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Real-world Effectiveness of Romosozumab: Bone Density Gains and Safety Outcomes in a Turkish Severe Osteoporosis Cohort – A Single-center Retrospective Cross-sectional Study

Romosozumabın Gerçek Yaşam Etkinliği: Türk Şiddetli Osteoporoz Kohortunda Kemik Yoğunluğu Artışı ve Güvenlilik Sonuçları – Tek Merkezli Retrospektif Kesitsel Bir Çalışma

Emre Ata, Aysu Girgin Güleşen, Mustafa Hüseyin Temel, Feyza Nur Yücel, Mehmet Akif Güler

University of Health Sciences Türkiye, Sultan 2. Abdülhamid Han Training and Research Hospital, Department of Physical Medicine and Rehabilitation, İstanbul, Türkiye

Abstract

Objective: To determine, in a real-world setting, the 12-month effects of romosozumab on bone mineral density (BMD) and T-scores in Turkish patients with severe osteoporosis.

Materials and Methods: This single-center, retrospective real-life cohort included 124 consecutive patients followed between October 2023 and March 2025. Twenty-nine patients met predefined exclusion criteria and were removed; the final analysis comprised 95 patients who had received monthly subcutaneous romosozumab 210 mg for 12 months. BMD of the lumbar spine (L1-L4 and L2–L4), femoral neck, and total hip was assessed by dual-energy X-ray absorptiometry at baseline, month 6, and month 12. Within-patient changes were analyzed using the Wilcoxon signed-rank test. Comparisons according to sex and prior anti-osteoporotic therapy (treatment-naïve vs. previously treated) were performed using the Mann-Whitney U test.

Results: Of the cohort, 89.5% were women and the median age was 73 years. Median baseline BMD at L1-L4 was 0.671 g/cm² (T-score -3.50) and increased to 0.762 g/cm² at 12 months (+13.6%, p<0.001). At L2–L4, BMD increased to 0.750 g/cm² (+14.9%, p<0.001). Femoral neck BMD rose to 0.548 g/cm² (+4.9%, p<0.001), and total hip BMD to 0.668 g/cm² (+3.7%, p<0.001). Corresponding median T-score gains were +0.47, +0.52, +0.11, and +0.08 SD units, respectively. The magnitude of BMD and T-score improvement did not differ by sex (women n=85, men n=10) or by prior treatment status (treatment-naïve n=24, previously treated n=71) (all p>0.05). Treatment was discontinued in one patient because of palpitations judged unrelated to the drug; nine patients (9.5%) reported mild adverse events such as nasopharyngitis, injection-site reactions, and low back pain.

Conclusion: In this real-world Turkish cohort with severe osteoporosis, 12 months of romosozumab was associated with rapid and clinically meaningful increases in spinal and hip BMD, maintained through 1-year and unaffected by sex or previous pharmacotherapy. The observed safety profile supports the use of romosozumab in high-risk patients.

Keywords: Osteoporosis, romosozumab, bone density, retrospective studies

Öz

Amaç: Bu çalışmanın amacı, gerçek yaşam koşullarında romosozumab tedavisinin bir yıllık sürede kemik mineral yoğunluğu (KMY) ve T-skorları üzerindeki etkilerini Türk şiddetli osteoporoz kohortunda değerlendirmektir.

Gereç ve Yöntem: Bu tek merkezli retrospektif kesitsel çalışmada, Ekim 2023-Mart 2025 tarihleri arasında takip edilen 124 ardışık hasta tarandı, dışlama kriterlerini karşılayan 29 hasta çalışma dışı bırakıldı. Kalan 95 hasta, 12 ay boyunca aylık 210 mg romosozumab tedavisi almıştı. Lomber omurga (L1-L4 ve L2-L4), femur boynu ve total kalça bölgelerinde KMY ölçümleri dual enerjili X-ışını absorbsiyometri yöntemiyle başlangıçta, 6. ayda ve 12. ayda yapılmıştı. Grup içi değişimler Wilcoxon işaretli sıralar testi, bağımsız gruplar arası karşılaştırmalar Mann-Whitney U testi ile değerlendirildi.

Corresponding Author/Sorumlu Yazar: Assoc. Prof. Emre Ata, University of Health Sciences Türkiye, Sultan 2. Abdülhamid Han Training and Research Hospital, Department of Physical Medicine and Rehabilitation, İstanbul, Türkiye
E-mail: emreata.ftr@gmail.com **ORCID ID:** orcid.org/0000-0002-8923-4158
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Bulgular: Katılımcıların %89,5'i kadındı ve medyan yaş 73 yıldı. Başlangıçta L1-L4 bölgesinde medyan KMY 0,671 g/cm² (T-skoru -3,50) iken, 12. ayda 0,762 g/cm²'ye yükseldi (+%13,6; p<0,001). L2-L4 bölgesinde KMY 0,750 g/cm²'ye (+%14,9; p<0,001), femur boynunda 0,548 g/cm²'ye (+%4,9; p<0,001) ve total kalçada 0,668 g/cm²'ye (+%3,7; p<0,001) yükseldi. T-skoru artışları sırasıyla +0,47, +0,52, +0,11 ve +0,08 standart sapma birimi oldu. Artışlar cinsiyete veya önceki tedavi durumuna göre farklılık göstermedi (tüm p>0,05). Bir hastada çarpıntı nedeniyle tedavi sonlandırılmıştı; dokuz hastada (%9,5) nazofarenjit, enjeksiyon bölgesi reaksiyonu ve bel ağrısı gibi hafif advers olaylar bildirilmişti.

Sonuç: Gerçek yaşam verilerine dayalı bu 95 hastalık kohortta romosozumab, omurga ve kalça KMY'sinde hızlı ve klinik olarak anlamlı artışlar sağlamış, bu kazanımlar 12 ay boyunca korunmuş ve cinsiyet ya da önceki farmakoterapiden bağımsız olmuştur. Olumlu güvenlilik profili, şiddetli osteoporozu olan hastalarda romosozumab kullanımını desteklemektedir.

Anahtar kelimeler: Osteoporoz, romosozumab, kemik mineral yoğunluğu, retrospektif çalışmalar

Introduction

Osteoporosis is a systemic skeletal disease characterized by reduced bone mass and microarchitectural deterioration, leading to increased bone fragility and fracture risk (1). It is a major public health concern, particularly in aging populations, with a significant socioeconomic and healthcare burden due to the morbidity and mortality associated with osteoporotic fractures (2). Despite advancements in early diagnosis, osteoporosis remains largely underdiagnosed and undertreated, with many patients only identified after a fragility fracture has occurred (3). The treatment landscape for osteoporosis includes antiresorptive agents such as bisphosphonates and denosumab, as well as anabolic agents like teriparatide, which aim to improve bone strength and reduce fracture risk (4). However, long-term adherence to these treatments remains suboptimal due to side effects, limited efficacy in severely osteoporotic patients, and concerns over rare adverse effects like atypical fractures and osteonecrosis of the jaw (5). Moreover, many current therapies predominantly act by either inhibiting bone resorption or stimulating bone formation, rather than simultaneously addressing both processes, creating a need for innovative therapies that provide more comprehensive skeletal benefits (6). Romosozumab, a monoclonal antibody that inhibits sclerostin, is a paradigm shift in osteoporosis therapy by providing novel synergy of anabolic and antiresorptive activity (7). Phase III trials have demonstrated that 12-month romosozumab therapy is followed by striking increases in hip and lumbar spine bone mineral density, outcompeting teriparatide and bisphosphonates on reduction of fracture risk (8). Exciting though these findings are, there have been cardiovascular safety issues that have led to regulatory restrictions, where there is requirement of post-marketing surveillance together with real-world efficacy studies (9).

While randomized controlled trials provide valuable evidence of efficacy, outcomes of treatments of osteoporosis can also vary by demographic, gene, lifestyle, and health system differences within populations (10). Real-world evidence produced within targeted countries is what confirms how these therapies operate within real-world practice, where compliance of patients, comorbidities, and habits of prescriptions can also vary compared to that of trial settings (11). The use of FRAX or other fracture risk assessments is also population-adjusted, hence population-based research is critical to personalize treatments and enhance outcomes of patients (12).

In light of the current evidence and the clinical need for real-world data, the aim of this single-center retrospective cross-sectional study was to assess the effectiveness and safety of 12-month romosozumab therapy in a Turkish cohort with severe osteoporosis. The primary outcomes were changes in bone mineral density (BMD) and T-scores at the lumbar spine, femoral neck, and total hip after 12 months of treatment.

Materials and Methods

Study Design and Ethical Considerations

This retrospective cross-sectional study was conducted at the University of Health Sciences Türkiye, Sultan 2. Abdülhamid Han Training and Research Hospital, Physical Medicine and Rehabilitation Clinic, between January 10, 2025, and February 20, 2025. Ethical approval was obtained from the University of Health Sciences Türkiye Hamidiye Clinical Trials Ethics Committee (approval number: 1/23, date: January 1, 2025). The study adhered to the ethical principles outlined in the Declaration of Helsinki.

Study Population

Patient records were retrospectively reviewed for individuals diagnosed with osteoporosis who presented to the physical medicine and rehabilitation outpatient clinic at our institution between August 25, 2023, and January 8, 2025. The study population consisted of patients classified as high fracture risk according to the Türkiye Osteoporosis Clinical Guidelines (13) and who were initiated on romosozumab therapy. Patients with secondary osteoporosis were excluded. Only patients with a diagnosis of primary osteoporosis were included in the analysis, in accordance with the Türkiye Osteoporosis Clinical Guidelines. All female participants were postmenopausal. No patients were receiving hormone replacement therapy or estrogen treatment during the study period.

Per the Türkiye Osteoporosis Clinical Guidelines, high-risk osteoporosis is defined as:

- Severe osteoporosis (T-score ≤-3.0) with one or more fragility fractures
- Multiple vertebral fractures
- Imminent fracture risk due to a combination of clinical and densitometric risk factors

Treatment Administration

Romosozumab therapy was administered by monthly subcutaneous administration of 12 doses of 12 months utilizing the same dosing regimen that had been created by conducting clinical trials (14). The monthly dose of romosozumab totaled 210 mg that had been administered by two consecutive injections of 105 mg each taken separately by anatomically distinct locations (e.g., abdominal region, thigh, or upper extremity) (15).

All patients received concurrent calcium and vitamin D supplementation during romosozumab treatment. A daily fixed-dose supplement containing 600 mg calcium and 400 IU vitamin D3 was prescribed. For patients with baseline 25(OH) D levels below 30 ng/mL, vitamin D deficiency was corrected using 20,000 IU cholecalciferol twice weekly for 7 weeks, followed by a maintenance dose of 20,000 IU once weekly. Prior to treatment initiation, serum calcium levels were assessed in all patients. Those with suboptimal levels received calcium replacement therapy before romosozumab was initiated.

Adherence to supplementation was monitored during routine outpatient follow-up visits at 3-month intervals. Electronic prescription refill records were reviewed through the national e-prescription system to verify continuous use. Any deficiencies identified during follow-up were corrected in accordance with standard clinical practice. All romosozumab administrations were scheduled as monthly outpatient visits at the study center. During each visit, calcium and vitamin D supplementation status was also checked, and serum levels were monitored in accordance with standard clinical practice guidelines (13). Adherence was reinforced at each visit.

Data Collection and Assessments

Patient records were systematically evaluated to gather demographic and anthropometric data, that is, age, gender, weight, and height. Femoral neck, total femur, L2-L4, and L1-L4 BMD with corresponding T-scores were obtained by means of dual-energy X-ray absorptiometry (DXA) Since a site-specific precision assessment has not yet been performed in our facility, we referenced the International Society for Clinical Densitometry (ISCD) guidelines for acceptable least significant change (LSC) values. According to ISCD best practices, the maximum recommended LSC is 5.3% for the lumbar spine, 5.0% for the total hip, and 6.9% for the femoral neck (16). These thresholds were used to interpret changes in BMD over time in our study. DXA results were recorded from the following time intervals: At the beginning of treatment, at the 6th month of treatment, and at the 12th month of the follow-up time frame. Besides this information, the medical record of the prior treatment of osteoporosis was also documented with reference to the administration of pharmacological therapy with a description of the specific medications that were administered to the patient. The presence of fragility fractures was confirmed through review of existing medical records and radiology reports or newly obtained spinal and skeletal radiographs where necessary during screening.

BMD and T-score Measurement

Bone mineral content and T-score values were measured by using the Hologic DXA scanner (Hologic Inc., Marlborough, MA, USA). For DXA scans, there were standardized positioning protocols followed to ensure maximum reproducibility and accuracy. For lumbar spine DXA, patients were seated supine with hip and knee flexion over a cushion to flatten out lordosis of the lumbar region, ensuring clear visualization of the scan of the T12 to L5 vertebral bodies within the scan region. For hip DXA, patients were seated supine with internally rotated femur (15-20°) using a positioning apparatus to ensure maximum accuracy of measurement and to ensure visualization of the lesser trochanter is minimized. Appropriate patient positioning was carefully adhered to within both tests to ensure maximum precision and reduction of artifacts, ensuring valid BMD measures (17).

Patient Monitoring, Treatment Adherence and Adverse Event Surveillance

All injections were administered by the same physician. Following the injections, patients were scheduled for their subsequent romosozumab administration. Those who missed their appointments or were unable to attend were contacted by phone and invited to continue their treatment.

The immediate hypersensitivity or acute adverse effects were assessed within patients within 30 minutes of administration of injections (18). Patients were screened out of possible contraindications, including history of cardiovascular complications and hypocalcemia, prior to each administration session, adhering to predetermined safety protocols (19).

Adverse events were defined as minor adverse events and major adverse events, utilizing earlier operational definitions of adverse events within clinical research. Minor adverse events were operationalized as non-serious, transient signs that were not medically intervened upon, e.g., mild nausea, transient headache, fatigue, or focal discomfort on administration site (20). Major adverse events were operationalized as severe complications that hospitalized, permanently disabled, threatened life, or led to death, utilizing guidelines by regulators (21).

To ensure systematic AE monitoring, patients were questioned before each treatment session regarding the occurrence of any adverse events since their last visit. Standardized questionnaires and structured interviews were used to document and categorize reported AEs. In cases where patients reported symptoms, clinical assessments were performed to determine the severity and potential causality of the event (22).

Statistical Analysis

Statistical analyses were performed using IBM SPSS (Statistical Package for the Social Sciences, Version 27.0, Armonk, NY, IBM Corp.) and Python (version 3.11.10). The distributional properties of continuous variables were assessed with the Shapiro-Wilk test. Descriptive data are summarized as mean ± standard deviation or as median and interquartile range, according to distributional characteristics. Within-group changes over time

were evaluated using the Wilcoxon signed-rank test. Between-group comparisons of continuous outcomes were performed with the Wilcoxon Rank-Sum test. Adjustment for multiple hypothesis testing was carried out using the Holm-Bonferroni method for the primary subgroup analyses. A two-tailed p-value <0.05 was considered statistically significant. "Plotly" library was used for visualizations.

Results

The cohort was predominantly female (89.5%) with a median age of 73 years (68-77.5). At baseline, lumbar spine (L1-L4) BMD was 0.671 g/cm² (0.592-0.764), and the corresponding T-score was -3.50 (-4.10 to -2.60). Among the 95 patients, 71 (74.7%) had received at least one osteoporosis treatment before enrollment. The median total prior treatment duration was 4.0 years. Prior use by agent was as follows: alendronate 23 patients (24.2%), 2.0 years; zoledronic acid 37 (38.9%), 2.0 years; ibandronate 29 (30.5%), 2.0 years; risedronate 13 (13.7%), 2.0 years; denosumab 20 (21.1%), 2.0 years; and teriparatide 10 (10.5%), 2.0 years. No significant differences in demographic, biochemical, or densitometric characteristics were observed by sex or treatment history (p>0.05). Laboratory parameters—including serum albumin, calcium, and 25-hydroxyvitamin D—as well as all additional baseline characteristics are summarized in Table 1.

Table 1. Baseline characteristics of the study cohort

Characteristic	Value
Age, yr	73.0 (68.0-77.5)
Sex, n (%)	85 female/10 male (89.5% F)
BMI, kg m^{-2}	26.8±5.5
eGFR, mL min^{-1} 1.73 m^{-2}	70.6±26.9
Albumin, g L^{-1}	43.2±2.3
Serum calcium, mg dL^{-1}	9.45±0.33
25-OH-vitamin D, µg L^{-1}	45.5±12.3
Lumbar spine (L1-L4) BMD, g cm^{-2}	0.671 (0.592-0.764)
Lumbar spine (L1-L4) T-score	-3.50 (-4.10- -2.60)
Lumbar spine (L2-L4) BMD, g cm^{-2}	0.653 (0.592-0.774)
Lumbar spine (L2-L4) T-score	-3.90 (-4.45- -2.80)
Femoral neck BMD, g cm^{-2}	0.522 (0.453-0.605)
Femoral neck T-score	-2.90 (-3.60- -2.20)
Total hip BMD, g cm^{-2}	0.648 (0.606-0.713)
Total hip T-score	-2.40 (-2.80- -1.90)
Treatment-naïve, n (%)	24 (25.3)
Any prior osteoporosis therapy, n (%)	71 (74.7)
Bisphosphonate only	47 (49.5)
Denosumab only	4 (4.2)
Denosumab following bisphosphonate	10 (10.5)
Teriparatide following bisphosphonate	4 (4.2)
Teriparatide following denosumab and bisphosphonate	6 (6.3)

BMD: Bone mineral density, BMI: Body mass index, eGFR: Estimated glomerular filtration rate, SD: Standard deviation, IQR: Interquartile range. Continuous variables with normal distribution (BMI, eGFR, albumin, calcium, 25-hydroxyvitamin D) are presented as mean ± SD; all other variables are reported as median (IQR)

Overall Treatment Response

During 12 months of romosozumab therapy, significant improvements were observed in both (BMD and T-scores across all measured skeletal sites (Table 2).

At the lumbar spine (L1-L4), median BMD increased from 0.671 g/cm² (0.592-0.764) at baseline to 0.727 g/cm² (0.601-0.872) at 6 months [+8.6% (1.7-14.2%)] and to 0.762 g/cm² (0.641-0.903) at 12 months [+13.6% (8.4-17.9%)] (p<0.001 for both intervals). The corresponding median T-score improved from -3.50 (-4.10 to -2.60) at baseline to -3.17 (-3.71 to -2.35) at 6 months and -3.03 (-3.55 to -2.25) at 12 months (p<0.001 for both comparisons).

For the lumbar spine (L2-L4), BMD increased from 0.653 g/cm² (0.593-0.774) at baseline to 0.711 g/cm² (0.623-0.870) at 6 months [+8.6% (5.0-13.1%)] and to 0.750 g/cm² (0.679-0.878) at 12 months [+14.7% (14.2-15.1%)] (p<0.001). The T-score for this region improved from -3.90 (-4.45 to -2.80) at baseline to -3.53 (-4.04 to -2.54) at 6 months and -3.36 (-3.85 to -2.42) at 12 months (p<0.001).

At the femoral neck, BMD rose from 0.522 g/cm² (0.453-0.605) at baseline to 0.539 g/cm² (0.470-0.626) at 6 months [+3.6% (3.3-3.9%)] and 0.548 g/cm² (0.475-0.634) at 12 months [+4.5% (4.1-5.0%)] (p<0.001). The corresponding T-score increased from -2.90 (-3.60 to -2.20) to -2.84 (-3.52 to -2.15) at 6 months and -2.79 (-3.47 to -2.12) at 12 months (p<0.001).

For the total hip, median BMD improved from 0.648 g/cm² (0.606-0.713) at baseline to 0.668 g/cm² (0.619-0.731) at 6 months [+2.3% (2.0-2.6%)] and 0.668 g/cm² (0.623-0.733) at 12 months [+2.9% (2.6-3.2%)] (p<0.001). The corresponding T-score increased from -2.40 (-2.80 to -1.90) at baseline to –2.34 (-2.73 to -1.86) at 6 months and -2.32 (-2.70 to -1.84) at 12 months (p<0.001).

Sex-specific Treatment Response

The median percentage increase in BMD from baseline to 12 months was comparable between sexes at the lumbar spine L1-L4 (13.6% in women vs. 14.0% in men; p=0.68), lumbar spine L2-L4 (14.7% vs. 14.4%; p=0.41), femoral neck (4.48% vs. 4.85%; p=0.13), and total hip (2.82% vs. 3.08%; p=0.040). Similarly, absolute changes in T-score were nearly identical in women and men for each region (L1-L4: +0.47 vs. +0.48 SD units, p=0.13; L2-L4: +0.52 vs. +0.53, p=0.17; femoral neck: +0.11 vs. +0.09, p=0.23; total hip: +0.08 vs. +0.08, p=0.72) (Figure 1). No significant differences in densitometric response to romosozumab were identified between women and men at any of the evaluated skeletal sites.

Table 2. Changes in bone mineral density and T-score at 6 and 12 months of romosozumab therapy

Region/outcome	T0 median (IQR)	T6 median (IQR)	T12 median (IQR)	%Δ T0→T6	%Δ T6→T12	%Δ T0→T12	p T0→T6	P T6→T12	p T0→T12
Lumbar spine (L1-L4) BMD (g cm^{-2})	0.671 (0.592-0.764)	0.727 (0.601-0.872)	0.762 (0.641-0.903)	8.32%	4.86%	13.58%	<0.001	<0.001	<0.001
Lumbar spine (L1-L4) T-score (SD)	-3.50 (-4.10 to -2.60)	-3.17 (-3.71 to -2.35)	-3.03 (-3.55 to -2.25)	9.50%	4.34%	13.43%	<0.001	<0.001	<0.001
Lumbar spine (L2-L4) BMD (g cm^{-2})	0.653 (0.593-0.774)	0.711 (0.623-0.870)	0.750 (0.679-0.878)	8.81%	5.56%	14.86%	<0.001	<0.001	<0.001
Lumbar spine (L2-L4) T-score (SD)	-3.90 (-4.45 to -2.80)	-3.53 (-4.04 to -2.54)	-3.36 (-3.85 to -2.42)	9.39%	4.78%	13.72%	<0.001	<0.001	<0.001
Femoral neck BMD (g cm^{-2})	0.522 (0.453-0.605)	0.539 (0.470-0.626)	0.548 (0.475-0.634)	3.33%	1.55%	4.94%	<0.001	<0.001	<0.001
Femoral neck T-score (SD)	-2.90 (-3.60 to -2.20)	-2.84 (-3.52 to -2.15)	-2.79 (-3.47 to -2.12)	2.14%	1.39%	3.67%	<0.001	<0.001	<0.001
Total hip BMD (g cm^{-2})	0.648 (0.606-0.713)	0.668 (0.619-0.731)	0.668 (0.623-0.733)	3.08%	0.63%	3.72%	<0.001	<0.001	<0.001
Total hip T-score (SD)	-2.40 (-2.80 to -1.90)	-2.34 (-2.73 to -1.86)	-2.32 (-2.70 to -1.84)	2.50%	0.85%	3.27%	<0.001	<0.001	<0.001

BMD: Bone mineral density, IQR: Interquartile range, SD: Standard deviation, %Δ: Percent change; T0, baseline; T6, 6 months; T12, 12 months. P-values from paired Wilcoxon signed-rank tests. Bonferroni-corrected significance threshold =0.0021 (0.05/24 comparisons)

Effect of Any Prior Osteoporosis Therapy on Romosozumab Response

Treatment-naïve patients (n=24) showed numerically larger densitometric gains than those with any prior anti-osteoporotic therapy (n=71), yet the differences were not statistically significant. Over 12 months, median BMD increased by 16.3% (IQR, 10.6-18.3) at the lumbar spine L1-L4, 14.6% (14.0-15.2) at L2-L4, 4.5% (4.2-4.9) at the femoral neck, and 2.95% (2.66-3.22) at the total hip; the corresponding gains among previously treated patients were 13.3% (8.0-17.8), 14.7% (14.3-15.1), 4.48% (4.12-4.97), and 2.89% (2.58-3.22), respectively (p=0.14, 0.67, 0.86, and 0.86, respectively).

T-score improvements paralleled these findings. In treatment-naïve individuals, median T-score rose by 0.54 SD units (0.42-0.66) at L1-L4, 0.57 (0.45-0.69) at L2-L4, 0.12 (0.09-0.15) at the femoral neck, and 0.09 (0.07-0.11) at the total hip. Previously treated patients exhibited median increases of 0.45 (0.33-0.57), 0.52 (0.40-0.63), 0.11 (0.08-0.14), and 0.08 (0.06-0.10) SD units, respectively, with no significant between-group differences (p=0.18, 0.39, 0.81, and 0.90, respectively) (Figure 2).

Between-group analyses of percentage BMD change and T-scores at 12 months were performed across prior osteoporosis therapy categories. Kruskal-Wallis tests showed no significant differences among groups at the lumbar spine L1-L4, L2-L4, femoral neck, or total hip (all $p \geq 0.05$).

Adverse Events

No major AEs were reported. At least one AE occurred in 9 patients. Specifically, 1 had experienced palpitations and breathing difficulty, 2 had experienced injection site reactions, 3 had experienced backache, and 3 had experienced nasopharyngitis diagnosed. In addition, 38 patients demonstrated non-treatment compliance and had also defaulted on follow-up. By month 12, incident vertebral fractures were observed in two patients (2.1%; 1 vertebra each), although both had shown gains in BMD and T-scores.

Discussion

This study demonstrates real-world outcomes of romosozumab's activity on a population of individuals with osteoporosis within Türkiye, closing a key literature gap. While randomized controlled trials have validated its efficacy, real-world evidence is important to establish outcomes of therapy, compliance, and efficacy within real-world populations. Our findings reinforce significant increases within diverse skeletal locations, particularly of the lumbar spine, confirming romosozumab's dual function of inducing anabolism and inhibiting resorption.

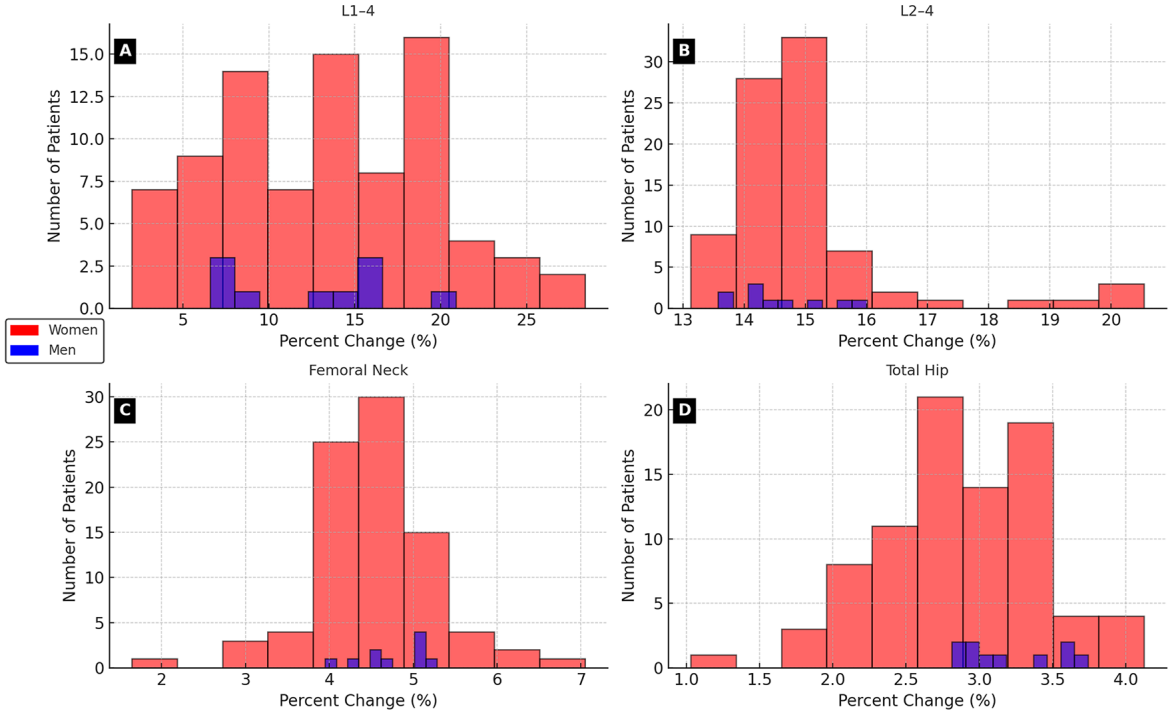

Figure 1. Distribution of 12-month percent BMD an T-score change by sex. Panels A through D show histograms for the lumbar spine (L1-4), lumbar spine (L2-4), femoral neck, and total hip, respectively. Red bars represent women (n=85) and blue bars represent men (n=10). Bin widths are identical across panels (10 bins) to permit direct visual comparison. The overlapping distributions for each skeletal site corroborate the non-significat sex differences
BMD: Bone mineral density

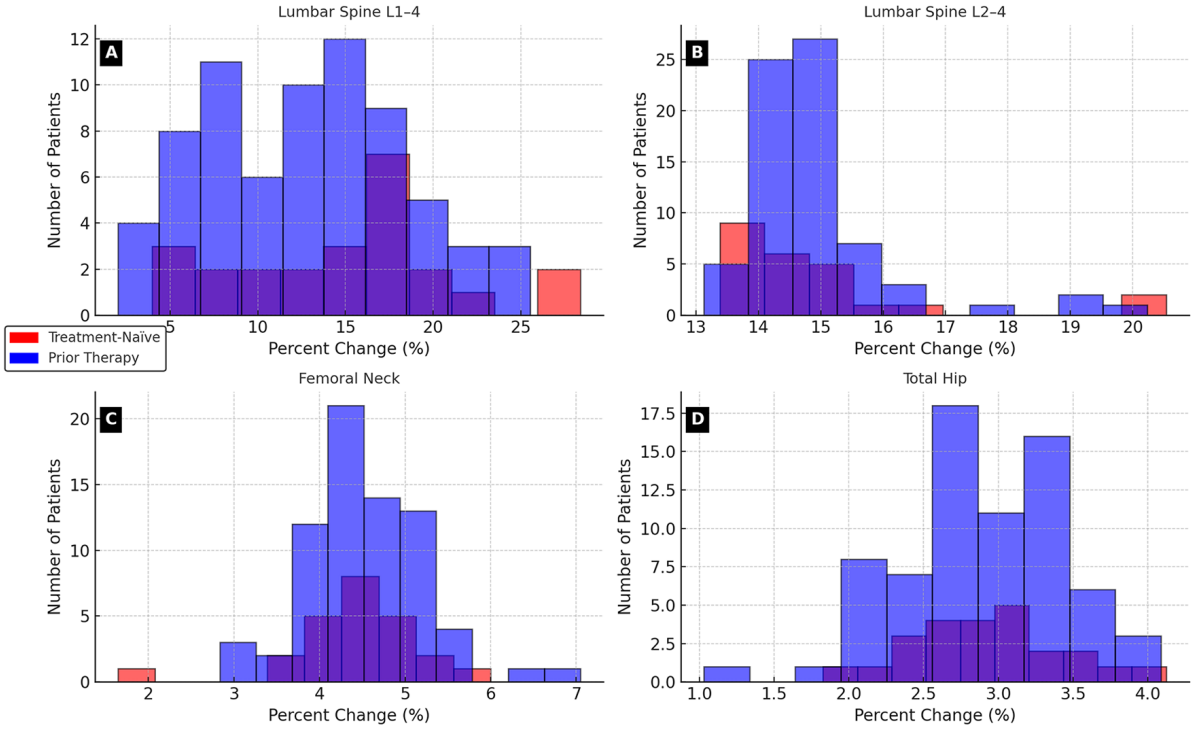

Figure 2. Distribution of 12-month percent BMD and T-score change by prior osteoporosis therapy. Panels A through D depict histograms of 12-month percentage change in BMD at the lumbar spine (L1-4), lumbar spine (L2-4), femoral neck, and total hip, respectively. Red bars represent treatment-naïve patients (n=24); blue bars represent patients who had received any previous anti-osteoporotic therapy (n=71)
BMD: Bone mineral density

With issues of non-adherence to therapy of osteoporosis and maintaining long-term skeletal health, these findings reinforce romosozumab's use within practice and provide region-specific evidence helpful within Türkiye's management of osteoporosis.

The observed significant increases in femoral neck and total femur BMD and T-scores align well with previous studies although there are variations in amount of increase in those scores in literature. For example, Ishibashi et al. (23) reported a 3.8% increase in femoral neck BMD at 12 months, which is slightly lower to the 4.94% increase observed in our study. Similarly, Dilshani et al. (24) found a 4.8% increase in total femoral BMD, which is lower than our findings. They also reported a 4.1% increase in femur neck BMD, which is slightly lower than our results. A multicenter real-world study found a 6.0% increase in femoral neck BMD over 12 months (25), which is higher than our findings. A meta-analysis confirmed that romosozumab significantly increases femoral neck BMD by approximately 5.18% at 12 months (26).

Similarly, romosozumab's impact on the lumbar spine observed in this study had parallel results compared to literature. A 16.9% BMD of the lumbar spine after 12 months has been reported by Ishibashi et al. (23), compared to our 13.58% BMD of L1-4 and 14.86% of BMD of L2-4. Similarly, Anno et al. (27) also reported that BMD of the lumbar spine is elevated by 10.8% after 12 months, which is above our findings. Our findings also exceed the 10.8% lumbar spine BMD increase observed in rheumatoid arthritis patients receiving romosozumab (28), and a parallel results yielding a 15.3% gain in osteoporotic patients undergoing hemodialysis (29). Additionally, a study comparing romosozumab and teriparatide found a 10.2% increase in lumbar spine BMD after 12 months, also lower than our results (30).

The differences in the magnitude of BMD and T-score increases at the lumbar spine, femoral neck, and total hip observed in our study compared with previous reports may be attributed to multiple factors. These include the severity of baseline osteoporosis, the specific characteristics of the patient population, and adherence patterns in real-world clinical settings. For example, previous reports indicate that variations in femoral neck and total femur outcomes could reflect regional and ethnic differences, as well as potential influences from prior osteoporosis treatments, both of which have been shown to affect treatment response (31,32). Collectively, these factors likely account for the observed variations in femur neck and femur total BMD and T-scores relative to earlier literature.

The observed greater increases in lumbar spine BMD and T-scores compared to femoral neck and total femur align with prior findings. A study comparing romosozumab with denosumab in rheumatoid arthritis patients found lumbar spine BMD increase by 10.2% with romosozumab, while femoral neck and total hip BMD increased by 3.6% (30). Similarly, a multicenter real-world study found a 14.1% increase in lumbar spine BMD after 12 months of romosozumab, while total hip BMD increased by 5.7% (33). Another phase 2 study reported that romosozumab led to a 15.1% gain in lumbar spine BMD and a 5.4% gain in total hip BMD over 24 months (7). This discrepancy could be attributed to differences in bone composition and remodeling dynamics, as trabecular-rich sites such as the vertebral column exhibit higher metabolic activity and faster turnover than cortical-dominant regions like the femur which results to a greater response to anabolic stimuli (23).

The observation that prior osteoporosis therapy did not have a statistically significant effect on changes in BMD or T-score following romosozumab treatment in our cohort contrasts with several previous reports, though real-world variability in patient response may account for this discrepancy. Notably, while statistical significance was not reached, our treatment-naïve subgroup demonstrated a trend toward greater improvements in BMD and T-score compared to those with prior anti-osteoporotic therapy, and the relatively small sample size may have limited our ability to detect significant differences. Ebina et al. (34) reported that increases of BMD of the lumbar spine after 6-12 months were greater in individuals without previous therapy compared to individuals on previous therapy of bisphosphonates, denosumab, or teriparatide. Ebina et al. (32) also reported that early increases of BMD of the lumbar spine after 6 months were also significantly affected by previous therapy but that most increases occurred in individuals without previous therapy. In contrast, Anno et al. (27) reported that romosozumab increased BMD of the lumbar and femoral sites regardless of previous therapy of osteoporosis, agreeing with our findings.

The absence of major AEs and the low incidence of minor AEs in our study is consistent with previous clinical trials and pharmacovigilance analyses, which have generally reported a favorable safety profile for romosozumab. A meta-analysis by Mariscal et al. (35) found that romosozumab had a similar overall safety profile to bisphosphonates, except for an increased risk of mild injection site reactions. Similarly, Chen et al. (36) identified injection site pain, back pain, and nasopharyngitis as the most reported non-serious AEs, aligning with our findings. The lack of severe AEs, particularly cardiovascular events, may be attributed to careful patient selection and exclusion of high-risk individuals, as major cardiovascular events have been primarily reported in high-risk populations (37). The high rate of non-compliance and follow-up was notable, as adherence challenges have been reported in real-world romosozumab use and may impact treatment outcomes (38).

Study Limitations

This study has several limitations that must be acknowledged. Its retrospective design introduces potential sources of bias, including selection bias and incomplete data, which may affect the reliability of the findings. The absence of a control group limits the ability to directly compare romosozumab with other osteoporosis treatments. Adherence to therapy and lifestyle factors, such as physical activity and nutrition, were not systematically assessed and may have influenced BMD outcomes. Although significant improvements in BMD were observed,

fracture incidence was not recorded, making it unclear whether these gains translated into reduced fracture risk. The 12-month follow-up period does not allow for assessment of long-term bone mass retention following cessation of therapy. Furthermore, the single-center design and inclusion of only patients from Türkiye may limit the generalizability of the results to populations with differing genetic, dietary, and healthcare profiles. Another limitation is the absence of a site-specific precision study in our facility to determine LSC values for BMD. Instead, we relied on published LSC thresholds for Hologic DXA systems. In addition, bone turnover markers such as procollagen type 1 N-terminal propeptide and C-terminal telopeptide of type 1 collagen were not measured, as they are not included in routine clinical testing for osteoporosis. Future prospective, randomized, multi-center studies with extended follow-up durations and comprehensive biochemical and fracture outcome assessments are needed to validate and expand upon these findings.

Conclusion

In conclusion, our real-world findings underscore romosozumab's therapeutic effects, as evidenced by marked increases in BMD and T-scores at multiple skeletal sites among high-risk Turkish patients with osteoporosis. Notably, we observed particularly pronounced improvements at the lumbar spine, reflecting the therapy's greater impact in trabecular-rich regions, along with significant gains at the femoral neck and total femur. Romosozumab also exhibited a favorable safety profile; no major adverse events occurred, and minor adverse events were uncommon. Contrary to some prior reports, previous osteoporosis therapies did not substantially alter romosozumab's effectiveness in our cohort, pointing to consistent benefits across varied treatment histories. While limitations such as a single-center design and relatively small sample size warrant caution, these findings add valuable real-world evidence to support romosozumab's promise in managing osteoporosis in the Turkish context, reinforcing the need for more extensive, multi-center studies to confirm these positive outcomes.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Türkiye Hamidiye Clinical Trials Ethics Committee (approval number: 1/23, date: January 1, 2025). The study adhered to the ethical principles outlined in the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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

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