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Effects of teriparatide compared with risedronate in the treatment of osteoporosis

A meta-analysis of randomized controlled trials

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Abstract

Background: This meta-analysis was conducted to compare the effects and safety of teriparatide with risedronate in the treatment of osteoporosis.

Material and methods: PubMed, Embase, Web of Science and Cochrane library database were systematically reviewed for studies published up to February 24, 2019. Eligible studies that compared the effects of teriparatide with risedronate in osteoporosis were included in this meta-analysis. The outcomes included percentage change in bone mineral density (BMD) of lumbar spine, femoral neck, and total hip, the incidence of clinical fractures, serum bone markers, and adverse events. A random-effects or fixed-effects model was used to pool the estimate, according to the heterogeneity among the included studies.

Results: Seven studies were included in this meta-analysis. Compared with risedronate, teriparatide was associated with a significant increase in lumbar spine BMD [weight mean difference (WMD)=4.24, 95%CI: 3.11, 5.36; $P < .001$], femoral neck BMD (WMD=2.28, 95%CI: 1.39, 3.18; $P < .001$), and total hip BMD (WMD = 1.19, 95%CI: 0.47, 1.91; $P = .001$). Moreover, patients in teriparatide group had significantly lower incidences of clinical fracture (risk ratio [RR] = 0.48, 95%CI: 0.32, 0.72; $P < .001$), new vertebral fracture (RR = 0.45, 95%CI: 0.32, 0.63; $P < .001$), and non-vertebral fracture (RR = 0.63, 95%CI: 0.40, 0.98; $P = .042$) than those in risedronate group. There were significant differences between the 2 groups in serum change, including P1NP (WMD = 122.34, 95%CI: 68.89, 175.99; $P < .001$), CTx (WMD = 0.62, 95%CI: 0.29, 0.96; $P < .001$), and iPTH (WMD = -13.18, 95%CI: -15.04, -11.33; $P < .001$). The incidence of adverse events was similar between the 2 groups (RR = 0.93, 95%CI: 0.69, 1.25; $P = .610$).

Conclusion: This study suggested that teriparatide was more effective than risedronate for increasing the BMD in lumbar spine, femoral neck, and total hip, as well as reducing the incidences of clinical fracture, new vertebral fracture and non-vertebral fracture. There was no significant difference in incidence of adverse events between the 2 drugs. Considering the potential limitations in the present study, further large-scale, well-performed randomized trials are needed to verify our findings.

Abbreviations: BMD = bone mineral density, CIs = confidence intervals, RCTs = randomized controlled trials, RR = risk ratio, WMD = weight mean difference.

Keywords: meta-analysis, osteoporosis, risedronate, teriparatide

1. Introduction

Osteoporosis is a worldwide disease associated with decreased bone strength and quality and increased risk for fracture. Approximately 20% of women in North America will experience a hip fracture in their lifetime.[1] For patients who were older than 55 years, the 1-year mortality rate was up to 39% if they had hip fractures; whereas, for the survivors, the frailty would decrease their life expectancy, reduce physical function, and impair quality

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CY and GL the 2 authors contributed equally to this manuscript

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of life.[2,3] There are two major categories of pharmacological treatments that have been used for osteoporosis, including antiresorptive and bone anabolic medications. These osteoporosis medications could increase bone mineral density (BMD), reduce bone loss, and thereby reducing the risk of fractures.[4]

Teriparatide is a bone-forming medication that preferentially stimulates osteoblasts to improve bone quality and reduce the risk of vertebral and nonvertebral fractures.[5] Two previous clinical trials have reported the effects of teriparatide in patients with prevalent vertebral fractures and preexisting back pain.[6,7] Their results showed that the back pain had been significantly reduced after 6 months of teriparatide treatment, and this effect lasted through 24 months,[8] or 18 months of treatment.[9]

Risedronate is a potent antiresorptive agent, which is used for the prevention and treatment of osteoporosis. It inhibits osteoclast activity and induces their apoptosis, thereby maintaining BMD and reducing the risk of fractures.[10]

Although several studies[11–13] have compared the effects of teriparatide and risedronate on BMD in osteoporosis patients; no meta-analysis that compared the effects and safety of teriparatide versus risedronate has been performed. Therefore, we conducted this meta-analysis of randomized controlled trials (RCTs) of teriparatide versus risedronate to fully characterize the effect of the two drugs on changes in lumbar spine, femoral neck, and total hip BMD, incidences of vertebral and nonvertebral fractures, bone turnover markers, and adverse events in osteoporosis patients.

2. Materials and methods

2.1. Ethics approval and consent to participate

Since this study is a meta-analysis of previously published studies, ethics approval and informed consent are not applicable.

2.2. Search strategy and data source

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and meta-analysis criteria.[14] Electronic databases, including PubMed, Web of Science, Embase, and Cochrane library were systematically searched until February 24, 2019, with no language restrictions. The following initial search items were used:("osteoporosis, postmenopausal" [MeSH terms] OR ("osteoporosis" [All fields] AND "postmenopausal" [All Fields]) OR "postmenopausal osteoporosis"[All Fields] OR "osteoporosis" [All Fields] OR "osteoporosis" [MeSH Terms]) AND ("teriparatide" [MeSH Terms] OR "teriparatide" [All Fields]) AND ("risedronic acid"[MeSH Terms] OR ("risedronic" [All Fields] AND "acid"[-All Fields]) OR "risedronic acid"[All Fields] OR "risedronate"[All Fields]). We also manually searched the references of related reviews and eligible studies until no potential studies were found. Discrepancies were resolved by discussion and consensus between the 2 investigators.

2.3. Study inclusion and exclusion criteria

The inclusion criterion for a study to be included in this meta-analysis was that it should meet the following inclusion criteria:

(1) Study design: RCT;
(2) Study subjects: adult osteoporosis patients;
(3) Study intervention: teriparatide or risedronate;
(4) Outcomes: percentage changes in lumbar spine, femoral neck, and total hip BMD, incidences of clinical fracture, new vertebral fracture, and non-vertebral fractures, biochemical markers of bone turnover, and adverse events.

We would contact the corresponding authors for missing information when necessary. Exclusion criteria included studies that published with any of the following type: reviews, case report, editorials, and letters; or studies that used other drugs for osteoporosis; or studies that were related with our topics but did not present data of our interest.

2.4. Data extraction and risk of bias assessment

Two independent investigators extracted the following information from the included studies: first author's name, year of publication, study design, number of patients in each group, patient characteristics (gender, age, race, weight, and body mass index), and outcomes. In case that several articles from the same trial were published, we only included the study that had the most relevant information or the longest follow-up period.

We used the method recommended by Cochrane Collaboration to assess the risk of bias for RCTs.[15] This method consists of the following items to evaluate the risk bias: random sequence generation; allocation concealment; blinding of outcome participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting and other bias.[15] Each study was regarded as "high", "low", or "unclear" risk of bias according to the criteria mentioned above.

2.5. Statistical analysis

For continuous variables (ie, percentage changes in lumbar spine, femoral neck, and total hip BMD), the mean value and standard deviation were extracted from the included studies. Thereafter, the weighted mean difference (WMD) with 95% confidence intervals (CIs) was calculated. For dichotomous variables (ie, incidences of clinical fracture, new vertebral fracture, and non-vertebral fractures, and adverse events), they were expressed as risk ratio (RR) with 95%CIs. Before the data were synthesized, Cochrane Q and I^2 statistic[16] were used to test the heterogeneity among the included studies, in which $P < .1$ or $I^2 > 50\%$ were considered to be significant.[16] A fixed-effect model[17] was employed for studies which showed no evidence of heterogeneity, while a random-effects model[18] was used for those with heterogeneity. We also conducted sensitivity to assess the stability of synthesis results and explore the sources of heterogeneity by removing every single study at 1 time. Subgroup analysis was performed based on the gender and treatment duration. Publication bias was evaluated using the Begg[19] and Egg[20] test. A P value less than .05 was judged as statistically significant except where a certain P-value had been given. All statistical analyses were performed using STATA version 12.0 (Stata Corporation, College Station, TX).

3. Results

3.1. Study selection

The diagram of meta-analysis search strategy and selection process is presented in Figure 1. A total of 937 records were discovered in the electronic database, of which 582 were removed because of duplicate records. After checking for title/abstract

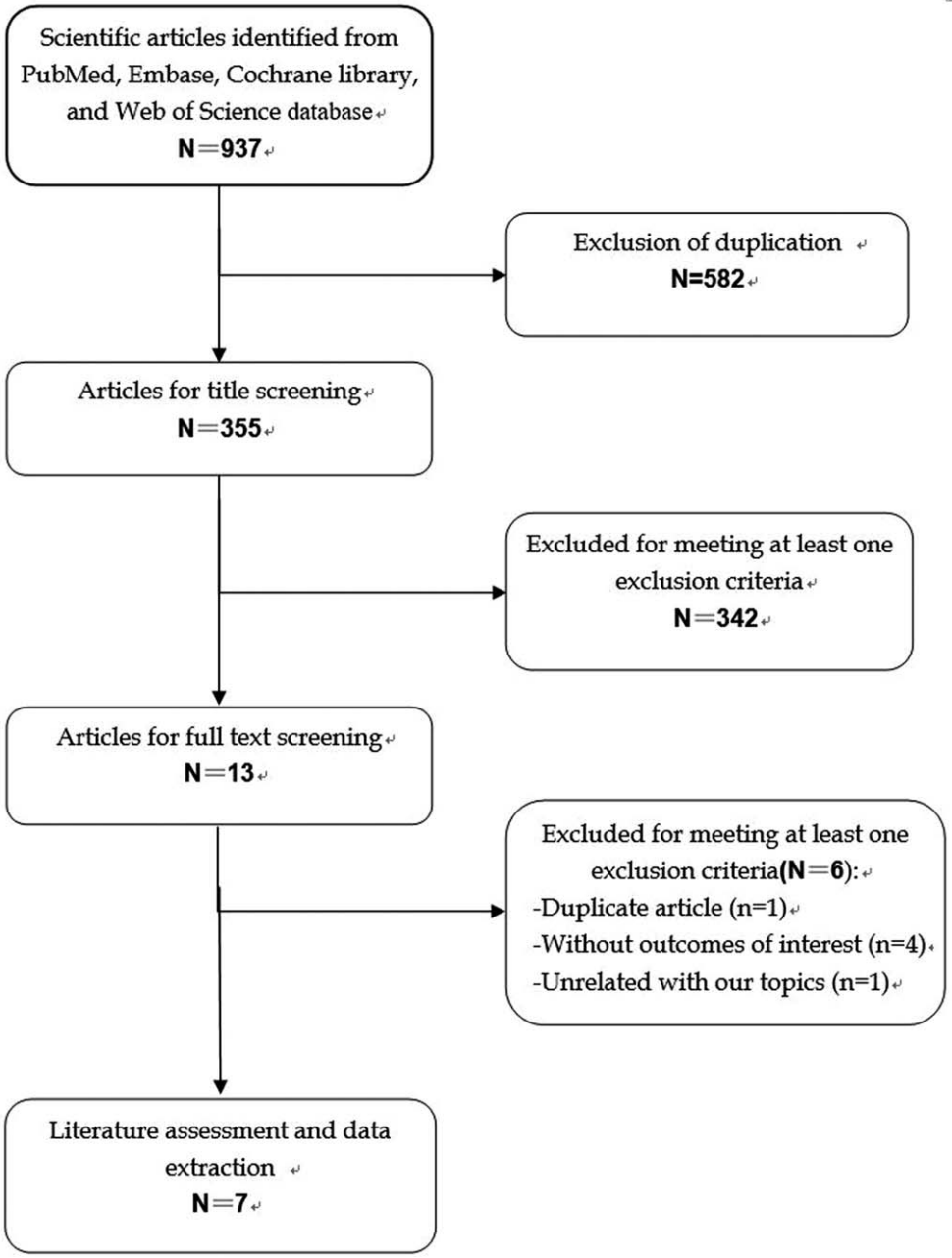

Figure 1. Eligibility of studies for inclusion in meta-analysis.

review, 342 records were excluded because they were incompatible with our inclusion criteria. Then 13 studies were left for the full-text information screening. Of them, 6 studies were excluded because 4[11–13,21] did not provide outcomes of our interest, 1 was unrelated with our topics,[22] and 1[23] was a duplicate article with another publication. Finally, seven studies[24–30] met the inclusion criteria and were included in this meta-analysis.

3.2. Study characteristics

The main characteristics of the included studies are presented in Table 1. The total number of patients was 1949, and the sample size across studies ranged from 19 to 1360. All the included studies were RCT. Three of the included studies enrolled only post-menopausal women,[24–26] and 2 enrolled only men.[27,29] The demographic and clinical characteristics of patients in each trial were well balanced. The mean age of patients was older than 50-years old. The treatment duration ranged from 12 months to 24 months in each trial.

3.3. Risk of bias of included studies

The details of risk bias are summarized in Figure 2. Overall, 5 RCTs were considered as being at low risk of bias,[24,26,28–30] 1 at unclear risk of bias,[27] and 1 at high risk of bias.[25] The reason for the study[25] at high risk of bias was that blinding of participants and personnel, as well as the blinding of outcome

Table 1

Baseline characteristics of patients in the trials included in the meta-analysis.

Study	Country	Study population	Treatment regimen	No. of patients	Male/ female	Age (mean ± SD, y)	Duration (mo)
Hadji P[24]	Multiple countries	Postmenopausal women with osteoporotic vertebral fractures	Teriparatide 20 μg/d	45	0/45	57.5 ± 12.8	18
			Risedronate 35mg/wk	47	0/47	55.1 ± 15.5	18
Anastasilakis AD[25]	Greece	Postmenopausal women with osteoporosis	Teriparatide 20 μg/d	22	0/22	65.4 ± 1.6	12
			Risedronate 35mg/wk	22	0/22	64.7 ± 1.5	12
Kendler DL[26]	Multiple countries	Postmenopausal women with severe osteoporotic vertebral fractures	Teriparatide 20 μg/d	680	0/680	72.6 ± 8.77	24
			Risedronate 35mg/wk	680	0/680	71.6 ± 8.58	24
Glüer CC[27]	Multiple countries	Men with glucocorticoid-induced osteoporosis	Teriparatide 20 μg/d	45	45/0	57.5 ± 12.8	18
			Risedronate 35mg/wk	47	47/0	55.1 ± 15.5	18
Malouf-Sierra J[28]	Multiple countries	Men and postmenopausal women with low bone mass who had sustained a recent unilateral pertrochanteric fracture	Teriparatide 20 μg/d	86	20/66	77.2 ± 8	18
			Risedronate 35mg/wk	85	19/66	76.4 ± 7.5	18
Walker MD[29]	USA	Men with low bone mineral density	Teriparatide 20 μg/d	9	9/0	51.6 ± 3.9	18
			Risedronate 35mg/wk	10	10/0	56.7 ± 4.9	18
Aspenberg P[30]	Multiple countries	Men and women with a recent pertrochanteric hip fracture	Teriparatide 20 μg/d	86	20/66	77.2 ± 8.0	18
			Risedronate 35mg/wk	85	19/66	76.4 ± 7.5	18

mo = month, SD = standard deviation.

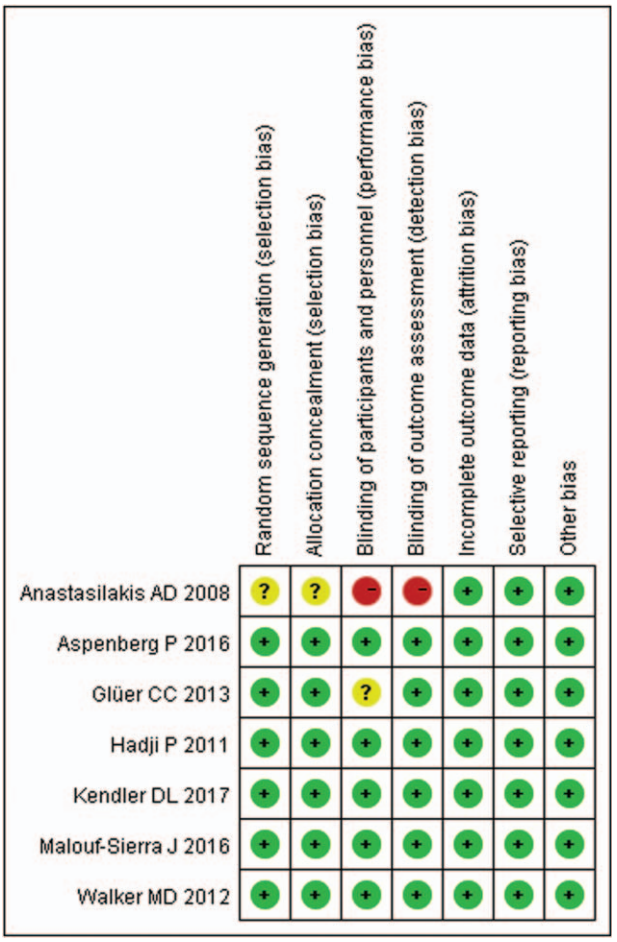

Figure 2. Risk of bias summary.

assessment were not adequately performed. The reason for the study[27] at unclear risk of bias was that it did not describe the method for the blinding of participants and personnel.

3.4. BMD of lumbar spine

Five studies[24,25,27–29] reported the data of percentage change in lumbar spine BMD. Pooled estimate suggested that patients treated with teriparatide had a greater percentage change in lumbar spine BMD compared with those with risedronate (WMD = 4.24, 95%CI: 3.11, 5.36; $P < .001$) (Fig. 3). There was significant heterogeneity among the included studies ($I^2 = 99.0\%$, $P < .001$). Therefore, we conducted sensitivity analysis. When we excluded the trial with outlier,[27] the overall estimate did not change substantially (WMD = 3.47, 95%CI: 2.33, 4.61; $P < .001$), but the heterogeneity was still present ($I^2 = 99.1\%$, $P < .001$). When we excluded the trial with small sample size,[29] the overall result changed slightly (WMD = 4.58, 95%CI: 3.24, 5.91; $P < .001$), but the heterogeneity did not disappear ($I^2 = 85.3\%$, $P < .001$). When we further excluded any other single study, the overall estimate and heterogeneity did not change substantially (data not shown).

Subgroup analysis stratified by treatment duration suggested that teriparatide was associated with a greater percentage change in lumbar spine BMD as compared with risedronate when it was administered for 6 months (WMD = 2.44, 95%CI: 2.26, 2.61; $P < .001$), 12 months (WMD = 3.76, 95%CI: 2.26, 5.25; $P < .001$), and 18 months (WMD = 5.74, 95%CI: 4.33, 7.14; $P < .001$) (Fig. 3).

Subgroup analysis stratified by gender indicated that teriparatide was associated with a greater percentage change in lumbar spine BMD than risedronate. And this significant difference was observed in both male (WMD = 4.96, 95%CI: 1.57, 8.36; $P < .001$) and female (WMD = 3.64, 95%CI: 0.53, 6.74; $P < .001$) patients.

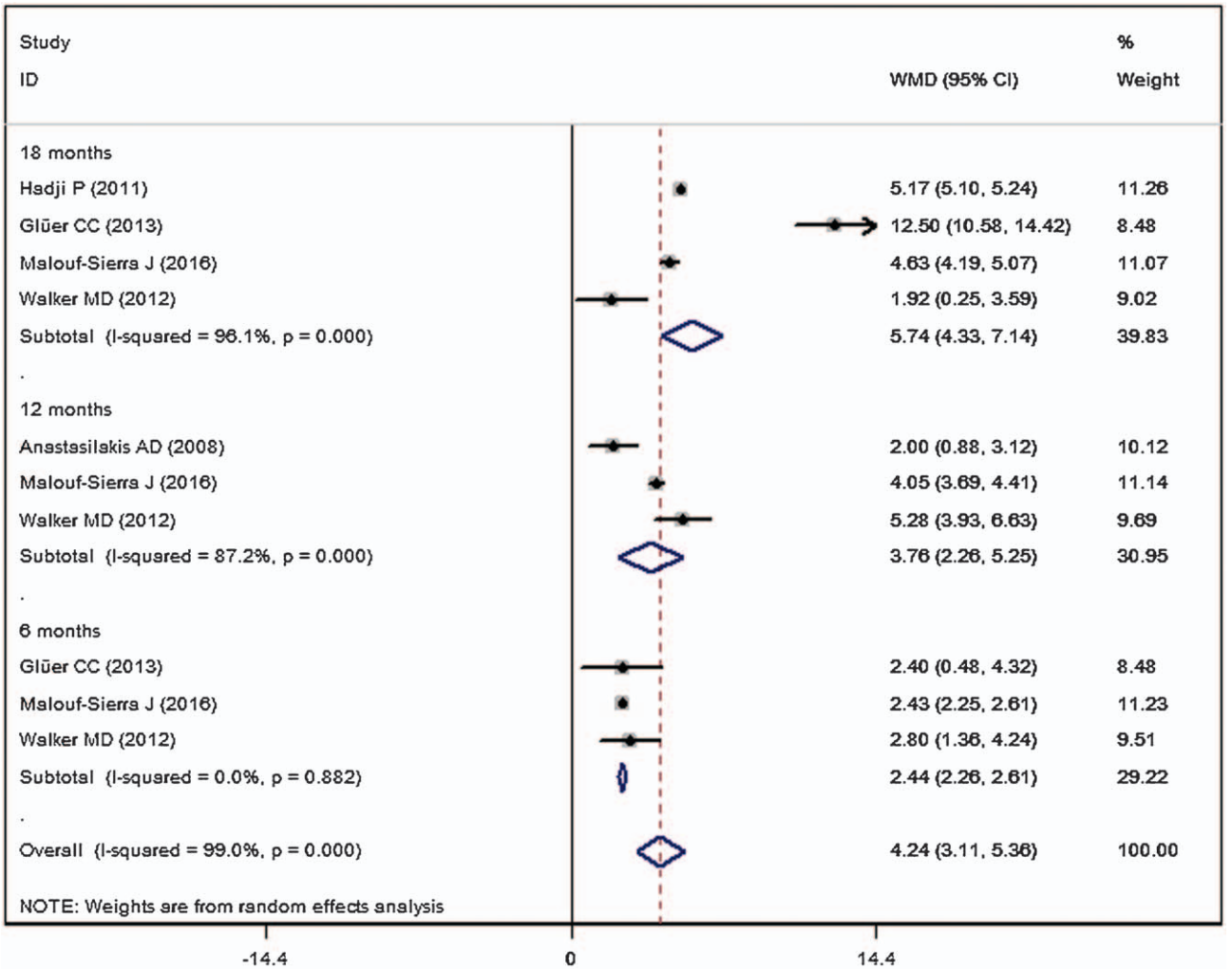

Figure 3. Forest plot showing the comparison between teriparatide with risedronate on the percentage change in lumbar spine BMD. BMD = bone mineral density.

3.5. BMD of femoral neck

Two studies[28,29] reported the data of percentage change in femoral neck BMD. The summarized result demonstrated that patients treated with teriparatide had a greater percentage change in femoral neck BMD compared with those with risedronate (WMD = 2.28, 95%CI: 1.39, 3.18; $P < .001$) (Fig. 4). The test for heterogeneity showed that significant heterogeneity was observed among the included studies ($I^2 = 98.1\%$, $P < .001$). however, because the number of included studies was small, we did not perform the sensitivity analysis.

Subgroup analysis based on treatment duration showed that the percentage change in femoral neck BMD was significantly greater in teriparatide group than in risedronate group when the treatment lasted for 6 months (WMD = 2.37, 95%CI: 1.25, 3.50; $P < .001$), 12 months (WMD = 1.09, 95%CI: 0.67, 1.52; $P < .001$), or 18 months (WMD = 3.15, 95%CI: 2.95, 3.36; $P < .001$) (Fig. 4).

3.6. BMD of total hip

Three studies[24,28,29] reported the data of percentage change in total hip BMD. The pooled result suggested that, patients treated with teriparatide had a greater percentage change in total hip BMD compared with those with risedronate (WMD = 1.19, 95%CI: 0.47, 1.91; $P = .001$) (Fig. 5). There was significant heterogeneity among the included studies ($I^2 = 98.8\%$, $P < .001$).

Subgroup analysis stratified by treatment duration suggested that percentage change in total hip BMD was significantly greater in teriparatide group than in risedronate group when the treatment lasted for 18 months (WMD = 1.60, 95%CI: 0.51, 2.68; $P = .004$), but not for 6 months (WMD = 0.81, 95%CI: -0.74, 2.36; $P = .304$) and 12 months (WMD = 0.93, 95%CI: -0.35, 2.20; $P = .154$) (Fig. 5).

3.7. Incidence of clinical fracture, vertebral fracture, and non-vertebral fracture

Five studies[24,26,28–30] reported the data of vertebral and non-vertebral fractures. Pooled estimate indicated that patients treated with teriparatide had significantly lower incidences of clinical fracture (RR = 0.48, 95%CI: 0.32, 0.72; $P < .001$), new vertebral fracture (RR = 0.45, 95%CI: 0.32, 0.63; $P < .001$), and non-vertebral fracture (RR = 0.63, 95%CI: 0.40, 0.98; $P = .042$) (Fig. 6). There was no evidence of heterogeneity among the included studies ($I^2 = 0.0\%$, $P = .992$).

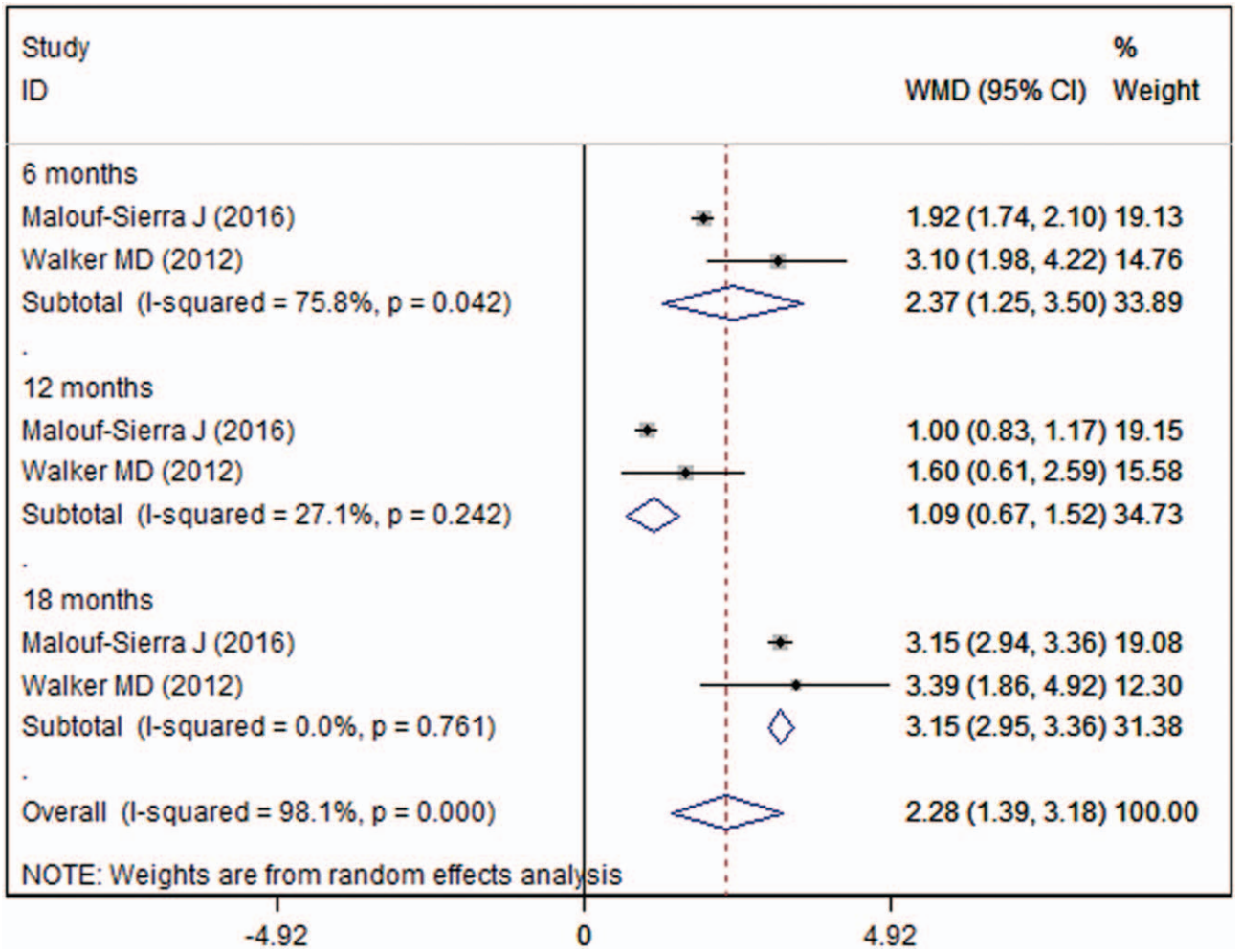

Figure 4. Forest plot showing the comparison between teriparatide with risedronate on the percentage change in femoral neck BMD. BMD = bone mineral density.

3.8. Serum bone markers

Three studies[25,27,29] reported the data of serum bone markers. The serum P1NP, CTx, and ALP levels increased significantly in teriparatide group and decreased significantly in risedronate group. However, the iPTH significantly reduced in both teriparatide and risedronate groups. Pooled estimate showed that there was significant differences between the 2 groups in terms of the serum change in P1NP (WMD = 122.34, 95%CI: 68.89, 175.99; $P < .001$), CTx (WMD = 0.62, 95%CI: 0.29, 0.96; $P < .001$), and iPTH (WMD = -13.18, 95%CI: -15.04, -11.33; $P < .001$). But the serum ALP level was not significant difference between the 2 groups (WMD = 22.58, 95%CI: -1.53, 46.69; $P = .066$).

3.9. Adverse events

All the included studies[24–30] reported the data of adverse events. Pooled estimate showed that, there was no significant difference in incidence of adverse events between teriparatide and risedronate groups (RR = 0.93, 95%CI: 0.69, 1.25; $P = .610$). The most frequently seen adverse events of teriparatide and risedronate were presented in Table 2.

4. Discussion

To the best of our knowledge, this meta-analysis is the first to compare the effect and safety of teriparatide versus risedronate in the treatment of osteoporosis. The present meta-analysis from seven RCTs, provided relatively high level of evidence, showing that the percentage changes in lumbar spine, femoral neck, and total hip BMD were significantly greater in teriparatide group than in risedronate group. The incidences of clinical fracture, vertebral fracture, and non-vertebral fracture were significantly lower in teriparatide group than in the risedronate group. Moreover, teriparatide also had benefit effects than risedronate in serum bone markers, including P1NP, CTx, and iPTH. The incidence of adverse events was comparable between the 2 drugs.

This meta-analysis suggested that teriparatide was associated with significantly greater increases in lumbar spine, femoral neck, and total hip BMD as compared with risedronate. Moreover, subgroup analysis also indicated the effects of teriparatide in lumbar spine and femoral neck BMD when it was administrated for 6-,12-, and 18-month. Our findings were in consistent with the previously published studies.[24,27,29] Hadji P, et al[24] performed an 18-month randomized, double-blind,

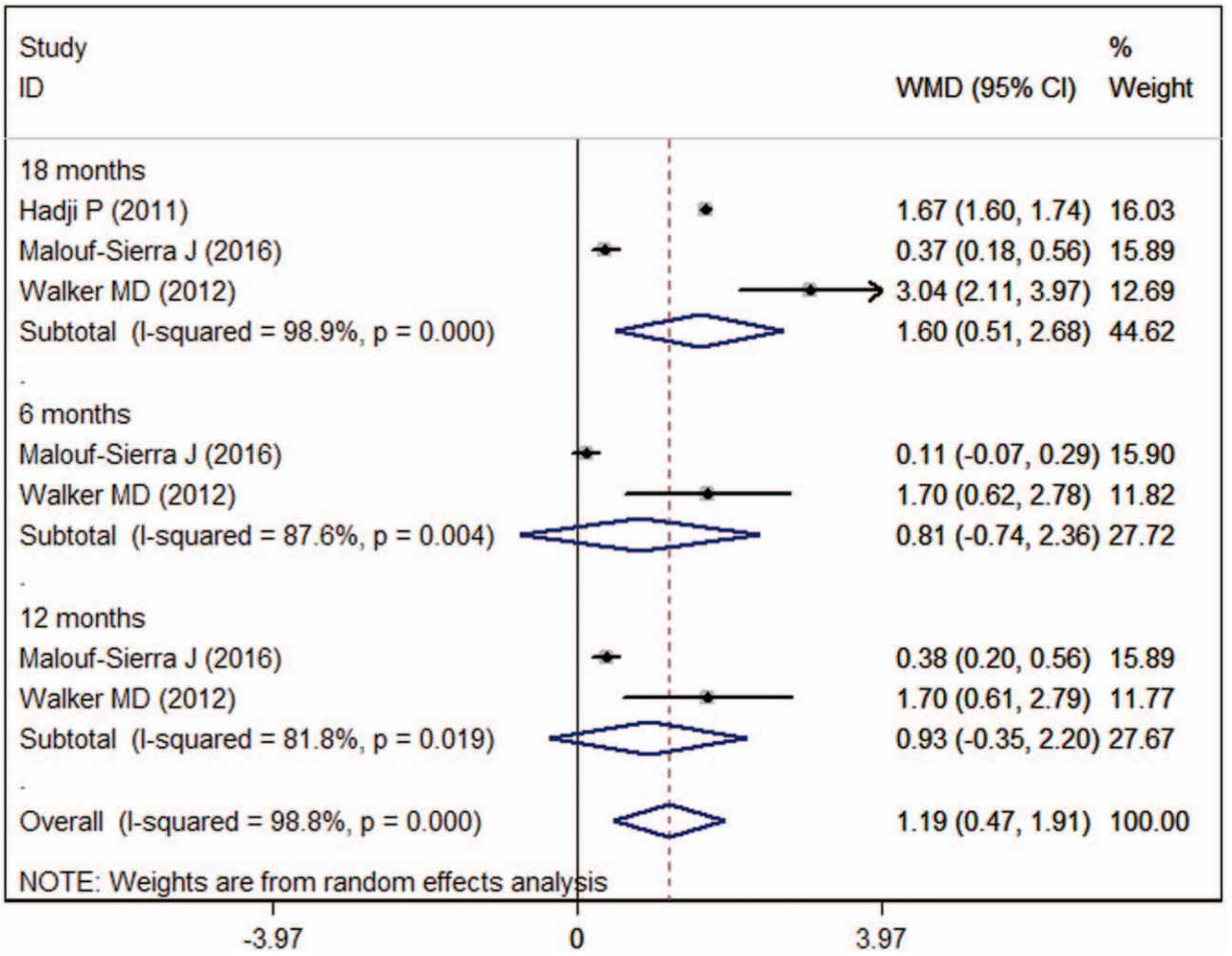

Figure 5. Forest plot showing the comparison between teriparatide with risedronate on the percentage change in total hip BMD. BMD = bone mineral density.

double-dummy trial in postmenopausal women who had osteoporosis vertebral fractures. At the treatment of 18 months, patients in teriparatide group achieved greatly increased BMD in lumbar spine (7.8 ± 0.5% vs 2.63 ± 0.5%, $P < .001$) and femoral neck (2.11 ± 9.4% vs 0.77 ± 0.4%, $P = .02$) than those in teriparatide group.[24] Moreover, the percentage change in total hip BMD was greater in teriparatide group (2.05 ± 0.4%) than in risedronate group (0.83 ± 0.5%).[24] Similar results were reported by Gluer CC et al,[27] who carried out a randomized, open-label trial in glucocorticoid-induced osteoporosis men. In that study, the authors demonstrated a greater increase in lumbar spine BMD in teriparatide-treated patients (16.3 ± 4.2%) than in risedronate-treated patients (3.8 ± 4.1%) after 18 months of treatment.[27]

Contrary to the positive results, Anastasilakis AD et al[25] found that the change in lumbar spine BMD was not significant difference between teriparatide and risedronate groups in women who had postmenopausal osteoporosis. In that study, 44 patients were enrolled for the treatment of teriparatide (n = 22) or risedronate (n = 22). At the 12 months, both groups showed increased percentage in lumbar spine BMD (teriparatide: 0.809 ± 0.020 g/cm^2, risedronate: 0.782 ± 0.020 g/cm^2), but the difference between them was not significant ($P = .075$).[25] The authors thought that their negative results could be explained by the following possible reasons:

(1) The measurement of BMD by dual-energy X-ray absorptiometry is more obvious at 18 months rather than at 12 months;[5,31] thus, the difference might not be detected at the 12 months;
(2) The sample size in the 2 groups was not large enough to detect the statistical difference.

There were several published studies reporting that teriparatide and risedronate significantly reduced the risk of fracture,[24,26,28–30] and their results were in consistent with ours. Kendler, D.L et al[26] found that the incidence of clinical fracture was significantly lower in teriparatide group (4.8%) than in risedronate group (9.8%) (hazard ratio = 0.48, 95%CI: 0.32, 0.74; $P = .009$). Moreover, there were fewer patients in in teriparatide group (4.0%) than in risedronate group (6.1%) that developed non-vertebral fractures.[26]

There have been 2 studies suggested that, teriparatide is associated with a transient decrease in BMD at cortical-rich skeletal sites, when it is used in patients who have long-term treatment of anti-resorptive drugs.[32,33] Thus, some researchers hypothesized that this process might reduce the bone strength,

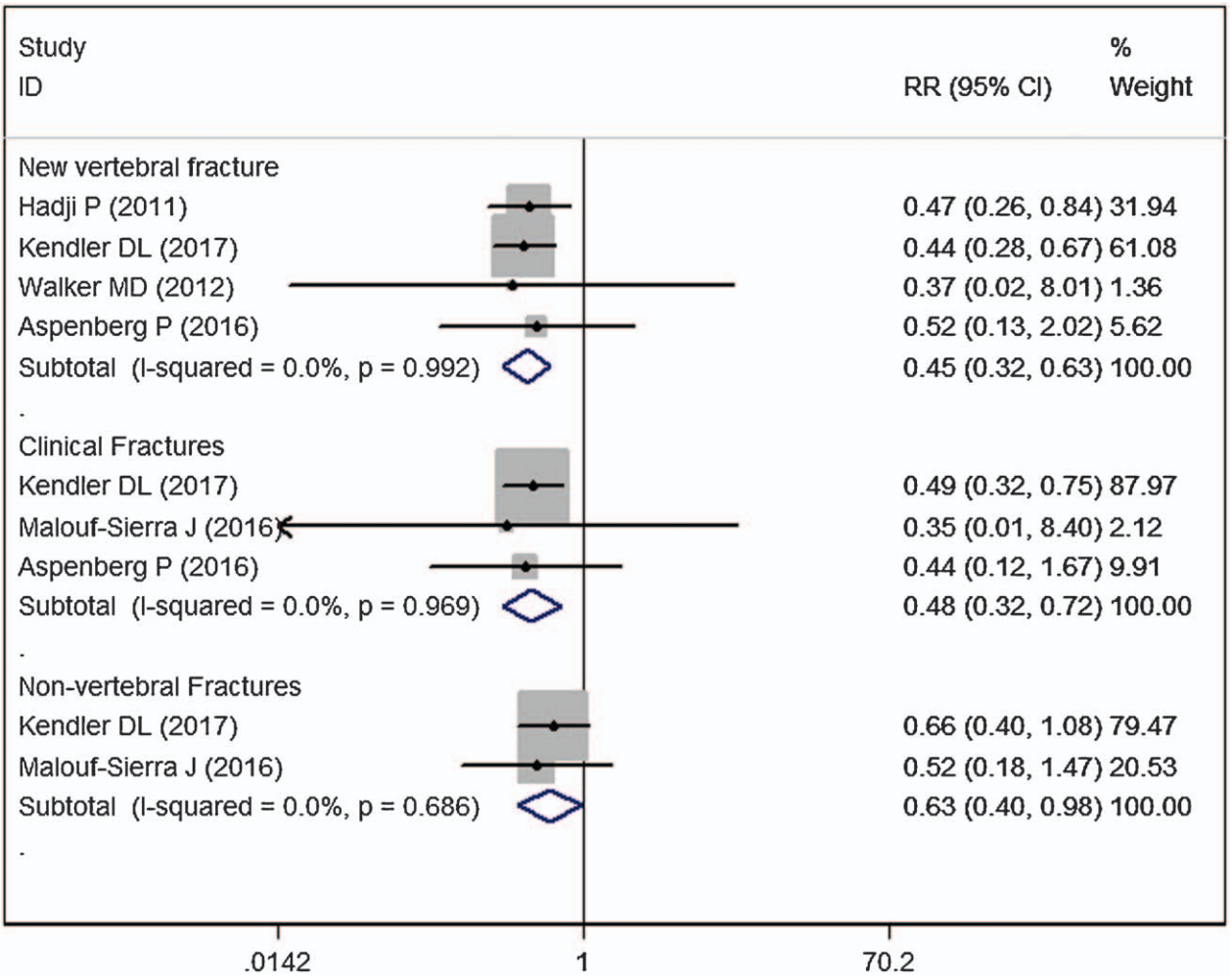

Figure 6. Forest plot showing the comparison between teriparatide with risedronate on the incidences of clinical fracture, new vertebral fracture, and non-vertebral fracture. BMD = bone mineral density.

Table 2

Summary of the risk ration (RR) of adverse events in osteoporosis patients treated with teriparatide or risedronate.

Adverse events	Risk ratio (RR)	95% CI	*P* value
Dizziness	2.60	1.37–4.95	.004
Nausea	1.26	0.77–2.08	.357
Epigastric pain	0.20	0.01–3.94	.290
Flushes	3.00	0.13–69.87	.494
Hypercalcaemia	2.38	1.84–3.07	<.001
Back pain	0.92	0.68–1.23	.555
Arthralgia	0.86	0.59–1.27	.457
Nasopharyngitis	0.94	0.58–1.52	.798
Osteoarthritis	1.38	0.79–2.40	.251
Bronchitis	0.93	0.56–1.56	.785
Hypertension	0.79	0.46–1.36	.397
Dental caries	13.00	0.73–230.31	.080
Hyperuricaemia	1.69	1.33–2.13	<.001
Hypomagnesaemia	6.13	2.14–17.55	.001
Fatigue	0.37	0.02–8.01	.524
Gastroesophageal reflux	0.16	0.01–2.68	.201
Leg cramps	1.11	0.08–15.28	.937

CI = confidence interval, RR = risk ratio.

predisposing patients to fractures.[34] However, this hypothesis was not supported by some studies which used teriparatide or risedronate in non-vertebral fractures.[26,35,36] Kendler DL[26] and McClung MR[36] reported that, risedronate reduced non-vertebral fractures by 59% as compared with placebo, and hip fracture by 60% in postmenopausal women after 3 years of treatment.[26,36] In the present study, our findings suggested that teriparatide was associated with a 37% reduction (RR = 0.63, 95%CI: 0.40, 0.98; $P = .042$) in non-vertebral fractures and 55% reduction (RR = 0.45, 95%CI: 0.32, 0.63; $P < .001$) in new vertebral fractures, which supported the effect of teriparatide in decreasing the risk of fractures.

The safety profiles of teriparatide versus risedronate in this study were in consistent with the previous studies, with similar incidence of adverse events between the 2 treatments. The most common reported adverse events associated with teriparatide were dizziness, hypercalcemia, hyperuricemia, and hypomagnesaemia. Malouf-Sierra, J et al[28] showed that patients treated with teriparatide had a significant increase in hyperuricemia at 6 weeks (15.9%) and hypercalcemia at 26 weeks (12.9%) as compared with those with risedronate.[28] The most common adverse event leading to discontinuation was nausea. Kendler,

DL et al[26] reported that 22 patients died during the study, however, all of them were considered unrelated to the study drug.

Several potential limitations in this meta-analysis should be considered when interpreting our results. First, there were substantial heterogeneity among the included studies for several outcomes, such as the percentage change in BMD of lumbar spine, femoral neck, and total hip. Although we conducted sensitivity analysis and subgroup analysis to explore the potential sources of heterogeneity, no useful information was identified. For some other factors, such as patient characteristics (age, gender, history of fragility fracture, and prior anti-resorptive treatment), and study design, these factors may increase the heterogeneity and affect the results. Second, among the included studies, 2 studies had a relatively small sample size ($n < 50$). It was reported that studies with small sample size were more likely to overestimate the treatment effect as compared with larger trials. Thus, interpreting our results should be caution, especially in these outcomes that involved small sample studies.

In summary, the current meta-analysis suggests that teriparatide may be superior to risedronate in osteoporosis since it increased the BMD of lumbar spine, femoral neck, and total hip, as well as reduced the risk of new clinical fractures. Moreover, the incidence of adverse events was comparable between the 2 drugs. Considering the potential limitations in this meta-analysis, more large-scale, well-performed RCTs are needed to verify our findings.

Author contributions

Conceptualization: Chengzhi Yang, Renjie Wei, Xinli Zhan.
Data curation: Chengzhi Yang, Jingli Tang.
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References

[1] Kanis JA, Johansson H, Oden A, et al. A meta-analysis of prior corticosteroid use and fracture risk. J Bone Miner Res 2004;19:893–9.
[2] Canalis E, Mazziotti G, Giustina A, et al. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. Osteoporos Int 2007;18:1319–28.
[3] Ito M, Ikeda K, Nishiguchi M, et al. Multi-detector row CT imaging of vertebral microstructure for evaluation of fracture risk. J Bone Miner Res 2005;20:1828–36.
[4] Black DM, Rosen CJ. Clinical practice. Postmenopausal osteoporosis. N Engl J Med 2016;374:254–62.
[5] Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344:1434–41.
[6] Nenonen A, Cheng S, Ivaska KK, et al. Serum TRACP 5b is a useful marker for monitoring alendronate treatment: comparison with other markers of bone turnover. J Bone Miner Res 2005;20:1804–12.
[7] Hodsman AB, Bauer DC, Dempster DW, et al. Parathyroid hormone and teriparatide for the treatment of osteoporosis: a review of the evidence and suggested guidelines for its use. Endocr Rev 2005;26:688–703.
[8] Lyritis G, Marin F, Barker C, et al. Back pain during different sequential treatment regimens of teriparatide: results from EUROFORS. Curr Med Res Opin 2010;26:1799–807.
[9] Fahrleitner-Pammer A, Langdahl BL, Marin F, et al. Fracture rate and back pain during and after discontinuation of teriparatide: 36-month data from the European Forsteo Observational Study (EFOS). Osteoporos Int 2011;22:2709–19.
[10] Fleisch H. Bisphosphonates: mechanisms of action. Endocr Rev 1998;19:80–100.
[11] Polyzos SA, Anastasilakis AD, Bratengeier C, et al. Serum sclerostin levels positively correlate with lumbar spinal bone mineral density in postmenopausal women–the six-month effect of risedronate and teriparatide. Osteoporos Int 2012;23:1171–6.
[12] Anastasilakis AD, Goulis DG, Polyzos SA, et al. Serum osteoprotegerin and RANKL are not specifically altered in women with postmenopausal osteoporosis treated with teriparatide or risedronate: a randomized, controlled trial. Horm Metab Res 2008;40:281–5.
[13] Miller PD, Delmas PD, Lindsay R, et al. Early responsiveness of women with osteoporosis to teriparatide after therapy with alendronate or risedronate. J Clin Endocrinol Metab 2008;93:3785–93.
[14] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Bmj 2009;339:b2535.
[15] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[16] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[17] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719–48.
[18] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
[19] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.
[20] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[21] Misof BM, Paschalis EP, Blouin S, et al. Effects of 1 year of daily teriparatide treatment on iliacal bone mineralization density distribution (BMDD) in postmenopausal osteoporotic women previously treated with alendronate or risedronate. J Bone Miner Res 2010;25:2297–303.
[22] Chevalier Y, Quek E, Borah B, et al. Biomechanical effects of teriparatide in women with osteoporosis treated previously with alendronate and risedronate: results from quantitative computed tomography-based finite element analysis of the vertebral body. Bone 2010;46:41–8.
[23] Geusens P, Marin F, Kendler DL, et al. Effects of Teriparatide Compared with Risedronate on the Risk of Fractures in Subgroups of Postmenopausal Women with Severe Osteoporosis: the VERO Trial. J Bone Miner Res 2018;33:783–94.
[24] Hadji P, Zanchetta JR, Russo L, et al. The effect of teriparatide compared with risedronate on reduction of back pain in postmenopausal women with osteoporotic vertebral fractures. Osteoporos Int 2012;23:2141–50.
[25] Anastasilakis AD, Goulis DG, Polyzos SA, et al. Head-to-head comparison of risedronate vs. teriparatide on bone turnover markers in women with postmenopausal osteoporosis: a randomised trial. Int J Clin Pract 2008;62:919–24.
[26] Kendler DL, Marin F, Zerbini CAF, et al. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet 2018;391:230–40.
[27] Gluer CC, Marin F, Ringe JD, et al. Comparative effects of teriparatide and risedronate in glucocorticoid-induced osteoporosis in men: 18-month results of the EuroGIOPs trial. J Bone Miner Res 2013;28:1355–68.
[28] Malouf-Sierra J, Tarantino U, Garcia-Hernandez PA, et al. Effect of teriparatide or risedronate in elderly patients with a recent pertrochanteric hip fracture: final results of a 78-week randomized clinical trial. J Bone Miner Res 2017;32:1040–51.
[29] Walker MD, Cusano NE, Sliney JJr, et al. Combination therapy with risedronate and teriparatide in male osteoporosis. Endocrine 2013;44:237–46.
[30] Aspenberg P, Malouf J, Tarantino U, et al. Effects of teriparatide compared with risedronate on recovery after pertrochanteric hip fracture: results of a randomized, active-controlled, double-blind clinical trial at 26 weeks. J Bone Joint Surg Am 2016;98:1868–78.

[31] McClung MR, San Martin J, Miller PD, et al. Opposite bone remodeling effects of teriparatide and alendronate in increasing bone mass. Arch Intern Med 2005;165:1762–8.
[32] Tsai JN, Uihlein AV, Lee H, et al. Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. Lancet 2013;382:50–6.
[33] Obermayer-Pietsch BM, Marin F, McCloskey EV, et al. Effects of two years of daily teriparatide treatment on BMD in postmenopausal women with severe osteoporosis with and without prior antiresorptive treatment. J Bone Miner Res 2008;23:1591–600.
[34] Burr DB. Does early PTH treatment compromise bone strength? The balance between remodeling, porosity, bone mineral, and bone size. Curr Osteoporos Rep 2005;3:19–24.
[35] Harrington JT, Ste-Marie LG, Brandi ML, et al. Risedronate rapidly reduces the risk for nonvertebral fractures in women with postmenopausal osteoporosis. Calcif Tissue Int 2004;74:129–35.
[36] McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip intervention program study group. N Engl J Med 2001;344:333–40.