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Revista de Osteoporosis y Metabolismo Mineral

Revisión

Efficacy of teriparatide combination therapies on bone mineral density in postmenopausal osteoporosis: a network meta-analysis

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Abstract

Introduction: teriparatide (TPTD) is an effective anabolic agent for osteoporosis; however, its comparative efficacy when combined with antiresorptive drugs or other interventions remains uncertain. This network meta-analysis (NMA) aimed to compare the effects of various TPTD combination therapies and monotherapies on bone mineral density (BMD) in patients with postmenopausal osteoporosis.

Methods: Bayesian random-effects models were used. Primary endpoints were mean differences (MDs) in percentage change in BMD at the lumbar spine, femoral neck, and total hip. We estimated MDs with 95 %CrIs and ranked treatments using SUCRA probabilities.

Results: a total of 10 studies were included in this analysis. No combination therapy demonstrated statistically significant improvements in mean BMD across skeletal sites. At the lumbar spine, denosumab (DEN) + TPTD showed the largest estimated effect (MD, 3.12; 95 %CrI, -1.65 to 7.83). For the total hip, zoledronic acid (ZOL) + TPTD yielded the highest estimated mean change (MD, 6.75; 95 %CrI, -1.65 to 15.10). At the femoral neck, DEN + TPTD had the greatest estimated effect (MD, 3.71; 95 %CrI, -3.08 to 10.5). SUCRA rankings indicated DEN + TPTD as the most effective treatment for the lumbar spine (79.32) and femoral neck (76.45), whereas ZOL + TPTD ranked highest for the total hip (83.77).

Conclusions: this NMA indicates that TPTD combination therapies may offer potential benefits in improving BMD, with DEN + TPTD and ZOL + TPTD ranking highest across different skeletal sites. However, the absence of statistically significant differences underscores the need for further studies.

Keywords:
Combination therapy.
Osteoporosis.
Teriparatide.
Postmenopausal osteoporosis.

Received: 20/01/2026 • Accepted: 22/03/2026

Authors' contribution: H. N.: conceptualization, methodology, software, investigation, validation, formal analysis, funding acquisition, visualization, project administration, resources, supervision, writing—original draft, writing—review and editing. S. A.: conceptualization, methodology, software, investigation, validation, formal analysis, funding acquisition, visualization, project administration, resources, supervision, writing—original draft, writing—review and editing. O. W.: conceptualization, methodology, investigation, writing—original draft, writing—review and editing. I. B.: conceptualization, methodology, investigation, writing—original draft, writing—review and editing.

Statement of authorship: All authors certified fulfillment of ICMJE authorship criteria.

Data availability statement: Datasets generated and analyzed during the current study are included in the published article.

Conflicts of interest: The authors declare no conflict of interest.

Artificial intelligence: The authors declare that no generative artificial intelligence (AI) or AI-assisted technologies were used in the writing or preparation of this manuscript.

Nugroho H, Alvianto S, Wangidjaja O, Beatric I. Efficacy of teriparatide combination therapies on bone mineral density in postmenopausal osteoporosis: a network meta-analysis. Rev Osteoporos Metab Miner 2026;18(4):156-164

DOI: 10.20960/RevOsteoporosMetabMiner.00115

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INTRODUCTION

Postmenopausal osteoporosis (PMO) is clinically characterized by low bone mineral density (BMD), microarchitectural deterioration, and increased susceptibility to fragility fractures due to estrogen deficiency (1). It remains a major global health burden, as postmenopausal women (PMW) experience a 15.17-fold higher mortality rate, a 5.84-fold greater burden in disability-adjusted life years (DALYs), and a 6.29-fold greater burden in years lived with disability (YLDs) compared with premenopausal populations, underscoring the urgent need for more effective therapeutic strategies (2). Although antiresorptive agents remain widely used as first-line therapies, their predominant suppression of bone resorption may be insufficient to rapidly restore skeletal mass and strength in women at very high fracture risk, prompting greater reliance on bone-forming approaches and optimized treatment sequencing (3). Teriparatide (TPTD), a recombinant human parathyroid hormone (PTH) 1-34, is a prototypical anabolic agent with well-established antifracture efficacy in severe PMO, including significant reductions in vertebral and nonvertebral fractures (4). It was the first anabolic therapy approved by the US Food and Drug Administration (FDA) for osteoporosis treatment (5).

An ideal antiosteoporosis agent would theoretically both suppress bone resorption and stimulate new bone formation; however, neither currently available antiresorptive therapies nor PTH analogs achieve this dual action. Consequently, combining anabolic and antiresorptive therapies has been proposed as a practical alternative, based on the rationale that stimulating bone formation while simultaneously inhibiting resorption could yield greater gains in bone mass and strength than either approach alone (6,7). However, the 2020 guidelines of the American Association of Clinical Endocrinologists and the American College of Endocrinology state that, until the effects of combination therapy on fracture risk are better understood, the concomitant use of multiple osteoporosis agents is generally not recommended for osteoporosis treatment (8). Moreover, when anabolic agents are used, current guidelines recommend transitioning to sequential therapy with an antiresorptive agent, such as a bisphosphonate or denosumab, after discontinuation of the anabolic course to preserve gains in BMD and reduce the risk of subsequent fractures (8,9).

Therefore, given the limited available data and the lack of comprehensive head-to-head comparisons among TPTD combination therapies and other interventions, a network meta-analysis (NMA) is warranted to rank therapeutic strategies according to their efficacy on BMD outcomes, while also emphasizing the need for further evidence regarding the clinical effectiveness of TPTD-based combination approaches.

METHODS

This systematic review and NMA were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRDxx) on 10 November 2025.

SEARCH STRATEGY

A comprehensive literature search was conducted across multiple electronic databases, including Cochrane, MEDLINE, and ClinicalTrials.gov. The search was independently performed by HN, SA, and OW using predefined keywords and Medical Subject Headings (MeSH), including "Teriparatide," "Parathyroid Hormone," "Combination Therapy," "Osteoporosis," and "Postmenopausal Osteoporosis" (Supplementary material: https://www.revistadeosteoporosisymetabolismomineral.com/files/526/ADMA1-00115-02.docx). The search strategy was developed according to the PICOTS-SD framework as follows:

- Population: adults (≥ 18 years) with PMO.
- Intervention: TPTD-based combination therapy.
- Comparator: TPTD monotherapy, other active monotherapies, or alternative TPTD-containing combination regimens.
- Outcomes: mean change in BMD at the lumbar spine, total hip, and femoral neck.
- Time: no restrictions applied.
- Setting: all relevant clinical settings.
- Study design: randomized controlled trials (RCTs).

ELIGIBILITY CRITERIA

Types of studies

Only RCTs were eligible for inclusion. Observational studies, case series, case reports, narrative reviews, systematic reviews, book chapters, editorials, commentaries, as well as in vitro and in silico studies, were excluded.

Outcomes of interest

The primary endpoint of this study was to compare and rank the efficacy of TPTD-based combination therapies relative to TPTD monotherapy and other treatment strategies in improving BMD at the femoral neck, total hip, and lumbar spine.

Study selection

Studies were identified through a structured screening process. After duplicate records were removed using Zotero (version 7.0.15; Corporation for Digital Scholarship, Virginia, USA) on 10 November 2025, HN, SA, and OW independently screened titles and abstracts for relevance. Full-text articles of potentially eligible studies were subsequently assessed according to predefined inclusion criteria. Reference lists of included studies were manually reviewed to identify additional eligible reports. Final study inclusion was determined by reviewer consensus.

Data collection process

Data were extracted using a standardized form by 2 reviewers (HN and SA). Extracted variables included study characteristics, sample size, participant age, intervention details, daily treatment regimens, and follow-up duration.

Summary measures

Changes in BMD were analyzed as continuous outcomes using mean differences (MDs) as the summary effect measure.

Risk of bias assessment

Two reviewers (OW and IB) independently evaluated study quality using the Cochrane Risk of Bias tool, version 2 (RoB 2).10 Disagreements were resolved through consensus.

Synthesis of results and statistical analysis

For studies reporting outcomes only in graphical form, numerical values were extracted using WebPlotDigitizer (version 4.8; Autometris LLC; https://apps.automeris.io/wpd4/). A Bayesian NMA was conducted using the MetaInsight platform (version 6.4.0; NIHR Complex Reviews Support Unit; https://crsu.shinyapps.io/MetaInsight/) accessed on 20 November 2025.11 Results were summarized using forest plots, with between-study heterogeneity addressed through a random-effects model. Inconsistency and sensitivity analyses were also conducted. Treatment rankings were generated using the surface under the cumulative ranking curve (SUCRA), with higher values indicating greater efficacy. Studies identified as having a high risk of bias, as well as poorly fitting studies based on leverage plots falling outside the threshold line at $c = 3$, were excluded when present. Inconsistency was further assessed using the node-splitting model.

RESULTS

STUDY SELECTION

The study selection process is summarized in figure 1. Following an initial retrieval of 717 records from the database search, screening based on predefined criteria resulted in 35 articles undergoing full-text assessment. Of these, exclusions were made for mismatched interventions ($n = 13$), inappropriate comparators ($n = 8$), and outcomes not aligned with the study objectives ($n = 4$). Consequently, 10 studies fulfilled all inclusion criteria and were incorporated into the NMA for data synthesis.

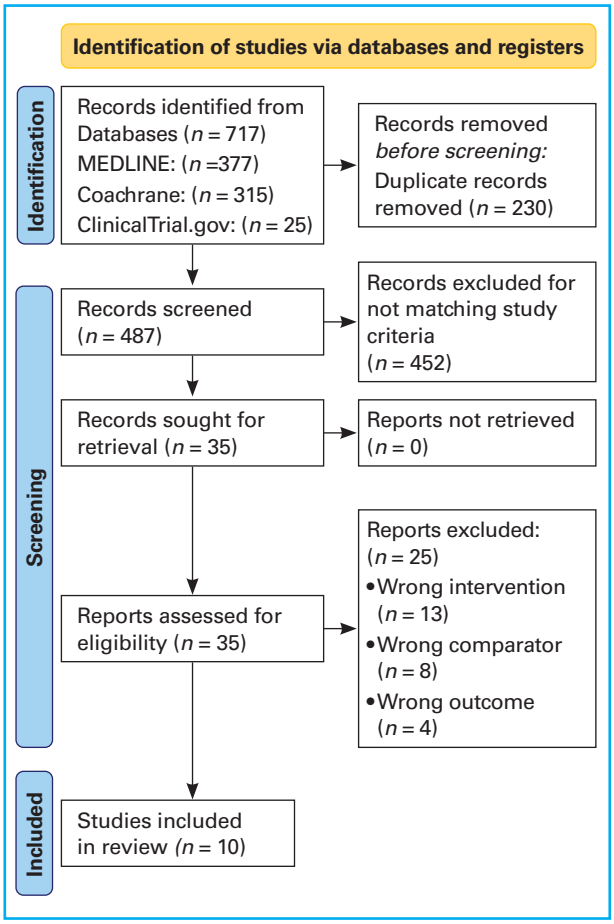

Figure 1. PRISMA flowchart diagram.

CHARACTERISTICS OF THE INCLUDED STUDIES

A total of 1459 participants from 10 RCTs were included. The studies enrolled PMW with osteoporosis from the United States, Europe, China, and multinational cohorts. Sample sizes ranged from 33 to more than 412 participants, with mean ages predominantly in the sixth to seventh decades of life. All trials evaluated TPTD-based combination therapies versus TPTD monotherapy, with some including additional active comparators such as alendronate (ALD), raloxifene (RAL), zoledronic acid (ZOL), denosumab (DEN), or nonpharmacological interventions (pulsed electromagnetic fields [PEMFs] or whole-body vibration [WBV]). TPTD (20-100 µg/day) was most frequently combined with antiresorptive agents, and calcium and vitamin D supplementation was routinely provided. Follow-up periods ranged from 6 to 30 months, most commonly 12 months. Overall, study quality was acceptable, with several trials at low risk of bias and the remainder showing some concerns. Further details are shown in table I.

NETWORK META-ANALYSIS RESULTS

Figure 2 and figure 3 illustrate the network and forest plots for BMD changes at the lumbar spine, total hip, and femoral neck. No intervention showed a statistically significant difference in mean BMD change across these skeletal sites. At the lumbar spine, the largest estimated effect was observed with DEN + TPTD (MD, 3.12; 95 %CrI, -1.65 to 7.83), followed by PEMF + TPTD (MD, 2.48; 95 %CrI, -3.83 to 8.72). For the total hip, ZOL + TPTD demonstrated the highest estimated mean change (MD, 6.75; 95 %CrI, -1.65 to 15.1), with DEN + TPTD ranking second (MD, 4.27; 95 %CrI, -4.32 to 12.7). At the femoral neck, DEN + TPTD showed the greatest estimated effect (MD, 3.71; 95 %CrI, -3.08 to 10.5), followed by ZOL + TPTD (MD, 3.17; 95 %CrI, -3.56 to 9.92). SUCRA-based ranking indicated that DEN + TPTD had the highest probability of being the most effective intervention for lumbar spine BMD (SUCRA, 79.32) and femoral neck BMD (SUCRA, 76.45), whereas ZOL + TPTD ranked highest for total hip BMD (SUCRA, 83.77). Detailed SUCRA rankings are presented in table II and figure 4.

SENSITIVITY AND INCONSISTENCY ANALYSES

No studies were identified as having a high risk of bias or as poorly fitting according to the leverage plots. Inconsistency assessments using node-splitting analyses likewise revealed no significant findings, except at the femoral neck. A significant local inconsistency emerged between RAL + TPTD and ALD + TPTD (P = .0043). While direct evidence indicated a significant benefit of RAL + TPTD, indirect evidence pointed in the opposite direction. This discrepancy resulted in a non-significant overall network estimate at the femoral neck. Further details are provided in the supplementary material (https://www.revistadeosteoporosisymetabolismomineral.com/files/526/ADMA1-00115-02.docx).

PUBLICATION BIAS

Publication bias was evaluated qualitatively using funnel plots and quantitatively using Egger regression tests. In this analysis, lumbar spine, total hip, and femoral neck plots appeared asymmetrical; however, Egger regression tests showed no significant bias, with P = .2121, P = .9783, and P = .4635 for the lumbar spine, total hip, and femoral neck, respectively, as illustrated in the supplementary material (https://www.revistadeosteoporosisymetabolismomineral.com/files/526/ADMA1-00115-02.docx). Such discrepancies may reflect small-study effects and heterogeneity, particularly given the limited number of included studies. Because funnel plots are less reliable with small sample sizes, the observed asymmetry is more likely attributable to heterogeneity.

DISCUSSION

The main strength of this study is that it represents the first comprehensive NMA comparing the effectiveness of various TPTD combination therapies, including both pharmacological and nonpharmacological interventions, in patients with PMO. Although the comparative analysis revealed no statistically significant differences in increasing BMD across interventions, this study demonstrated that several TPTD-based combination therapies consistently showed larger estimated mean changes in BMD vs other interventions in PMO.

In particular, the combination of DEN + TPTD demonstrated the greatest estimated effects at the lumbar spine and femoral neck, while ranking second at the total hip. The direction of effect observed in this study is consistent with a meta-analysis by Sun et al. (2022), which reported that combination therapy with TPTD + DEN in PMO was associated with greater BMD gains than monotherapy, including statistically significant mean percentage increases of approximately 2.91 % at the lumbar spine and 3.19 % at the hip (12). The overall beneficial effect may be attributed to DEN's ability to fully inhibit the proresorptive effects of TPTD through suppression of the RANKL pathway, while still allowing TPTD-induced stimulation of bone formation via activation of parathyroid hormone receptors. This combination thereby establishes a dynamic balance between bone formation and resorption (13).

Table I. Study characteristics

No.	Study ID	Participants (n)	Age	Intervention	Basic treatment/day	Follow-up (months)	RoB 2
1	Deal 2005 (24)	I: RAL + TPTD: 69 C: TPTD: 68	I: 66.6 ± 7.5 C: 66.1 ± 7.8	I: RAL 60 mg/day orally + TPTD 20 µg/day IM C: TPTD 20 µg/day IM	Calcium 1000 mg Vitamin D 400-800 IU/day	6	Low
2	Finkelstein 2010 (25)	I: ALD + TPTD: 20 C: TPTD: 20 ALD: 29	I: 62 ± 7 C: 65 ± 7 ALD: 64 ± 6	I: ALD 10 mg/day orally + TPTD 100 µg/day IM C: TPTD 56.5 µg/day IM ALD 10 mg/day orally	Calcium 1000-1200 mg Vitamin D 400 IU	30	Some concerns
3	Cosman 2011 (14)	I: ZOL + TPTD: 137 C: TPTD: 138 ZOL: 137	I: 65 ± 8.8 C: 63.8 ± 9.1 ZOL: 66.1 ± 9.0	I: ZOL 5 mg/year IV infusion + TPTD 20 µg/day IM C: TPTD 20 µg/day IM ZOL 5 mg/year IV infusion	Calcium 1000-1200 mg Vitamin D 400-800 IU	12	Some concerns
4	Muschitz 2013 (26)	I: ALD + TPTD: 41 RAL + TPTD: 37 C: TPTD: 47	I: 71.6 ± 8.5 C: 71.7 ± 9.3	I: ALD 70 mg/week orally + TPTD 20 µg/day IM RAL 60 mg/day orally + TPTD 20 µg/day IM C: TPTD 20 µg/day IM	Calcium 1000 mg Vitamin D 800 IU	18	Some concerns
5	Tsai 2013 (27)	I: DEN + TPTD: 30 C: TPTD: 29 DEN: 33	I: 65.9 C: 65.5 ± 7.9	I: DEN 60 mg/6 months + TPTD 20 µg/day IM C: TPTD 20 µg/day IM	Calcium 1200 mg Vitamin D 400 IU	12	Low
6	Muschitz 2014 (The CONFORS Study) (28)	I: ALD + TPTD: 41 RAL + TPTD: 37 C: TPTD: 47	I: 72.4 ± 9.1 70.5 ± 8.4 C: 72.8 ± 8.9	I: ALD 70 mg/week orally + TPTD 20 µg/day IM RAL 60 mg/day orally + TPTD 20 µg/day IM C: TPTD 20 µg/day IM	Calcium Vitamin D	12	Some concerns
7	Leder 2014 (The DATA Extension Study) (29)	I: DEN + TPTD: 24 C: TPTD: 28 DEN: 31	I: 65.9 ± 9.0 C: 65.5 ± 7.9 DEN: 66.3 ± 8.3	I: DEN 60 mg/6 months + TPTD 20 µg/day IM C: TPTD 20 µg/day IM DEN 60 mg/6 months	Calcium 1200 mg Vitamin D 20 ng/mL	24	Some concerns
8	Xuan 2025 (30)	I: PEMF + TPTD: 15 C: TPTD: 113 PEMFs: 108	I: 65.04 ± 7.10 C:65.23 ± 7.07 PEMFs: 65.37 ± 7.38	I: PEMF for 5 months followed 1 month later by TPTD 20 µg/day IM C: TPTD 20 µg/day IM PEMF monotherapy	Calcium 600 mg Vitamin D 125 IU	18	Some concerns
9	Jepsen 2019 (PaVOS study) (31)	I: WBV + TPTD: 15 C: TPTD: 18	I: 69 ± 5 C: 69 ± 8	I: WBV training protocol consisting of 12 minutes of training with a WB-V:rest ratio of 1:1 minute, including 6 minutes of vibration, 3 days/week with 1 day between sessions + TPTD 20 µg/day IM C: TPTD 20 µg/day IM	Calcium 800 mg Vitamin D 400-800 IU	12	Some concerns
10	Wei 2021 (32)	I: ZOL + TPTD: 48 C: TPTD: 48	I/C:64.31 ± 2.56	I: ZOL 5 mg/day IV + TPTD 20 µg/day IM C: TPTD 20 µg/day IM	Calcium carbonate 600 mg Vitamin D 125 IU	6	Some concerns

ALD: alendronate; DEN: denosumab; PEMFs: pulsed electromagnetic fields; RAL: raloxifene; RID: risedronate; TPTD: teriparatide; WBV: whole-body vibration; ZOL: zoledronic acid.

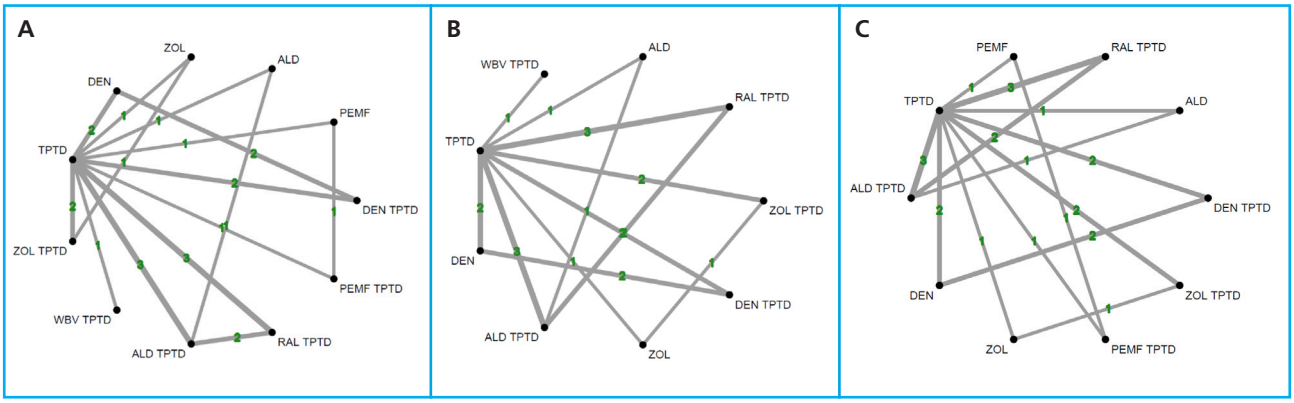

Figure 2. Network plots for BMD at the: (A) lumbar spine; (B) total hip; and (C) femoral neck.

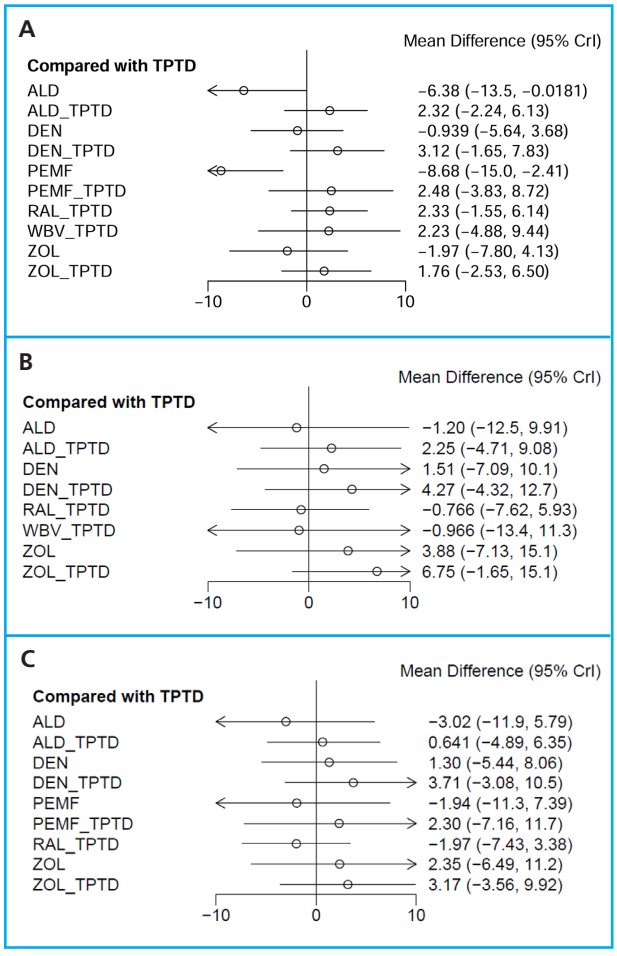

Figure 3. Forest plots of the NMA for: (A) lumbar spine; (B) total hip; and (C) femoral neck.

Table II. SUCRA rankings

Treatment	Lumbar spine	Total hip	Femoral neck
ALD	10.57	30.85	22.27
ALD + TPTD	70.97	56.13	50.89
DEN	35.85	48.08	55.05
DEN + TPTD	79.32	69.70	76.45
PEMF	3.98	N/A	29.41
PEMF + TPTD	71.59	N/A	63.47
RAL + TPTD	71.56	29.83	24.88
TPTD	42.97	34.34	42.46
WBV + TPTD	67.81	33.50	N/A
ZOL	29.75	63.81	63.14
ZOL + TPTD	65.61	83.77	71.97

At the total hip, the combination of ZOL + TPTD produced the greatest estimated improvement in BMD. Whereas TPTD exerts a distinctive adverse effect on cortical bone by increasing cortical porosity, the addition of ZOL appears to mitigate this remodeling process by reinforcing cortical structure, thereby enhancing hip BMD. Nevertheless, in the clinical trial setting, the absence of sustained BMD gains during the final 6 months may reflect renewed cortical remodeling and increasing cortical porosity as the antiresorptive effect of ZOL diminishes (14).

Furthermore, combining TPTD with nonpharmacological therapies (PEMF/WBV) was also associated with improvements in lumbar spine and femoral neck BMD, with outcomes comparable to those achieved with TPTD combined with antiresorptive agents. However, no improvement was observed in total hip BMD. WBV delivered through a vibration platform transmits mechanical signals across the skeletal muscle system via centrifugal conduction from the lower limbs. This stimulation triggers widespread neuromuscular activation and contributes to the regulation of bone metabolism. Its benefits appear even greater when paired with pharmacological treatments such as TPTD, in which synergistic effects have been reported (15). A meta-analysis also found that the use of PEMF to-

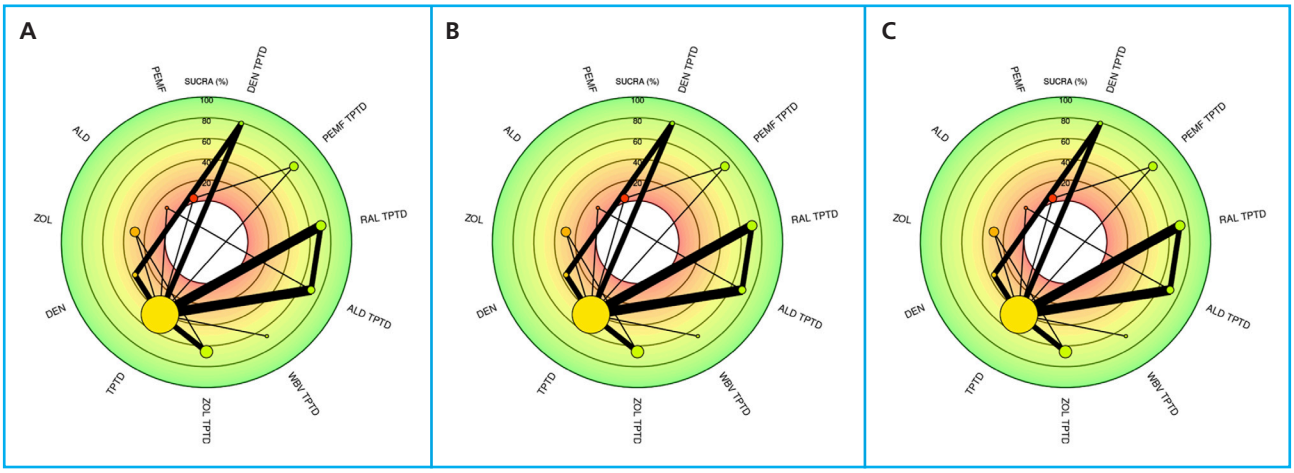

Figure 4. SUCRA plots of the NMA for: (A) lumbar spine; (B) total hip; and (C) femoral neck.

gether with standard medications resulted in significant increases in lumbar spine and femoral BMD (16). PEMFs enhance osteoblast activity, inhibit osteoclast formation, and modulate bone marrow stromal cells and osteocytes, thereby preserving bone mass and strength (17).

Emerging evidence from previous meta-analyses suggests potential benefits of combination therapy. A meta-analysis by Lou et al. (2019) demonstrated that combination regimens were superior to monotherapy, whereas more recent data from Jin et al. (2025) indicated that the DEN + TPTD combination may be clinically preferable for BMD enhancement (6,13). Consistent with these findings, our NMA identified a trend favoring combination therapy for BMD improvement, with the highest rank probabilities observed for DEN + TPTD and ZOL + TPTD.

A key limitation of this study is that, although several TPTD-based combination strategies achieved high SUCRA rankings, the corresponding credible intervals were wide and consistently crossed the null effect. This finding reflects substantial uncertainty in the estimated treatment effects and indicates that these rankings should be interpreted cautiously. The observed imprecision is likely attributable to small sample sizes, the limited number of included studies, heterogeneity in interventions and follow-up durations, and reliance on indirect comparisons inherent to the NMA framework. A local inconsistency at the femoral neck was also identified, further indicating that the rankings should be interpreted with caution. Consequently, although relative treatment rankings provide insight into potential comparative performance, the absence of statistically significant differences highlights the need for larger, adequately powered RCTs to more precisely define the effects of combination therapies on site-specific BMD outcomes.

This study focused exclusively on TPTD-based combination strategies and did not address other anabolic agents, such as abaloparatide (ABL) or romosozumab (ROMO). Evidence regarding ROMO in combination therapy for PMO remains limited. Meta-analyses have suggested that ROMO demonstrates superior efficacy compared with TPTD (18). This monoclonal antibody targets sclerostin and acts through a dual mechanism, promoting bone formation while simultaneously reducing bone resorption (19). Observational data indicate that the addition of ROMO to ongoing DEN therapy produced significant gains in lumbar spine BMD (20). Preliminary analyses further suggest that ROMO combined with DEN resulted in greater improvements in BMD and required fewer injections compared with DEN plus TPTD (21). Meta-analyses evaluating ABL have demonstrated beneficial effects on BMD and a lower risk of adverse events compared with TPTD (22). However, clinical trials investigating ABL in combination therapy remain limited and are still ongoing, including NCT04467983 (23). Future studies comprehensively comparing combination therapies for PMO are warranted to better define optimal treatment strategies. In addition, comparisons between sequential TPTD therapy and combination therapy have not yet been adequately evaluated, highlighting the need for future direct head-to-head trials.

CONCLUSIONS

This NMA highlights a favorable trend for TPTD combination therapies in improving BMD, with DEN + TPTD and ZOL + TPTD emerging as leading candidates in relative treatment rankings. However, the absence of statistically significant differences underscores the need for larger, adequately powered clinical trials.

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