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Review

Teriparatide versus bisphosphonates for treatment of postmenopausal osteoporosis: A meta-analysis

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ABSTRACT

Objective: This meta-analysis aims to compare the efficacy of teriparatide and bisphosphonates for reducing vertebral fracture risk and bone mineral density (BMD) in lumbar spine and femoral neck in postmenopausal women with osteoporosis.

Methods: We searched the literature, via PubMed, Embase, Cochrane Library, Web of Science and Google database to screen citations from inception to April 2018 for inclusion in this study. Only randomized controlled trials that compared teriparatide and bisphosphonates for reducing vertebral fracture risk in postmenopausal women with osteoporosis were included. Stata 12.0 was used for meta-analysis.

Results: Our meta-analysis results indicated that, compared with bisphosphonates, teriparatide was associated with a reduction of the vertebral fracture risk (risk ratio (RR) = 0.57, 95% confidence interval (CI): 0.35, 0.93, P = 0.024). Furthermore, teriparatide therapy increased the mean percent change in BMD in lumbar spine of 6 months, 12 months and 18 months than bisphosphonates with statistically significant ($P < 0.05$). And, teriparatide has only beneficial in increasing the mean percent change in BMD in femoral neck of 18 months ($P < 0.05$). There was no significant difference between teriparatide and bisphosphonates in terms of the adverse events (AEs, RR = 1.09, 95% CI 0.89, 1.33, P = 0.424).

Conclusions: Teriparatide is an effective agent in reducing the risk of vertebral fracture in postmenopausal women with osteoporosis. Furthermore, teriparatide can increase the BMD in lumbar spine and femoral neck in long-terms duration.

1. Introduction

Postmenopausal osteoporosis is the most common bone disease in elderly women [1]. It comprises a major risk factor for fracture, which leads to considerable morbidity, mortality and economic costs [2,3]. It was suggested that approximately 30% of women in the United States are at risk for osteoporosis [4]. Furthermore, nearly 9 million fractures associated with osteoporosis occur annually [5]. Currently, bisphosphonates are considered the first-line treatment option in patients with osteoporosis [6]. The mechanism of bisphosphonates for treatment with osteoporosis was main through inhibit osteoclast-mediated bone resorption [7]. Recently, teriparatide has been shown that directly promote bone formation [8]. Teriparatide induces differentiation of preosteoblasts into osteoblasts, stimulates preexisting osteoblasts to form new bone and decreases osteoblast apoptosis. The effects of teriparatide versus bisphosphonates for preventing vertebral fracture was still controversial.

Several relevant meta-analysis has been published [9,10]. Zhang et al. [9] used an indirection method to compare the clinical effects of teriparatide versus bisphosphonates in reducing vertebral fracture. Results shown that teriparatide has comparable vertebral fracture rate when compared with bisphosphonates. Liu et al. [10] conducted a direct head to head comparison between teriparatide and bisphosphonates in osteoporosis patients. However, glucocorticoid-induced osteoporosis patients were also included and thus a large clinical heterogeneity was existed in this meta-analysis. Several more RCTs on this subject have been published without conclusive results [11]. Considering all these issues, it is impossible to give clear advice on which method to adopt.

Thus, we undertook a further meta-analysis to evaluate whether teriparatide is superior to bisphosphonates with respect to: (1) vertebral fracture; (2) non-vertebral fracture; (3) mean bone mineral density

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(BMD) change in lumbar spine in different duration; (4) mean BMD change in femoral neck in different duration; (5) adverse events (AEs).

2. Materials and methods

The current meta-analysis was performed according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and was reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [12] and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines.

2.1. Literature search

We performed a systematic electronic search in PubMed, Embase, Cochrane Library, Web of Science and Google database from inception through April 2018. Key word and corresponding Medical Subject Headings (MeSH) terms were used for searching databases. Search terms were as follows: ((((“Osteoporosis, Postmenopausal"[Mesh]) OR Postmenopausal osteoporosis)) AND ((((zoledronic acid) OR alendronate) OR risedronate) OR bisphosphonates)) AND (((((((Forteo) OR Teriparatide Acetate) OR Parathar) OR Human Parathyroid Hormone (1 − 34)) OR hPTH (1 − 34)) OR “Teriparatide"[Mesh]) OR teriparatide). We also manually checked the bibliographies of previous meta-analysis and included trials to identify other potentially eligible trials.

2.2. Selection criteria

Published RCTs meeting the following criteria were included:

(1) Population: Postmenopausal osteoporosis; (2) intervention: administration with teriparatide; (3) comparison: administration with bisphosphonates; and (4) ≥ 1 of the following outcomes: vertebral fracture, non-vertebral fracture, mean BMD change in lumbar spine, femoral neck in different duration and AEs.

2.3. Data extraction

Data extraction was performed by **XXX**. and XXX and disagreement was confirmed by other authors (**XXX**). Collected data included the following: first author, year of publication, country, sample and mean age of patients, dose and interval of comparison and controls, adjunct therapy, follow-up and outcomes. Extracted data were entered into a standardized Excel (Microsoft Corporation, Redmond, Washington, USA) file. Discrepancies were resolved by consulted from third reviewer (X.-L. M). Predefined primary outcome was the incidence of vertebral fracture. Other outcomes including incidence of non-vertebral fracture, mean percent changes in BMD in lumbar spine and femoral neck of 6, 12 and months duration and adverse events (AEs).

2.4. Risk of bias assessment

Two authors (**XX**. and XX) independently assessed risk of bias using the Cochrane risk-of-bias tool. We reviewed each trial and scored as high, low, or unclear risk of bias to the following criteria: random sequence generation; allocation concealment; blinding of participants and personnel to the study protocol; blinding of outcome assessment; incomplete outcome data; selective reporting; and other bias. Trials with high risk of bias for > 1 key domains were considered to be at high risk of bias whereas trials with low risk of bias for all key domains were considered to be at low risk of bias; otherwise they were considered to be at unclear risk of bias.

2.5. Grading quality of evidence

Two authors (XX. and XXX**)** independently evaluated the quality of evidence for primary and secondary outcomes according to Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [13] methodology for risk of bias, inconsistency, indirectness, imprecision, and publication bias, classified as very low, low, moderate, or high. Summary tables were constructed using the GRADE Profiler (version 3.6, GRADEpro).

2.6. Statistical analysis

We calculated risk ratios (RR) with 95% confidence intervals (CIs) for dichotomous outcomes and weighted mean differences (WMD) with 95% CIs for continuous outcomes. Heterogeneity across studies was quantified using the I^2 statistic; $I^2 > 50\%$ indicated significant heterogeneity. We pooled outcome data using a random-effects model accounting for clinical heterogeneity. To check the influence of various factors on the vertebral fracture, we further performed post hoc subgroup analyses according to dose of teriparatide (20 μg vs 40 μg), drugs of bisphosphonates (teriparatide vs risedronate or teriparatide vs alendronate), risk of bias (low vs unclear/high) and follow-up duration (≤18 months vs > 18 months). Only subgroup analyses showing a statistically significant test of interaction ($P < 0.05$) were considered to provide evidence of an intervention effect.

$P < 0.05$ was considered statistically significant. Publication bias was assessed by visually inspecting a funnel plot, and also evaluated using the tests of Begg's test. All statistical analyses were performed using Stata 12.0 (Stata Corp., College Station, TX).

3. Results

3.1. Search results

The PRISMA statement flowchart shows the process of literature screening, study selection, and reasons for exclusion (Fig. 1). Our initial search yielded 493 records. After removing duplicates and screening the titles and abstracts, 26 articles were thought to be potentially eligible for inclusion. After reviewing the full text, 11 randomized controlled trials (RCTs) [11–14] were finally included in the meta-analysis. Data on first-attempt failure were obtained by contacting with authors in one trial.

3.2. Trials characteristics

The main characteristics of the included trials are summarized in Table 1. These trials were published from 2002 to 2018. Population sizes ranged from 21 to 680, with a total of 4323 patients (teriparatide = 2166; bisphosphonates = 2157). Among the included trials, 3 of 11 trials compared teriparatide with risedronate, six compared teriparatide with alendronate, and one compared teriparatide with zoledronic acid. Two studies used 40 μg teriparatide as intervention group.

3.3. Risk of bias assessment

Figs. 2 and 3 summarize details of risk of bias. Overall, three trials were categorized as being at low risk of bias, four as being unclear, and four as being at high risk of bias. An adequate randomized sequence was generated in eight trials and appropriate allocation concealment was reported in five. Blinding of outcome assessments was unclear or seldom reported in five trials.

3.4. Primary outcome

3.4.1. Incidence of vertebral fracture

This analysis involved four trials [11–16] with a total of 3576 patients. The teriparatide therapy demonstrated a significant advantage over bisphosphonates in incidence of vertebral fracture (RR = 0.57, 95% CI: 0.35, 0.93, P = 0.024, Fig. 4). Subgroup analysis can be obtained in Table 2. The findings of incidence of vertebral fracture were

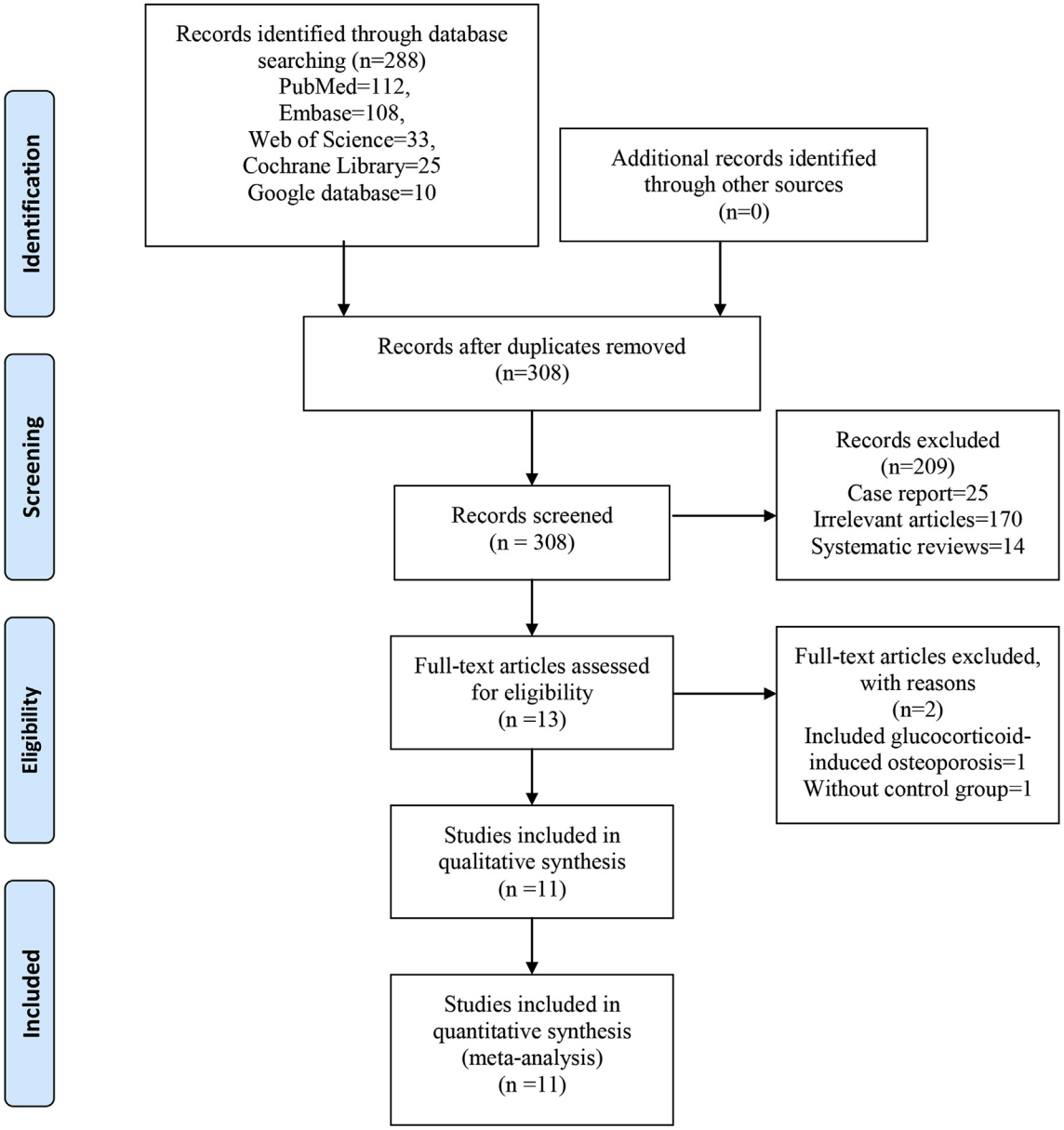

Fig. 1. The flow diagram of study selection.

consistent in all subgroup analyses except for the drug of bisphosphonates and follow-up duration.

3.4.2. Incidence of non-vertebral fracture

This analysis involved four trials [11–16] with a total of 2419 patients. The effect of the teriparatide therapy was equal to the bisphosphonates therapy at the incidence of non-vertebral fracture (RR = 0.66, 95% CI: 0.37, 1.17, P = 0.153, Fig. 5).

3.4.3. Mean percent changes in BMD in lumbar spine of 6 months duration

Six trials [15–18] with 768 patients provided the BMD data and were included in the analysis. Compared with the bisphosphonates therapy, teriparatide therapy improve the BMD at the lumbar spine (WMD = 1.35, 95% CI: 0.46, 2.24, P = 0.003, Fig. 6).

3.4.4. Mean percent changes in BMD in lumbar spine of 12 months duration

Five trials [16–18] with 726 patients provided the BMD data and were included in the analysis. Compared with the bisphosphonates therapy, teriparatide therapy improve the BMD at the lumbar spine (WMD = 3.51, 95% CI: 1.99, 5.03, P = 0.000, Fig. 7).

3.4.5. Mean percent changes in BMD in lumbar spine of 18 months duration

Four trials [18–20] with 1015 patients provided the BMD data and were included in the analysis. Compared with the bisphosphonates therapy, teriparatide therapy improve the BMD in lumbar spine of 18 months (WMD = 5.10, 95% CI: 5.07, 5.13, P = 0.000, Fig. 8).

3.4.6. Mean percent changes in BMD in femoral neck of 12 months duration

Three studies [16–18] with 398 patients reported the mean percent changes in BMD in femoral neck of 6 months duration. Patients treated with teriparatide has no beneficial in improving mean percent changes in BMD in femoral neck of 6 months duration than bisphosphonates (WMD = 1.71, 95% CI: 0.35, 3.77, P = 0.104, Fig. 9).

3.4.7. Mean percent changes in BMD in femoral neck of 18 months duration

Five studies with 398 patients reported the mean percent changes in

Table 1
General characteristic of the included studies.

Author	Country	Sample		Age		Dose and interval		Adjuvant	Follow-up	Outcomes
		Teriparatide	Other treatments	Teriparatide	Other treatments	Teriparatide	Other treatments			
Anastasilakis 2008	Greece	22	risedronate(n = 22)	65.4	64.7	20 μg SC daily	35 mg once weekly	Calcium/Vit D	12 months	1,3,4
Arlot 2005	France	21	alendronate (n = 21)	60.9	65.5	20 μg SC daily	alendronate 10 mg	Calcium/Vit D	18 months	1
Body 2002	India	73	alendronate (n = 73)	66	65	40 μg SC daily	alendronate 10 mg	Calcium/Vit D	12 months	1
Cosman 2011	USA	138	zoledronic acid n = 137	63.8	66.1	20 μg SC daily	zoledronic acid 5 mg	Calcium/Vit D	12 months	1
Finkelstein 2010	USA	20	alendronate (n = 29)	65	64	40 μg SC daily	alendronate 10 mg daily	Calcium/Vit D	30 months	1
Geusens 2018	Netherlands	680	risedronate (n = 680)	NS	NS	20 μg SC daily	risedronate 35 mg	Calcium/Vit D	24 months	2
Hadji 2012	Germany	360	risedronate (n = 350)	70.5	71.6	20 μg SC daily	risedronate 35 mg	Calcium/Vit D	6 months	3
Keaveny 2007	USA	28	alendronate (n = 25)	64.5	62.5	20 μg SC daily	alendronate 10 mg	Calcium/Vit D	18 months	3
Kendler 2017	Canada	680	680	72.6	71.6	20 μg SC daily	risedronate 35 mg	Calcium/Vit D	24 months	2
McClung 2005	Brazil	102	alendronate (n = 101)	65.3	66.6	20 μg SC daily	alendronate 10 mg	Calcium/Vit D	18 months	2,3,4
Panico 2011	Italy	42	alendronate n(n = 39)	65	60	20 μg SC daily	alendronate 10 mg	Calcium/Vit D	18 months	2,3,4

Fig. 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

BMD in femoral neck of 18 months duration. Patients treated with teriparatide has a beneficial role in improving mean percent changes in BMD in femoral neck of 18 months duration than bisphosphonates (WMD = 1.07, 95% CI: 0.06, 2.08, P = 0.038 Fig. 10).

3.4.8. AEs

Seven studies with patients reported the AEs. There was no significant difference between the teriparatide and bisphosphonates in terms of the AEs (RR = 1.09, 95% CI 0.89, 1.33, P = 0.424, Fig. 11).

3.4.9. GRADE profile evidence and publication bias

Supplement S1 shows the GRADE evidence profiles for the outcomes. The GRADE Working Group level of evidence is low for the incidence of vertebral fracture, incidence of non-vertebral fracture, mean percent changes in BMD in lumbar spine of 12 months duration and AEs. The GRADE Working Group level of evidence is high for the mean percent changes in BMD in lumbar spine of 18 months duration and moderate for Mean percent changes in BMD in femoral neck of 12 and 18 months duration.

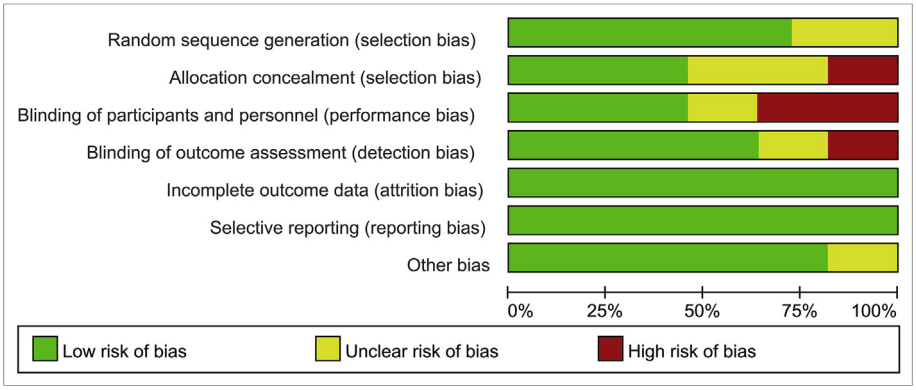

Fig. 3. Risk of bias summary for included studies. +, no bias; –, bias; ?, bias unknown.

For the meta-analysis of the effects of teriparatide versus bisphosphonates on the incidence of vertebral fracture, there was no evidence of publication bias according to inspection of the funnel plot (Fig. 12) and formal statistical tests (Egger test, P = 0.085; Begg test, P = 0.104). We performed a sensitivity analysis to assess the stability of the pooled results. Among the most studies, the heterogeneity results was not obviously altered after sequentially omitting each study, indicating that our results were statistically reliable (Fig. 13).

4. Discussion

Current meta-analysis indicated that, compared with bisphosphonates, teriparatide was associated with a reduction of the vertebral fracture. Furthermore, tereparatide was shown to increase the BMD in lumbar spine at short duration (6 months) and long terms duration (12 months and 18 months). And tereparatide only has a beneficial role in improving the BMD in femoral neck in long term duration (18 months). There was no significant difference in the occurrence of AEs between tereparatide and bisphosphonates.

Several previous systematic reviews comparing tereparatide and other treatments have been published [10–24]. However, difference between with previous meta-analyses should be noted. A meta-analysis of tereparatide versus alendronate in patients with osteoporosis showed

Table 2
Subgroup analysis for teriparatide compared with bisphosphonates for vertebral fracture.

Subgroup	Risk ratio (95% CI)	P value	I^2(%)	Test ofinteraction, P
Total				
Dose of teriparatide				
20 μg	0.45(0.35,0.58)	0.000	15.7	0.104
40 μg	0.57(0.42,0.93)	0.000	68.5	
Drug of bisphosphonates				
T vs ALE	3.33(0.96,11.62)	0.059	12.5	0.008
T vs RIS	0.45(0.35,0.58)	0.000	25.9	
Risk of bias				
Low	0.52(0.39,0.83)	0.015	39.4	0.063
Unclear/high	0.59(0.45,0.73)	0.027	52.1	
Follow-up				
≤18 months	0.71(0.43,1.15)	0.163	87.2	0.000
> 18 months	0.45(0.39, 0.63)	0.000	0.0	

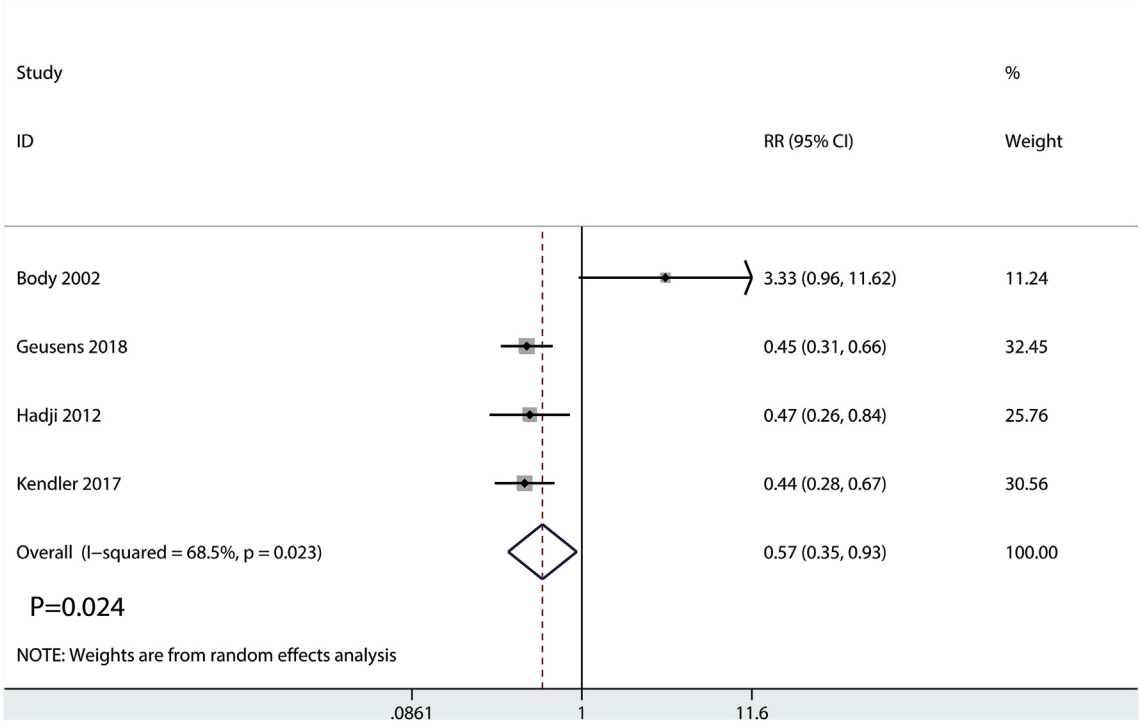

Fig. 4. Forest plot for comparing teriparatide versus bisphosphonates in terms of incidence of vertebral fracture.

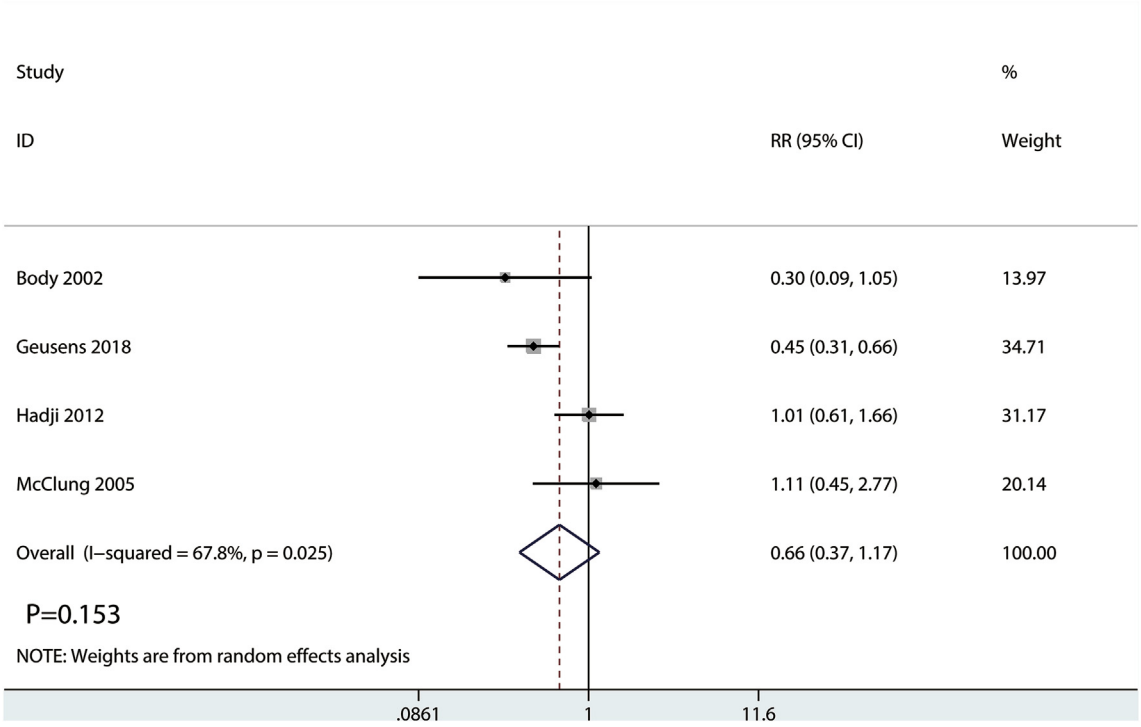

Fig. 5. Forest plot for comparing teriparatide versus bisphosphonates in terms of incidence of non-vertebral fracture.

no significant difference in the occurrence of vertebral fracture [24]. Liu et al. [10] conducted a meta-analysis comparing tereparatide and bisphosphonates in osteoporosis patients. However, glucocorticoid-induced osteoporosis patients were also included in meta-analysis. Clinical heterogeneity was obvious in that meta-analysis.

In this meta-analysis, we identified the vertebral fracture as the primary outcome. Result shown that tereparatide was superior than bisphosphonates in reducing the vertebral fracture rate. Compared with bisphosphonates, teriparatide was associated with a reduction of the rate of vertebral fracture by nearly 5.13% (5.08% vs 10.21%). Nevitt et al. [25] revealed that tereparatide was associated with a reduction of the back pain following teriparatide treatment in osteoporotic vertebral fracture. Murad et al. [26] conducted a network meta-analysis and found that teriparatide had the highest risk reduction of fractures.

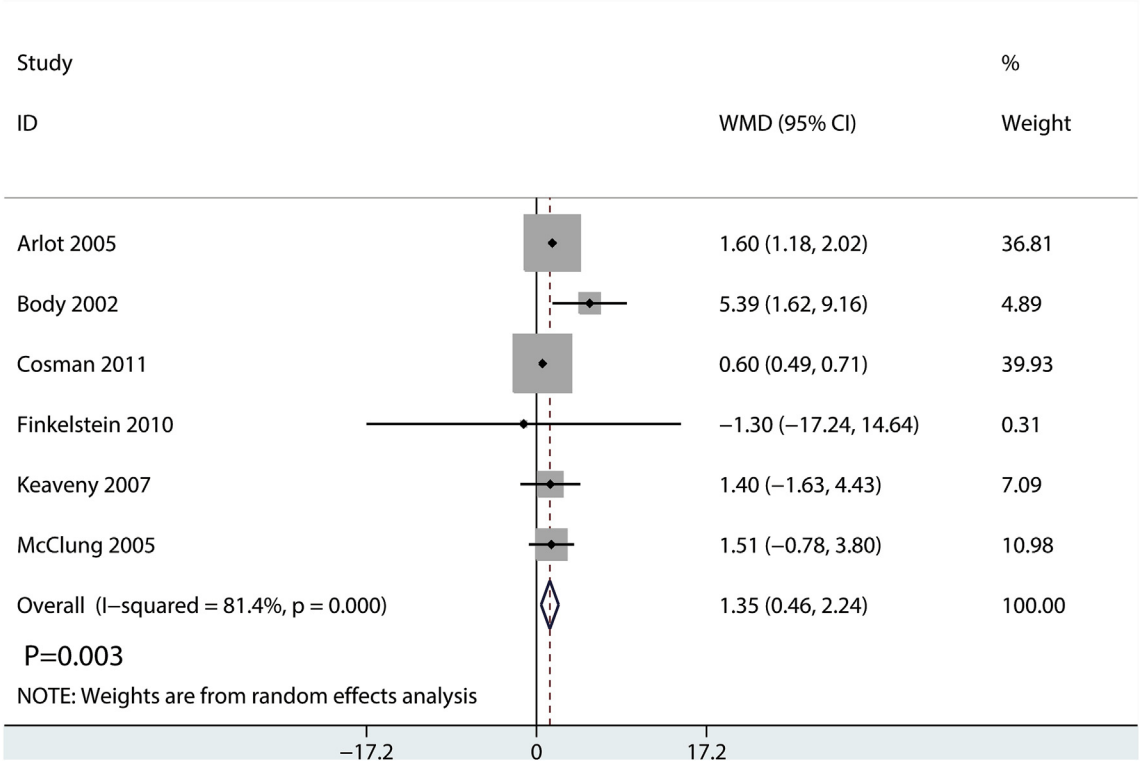

Fig. 6. Forest plot for comparing teriparatide versus bisphosphonates in terms of mean percent changes in BMD in lumbar spine of 6 months duration.

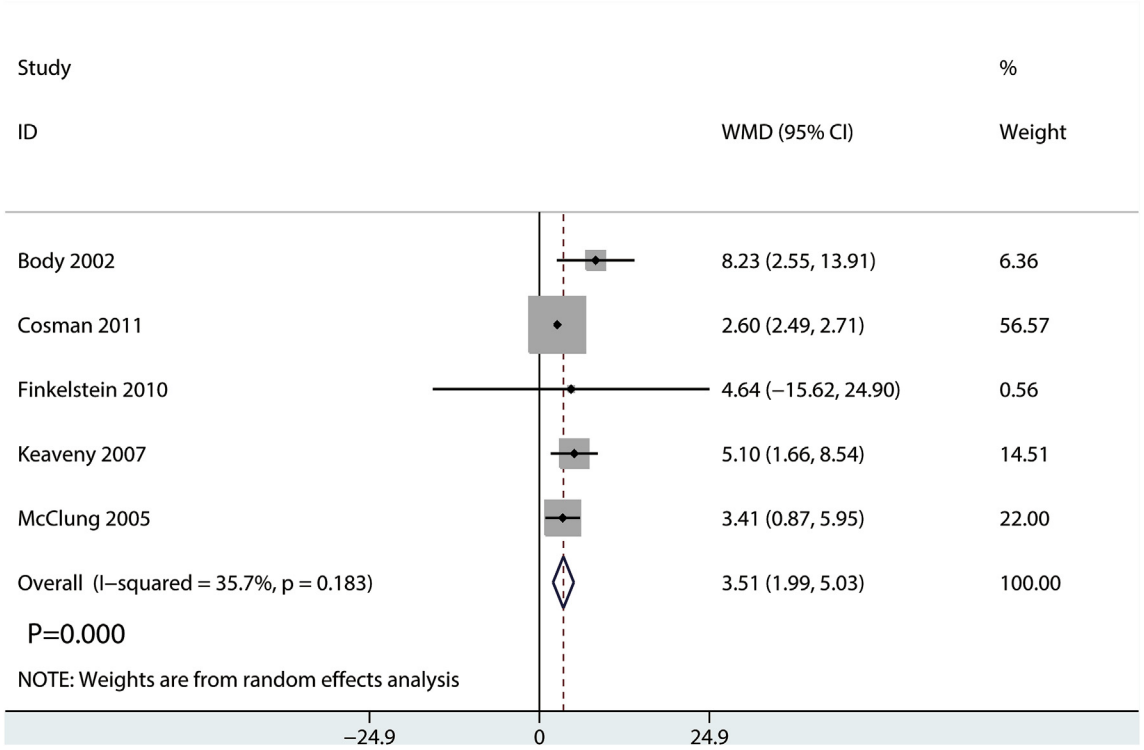

Fig. 7. Forest plot for comparing teriparatide versus bisphosphonates in terms of mean percent changes in BMD in lumbar spine of 12 months duration.

Zhang et al. [9] performed an indirect comparison between four different drugs for preventing vertebral fracture in osteoporosis patients. And teriparatide, denosumab, alendronate, and risedronate are effective in reducing the risk of vertebral and non-vertebral fracture in osteoporosis patients. Shi et al. [27] found that administration of teriparatide following fracture lacked the effectiveness for fracture healing. Our study adds to the body of literature regarding the influence of teriparatide versus bisphosphonates on vertebral fracture. We further collected relevant data about the non-vertebral fracture. However, no significant difference was found between teriparatide and bisphosphonates. Balani et al. [28] revealed that teriparatide increases the numbers of early cells of the osteoblast lineage, hastens their differentiation into osteoblasts, and suppresses their differentiation into adipocytes in vivo.

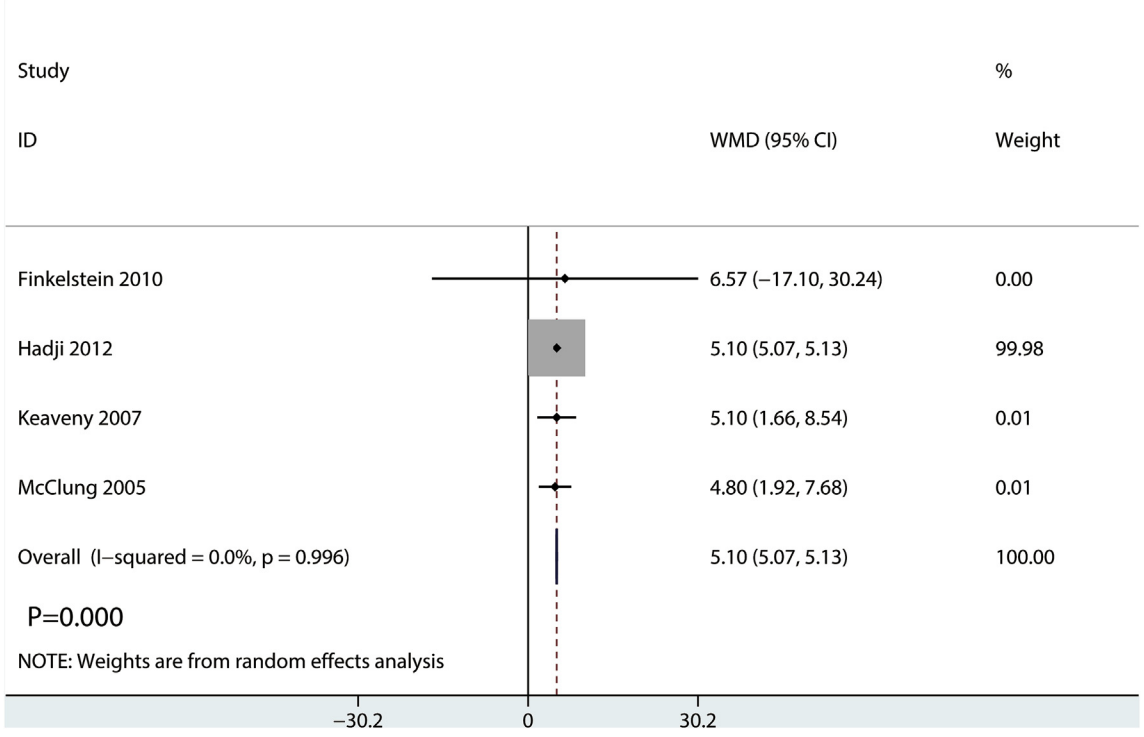

Fig. 8. Forest plot for comparing teriparatide versus bisphosphonates in terms of mean percent changes in BMD in lumbar spine of 18 months duration.

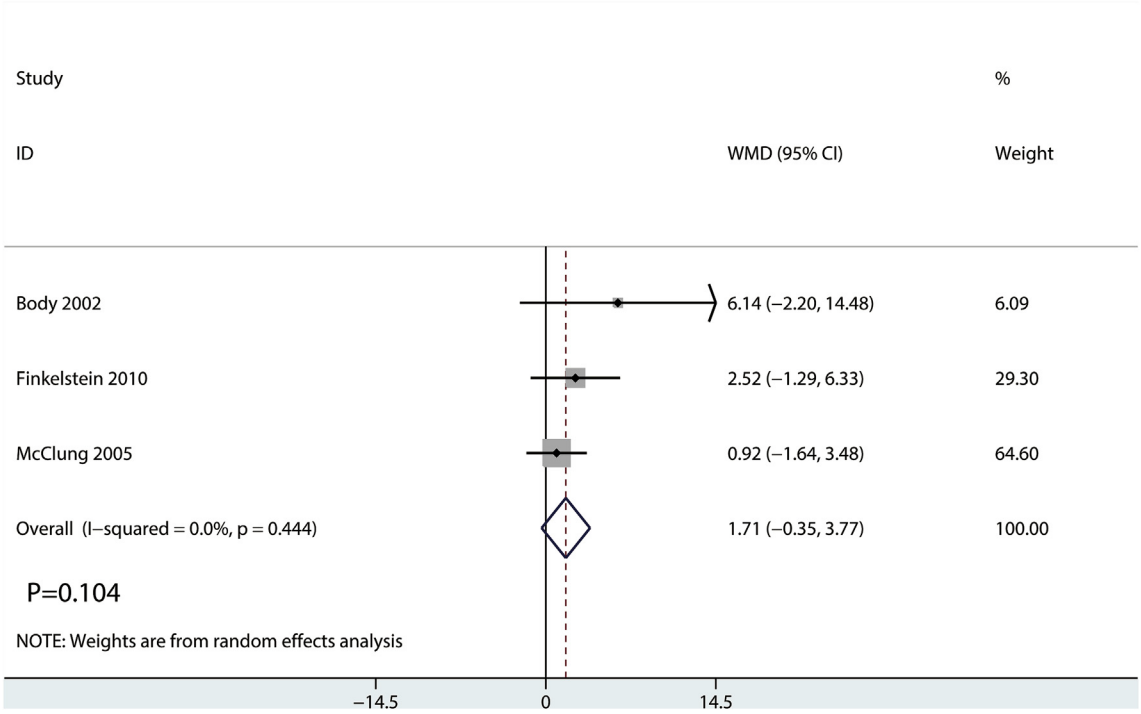

Fig. 9. Forest plot for comparing teriparatide versus bisphosphonates in terms of mean percent changes in BMD in femoral neck of 12 months duration.

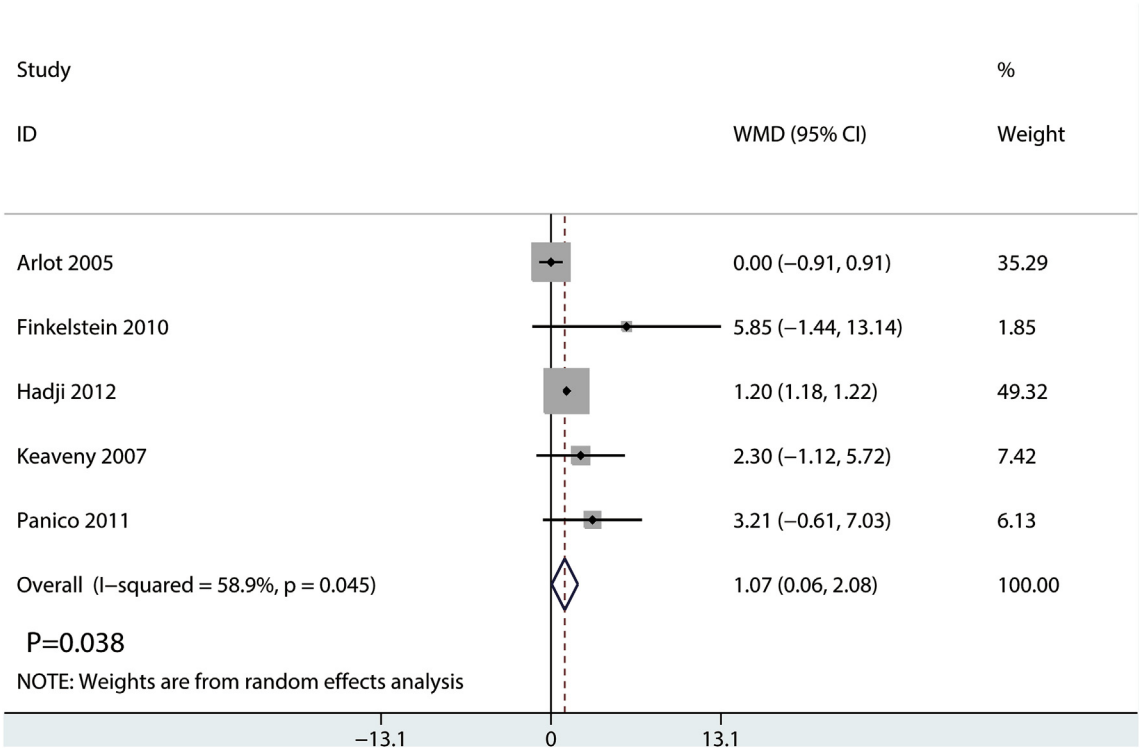

Fig. 10. Forest plot for comparing teriparatide versus bisphosphonates in terms of mean percent changes in BMD in femoral neck of 18 months duration.

We then measured the BMD in lumbar spine and femoral neck at short duration (6 months) and long terms duration (12 months and 18 months). Teriparatide was superior to bisphosphonates in improving BMD in lumbar spine at short duration and long terms duration. Han et al. found that teriparatide significantly increased spine and hip BMD, clinical heterogeneity and potential bias could not be eliminated [29]. In accordance with our findings, previous studies have also shown that teriparatide could increase BMD and femoral neck of postmenopausal women with osteoporosis by nearly 9.7% [30,31].

Tereparatide has a beneficial role in improving the BMD in femoral neck in long term duration (18 months). In contrast with our meta-analysis, Shen et al. revealed that teriparatide could increase the femoral neck BMD in a dose-dependent manner [31].

Finally, we compared total AEs between teriparatide and bisphosphonates at final follow-up. Results shown that there was no significant difference between the teriparatide and bisphosphonates in

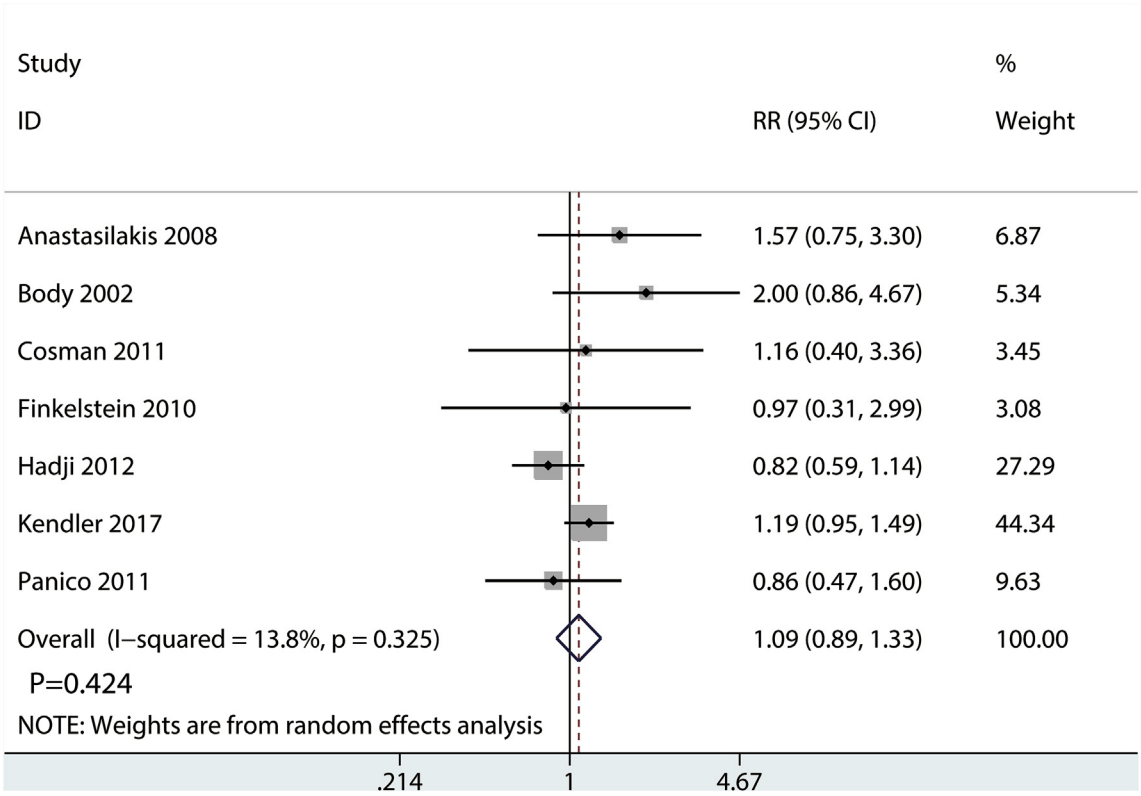

Fig. 11. Forest plot for comparing teriparatide versus bisphosphonates in terms of adverse events.

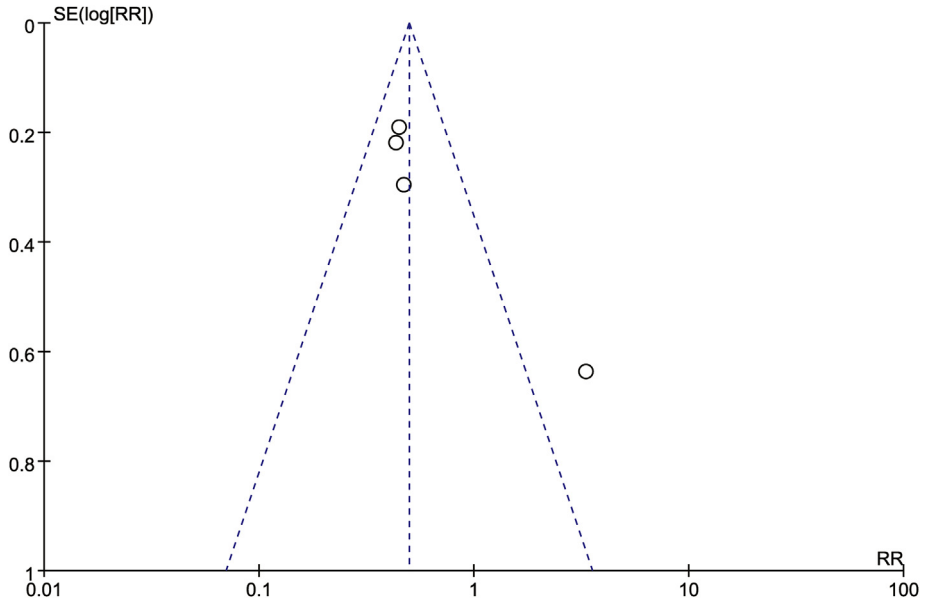

Fig. 12. Funnel plot of the incidence of vertebral fracture.

terms of the AEs ($P > 0.05$). AEs were balanced in the two groups and both teriparatide and bisphosphonates were well tolerated. The most common AEs in teriparatide group were back pain, nausea and dizziness in the first month of treatment. Furthermore, hypercalcaemia, hyperuricaemia, and hypomagnesaemia were more common in teriparatide group than in bisphosphonates group. While the most common AEs in bisphosphonates group were abdominal pain, arthralgia and dyspepsia.

The strength of this meta-analysis lies in the preplanned parallel comparison of vertebral fracture as the primary outcome in homogeneous set of participants (patients were diagnosed with postmenopausal osteoporosis) receiving teriparatide versus bisphosphonates. Moreover, this meta-analysis assesses the dose of teriparatide and different bisphosphonates in different subgroups for further analysis. Additionally, all of the included trials reported long-term follow-up data (at least 6 months).

Several limitations in this meta-analysis should be noted. First, only two studies included 40 μg teriparatide as comparison and other studies were all administration with 20 μg teriparatide. Though we performed a subgroup analysis, the real effects of different dose of teriparatide for

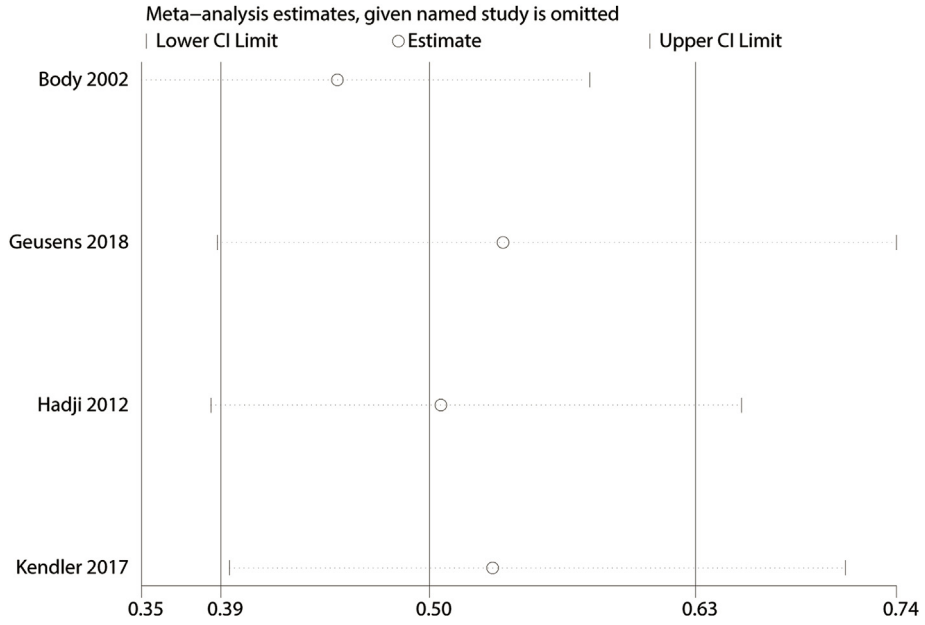

Fig. 13. Sensitivity analysis of the incidence of vertebral fracture.

osteoporosis was undefined. Second, duration of these two drugs were different and may affect final outcomes. Third, vertebral fracture rates were assessed in different follow-up and thus need for more studies to identify teriparatide versus bisphosphonates for vertebral fracture rates in a same duration of follow-up. Fourth, the adjuvant therapy (Calcium or Vit D supplement) was different and thus may cause heterogeneity for final clinical outcomes. At last, direct comparison between teriparatide and alendronate, risedronate and zoledronic acid need for more studies to identify.

5. Conclusion

In patients with postmenopausal osteoporosis, when compared with bisphosphonates, teriparatide decreases the risk of vertebral fracture and increase the BMD change in lumbar spine and femoral neck. The complications rates in teriparatide and bisphosphonates was comparable.

Ethical approval

None.

Author contribution

Fei Yuan and Wen Peng: data collections, data analysis and writing. Caihong Yang and Jinping Zheng: data collections and data analysis. Fei Yuan: study design, data collections.

Conflicts of interest

None.

Trial registry number

Reviewregistry663.

Guarantor

Fei Yuan.

Data statement

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Provenance and peer review

Not commissioned, externally peer-reviewed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.03.004.

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