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

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

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Abstract

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

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

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

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

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

Öz

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

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

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

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

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

Introduction

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

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

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

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

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

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

Materials and Methods

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

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

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

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

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

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

Statistical Analysis

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

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

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

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

Results

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

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

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

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

Table 2. Comparison of newly diagnosed and treated patients (non-parametric variables)			
Variable	**Newly diagnosed (n=53)**	**Treated (n=47)**	**p-value**
Fracture duration (months)	3 (5)	12 (38)	<0.05
Vitamin D (ng/mL)	23.4 (20.4)	38.9 (27.9)	<0.05

Note: Data are presented as median (interquartile range). Between-group comparisons were performed using the Mann-Whitney U test. Statistical significance was defined as p<0.05

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

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

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

Discussion

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

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

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

Pearson correlation analysis was used. Only statistically significant correlations (p<0.05) are shown. BMD: Bone mineral density, eGFR: Estimated glomerular filtration rate

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

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

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

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

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

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

Study Limitations

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

Conclusion

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

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

Ethics

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

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

Footnotes

Authorship Contributions

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

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