interval

This is, to our knowledge, the first evidence in postmenopausal North Indian women demonstrating a significant link with serotonin transporter polymorphisms (5HTTVNTR & 5HTTLPR), their circulating serotonin levels, and BMD which providing a multiple aspect understanding of the potential genetic and molecular mechanisms underlying osteoporosis. It will also help us better understand the onset and progression of this disease.

Study Limitations

There are certain limitations to our study that should be acknowledged, all subjects were enrolled from a single medical center within the same geographic region, & the results may not be fully generalizable to the wider Indian population due to differences in environmental conditions across regions. Second, the relatively small sample size may have influenced the results, and the observed effects may differ from those in larger and more diverse group.

Future Direction

This regionally focused investigation provides a methodological and conceptual framework for future multicentric and large-scale genetic studies on osteoporosis in diverse Indian populations. A prospective longitudinal design should be used to better clarify the causal relationship between 5HTTVNTR & 5HTTLPR genotypes, serum serotonin levels, and variations in BMD over time. Future studies should also systematically control for possible confounding variables, like lifestyle parameters, dietary pattern, comorbid conditions, and the use of medications, which can affect both serotonin levels and bone metabolism. Collectively, these measures will enhance mechanistic understanding and facilitate the development of targeted preventive and therapeutic interventions for postmenopausal osteoporosis.

Conclusion

We conclude that homozygous mutant genotype 12/12 of 5HTTVNTR and LL of 5HTTLPR lower serum serotonin levels thereby reducing BMD at hip, forearm, femoral neck & Lumbar spine in North Indian postmenopausal female.

A more detailed investigation of genetic factors will enhance our insight of the underlying of osteoporosis pathogenesis, as well as the inter-individual variability observed in its onset and progression. In clinical practice, identifying and mapping genes that influence BMD could lead to the discovery of novel molecular pathways for developing treatments in bone-related disorders. Although the contribution of individual genetic variants may be modest, their associated signaling pathways are likely to play a significant role in metabolic processes of bone. Consequently, these pathways represent promising targets for the creation of new pharmaceutical interventions aimed at the prevention and therapy of osteoporosis and other skeletal diseases. Furthermore, advances in osteoporosis genetics may also contribute to the establishment of improved diagnostic and predictive approaches for assessing individual disease risk.

Ethics

Ethics Committee Approval: The study received ethical approval from the Institutional Ethics Committee of King George's Medical University, Lucknow, India (approval number: 1094, dated: 29.07.2019).

Informed Consent: Before participating in this study, we obtained a questionnaire from each participant's current health status and medical history with informed consent.

Footnotes

Authorship Contributions

Concept: P.D., I.A., S.W., T.J., Design: P.D., I.A., S.W., T.J., Data Collection or Processing: P.D., I.A., S.W., T.J., Writing: P.D., I.A., S.W., T.J.

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

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Assessment of Bone Mineral Density in Individuals with Chronic Respiratory Diseases and Its Relationship with Thyroid Function

Kronik Solunum Sistemi Hastalığı Olan Bireylerde Kemik Mineral Yoğunluğunun Değerlendirilmesi ve Tiroid Fonksiyonları ile İlişkisi

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Abstract

Objective: Decreased bone mineral density (BMD) in patients with chronic respiratory diseases is a significant complication that increases the risk of osteoporosis and fractures. In this study, the effect of variability in thyroid function tests, including thyroid-stimulating hormone (TSH) and free thyroxine (FT4) levels, on BMD was evaluated, and the implications of the interaction between the endocrine and respiratory systems for bone health were examined.

Materials and Methods: Between July 2024 and July 2025, data (thyroid function tests and BMD results) from 124 patients with chronic respiratory diseases [chronic obstructive pulmonary disease, asthma, interstitial lung diseases (ILDs)] who were referred to pulmonary rehabilitation at Aydın Adnan Menderes University in Aydın were retrospectively evaluated. Patients were classified as normal, osteopenic, or osteoporotic according to the World Health Organization criteria. The relationship between thyroid function and BMD in the femur and lumbar regions was examined using Spearman correlation analysis.

Results: The study included 124 patients with a mean age of 65.07±9.70 years. 49.2% of patients were diagnosed with chronic obstructive pulmonary disease, 29.8% with asthma, and 21.0% with ILD. A negative correlation was observed between FT4 level and femoral neck BMD (r=-0.212, p=0.025), whereas TSH level was positively correlated with total femoral BMD (r=0.201, p=0.032).

Conclusion: This study found that the prevalences of osteopenia and osteoporosis are high among individuals with respiratory disease and that these prevalences are negatively correlated with T4 levels and positively correlated with TSH levels. These results emphasize the need to consider thyroid function when screening for osteoporosis in this disease group.

Keywords: Osteoporosis, bone mineral density, thyroid hormones, chronic obstructive pulmonary disease, asthma, interstitial lung disease

Öz

Amaç: Kronik solunum sistemi hastalıklarında kemik mineral yoğunluğunda (KMY) azalma, osteoporoz ve kırık riskini artıran önemli bir komplikasyondur. Bu çalışmada, tiroid uyarıcı hormon (TSH) ve serbest tiroksin (FT4) düzeylerini içeren tiroid fonksiyon testlerindeki değişkenliğin KMY üzerindeki etkisi değerlendirilerek endokrin ve solunum sistemleri arasındaki etkileşimin kemik sağlığına yansımaları incelenmiştir.

Gereç ve Yöntem: Temmuz 2024 ve Temmuz 2025 arasında Aydın Adnan Menderes Üniversitesi'nde kronik solunum sistemi hastalığı (kronik obstrüktif akciğer hastalığı, astım, interstisyel akciğer hastalıkları) olan, pulmoner rehabilitasyona yönlendirilen 124 hastanın verileri (tiroid fonksiyon testleri ve KMY sonuçları) retrospektif değerlendirildi. Hastalar, Dünya Sağlık Örgütü kriterlerine göre normal, osteopenik ve osteoporotik olarak sınıflandırıldı. Tiroid fonksiyonları ile femur ve lomber bölgelerdeki KMY ilişkisi Spearman korelasyon analizi ile incelendi.

Bulgular: Çalışmaya, yaş ortalaması 65,07±9,70 yıl olan 124 hasta dahil edildi. Hastaların %49,2'si kronik obstrüktif akciğer hastalığı, %29,8'i astım ve %21,0'i ınterstisyel akciğer hastalığı tanısı almıştı. FT4 düzeyi ile femur boyun KMY arasında negatif (r=-0,212; p=0,025), TSH düzeyi ile femur total KMY arasında pozitif ilişki (r=0,201; p=0,032) saptandı.

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Sonuç: Bu çalışmada solunum sistemi hastalığı bulunan kişilerde osteopeni ve osteoporoz prevalansının yüksek olduğu ve bu değerlerin FT4 düzeyleri ile negatif, TSH düzeyleri ile pozitif korelasyon gösterdiği saptandı. Bu sonuçlar, bu hastalık grubunda osteoporoz taramalarında tiroid fonksiyonlarının da dikkate alınmasının gerekliliğini vurgulamaktadır.

Anahtar kelimeler: Osteoporoz, kemik mineral yoğunluğu, tiroid hormonları, kronik obstrüktif akciğer hastalığı, astım, intertisyel akciğer hastalığı

Introduction

Osteoporosis is a skeletal disease characterized by deterioration in the microarchitecture of bone tissue and a decrease in bone mass (1). Approximately 200 million people worldwide are affected by osteoporosis, and this number is steadily increasing. A meta-analysis conducted in China reported a prevalence of osteoporosis of 25% among women and 15% among men (2). Estimates indicate that the number of osteoporotic fractures in Europe will reach 5.3 million by 2034, whereas approximately 2.1 million osteoporosis-related fractures occur each year in the United States (3). This makes osteoporosis a public health issue as significant as cardiovascular disease and diabetes. Therefore, early diagnosis and identification of risk factors are critical in reducing both mortality and healthcare costs.

Bone mineral density (BMD) is significantly lower in patients with chronic respiratory diseases than in the general population (4). It has been reported that the risk of osteoporosis is approximately fourfold higher in severe cases of chronic obstructive pulmonary disease (COPD), and it has been suggested that medications used to treat asthma may adversely affect bone mass (5,6). These findings indicate that the risk of osteopenia and osteoporotic fractures is increased among individuals with respiratory diseases and underscore the need for regular monitoring of bone health in this population. It has been reported that the mechanism of bone loss associated with COPD is multifactorial; chronic hypoxia, nutritional deficiencies, and glucocorticoid use play a role in this process (7). Although the global initiative for chronic obstructive lung disease guidelines recommend inhaled corticosteroids as a standard treatment to reduce exacerbations and inflammation, data on the effects of inhaled corticosteroids on fracture risk and osteoporosis remain conflicting (8,9).

Thyroid hormones play a critical role in regulating energy metabolism and bone health. They control the bone formation-resorption cycle by affecting the balance between osteoblast and osteoclast activity (10,11). Even small changes in these hormones can have clinically significant effects on BMD (11). Studies conducted in postmenopausal women have shown that an increase in free thyroxine (FT4) levels is associated with impairment in trabecular microarchitecture (12). Similarly, thyroid-stimulating hormone (TSH) levels have been reported to be positively correlated with trabecular bone score (13). Meta-analyses have demonstrated an increased risk of fractures in subclinical hyperthyroidism, particularly when TSH levels are below 0.10 mIU/L (14). However, it remains unclear whether treatment for this condition can prevent fractures. Large cohort studies of euthyroid individuals have reported that lower TSH and higher FT4 levels are associated with an increased risk of hip fracture (15,16). However, there is no clear consensus on the relationship between hypothyroidism and subclinical hypothyroidism, and BMD (13).

Current data suggest that the risk of osteoporosis in chronic respiratory diseases cannot be explained solely by classic factors such as pharmacological treatments and hypoxia; variability in thyroid hormone levels may also play an important role in osteoporosis risk. Therefore, investigating the association between thyroid function and BMD in individuals with respiratory dysfunction will increase awareness of the clinical management strategies for this group of patients.

Materials and Methods

Ethical Approval

Ethical approval for this research was obtained from the Aydın Adnan Menderes University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee protocol number: 2025/221, dated: 11.07.2025), and all procedures adhered to the ethical principles of the Declaration of Helsinki. Since the study involved a retrospective data review, the ethics committee approved the study and waived the requirement for participant consent.

Study Design and Patient Selection

This retrospective observational study was conducted between July 1, 2024, and July 1, 2025, at the Physical Medicine and Rehabilitation Outpatient Clinic of the Faculty of Medicine, Aydın Adnan Menderes University, Aydın, Türkiye. The study used electronic medical records of patients who were diagnosed with asthma, COPD, interstitial lung disease, or sarcoidosis and referred to the department of physical medicine and rehabilitation for pulmonary rehabilitation. Patients aged 40 years or older with respiratory dysfunction, no active infection, and no history of thyroid disease were included in the study. Patients diagnosed with thyroid disease, receiving thyroid hormone treatment, under the age of 40, or with missing data were excluded from the study. A total of 128 patients were evaluated; 124 with complete data were included in the final analysis.

Data Collection and Measurements

Patients' demographic data (age, gender, height, weight), thyroid function tests—TSH (0.35-4.94 uIU/mL) and (FT4; 0.70-1.48 ng/mL)—and BMD results were obtained from electronic patient records. Thyroid function tests were evaluated according to laboratory reference ranges, and those tests with values outside these ranges were classified into relevant categories.

Bone Mineral Density Assessment and Classification

BMD measurements were performed using dual-energy X-ray absorptiometry (DEXA). DEXA is the method accepted by the World Health Organization (WHO) as the standard for diagnosing

osteoporosis and is preferred because of its short screening time, low radiation exposure, and high accuracy. Measurements were taken in the femoral and lumbar vertebral regions. According to the WHO classification, patients were categorized as having normal bone mass (T-score ≥-1.0), osteopenia (T-score between -1.0 and -2.5), or osteoporosis (T-score ≤-2.5) (17).

Statistical Analysis

The statistical evaluation of the data was performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). To examine whether continuous variables followed a normal distribution, the Kolmogorov-Smirnov test was applied. Parameters exhibiting a normal distribution were reported as the arithmetic mean and standard deviation, whereas non-normally distributed variables were reported as the median and interquartile range (25^{th}-75^{th} percentiles). Categorical data were summarized as frequencies and percentages. For group comparisons, normally distributed data were analyzed using One-Way ANOVA, and the Kruskal-Wallis test was used for data not conforming to a normal distribution. Associations between categorical variables were assessed using the chi-square test. Spearman's rank-order correlation coefficient was used to evaluate associations between continuous variables. A significance level of $p<0.05$ was adopted as the threshold for statistical significance.

Results

A total of 124 participants were analyzed; 54.8% were men and 45.2% were women. The mean age of the study population was 65.07±9.70 years. 49.2% of patients were diagnosed with COPD, 29.8% with asthma, and 21.0% with interstitial lung disease (ILD). Among the 26 patients in the ILD group, 30.8% had idiopathic pulmonary fibrosis (IPF), 26.9% had sarcoidosis, 30.8% had ILD associated with connective tissue diseases, 7.7% had drug-related ILD, and 3.8% had other idiopathic ILD. The patients' demographic characteristics and distribution of diagnoses are presented in Table 1.

Table 1. Participants' demographic characteristics and diagnosis distribution

Characteristic	n	%
Total number of patients	124	100.0
Age (years)	65.07±9.70 (42-88)	-
Gender		
Male	68	54.8
Female	56	45.2
Diagnosis groups		
COPD	61	49.2
Asthma	37	29.8
ILD	26	21.0
Subgroups of ILD		
Idiopathic pulmonary fibrosis	8	30.8
Sarcoidosis	7	26.9
ILD associated with connective tissue diseases	8	30.8
Drug-induced ILD	2	7.7
Other idiopathic ILD	1	3.8

COPD: Chronic obstructive pulmonary disease, ILD: Interstitial lung disease

Among all patients included in the study, evaluation of BMD showed that 22.6% were classified as having normal BMD, 46.0% as having osteopenia, and 31.5% as having osteoporosis. The detailed distribution of BMD categories is presented in Table 2.

When the disease groups were compared, 18.0% of patients with COPD had normal bone density, 42.6% had osteopenia, and 39.4% had osteoporosis. In the asthma group, 21.6% had normal BMD, 56.8% had osteopenia, and 21.6% had osteoporosis. In the ILD group, 34.6% were normal, 38.5% had osteopenia, and 26.9% had osteoporosis. However, no statistically significant differences were found in BMD distributions among disease groups (p=0.188). The distribution of BMD across disease groups is presented in Table 3.

When comparing T-scores across respiratory diseases, significant differences were observed between patients with COPD and those with asthma for both femoral neck T-scores (p=0.026) and total femur T-scores (p=0.006). In contrast, no significant differences were found between COPD and ILD patients in femoral neck (p=0.174) and total femur T-scores (p=0.235), or between asthma and ILD patients in femoral neck (p=0.869) and total femur T-scores (p=0.224). No significant differences were detected in lumbar total T-scores among the three disease groups (p>0.05). The corresponding data are presented in Table 4.

According to the results of the Spearman correlation analysis, a statistically significant negative correlation was observed between FT4 levels and both femoral neck T-score (r=-0.212, p=0.025) and femoral neck BMD (r=-0.204, p=0.032). In addition, significant positive correlations were found between TSH levels and both total femur T-score (r=0.201, p=0.032) and total femur BMD (r=0.190, p=0.043). The correlations between thyroid function parameters and BMD are presented in Figure 1.

Discussion

This study investigated the relationship between thyroid function and BMD in individuals with chronic respiratory diseases and found that FT4 levels were negatively correlated with femoral neck BMD, whereas TSH levels were positively correlated with total femoral BMD. These findings suggest that the risk of

Table 2. Distribution of participants according to bone mineral density classification

BMD class	n	%
Normal (T-score ≥-1.0),	28	22.6
Osteopenia (-1.0> T-score >-2.5)	57	46.0
Osteoporosis (T-score ≤-2.5)	39	31.5
Total	124	100.0

Participants were classified according to WHO criteria
BMD: Bone mineral density, WHO: World Health Organization

Table 3. Bone mineral density classification by disease groups

		Normal n (%)	Osteopenia n (%)	Osteoporosis n (%)	Total
Disease	COPD	11 (18%)	26 (42.6%)	24 (39.4%)	61 (100%)
	Asthma	8 (21.6%)	21 (56.8%)	8 (21.6%)	37 (100%)
	ILD	9 (34.6%)	10 (38.5%)	7 (26.9%)	26 (100%)
Total		28 (22.6%)	57 (46%)	39 (31.4%)	124 (100%)

No significant difference was observed among disease groups, p=0.188
COPD: Chronic obstructive pulmonary disease, ILD: Interstitial lung disease

Table 4. Comparison of femur and lumbar vertebra bone mineral density and T-score values according to respiratory system diseases

	COPD	Asthma	ILD	p-value
Femur neck	-1.389±1.15	-0.809±0.88	-0.946±0.98	**0.026***
Femur neck BMD	0.732±0.15	0.769±0.11	0.753±0.11	0.394
Total femur	-1 (-2.1- -0.150)	-0.200 (-1.025-0.098)	-0.900 (-1.175-0.50)	**0.22****
Total femur BMD	0.868 (0.698-0.959)	0.92 (0.838-1)	0.867 (0.798-0.944)	0.143
L1-L4 total	-1.434±1.72	-1.435±1.41	-0.935±1.58	0.374
L1-L4 total BMD	0.926±0.19	0.894±0.16	0.919±0.23	0.738

*: A statistically significant difference was found between COPD and asthma patients in terms of femoral neck T-score (p=0.026). In contrast, no statistically significant difference was found in femoral neck T-scores between COPD and ILD patients (p=0.174) and between asthma and ILD patients (p=0.869).
**: A statistically significant difference was found between COPD and asthma patients in terms of femur total T-score (p=0.006). In contrast, there was no statistically significant difference in total T-scores of the femur between COPD and ILD patients (p=0.235) and between asthma and ILD patients (p=0.224).
COPD: Chronic obstructive pulmonary disease, ILD: Interstitial lung disease, BMD: Bone mineral density

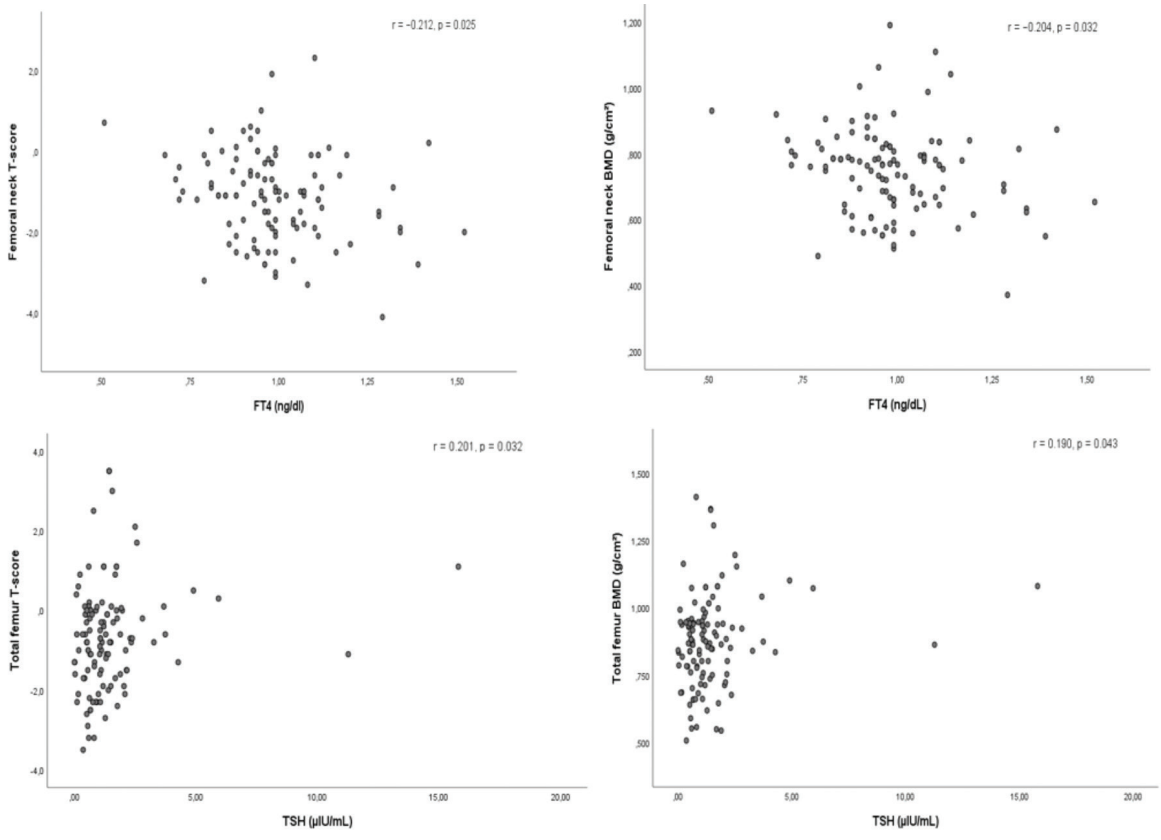

Figure 1. Correlation between thyroid function parameters and bone mineral density values
TSH: Thyroid-stimulating hormone, FT4: Free thyroxine

osteoporosis in individuals with chronic respiratory diseases may be related not only to the chronic disease itself or to the medications used for treatment, but also to alterations in the patients' endocrine systems.

Numerous studies published over many years have examined bone health in patients with chronic respiratory diseases (18-21). Osteoporosis is common in these patients due to hypoxia and the resulting increase in free oxygen radicals, caused by factors such as the medications used, particularly corticosteroids, nutritional deficiencies, and immobility associated with the disease (7,18).

In our study, 42.6% of COPD patients had osteopenia and 39.4% had osteoporosis; this distribution is consistent with previously published data. Indeed, a 2019 meta-analysis reported that the prevalence of osteoporosis ranged from 14% to 66%, with mean prevalences of 39% for osteopenia and 37% for osteoporosis (21). Pobeha et al. (22) reported that osteopenia or osteoporosis occurred in 50-70% of patients with COPD. In an epidemiological study conducted in Taiwan, this rate was found to be 21.21% (23).

Similar to findings in COPD, the susceptibility of individuals with asthma to osteoporosis is a noteworthy topic in the literature. In Jung et al.'s (24) retrospective study involving 7,034 patients, the prevalence of osteoporosis was significantly higher in individuals with a history of asthma than in those without asthma. In another study of respiratory diseases, the prevalence of osteoporosis was 53.6% among patients with asthma and 65.0% among patients with COPD, with an overall prevalence of 60.1% (19). In addition, Soen et al. (20) reported an increase in BMD measurements and in bisphosphonate prescription rates among asthma patients in clinical practice. In our study, only 21.6% of asthma patients had normal BMD, while 56.8% had osteopenia and 21.6% had osteoporosis. Although these rates are lower than those reported in some epidemiological studies, they appear to be consistent with the prevalence of osteoporosis reported in clinical practice. We believe that the decrease in BMD observed in patients with COPD and asthma may be attributed not only to the systemic effects of these diseases but also to their treatments and other risk factors.

BMD loss, observed in COPD and asthma patients, also represents a clinical problem in ILD patients. In a study of 196 newly diagnosed ILD patients, osteoporosis was detected in 44% and osteopenia in 36%. They reported these patients had a significantly increased risk of osteoporosis and required an aggressive approach involving early screening and various anti-resorptive treatments (25).

Similarly, Ikezoe et al. (26) compared 55 steroid-naive male IPF patients with equal numbers of patients in the COPD and smoker groups. Thoracic vertebral BMD was measured by computed tomography. In this study, 27.2% of patients had mean BMD values 2.5 standard deviations below the young-adult mean, suggesting that osteoporosis may develop not only as a result of pharmacological treatments but also via disease-specific mechanisms (26). In our study, the finding that 26.9% of the ILD group had osteoporosis, regardless of treatment status and year of illness, indicates that this patient group is at high risk. Consistent with the literature, this group should be screened early, and other factors that may affect osteoporosis should be examined to enable early treatment.

Our study found no statistically significant differences in the prevalence of osteoporosis among the asthma, COPD, and ILD groups. However, when BMD and T-scores were compared across regions, significant differences were found between patients with COPD and those with asthma in both femoral neck and total femur T-scores. This finding suggests that bone loss may be more pronounced in patients with COPD than in those with asthma. Conversely, the absence of a significant difference between diseases in lumbar measurements indicates that this difference is particularly pronounced in the femur.

In addition, the high prevalence of osteopenia and osteoporosis across all groups (77.5%) underscores the need for regular osteoporosis screening in this patient population. This high rate necessitates consideration of comorbid hormonal disorders that may affect skeletal health. Thyroid hormones are essential for maintaining bone metabolism in adults; however, thyroid dysfunction can have adverse effects on bone structure. Hyperthyroidism reduces bone mass by increasing bone turnover and thereby increases the risk of high-turnover osteoporosis (13). Evidence increasingly indicates that subclinical hyperthyroidism is associated with decreased BMD and increased fracture risk, particularly in postmenopausal women (27). Hypothyroidism is associated with low bone turnover and increased mineralization by reducing both osteoclastic resorption and osteoblastic activity; however, no consistent relationship between hypothyroidism and BMD has been demonstrated in adults (13). Despite these clinical findings, the cellular and molecular effects of thyroid hormones on bone have not yet been fully elucidated (27).

Several studies have indicated a higher prevalence of thyroid dysfunction among individuals with respiratory disorders than in the general population (15,28-31). In a study conducted by Chaudhary et al. (28), the prevalence of thyroid dysfunction in COPD patients was found to be 25%, and it was reported that thyroid dysfunction in COPD leads to a decrease in quality of life by increasing the frequency of exacerbations (28). In animal studies, it has been shown that osteogenesis decreases as the severity of COPD increases (32). In a review of thyroid function in COPD patients, the prevalence of thyroid dysfunction was reported to be 42.1%. It has been underlined that thyroid dysfunction can affect lung function and therefore patients should be screened regularly (29). They have reported that the risk of developing hyperthyroidism is high in patients with asthma, and that this is particularly true in patients over the age of 30 and in the first 3 years after the diagnosis of asthma (31). It has been reported that thyroid dysfunction has a higher prevalence in IPF patients compared to the general population and may predict mortality (30).

Thyroid function can have significant effects not only on the respiratory system but also on bone health. A large-scale study has shown that low TSH and high FT4 levels are associated with an increased risk of hip fracture (15). In the present study, the negative association observed between FT4 and femoral neck BMD is consistent with previous reports. In addition, TSH levels have been shown to be positively associated with bone microarchitecture and negatively associated with new fractures (13). The positive correlation between TSH and total femoral BMD observed in our study also supports these findings.

A clinically significant implication of our study is that osteoporosis screening in patients with chronic respiratory diseases should be based not only on age, gender, and steroid use but also on thyroid function. Especially in patients with high normal FT4 levels or low TSH levels, closer monitoring of BMD may be valuable in preventing osteoporotic fractures.

Study Limitations

This study has some limitations. Firstly, the results are limited in generalizability because data collection and analysis were performed at a single medical facility and involved a limited number of patients. Secondly, it has a retrospective design and examines only thyroid function among the factors affecting osteoporosis in this patient group. Therefore, to better understand the significance and specifics of this issue, multicenter prospective studies involving a substantially larger number of patients are needed to examine the many factors affecting osteoporosis.

Conclusion

In individuals with chronic respiratory diseases, osteoporosis should be considered related not only to hypoxia, corticosteroid use, or immobility, but also to alterations in the endocrine system. Our study showed that FT4 levels were negatively associated with femoral neck BMD, while TSH levels were positively associated with total femoral BMD. The clinically significant finding of our study is that osteoporosis screening in this group of patients should not be based solely on age, gender, and medication use; thyroid function tests should also be included in the evaluation. Patients with high-normal FT4 levels or low TSH levels should be monitored more closely, as this may help prevent osteoporotic fractures at an early stage.

Ethics

Ethics Committee Approval: Ethical approval for this research was obtained from the Aydın Adnan Menderes University Faculty of Medicine Non- Interventional Clinical Research Ethics Committee (protocol number: 2025/221, dated: 11.07.2025), and all procedures adhered to the ethical principles of the Declaration of Helsinki.

Informed Consent: The ethics committee waived the requirement for individual informed consent due to the retrospective design of the study.

Footnotes

Authorship Contributions

Concept: E.E., Ş.D.Y., Design: E.E., Ş.D.Y., Data Collection or Processing: Ş.D.Y., Analysis or Interpretation: E.E., Ş.D.Y., Literature Search: E.E., Ş.D.Y., Writing: E.E., Ş.D.Y.

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The Relationship Between Postural Balance, Posture and Postural Awareness in Patients Diagnosed with Osteoporosis

Osteoporoz Tanılı Hastalarda Postüral Denge, Duruş ve Postüral Farkındalık Arasındaki İlişki

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Abstract

Objective: Osteoporosis, characterized by low bone mass and microarchitectural deterioration, leads to increased fracture risk. Beyond skeletal fragility, it is associated with postural deformities, balance impairments, and potentially diminished postural awareness, which are critical factors for fall prevention. This study aims to investigate the relationship between postural balance, posture, and postural awareness in postmenopausal women diagnosed with osteoporosis compared to those with osteopenia.

Materials and Methods: A cross-sectional study was conducted with 32 postmenopausal women (osteoporosis, n=16; osteopenia, n=16). Participants were assessed using the timed up and go (TUG) test for functional mobility, the Berg balance scale (BBS) for balance, the New York posture scale (NYPS) for postural alignment, and the postural awareness scale (PAS) for body awareness. Bone mineral density was determined by lumbar spine T-scores. Statistical analyses included the Mann-Whitney U test for group comparisons and Spearman's correlation to examine relationships between variables.

Results: The osteoporosis group demonstrated significantly lower postural awareness (PAS), poorer balance (BBS), longer TUG times, and more postural deviations (NYPS) compared to the osteopenia group ($p<0.05$), despite similar age and body mass index. Lumbar T-scores were significantly correlated with better PAS, BBS, and NYPS scores ($p<0.01$), and negatively correlated with TUG times ($p<0.01$), with stronger correlations observed in the osteoporosis group. A significant proportion of the osteoporosis group was classified as having low awareness, high fall risk, and poor posture.

Conclusion: Osteoporosis is associated with significantly impaired postural awareness, poorer postural alignment, and reduced balance compared to osteopenia. The strong correlations between bone mineral density and functional parameters underscore the interconnection between skeletal and neuromuscular health. These findings highlight the necessity of integrating functional assessments and targeted interventions, such as balance training and postural awareness education, into standard osteoporosis management to reduce fall risk and improve quality of life.

Keywords: Osteoporosis, postural balance, posture, awareness, osteopenia, fall risk

Öz

Amaç: Kemik kütlesinin azalması ve mikro-mimari bozulma ile karakterize osteoporoz, kırık riskini artırır. Osteoporoz; postüral deformiteler, denge bozuklukları ve düşmeyi önlemede kritik olan postüral farkındalıkta azalma ile ilişkili olabilir. Bu çalışmanın amacı, osteoporoz tanılı postmenopozal kadınlarda postüral denge, postür ve postüral farkındalığın osteopenili kadınlara göre farklılığını ve bu değişkenler arasındaki ilişkileri incelemektir.

Gereç ve Yöntem: Kesitsel çalışmaya 32 postmenopozal kadın dahil edildi (osteoporoz n=16; osteopeni n=16). Fonksiyonel mobilite timed up and go (TUG) testi ile, denge Berg denge skalası (BDS) ile, postür New York postür skalası (NYPS) ile ve postüral farkındalık postüral farkındalık skalası (PFS) ile değerlendirildi. Kemik mineral yoğunluğu lomber omurga T-skoru ile belirlendi. Gruplar arası karşılaştırmalarda Mann-Whitney U testi, değişkenler arası ilişkilerde Spearman korelasyon analizi kullanıldı.

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Bulgular: Gruplar yaş ve vücut kitle indeksi açısından benzerdi. Osteoporoz grubu osteopeni grubuna göre anlamlı derecede daha düşük postüral farkındalık (PFS), daha kötü denge (BDS), daha uzun TUG süreleri ve daha fazla postüral sapma (NYPS) gösterdi (p<0,05). Lomber T-skoru; PAS, BBS ve NYPS ile pozitif (p<0,01), TUG süresi ile negatif yönde anlamlı korelasyon gösterdi (p<0,01) ve bu ilişkiler osteoporoz grubunda daha güçlüydü. Osteoporoz grubunun önemli bir kısmı düşük farkındalık, yüksek düşme riski ve kötü postür sınıflamasındaydı.

Sonuç: Osteoporoz, osteopeniye kıyasla postüral farkındalıkta belirgin azalma, postüral hizalanmada bozulma ve dengede zayıflama ile ilişkilidir. Kemik mineral yoğunluğu ile fonksiyonel parametreler arasındaki güçlü ilişkiler, iskelet ve nöromusküler sağlık arasındaki bağlantıyı desteklemektedir. Düşme riskini azaltmak ve yaşam kalitesini artırmak için fonksiyonel değerlendirmelerin ve denge eğitimi ile postüral farkındalık eğitimini içeren hedef müdahalelerin standart osteoporoz yönetimine entegre edilmesi önerilir.

Anahtar kelimeler: Osteoporoz, postüral denge, postür, farkındalık, osteopeni, düşme riski

Introduction

Osteoporosis is a chronic and progressive disease characterised by low bone mass and deterioration of the bone's microarchitecture, resulting in brittle bones (1). Osteoporosis is considered a silent disease because it usually does not cause symptoms until the first fracture occurs (2). Bone density decreases with age, and the incidence of fractures increases (3). Osteoporosis is one of the musculoskeletal problems commonly seen in women during menopause (4). One of the most significant changes observed in the musculoskeletal system due to ageing and osteoporosis is postural deformities. Postural changes in osteoporotic cases can lead to complications such as falls, balance problems, and vertebral fractures (5).

Decreased bone mass, vertebral fractures, and spinal deformities can lead to loss of vertebral height. Granito et al. (6) noted an increase in thoracic kyphosis associated with low bone mineral density (BMD). The sagittal vertical axis, pelvic tilt, lumbar lordosis, and thoracic kyphosis were all found significantly different between osteoporotic patients and the control group (7). In addition to postural abnormalities, spinal deformities like thoracic and/or lumbar kyphosis can result in decreased spinal mobility and range of motion. Osteoporotic patients with spinal kyphosis use their hip or ankle joints more (8). However, a shift in the center of gravity and impaired balance control due to postural changes can make it more difficult for the person to stand and walk. Furthermore, because kyphosis changes the center of mass of the body, it results in a relatively unstable posture. These factors may affect control over the centre of mass position and the ability to compensate for balance changes (9). In osteoporosis patients, reduced muscle mass and deformities in the spinal structure can disrupt postural balance and increase posture disorders. In such cases, postural awareness is important for the individual to develop and maintain correct posture habits in their daily life (10).

Postural awareness is the ability to recognise changes in posture and body position that an individual makes in daily life. This awareness is crucial for maintaining healthy postural habits and preventing poor posture. Good posture ensures minimal stress on the joints (11), while poor posture leads to increased stress on the joints due to misalignment of body parts (12).

In the prevention and management of osteoporosis, it is important to determine the level of knowledge, particularly among postmenopausal women who are at risk for this disease (13). Identifying individuals' knowledge and attitudes regarding osteoporosis may contribute to the development of public health programs aimed at effective prevention of osteoporosis (14). While the relationship between osteoporosis, progressive postural deformities such as kyphosis, and subsequent impairments in balance and fall risk is well-established in the literature, the impact of these physical changes on an individual's postural awareness remains a significant and under-investigated gap. Postural awareness is a critical component for maintaining healthy posture and executing compensatory strategies to prevent falls. This study, therefore, moves beyond the well-documented pathophysiology to investigate the specific relationship between objective postural balance, spinal alignment, and the level of postural awareness in individuals with osteoporosis. By quantitatively assessing this triad, our research aims to provide original insights that could inform the development of targeted rehabilitation programs, shifting the focus from strength and bone health alone to include the enhancement of body perception and proprioceptive feedback for better postural control and fracture prevention. Investigating the effects of osteoporosis on postural awareness and balance may contribute to the development of education and exercise programs aimed at increasing postural awareness. Therefore, the aim of this study is to investigate the relationship between postural balance, posture, and postural awareness in individuals with osteoporosis.

Materials and Methods

The study included postmenopausal women diagnosed with osteoporosis and osteopenia who were under follow-up at Elazığ Medical Hospital. The required sample size and power calculation for the study were calculated using the G*Power Ver.3.1.9.4 program. The sample volume representing the population was determined based on the conditions of α= 0.05 risk and 1-α =0.80 accuracy rate, using the results of the comparison of the mean Berg balance scale (BBS) scores in the study by Alshahrani and Reddy (15). Based on the results of the power analysis, the effect size was 1.09 and the actual power was 0.82, indicating that the sample size for the study required a minimum of 15 participants in each group.

This study had ethical approval from the Fırat University Ethics Committee (approval number: 2024/15-32, date: 19.12.2024). The study was completed with 32 participants. At the beginning of the study, the participants' medical histories were

obtained through face-to-face interviews. Fracture history was obtained through a structured interview and, when available, verified by reviewing medical records and/or imaging reports. Informed consent forms were obtained from the participants who volunteered to participate in the study. Information on the duration of osteoporosis diagnosis, age, occupation, body mass index, duration of menopause, history of vertebral or non-vertebral fractures, and comorbidities was obtained and recorded. Dynamic and functional balance was measured using the timed up and go (TUG) test and the BBS. Postural awareness was measured using the postural awareness scale (PAS). Posture was assessed using the New York posture scale.

Women in the postmenopausal period, patients diagnosed with osteoporosis or osteopenia according to World Health Organization criteria, and patients who could stand independently were included in the study. Patients with any ongoing orthopaedic or neurological disease, lower extremity pain that prevented standing and bearing weight, any other systemic chronic disease that could affect posture or balance, cognitive dysfunction, and a history of vertebral surgery were excluded from the study. In addition, participants using medications known to impair balance (e.g., sedatives/hypnotics or other centrally acting agents) were excluded.

Balance Assessment

Dynamic balance and functional mobility were evaluated using the TUG. The person was instructed to get up from a seated position, walk three meters at a normal and safe pace, turn around, walk back, and then sit down once more. The time was noted in seconds (s). The patient started the test with their arms resting on the chair's armrests and their feet flat on the ground. To finish the task, patients were instructed to walk at a pace that felt safe to them. For people with mobility impairments or the elderly, 10-20 seconds is acceptable, while less than 10 seconds is regarded as normal mobility (16).

The patient's performance was observed and scored on a scale of 0-4 for each of the 14 instructions in the BBS, a measure of balance. If the patient cannot complete the task at all, they receive a score of 0, and if they can finish it on their own, they receive a score of 4. A score of 0-20 indicates impaired balance, 21-40 indicates acceptable balance, and 41-56 indicates good balance. The maximum score is 56. The scale takes ten to twenty minutes to complete (17).

Postural Awareness Evaluation

Postural awareness, a German measure created by Cramer et al. (18), was assessed using the PAS. Twelve items make up the PAS, and each one is scored on a Likert-style scale that goes from 1 (not applicable to me at all) to 7 (completely applicable to me). The structure of the PAS scale is two-factor. Need for attention regulation with postural awareness is the second factor, and ease/familiarity with postural awareness is the first. Each of the twelve items on the scale has a score ranging from 1 (not applicable to me at all) to 7 (completely applicable to me). The PAS scale has reverse scoring for items 1, 2, 3, 4, 5, and 12. Item 12 has been omitted from the Turkish adaptation of the PAS. The Turkish adaptation of the PAS consists of 11 items. A minimum of 11 and a maximum of 77 points can be obtained on the scale (19).

Posture Assessment

Thirteen distinct sections of the body were assessed for potential posture changes using the New York Posture Scale. Five points are awarded for proper posture, three points for moderately impaired posture, and one point for severely impaired posture. The final test score falls between 13 and 65. Good posture is indicated by a high score. The New York posture assessment scale is used to measure changes in posture from the lateral (neck, chest, shoulders, upper back, torso, abdomen, waist) and posterior (head, shoulders, back, hips, feet, and heels) perspectives (20).

Statistical Analysis

The data obtained in the study were analysed using the SPSS for Windows 22.0 (Statistical Package for the Social Sciences) program. The data was analyzed using descriptive statistical techniques, including number, percentage, median, minimum, and maximum values. The data did not exhibit a normal distribution, according to the Shapiro-Wilk normality test, which was used to assess whether continuous variables did. As a result, the chi-square test was employed for categorical data analysis and the Mann-Whitney U test for intergroup comparisons. Whereas categorical data are displayed as numbers and percentages [n (%)], continuous variables are displayed as medians (25^{th}-75^{th} percentile); minimum-maximum. The relationship between the variables was assessed using Spearman's rank correlation coefficient. All tests were conducted bilaterally (two-tailed), with a significance level of $p<0.05$.

Results

The comparative results of the demographic, clinical, and functional characteristics of the osteoporosis and osteopenia groups are summarized in Table 1. None of the participants had a history of vertebral or non-vertebral fracture. While no significant difference was found between the groups in age, body mass index, and duration of menopause, lumbar spine T-scores were found to be significantly lower in the osteoporosis group. Furthermore, postural awareness levels, balance, and mobility performance were found to be significantly weaker in individuals in this group compared to the osteopenia group.

The categorical distributions of participants were compared according to postural awareness levels, fall risk, postural alignment, and balance levels (Table 2). A significant proportion of individuals in the osteoporosis group had low awareness levels, high fall risk, and poor posture, while most of these parameters were better in the osteopenia group. Significant differences were also observed between the groups in terms of balance level.

The relationships between functional and clinical parameters were analysed separately for each group (Table 3). In both groups,

Table 1. Comparison of demographic, clinical, and functional parameters between osteoporosis and osteopenia groups

Parameters median (percentile 25-75); (min-max)	Osteoporosis group (n=18)	Osteopenia group (n=18)	p*
Age/years	63.00 (56.00-66.00); (53.00-75.00)	62.00 (53.00-68.00); (52.00-75.00)	0.563
BMI/kg/cm^2	30.60 (29.80-32.39); (26.10-34.90)	29.47 (27.30-30.80); (25.60-37.10)	0.181
Osteoporosis diagnosis time/years	3.00 (2.00-4.00); (1.00-7.00)		
Duration of menopause/years	10.00 (5.00-13.00); (2.00-20.00)	10.00 (3.00-13.00); (2.00-20.00)	0.650
Lumbar spine (L1-L4) T-score	-2.63 (-2.90- -2.50); (-3.75- -2.50)	-1.93 (-2.10- -1.70); (-2.30- -1.40)	**<0.001**
OAS	31.00 (29.00-32.00); (22.00-45.00)	42.50 (36.00-49.00); (32.00-52.00)	**<0.001**
TUG test/seconds	15.00 (14.00-17.00); (12.00-22.00)	11.00 (10.00-12.00); (10.00- 16.00)	**<0.001**
NYPRC	40.50 (39.00-45.00); (37.00-51.00)	51.00 (47.00-53.00); (40.00- 61.00)	**<0.001**
BBS	41.50 (36.00-45.00); (34.00-46.00)	48.00 (47.00-50.00); (40.00-55.00)	**<0.001**

PAS: Posture awareness scale, TUG: Timed up and go, NYPRC: New York posture rating chart, BBS: Berg balance scale, *: Mann-Whitney U test, BMI: Body mass index, OAS: Osteoporosis awareness scale

Table 2. Distribution of postural awareness, fall risk, postural alignment, and balance subgroups between osteoporosis and osteopenia groups

Parameters		Osteoporosis group (n=18)	Osteopenia group (n=18)	χ^2	p**
PAS	Low postural awareness	7 (38.9%)	0 (0%)	9.926	**0.007**
	Moderate postural awareness	11 (61.1%)	16 (88.9%)		
	High postural awareness	0 (0%)	2 (11.1%)		
TUG	Low/acceptable risk (≤13.5 s)	4 (22.2%)	17 (94.4%)	19.314	**<0.001**
	High fall risk (>13.5 s)	14 (77.8%)	1 (5.6%)		
NYPRC	Moderate posture	5 (27.8%)	0 (0%)	14.761	**0.001**
	Good posture	7 (38.9%)	1 (5.6%)		
	Very good posture	6 (33.3%)	17 (94.4%)		
BBS	Acceptable balance	7 (38.9%)	1 (5.6%)	5.786	**0.016**
	Good balance	11 (61.1%)	17 (94.4%)		

PAS: Posture awareness scale, TUG: Timed up and go, NYPRC: New York posture rating chart, BBS: Berg balance scale, χ^2: Chi-square value, **: Chi-square test

positive and significant correlations were found between the T-score and awareness, posture, and balance scores. The TUG, however, demonstrated a negative and significant relationship with these parameters. These relationships were particularly stronger in the osteoporosis group.

Discussion

This study examined the relationship between posture, balance, and postural awareness levels in postmenopausal women diagnosed with osteoporosis. The findings indicate that osteoporosis is not limited to a decrease in BMD; it also affects important functional areas such as balance, posture, and body awareness.

This study concluded that individuals in the osteoporosis group had significantly lower levels of postural awareness. It implies that these women are navigating their world with an inaccurate "internal postural map". As thoracic kyphosis increases and the body's center of gravity shifts, proprioceptive feedback from the spine and trunk muscles may become unreliable. The individual may thus lose the ability to sense their own slump, allowing minor, uncorrected postural errors to accumulate into fixed deformities. This places them in a precarious position as they are less likely to consciously engage protective strategies to maintain stability. This result suggests that changes in the spinal structure may negatively affect the body's ability to perceive its position. In particular, the shift of the body's centre of gravity forward, accompanied by an increase in thoracic kyphosis, may prevent individuals from receiving adequate proprioceptive feedback. As a result, individuals may not notice the deterioration in their posture, which may lead to more serious postural problems over time. Osteoporosis is associated with more pronounced postural

Table 3. Spearman correlations between functional and clinical parameters in osteoporosis and osteopenia

Parameters r (p)	Osteoporosis group (n=18)					Osteopenia group (n=18)				
	Lumbar spine (L1-L4) T-score	**PAS**	**TUG test**	**NYPRC**	**BBS**	**Lumbar spine (L1-L4) T-score**	**OAS**	**TUG test**	**NYPRC**	**BBS**
Lumbar spine (L1-L4) T-score	1 (.)	0.940 **(<0.001)**	-0.898 **(<0.001)**	0.941 **(<0.001)**	0.930 **(<0.001)**	1 (.)	0.876 **(<0.001)**	-0,932 **(<0.001)**	0.874 **(<0.001)**	0.875 **(<0.001)**
OAS	0.940 **(<0.001)**	1 (.)	-0.927 **(<0.001)**	0.964 **(<0.001)**	0.967 **(<0.001)**	0.876 **(<0.001)**	1 (.)	-0.734 **(<0.001)**	0.977 **(<0.001)**	0.986 **(<0.001)**
TUG test	-0.898 **(<0.001)**	-0.927 **(<0.001)**	1 (.)	-0.954 **(<0.001)**	0.976 **(<0.001)**	-0,932 **(<0.001)**	-0.734 **(<0.001)**	1 (.)	-0.763 **(<0.001)**	-0.734 **(<0.001)**
NYPRC	0.941 **(<0.001)**	0.964 **(<0.001)**	-0.954 **(<0.001)**	1 (.)	-0.969 **(<0.001)**	0.874 **(<0.001)**	0.977 **(<0.001)**	-0.763 **(<0.001)**	1 (.)	0.970 **(<0.001)**
BBS	0.930 **(<0.001)**	0.967 **(<0.001)**	-0.969 **(<0.001)**	0.976 **(<0.001)**	1 (.)	0.875 **(<0.001)**	0.986 **(<0.001)**	-0.734 **(<0.001)**	0.970 **(<0.001)**	1 (.)

PAS: Posture awareness scale, TUG: Timed up and go, NYPRC: New York posture rating chart, BBS: Berg balance scale, r: Spearman's correlation coefficient, p: Spearman correlation test

changes, such as increased thoracic kyphosis and reduced spinal length, which are less severe or absent in osteopenia. These structural changes further impair postural awareness and stability (9). In addition, the worsening of postural awareness in osteoporosis is linked to lower BMD, vertebral deformities, and muscle weakness, which are less pronounced in osteopenia (21,22). Women with osteoporosis exhibit significantly greater postural sway (both anteroposterior and mediolateral) than those with osteopenia or normal bone density, indicating worse postural control. The osteoporosis group consistently demonstrated the highest instability across all tested positions, while the osteopenia group had intermediate values between osteoporosis and healthy controls (23).

This study was concluded that individuals in the osteoporosis group had lower balance levels and higher risk of falling according to the results of BBS and TUG. These findings reveal that osteoporosis may negatively affect individuals' ability to safely perform daily living activities. This study corroborate that osteoporosis does not merely weaken the skeleton; it undermines the very system designed to protect it, creating a perfect storm for fracture. In particular, the negative effects of spinal deformities on static and dynamic balance are consistent with previous literature. People with osteoporosis consistently demonstrate poorer balance compared to those without osteoporosis. This includes greater postural sway, altered balance control strategies, and reduced ability to maintain stability, especially in challenging positions (8,24). Muscle weakness, increased spinal kyphosis, and vertebral fractures further compromise balance in osteoporosis, making postural control more difficult (5,24,25). In some studies, balance impairment is a stronger predictor of future fractures than BMD itself, highlighting its clinical importance (26). Studies found that individuals with osteoporosis have significantly worse balance than those with osteopenia, which is parallel to this study. Osteoporotic patients demonstrate greater postural sway (both anteroposterior and mediolateral) and more pronounced instability in all tested positions compared to osteopenic and healthy individuals (22,27). Objective and behavioral balance tests reveal a higher proportion of abnormal results in osteoporosis, and vestibular dysfunction is more prevalent in this group (28).

The study indicates that individuals in the osteoporosis group have significant posture abnormalities. Osteoporosis leads to vertebral fractures and spinal deformities, which shift the body's center of gravity forward, increasing instability and the risk of falls. Muscle weakness, proprioceptive deficits, and pain further contribute to postural problems (29). The weakening of the vertebral structure not only affects bone health but also disrupts the functional integrity of posture, thereby reducing the individual's mobility and quality of life. Recent genetic and clinical studies confirm a causal association between low bone BMD in osteoporosis and increased postural instability. Lower BMD, especially at the femoral neck and lumbar spine, is significantly associated with greater postural instability and impaired balance (30). Postural deficits in osteoporosis are a major contributor to increased fall and fracture risk, making their assessment and management crucial in clinical practice (31). Postural deformities and reduced spinal mobility in osteoporosis are strongly linked to lower quality of life, greater fear of falling, and reduced functional independence (9).

The positive relationships observed between T-score, postural awareness, posture and balance have revealed that decreases in BMD have a significant effect on these three parameters in this study. Lower BMD is associated with postural changes such as increased thoracic kyphosis, spinal deformities, and altered body alignment. These changes further compromise postural control and awareness (32). Poor balance and postural deficits in those with low BMD are strong predictors of falls and fractures. Balance and functional mobility tests independently predict

BMD status and fracture risk (33). Large-scale genetic and clinical studies confirm a significant negative correlation between BMD (especially at the femoral neck and lumbar spine) and postural instability. Lower BMD increases the risk of postural instability and impaired balance, making individuals with osteoporosis more susceptible to falls (31). In contrast, a negative relationship was found between TUG duration and these parameters. This indicates that movement safety decreases alongside a reduction in functional capacity. Studies concluded that women with lower BMD have greater postural sway, reduced limits of stability, and poorer performance on balance tests. These deficits are more pronounced in osteoporosis than in osteopenia or normal BMD (34).

The current findings have important clinical implications. The identification of high fall risk in osteoporosis patients highlights the urgent need for targeted fall-prevention strategies. Interventions should not only aim to improve bone density through pharmacological treatment but also incorporate physiotherapy programs that enhance balance, postural control, and functional awareness. Previous studies have shown that exercise interventions focusing on strength, balance, and proprioception significantly reduce fall incidence and improve functional performance in osteoporotic populations (35). Finally, the findings support the concept of tailored rehabilitation approaches. Given the inter-individual variability observed in postural and functional parameters, exercise interventions should be personalised according to baseline performance and awareness levels. This aligns with current perspectives in precision rehabilitation, advocating for interventions that address both skeletal and neuromuscular dimensions of osteoporosis.

Study Limitations

This study has several limitations. The sample size was relatively small, which may limit the generalisability of findings. Furthermore, the cross-sectional design precludes causal inference regarding the relationship between bone density and functional performance. Longitudinal studies are needed to clarify the directionality of these associations and to examine whether improvements in postural awareness and balance can mitigate bone loss or reduce fracture risk. Future research should also explore the role of psychosocial factors, such as fear of falling, which may further influence the interaction between osteoporosis and functional decline.

Conclusion

In conclusion, this study shows that, in contrast to osteopenia, osteoporosis is linked to significantly worse postural awareness, poorer postural alignment, and decreased balance. The interdependence of skeletal and neuromuscular health is highlighted by the strong relationships found between BMD and functional parameters. To maintain independence and lower fall-related morbidity in this population, these findings emphasize the necessity of comprehensive rehabilitation strategies that combine functional training with traditional osteoporosis management.

Ethics

Ethics Committee Approval: This study had ethical approval from the Fırat University Ethics Committee (approval number: 2024/15-32, date: 19.12.2024).

Informed Consent: Informed consent forms were obtained from the participants who volunteered to participate in the study.

Footnotes

Authorship Contributions

Concept: M.Ş.E., K.Ç., S.B.Y., Design: K.Ç., S.B.Y., Data Collection or Processing: M.Ş.E., K.Ç., Analysis or Interpretation: M.Ş.E., Literature Search: K.Ç., S.B.Y., Writing: M.Ş.E., S.B.Y.

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DXA Çekimlerinde Tekrar Oranları ve Hizmet Dağılımının Değerlendirilmesi: 35.827 Çekimlik Retrospektif Analiz

Evaluation of Repeat Scan Rates and Service Utilization Patterns in DXA Examinations: A Retrospective Analysis of 35,827 Scans

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Öz

Amaç: Bu çalışmada, Sağlık Bilimleri Üniversitesi, Sincan Eğitim ve Araştırma Hastanesi'nde üç yıllık dönemde gerçekleştirilen dual-enerji X-ışını absorbsiyometrisi (DXA) çekimlerinin kullanım paternleri incelendi. Çalışmanın amacı, çekimlerin dağılımını, tekrar aralıklarını ve tanı gruplarına göre kullanım özelliklerini ortaya koymaktır.

Gereç ve Yöntem: Retrospektif olarak planlanan çalışmaya 1 Ocak 2022-31 Aralık 2024 tarihleri arasında yapılan toplam 35.827 DXA çekimi ve 17.857 hasta dahil edildi. Demografik veriler, hizmet türleri, istek-çekim aralıkları ve ICD-10 tanı grupları değerlendirildi. Tekrar çekimler zaman aralıklarına göre sınıflandırıldı. Tanımlayıcı istatistikler ve gruplar arası karşılaştırmalar yapıldı.

Bulgular: Hastaların ortalama yaşı 61 (çeyrekler arası aralık: 52-70) yıl olup, %78'i kadındı. Çekimlerin %52'si lomber omurga, %33'ü femur ve %15'i tüm vücut bölgesine yönelikti. Hastaların %22'sinde en az bir tekrar çekim mevcuttu. Tekrarların %2,8'i 7 gün içinde (teknik tekrar), %14,4'ü ilk yıl içinde, %12,2'si ise ≥2 yıl sonrasında gerçekleşti. Osteoporoz (M81) ve postmenopozal durum (N95) tanılı hastalarda tekrar oranları diğer gruplara kıyasla anlamlı derecede daha yüksek bulundu (p<0,001). İstek-çekim aralığının medyanı 5 gün hesaplandı.

Sonuç: Bu çalışma, DXA hizmet kullanımında yalnızca ölçüm sonuçlarını değil, kullanım paternlerini de ortaya koymuştur. Bulgular, teknik tekrarların ve kılavuzlardan daha erken yapılan kontrollerin dikkate değer bir orana ulaştığını göstermektedir. DXA hizmetlerinin verimliliğini artırmak için klinik endikasyonlara sıkı bağlı kalınması, tekrar çekim endikasyonlarının gözden geçirilmesi ve kalite kontrol süreçlerinin güçlendirilmesi önerilmektedir.

Anahtar kelimeler: DXA, dual-enerji X-ışını absorbsiyometrisi, tekrar çekim sıklığı, osteoporoz, postmenopozal durum, sağlık hizmeti kullanımı

Abstract

Objective: This study aimed to investigate the utilization patterns of dual-energy X-ray absorptiometry (DXA) scans performed over a three-year period at University of Health Sciences Türkiye, Sincan Training and Research Hospital by evaluating the distribution of scan types, repeat intervals, and utilization characteristics across diagnostic groups.

Materials and Methods: This retrospective study included 35,827 DXA scans from 17,857 unique patients performed between January 1, 2022, and December 31, 2024. Demographic data, scan types, request-to-scan intervals, and ICD-10 diagnostic codes were evaluated. Repeat scans were classified by time interval. Descriptive statistics and intergroup comparisons were performed.

Results: The mean patient age was 61 years (interquartile range: 52-70), and 78% were female. Lumbar spine scans were the most frequent (52%), followed by femoral (33%) and whole-body scans (15%). At least one repeat scan was observed in 22% of patients. Among repeats, 2.8% were technical repeats (within 7 days), 14.4% occurred within the first year, and 12.2% after ≥2 years. Repeat rates were significantly higher in patients with osteoporosis (M81) and postmenopausal status (N95) compared to other groups (p<0.001). The median request-to-scan interval was 5 days.

Conclusion: Our analysis revealed that technical repeats and early follow-up scans constitute a considerable proportion of DXA services. Reinforcing adherence to clinical indications, re-evaluating repeat scan criteria, and strengthening quality control processes are recommended to improve the efficiency of DXA utilization and optimize healthcare resources.

Keywords: DXA, dual-energy X-ray absorptiometry, repeat scans, osteoporosis, postmenopausal status, healthcare utilization

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Giriş

Osteoporoz, düşük kemik kütlesi ve bozulmuş mikro-mimari yapı sonucu kırık riskinde artış ile karakterize edilen, prevalansı yaşla birlikte yükselen önemli bir sağlık sorunudur. Tanı ve izlemde en sık kullanılan yöntem dual-enerji X-ışını absorbsiyometrisi (DXA) olup, kemik mineral yoğunluğunu (BMD) ölçmede referans standart kabul edilmektedir (1-3). DXA sonuçlarının güvenilirliği için çekim kalitesi, rapor standartları ve tekrar aralıklarının uluslararası kılavuzlarla uyumlu olması önerilmektedir (4-7). DXA kullanımında çeşitli sınırlılıklar ve hata kaynakları bildirilmiştir. Lomber omurga dejeneratif değişikliklerinin ölçüm sonuçlarını etkileyebildiği (8), raporlama sürecinde hataların sık görüldüğü (9), raporların kılavuzlara yeterince uymadığı belirtilmiştir (10). Bu nedenle, ilgili dernekler rapor standardizasyonu ve kalite kontrolünün önemini vurgulamış, DXA tekrarlarının klinik bağlama göre düzenlenmesini önermiştir (5,6,11). Hizmet kullanımına ilişkin veriler, ülkeler ve sağlık sistemleri arasında farklılık göstermektedir. Kanada'da yapılan geniş ölçekli bir analizde, DXA'nın kullanım sıklığı ve tekrar aralıklarının sağlık politikaları ile ilişkili olduğu raporlanmıştır (12). Klinik düzeyde ise, izlem altındaki hastalarda BMD ölçümlerinin sıklığının hasta özellikleri ve tedavi durumuna göre değiştiği gösterilmiştir (13,14). DXA ayrıca vücut kompozisyonu ve trabeküler kemik skorunun (TBS) değerlendirilmesinde de kullanılabilmektedir. TBS'nin BMD'ye ek olarak kırık riskini öngörmede yararlı olabileceği (13), tüm vücut DXA ile yağ ve kas dağılımının değerlendirilebileceği bildirilmiştir (14). Ancak bu parametrelerin klinik kullanımı henüz sınırlıdır. Bu çalışmada, bir eğitim ve araştırma hastanesinde 2022-2024 yılları arasında yapılan DXA çekimlerinin incelenmesi amaçlanmıştır. Hizmet türü dağılımları, tekrar çekim aralıkları, tanı grupları ve erişim göstergeleri değerlendirilmiştir.

Gereç ve Yöntem

Çalışma retrospektif, gözlemsel ve tanımlayıcı tasarımlıdır. 1 Ocak 2022-31 Aralık 2024 tarihleri arasında Sağlık Bilimleri Üniversitesi, Sincan Eğitim ve Araştırma Hastanesi'nde gerçekleştirilen tüm DXA çekimleri dahil edilmiştir. Toplam 35.827 çekim ve 17.857 hasta analiz edilmiştir.

Tüm DXA ölçümleri, GE Lunar Prodigy Pro (GE Healthcare, Madison, WI, USA) cihazı ile gerçekleştirilmiştir. Cihaz günlük kalite kontrol testlerinden geçirilmiş olup, ölçümler üretici tarafından önerilen kalibrasyon standartlarına göre yapılmıştır. Verilerden elde edilen değişkenler: Demografik bilgiler, çekim tarihleri, hizmet türü (lomber omurga, femur, tüm vücut, ön kol, diğer), ICD-10 tanı grupları, istek-çekim aralığı, PACS imaj ve rapor varlığı, tekrar çekim sınıfları.

Bu çalışma, Sağlık Bilimleri Üniversitesi, Sincan Eğitim ve Araştırma Hastanesi Bilimsel Araştırmalar Etik Kurulu tarafından onaylanmıştır (karar no: SEAH-BAEK-2025-136, tarih: 23.12.2025). Çalışmanın retrospektif tasarımı nedeniyle bireysel hasta onamı etik kurul tarafından muaf tutulmuştur.

İstatistiksel Analiz

Tanımlayıcı istatistikler medyan [çeyrekler arası aralık (ÇAA)] ve yüzde değerleri ile verilmiştir. Gruplar arası karşılaştırmalarda Kruskal-Wallis ve ki-kare testleri uygulanmıştır. Anlamlılık düzeyi $p<0,05$ olarak kabul edilmiştir.

Bulgular

Çalışma dönemi boyunca hastanemizde toplam 35.827 DXA çekimi, 17.857 hastaya ait olarak gerçekleştirildi. Hastaların ortalama yaşı 61 yıl (ÇAA: 52-70) olup, %78'i kadındı.

Hizmet Türü Dağılımı

DXA çekimlerinin türlere göre dağılımı incelendiğinde, en sık lomber omurga çekimleri yapıldı (n=18.600, %52,0). Bunu sırasıyla femur (n=11.800, %33,0) ve tüm vücut çekimleri (n=5,200, %15,0) izledi. Ön kol (n=200, %0,6) ve diğer bölge (n=27, %0,1) çekimleri ise oldukça sınırlı oranda talep edildi (Tablo 1, Şekil 1).

Tekrar Çekim Analizleri

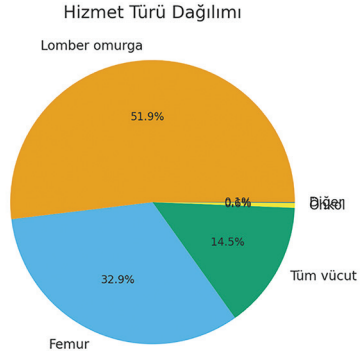
Toplam hastaların yaklaşık %22'sinde (n=3,930) en az bir kez tekrar DXA çekimi yapıldığı tespit edildi. Tekrarların %2,8'ini (n=1,250) ≤7 gün içinde aynı hizmette yapılan teknik tekrarlar, %0,7'sini (n=320) ≤7 gün içinde farklı hizmette yapılan kısa aralıklı incelemeler oluşturdu. Bunun dışında tekrar çekimler sırasıyla:

- %4,3 (n=1,900) 8-90 gün arası kısa dönem tekrar,
- %4,7 (n=2,100) 91-180 gün arası orta dönem kontrol,
- %6,4 (n=2,800) yıllık kontrol (181-365 gün),
- %7,1 (n=3,100) 12-24 ay kontrol,
- %5,1 (n=2,300) ≥2 yıl kontrol şeklinde sınıflandırıldı (Tablo 2, Şekil 2).

Tablo 1. Hizmet türlerinin dağılımı

Hizmet türü	n	%
Lomber omurga	18600	52
Femur (tek taraf)	11800	33
Tüm vücut	5200	15
Ön kol	200	0,6
Diğer	27	0,1

Hastaların DXA hizmet türlerine göre dağılımı. n: Hasta sayısı, %: Yüzdelik oran, DXA: Dual-enerji X-ışını absorbsiyometrisi



Şekil 1. Hizmet türü dağılımı (pasta grafik)
DXA hizmet türlerinin yüzdesel dağılımı. Lomber omurga en sık talep edilen hizmettir (%52)
DXA: Dual-enerji X-ışını absorbsiyometrisi

Branşlara Göre DXA İstem Dağılımı

DXA tetkiklerinin büyük çoğunluğu fizik tedavi birimleri tarafından istenmiştir (%57,7). Bunu sırasıyla kadın hastalıkları ve doğum (%26,7), ortopedi (%5,9), iç hastalıkları (%3,5) ve endokrinoloji (%2,7) branşları izlemiştir. Diğer branşların katkısı oldukça sınırlı orandadır (<%1). Bu dağılım, DXA'nın öncelikli olarak osteoporoz ve menopoz izleminde, fizik tedavi ve kadın doğum kliniklerinde yoğun kullanıldığını göstermektedir (Tablo 3).

Tanı Gruplarına Göre Tekrar Oranları

Tanı grupları açısından değerlendirildiğinde, osteoporoz (M81) ve postmenopozal durum (N95) tanılı hastalarda tekrar oranlarının diğer gruplara kıyasla anlamlı derecede yüksek olduğu görüldü (p<0,001). Bu farklılık Şekil 3'te çubuk grafik ile gösterilmiştir.

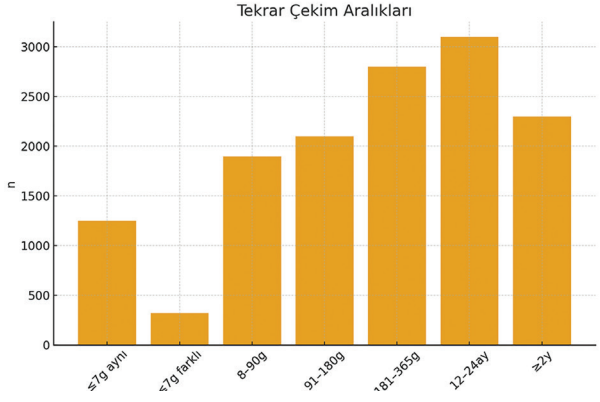
İstatistiksel Karşılaştırmalar

Gruplar arası karşılaştırmalarda, tanı grupları ve hizmet türlerine göre tekrar oranlarında, ayrıca yaş ve cinsiyet değişkenleriyle ilişkili olarak istatistiksel açıdan anlamlı farklılıklar saptandı (p<0,05).

Tablo 2. Tekrar çekim sınıfları

Tekrar çekimlerin zaman aralıklarına göre sınıflandırılması. Teknik tekrar: ≤7 gün aynı hizmet; kısa aralıklı ek inceleme: ≤7 gün farklı hizmet.

Sınıf	n	%
Teknik tekrar (≤7 g, aynı hizmet)	1250	2,8
Kısa aralıklı ek inceleme (≤7 g, farklı hizmet)	320	0,7
Kısa dönem tekrar (8-90 g)	1900	4,3
Orta dönem kontrol (91-180 g)	2100	4,7
Yıllık kontrol (181-365g)	2800	6,4
12-24 ay kontrol	3100	7,1
≥2 yıl kontrol	2300	5,1



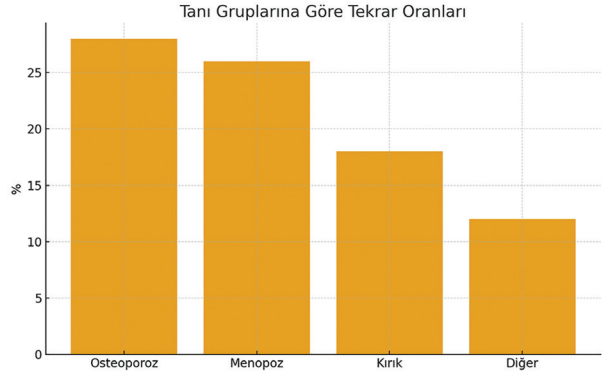
Şekil 2. Tekrar çekim aralıkları (histogram)
Tekrar çekimlerin zaman aralıklarına göre dağılımı. Erken tekrarlar (%14, ≤1 yıl) belirgin orandadır

Tartışma

Bu çalışmada, üç yıllık dönemde bir eğitim ve araştırma hastanesinde gerçekleştirilen 35.827 DXA çekimi ve 17.857 hasta analizi incelenmiştir. Bulgular, hizmet türü dağılımları, tekrar çekim aralıkları ve tanı gruplarına göre kullanım paternleri açısından literatürde bildirilen eğilimlerle karşılaştırıldığında hem benzerlikler hem de farklılıklar göstermektedir. DXA, osteoporoz tanı ve izleminin temel yöntemi olmakla birlikte (1-3), ölçümlerin güvenilirliği çeşitli sınırlılıklar ve teknik kısıtlılıklardan etkilenebilir (4,5). Çalışmamızda tekrar çekimlerin %2,8'inin ≤7 gün içinde aynı hizmetten oluşması, olası teknik hataları veya raporlama sorunlarını düşündürmektedir. Literatürde de benzer şekilde çekim hataları ve raporlardaki eksikliklerin DXA güvenilirliğini sınırladığı bildirilmiştir (6,7). Ayrıca lomber omurga bölgesinde dejeneratif değişikliklerin ölçüm değerlerini etkilediği belirtilmiş olup (8), tekrarların bu bölgede daha sık olması bu sınırlılığı destekleyebilir. Uluslararası kılavuzlarda DXA tekrar aralıklarının klinik bağlama göre düzenlenmesi önerilmektedir (5,9). ISCD 2019 pozisyon bildirisine göre tedavi altındaki veya yüksek riskli hastalarda daha kısa aralıklarla ölçüm yapılabilirken, düşük riskli hastalarda bu süre daha uzun olmalıdır (8). Çalışmamızda tekrarların

Tablo 3. İstem yapan branşlarının dağılımı

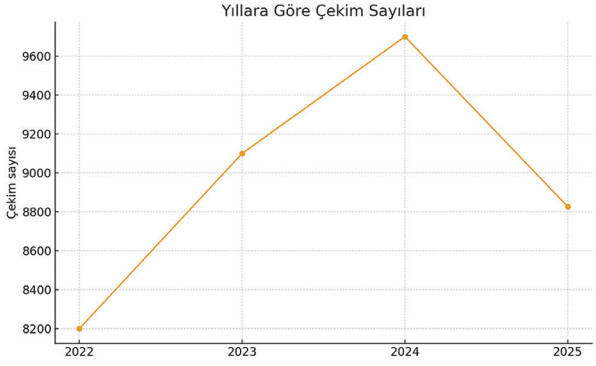
Branş	n	%
Fizik tedavi	20,678	57,7
Kadın doğum	9,582	26,7
Ortopedi	2,109	5,9
İç hastalıkları	1,243	3,5
Endokrinoloji	978	2,7
Beyin ve sinir cerrahisi	415	1,2
Enfeksiyon hastalıkları	174	0,5
Nöroloji	106	0,3
Geriatri	93	0,3
Genel cerrahi	77	0,2



Şekil 3. Tanı gruplarına göre tekrar oranları (çubuk grafik)
Osteoporoz (M81) ve postmenopozal durum (N95) tanılı hastalarda tekrar oranlarının diğer tanı gruplarına göre daha yüksek olduğu görülmektedir (p<0,001)

%14'ünün bir yıl içinde, %6'sının ise iki yıl veya daha uzun sürede gerçekleşmesi, kısmen bu önerilerle uyumlu bulunmuştur. Ancak bir yıl içinde yapılan tekrarların oranı, klinik gereklilik dışında erken çekimlerin de olabileceğini düşündürmektedir.

Çalışmamızda DXA çekimi için istek-çekim arasındaki ortalama sürenin 5 gün olarak bulunması, hizmete erişimin nispeten hızlı olduğunu ve bekleme listesi probleminin bulunmadığını göstermektedir. Bu durum, hastane kaynaklarının etkin kullanımı açısından olumlu bir gösterge olarak değerlendirilebilir. Ayrıca, incelenen üç yıllık dönemde toplam DXA çekim sayısında gözlemlenen artış eğilimi (Şekil 4), osteoporoz tarama ve takip farkındalığının giderek arttığına işaret ediyor olabilir. Bununla birlikte, bu artan talebin, erken ve gereksiz tekrar çekim oranları üzerindeki olası etkisi de göz ardı edilmemelidir. DXA çekimlerinin tekrar sıklığı yalnızca klinik açıdan değil, sağlık hizmetleri planlaması ve maliyetler açısından da önemlidir. Erken dönemde yapılan tekrarların, özellikle klinik gereklilik dışında olduğunda, sağlık sistemi üzerinde ek yük oluşturabileceği bildirilmiştir (10). Çalışmamızda bir yıl içinde gerçekleştirilen tekrarların oranı %14 olarak bulunmuştur. Bu oran, teknik gereklilik dışında yapılan çekimlerin olabileceğini düşündürmektedir. Bu bulgu, DXA kullanımının yalnızca klinik endikasyonlarla sınırlı tutulması ve sağlık kaynaklarının daha verimli kullanılması gerektiğini göstermektedir. Sağlık sistemi düzeyinde, DXA kullanım paternleri farklı ülkelerde değişkenlik göstermektedir. Ontario'da yapılan geniş ölçekli analizde, tekrar aralıkları ve hizmet kullanım sıklığının sağlık politikaları ile yakından ilişkili olduğu rapor edilmiştir (10). Bizim çalışmamızda bekleme sürelerinin kısa (ortalama 5 gün) bulunması, erişim açısından avantajlı bir durum olmakla birlikte, yoğun kullanımın erken tekrar oranlarını artırabileceği de göz önünde bulundurulmalıdır. Klinik izlem verileri de, tekrar çekim sıklığının hasta özelliklerine göre değiştiğini göstermektedir. Leslie ve ark. (11), antiosteoporoz tedavi altındaki hastalarda izlem sıklığının daha yüksek olduğunu, Park ve ark. (12) ise Asya popülasyonunda osteoporoza geçiş riskine göre tarama aralıklarının farklılık gösterdiğini bildirmiştir. Çalışmamızda osteoporoz (M81) ve menopoz (N95) tanı gruplarında tekrar oranlarının diğer tanılara göre daha yüksek bulunması bu literatür ile uyumludur.



Şekil 4. Yıllara göre çekim sayıları
Çalışma yıllarına göre toplam DXA çekim sayıları. Çekim hacminde artış eğilimi gözlenmektedir
DXA: Dual-enerji X-ışını absorbsiyometrisi

Çalışmanın Kısıtlılıkları

Bu çalışmanın bazı kısıtlılıkları bulunmaktadır. Retrospektif tasarım nedeniyle klinik endikasyonlar, tedavi durumu ve hastaların klinik sonuçları tam olarak değerlendirilememiştir. T ve Z-skorları çalışmaya dahil edilmemiştir; bu nedenle bulgular yalnızca hizmet kullanım paternleriyle sınırlı kalmıştır. Ayrıca tek merkezli bir veri seti kullanılmış olup, sonuçların genelleştirilebilirliği sınırlı olabilir. PACS raporlarının varlığı değerlendirilmiş ancak rapor içeriklerinin ayrıntılı analizi yapılmamıştır. Bu faktörler, sonuçların yorumlanmasında göz önünde bulundurulmalıdır.

Sonuç

Bu çalışmada, üç yıllık dönemde geniş bir hasta grubuna ait 35.827 DXA çekiminin incelenmesiyle, hizmet kullanım paternleri değerlendirilmiştir. Çekimlerin büyük çoğunluğunu lomber omurga ve femur incelemeleri oluşturmuş, hastaların yaklaşık beşte birinde ise tekrar çekim yapıldığı tespit edilmiştir. Özellikle osteoporoz ve postmenopozal durum tanılı hastalardaki yüksek tekrar oranları, bu gruplarda izlemin daha yoğun olduğunu göstermektedir.

Tekrar çekimlerin sınıflandırılması, klinik pratikte hem yüksek riskli hastaların yakın takibini hem de erken dönemdeki teknik tekrarlar gibi optimize edilebilecek süreçleri ortaya koymuştur. İstek-çekim aralıklarının kısa olması hizmete erişimin etkin olduğunu düşündürse de, bulgularımız DXA kullanımının yalnızca tanısal bir araç olarak değil, aynı zamanda sağlık hizmeti sunumunun organizasyonu ve klinik karar süreçlerinin bir yansıması olarak değerlendirilmesi gerektiğine işaret etmektedir. Sonuç olarak, bu veriler DXA hizmetlerinin kalite kontrolünün güçlendirilmesi ve kaynak kullanımının optimize edilmesi için değerli bir altyapı sunmaktadır. Erken dönemde yapılan tekrarların belirgin bir oran oluşturması, sağlık sistemi açısından ayrıca önemlidir. Klinik gerekliliği olmayan tekrarların azaltılması, hem maliyetlerin düşürülmesine hem de sağlık kaynaklarının daha verimli kullanılmasına katkı sağlayabilir. Bu nedenle, DXA hizmetlerinin planlanmasında klinik endikasyonlara dayalı yaklaşımların güçlendirilmesi ve kalite kontrol süreçlerinin geliştirilmesi faydalı olacaktır.

Etik

Etik Kurul Onayı: Bu çalışma, Sağlık Bilimleri Üniversitesi, Sincan Eğitim ve Araştırma Hastanesi Bilimsel Araştırmalar Etik Kurulu tarafından onaylanmıştır (karar no: SEAH-BAEK-2025-136, tarih: 23.12.2025).

Hasta Onayı: Çalışmanın retrospektif tasarımı nedeniyle bireysel hasta onamı etik kurul tarafından muaf tutulmuştur.

Dipnot

Yazarlık Katkıları

Cerrahi ve Medikal Uygulama: N.Y., A.S.N., Konsept: S.E.E., Dizayn: S.E.E., N.K.Ü., Veri Toplama veya İşleme: N.Y., M.O.A.,

Analiz veya Yorumlama: S.E.E., N.K.Ü., Literatür Arama: A.S.D., M.O.A., Yazan: S.E.E.

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The Circulating Levels of Osteoprotegerin and RANKL in Transfusion-dependent Beta-thalassemia Patients

Transfüzyona Bağımlı Beta Talasemi Hastalarında Dolaşımdaki Osteoprotegerin ve RANKL Düzeyleri

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Abstract

Objective: β-thalassemia is a lifelong blood disorder with anemia and systemic effects. One of the complications commonly encountered in β-thalassemia, particularly with advancing age, includes weakened bones. The roles of osteoprotegerin (OPG) and receptor activator for nuclear factor B ligand (RANKL) in age-related osteoporosis, as well as β-thalassemia-related bone disease, have been studied. This study aimed to compare the levels of OPG and RANKL in transfusion-dependent β-thalassemia (TDT) patients with healthy controls (HCs).

Materials and Methods: This study comprised 120 TDT and 60 HCs, whose blood counts and biochemical profiles were assessed, followed by ELISA for OPG and RANKL according to the manufacturer's guidelines. Data were analysed using the Mann-Whitney U test and Spearman's correlation, with a p-value of ≤0.05 considered statistically significant.

Results: The median age was slightly higher in HCs, with overall more male representation. Blood counts were comparable in both groups, except slightly higher WBC count. High serum ferritin, suggestive of iron overload, was noted in TDT. Findings suggest a reduced OPG and RANKL level in TDT patients compared to HCs. OPG was reduced in both male and female TDT patients, while RANKL was reduced in male TDT patients only. A very weak to no correlation of OPG or RANKL was determined with age and serum ferritin.

Conclusion: Our results show reduced OPG and RANKL levels in TDT patients, particularly in males, with a very weak correlation with age and serum ferritin. However, further studies to explore their role in bone metabolism and association with bone density are needed.

Keywords: Beta-thalassemia, transfusion dependent β-thalassemia, TDT, OPG, RANKL, bone disease

Öz

Amaç: β-talasemi, anemi ve sistemik etkilerle seyreden, yaşam boyu devam eden bir kan hastalığıdır. Özellikle yaş ilerledikçe, β-talasemide sık karşılaşılan komplikasyonlardan biri kemik zayıflığıdır. Osteoprotegerin (OPG) ve RANKL'nin yaşa bağlı osteoporozdaki ve β-talasemiye bağlı kemik hastalığındaki rolleri daha önce incelenmiştir. Bu çalışma, transfüzyona bağımlı β-talasemi (TDT) hastaları ile sağlıklı kontrollerde (SK) OPG ve nükleer faktör B ligandı için reseptör aktivatörü (RANKL) düzeylerini karşılaştırmayı amaçlamıştır.

Gereç ve Yöntem: Bu çalışmaya kan sayımları ve biyokimyasal profilleri değerlendirilen, ardından üretici talimatlarına göre OPG ve RANKL için ELISA yapılan 120 TDT hastası ve 60 SK dahil edilmiştir. Veriler Mann-Whitney U testi ve Spearman korelasyonu ile analiz edilmiş; p≤0,05 istatistiksel olarak anlamlı kabul edilmiştir.

Bulgular: Sağlıklı kontrollerin medyan yaşı biraz daha yüksek olup, genel olarak erkek oranı daha fazlaydı. Her iki grubun kan sayımları karşılaştırılabilir düzeydeydi, ancak beyaz kan hücresi sayısı SK'da biraz daha yüksekti. TDT grubunda demir yüklenmesini düşündüren yüksek

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serum ferritin düzeyleri saptandı. Bulgular, TDT hastalarında SK'lara kıyasla OPG ve RANKL düzeylerinin azaldığını göstermektedir. OPG düzeyi hem erkek hem kadın TDT hastalarında düşükken, RANKL düzeyi yalnızca erkek TDT hastalarında düşüktü. OPG ve RANKL'nin yaş ve serum ferritin ile çok zayıf ya da hiç korelasyon göstermediği belirlendi.

Sonuç: Sonuçlarımız, TDT hastalarında özellikle erkeklerde OPG ve RANKL düzeylerinin azaldığını ve bu parametrelerin yaş ile serum ferritinle çok zayıf bir ilişki gösterdiğini ortaya koymaktadır. Bununla birlikte, bu moleküllerin kemik metabolizmasındaki rollerini ve kemik yoğunluğu ile ilişkilerini araştırmak için ileri çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Beta-talasemi, transfüzyona bağımlı β-talasemi, TDT, OPG, RANKL, kemik hastalığı

Introduction

Beta-thalassemia (β-thalassemia) is an inherited blood disorder due to defective β-globin chains resulting in anemia and systemic effects (1). β-thalassemia is clinically classified into transfusion dependent (TDT) and non-transfusion dependent β-thalassemia (NTDT) based mainly on the transfusion frequency. Systemic complications include organomegaly, endocrine problems and skeletal changes (2,3). β-thalassemia is the most common hemoglobinopathy worldwide and in Pakistan, though the exact prevalence remains unknown, ~5000 births per annum are reported (4).

Patients are treated with regular blood transfusions or drugs with potential to induce fetal hemoglobin (HbF) production to ameliorate the anemia and related complications (5). In the recent years, improved healthcare facilities have increased the lifespan of β-thalassemia patients, however, the long-term consequences remain a challenge (6-8). One of the major complications include bone disease which comprises of weakened bones, skeletal changes and increased risk of fractures (9-14). The pathogenesis of bone disease in β-thalassemia is complex with several risk factors which includes low calcium and vitamin D, endocrine problems, iron overload and the use of iron chelation therapy (15-18). Bone remodeling is a tightly regulated process with a balance between bone formation and resorption (19). Any dysregulation in this process results in bone diseases resulting in osteopenia and osteoporosis as debilitating illnesses. The pathway involving osteoprotegerin (OPG) and receptor activator for nuclear factor B ligand (RANKL) has been associated with bone disease (20,21). The OPG/RANKL ratio has been found to be a key regulator of bone mass and bone homeostasis (20,22). Similar to other conditions associated with bone disease, the role of OPG/RANKL ratio has also been studied in β-thalassemia (23-25). Dysregulated OPG/RANKL with increased osteoclastic activity results in bone weakening and increases the risk of bone related complications. The objective of this study was to determine the circulating levels of OPG and RANKL in TDT β-thalassemia patients. The findings of this study would be beneficial in understanding the role of OPG and RANKL in TDT who are at risk of bone related complications.

Materials and Methods

Study Participants

This study included 120 TDT patients and 60 healthy controls (HCs) of age ≥1 years regardless of gender and ethnicity, after informed consent from participants or their parents/guardians. NTDT and hemoglobinopathies other than β-thalassemia were excluded. This study was conducted at the Thalassemia Center Al-Khidmat Hospital, Peshawar and Blood Diseases Clinic, Peshawar Institute of Medical Sciences, Peshawar after ethical approval from the Institutional Ethical Committee of Institute of Pathology and Diagnostic Medicine, Khyber Medical University, Peshawar, Pakistan (ref: # KMU/IPDM/IEC/2024/27; dated: 12.12.2024).

Laboratory Parameters

Serum samples were collected from TDT patients and HCs and stored at -80 °C freezer for later use. Sandwich ELISA was done for the estimation of OPG and RANKL levels as per the manufacturer protocols (IDEAL company). Serum ferritin levels were determined as per standard protocol. Were also determined as per standard protocol (Cobas® c311 analyser, Roche Diagnostics International Ltd, Switzerland). Complete blood counts were performed on each blood sample collected in EDTA tube using Automated Hematology Sysmex analyser XP-100.

Statistical Analysis

Data were statistically analysed using Graph Pad Prism (version 10.6.0). Categorical variables are represented as frequency and percentages while numerical variable as median and interquartile range or range. Data normality was determined by Shapiro-Wilk test and Mann-Whitney U test was applied for comparison between two groups. Spearman's correlation analysis was done to determine the association of age and serum ferritin with serum OPG and RANKL levels. A p-value of ≤0.05 was considered as statistically significant.

Results

Demographic and Clinical Characteristics

This study included TDT (n=120) and HCs (n=60) with median age of eight and ten years, respectively, with male preponderance. Splenomegaly was noted in 20% of TDT patients with 10.83% had splenectomy done prior to inclusion in this study. Serum ferritin was higher in TDT patients compared to HCs (median: 2636 vs. 56.50 ng/mL, p<0.0001). Hb and platelet count were lower in TDT patients while WBC count was comparable between TDT patients and HCs. Data are summarized in Table 1.

Serum OPG and RANKL Levels

In this study, the median serum OPG levels were lower in TDT patients compared to HCs (204.3 vs. 277.5; p<0.0001), shown in Figure 1a. Similarly, the median serum RANKL levels were also

Table 1. Demographic and clinical characteristics of study participants			
Characteristics	**TDT patients (n=120)**	**HCs (n=60)**	**p-value (Mann-Whitney U test)**
Age in years Median (range)	8.0 (2-19)	10.0 (4-17)	0.001
Gender Females, n (%) Males, n (%)	52 (43.33) 68 (56.67)	23 (38.34) 37 (61.66)	-
Spleen status Splenomegaly, n (%) Splenectomy, n (%)	24 (20.0) 13 (10.83)	N/A	-
Serum ferritin (ng/mL) Median (range)	2636 (41.4-10595)	56.50 (28-104)	<0.0001
Hb (g/dL) Median (range)	7.4 (2-10.6)	12.75 (10.2-15.6)	<0.0001
WBC count Median (range)	7.3 (1.5-123.5)	8.45 (4.1-11)	0.408
Platelet count Median (range)	258.5 (31-791)	310.0 (152-672)	0.020
TDT: Transfusion-dependent β-thalassemia, Hb: Hemoglobin, WBC: White blood cell, N/A: Not applicable			

lower in TDT patients as compared to HCs (319.0 vs. 392.3; p<0.0001), as in Figure 1b. In addition, the levels of OPG and RANKL were lower in TDT patients and HCs in both female and male participants except RANKL in females (Figure 1c-f). No to weak correlation was determined between OPG or RANKL and serum ferritin or age. Data shown in Table 2.

Discussion

β-thalassemia is a lifelong blood disorder with multiorgan involvement including weakened bones and risk of fractures (26,27). The pathogenesis of bone disease in β-thalassemia is complex with several proposed mechanisms, ranging from nutritional deficiencies to disrupted bone metabolism pathways. Transfusion frequency, chronic anemia, iron overload and the use of iron chelation have been associated with reduced bone density (18,28). Despite nutritional supplementation with calcium, zinc, phosphorus, vitamin D and use of drugs to strengthen bones such as bisphosphonates, the risk of bone related complications remain a challenge (29,30). In order to improve the bone health and minimise the risk of complications, it is critical to understand the pathogenesis of bone disease in β-thalassemia. The role of OPG and RANKL mediated impaired bone metabolism have been shown to play an important role in age-related and β-thalassemia related bone disease (21,24,25). Alterations in the OPG and RANKL have been associated with increased osteoclastic activity resulting in weakened bones (31). To determine the OPG and RANKL levels in TDT patients, this study was conducted comprising of 120 TDT patients and 60 HCs. The median age of TDT patients and HCs were eight and ten years, respectively and slightly more male representation. Anemia, iron overload, splenomegaly and history of splenectomy was present in TDT patients similar to previously published studies (32). Overall, the serum OPG and RANKL levels were

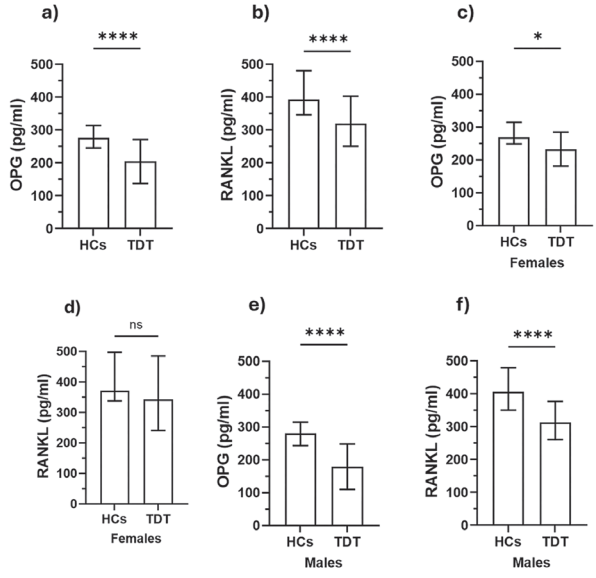

Figure 1. Serum OPG and RANKL levels in TDT patients and HCs. Serum OPG (a) and serum RANKL (b) levels were compared between TDT patients (n=120) and HCs (n=60) using Mann-Whitney U test. Serum OPG and RANKL were compared between female (c, d) and male (e, f) participants of each group using Mann-Whitney U test
*Data are represented as median with interquartile range using Box and Whisker plots and p-value denoted as ns: Non-significant, *: <0.05, ****: <0.0001, OPG: Osteoprotegerin, RANKL: Receptor activator for nuclear factor B ligand, TDT: Transfusion-dependent β-thalassemia, HCs: Healthy controls*

reduced in TDT patients compared to HCs in this study. Previous studies have shown reduced OPG in TDT patients, however, an increased level of RANKL (23,25,31). In contrast, increased levels of OPG and RANKL were determined in TDT patients in a study by Pietrapertosa et al. (33). Additionally, previous studies have

Table 2. Correlation analysis of age and serum ferritin with serum OPG and RANKL levels

Characteristics	TDT patients (n=120)		HCs (n=60)	
	OPG	RANKL	OPG	RANKL
Age in years				
Coefficient of correlation	0.173	0.153	-0.011	-0.052
p-value	0.058	0.093	0.933	0.693
Serum ferritin (ng/mL)				
Coefficient of correlation	0.012	-0.083	-0.109	-0.179
p-value	0.896	0.370	0.404	0.171

TDT: Transfusion-dependent β-thalassemia, OPG: Osteoprotegerin, RANKL: Receptor activator for nuclear factor B ligand, HCs: Healthy controls

not found any difference in the levels of OPG and RANKL in TDT and HCs based on the gender (31). However, our results show a significantly reduced OPG and RANKL levels in male TDT patients compared to male HCs ($p<0.0001$) while slightly reduced OPG in female TDT patients ($p<0.05$) and no difference in RANKL compared to HCs ($p>0.05$). The effect of gender, endocrine profile, vitamin D and calcium have been shown to modulate OPG/RANKL mediated bone metabolism (21). Although the factors affecting bone health in TDT were not determined in this study, it is not uncommon to have bone related complications in these patients (16,34). In β-thalassemia, the bone related complications such as osteopenia and osteoporosis increase with advancing age, our study found weak to no correlation of age with serum levels of OPG and RANKL. Moreover, a very weak to no correlation was found between serum ferritin and serum levels of OPG and RANKL.

Limited data are available on the effect of iron overload on the levels of OPG or RANKL. However, studies have shown an association of iron overload and iron chelating drugs with reduced bone density in TDT (18).

Interestingly, the role of OPG and RANKL are not limited to bone metabolism but shown to regulate several physiological and pathological mechanisms including immunity, cancers, cardiomyopathies and oral health (35-37). TDT is a complex disease with multisystem involvement and the possible systemic involvement of OPG and RANKL such as cardiomyopathy along with bone metabolism (38). Keeping in view the variations noted in OPG and RANKL levels in TDT among ours and previous studies, several factors such as transfusion frequency, bone density and use of bisphosphonate, vitamin D, corticosteroid or HbF inducing drugs could influence the levels. Furthermore, the role of the endocrine profile particularly thyroid and parathyroid hormones on bone metabolism needs consideration. Therefore, further studies are needed to understand the pathogenesis of bone disease in TDT including the role of OPG and RANKL mediated bone metabolism and systemic effects with above mentioned limitations taken into account.

Conclusion

Overall, the level of OPG and RANKL were reduced in TDT patients compared to HCs. OPG levels were reduced in both female and male TDT patients compared to HCs while RANKL was only reduced in TDT males. Age and serum ferritin levels had a very weak to no correlation with OPG or RANKL levels.

Ethics

Ethics Committee Approval: This study was conducted at the Thalassemia Center Al-Khidmat Hospital, Peshawar and Blood Diseases Clinic, Peshawar Institute of Medical Sciences, Peshawar after ethical approval from the Institutional Ethical Committee of Institute of Pathology and Diagnostic Medicine, Khyber Medical University, Peshawar, Pakistan (ref: #KMU/IPDM/IEC/2024/27; dated: 12.12.2024).

Informed Consent: Informed consent was taken from participants or their parents/guardians.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: N.S., M.I.K., G.F.R., Concept: A.H., G.F.R., Design: K.S., A.H., G.F.R., Data Collection or Processing: K.S., N.S., G.F.R., Analysis or Interpretation: A.H., A.J.M., Q.A., M.I.K., Literature Search: K.S., A.H., A.J.M., Q.A., N.S., G.F.R., Writing: K.S., A.H., A.J.M., Q.A., N.S., M.I.K., G.F.R.

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Does Hypermobility Syndrome Affect Bone Density?

Hipermobilite Sendromu Kemik Yoğunluğunu Etkiler mi?

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Abstract

Objective: This study aimed to examine whether benign joint hypermobility syndrome (BJHS) affects bone mineral density (BMD).

Materials and Methods: A cross-sectional controlled design was used. Seventy-two participants were enrolled: 36 patients diagnosed with BJHS (group 1) and 36 healthy individuals (group 2). Participants aged ≥18 years were included. BJHS was diagnosed according to Beighton criteria with a score ≥4. Individuals with secondary osteoporosis, inflammatory rheumatic disease, systemic illness, pregnancy, liver or kidney failure, spinal or hip fractures, metal implants, or the use of medications affecting bone metabolism were excluded. BMD of the lumbar spine and femur was measured by dual-energy X-ray absorptiometry and reported as absolute values and T and Z-scores.

Results: Group 1 and group 2 had mean ages of 29.74±7.97 and 32.02±7.73 years, and mean body mass index (BMI) values of 23.51±2.84 and 24.76±3.17, respectively. No significant differences were found between groups regarding age, sex, BMI, or biochemical parameters. All T and Z-scores were significantly lower in BJHS patients compared with healthy controls ($p<0.05$).

Conclusion: Patients with BJHS demonstrated reduced BMD, suggesting that hypermobility may negatively affect bone structure. Individuals with BJHS should be assessed for osteopenia or osteoporosis as part of routine evaluation.

Keywords: Joint hypermobility, benign joint hypermobility syndrome, bone density, dual-energy X-ray absorptiometry

Öz

Amaç: Bu çalışmanın amacı, benign eklem hipermobilite sendromunun (BJHS) kemik mineral yoğunluğunu (KMY) etkileyip etkilemediğini incelemektir.

Gereç ve Yöntem: Çalışma kesitsel kontrollü tasarımda yürütüldü. Toplam 72 katılımcı değerlendirildi: BJHS tanısı alan 36 hasta (grup 1) ve 36 sağlıklı birey (grup 2). Çalışmaya ≥18 yaş bireyler dahil edildi. BJHS tanısı, Beighton kriterlerine göre ≥4 puan ile doğrulandı. Sekonder osteoporoz, enflamatuvar romatizmal hastalık, sistemik hastalık, gebelik, karaciğer veya böbrek yetmezliği, omurga veya kalça kırığı öyküsü, metal implant varlığı ve kemik metabolizmasını etkileyen ilaç kullanımı dışlama kriterlerini oluşturdu. Lomber omurga ve femur KMY ölçümleri çift enerjili X-ışını absorbsiyometrisi ile yapıldı ve mutlak değerler ile T ve Z-skorları olarak raporlandı.

Bulgular: Grup 1 ve grup 2'nin sırasıyla ortalama yaşları 29,74±7,97 ve 32,02±7,73 yıl, vücut kitle indeksi (VKİ) değerleri 23,51±2,84 ve 24,76±3,17 idi. Yaş, cinsiyet, VKİ ve biyokimyasal parametreler açısından gruplar arasında anlamlı fark saptanmadı. Tüm T ve Z-skorlarının BJHS grubunda sağlıklı kontrollere kıyasla anlamlı düzeyde daha düşük olduğu belirlendi ($p<0,05$).

Sonuç: BJHS'li hastalarda KMY'nin azalmış olması, hipermobilitenin kemik yapısını olumsuz etkileyebileceğini düşündürmektedir. Bu nedenle BJHS'li bireylerin rutin değerlendirme kapsamında osteopeni veya osteoporoz açısından taranması önerilir.

Anahtar kelimeler: Eklem hipermobilitesi, benign eklem hipermobilite sendromu, kemik yoğunluğu, çift enerjili X-ışını absorbsiyometrisi

Introduction

Joint hypermobility is defined as the ability of a joint to move "beyond normal limits along physiological axes" (1). Benign joint hypermobility syndrome (BJHS) is characterized by an increase in general joint laxity, defined as joints having a range of motion above normal without any diagnosis of systemic rheumatological disease. The prevalence of BJHS varies according to gender and age, being more common in young women and decreasing in frequency with age. Although the pathophysiology of BJHS is not fully understood, it is considered a systemic abnormality of collagen (2,3).

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It is reported that proprioception is decreased in patients with BJHS, making joints more susceptible to trauma (4-6). The increase in joint laxity and decrease in proprioception in BJHS lead to balance disorders and increased risk of falling in patients (7). Clinical findings in BJHS are characterized by chronic pain, fatigue, and decreased physical activities. These clinical findings cause patients to maintain a sedentary lifestyle, leading to a reduction in load on bones and resulting in secondary deterioration of bone parameters (8-12). Additionally, the decrease in tendon stiffness of patients leads to a reduction in muscle strength and force transmission, creating a negative effect on bone structure (13,14). BJHS increases the risk of fractures in patients due to both the negative effects of BJHS on bone structure and the increased risk of falling. Therefore, it is important to evaluate the bone structure of patients with BJHS (15).

Studies evaluating the bone structure of BJHS patients have reported decreased bone mineral density (BMD), while some recent studies have reported no change in BMD (16-21). While previous studies have primarily evaluated dual energy X-ray absorptiometry (DEXA) derived Z-scores from either lumbar or femoral regions, often focusing on premenopausal or postmenopausal women and including patients with hypermobile Ehlers-Danlos syndrome (hEDS), the present study adopts a broader methodological approach (2,16,17,19). By including adults aged 18 years and older of both sexes diagnosed with BJHS, assessing both lumbar and femoral regions, and evaluating both T-scores and Z-scores, this study aims to provide more comprehensive and generalizable evidence regarding the relationship between joint hypermobility and BMD.

The aim of our study is to investigate the relationship between BJHS and BMD.

Materials and Methods

Study Participants and Design

This cross-sectional controlled study was reviewed and approved by the Clinical Research Ethics Committee of Balıkesir University (decision number: 2024/39, date: 26.04.2024), and written informed consent was obtained from all participants. The study was also conducted in accordance with the principles of the Declaration of Helsinki.

A total of 72 participants were included in the study, comprising 36 patients diagnosed with BJHS at the outpatient clinic of Physical Medicine and Rehabilitation at Balıkesir University Health Practice and Research Hospital, and 36 healthy participants to form the control group. In the study, patients diagnosed with BJHS were designated as group 1, while the control group consisting of healthy participants was designated as group 2. The study included individuals aged 18 and over, patients diagnosed with BJHS according to Beighton diagnostic criteria, patients with a Beighton score ≥4, and healthy participants without any known disease. All female participants were premenopausal, and no patients with natural or surgically induced menopause were included. Those who were pregnant, had secondary osteoporosis, had inflammatory rheumatic diseases, had fractures or metal implants in the back, waist and hip region, had liver and kidney failure, had systemic diseases and were using drugs that affected bone metabolism were excluded from the study.

The Beighton criteria (a 0-9 point scale) were used to assess the hypermobility of the participants included in the study (22). The Beighton criteria consist of five maneuvers: passive dorsiflexion of the fifth finger ≥90°, passive apposition of the thumb to the forearm, hyperextension of the elbows and knees ≥10°, and touching the floor with the palmar surface of the hand while keeping the knees fully extended. The first 4 maneuvers are evaluated for both extremities and each is scored as 0 or 1 point. According to the Beighton score, the total score ranges from 0 (inability to perform any of these maneuvers) to 9 (ability to perform all of these maneuvers). The Beighton score was calculated based on the results of the clinical examination of these maneuvers, and patients with a total score of ≥4 were included in the study.

Interventions

Sociodemographic characteristics, age, gender, occupation, marital status and systemic diseases of the participants who met the study inclusion criteria were recorded. Participants' body weights were measured using an MC-780 Tanita™ device (Tokyo, Japan) with a capacity of 150 kg and sensitivity of 0.1 kg, while height was measured using a non-stretch measuring tape in accordance with the method. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2).

BMD measurements were obtained at the lumbar spine (L1-L4 and L2-L4) and proximal femur (femoral neck, trochanter, and Ward's triangle) using DEXA device. BMD measurements were performed at the Department of Radiology, Balıkesir University Faculty of Medicine, using a GE Healthcare Lunar DXA device (General Electric Company, Coventry, United Kingdom). To minimize inter-device and inter-operator variability, all scans were performed at a single center using the same DEXA device by the same experienced technician. The results were reported as absolute BMDs (in grams per square centimeter) and as T and Z-scores. BMD classifications were based on World Health Organization criteria, whereby T-scores—reflecting the number of standard deviations from the mean BMD of a young adult reference population—were defined as normal (≥-1.0), osteopenic (between -1.0 and -2.5), or osteoporotic (≤-2.5) (23). Demographic information, physical examinations, evaluation of test results, and data collection for all participants were conducted by the same physical medicine and rehabilitation specialist. BMD measurements, aspartate aminotransferase, alanine aminotransferase, creatinine, urea, calcium, phosphorus, alkaline phosphatase, thyroid-stimulating hormone, free thyroxine, parathyroid hormone, and cholecalciferol values were recorded from participants' files.

Statistical Analysis

Data analysis was conducted using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics for continuous variables were presented as mean, standard deviation, minimum, median, and maximum values. The normality of data distribution was evaluated using analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Group comparisons were performed using the independent samples t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. As Beighton scores did not show a normal distribution, the association between Beighton scores and BMD T-scores was assessed using Spearman's rank correlation analysis. All tests were two-tailed, and statistical significance was set at $p<0.05$. The required sample size was calculated as 72 participants based on an effect size of 0.60, a type I error rate (α) of 0.05, and a statistical power (1-β) of 80%. Sample size estimation was performed using G*Power software version 3.1.9.7 (24).

Results

The gender distribution of participants in the study was 31 females and 5 males in group 1, 32 females and 4 males in group 2. The mean age was 29.74±7.97 in group 1 and 32.02±7.73 in group 2, while the mean BMI was 23.51±2.84 in group 1 and 24.76±3.17 in group 2 (Table 1). In the study, the mean serum cholecalciferol (ng/mL) values were 19.53±6.78 in group 1 and 20.92±7.87 in group 2. Blood biochemistry parameters including calcium, phosphorus, alkaline phosphatase, TSH, free T4, and parathormone values were within normal ranges for both groups. There were no statistically significant differences between the groups in terms of age, gender, BMI, and blood biochemistry parameter values ($p>0.05$) (Table 1).

In the study, one patient in group 1 diagnosed with BJHS exhibited BMD values within the osteoporotic range, whereas no participants in the control group met the criteria for osteoporosis. Low bone density was defined as the presence of osteopenia or osteoporosis in at least two skeletal regions based on T-score assessments. According to this definition, 16 patients (~45%) in group 1 were classified as having low bone density, compared with 4 patients (~12%) in the control group. This difference between groups was statistically significant ($p<0.05$) (Table 1). All BMD t and z scores obtained by DEXA from both the lumbar spine and femoral regions were significantly lower in patients with BJHS in group 1 compared with the control group ($p<0.05$) (Table 2).

In the BJHS group (n=36), the Beighton score demonstrated statistically significant negative correlations with BMD T-scores across multiple skeletal sites. Specifically, moderate inverse correlations were identified at the total femur (Spearman's ρ=-0.493, p=0.002), femoral neck (ρ=-0.539, p=0.001), lumbar spine L2-L4 (ρ=-0.528, p=0.001), and total lumbar spine (ρ=-0.492, p=0.002) (Table 3).

Discussion

In our study, we found that BMD decreased in both the lumbar spine and femoral regions of patients with BJHS. While studies evaluating BMD in BJHS patients have reported decreased BMD in patients with hypermobility, recent results also indicate no change in BMD (2,8,12,16,17,19).

Table 1. Subjects' characteristics

	Hypermobility group (n=36)	Control group (n=36)	p-value
Gender (female/male)	31/5	32/4	
Age (year)	29.74±7.97	32.02±7.73	0.228
Body height (m)	1.63±0.07	1.64±0.08	0.928
Body weight (kg)	64.61±9.44	66.82±10.54	0.411
BMI (kg/m^2)	23.51±2.84	24.76±3.17	0.603
Calcium (mg/dL)	9.50±0.27	9.51±0.35	0.821
Phosphorus (mg/dL)	3.59±0.48	3.60±0.47	0.941
Alkaline phosphatase (IU/L)	72.37±22.64	64.20±20.95	0.122
TSH (mIU/L)	1.85±0.81	1.78±0.83	0.705
Thyroxine (T4), free (ng/dL)	2.90±3.49	2.35±1.96	0.226
PTH (pg/mL)	59.03±36.45	63.09±25.20	0.590
Cholecalciferol (ng/mL)	19.53±6.78	20.92±7.87	0.432
Osteopenic patients (n)	16	4	
Osteoporotic patients (n)	1	0	
Patients with low bone mass (n)	17	4	

BMI: Body mass index, TSH: Thyroid-stimulating hormone, PTH: Parathormone, m: Meter, kg: Kilogram, ng: Nanogram, pg: Picogram, L: Liter, dL: Deciliter, mL: Milliliter, IU: International unit, mIU: National-international unit, *: p<0.05; significant difference between groups

Table 2. BMD parameters in both groups

BMD	Hypermobility group (n= 36)	Control group (n= 36)	p-value
Lumbar L2-L4 t	-0.75±0.80	0.13±0.97	<0.001*
Lumbar L2-L4 z	-0.72±0.79	0.11±0.95	<0.001*
Lumbar L1-L4 t	-0.74±0.76	0.13±0.95	<0.001*
Lumbar L1-L4 z	-0.71±0.75	0.10±0.93	<0.001*
Femoral neck t	-0.64±0.87	0.09±1.11	0.003*
Femoral neck z	-0.62±0.79	0.21±1.12	0.001*
Femoral total t	-0.70±0.80	0.15±1.09	<0.001*
Femoral total z	-0.66±0.74	0.24±1.04	<0.001*

BMD: Bone mineral density, *: p<0.05; significant difference between groups

Table 3. Spearman correlation between Beighton score and BMD T-scores in the BJHS group

BMD parameter (T-score)	Spearman's ρ	p-value
Femoral neck t	-0.539	0.001
Femoral total t	-0.493	0.002
Lumbar L2-L4 t	-0.528	0.001
Lumbar total (L1-L4) t	-0.492	0.002

BMD: Bone mineral density. Values are Spearman's rank correlation coefficients (two-tailed), p<0.05 considered statistically significant

Mishra et al. (19) evaluated BMD in their study investigating the extra-articular features of BJHS. The study was conducted with 58 BJHS patients and a control group of 30 healthy participants matched for age and gender. BMD measurements were taken from the lumbar spine (L1-L4) and femoral region using DEXA, and Z-scores were recorded. The study results showed that BMD decreased in both the lumbar spine and femoral regions of BJHS patients, although not at a statistically significant level. Gulbahar et al. (2) evaluated BMD in premenopausal women with BJHS in their study. The study included a total of 48 participants: 25 patients diagnosed with BJHS and 23 healthy controls matched for age and gender. Participants' BMD measurements were obtained from the lumbar spine (L1-L4) and femoral region (neck, trochanter, and Ward's triangle) using DEXA, and T and Z-scores were recorded. Their study found that both lumbar spine and femoral region T and Z-scores were lower in the BJHS group compared to the control group (p<0.05). Additionally, the risk of bone mass reduction in the hypermobility group was found to increase by 1.8 times. Our study is methodologically different from these studies because Mishra et al. (19) evaluated only Z-scores in BMD measurement and Gulbahar et al. (2) selected premenopausal women. However, despite these differences, the finding of decreased BMD values in the lumbar spine and femur region in individuals with hypermobility in both studies supports our results.

Dolan et al. (17) investigated whether hypermobility was associated with a tendency towards osteoporosis in the normally aging population. The study included 716 postmenopausal women aged 53 to 72 years. In the hypermobility assessment, 79 subjects had a Beighton score >1/9, and 82 had a Contompasis score >22. Only a participant had BJHS (Beighton score 4/9). Therefore, the study used the Contompasis score and considered subjects with localized hypermobility as hypermobile. In the hypermobile group, total hip BMD was found to be 3% higher compared to controls. However, it was noted that the physical activity scores of the hypermobile group were also higher than the controls. Dolan et al.'s (17) study differs from ours in that it was conducted on postmenopausal women over 50 years old and there were differences in physical activity levels. Contrary to our study results, the higher hip BMD values of participants with hypermobility in the study by Dolan et al. (17) may be due to the higher physical activity levels of hypermobile subjects.

In 2017, new diagnostic criteria for joint hypermobility were developed by the Ehlers-Danlos Society. According to these criteria, patients with hypermobility were classified as hEDS or hypermobility spectrum disorders (HSD) (1,12,25). In this classification, BJHS is included within the HSD classification. However, the term BJHS is still widely used and generally indicates the presence of hypermobility (21).

Recent studies on hypermobility have been conducted on patients diagnosed with hEDS and HSD. In these studies, DiFrancisco-Donoghue et al. (16) found that Z-scores obtained by DEXA from the lumbar spine and both femur regions of patients with hypermobility were statistically significantly lower compared to the control group (p<0.05). In the study by Coussens et al. (8,12), no significant difference was found between groups in BMDmeasurement values obtained by DEXA in patients with hypermobility. However, in the results obtained by peripheral quantitative computed tomography (pQCT), it was found that patients with hypermobility had decreased cortical bone mineral content and thickness, decreased trabecular bone mass and density, and a higher fracture prevalence (p<0.05)

(8,12). Unlike our study, these studies were conducted on female participants. The detection of decreased BMD values in DiFrancisco-Donoghue et al.'s (16) study is similar to our study results. On the other hand, the lack of significant change in BMD measurement values in Coussens et al.'s (8,12) study does not support our study results. Unlike our study, in Coussens et al.'s (8,12) studies, DEXA measurements were obtained from different body regions, and area BMD measurement scores were used instead of T or Z-scores for bone density measurement. Therefore, the fact that the results of the studies by Coussens et al. (8,12) and our study do not support each other may be due to differences in methodological methods. Nevertheless, the results of these studies show that the bone structure of patients with hypermobility is negatively affected.

Study Limitations

This study has certain limitations. Physical activity level, daily calcium and vitamin D intake, and lifestyle-related factors known to affect BMD were not systematically assessed, which may have resulted in residual confounding. In addition, reproductive and hormonal variables such as age at menarche, pregnancy and breastfeeding history, as well as smoking, alcohol consumption, prior fracture history, and family history of osteoporosis were not evaluated. Although sex distribution differed slightly between groups, the difference was not statistically significant, and no sex-stratified analyses were performed. These limitations should be considered when interpreting the findings. Future studies with larger sample sizes and comprehensive assessment of confounding factors are warranted.

Conclusion

In conclusion, the findings of this study suggest that bone structure may be adversely affected in patients with joint hypermobility, as reflected by lower BMD values. Individuals with BJHS appear to be at increased risk for reduced bone mass, potentially predisposing them to osteopenia, osteoporosis, and fracture. Accordingly, assessment of BMD using DEXA, given its clinical accessibility and cost-effectiveness, may be considered a useful tool for the evaluation and follow-up of bone health in this patient population.

Ethics

Ethics Committee Approval: This cross-sectional controlled study was reviewed and approved by the Clinical Research Ethics Committee of Balıkesir University (decision number: 2024/39, date: 26.04.2024).

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

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

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

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Kalçanın Geçici Osteoporozu ve Ankilozan Spondilit Birlikteliği: Bir Olgu Sunumu

Transient Osteoporosis of the Hip and Ankylosing Spondylitis: A Case Report

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Öz

Kalçanın geçici osteoporozu (KGO) nadir görülen, etiyolojisi bilinmeyen, kendini sınırlayan bir hastalıktır. Primer kemik iliği ödem sendromları içinde yer alan KGO şiddetli ağrı, antaljik yürüyüş, eklem hareket açıklığında kısıtlılık ve yük aktarımında zorlanma şikayetlerine neden olabilir. Avasküler nekroz, stres fraktürleri, enfeksiyon ayırıcı tanıda yer alır. KGO ve ankilozan spondilit birlikteliği, klinik tablo ve kemik iliği ödemi, entezit, erken artrit evresi, osteonekroz veya steril osteomiyelit gibi spondiloartropati ile ilişkili çeşitli nedenlere bağlanabileceğinden tanısal zorluklara yol açabilir. Aktif sakroileit ve entezit bulgularının eşlik ettiği diffüz kalça kemik iliği ödemi olguları sınırlı sayıda bildirilmiştir. Bu olgu sunumu, genç erişkinlerde spondiloartropati varlığının KGO tanısını dışlamadığını vurgulamayı amaçlamaktadır.

Anahtar kelimeler: Kalça ağrısı, spondiloartropati, geçici osteoporoz, kemik iliği ödemi

Abstract

Transient osteoporosis of the hip (THO) is a rare, self-limiting disease of unknown etiology. THO, a primary bone marrow edema syndrome, can cause severe pain, antalgic gait, limited range of motion, and difficulty with weight bearing. Avascular necrosis, stress fractures, and infection are included in the differential diagnosis. The coexistence of THO and ankylosing spondylitis can present diagnostic challenges because the clinical presentation and various causes associated with spondyloarthropathy, such as bone marrow edema, enthesitis, early arthritis, osteonecrosis, or sterile osteomyelitis, can be attributed to the underlying cause. This case report aims to present the association of THO and spondyloarthropathy.

Keywords: Hip pain, spondyloarthropathy, transient osteoporosis, bone marrow edema

Giriş

Kalça ağrısı toplumda sık görülen ve yaş grupları ile etiyolojiye göre görülme sıklığı değişkenlik gösteren bir klinik durumdur. Ağrı, kalça eklemini oluşturan yapılardan kaynaklanabileceği gibi, bu bölgedeki derin yapılardan yansıyan ağrı şeklinde de ortaya çıkabilir. Ayırıcı tanıda mekanik, enflamatuvar, metabolik ve travmatik nedenler birlikte değerlendirilmelidir. Radyografik sakroileit, ankilozan spondilitin (AS) ayırt edici özelliklerinden biri olup, akut sakroileitin saptanması AS'nin erken tanısı açısından kritik öneme sahiptir (1,2). Kalçanın geçici osteoporozu (KGO) ise her iki cinsiyette görülebilen, nadir ve kendini sınırlayan bir klinik tablodur. Gebelikte özellikle üçüncü trimester ve emzirme döneminde daha sık izlenmekle birlikte, gebelikle ilişkili patofizyolojik mekanizmalar henüz net olarak ortaya konmamıştır. Alkol kullanımı, kortikosteroid tedavisi, hipotiroidizm, D vitamini eksikliği ve hipofosfotazya etiyolojide yer alan diğer faktörler arasındadır (3). KGO sıklıkla gözden kaçabilen bir durum olup, manyetik rezonans görüntüleme (MRG) erken tanı ve ayırıcı tanıda altın standart görüntüleme yöntemi olarak kabul edilmektedir. Kronik inflamatuvar hastalıklarda, özellikle spondiloartropatilerde, sitokin aracılı enflamasyon, immobilizasyon ve lokal dolaşım bozukluklarının kemik metabolizması üzerinde olumsuz etkiler oluşturarak kemik iliği ödemi gelişimine zemin hazırlayabilir. KGO ve AS'nin tek başına nadir olmadığı bilinmekle birlikte, bu iki tablonun birlikteliğinde kalça MRG'sinde kemik iliği ödemi ve eşlik eden inflamatuvar aksiyel bulgular saptanan hastalarda,

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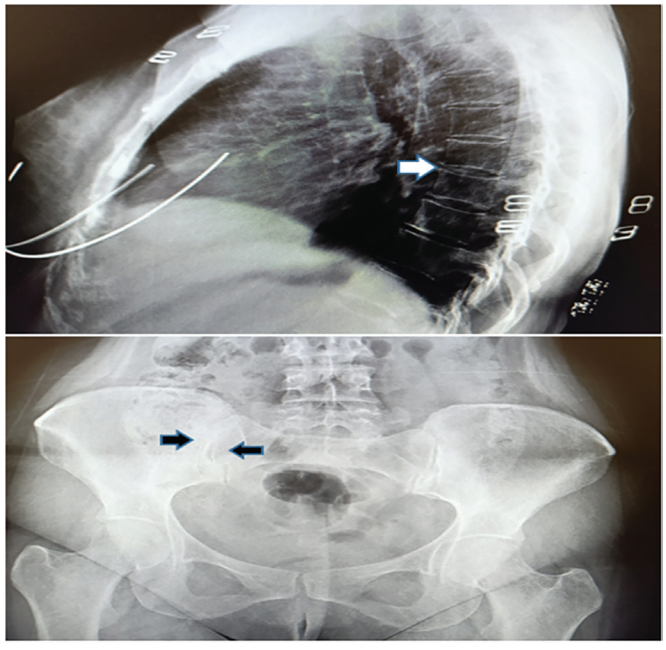
bulgular sıklıkla osteonekroz veya spondiloartropatiye bağlı tutulum şeklinde yorumlanabilmekte ve KGO tanısı gözden kaçabilmektedir. Bu olgu sunumunda, kalça ağrısı ile başvuran bir hastada AS ile osteonekroz ve KGO ayırıcı tanısındaki zorlukların vurgulanması amaçlanmaktadır.

Olgu Sunumu

Otuz üç yaşında kadın hasta, sol kalça ağrısı şikayetiyle polikliniğimize başvurdu. Hasta öyküsünde bu yakınmasının yaklaşık 3 ay önce başladığını, sürekli olduğunu, gece uykudan uyandırdığını, medikal tedaviyle gerilemediğini belirtti. Bu şikayetlerle dış merkezde fizyoterapiye alındığını, şikayetlerinin giderek arttığını, ağrının yürüme ve yük verme ile şiddetlendiğini ifade etti. Başvuru sırasında fizyoterapisinin devam ettiği, kalça eklemine minör ozon tedavisinin yapıldığı ve fayda görmediği öğrenildi. Ev hanımı olan hastanın herhangi bir travma öyküsü ve soygeçmişinde özellik yoktu. Özgeçmişinde ek hastalık ve sürekli ilaç kullanım öyküsü yoktu. Her iki dizde meniskopati nedeni ile operasyon öyküsü vardı. Sigara kullanan (3 paket/yıl) hastanın alkol kullanımı yoktu. On üç yıl önce bir doğum öyküsü olan hastanın romatolojik sorgulamasında bir abortus öyküsü ve aralıklı inflamatuvar özellikte bel ağrısı dışında ek bulgu yoktu. Hastanın genel sistem muayenesi normaldi. Kas iskelet sistemi muayenesinde kas gücü bilateral alt ve üst ekstremitede 5/5 idi. Sol kalça abdüksiyonu 50 derece ve diğer eklem hareket açıklığı tamdı. FABER testi sol tarafta pozitifti. Eklemlerinde artrit ile uyumlu bulgu yoktu. Hastanın mevcut şikayetlerine yönelik yapılan laboratuvar tetkiklerinde lökosit sayısı 6,62x10³/mm³, trombosit sayısı 374x10³/mm³, C-reaktif protein: 1,10 mg/L (0-0,5 mg/L), eritrosit sedimantasyon hızı: 12 mm/saat (0-25 mm/saat), romatoid faktör düzeyi 8,03 IU/mL, antisiklik sitrulin peptid (<7 U/mL), ENA profili (antiSM-RNP), HLA-B27, hepatit markerları ve *Brusella* negatifti. Hastanın sakroiliyak eklem ve torakolomber direkt radyografisinde torakal vertebralarda sindesmofit, sakroiliyak eklemlerde düzensizlik ve skleroz artışı izlendi (Şekil 1). Hastanın polikliniğimize başvurusundan önce yapılmış kalça ve sol femura ait MRG'de koksafemoral eklem bileşkesinde minimal sıvı artışı, femur baş ve boyun bölgesinde kemik iliği ödemi mevcuttu. Spondiloartropati ve avasküler nekroz (AVN) ön tanıları ile kalça ve sakroiliyak eklem MRG yapıldı. Kontrastlı sakroiliyak MRG incelemesinde sakroiliyak eklem orta zon anterior kesime komşu sakral yüzde sıvı duyarlı sekanslarda fokal subkortikal sinyal artışı ve kontrastlanma fokal aktif sakroileit ile uyumlu idi (Şekil 2). Kontrastlı kalça MRG incelemesinde sol femur baş-boyun kesimi ve intertrokanterik mesafede T1'de heterojen sinyal kaybı, sıvı duyarlı sekanslarda heterojen sinyal artışı ve kontrastlanma izlendi. Bulgular sol kalçada KGO ile uyumlu idi (Şekil 3). Hastanın kemik mineral yoğunluğu ölçümünde, yaşa göre değerlendirme amacıyla Z-skorları dikkate alındı. L1-L4 bölgesinde Z-skoru -1,0; femur boynunda -1,2 ve total femurda -1,4 olarak saptandı. Hastanın medikal tedavisi indometazin 3x1, 1000 mg elementer kalsiyum, 880 IU vitamin D3 ve sülfasalazin 500 mg 2x2 şeklinde düzenlendi. İstirahat ve bir çift kanedyen kullanımıyla kalçaya yük vermeme önerildi. Polikliniğimizde takip edilmesi planlanan hasta takiplerine gelmedi. Üç ay sonra bilateral göğüs bölgesinde ele gelen şişlik ve 2 ve 3. kostosternal bileşkede ağrı şikayeti ile tekrar başvurduğunda indometazin ve sülfasalazin tedavilerine devam etmediği görüldü. Konservatif tedavi ile ortopedi tarafından takip edildiği öğrenildi. Hastanın 3. ay kontrolünde sol kalça eklem hareket açıklığı tam ve ağrısızdı. Sternum/sternoklavikular MRG incelemesinde 1 ve 2. sternokostal eklem düzeyinde sternumda, komşu sternoklavikular eklem yüzlerine uzanan T1AG'de hipointens, T2AG'de hiperintens patolojik

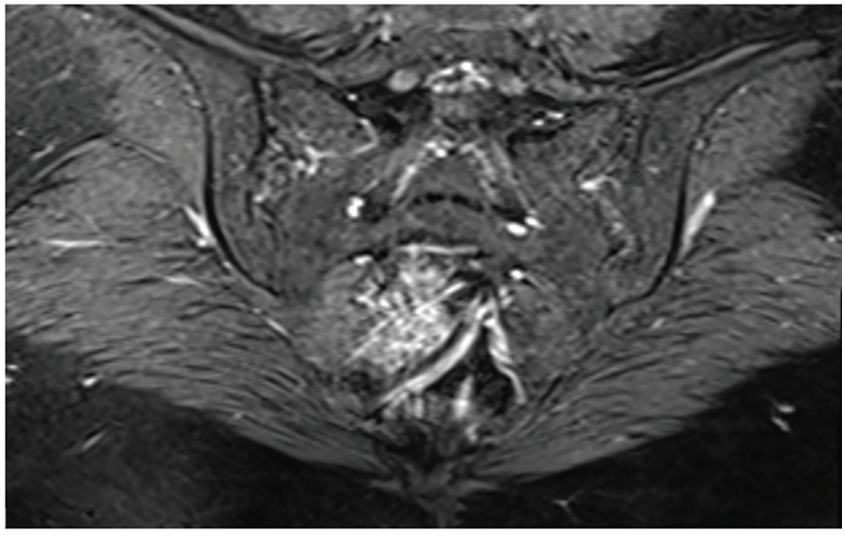


Şekil 1. Sakroiliyak eklem ve torakolomber radyografi bulguları

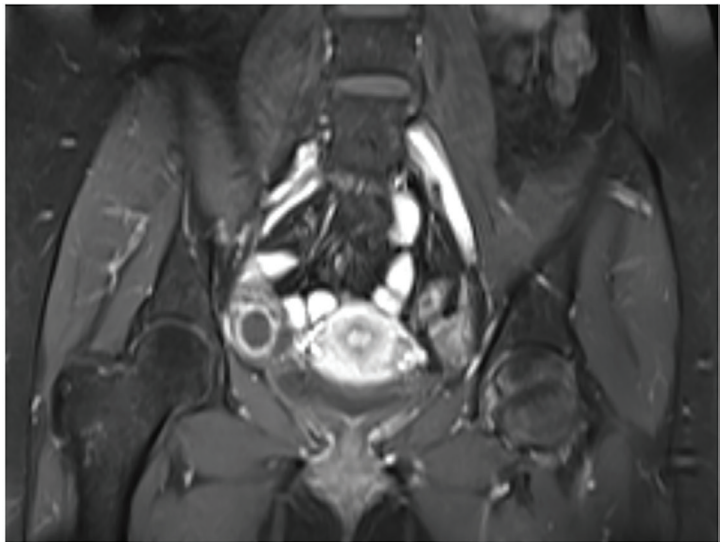
meduller sinyal değişikliği; manubriosternal eklemin karşılıklı yüzlerinde düzensizlik ve patolojik kemik iliği reaksiyonu vardı (Şekil 4). Meme ultrasonografisi ve toraks tomografisi normaldi. Bulgular entezit ile uyumlu değerlendirildi ve hastaya sülfasalazin ve indometazin tedavisi tekrar başlandı. Artrit, entezit, enflamatuvar bel ve kalça ağrısı olmayan hastanın romatolojik takip ve tedavisi devam etmektedir.

Tartışma

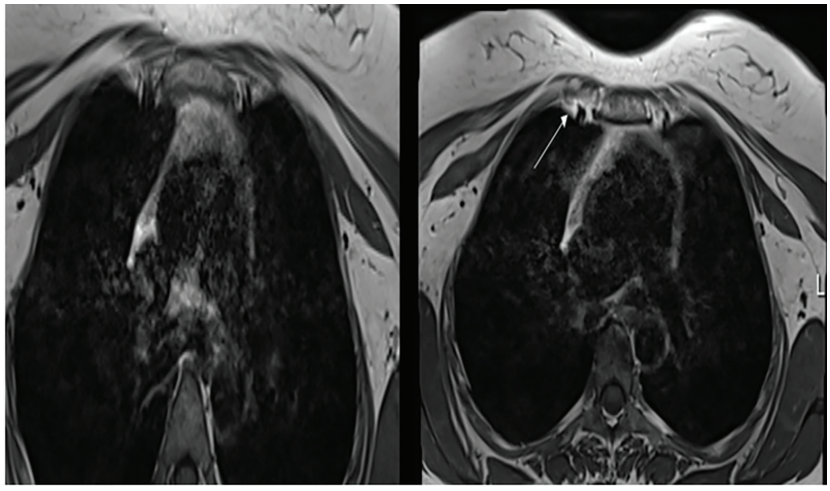
KGO, çoğunlukla orta yaş erkeklerde ve gebeliğin üçüncü trimesterinde kadınlarda görülen kendini sınırlayan nadir bir kemik iliği ödem sendromudur. Klinik olarak ani başlayan ve birkaç ay içinde giderek artan kalça ağrısı, yük verme ile şiddetlenme ve antaljik yürüme ile seyreder. Radyografiler sıklıkla normal iken MRG ile femur baş ve boynunda diffüz kemik iliği ödemi saptanması tanı için belirleyicidir (4). Primer kemik iliği ödem sendromları içinde yer alan KGO etiyolojisi tam olarak açıklanamamış olmakla birlikte; lokal iskemik olaylar, mekanik aşırı yüklenme, metabolik ve endokrin bozukluklar, genetik yatkınlık, venöz dolaşım bozukluğu, C vitamin eksikliği ve düşük kemik mineral yoğunluğunun rol oynayabileceği bildirilmektedir. MRG bulguları, geçici osteoporoz ile osteonekroz ayrımında kritik öneme sahiptir. KGO'de iyi prognozla tedavisi mümkünken, ayırıcı tanıda yer alan AVN'nin seyri progresiftir. Geçici osteoporozda T1 ağırlıklı görüntülerde femur baş ve boynunda diffüz veya yamalı sinyal kaybı, T2 yağ baskılı/STIR sekanslarda ise subkondral bölgeyi de içeren yaygın hiperintens kemik iliği ödemi izlenir; subkondral kemik plağı genellikle korunmuştur ve femur başında çökme saptanmaz. Buna karşılık AVN'de



Şekil 2. MRG'de sakroiliyak eklemin sakral yüzünde aktif sakroilit ile uyumlu fokal kemik iliği ödemi
MRG: Manyetik rezonans görüntüleme



Şekil 3. T2 yağ baskılı MRG kesitinde sol femur başı ve boynunda transient osteoporoz ile uyumlu artmış sinyal intensitesi izlenmektedir
MRG: Manyetik rezonans görüntüleme



Şekil 4. Birinci ve ikinci sternkostal eklem düzeyinde sternumda T1'de hipointens, T2'de hiperintens medüller sinyal değişikliği ve manubriosternal eklem yüzlerinde düzensizlik

subkondral bölgede serpiginöz sınır çizen, çift çizgi bulgusu ile karakterize sınırlı lezyonlar ve ilerleyen olgularda femur başında çökme ön plandadır. Bu olguda femur baş-boyun ve intertrokanterik bölgeye uzanan yaygın kemik iliği ödemi, eklem yüzeyinde çökme olmaması ve izlemler sırasında radyolojik geri dönüş osteonekrozdan çok KGO ile uyumlu bulunmuştur. Ayrıca olgumuzda ağrının istirahatle azalmadığı; kortikosteroid kullanımı, alkolizm, travma veya hemoglobinopatiler gibi AVN gelişimine predispoze durumların bulunmaması klinik bulguların sadece KGO ile açıklanamayacağını düşündürmüştür.

Spondiloartropatilerde aksiyel iskelet tutulumu ile birlikte kalça eklem tutulumu sık görülmekte olup, kalça ağrısının yalnızca dejeneratif veya mekanik nedenlere bağlanması tanıda gecikmeye yol açabilmektedir. Ankilozan spondilit ve aksiyel spondiloartritte sakroiliyak eklemlerdeki aktif enflamasyonun erken döneminde konvansiyonel radyografiler çoğu zaman yetersiz kalmakta, şüpheli olgularda sakroiliyak eklem MRG erken tanı için önemlidir (5). MRG'de kemik iliği ödemi aktif sakroileitin en önemli bulgularından biri olup erozyon, yağlanma ve skleroz gibi yapısal değişikliklerle birlikte değerlendirilmesi önerilmektedir. Spondiloartropati tanısında HLA-B27 pozitifliği, klinik bulgular ve görüntüleme yöntemleri önemlidir. ASAS sınıflama kriterleri, kronik bel ağrısı olan hastalarda radyografik bulgu olsun ya da olmasın MRG ile gösterilen sakroileit ve beraberindeki SpA özelliklerine dayanarak aksiyel spondiloartriti sınıflamayı mümkün kılmıştır. Bizim olgumuzda HLA-B27 negatif olmasına rağmen radyografik sakroileit, sakroiliyak MRG'de aktif sakroilit bulguları ve takipte sternokostal bölgede entezit gelişimi, spondiloartropati tanısını desteklemektedir. Bu durum, HLA-B27 negatif olgularda da klinik, radyolojik ve MRG bulgularının birlikte değerlendirilmesinin önemini ortaya koymaktadır (6). Spondiloartropatilerde hem kronik enflamasyon hem de immobilizasyon, osteoporoz gelişimini kolaylaştırmakta ve kemik iliğinde ödem gelişimine zemin hazırlayabilmektedir. Buna karşın literatürde KGO ile spondiloartropatinin eş zamanlı olduğu olgu sayısı oldukça sınırlıdır; mevcut yayınlar çoğunlukla izole KGO veya gebelikle ilişkili kalça ağrısına odaklanmaktadır. Olgumuzda hem radyografik ve MRG ile gösterilmiş sakroileit hem de femur baş-boyun ve intertrokanterik bölgede KGO'ya özgü yaygın kemik iliği ödemi bulunması, klinik tabloyu karmaşıklaştırmış ve başlangıçta ayırıcı tanıyı güçleştirmiştir.

KGO'nun doğal seyri genellikle 3-6 ay içinde spontan düzelme yönünde olmakla birlikte, yoğun ağrı ve belirgin fonksiyon kaybı hastaların yaşam kalitesini ciddi şekilde bozabilmektedir. Temel tedavi yaklaşımı; etkilenen ekstremitenin yükten korunması, analjezik/non-steroidal anti-inflamatuvar ilaç (NSAİİ) kullanımı ile ağrı ve enflamasyonun kontrolü ile kalsiyum-D vitamini desteğidir. Son yıllarda kemik iliği ödem sendromlarında bifosfonatların, özellikle tek doz intravenöz zoledronik asitin, ağrıyı daha hızlı gerilettiği ve MRG'deki ödemin çözülmesini hızlandırdığı bildirilmiştir (7). Bu olgu, aktif aksiyel spondiloartrit bulguları olan genç erişkinlerde kalça MRG'sinde saptanan diffüz kemik iliği ödeminin, sıklıkla osteonekroz veya inflamatuvar tutulum olarak yorumlanabildiğini; bu durumun KGO tanısının gözden kaçmasına yol açabileceğini göstermektedir. Özellikle subkondral çökme olmaksızın femur baş-boyun ve intertrokanterik bölgeye uzanan diffüz ödem varlığında, spondiloartropati eşlik etse dahi KGO mutlaka ayırıcı tanıda düşünülmelidir. Olgumuzda da NSAİİ ve kalsiyum-D vitamini ile uygulanan konservatif tedavi sonucunda yaklaşık üç aylık izlemde kalça ağrısının gerilemesi ve eklem hareket açıklığının normale dönmesi, literatürde bildirilen kendini sınırlayan seyirle uyumludur. Bununla birlikte, hastanın başlangıçta düzenli klinik ve radyolojik takiplere devam etmemesi ve tedaviye uyumsuzluğu, uzun dönem sonuçların değerlendirilmesini sınırlandıran önemli bir kısıtlılık olarak değerlendirilmelidir.

Sonuç

Kalça ağrısıyla başvuran olgularda, ağrı yalnızca tek bir yapıdan değil, eklemi oluşturan farklı yapılardan kaynaklanabilir. Bu olgu,

kalça ağrısı ile başvuran genç erişkinlerde spondiloartropati varlığının, KGO gibi kemik iliği ödem sendromlarını dışlamadığını; aksine bu iki tablonun eş zamanlı varlığının ayırıcı tanıyı zorlaştırabileceğini göstermektedir. Kalça MRG'sinde diffüz kemik iliği ödemi saptanan ve osteonekroz düşünülen hastalarda, subkondral çökme olmaması, lezyonun femur boynu ve intertrokanterik bölgeye uzanımı ile klinik ve laboratuvar bulguların birlikte değerlendirilmesi durumunda KGO mutlaka akılda tutulmalıdır. Öte yandan inflamatuvar bel ağrısı, entezit veya radyografik sakroileit bulguları olan hastalarda, yalnızca kalça eklemi patolojisine odaklanmak yerine aksiyel spondiloartrit olasılığı da değerlendirilmelidir. Özellikle HLA-B27 negatif olgularda, ayrıntılı anamnez, dikkatli fizik muayene, konvansiyonel radyografi ve MRG'nin birlikte değerlendirilmesi tanı ve tedavi stratejisini belirlemede kritik önem taşımaktadır.

Etik

Hasta Onayı: Olgu raporunun ve eşlik eden görsellerin yayınlanması için yazılı bilgilendirilmiş onam alındı.

Dipnot

Yazarlık Katkıları

Konsept: T.E.S., Dizayn: T.E.S., Veri Toplama veya İşleme: T.E.S., Ö.Y., Analiz veya Yorumlama: T.E.S., Ö.Y., Literatür Arama: T.E.S., Ö.Y., Yazma: T.E.S., Ö.Y.

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Kinesiotaping for Mechanical Stabilization in Slipping Rib Syndrome: A Case Report

Slipping Rib Sendromunda Mekanik Stabilizasyon Amaçlı Kinesiotaping: Olgu Sunumu

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Abstract

Slipping rib syndrome (SRS) is an underrecognized cause of lower anterior chest wall pain resulting from hypermobility of the 8th-10th costal cartilages. Because the condition represents a dynamic instability, conventional imaging is often normal, and the diagnosis is primarily clinical. A 45-year-old woman presented with sharp pain localized to the right 8th-10th costal margin, aggravated by trunk movements. Laboratory and radiologic evaluations were unremarkable, and hepatobiliary causes were excluded. The patient did not respond to oral or topical non-steroidal anti-inflammatory drugs or conventional physical therapy. At follow-up, the hooking maneuver reproduced the pain and demonstrated anterior rib displacement, confirming the clinical diagnosis of SRS. Kinesiotaping was applied to provide mechanical stabilization of the affected rib segment. The patient experienced a rapid reduction in pain, with the VAS score decreasing from 8 to 3 within one week and complete symptom resolution by the third week. A recurrence one year later responded successfully to the same stabilization protocol. This case highlights the diagnostic challenges of imaging-negative SRS and suggests that targeted mechanical stabilization using kinesiotaping may be an effective, reproducible, non-invasive, conservative treatment option prior to invasive interventions.

Keywords: Slipping rib syndrome, anterior chest wall pain, kinesiotaping, rib instability, conservative treatment

Öz

Slipping rib sendromu (SRS), 8.-10. kostal kıkırdakların hipermobilitesine bağlı gelişen ve alt anterior göğüs duvarı ağrısının sıklıkla gözden kaçan bir nedenidir. Bu durum dinamik bir instabiliteyi temsil ettiğinden, konvansiyonel görüntüleme yöntemleri çoğu zaman normaldir ve tanı esas olarak klinik değerlendirmeye dayanır. Kırk beş yaşında bir kadın hasta, gövde hareketleriyle artan ve sağ 8.-10. kostal kenara lokalize keskin ağrı şikaayeti ile başvurdu. Laboratuvar ve radyolojik değerlendirmeleri normaldi ve hepatobiliyer nedenler dışlandı. Hasta oral veya topikal non-steroid anti-enflamatuvar ilaçlara ve konvansiyonel fizik tedavi uygulamalarına yanıt vermedi. İzlem sırasında uygulanan hooking manevrası ağrıyı yeniden oluşturdu ve kostanın anterior yönde yer değiştirdiğini göstererek SRS klinik tanısını doğruladı. Etkilenen kosta segmentinin mekanik stabilizasyonunu sağlamak amacıyla kinesiotaping uygulandı. Hastada hızlı bir ağrı azalması gözlendi; vizüel analog skala skoru bir hafta içinde 8'den 3'e geriledi ve üçüncü haftada hastanın semptomları tamamen düzeldi. Bir yıl sonra gelişen nüks aynı stabilizasyon protokolü ile başarıyla tedavi edildi. Bu olgu, görüntüleme yöntemlerinin negatif olduğu SRS'nin tanısal güçlüklerini vurgulamakta ve kinesiotaping ile sağlanan hedefe yönelik mekanik stabilizasyonun, invaziv girişimler düşünülmeden önce etkili, tekrarlanabilir ve non-invaziv bir konservatif tedavi seçeneği olabileceğini düşündürmektedir.

Anahtar kelimeler: Slipping rib sendromu, göğüs ön duvarı ağrısı, kinesiotaping, kosta instabilitesi, konservatif tedavi

Introduction

Slipping rib syndrome (SRS) is a frequently overlooked cause of lower chest wall or upper abdominal pain attributed to hypermobility of the 8th-10th costal cartilages (1,2). Excessive rib excursion may result in intermittent subluxation and irritation of the intercostal nerve, producing sharp, movement-dependent pain (3).

Because SRS represents a dynamic mechanical instability rather than a fixed structural abnormality, static imaging

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modalities such as radiography, computed tomography, or routine ultrasonography are often normal (4). Consequently, diagnosis relies predominantly on clinical evaluation. The hooking maneuver—manual traction beneath the costal margin to reproduce symptoms—is considered highly suggestive of SRS (2,5).

While surgical resection of the affected costal cartilage has been described in refractory cases (6,7), conservative approaches are recommended as first-line management (3). These include activity modification, analgesics, manual therapy, and external stabilization. However, evidence regarding structured non-invasive mechanical stabilization remains limited.

Kinesiotaping (KT) is an elastic therapeutic taping method designed to provide dynamic support while preserving functional range of motion (8). Proposed mechanisms include cutaneous mechanoreceptor stimulation, neuromuscular facilitation, and mild mechanical constraint of excessive segmental motion (8,9). Although it is widely used in musculoskeletal conditions, its role in rib instability syndromes has not been well established.

We present a case of recurrent imaging-negative SRS that was successfully managed with targeted KT stabilization after failure of conventional physical therapy.

Case Report

A 45-year-old woman presented with a three-week history of sharp, anterior chest wall pain localized to the right 8th-10th costal margin. Pain intensified with walking, trunk rotation, sudden movements, and rising from bed. There was no history of trauma. The patient had initiated a Pilates exercise program three months before symptom onset.

All laboratory parameters, including liver function tests, were within normal limits. In view of the patient's right upper quadrant pain, hepatobiliary pathologies were excluded based on laboratory and radiologic findings. Direct radiography, thoracic computed tomography, and ultrasonography were unremarkable. There was no clinical response to conservative medical treatment, including oral and topical non-steroidal anti-inflammatory drugs (NSAIDs) and local anesthetic injections. Prior evaluations had considered intercostal neuralgia and costochondral inflammation. Conventional physical therapy modalities, including superficial heat, transcutaneous electrical nerve stimulation, and therapeutic ultrasound, failed to provide relief. At follow-up after completion of physical therapy, the hooking maneuver reproduced the patient's sharp pain and demonstrated anterior rib displacement at the 8th-10th costal margin. Based on characteristic clinical findings and normal imaging, a diagnosis of SRS was established.

A biomechanical hypothesis was formulated: dynamic hypermobility of the lower costal cartilage causes repetitive intercostal nerve irritation. External mechanical stabilization was therefore considered.

The material used for KT was Kinesio® Tex Gold™ (Kinesio Holding Corp., NM, USA), a 100% cotton, latex-free, 5-cm-wide elastic band. KT was applied using a combined Y-strip and I-strip configuration (Figure 1). A Y-strip was anchored proximally, with its two tails positioned to cradle the symptomatic 8th-10th costal margin, leaving the painful segment centered between its limbs at minimal to moderate tension (approximately 10-20%). An I-strip was subsequently applied over the same region, with high tension across the central portion (approximately 75-100%), while the terminal ends were laid down without tension to minimize skin irritation. The configuration aimed to limit excessive anterior rib excursion while preserving functional mobility. Applications were carried out three times, at five-day intervals. Activity modification and short-term NSAID therapy were also recommended. Pain intensity decreased from 8 to 3 on the visual analog scale (VAS) within one week. By week three, the patient reported complete resolution of symptoms and full return to daily activities.

She remained asymptomatic for one year. Following intense physical exertion during sporting activity, similar symptoms recurred. Reapplication of the same stabilization protocol resulted in symptom resolution, demonstrating a reproducible therapeutic response.

Written informed consent was obtained from the patient for publication of clinical information and accompanying images.

Discussion

SRS remains an underrecognized cause of lower anterior chest wall pain, largely because its clinical presentation overlaps with more common entities such as intercostal neuralgia or costochondritis (1,3). The frequent absence of abnormalities on radiographic imaging contributes to diagnostic delay, as SRS represents a dynamic instability rather than a fixed structural lesion (4). In such contexts, clinical examination—particularly the hooking maneuver—becomes central to diagnosis (2,5). Some

Figure 1. Kinesiotaping stabilization technique applied over the 8th-10th costal margin. A Y-strip was positioned to cradle the symptomatic segment, and an I-strip was applied under high tension across its central portion to enhance mechanical constraint while leaving the terminal ends without tension

authors have reported secondary sonographic findings, such as reduced thickness of the ipsilateral rectus abdominis muscle, which possibly reflects chronic segmental denervation. Although such findings are not required for diagnosis, they may increase clinical suspicion in patients with unexplained chest wall pain (7). In the present case, the patient failed to respond to conventional physical therapy modalities (superficial heat, transcutaneous electrical nerve stimulation, and therapeutic ultrasound), as well as to NSAIDs and local anesthetic injections. These findings suggest that the dominant pain generator was unlikely to be primarily inflammatory or purely neuropathic. NSAIDs primarily target inflammatory pathways, whereas conventional modalities largely provide nociceptive modulation and enhance circulation. The lack of improvement with these interventions supports the possibility of a biomechanical source of repetitive mechanical irritation.

The onset of symptoms following the initiation of a Pilates program further supports a mechanical cause. Pilates involves controlled trunk flexion, rotation, and deep breathing, all of which may increase rib cage excursion. In individuals with latent costal cartilage hypermobility, repetitive loading may precipitate symptomatic instability.

KT was therefore selected as a non-rigid external stabilization strategy. Unlike rigid bracing, elastic therapeutic taping allows functional movement while providing graded mechanical constraint. Several mechanisms may account for its benefit in SRS. First, elastic recoil may limit excessive anterior rib translation, reducing repetitive intercostal nerve irritation. Second, cutaneous stimulation may enhance proprioceptive feedback and improve segmental neuromuscular control. Third, afferent stimulation may contribute to pain modulation via gate-control mechanisms (8-10).

Importantly, the patient demonstrated a rapid and clinically meaningful improvement following stabilization, with a VAS reduction from 8 to 3 within one week. Furthermore, the recurrence of symptoms after intense physical strain and their subsequent resolution following reapplication of the same taping protocol provide reproducible clinical evidence that mechanical instability is the underlying mechanism. This pattern makes it less likely that the observed improvement was solely attributable to placebo effects or non-specific analgesic mechanisms.

Although surgical costal cartilage resection has been described for refractory SRS (6), invasive approaches carry inherent risks and are typically reserved for persistent cases. The present case suggests that structured conservative mechanical stabilization should be considered before surgical intervention, particularly in imaging-negative presentations.

From a clinical standpoint, this report emphasizes that SRS should remain in the differential diagnosis of movement-related chest wall pain despite normal imaging. Lack of response to NSAIDs and conventional modalities may signal a mechanical, rather than inflammatory, etiology; targeted external stabilization can offer a low-risk, reproducible conservative treatment option. Nevertheless, several limitations of this report should be acknowledged. In a single-case observation, a causal relationship between rib stabilization and symptom resolution cannot be definitively established. Second, objective dynamic imaging was not performed to directly visualize rib hypermobility; instead, the diagnosis relied on clinical examination and reproduction of symptoms using the hooking maneuver. Although the patient demonstrated reproducible improvement following re-stabilization, the contribution of non-specific factors such as natural history cannot be entirely excluded. Prospective studies incorporating dynamic imaging and standardized stabilization protocols are needed to better define the role of non-invasive mechanical support in SRS.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of clinical information and accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.Y., F.A.K., Concept: N.Y., Design: N.Y., Data Collection or Processing: N.Y., F.A.K., Analysis or Interpretation: N.Y., F.A.K., Literature Search: N.Y., F.A.K., Writing: N.Y., F.A.K.

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High Visibility, Low Citability? The Challenge of Artificial Intelligence in Osteoporosis Research

Yüksek Görünürlük, Düşük Alıntılanabilirlik? Osteoporoz Araştırmalarında Yapay Zekanın Zorluğu

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Keywords: Altmetric score, artificial intelligence, osteoporosis
Anahtar kelimeler: Altmetrik skor, osteoporoz, yapay zeka

Dear Editor,

Artificial intelligence (AI) is increasingly appreciated and there are many studies of AI in osteoporosis in the field of prediction of the disease, early diagnosis for personalized treatment planning and risk assessment (1,2). Utilization of AI may lead to better fracture risk prediction, enhanced evaluation of bone mineral density, and improved therapeutic decision-making with the help of machine learning algorithms, advanced deep learning models, and automated image analysis (1,3). With the increasing interest in AI-enabled advances in osteoporosis research, it is necessary to evaluate the academic landscape and the research impact of this emerging field. A bibliometric analysis was performed on the AI-related osteoporosis research indexed in Web of Science, which showed a total of 256 articles with 90 articles being included after the application of inclusion criteria. The selection of articles was based on their relevance to AI applications in osteoporosis research, particularly in terms of fracture risk assessment, bone mineral density analysis, and osteoporosis related clinical decision making.

The most cited study, "Evaluation of Transfer Learning with Deep Convolutional Neural Networks for Classifying Osteoporotic Vertebral Fractures" (2020) has 101 citations in total and 16.83 average citation per year (1). Conclusively, our study suggests the promise of deep learning in vertebral fracture classification with extensive academic acknowledgement. Yet despite the high citation impact, the paper has an Altmetric score of just 1.0, implying very little online interest. "The Machine Learning solutions for Osteoporosis—A review" (2021) is the paper with the highest citation index (18.6 citations per year) which indicates it as a prominent reference for AI-based osteoporosis studies (3). As a supplement to existing AI, radiology, and musculoskeletal literature, it has been referenced extensively in these fields, establishing strong foundations for future investigations (4). It's altmetric score (9.0), however, is modest, suggesting that AI in osteoporosis is still mostly an academic conversation rather than a clinical front-page issue.

A correlation analysis between total citations, average citation rate, and altmetric scores provides further insight into the relationship between academic influence and public engagement. The correlation of 0.96 between total citations and average citations per year indicates a very strong positive correlation, indicating that highly cited articles are consistently receiving references and reinforcing their academic impact in the long run. However, the correlation between Altmetric scores and total citations (r=0.048) is weak, indicating that articles with high online engagement do not necessarily receive high citations

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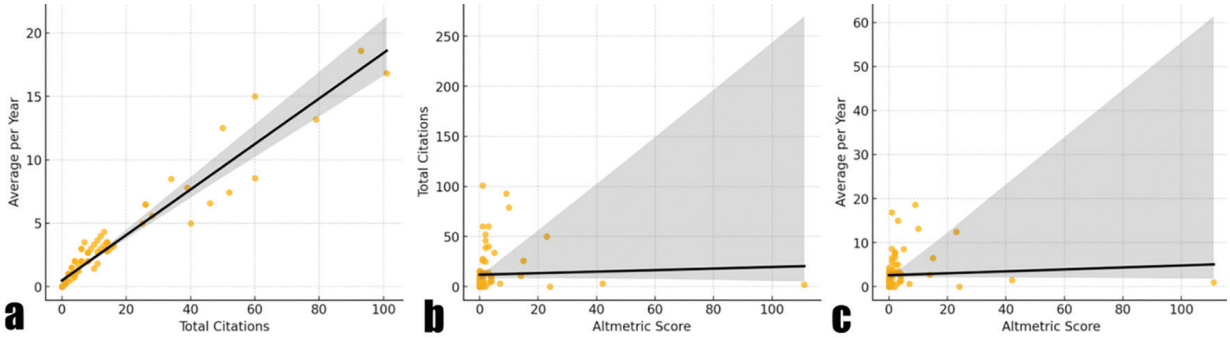

Figure 1. (a) Relationship between total citations and average citations per year, **(b)** Relationship between Altmetric scores and total citations, **(c)** Relationship between Altmetric scores and average citations per year

(5). Similarly, the correlation between Altmetric scores and yearly citations (r=0.075) remains low, suggesting that articles gaining media attention or social shares may not yet be widely cited in academic literature (Figure 1).

These findings underscore the discrepancy between AI's online engagement and its adoption within academic circles, underscoring the necessity for structured development in osteoporosis research and clinical contexts. In order to address this discrepancy, there is a necessity for the prioritisation of several high-impact strategies.

It is clear that AI models need to move from being tested in experiments to being used in the real world. This change is very important for improving how we combine clinical practice, which means moving from just trying things out to actually putting them into practice in the real world. Additionally, in the rapidly evolving field of AI, older research becomes outdated more quickly than other research. It is essential to maintain currency of information.

The establishment of consistent validation criteria is of highly importance in ensuring the uniformity and reliability of research outcomes. This methodological standardisation is a crucial aspect of scientific practice, as it fosters trust and reproducibility in research findings.

It is evident that there is a necessity for collaboration between AI researchers, clinicians, and policymakers in order to facilitate the adoption of AI.

AI-driven osteoporosis research is advancing rapidly; however, a disparity persists between its academic impact and public engagement. It is imperative that the Altmetric-Citation gap is closed through clinical validation, interdisciplinary collaboration, and methodological transparency in order to ensure the effective integration of AI into osteoporosis management.

Footnotes

Authorship Contributions

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

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