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ORIGINAL RESEARCH

Synergistic Efficacy of Calcitriol Combined with Denosumab versus Calcitriol Alone in Postmenopausal Osteoporosis: A Retrospective Cohort Study

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Objective: To evaluate the efficacy and safety of calcitriol combined with denosumab versus calcitriol alone in postmenopausal osteoporosis (PMO).

Methods: In this retrospective cohort study, 306 postmenopausal women with PMO were divided into two groups: an intervention group (n = 144) receiving calcitriol, denosumab, and calcium/vitamin D3, and a control group (n = 162) receiving calcitriol and calcium/vitamin D3 only, over 12 months. Outcomes included bone mineral density (BMD), bone turnover markers, calcium-phosphate homeostasis, patient-reported outcomes (VAS, ODI, BI), and adverse events.

Results: The intervention cohort demonstrated more pronounced enhancements in BMD measured at the lumbar spine, femoral neck, and total hip (all $P < 0.05$). Additionally, there was a more marked reduction in bone turnover markers, namely β-C-terminal telopeptide of type I collagen (β-CTX), Tartrate-resistant acid phosphatase 5b (TRACP-5b), Procollagen type I N-terminal propeptide (P1NP), and Bone Gla Protein (BGP) ($P < 0.05$). Superior regulation of calcium-phosphate homeostasis—reflected by Parathyroid Hormone (PTH) and 25-hydroxyvitamin D [25(OH)D] levels—was also observed in this group ($P < 0.05$). Patient-reported outcomes (VAS, ODI, BI) also improved more markedly ($P < 0.05$). The incidence of adverse events was low and comparable between groups, with no serious events reported.

Conclusion: Calcitriol combined with denosumab synergistically enhances BMD, suppresses bone turnover, improves functional outcomes, and maintains a favorable safety profile in PMO, representing a promising therapeutic strategy.

Keywords: postmenopausal osteoporosis, denosumab, calcitriol, bone mineral density, bone turnover markers

Introduction

Postmenopausal osteoporosis (PMO) is a common bone disease resulting from estrogen deficiency after menopause. This hormonal change disrupts the normal bone remodeling cycle, leading to progressive bone loss, increased bone fragility, and a markedly elevated risk of fractures even after minor falls or injuries.[1,2] Epidemiological data from China show that primary osteoporosis affects approximately 18.2% of the Chinese population, with a notable sex disparity: 23.4% in women versus 11.5% in men.[3] The prevalence in women rises sharply with age, from 22.6% at 50–59 years to 44.1% at 60–69 years, and exceeds 55% among those aged ≥70 years.[3] Globally, a systematic review and meta-analysis reported a prevalence of osteoporosis of 21.7% among older adults (≥50 years), with a much higher rate in elderly women (35.3%) than in elderly men (12.5%).[4] These growing figures highlight the urgent need for safer and more effective therapeutic strategies to preserve bone health and maintain patient well-being.[5]

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Despite the availability of a number of pharmacological choices, the capacity of existing treatments to concurrently optimize safety and efficacy is restricted. Strong antifracture efficacy has been shown for denosumab, a powerful RANKL inhibitor,[6,7] but it poses a significant risk of hypocalcemia, requiring careful monitoring.[8,9] Calcitriol promotes bone mineralization and enhances intestinal calcium absorption,[10] but it alone is insufficient for effective fracture prevention.[11] The obvious discrepancy between metabolic safety and antiresorptive potency emphasizes the urgent need for integrated treatment strategies that can improve therapeutic results while lowering hazards.

The combination of denosumab and calcitriol is a logical treatment approach to address this unmet need; denosumab offers strong antifracture protection, while calcitriol may reduce denosumab-induced hypocalcemia by preserving calcium homeostasis. Although there is currently little direct clinical evidence from carefully planned studies assessing this particular combination, such a strategy makes use of the complimentary mechanisms of both drugs and may produce synergistic effects.[12] Notably, calcitriol monotherapy has been used as an active comparator in Chinese postmenopausal osteoporosis studies;[13,14] therefore, comparing the combination against calcitriol alone allows us to assess the incremental benefit of adding denosumab. However, most existing studies on this combination are limited to basic research or small-sample clinical observations, and large-scale retrospective or randomized controlled trials focusing on the Chinese postmenopausal population remain scarce.

To capture both clinical and patient-centered benefits, we assessed objective outcomes (bone mineral density, bone turnover markers, and calcium-phosphate homeostasis) alongside patient-reported outcomes (pain, function, and activities of daily living). This retrospective cohort study therefore aimed to compare the efficacy and safety of calcitriol combined with denosumab versus calcitriol alone in postmenopausal osteoporosis, thereby providing evidence to inform therapeutic strategies.

Materials and Methods

Study Design

Female patients diagnosed with primary osteoporosis following menopause were retrospectively enrolled from Zhoupu Hospital, located in Shanghai's Pudong New Area, between July 2020 and May 2025. Case identification was performed by extracting relevant diagnostic codes from the hospital's electronic medical record system. The diagnosis of osteoporosis was established in accordance with the criteria set forth in the Chinese Guidelines for the Diagnosis and Treatment of Primary Osteoporosis (2022 Edition),[15] These guidelines specify that a diagnosis can be made upon meeting one or more defined clinical or densitometric criteria, supported by a comprehensive clinical assessment. (1) experience a fragility fracture of the hip or vertebrae, irrespective of bone mineral density; (2) present a bone mineral density T-score of −2.5 or lower at the femoral neck, lumbar spine (L1-L4), or total hip; or (3) have low bone mass (a T-score between −2.5 and −1.0) accompanied by a fragility fracture of the proximal humerus, distal forearm, or pelvis.

The study protocol was approved by the Institutional Review Board (IRB) of Shanghai Pudong New Area Zhoupu Hospital (Approval No.: 2025-C-236-E01). All patient information was de-identified prior to analysis.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) age 50–75 years with natural amenorrhea ≥12 months; (2) completion of ≥12 months of continuous treatment; (3) complete baseline and 12-month follow-up data available.

Exclusion criteria: (1) secondary osteoporosis (including prolonged glucocorticoid therapy with prednisone ≥5 mg/day for >3 months, hyperthyroidism, or hyperparathyroidism); (2) severe hepatic impairment (Child-Pugh class C) or renal insufficiency (eGFR <30 mL/min/1.73 m^2); (3) active malignancy or bone metastases within 5 years; (4) use of other bone-active medications (eg, bisphosphonates, teriparatide, selective estrogen receptor modulators, romosozumab) within 12 months before baseline.

Sample Size Calculation

A preliminary power calculation was performed with PASS 15 software. The analysis was configured to detect a 25% absolute difference in the primary endpoint (percentage of participants achieving a lumbar spine BMD increase ≥3%). Assumed response rates were 75% for the combination group[16] and 50% for the calcitriol-alone group.[9] With $\alpha = 0.05$

and 80% power, 55 participants per group (110 total) were required. Our final cohort of 306 participants (144 vs. 162) exceeded this estimate.

Treatment Regimens

According to the therapeutic regimens administered during the observation period, eligible participants were categorized into two cohorts: an observation group receiving combination therapy with denosumab and calcitriol (n = 144), and a control group receiving calcitriol monotherapy (n = 162). In the observation group, patients received subcutaneous denosumab (Prolia®; 60 mg) once every 6 months (at baseline and month 6), oral calcitriol (Rocaltrol®; 0.25 μg) twice daily, and a daily oral supplement of 600 mg elemental calcium and 400 IU cholecalciferol. Patients in the control group received the same oral calcitriol and calcium/vitamin D_3 supplement without denosumab. The treatment duration was 12 months.

Outcome Measures and Assessment Methods

All study endpoints were evaluated at baseline and at the 12-month follow-up. BMD at the lumbar spine (L2-L4), femoral neck, and total hip was measured using a Hologic Discovery Wi dual-energy X-ray absorptiometry (DXA) system with daily quality control calibration. All scans were performed by certified radiologic technologists. Fasting morning venous blood samples (8:00–10:00 a.m) were collected to minimize diurnal variability. Serum levels of bone resorption markers (β-CTX, TRACP-5b), bone formation markers (P1NP, BGP), intact parathyroid hormone (PTH), and 25-hydroxyvitamin D [25(OH)D] were quantified using electrochemiluminescence immunoassay (Roche platform) and chemiluminescence immunoassay (Siemens platform).

Functional and symptomatic status was measured using three standardized instruments: the Visual Analogue Scale (VAS) for pain severity,[17] the Oswestry Disability Index (ODI) for back-specific functional impairment,[18] and the Barthel Index (BI) for assessing activities of daily living.[19]

Overall Clinical Efficacy Assessment

Overall clinical efficacy was assessed using a composite endpoint comprising functional improvement, pain relief, and BMD enhancement, categorized into three levels: "Significant improvement", "Effective", and "Ineffective". Specific grading criteria were: (1) Significant improvement: ODI improvement ≥30%,[20] BMD increase ≥5%,[21] and VAS score reduction ≥30%;[22] (2) Effective: ODI improvement 15%–30%, BMD increase 2%–5%, and VAS reduction 25%–50%; (3) Ineffective: failure to meet the criteria for "Effective".

Adverse Events

Data concerning prespecified adverse events of special interest (AESI) were systematically collected from electronic medical records. The monitored AESIs included hypocalcemia, musculoskeletal pain, pyrexia, serious cardiovascular events, osteonecrosis of the jaw, atypical femoral fractures, and hepatic or renal impairment. Causality was assessed by investigators based on temporal relationship and clinical context. Serious adverse events (SAEs) were defined as any event that was fatal, life-threatening, required inpatient admission or prolonged hospitalization, or resulted in significant disability.

Medication adherence was assessed using electronic medical records and pharmacy refill data. Adherence was defined as receipt of at least 80% of prescribed doses. For denosumab, adherence required both scheduled injections (months 0 and 6). Patients with documented poor adherence were excluded from the primary analysis.

Statistical Analysis

Statistical evaluations were conducted using IBM SPSS Statistics for Windows (Version 26.0). Missing data were handled using multiple imputation. The normality of continuous variables was examined with the Shapiro–Wilk test. Based on this assessment, normally distributed data are summarized as mean ± standard deviation, while non-normally distributed data are reported as median and interquartile range. Group comparisons for normally distributed variables employed the independent samples *t*-test, with outcomes presented as mean difference (MD) and 95% confidence interval (CI). For non-normally distributed variables, the Mann–Whitney *U*-test was applied, and results are given as the median difference along with its 95% CI. Categorical variables are described as counts and percentages (n, %) and were compared using the Pearson Chi-square test

or Fisher's exact test, as appropriate. To evaluate treatment efficacy longitudinally within each cohort, intra-group comparisons between baseline and the 12-month evaluation point were performed. Depending on data distribution, either the paired-samples *t*-test or the Wilcoxon signed-rank test was employed. A two-tailed p-value below the predefined alpha level of 0.05 was considered indicative of statistical significance.

Results

Patient Baseline Characteristics

The final analytical cohort comprised 306 patients, with 144 assigned to the observation group and 162 to the control group. Comparative analysis demonstrated that the groups were well-balanced at baseline, showing no statistically significant disparities in demographic characteristics (age, age at menopause, body mass index), lifestyle factors (smoking history, alcohol consumption, exercise frequency), clinical history (prior fragility fractures, comorbidities including diabetes and rheumatoid arthritis, previous use of anti-osteoporosis medications, parental history of hip fracture), or initial laboratory values (serum calcium, phosphorus, and creatinine) (all $P > 0.05$; Table 1).

Table 1 Baseline Characteristics of the Observation and Control Groups

Variable	Observation Group (n = 144)	Control Group (n = 162)	t/χ^2	*P*
Age (years, $\bar{x} \pm s$)	57.78 ± 2.31	57.82 ± 2.13	0.158	0.895
Age at menopause (years, $\bar{x} \pm s$)	8.49 ± 1.80	8.47 ± 1.72	0.099	0.921
Body mass index (kg/m^2, $\bar{x} \pm s$)	25.15 ± 3.47	24.67 ± 3.25	1.249	0.213
Smoking history (n, %)			1.927	0.165
Yes	8 (5.56)	4 (2.47)		
No	136 (94.44)	158 (97.53)		
Alcohol use history (n, %)			0.531	0.466
Yes	18 (12.50)	16 (9.88)		
No	126 (87.50)	146 (90.12)		
Exercise frequency (n, %)			0.059	0.809
Yes	26 (18.06)	31 (19.14)		
No	118 (81.94)	131 (80.86)		
History of fragility fracture (n, %)			0.444	0.505
Yes	32 (22.22)	31 (19.14)		
No	112 (77.78)	131 (80.86)		
Diabetes mellitus (n, %)			0.378	0.539
Yes	22 (15.28)	29 (17.90)		
No	122 (84.72)	133 (82.10)		
Rheumatoid arthritis (n, %)			0.261	0.609
Yes	12 (8.33)	11 (6.79)		
No	132 (91.67)	151 (93.21)		
Prior anti-osteoporotic drug use (n, %)			0.049	0.826
Yes	34 (23.61)	40 (24.69)		
No	110 (76.39)	122 (75.31)		
Parental history of hip fracture (n, %)			0.847	0.358
Yes	16 (11.11)	13 (8.02)		
No	128 (88.89)	149 (91.98)		
Serum calcium (mmol/L, $\bar{x} \pm s$)	2.34 ± 0.23	2.35 ± 0.22	0.389	0.698
Serum phosphorus (mmol/L, $\bar{x} \pm s$)	1.26 ± 0.23	1.23 ± 0.23	1.139	0.256
Serum creatinine (μmol/L, $\bar{x} \pm s$)	68.46 ± 12.38	67.93 ± 12.26	0.376	0.707

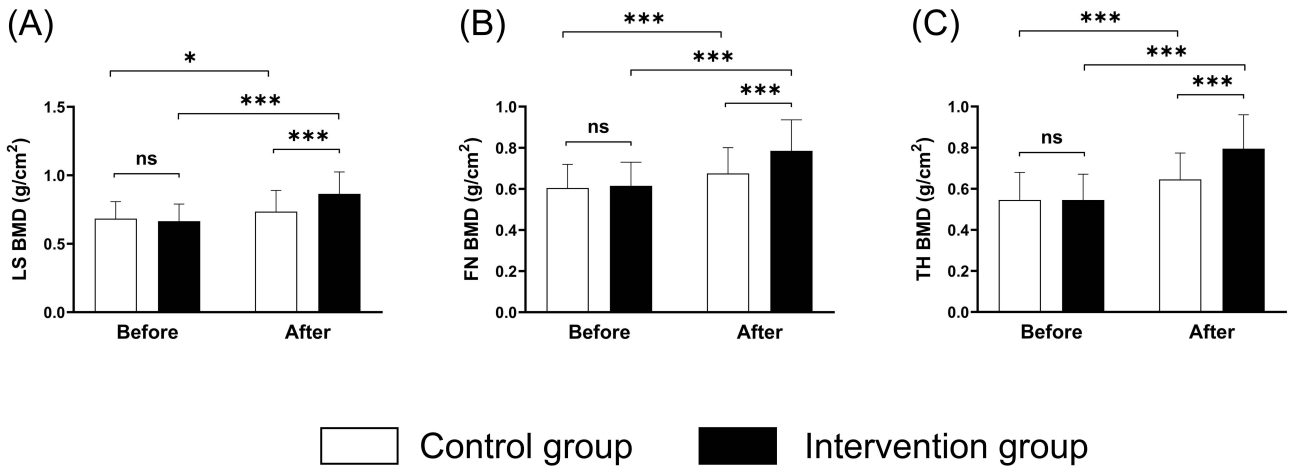

Figure 1 Comparison of bone mineral density changes between the observation group and the control group. Data are presented as bar graphs showing mean ± standard deviation (SD). BMD was measured at (**A**) lumbar spine (L2-L4) (LS BMD), (**B**) femoral neck (FN BMD), and (**C**) total Hip (TH BMD) before and after the treatment period. Statistical significance between groups at the post-treatment time point is indicated (ns, not significant; *$P < 0.05$; ***$P < 0.001$.

Changes in Bone Mineral Density

As depicted in Figure 1, baseline BMD measurements were comparable between the two groups. Following the intervention, both cohorts exhibited statistically significant gains in BMD at the lumbar spine, femoral neck, and total hip. However, the magnitude of increase at all three skeletal sites was markedly more pronounced in the observation group relative to the control group by the conclusion of the 12-month treatment period ($P < 0.05$).

Serum Bone Turnover Biomarkers

Serum concentrations of bone turnover markers before and following treatment are displayed in Figure 2. After the 12-month intervention, both treatment groups demonstrated a significant reduction in the levels of bone resorption markers (β-CTX and TRACP-5b) and bone formation markers (P1NP and BGP). The observation group demonstrated a more pronounced reduction in all four biomarkers compared to the control group, with the differences being statistically significant ($P < 0.05$).

Calcium-Phosphate Homeostasis

The effects on the calcium-phosphate metabolism regulatory axis are shown in Figure 3. Following the treatment period, notable alterations in calcium-phosphate homeostasis were observed. PTH levels demonstrated a significant decline, whereas 25(OH)D concentrations increased substantially in both cohorts. However, the reduction in PTH and the elevation in 25(OH)D were both more pronounced in the observation group compared to the control group ($P < 0.05$).

Patient-Reported and Functional Outcomes

Improvements in clinical functional scores are displayed in Figure 4. At the 12-month evaluation, both cohorts demonstrated statistically significant improvements in functional outcomes, including reduced pain severity (VAS score), diminished disability (ODI index), and enhanced capacity for activities of daily living (BI index). The magnitude of these enhancements across all three functional metrics was significantly more pronounced in the observation group than in the control group ($P < 0.05$).

Overall Treatment Response

A statistically significant difference in overall clinical efficacy was observed between the two groups ($\chi^2 = 13.791$, $P = 0.001$). As documented in Table 2, the observation group exhibited a substantially greater proportion of patients achieving "Significant improvement" (56.25%) relative to the control group (37.04%). In contrast, the incidence of ineffective treatment was lower in the observation group (8.33%) compared to the control group (19.14%).

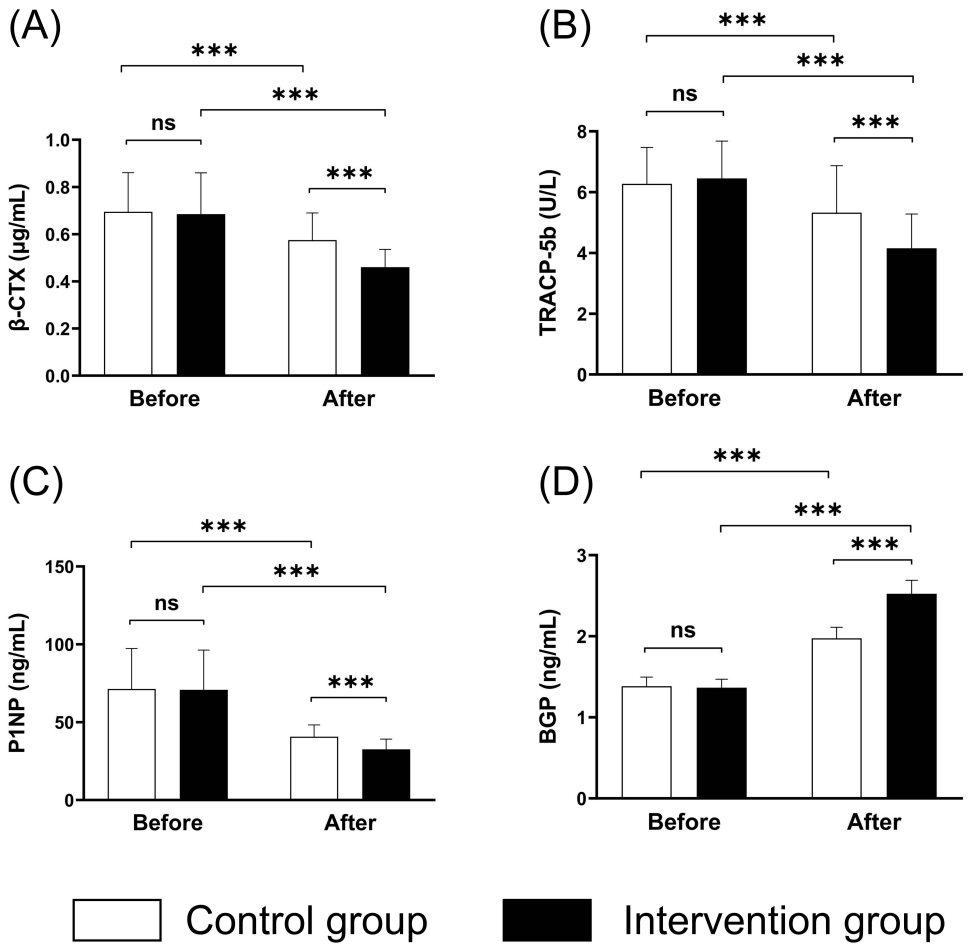

Figure 2 Comparison of bone turnover marker levels between the observation group and the control group. Data are presented as bar graphs showing mean ± standard deviation (SD). Serum levels of (**A**) β-C-terminal telopeptide of type I collagen (β-CTX), (**B**) Tartrate-resistant acid phosphatase 5b (TRACP-5b), (**C**) Procollagen type I N-terminal propeptide (P1NP), and (**D**) Bone gla protein (BGP, Osteocalcin) were measured before and after the treatment period. Statistical significance between groups at the post-treatment time point is indicated (ns, not significant; ***$P < 0.001$).

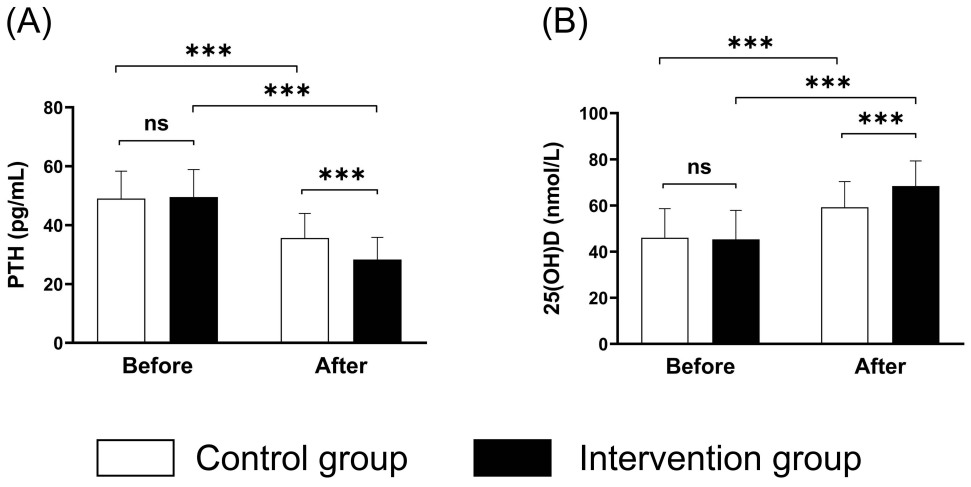

Figure 3 Comparison of calcium-phosphate metabolism regulatory axis between the observation group and the control group. Data are presented as bar graphs showing mean ± standard deviation (SD). Serum levels of (**A**) Parathyroid hormone (PTH) and (**B**) 25-hydroxyvitamin D [25(OH)D] were measured before and after the treatment period. Statistical significance between groups at the post-treatment time point is indicated (ns, not significant; ***$P < 0.001$).

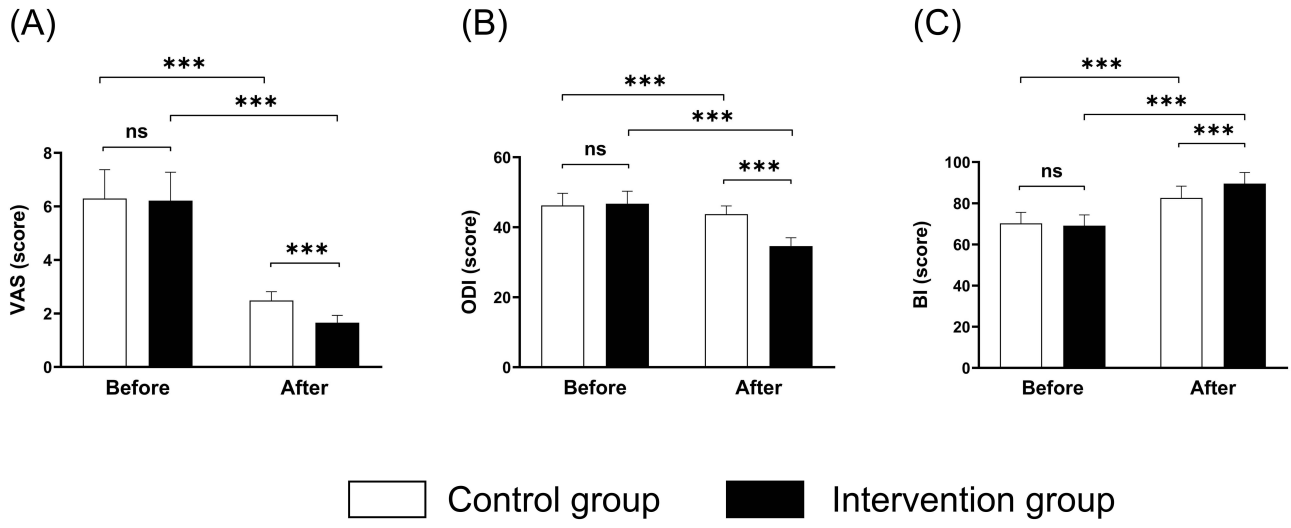

Figure 4 Comparison of clinical functional scores between the observation group and the control group. Data are presented as bar graphs showing mean ± standard deviation (SD). (**A**) Visual Analogue Scale (VAS) score, (**B**) Oswestry Disability Index (ODI), and (**C**) Barthel Index (BI) were assessed before and after the treatment period. Statistical significance between groups at the post-treatment time point is indicated (ns, not significant; ***$P < 0.001$).

Adverse Events and Safety Profile

As shown in Table 3, the total rate of adverse reactions was 5.56% (8 out of 144 patients) in the observation group and 2.47% (4 out of 162 patients) in the control group. A comparison between the groups revealed that the difference was not statistically significant ($\chi^2 = 1.927$, $P = 0.165$). Hypocalcemia was the most common adverse event, occurring in 6 patients (4.17%) in the Observation group and 2 patients (1.23%) in the control group. Arthralgia or limb pain was reported by two (1.39%) and two (1.23%) patients, respectively, in the observation and control groups. No significant adverse events, such as osteonecrosis of the jaw, atypical femoral fractures, serious cardiovascular events, or significant liver/renal dysfunction, occurred in either group during the study duration.

Table 2 Comparison of Clinical Efficacy Between the Two Groups [n (%)]

Group	Ineffective	Effective	Significant Improvement	χ^2	*P*
Observation (n = 144)	12 (8.33)	51 (35.42)	81 (56.25)	13.791	0.001
Control (n = 162)	31 (19.14)	71 (43.83)	60 (37.04)		

Table 3 Comparison of Safety Events Between the Two Groups [n (%)]

Adverse Event	Observation Group (n = 144)	Control Group (n = 162)	χ^2	*P*
Overall incidence	8 (5.56)	4 (2.47)	1.927	0.165
Hypocalcemia	6 (4.17)	2 (1.23)		
Arthralgia/Limb pain	2 (1.39)	2 (1.23)		
Fever	0 (0.00)	0 (0.00)		
Serious cardiovascular events	0 (0.00)	0 (0.00)		
Osteonecrosis of the jaw	0 (0.00)	0 (0.00)		
Atypical femoral fracture	0 (0.00)	0 (0.00)		
Liver or renal dysfunction	0 (0.00)	0 (0.00)		

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Discussion

Denosumab is essential for reducing the risk of fracture in people with postmenopausal osteoporosis, but its clinical results still need to be significantly improved.[12,23] According to current studies, the clinical management of osteoporosis is improved when calcitriol is added to denosumab medication. Increased bone mineral density at the lumbar spine, femoral neck, and total hip; increased suppression of bone formation and resorption markers; improved regulation of calcium-phosphate homeostasis; and superior improvements in patient-centered measures like pain relief, functional capacity, and everyday independence were all results of this combined approach. Consequently, a substantially higher proportion of patients had a "significant improvement" in their overall clinical response. This excellent efficacy was accompanied by a manageable safety profile because all episodes of hypocalcemia were mild and quickly treated, and there was no appreciable increase in overall adverse events. These results establish the calcitriol-denosumab regimen as a way to optimize anti-fracture efficacy.

In the present retrospective study, the proportion of patients achieving marked clinical improvement was higher in the combination group than in the calcitriol monotherapy group, suggesting better functional recovery, pain relief, and BMD gains. The complementary mechanisms of calcitriol and denosumab may explain this observation:[24,25] calcitriol enhances intestinal calcium absorption and neuromuscular function, while denosumab suppresses osteoclast-mediated bone resorption. Meta-analyses have confirmed that denosumab monotherapy increases BMD and reduces fracture risk compared with placebo or bisphosphonates.[6,26] However, clinical data on combining denosumab with active vitamin D are limited. A 2025 study reported that adding calcitriol to denosumab improved lumbar spine BMD and bone turnover markers.[27] Our findings extend this evidence by suggesting, in a Chinese postmenopausal cohort, that the combination may also improve patient-reported outcomes (VAS, ODI, BI). Given the retrospective design, these results should be interpreted as hypothesis-generating.

In the present retrospective study, the combination group showed greater BMD improvements at all skeletal sites than the calcitriol monotherapy group, likely due to the complementary mechanisms of denosumab and calcitriol.[2,28] Denosumab was given at the standard 6-month interval (two doses over 12 months), and previous trials have shown that such a regimen increases BMD as early as 6 months.[16,28] Denosumab inhibits RANKL, reducing bone resorption markers (β-CTX, TRACP-5b) and, secondarily, formation markers (P1NP, BGP), which is consistent with the coupled process of bone remodeling. Our findings align with previous reports that denosumab suppresses bone turnover and increases BMD more effectively than oral bisphosphonates.[6,28] Calcitriol did not interfere with denosumab's antiresorptive effect; rather, by enhancing intestinal calcium absorption, it may support bone mineralization when bone turnover is low. The combination therefore may produce a net gain in bone mass, although the retrospective design precludes causal inference. While marked suppression of bone turnover reflects the potent antiresorptive effect of denosumab, long-term very low bone turnover has been associated with rare but serious adverse events such as atypical femoral fractures or osteonecrosis of the jaw.[26,28] The 12-month follow-up in this study is too short to capture these potential risks, which deserve attention in future longer-term studies.

Improvements in patient-reported outcomes were also observed in this study. Increased bone mineral density may alleviate pain associated with fragile bone structure.[29] Calcitriol has been shown to enhance neuromuscular function by regulating calcium homeostasis, potentially improving muscle strength, balance, and endurance.[2] A meta-analysis comparing denosumab and bisphosphonates confirmed that denosumab is generally well-tolerated, with certain adverse events potentially attributable to its beneficial effects on bone metabolism.[26] Furthermore, clinical practice guidelines recommend considering adjunctive active vitamin D in patients receiving potent antiresorptive agents, particularly those with impaired renal function or vitamin D resistance.[30,31] Consistent with contemporary integrated care models, combining pharmacological treatment with rehabilitation and patient education may holistically address both bone strength and physical function.[5] Given the retrospective design, these observations should be interpreted as hypothesis-generating and warrant prospective validation.

In this study, hypocalcemia occurred in 4.17% of the combination group, which is lower than the 5–10% range reported in some previous denosumab studies.[9,31] This lower incidence may be attributed to the concurrent use of calcitriol (0.25 μg twice daily), which actively enhances intestinal calcium absorption, together with routine calcium/

vitamin D_3 supplementation and normal baseline serum calcium levels in our cohort. Lower parathyroid hormone (PTH) levels in the intervention group suggest that calcitriol enhanced intestinal calcium absorption, preventing a compensatory PTH rise and maintaining calcium homeostasis.[10,29] This mechanism ensures a steady mineral supply for bone formation and preserves ionic balance for neuromuscular function.[10] Calcitriol may also directly promote bone formation by activating osteoblasts, osteocytes, and mesenchymal stem cells.[32] However, denosumab-induced hypocalcemia is not completely prevented by calcium and vitamin D alone, especially within the first three months.[33] Adding active vitamin D (eldecalcitol) to denosumab suppressed bone turnover markers more than native vitamin D, though BMD gains did not differ significantly.[34] Zinc supplementation also enhanced BMD benefits of denosumab and eldecalcitol in patients with hypozincemia, suggesting mineral co-factors may further optimize outcomes.[35] Given the retrospective design, our observations on calcitriol's preventive effect against hypocalcemia should be interpreted as hypothesis-generating and require prospective validation.

Previous studies have suggested that denosumab plus native vitamin D is associated with increased BMD and reduced fracture risk.[6,26] Regarding the addition of active vitamin D, Suzuki et al reported that combination therapy with denosumab and eldecalcitol (ELD) could improve femoral neck BMD more effectively than denosumab plus native vitamin D.[34] Our retrospective findings extend these observations by showing that adding calcitriol (0.25 μg twice daily) to denosumab was associated with not only suppressed bone turnover but also greater improvements in patient-reported outcomes (VAS, ODI, BI)—outcomes that have not been systematically evaluated in previous combination studies. Furthermore, the hypocalcemia rate in our combination group (4.17%) was lower than the 5–10% range often reported with denosumab plus native vitamin D,[9,33] raising the possibility that proactive use of calcitriol may help maintain calcium homeostasis. Compared with bisphosphonate-based regimens, the calcitriol-denosumab combination offered the convenience of twice-yearly subcutaneous injection and was not associated with the gastrointestinal intolerance commonly seen with oral bisphosphonates in our cohort.[6] Based on these retrospective data, the potential advantages of this regimen may include: (1) more pronounced BMD gains across multiple skeletal sites; (2) better control of patient-reported pain and function; (3) a possibly lower risk of hypocalcemia through enhanced intestinal calcium absorption; and (4) favorable tolerability with no severe adverse events observed. However, head-to-head randomized trials are needed to confirm these potential benefits.

In this study, the safety profile of the combination therapy was consistent with expectations. Hypocalcemia occurred slightly more often in the denosumab plus calcitriol group (4.17%) than in the calcitriol monotherapy group (1.23%), a finding in line with previous reports.[9] This difference likely reflects the potent and rapid antiresorptive effect of denosumab. However, all hypocalcemic events were mild, asymptomatic, and managed with short-term adjustments of calcium or vitamin D supplementation; no patient discontinued the study drug. The favorable safety profile was further supported by laboratory findings: patients receiving combination therapy had higher 25(OH)D levels and lower PTH levels, suggesting that prophylactic calcitriol enhanced intestinal calcium absorption and mitigated denosumab induced calcium loss.[29] Recent evidence confirms that denosumab associated hypocalcemia is not fully prevented by standard calcium and vitamin D alone, particularly in the first three months of treatment.[33] Nevertheless, our results indicate that the addition of calcitriol may preserve calcium homeostasis and prevent secondary hyperparathyroidism. Given the retrospective design, these safety observations should be interpreted as hypothesis generating.

By evaluating treatment response in a number of areas, including bone density, bone turnover markers, calcium and phosphorus levels, pain scores, functional status, and daily living activities, this study was able to achieve a comprehensive evaluation. Nevertheless, the study has certain limitations. Firstly, because it was conducted at a single center and had a retrospective design, selection bias and residual confounding from unmeasured variables cannot be entirely ruled out, which may have led to overestimation or underestimation of the observed treatment effects. Patient-reported outcomes (VAS, ODI, BI) in particular could be influenced by coexisting conditions such as osteoarthritis or sarcopenia, which were not fully captured. Secondly, the 12-month observation duration and the relatively small sample size constitute a drawback. As a result, with limited sample size and only 12 months of follow-up, this study was unable to reliably assess rare but clinically critical endpoints such as fracture incidence, atypical femoral fractures, or osteonecrosis of the jaw. The absence of fracture data limits direct clinical interpretation, as BMD is a surrogate endpoint[5,16] Furthermore, tracking the long-term effects after discontinuing treatment was challenging due to the short

follow-up, which is a recognized issue with denosumab therapy. To provide more solid evidence, future prospective, randomized controlled trials with longer observation periods, larger sample sizes, and multicenter design are needed. For subsequent retrospective studies, analytical approaches such as propensity score matching or inverse probability of treatment weighting could help mitigate selection bias and balance covariates between groups.

Conclusion

In this retrospective study, adding calcitriol to denosumab was associated with better bone density, bone turnover, and functional outcomes than calcitriol alone, with mild and manageable hypocalcemia. From a clinical perspective, this combination may be considered for postmenopausal osteoporosis patients who require potent antiresorptive therapy, particularly those with prior fragility fractures or very low bone mineral density. The standard regimen is denosumab 60 mg every 6 months plus calcitriol 0.25 μg twice daily, with no routine dose adjustment except to withhold calcitriol if hypercalcemia occurs. Monitoring should include serum calcium, phosphorus, and renal function at baseline and periodically during treatment. Prospective trials are needed to confirm these potential benefits.

Data Sharing Statement

The data generated or analyzed during this investigation are available from the corresponding author (Yi Shen) upon reasonable request.

Ethics Approval and Consent to Participate

This retrospective cohort study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Shanghai University of Medicine & Health Sciences Affiliated Zhoupu Hospital (Approval No.: 2025-C-236-E01). Given the retrospective nature of the study, which utilized anonymized data from electronic medical records, the requirement for written informed consent was waived by the aforementioned IRB.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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