

Full Length Article

Effect of combination versus sequential teriparatide initiation on vertebral bone marrow microenvironment in postmenopausal women with prior denosumab treatment: A propensity score-matched study

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ABSTRACT

Background: The optimal strategy for transitioning from long-term denosumab (DMAB) to teriparatide (TPTD) in postmenopausal osteoporosis remains a clinical dilemma, as DMAB withdrawal can trigger a deleterious rebound in bone resorption. While bone mineral density (BMD) is the traditional benchmark, it fails to capture critical aspects of bone quality, such as the bone marrow microenvironment. This study investigated whether the method of TPTD initiation—adding it to ongoing DMAB (combination) versus switching after DMAB withdrawal (sequential)—differentially affects the vertebral bone marrow microenvironment, assessed by the MRI-derived vertebral bone quality (VBQ) score, a novel marker of marrow adiposity.

Methods: In this retrospective cohort study, postmenopausal women with osteoporosis who received TPTD for ≥ 12 months after at least 24 months of DMAB were included. Propensity score matching (1:1) yielded 60 patients in the combination group and 60 in the sequential group. The primary outcome was the percentage change in VBQ (Δ VBQ%) from baseline to 12 months.

Results: Combination therapy resulted in a significant improvement in the bone marrow microenvironment (Δ VBQ%: $-7.1\% \pm 3.0\%$), whereas sequential therapy did not ($-0.5\% \pm 5.4\%$), with an adjusted between-group difference of -6.5% (95%CI: -8.1 to -4.9 , $P < 0.001$). This was accompanied by superior gains in lumbar spine BMD ($+9.4\%$ vs. $+5.6\%$, $P < 0.001$) and trabecular bone score ($+4.8\%$ vs. $+1.5\%$, $P < 0.001$). Notably, the combination group maintained complete suppression of bone resorption (CTX), while the sequential group experienced a marked and sustained CTX rebound. Furthermore, in the combination group, the improvement in VBQ was significantly correlated with early bone formation activation (Δ PINP at M + 3, $r = -0.50$) and with gains in lumbar spine BMD ($r = -0.40$) and TBS ($r = -0.77$), suggesting a mechanistic link between modeling-based bone formation and microenvironmental restoration.

Conclusions: In postmenopausal women with long-term prior denosumab treatment, initiating teriparatide while continuing denosumab was associated with significantly greater improvement in the vertebral bone marrow microenvironment (greater VBQ reduction), more consistent gains in lumbar spine BMD and TBS, and better control of bone resorption markers over 12 months compared with a sequential switch after denosumab withdrawal. These findings suggest that the combination strategy may be more favorable than a sequential switch for improving vertebral bone quality. While our data provide mechanistic support for current guideline recommendations, confirmation in prospective randomized studies is required before clinical translation.

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Key points

1. In postmenopausal women with long-term prior denosumab treatment, initiating teriparatide while continuing denosumab (combination strategy) resulted in significantly greater improvement in the vertebral bone marrow microenvironment (greater VBQ reduction) compared with sequential teriparatide after denosumab withdrawal.
2. The combination strategy was associated with more consistent gains in lumbar spine BMD (+9.4% vs. +5.6%) and trabecular bone score (+4.8% vs. +1.5%) over 12 months.
3. The combination group maintained complete suppression of bone resorption (CTX), whereas the sequential group exhibited a marked and sustained rebound in bone resorption.
4. In the combination group, early bone formation marker activation (Δ PINP at month 3) was significantly correlated with subsequent improvements in VBQ, BMD, and TBS, suggesting a mechanistic link between early osteoblast activity and later bone quality restoration.
5. These findings provide novel evidence from the perspective of bone marrow microenvironment and bone quality that supports current guideline recommendations against direct transition from denosumab to anabolic therapy without antiresorptive cover. However, given the single-center retrospective design, the results should be interpreted with caution and require confirmation in prospective randomized studies.

1. Introduction

It should be noted that current international consensus advocates an “anabolic-first” strategy—prioritizing bone-forming agents when feasible, followed by consolidation with antiresorptive therapy—to maximize net gains in both bone mass and quality [1]. However, in real-world clinical practice, a substantial proportion of patients have already been on long-term antiresorptive therapy, particularly denosumab (DMAB), due to accessibility, comorbidities, or prior treatment pathways. Introducing teriparatide (TPTD) in this context is not a simple replication of the “anabolic-first” paradigm but presents practical challenges including withdrawal rebound, altered bone remodeling dynamics, and uncertain bone quality outcomes [2,32]. Therefore, clarifying the impact of different TPTD initiation strategies (combination vs. sequential) on bone marrow microenvironment and comprehensive bone quality parameters in patients with prior DMAB exposure retains direct clinical relevance.

Denosumab, a potent RANKL inhibitor, significantly reduces bone resorption and increases bone mineral density (BMD), making it a cornerstone of antiresorptive therapy for postmenopausal osteoporosis [3]. However, discontinuation or interruption of DMAB can lead to a rebound in bone turnover, rapid BMD loss, and an elevated risk of vertebral fractures [4,5]. In clinical settings where patients remain at high risk or exhibit inadequate bone mass/quality improvement after long-term DMAB treatment, transitioning to bone-forming agents such as TPTD is often considered [6]. Previous studies suggest that a direct sequential switch from DMAB to TPTD may result in an early surge in bone resorption and partial BMD decline, indicating that the initiation strategy may influence bone remodeling kinetics [7].

Beyond BMD, the bone marrow microenvironment—particularly marrow adipose tissue infiltration—is increasingly recognized as a critical factor linked to altered bone remodeling, trabecular microarchitecture, and skeletal fragility [8,9]. Although direct quantification of marrow fat is challenging in routine clinical practice, magnetic resonance imaging (MRI) signal intensities can reflect differences in fat and water composition. The vertebral bone quality (VBQ) score, derived from the ratio of vertebral body to cerebrospinal fluid signal on T1-weighted MRI, serves as a simple surrogate marker for vertebral marrow adiposity and has been associated with osteoporotic fracture risk and changes in bone quality [10,11]. Thus, VBQ may serve as an imaging biomarker to evaluate the impact of treatment strategies on the vertebral bone marrow microenvironment.

Currently, direct comparative evidence regarding the effects of different TPTD initiation strategies (combination vs. sequential) on bone marrow microenvironment and integrated bone quality parameters such as the trabecular bone score (TBS) in patients with prior DMAB treatment remains scarce. Based on a retrospective cohort with propensity score matching, this study aimed to compare the effects of combination versus sequential TPTD initiation on changes in VBQ, BMD, TBS, and bone turnover markers over a 12-month period.

It should be noted that current guidelines, including those from the National Osteoporosis Guideline Group (NOGG, 2024) [35] and the American Association of Clinical Endocrinologists (AACE, 2020) [36], do not recommend a direct switch from denosumab to teriparatide without antiresorptive bridging. However, in real-world practice, oral bisphosphonates may be poorly tolerated or contraindicated in patients with renal impairment; intravenous zoledronic acid may not be covered by local insurance or accessible in some settings; and the high cost of teriparatide often forces patients to choose a single drug rather than combination therapy. In such circumstances, some patients transition directly to teriparatide out of clinical necessity rather than preference. The sequential strategy examined here should therefore be understood as a reflection of these real-world constraints, not as a guideline-endorsed approach. Our aim is not to advocate for this strategy, but to evaluate its consequences.

2. Methods

2.1. Study design and ethics

This retrospective cohort study was conducted at a single tertiary spine center. The study protocol was approved by the local institutional review board and conducted in accordance with the Declaration of Helsinki and its subsequent amendments. Due to the retrospective nature of the study, the requirement for written informed consent was waived. The reporting of this study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines [12].

2.2. Study population

Inclusion criteria: Postmenopausal women (age ≥ 50 years) meeting the diagnostic criteria for osteoporosis; continuous use of denosumab for 24 months (± 3 months) prior to the initiation of teriparatide (defined as M0); continuous subcutaneous administration of teriparatide (20 μ g/day) for at least 12 months; availability of lumbar spine MRI and DXA scans within 3 months before TPTD initiation (M0) and at 12 months (M + 12); and availability of serum CTX and PINP measurements at M0, M + 3, M + 6, and M + 12.

Exclusion criteria: Secondary osteoporosis; history of malignancy or high risk of bone metastasis within the past 5 years; prior use of teriparatide or romosozumab; recent use of medications affecting bone metabolism (intravenous/oral bisphosphonates within 2/12 months, SERMs, strontium ranelate, or calcitonin within 6 months); long-term systemic glucocorticoid therapy; poor image quality affecting VBQ measurement; fewer than 2 evaluable vertebrae on DXA; and $> 20\%$ missing key variables (baseline BMD, VBQ, CTX, PINP).

2.3. Group definitions

The time of teriparatide initiation was defined as M0.

Combination group: The last denosumab dose was administered ≤ 6 months before M0, and denosumab was continued as scheduled every 6 months during the teriparatide treatment period.

Sequential group: The last denosumab dose was administered ≥ 7 months before M0, and no denosumab was given during the teriparatide treatment period.

Treatment strategies were determined by shared decision-making

between clinicians and patients; no randomization was performed.

2.4. Data collection and measurements

VBQ score: Based on T1-weighted lumbar spine MRI, regions of interest (ROIs) were placed in the central trabecular bone area of L1-L4 vertebrae, avoiding cortical bone, endplate sclerosis, hemangiomas, and focal lesions. CSF signal intensity was measured at the L3 level. VBQ was calculated as the median signal intensity (L1-L4) divided by the CSF signal intensity [10]. Two independent readers, blinded to clinical data, performed all measurements. The VBQ score has been previously validated as a reliable imaging surrogate for bone quality. Ehresman et al. demonstrated that higher VBQ scores were independently associated with lower DXA-based BMD and an increased risk of osteoporotic fragility fractures. Subsequent studies have further confirmed its good inter- and intra-observer reliability, supporting its applicability in longitudinal research settings. Intraclass correlation coefficients (ICC) were calculated in a random subset to assess inter- and intra-rater reliability.

BMD and TBS: BMD values at the lumbar spine (L1-L4), femoral neck, and total hip were extracted from DXA scans. TBS was calculated from lumbar spine DXA images using TBS iNsight® software (v3.1, Med-Imaps, France) following ISCD official guidelines [13].

Bone turnover markers: Fasting serum CTX and PINP were measured by electrochemiluminescence immunoassay (Roche Diagnostics) at M0, M + 3, M + 6, and M + 12.

All measurements were anchored to the M0 time point.

2.5. Outcome measures

Primary outcome: Percentage change in VBQ from M0 to M + 12 (Δ VBQ%).

Secondary outcomes: Percentage changes in lumbar spine, femoral neck, and total hip BMD (Δ BMD%); percentage change in TBS (Δ TBS%); trajectories of CTX and PINP over time; incidence of new clinical fractures; and safety events.

2.6. Statistical analysis

Propensity score matching (PSM): A logistic regression model was used to estimate propensity scores based on the treatment strategy. Covariates included age, BMI, duration of prior DMB treatment before TPTD initiation, baseline VBQ, baseline BMD, baseline TBS, baseline CTX, baseline PINP, and history of prior fractures. Nearest-neighbor 1:1 matching was performed with a caliper of 0.2 times the standard deviation of the logit propensity score. Covariate balance was assessed using standardized mean differences (SMD), with SMD <0.10 indicating good balance [14,15].

Baseline comparisons: Continuous variables were presented as mean $\pm$ standard deviation or median [interquartile range], and categorical variables as frequencies (%). Between-group comparisons were performed using *t*-tests or Mann-Whitney *U* tests for continuous variables, and chi-square or Fisher's exact tests for categorical variables.

Primary outcome analysis: Analysis of covariance (ANCOVA) was used to compare Δ VBQ% between the two groups, adjusting for pre-specified covariates including baseline VBQ, age, BMI, duration of prior DMB treatment before M0, and history of prior fractures. The adjusted between-group difference, 95% confidence interval (CI), and two-sided *P*-value were reported.

Secondary outcome analyses: Δ BMD% and Δ TBS% were analyzed using a similar ANCOVA framework, adjusting for corresponding baseline values and pre-specified covariates. Changes in CTX and PINP over time were analyzed using linear mixed-effects models for repeated measures (MMRM), with fixed effects for group, time, and group-by-time interaction, and random intercepts for individual subjects, adjusting for baseline levels. Correlations between Δ VBQ% and Δ PINP, Δ BMD %, and Δ TBS% were assessed using Pearson or Spearman correlation

coefficients.

Subgroup analyses: Prespecified subgroup analyses were performed in the matched sample based on baseline VBQ (median split), age (<70 vs. $\geq$ 70 years), history of prior fractures (yes vs. no), and baseline CTX (median split). Interaction terms (treatment $\times$ subgroup) were included in regression models to evaluate potential effect modification [16]. These analyses were considered exploratory and interpreted with caution.

Inverse probability of treatment weighting (IPTW) sensitivity analysis: Propensity scores were estimated using the full sample, and stabilized IPTW weights (truncated at the 1st and 99th percentiles) were constructed to estimate the average treatment effect. Covariate balance was reassessed using SMD in the weighted sample. The primary outcome was re-analyzed using weighted regression models. Additionally, a doubly robust model was applied by further including the prespecified baseline covariates in the weighted regression [17,18].

Statistical software: All analyses were performed using SPSS (IBM SPSS Statistics, version 27.0) and R (version 4.4.1). A two-tailed *P*-value <0.05 was considered statistically significant.

3. Results

3.1. Study population

A total of 438 patients were screened, and 200 met the inclusion criteria (120 in the combination group and 80 in the sequential group). After PSM, 120 patients (60 in each group) were included in the primary analysis (Fig. 1).

3.2. Baseline characteristics

After matching, baseline characteristics including age, BMI, duration of prior DMB treatment before M0, baseline VBQ, baseline BMD, TBS,

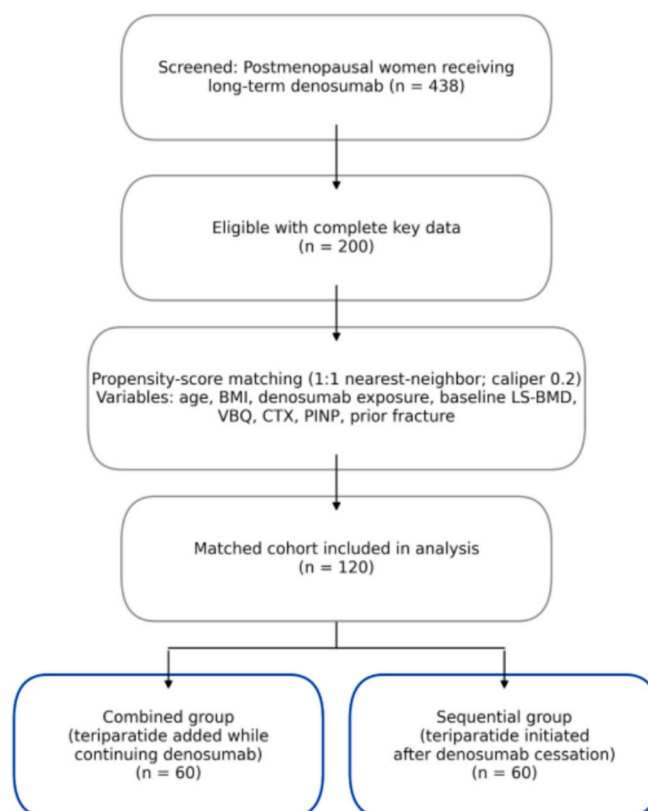


Fig. 1. Flowchart of patient screening.

baseline CTX, baseline PINP, and history of prior fractures were well-balanced between the two groups (all SMD <0.10; Table 1).

3.3. Primary outcome (Δ VBQ%)

At 12 months, the mean Δ VBQ% was $-7.10 \pm 3.03\%$ in the combination group and $-0.51 \pm 5.40\%$ in the sequential group. After adjusting for baseline VBQ, age, BMI, and duration of prior DMAB treatment, the combination strategy was associated with a significantly greater reduction in VBQ compared to the sequential strategy, with an adjusted between-group difference of -6.51 (95% CI: -8.12 to -4.91 , $P < 0.001$) (Fig. 2).

3.4. Secondary outcomes

The combination group showed greater improvements in lumbar spine BMD and TBS at 12 months (Table 2). After ANCOVA adjustment, the combination group showed a 3.59% greater increase in lumbar spine BMD ($P < 0.001$) and a 3.37% greater increase in TBS ($P < 0.001$) compared to the sequential group. Differences in femoral neck and total hip BMD were smaller and not statistically significant. (See Tables 3A and 3B.)

3.5. Bone turnover markers

CTX levels remained suppressed throughout the study period in the combination group. In contrast, the sequential group exhibited a significant increase in CTX from M + 3 onwards, reaching 0.393 ± 0.152 ng/mL at M + 12 ($P < 0.05$ vs. baseline and vs. the combination group). Both groups showed increases in PINP at M + 3, indicating activation of bone formation; however, the increase was significantly greater in the sequential group (80.55 ± 27.68 μ g/L vs. 57.08 ± 21.40 μ g/L, $P < 0.05$), and levels remained higher at M + 12 (Table 3, Fig. 3).

3.6. Subgroup analyses

The treatment effect of the combination strategy on Δ VBQ% was directionally consistent across prespecified subgroups defined by baseline VBQ, age, history of prior fractures, and baseline CTX (Fig. 4). Point estimates showed some variation, but confidence intervals overlapped, and no clear heterogeneity of treatment effect was observed. Given the small subgroup sample sizes, these analyses are exploratory and should not be used for confirmatory inference. Detailed stratification results and interaction tests between treatment effects and subgroup variables are provided in Supplementary Table S1.

3.7. Safety and fracture events

The incidence of adverse events was similar between the two groups. Two new vertebral fractures were observed in the sequential group during the 12-month follow-up, while none were observed in the

Table 1
Baseline characteristics of matched patients.

Variable	Combined (n = 60)	Sequential (n = 60)	SMD
Age (years)	68.5 $\pm$ 6.4	69.1 $\pm$ 6.6	0.09
BMI (kg/m ²)	23.8 $\pm$ 3.0	23.7 $\pm$ 3.1	0.03
Lumbar spine BMD(g/cm ²)	0.756 $\pm$ 0.081	0.770 $\pm$ 0.181	0.09
Total hip BMD(g/cm ²)	0.719 $\pm$ 0.092	0.728 $\pm$ 0.088	0.09
Femoral neck BMD(g/cm ²)	0.658 $\pm$ 0.089	0.643 $\pm$ 0.193	0.08
Denosumab exposure before M0 (months)	26.1 $\pm$ 2.9	26.2 $\pm$ 2.4	0.04
Baseline VBQ score	2.87 $\pm$ 0.38	2.85 $\pm$ 0.46	0.05
Prior fragility fracture, n (%)	20 (33.3)	22 (36.7)	0.07
Baseline CTX (ng/mL)	0.082 $\pm$ 0.02	0.081 $\pm$ 0.02	0.03
Baseline PINP (μ g/L)	37.85 $\pm$ 9.39	37.61 $\pm$ 11.43	0.02
Baseline TBS	1.225 $\pm$ 0.075	1.218 $\pm$ 0.074	0.09

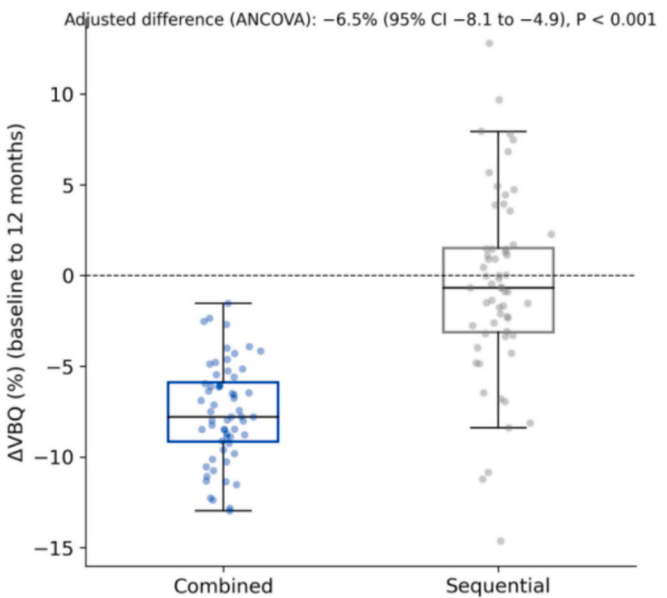


Fig. 2. Boxplot of Δ VBQ% in combination and sequential groups.

combination group. Due to the small number of events, this study is unable to make robust inferences regarding fracture risk differences; data are presented descriptively (Table 4).

3.8. Multivariable regression analysis

In the full sample ($N = 200$), multivariable linear regression confirmed that combination therapy was independently associated with greater Δ VBQ% improvement ($\beta = -6.1$, 95% CI: -7.4 to -4.8 , $P < 0.001$). Age, BMI, baseline BMD, and history of prior fractures were not significantly associated with Δ VBQ% (Table 5).

3.9. Correlation analysis

In the combination group ($n = 60$), Δ VBQ% was significantly negatively correlated with the change in PINP at M + 3 ($r = -0.50$, $P < 0.001$), while correlations with Δ PINP at M + 6 and M + 12 were not significant. Furthermore, Δ VBQ% was significantly negatively correlated with the 12-month changes in lumbar spine BMD ($r = -0.40$, $P = 0.002$) and TBS ($r = -0.77$, $P < 0.001$) (Fig. 5). These correlations suggest a coupled relationship between early bone formation response and subsequent improvements in bone marrow microenvironment and bone quality indices under the combination strategy. In contrast, no significant correlations were observed between Δ VBQ% and these parameters in the sequential group (all $P > 0.05$) (Table 6). Given the exploratory nature of these within-group analyses, the results are primarily descriptive and cannot infer causality.

3.10. IPTW analysis

The IPTW-weighted analysis confirmed that the combination group had a significantly greater Δ VBQ% reduction than the sequential group (between-group difference: -5.72 , 95% CI: -7.21 to -4.23 , $P < 0.001$). After further adjustment for prespecified baseline covariates in a doubly robust model, the treatment effect remained essentially unchanged (difference: -5.69 , 95% CI: -7.24 to -4.13 , $P < 0.001$), confirming the robustness of the primary findings.

4. Discussion

We fully acknowledge that current guidelines, including those from

Table 2
Primary and secondary outcomes at 12 Months.

Outcome	Combined (n = 60)	Sequential (n = 60)	Adjusted difference (95% CI)	P value
Primary outcome: ΔVBQ (%)	−7.10 ± 3.03	−0.51 ± 5.40	−6.51 (−8.12, −4.91)	< 0.001*
Lumbar spine BMD change (%)	9.35 ± 3.32	5.64 ± 4.23	3.59 (2.13, 5.04)	< 0.001*
Total hip BMD change (%)	2.14 ± 2.29	2.26 ± 2.41	−0.19 (−1.08, 0.70)	0.675
Femoral neck BMD change (%)	1.06 ± 2.48	1.93 ± 2.57	−0.85 (−1.80, 0.10)	0.078
TBS change (%)	4.80 ± 2.98	1.45 ± 3.04	3.37 (2.27, 4.48)	< 0.001*

Table 3A
CTX changes over time.

Group	M0	M + 3	M + 6	M + 12
Combined	0.082 ± 0.020	0.070 ± 0.021*	0.080 ± 0.019	0.080 ± 0.020
Sequential	0.081 ± 0.020	0.308 ± 0.047*#	0.346 ± 0.073*#	0.393 ± 0.152*#

Table 3B
PINP changes over time

Group	M0	M + 3	M + 6	M + 12
Combined	37.85 ± 9.39	57.08 ± 21.40*	49.70 ± 17.65*	43.51 ± 16.24*
Sequential	37.61 ± 11.43	80.55 ± 27.68*#	72.06 ± 27.95*#	63.09 ± 22.08*#

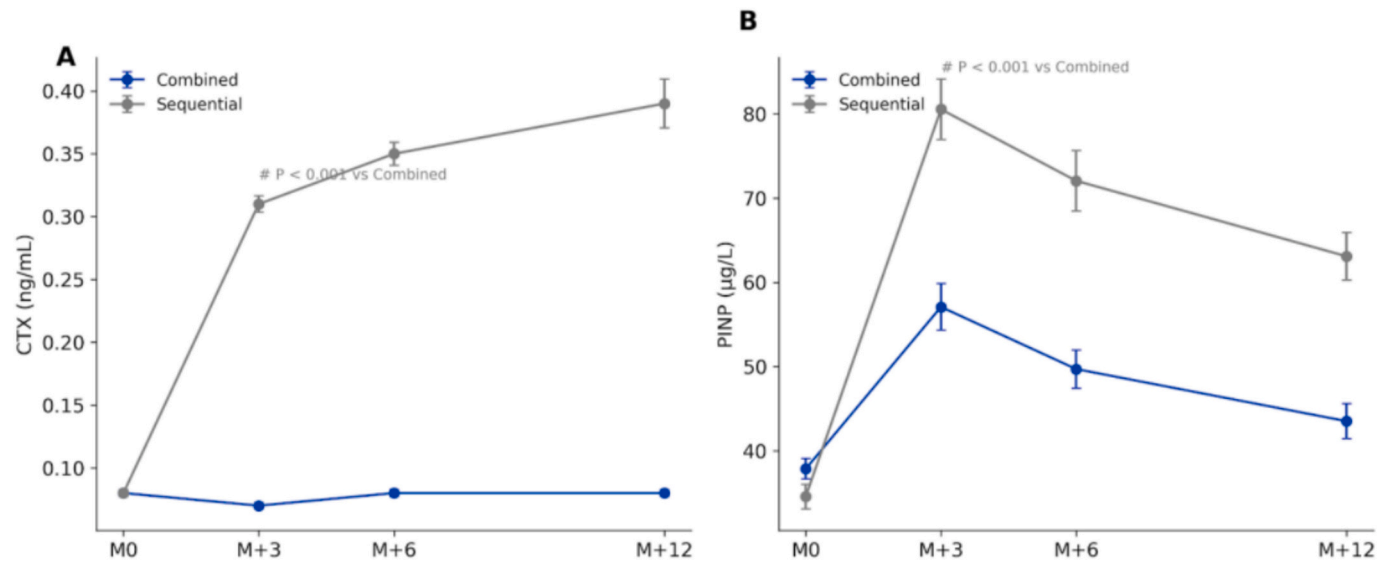


Fig. 3. A CTX trajectories over time; Fig. 3B PINP trajectories over time.

the National Osteoporosis Guideline Group (NOGG, 2024) [35] and the American Association of Clinical Endocrinologists (AACE, 2020) [36], do not recommend a direct switch from denosumab to teriparatide. The sequential group in this study reflects the real-world constraints described above. Our findings—showing significant CTX rebound and no VBQ improvement in this group—reinforce, rather than challenge, the rationale behind these guideline recommendations. This study is the first to systematically compare the impact of combination versus sequential teriparatide initiation on the vertebral bone marrow microenvironment in postmenopausal women with long-term prior denosumab exposure. The principal findings are that the combination strategy led to a significantly greater reduction in VBQ over 12 months, accompanied by more consistent improvements in lumbar spine BMD and TBS. At the biochemical level, the combination group maintained low CTX levels, whereas the sequential group exhibited a marked and sustained rebound in bone resorption. Converging evidence from multiple dimensions suggests that in the context of prior DMAB treatment, the method of TPTD initiation may influence bone remodeling

dynamics, thereby affecting vertebral bone marrow microenvironment and bone quality-related outcomes.

Bone formation can occur through two distinct pathways: the “remodeling-dependent” pathway, which requires prior resorption to create cavities subsequently filled by formation (predominant in adult bone turnover), and the “modeling-dependent” pathway, which involves direct deposition of new bone on quiescent surfaces without prior resorption [19,20]. Teriparatide, as a PTH analog, promotes osteoblast differentiation by activating Wnt/β-catenin signaling while simultaneously inhibiting the differentiation of mesenchymal stem cells into adipocytes. This dual action enables it to both increase bone mass and reduce marrow adiposity [21,22]. Long-term DMAB treatment profoundly suppresses bone resorption, leading to a relatively “frozen” remodeling space, evidenced by baseline CTX levels <0.12 ng/mL in both groups [23]. In this context, maintaining antiresorptive cover while adding TPTD may theoretically create a favorable window for net bone gain: on one hand, continued RANKL inhibition limits the rebound in bone resorption; on the other hand, TPTD-induced bone formation is

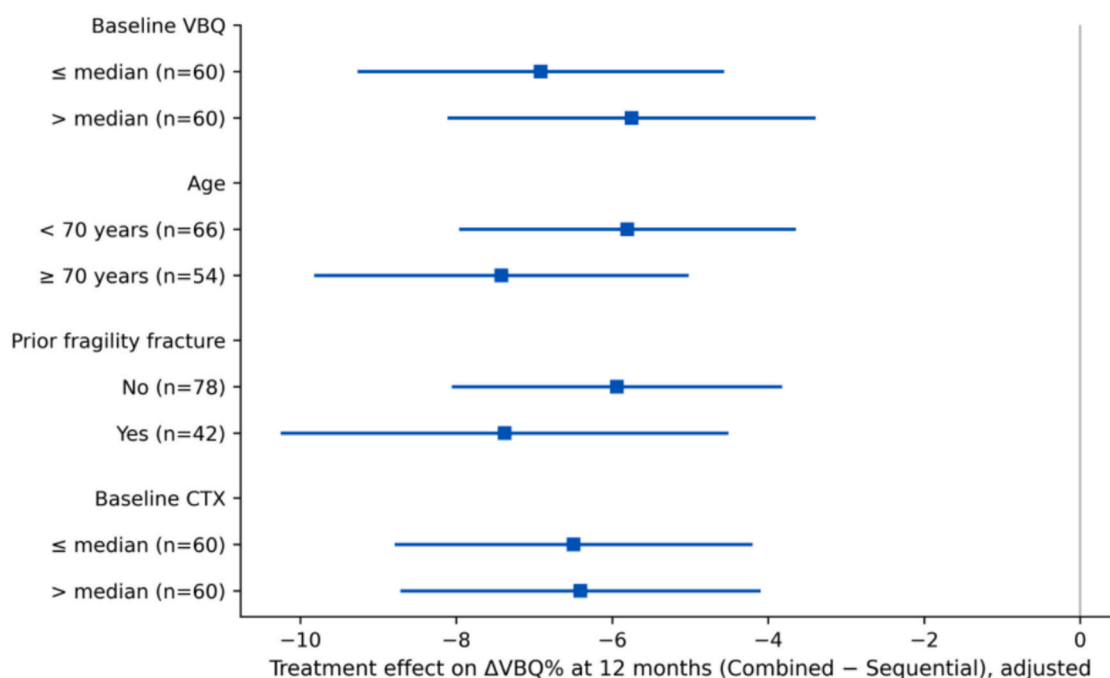


Fig. 4. Subgroup analysis forest plot: treatment effect is ΔVBQ% (combined – sequential).

Table 4

Safety outcomes.

Event	Combined (n = 60)	Sequential (n = 60)
Any adverse event	15 (25.0)	14 (23.3)
Injection-site reaction	7 (11.7)	4 (6.7)
Mild hypercalcemia	1 (1.7)	1 (1.7)
Nausea	5 (8.3)	5 (8.3)
Headache	5 (8.3)	4 (6.7)
New vertebral fracture	0 (0.0)	2 (3.3)
New non-vertebral fracture	0 (0.0)	0 (0.0)

Table 5

Multivariable linear regression for factors influencing ΔVBQ%.

Variable	β (95% CI)	P value
Combined vs Sequential	-6.1 (-7.4 to -4.8)	< 0.001*
Baseline VBQ (per unit)	-0.6 (-2.2 to 0.9)	0.412
Age (per 10 years)	0.7 (-0.3 to 1.7)	0.161
BMI (per 5 kg/m ²)	-0.3 (-1.4 to 0.7)	0.568
Baseline lumbar spine BMD (per 1 SD)	-0.1 (-0.7 to 0.6)	0.828
Prior fracture	0.6 (-0.7 to 1.9)	0.376

more likely to occur via direct surface deposition. This could translate into faster detectable improvements in structure and microenvironment, particularly in vertebrae rich in trabecular bone [24].

In the combination group, CTX remained suppressed while PINP was activated early. Moreover, within this group, the improvement in VBQ was significantly correlated with the early change in PINP and with the 12-month changes in TBS and lumbar spine BMD. This suggests a temporal relationship where early osteoblastic activation is followed by subsequent improvement in the bone marrow microenvironment. Conversely, in the sequential group, discontinuing DMAB led to a pronounced and sustained rebound in bone resorption (with CTX rising significantly from M + 3 onwards). Despite a larger increase in PINP, no improvement in VBQ was observed, and correlations between ΔVBQ% and other parameters were non-significant. This pattern implies that bone formation in the sequential group might be primarily engaged in countering the high resorption background (e.g., refilling resorption

cavities) rather than driving net optimization of the vertebral bone marrow microenvironment [25]. One potential biological pathway underlying this temporal relationship involves the Wnt/β-catenin signaling axis: under sustained RANKL inhibition, teriparatide-induced osteoblast differentiation may proceed predominantly via modeling-dependent bone formation, while simultaneously suppressing adipogenic differentiation of bone marrow mesenchymal stem cells. This resorption-independent mode of bone formation may be particularly efficient in translating early osteoblast activation into net improvements in bone mass, microarchitecture, and marrow adiposity. However, this mechanistic framework requires further experimental validation. Preclinical models combining RANKL inhibition with PTH analogs, incorporating paired histomorphometric and bone marrow adiposity analyses, would be valuable. In clinical settings, prospective studies with paired iliac crest bone biopsies and quantitative MRI-based fat measurement (such as PDFP or MRS) could provide direct evidence to confirm or refute this hypothesis.

Notably, the advantages of the combination strategy were most pronounced for vertebral-specific outcomes (VBQ, TBS, and lumbar spine BMD), while differences at the femoral neck and total hip were smaller and less consistent. This pattern aligns with the distinct biological characteristics of different skeletal sites. The vertebral body is rich in trabecular bone, which possesses a vast surface area, high metabolic activity, and abundant bone remodeling units, rendering it particularly sensitive to changes in remodeling dynamics [26]. In this context, by maintaining RANKL inhibition, the combination strategy allows teriparatide to deposit new bone directly on bone surfaces via modeling-dependent formation. This resorption-independent osteogenic pathway can be efficiently translated into measurable structural gains (such as TBS improvement) and microenvironmental optimization (such as VBQ reduction) in the highly trabecular vertebral bone. In contrast, the hip is predominantly composed of cortical bone, where renewal primarily relies on slow Haversian remodeling, and the contribution of modeling-dependent formation is limited [27,28]. Consequently, under the constraints of a 12-month follow-up period and the current sample size, stable between-group differences in hip BMD were more difficult to detect. This interpretation is indirectly supported by the observation that despite significant CTX rebound in the sequential group, hip BMD did not show corresponding deterioration, suggesting that the apparent

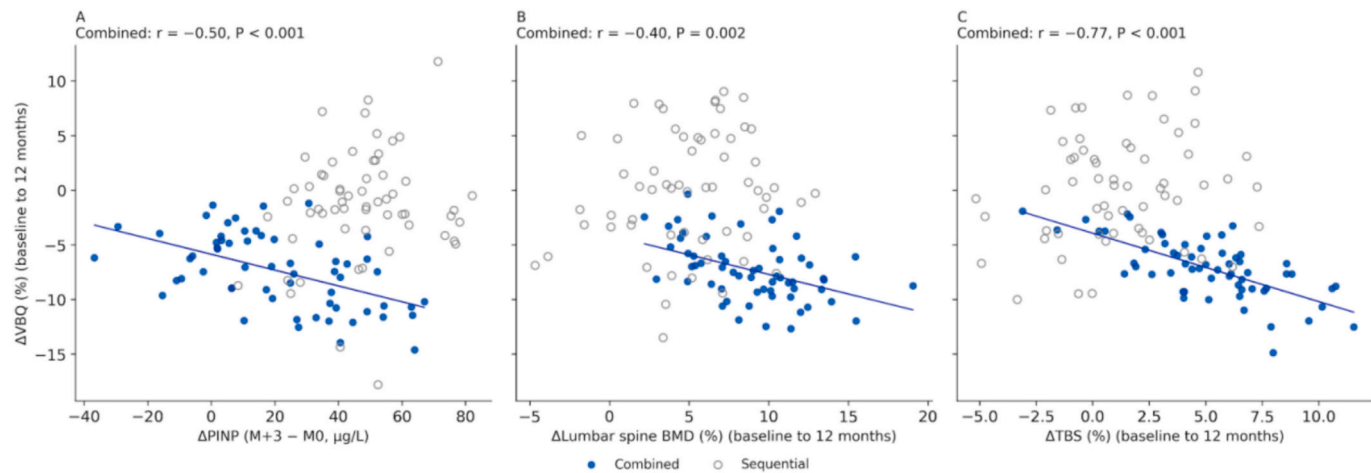


Fig. 5. Scatter plot matrix of correlations between ΔVBQ% and ΔPINP (M + 3), ΔLumbar Spine BMD% (M + 12), and ΔTBS% (M + 12) in the combination group.

Table 6
Summary of correlation analysis in the combination group.

Association	Time window	Combined (n = 60)	Sequential (n = 60)
ΔVBQ% vs ΔPINP	M + 3	$r = -0.50, p \leq 0.001^*$	$r = 0.06, p = 0.656$
	M + 6	$r = -0.09, p = 0.484$	$r = -0.22, p = 0.087$
	M + 12	$r = 0.02, p = 0.891$	$r = -0.18, p = 0.159$
ΔVBQ% vs ΔLumbar spine BMD%	M + 12	$r = -0.40, p = 0.002^*$	$r = -0.05, p = 0.695$
ΔVBQ% vs ΔTBS%	M + 12	$r = -0.77, p \leq 0.001^*$	$r = 0.16, p = 0.221$
ΔVBQ% vs ΔFemoral neck BMD%	M + 12	$r = -0.11, p = 0.167$	$r = -0.18, p = 0.163$
ΔVBQ% vs ΔTotal hip BMD%	M + 12	$r = -0.13, p = 0.322$	$r = 0.18, p = 0.172$

“stability” in hip BMD might mask underlying alterations in cortical microarchitecture [29].

Our findings are consistent with the small-sample study ($N = 23$) by Kumar et al. (2025), which also reported significantly greater lumbar spine BMD gains with combination versus sequential TPTD (+9.8% vs. +3.5%) [30]. However, the present study extends these findings in several important aspects: it is the first to incorporate VBQ as an imaging biomarker of the bone marrow microenvironment, demonstrating that combination therapy not only increases bone mass but also improves bone quality; it benefits from a larger sample size (120 vs. 23 patients), yielding more robust results; and it provides a comprehensive account of bone turnover marker trajectories, offering quantitative evidence for the proposed mechanistic explanation through correlation analyses. This study also resonates with the work of Adami et al. (2025) on combination denosumab/romosozumab, which similarly showed that adding romosozumab to ongoing denosumab preserves the anabolic effect, a pattern highly analogous to the TPTD effect observed in our combination group [31]. This suggests that regardless of the specific bone-forming agent used, maintaining an antiresorptive background may be key to maximizing bone quality improvement.

From a clinical perspective, this study offers a cautious inference that for high-risk patients on long-term DMAB who still require bone-forming therapy, initiating TPTD while continuing antiresorptive cover may be more conducive to achieving consistent improvements in vertebral bone quality parameters and reducing the uncertainty associated with bone resorption rebound. However, this study cannot infer fracture risk benefits (given the short follow-up and low event rate) and should not replace evidence-based strategies for transitioning off DMAB therapy.

Treatment decisions must be individualized, integrating the patient's fracture risk, treatment history, comorbidities, drug availability, and potential adverse effects (such as mild hypercalcemia) [32].

The strengths of this study include its focus on a common but under-investigated clinical scenario (“initiating TPTD after prior DMAB”) and its pioneering use of VBQ as an imaging surrogate for the vertebral bone marrow microenvironment, building a multi-dimensional chain of evidence alongside TBS, BMD, and bone turnover markers.

5. Limitations

Several limitations warrant consideration. First, the retrospective single-center design is subject to potential unmeasured confounding and selection bias, despite the use of propensity score methods to mitigate these issues. Second, VBQ is a derivative measure based on MRI signal ratios, which can be influenced by scanning parameters, field strength, and ROI placement [33];As an imaging-based surrogate marker of marrow adiposity, VBQ improvement should not be directly equated with fracture risk reduction. Its relationship with absolute marrow fat content and hard clinical outcomes requires further prospective validation. Third, the relatively short follow-up period and the low number of fracture events limit inferences regarding long-term clinical outcomes. Fourth, adverse events may be underreported in real-world medical records. Future multicenter, prospective studies employing standardized MRI protocols (potentially incorporating quantitative fat measurement techniques like PDFF/MRS) with extended follow-up to capture fracture endpoints are warranted. Further research should also explore baseline characteristics that might identify patients most likely to derive net benefit from a combination strategy [34]. Furthermore, as a single-center study, the findings may be influenced by local practice patterns, patient demographics, and imaging protocols, which may limit their generalizability to other populations and healthcare settings. Multi-center, international collaborative studies with standardized MRI acquisition protocols are needed to validate these findings across diverse clinical contexts.

6. Conclusion

In postmenopausal women with long-term prior denosumab treatment, initiating teriparatide while continuing denosumab (combination strategy) was associated with significantly greater improvement in the vertebral bone marrow microenvironment (greater reduction in VBQ) and more consistent gains in lumbar spine BMD and TBS over 12 months compared to a sequential switch after denosumab withdrawal. Bone turnover marker trajectories suggested that the combination strategy maintained a low resorption profile, whereas the sequential strategy was

characterized by sustained rebound in bone resorption. These findings suggest that the combination strategy may be associated with more favorable vertebral bone quality-related outcomes than a sequential switch after denosumab withdrawal. While our data provide mechanistic support for current guideline recommendations, confirmation in prospective randomized studies is required before clinical translation.

CRediT authorship contribution statement

Jie Hao: Writing – original draft, Data curation, Conceptualization. **Fayao Yan:** Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Yu Yao:** Writing – original draft, Visualization, Investigation. **Tongrui Zhang:** Writing – review & editing, Writing – original draft, Data curation. **Yongqi Zhang:** Writing – review & editing, Validation, Investigation. **Zheng Li:** Writing – review & editing, Investigation. **Hao Xu:** Writing – review & editing, Investigation. **Xingjie Jiang:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Funding acquisition, Conceptualization.

Ethical approval and informed consent

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was waived by the institutional review board of the Affiliated Hospital of Nantong University due to the retrospective nature of this study (Approval Number: 2026-K003-001).

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author(s) used ChatGPT to improve the language and readability of the manuscript. After using this tool, the author(s) reviewed and edited the content as needed and take (s) full responsibility for the content of the published article.

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Declaration of competing interest

Jie Hao, Fayao Yan, Yu Yao, Tongrui Zhang, Yongqi Zhang, Zheng Li, Hao Xu and Xingjie Jiang declare that they have no competing financial interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bone.2026.117955>.

Data availability

Data will be made available on request.

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