Effects of teriparatide versus alendronate for treatment of postmenopausal osteoporosis
A meta-analysis of randomized controlled trials

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Abstract
Objectives: Osteoporosis remains a clinical challenge. Teriparatide is an anabolic drug and alendronate is an antiresorptive agent; both are used in the treatment of osteoporosis. Comprehensive reviews investigating the comparative safety and efficacy of teriparatide versus alendronate are scarce. Therefore, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the safety and efficacy of teriparatide versus alendronate for the treatment of postmenopausal osteoporosis.

Methods: We conducted a comprehensive literature review of the PubMed, EMBASE, Cochrane Controlled Trials Registry, and the China Academic Journal Network Publishing databases for relevant RCTs of teriparatide versus alendronate in postmenopausal osteoporosis patients. Outcome measures were percentage change in lumbar spine and femoral neck bone mineral density (BMD) and incidence of vertebral and nonvertebral fractures. Effect size was reported as weighted mean differences (WMDs) for continuous outcomes and odds ratios (ORs) for dichotomous outcomes, with associated 95% confidence intervals (CIs).

Results: Six trials involving 618 patients were included. The meta-analysis demonstrated a significant increase in lumbar spine BMD (WMD: 3.46, 95% CI: 2.15–4.77, P<.00001), but not femoral neck BMD (WMD=1.50, 95% CI: 0.04–2.95, P=.04), in postmenopausal osteoporosis patients treated with teriparatide compared with alendronate for 6 to 18 months. These beneficial effects were apparent in the lumbar spine at 12 months of treatment (WMD: 4.49, 95% CI: 2.57–6.40, P<.01). Teriparatide was not superior to alendronate in reducing fracture risk (OR: −0.03, 95% CI: −0.12 to 0.07; P=.52).

Conclusion: Teriparatide may be superior to alendronate for increasing lumbar spine BMD in postmenopausal osteoporosis. The efficacy and safety of long-term teriparatide and alendronate treatment in postmenopausal osteoporosis should be further investigated in clinical trials.

Abbreviations: BMD = bone mineral density, CI = confidence interval, OR = odds ratio, PTH = parathyroid hormone, QALY = quality-adjusted life year, RCTs = randomized controlled trials, WMD = weighted mean difference.

Keywords: alendronate, meta-analysis, osteoporosis, postmenopausal, teriparatide

1. Introduction
Osteoporosis is a persistent public health problem that is common in older women. Approximately 30% of postmenopausal women have osteoporosis according to the World Health Organization definition of osteoporosis.[1,2] Despite therapy, fractures frequently occur in trabecular bone, predominantly in the lumbar spine and the femoral neck.[3,4] The most common osteoporotic fractures in postmenopausal women occur in the spine and hip. Among these, nonvertebral fractures are associated with the highest morbidity and mortality. The annual disability and mortality rates associated with hip fractures are estimated at 50% and 20%, respectively.[5]

Parathyroid hormone (PTH) is an anabolic agent that has widespread clinical application.[6] Teriparatide is a PTH that is approved for use in osteoporosis. Teriparatide induces the production of osteoblasts and inhibits osteoclast apoptosis, resulting in a rapid increase in bone microstructure and strength.[7] Bisphosphonates are widely used to prevent or treat osteoporosis as they induce osteoclast apoptosis and inhibit bone resorption.[8] Alendronate, a second-generation bisphosphonate, inhibits osteoclast activity, reduces bone resorption, and maintains the balance of bone resorption and formation. Alendronate may also stimulate osteoblast differentiation, and prevent or mitigate osteocyte and osteoblast apoptosis.[9,10] Alendronate is an effective and well-tolerated drug for prevention and treatment of postmenopausal osteoporosis, maintaining bone mineral density (BMD) and fracture benefits for up to 2 years.[3,11]

BMD is a major determinant of fractures and an essential parameter for the evaluation of anabolic and antosteoporotic drugs used in clinical therapy. An increasing number of studies
2. Materials and methods

2.1. Search strategy

Two researchers (Y-KW and WS) independently searched PubMed, EMBASE, the Cochrane Controlled Trials Registry, and the China Academic Journal Network Publishing Database from inception to March 1, 2015 using the following Keywords: osteoporosis; alendronate; teriparatide; bone mineral density or BMD; postmenopausal. Searches were restricted to studies published in the English language.

2.2. Inclusion and exclusion criteria

Inclusion criteria were RCTs of teriparatide versus alendronate, involving postmenopausal adult osteoporosis patients, treated for at least 6 months, and presenting changes in lumbar spine and femoral neck BMD and the incidence of vertebral and nonvertebral fractures as outcomes data, and reporting adverse effects of treatment. Corresponding authors of RCTs that presented incomplete data were contacted to obtain missing information, when necessary.

Exclusion criteria were RCTs that included children; RCTs that included patients with secondary osteoporosis caused by fetal diseases, or organ transplant recipients; RCTs that included patients with primary osteoporosis treated with other drugs that affected BMD; and non-RCTs, case reports, conference abstracts, or review articles.

Disagreement about study selection was resolved by discussion with a review author (Y-MZ) until consensus was reached.

2.3. Data extraction

Two researchers (Y-KW and WS) independently performed data extraction. Means were obtained from data tables or figures if no direct data were available from the article text or the corresponding author. Within-group and between-group standard deviations and the standard error of the difference in means were calculated according to the Cochrane Handbook for Systematic Reviews of Interventions (www.handbook.cochrane.org). Disagreements about data extraction were resolved by discussion with a review author (Y-MZ) until consensus was reached.

2.4. Assessment of study quality

Two researchers (Y-KW and WS) independently assessed the quality of the included studies. Risk of bias was evaluated using the modified Jadad scale.[12] Categories included: “Was the study described as randomized?” “Was the method used to generate the sequence of randomization described and appropriate (random numbers, computer-generated, etc.)?” “Was the study described as double-blind?” “Was the method of double-blinding described and appropriate (identical placebo, active placebo, dummy, etc.)?” and “Was there a description of withdrawals and drop-outs?” The Jadad scale is a 5-point scale; a score of 0 indicates poor quality evidence and a score of 5 indicates high-quality evidence; therefore, trials with a score of 4 or 5 were considered high methodological quality (Table 1). Disagreements about study quality were resolved by discussion with a review author (Y-MZ) until consensus was reached.

2.5. Statistical analysis

Data were analyzed using the Cochrane Collaboration software Review Manager 5.2. Weighted mean differences (WMDs) and their associated 95% confidence intervals (CIs) were calculated for the continuous outcome, change in BMD, while odds ratios (OR) and their associated 95% CIs were calculated for the dichotomous outcomes, incidence of bone fractures and adverse effects.

Heterogeneity was assessed using the I² test. A fixed-effects model was used to pool data if there was no evidence of significant heterogeneity (I² ≤ 50%). Otherwise, a random-effects model was used. Publication bias was assessed with funnel plots. Subgroup analyses were stratified by treatment duration (6, 12, and 24 months) and dose.

Ethics committee and/or institutional board approval was not required for this study.

3. Results

3.1. Trial characteristics

The searches identified 145 relevant articles. Of these, 6 RCTs were found eligible for inclusion according to our criteria for considering studies for this review.[13–18] (Fig. 1). A total of 618 patients with postmenopausal osteoporosis were included in the analyses. Among the 6 included trials, 4 were multicenter trials[13–16] and 2 were single-center trials.[17,18] Twenty micrograms teriparatide was administered in 3 trials,[14,15,18] 40 µg teriparatide was administered in 3 trials,[13,16,17] 10 mg/dalendronate was administered in 5 trials,[13–17] and 70 mg/wk alendronate was administered in 1 trial. These trials were considered comparable as evidence suggests that the efficacy of alendronate in the treatment of osteoporosis is equivalent when administered at a dose of 70 mg/wk or 10 mg/d.[19,20] Trial duration ranged from 18 to 30 months. The characteristics of the 6 included trials are summarized in Table 2.

3.2. BMD of the lumbar spine

Percentage change in lumbar spine BMD in postmenopausal osteoporosis patients treated with teriparatide versus alendronate for 6, 12, and 18 months is described in all 6 included trials (n = 574 patients).[13–18] The meta-analysis demonstrated that the percentage change in lumbar spine BMD was significantly greater.

| Table 1 | Jadad score[12] |
|---------|-----------------|
| Random allocation | Cited +1 | Described and appropriate +1 | Nonappropriate –1 |
| Double blind | Cited +1 | Described and appropriate +1 | Nonappropriate –1 |
| Dropouts and withdrawals | Described +1 | | |
in postmenopausal osteoporosis patients administered teriparatid compared to those administered alendronate (WMD: 3.46, 95% CI: 2.15–4.77, P < .00001; Fig. 2). There was evidence of significant heterogeneity between trials (P = .02, I² = 51%).

3.3. BMD of the femoral neck

Percentage change in femoral neck BMD in postmenopausal osteoporosis patients treated with teriparatid versus alendronate for 12 and 18 months is also described in all 6 trials (n = 574 patients). The meta-analysis demonstrated no significant difference in the percentage change in femoral neck BMD in postmenopausal osteoporosis patients administered teriparatid compared to those administered alendronate (WMD = 1.50, 95% CI: 0.04–2.95, P = .04; Fig. 3). There was no evidence of significant heterogeneity between trials (P = .17, I² = 34%).

3.4. Incidence of vertebral and nonvertebral fractures

The incidence of vertebral and nonvertebral fractures in postmenopausal osteoporosis patients treated with teriparatid versus alendronate for 6 to 24 months is described in 3 trials (n = 430 patients). The meta-analysis demonstrated no significant difference in the incidence of vertebral and/or nonvertebral fractures in postmenopausal osteoporosis patients administered teriparatid compared to those administered alendronate (overall OR: 0.03, 95% CI: 0.12 to 0.07; P = .52; Fig. 4). There was evidence of significant heterogeneity between trials (P = .0006, I² = 76%).

3.5. Subgroup and sensitivity analysis

Subgroup analyses stratified by treatment duration indicated that the percentage change in lumbar spine BMD was significantly

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Table 2

| Study         | Design | Mean age, y (alendronate/teriparatid) | Mean BMI, kg/m² (alendronate/teriparatid) | Type of population studied (teriparatid/alendronate) | Teriparatid, µg/d | Alendronate, mg/d | Duration, mo | Jadad scores |
|---------------|--------|---------------------------------------|------------------------------------------|-----------------------------------------------------|-----------------|-----------------|----------------|--------------|
| Body 2002     | RCT    | 65/66                                 | 24.4/23.9                                | 12 study sites (73/73)                               | 40              | 10              | 24             | 4            |
| Arlot 2005    | RCT    | 66/61                                 | 25.3/25.7                                | 6 clinical sites (21/21)                             | 20              | 10              | 18             | 5            |
| McClung 2005  | RCT    | 67/65                                 | 24.7/26.6                                | 19 clinical trial sites (102/101)                    | 20              | 10              | 18             | 5            |
| Keaveny 2007  | RCT    | 63/65                                 | 26.3/26.5                                | 19 clinical trial sites (28/25)                      | 20              | 10              | 18             | 5            |
| Finkelstein 2010 | RCT       | 64/65                                 | 25.6/24.9                                | Single university hospital (20/29)                  | 40              | 10              | 30             | 3            |
| Panico 2011   | RCT    | 60/65                                 | 22.8/24.5                                | Single university hospital (42/39)                  | 20              | 70 mg/wk        | 18             | 4            |

BMD = body mass index, RCT = randomized controlled trial.
greater in postmenopausal osteoporosis patients administered teriparatide compared to those administered alendronate for 6 months (WMD: 1.64, 95% CI: 1.22–2.05, \( P < .00001 \); \( I^2 = 0\% \); Fig. 2), 12 months (WMD: 4.49, 95% CI: 2.57–6.40, \( P < .00001 \); \( I^2 = 0\% \); Fig. 2), and 18 months (WMD: 5.15, 95% CI: 3.01–7.28, \( P < .00001 \); \( I^2 = 0\% \); Fig. 2) and indicated no significant difference in the percentage change in femoral neck BMD in postmenopausal osteoporosis patients administered teriparatide compared to those administered alendronate for 12 months (WMD = 1.71, 95% CI: –0.35 to 3.77 \( P = .44 \); \( I^2 = 0\% \); Fig. 3) or 18 months (WMD = 1.69, 95% CI: –0.58 to 3.95 \( P = .10 \); \( I^2 = 51\% \); Fig. 3).
Subgroup analyses stratified by teriparatide dose indicated that the percentage change in lumbar spine BMD was significantly greater in postmenopausal osteoporosis patients administered 20μg teriparatide (WMD = 5.45; 95% CI: 2.83–8.07; \( P < .0001 \); \( I^2 = 0\% \); Fig. 5A) and 40μg teriparatide (WMD = 5.95; 95% CI: 3.02–7.62; \( P < .0001 \); \( I^2 = 0\% \); Fig. 5A) compared to those administered 10mg alendronate. There was no significant difference in the percentage change in femoral neck BMD in postmenopausal osteoporosis patients administered 20μg teriparatide (WMD = 0.25; 95% CI: −0.58 to 1.09; \( P = .56 \); \( I^2 = 30\% \); Fig. 5B) compared to those administered 10mg alendronate; however, the difference in patients administered 40μg teriparatide was significant (WMD = 3.33; 95% CI: 0.42–6.23; \( P = .02 \); \( I^2 = 0\% \); Fig. 5B).

To confirm that our results are robust, we performed a sensitivity analysis, excluding 1 study at a time. Results showed that the overall findings of the meta-analysis were not affected by the inclusion/exclusion of any one particular study (Table 3).

### 3.6. Assessment of study quality

The level of evidence for each trial was graded as 3 to 5 according to the Jadad quality score. For publication bias, the shape of the funnel plot showed obvious asymmetry for trials investigating percentage change in lumbar spine BMD (Fig. 6A), but slight asymmetry for trials investigating percentage change in femoral neck BMD (Fig. 6B) and incidence of vertebral and nonvertebral fractures (Fig. 6C).

### 4. Discussion

This meta-analysis of 6 RCTs investigating the efficacy of teriparatide versus alendronate in postmenopausal osteoporosis patients showed that the percentage change in lumbar spine BMD was significantly greater in patients administered teriparatide for 6, 12, and 18 months compared to those administered alendronate. Subgroup analyses confirmed teriparatide efficacy was not duration or dose dependent. There was no significant difference in the percentage change in femoral neck BMD or the incidence of vertebral and/or nonvertebral fractures in patients administered teriparatide compared with alendronate.

Teriparatide is a once daily subcutaneous injection that is recommended for treatment of postmenopausal osteoporosis.\[21\] Our meta-analysis revealed that teriparatide increased lumbar spine BMD by 3.46% compared with alendronate. In accordance with our findings, previous meta-analyses have also shown that teriparatide versus placebo (calcium) can increase BMD in the spine and femoral neck of postmenopausal women with osteoporosis.\[22–24\] In contrast to our results, Shen et al\[25\] reported that PTH significantly increased femoral head BMD compared with bisphosphonates, and the effect was duration and dose-dependent. Furthermore, Neer et al\[26\] found that 20μg teriparatide increased femoral neck BMD by 9.7% versus placebo. Although 10mg of alendronate has proven efficacy for increasing lumbar spine and hip BMD after 2 to 3 years and 3 to 4 years of treatment, respectively, in postmenopausal osteoporosis versus placebo,\[27\] our data indicate teriparatide may be superior to alendronate for increasing lumbar spine BMD in postmenopausal osteoporosis.

The difference in the percentage increase in lumbar spine BMD resulting from teriparatide and alendronate treatment may be explained by their different mechanisms of action.\[28,29\] Teriparatide is a bone-forming agent, which increases biochemical markers of bone turnover. Previous reports show that teriparatide treatment increases markers of bone formation more rapidly and to a higher level than markers of bone resorption, suggesting an imbalance in bone turnover in favor of formation.\[30,31\] Furthermore, recombinant PTH may increase trabecular connectivity. By contrast, the majority of BMD increases observed with alendronate treatment result from increased mineralization of existing bone matrix.\[28\]
The effect of teriparatide and alendronate on the relative risk of fracture in postmenopausal osteoporosis patients is reported in several studies with varying magnitude. In accordance with our findings, Trevisani et al\[32\] found no significant difference in the incidence of vertebral or nonvertebral fractures in patients treated with teriparatide versus alendronate. However, the Fracture Prevention Trial showed that the incidence of new vertebral fractures and new nonvertebral fragility fractures was reduced in

| Table 3 |

| Sensitivity analyses excluding studies considered as contributing the most heterogeneity. |

| Outcome or subgroup | Studies | Excluded study | $\chi^2$ | $I^2$, % | $P$ | $P$ (test for overall effect) |
|---------------------|---------|----------------|--------|---------|-----|-------------------------------|
| 1.1 Lumbar spine    | 6       |                |        |         |     |                               |
| 1.1.1 at 6 mo       | 4       | McClung 2005   | 3.99   | 25      | .26 | .006                          |
| 1.1.2 at 12 mo      | 3       | Finkelstein 2010 | 2.46  | 19      | .29 | <.00001                      |
| 1.1.3 at 18 mo      | 3       | Excluded any one study | 0 |         |     | <.001                          |
| 1.2 Femoral neck    | 5       |                |        |         |     |                               |
| 1.2.1 at 12 mo      | 2       | Finkelstein 2010 | 1.37  | 27      | .24 | .35                           |
| 1.2.2 at 18 mo      | 3       | Arlot 2005     | 0.76   | 0       | .68 | .01                           |

Figure 5. Teriparatide versus alendronate for lumbar spine BMD (A) and femoral neck BMD (B): Subgroup analyses stratified by dose of teriparatide. BMD = bone mineral density.
postmenopausal women treated with teriparatide compared with placebo.\textsuperscript{1,2} Previous meta-analyses have shown that the incidence of vertebral or nonvertebral fractures was significantly reduced by alendronate in postmenopausal women without prevalent fractures and BMD levels below the World Health Organization threshold for osteoporosis compared with placebo.\textsuperscript{27,33} The discrepancies between our findings and the results of previous studies may be explained by our small sample size.

Only 1 study investigating teriparatide versus alendronate in postmenopausal osteoporosis reported adverse events associated with treatment. Panico et al showed that the most-common reported adverse events associated with teriparatide were back pain that worsened in the first month of treatment, nausea, and headache and dizziness. The most common adverse events associated with alendronate were abdominal pain, arthralgia, and dyspepsia; tolerability of alendronate was comparable to teriparatide.\textsuperscript{18}

In Sweden, for postmenopausal women (mean age: 70 years, total hip T-score: $-2.7$ and $3.3$ previous fractures), the cost per quality-adjusted life year (QALY) gained for teriparatide versus no treatment was estimated at €43,473.\textsuperscript{34} In the United States, for women with no additional fracture risk factors, the cost per QALY gained for alendronate ranged from 70,000 to 332,000 dollars, depending on patient age and femoral neck bone density.\textsuperscript{33} In Sweden, the cost-effectiveness ratios for teriparatide versus placebo were €36,995 and €43,473.\textsuperscript{34} In the United States, for postmenopausal women treated with teriparatide compared with placebo,\textsuperscript{2} the cost per QALY gained for teriparatide versus placebo was estimated at $€36,995$ and $€43,473$.\textsuperscript{34} Previous meta-analyses have shown that the incidence of vertebral or nonvertebral fractures was significantly reduced by alendronate in postmenopausal women without prevalent fractures and BMD levels below the World Health Organization threshold for osteoporosis compared with placebo.\textsuperscript{27,33} The discrepancies between our findings and the results of previous studies may be explained by our small sample size.

4.1. Limitations of study

This study is associated with some limitations. First, some of the included data were extracted from figures, which may limit its accuracy. Second, the sample size of 6 included studies was small.

5. Conclusions

The results of this meta-analysis suggest that teriparatide may be superior to alendronate for increasing lumbar spine BMD in postmenopausal osteoporosis. The efficacy and safety of long-term teriparatide and alendronate treatment in postmenopausal osteoporosis should be further investigated in clinical trials.

6. Figures

Figure 6. Funnel plots. (A) Lumbar spine BMD. (B) Femoral neck BMD. (C) Fracture incidence. BMD = bone mineral density, MD = mean difference, SE = standard error.
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