Comparison of Bisphosphonates Versus Teriparatide in Therapy of the Glucocorticoid-Induced Osteoporosis (GIOP): A Meta-Analysis of Randomized Controlled Trials

Authors

Bingzi Dong[1], Yue Zhou[1,2], Jun Wang[1], Chengqian Li[1], Zhengju Fu[1], Yajing Huang[1], Yangang Wang[1], Lili Xu[1]

Affiliations

1 Endocrinology and Metabolism, The Affiliated Hospital of Qingdao University, Qingdao, China

2 Endocrinology, Fudan University, Shanghai, China

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Georg Thieme Verlag, Rüdigerstraße 14, 70469 Stuttgart, Germany

Correspondence

Dr. Lili Xu

The Affiliated Hospital of Qingdao University,

Endocrinology and Metabolism,

16th Road Jiangsu

Shandong

266003 Qingdao

China

Tel: +86-0532-82911383

qdfyxll@qdu.edu.cn

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ABSTRACT

Osteoporosis (OP) is characterized as decreased bone mineral density (BMD) and increased risk of bone fracture. Secondary OP resulting from excess endogenous or exogenous glucocorticoid is defined as glucocorticoid-induced osteoporosis (GIOP). Current therapeutic strategies for GIOP are similar to menopausal osteoporosis, including calcium and vitamin D supplementation, bisphosphonates, and parathyroid hormone (PTH) analogues (teriparatide). Previously, several published meta-analyses compared anti-osteoporotic agents for the menopausal or aging-dependent OP. However, the physiopathologic bone metabolism of GIOP is different. In this study, we investigated the efficacy of BMD enhancement, bone fracture rate and safety of bisphosphonates versus teriparatide in the therapy of GIOP. We searched databases including PubMed, Embase, and the Cochrane Library until Jan 2023, and selected ten random clinical trials (RCT)s that compared the efficacy and/or safety of bisphosphonate versus teriparatide for GIOP patients. Teriparatide therapy increased lumber spinal BMD by 3.96 % (95 % CI 3.01–4.9 %, p < 0.00001), 1.23 % (95 % CI 0.36–2.1 %, p = 0.006) at total hip, and 1.45 % (95 % CI 0.31–2.58 %, p = 0.01) at femoral neck, respectively, compared to bisphosphonates at 18-month therapy for GIOP. Teriparatide also reduced bone fracture especially in vertebral bone (p = 0.0001, RR 6.27, 95 % CI 2.44–16.07), and increased bone formation and resorption marker levels. There was no difference in the incidence of adverse effects in bisphosphonate and teriparatide groups. Teriparatide showed better performance over bisphosphonate in BMD enhancement, bone fracture reduction, and bone remodeling improvement, without increasing the incidence of adverse effects.

Introduction

Osteoporosis (OP) is characterized as decreased bone mineral density (BMD) and deteriorated micro-architecture, resulting in increased risk of bone fracture [1]. Osteoporosis results in 1.5 million fractures per year in the United States, leading to poor quality of life and increased mortality risk [2]. Most of them are menopausal or age-dependent osteoporosis. However, secondary osteoporosis due to hypercortisolism, hyperparathyroidism, rheumatic disorders, malnutrition, diabetes mellitus, and multiple myeloma also account for a certain proportion. The persistently excess glucocorticoid, including both endogenous hypercortisolism such as Cushing's syndrome and the exogenous steroid medicine intake, leads

to glucocorticoid-induced osteoporosis (GIOP). The clinical characteristic of GIOP is rapidly decreased BMD, and increased bone fracture risk [3].

The anti-osteoporosis intervention for GIOP is based on the fracture risk. Computer-based fracture risk-assessment tool (FRAX) provides the probability of bone fracture for individuals using glucocorticoid. The anti-osteoporosis agents are classified into anti-resorptive agents, and anabolic agents and those affect both bone formation and resorption. Current therapeutic strategies for GIOP are similar to menopausal osteoporosis, including bisphosphonates, parathyroid hormone (PTH) analogues {recombinant human parathyroid hormone [rhPTH(1–34), teriparatide]}, a monoclonal antibody of RANKL (Denosumab), and selective estrogen receptor modulators (SERMs). Bisphosphonates, the classic anti-resorptive agents, are considered as the most common therapeutic option for GIOP [4]. A Cochrane review involving 12 RCTs and 1343 participants suggested that bisphosphonates had a 43 % lower risk of new vertebral fractures than calcium and vitamin D supplementation [5]. Teriparatide and abaloparatide (the analogous of PTH receptor) are anabolic agents to promote bone formation. PTH stimulates Wnt/beta-catenin signaling pathway, increases osteoblast differentiation and maturation, enhances BMD, and reduces bone fracture risk [6]. According to the pathophysiology of GIOP and mechanism of bisphosphonate and teriparatide action, they could be considered as effective therapeutic strategy for GIOP patients with high fracture risk.

Previously, several published meta-analyses compared anti-osteoporotic agents, nevertheless, some disadvantages existed in those studies [7–10]. Most of them studied on primary OP, mainly due to menopausal osteoporosis and aging. However, the physiopathologic mechanism of GIOP differs from primary OP, the former occurs due to the persistent excessive glucocorticoid. In this study, we focused on the comparison between bisphosphonate and teriparatide on the efficiency and safety and discuss the possible affecting factors of BMD and fracture rate, to help make decisions on pharmacotherapy for GIOP patients.

Materials and Methods

Search strategy

We performed this systematic review and meta-analysis based on the prespecified protocol and report our methods and results in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11].

We searched databases including PubMed, Embase, and the Cochrane Library until January 1st, 2023, to identify random clinical trials (RCT)s that reported the efficacy and/or safety of bisphosphonate vs teriparatide therapy for GIOP patients. Two reviewers (Dong B and Zhou Y) independently screened titles and abstracts of all records and full texts of potentially eligible studies. We searched using medical subject heading (MeSH) associated with terms relevant to “glucocorticoid-induced osteoporosis”, “steroid-induced osteoporosis”, “bisphosphonate”, “teriparatide” together with “randomized controlled trial”. Any disagreements were resolved by consensus with a third reviewer (Wang J).

Study inclusion and exclusion criteria

Studies included in this meta-analysis were required to meet the following inclusion criteria: (1) study design: RCT of GIOP with a comparison between bisphoshonate and teriparatide with a duration of at least 18 months; (2) study subjects: adult patients diagnosed with osteoporosis (T-score < –2.5) or osteopenia (T-score between –1.0 and –2.5) with or without prior fracture. Subjects also had received GC therapy at a dose of > 5 mg/day prednisone or its equivalent for at least three months; (3) study intervention: subjects received teriparatide 20 µg/d subcutaneously, or bisphosphonate treatment including oral aldendronate 10 mg/d or risedronate 35 mg/week for at least 18 months; and (4) the change of BMD could be measured by dual-energy X-ray absorptiometry (DXA) at the lumbar spine, total hip, or femoral neck. Trials were excluded if (1) malignant tumor exists with bone metastasis, metabolic osteopathy, or primary osteoporosis patients; (2) the same RCT was re-analyzed; (3) BMD were not evaluated by DXA; and (4) studies published as abstracts, reviews, editorials, and letters without available full texts.

Data collection process and quality assessment

Two independent reviewers (Dong B and Zhou Y) extracted data from the eligible studies, using predefined forms containing information on trial characteristics (first author, publication year, sample size, dose and varieties of agents, and treatment duration), participants’ baseline characteristics (age, gender, menopause state, previous fracture, base anti-osteoporotic treatment), and outcomes of interest mentioned above. Any resulting disagreements were judged by discussion with a third author (Wang J).

The quality of the involved study was assessed using the Cochrane Collaboration’s risk-of-bias assessment tool, which included random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants, and personal (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other potential sources of bias. The judgment for each entry involves answering a question, with low risk of bias, high risk of bias, and unclear indicating lack of information or uncertainty about the possibility of bias. Disagreements between authors were resolved with consensus.

Outcomes of measurements

The primary outcomes were the mean changes of BMD percentage from baseline at the lumbar spine, total hip, and femoral neck at 18 months. The secondary outcomes included: (1) overall incidence of vertebral and non-vertebral fractures; (2) the percentage changes of bone formation marker propeptide of type I procollagen (PINP) and bone resorption marker C-terminal telopeptide (beta-CTX) at 6 and 18 months; and (3) adverse events (Aes), severe adverse events (SAEs), and withdraw due to intolerance to AEs were also compared.

Data synthesis and statistical analysis

For each outcome measure of interest, the mean difference (MD) and its 95 % CI were applied for continuous variables (percentage changes of BMD at lumbar spine, total hip and femoral neck), while risk ratio (RR) and its 95 % CI were used for dichotomous outcomes

(risk for fracture and adverse events). Considering the differences in baseline participants' characteristics and drug administration, a random effects model was selected for analyses. A p-value < 0.05 for any test or model was considered statistically significant. The degree of between-study variability attributable to heterogeneity beyond chance was calculated using the I^2 statistic and Q statistic. Outcomes with I^2 levels from 0 % to 40 % were considered minimally heterogeneous, while I^2 > 50 % was considered an indication of statistically significant heterogeneity among included studies.

We conducted perspective meta-regression by study characteristics to address the clinical heterogeneity of included studies. We analyzed factors including age, sex, menopausal status, the ethnic difference (Caucasian percentage), previous bisphosphonate usage, steroid dosage, steroid duration, underlying diseases, previous vertebral or non-vertebral bone fracture, previous spinal or hip or femoral BMD (T-score).

Risk of bias assessment were performed by the Review Manager statistical software package (Version 5.3). The meta-analyses and regression-analyses were performed by the STATA statistical software package (Version 12.0).

Results

Search results

A total of 130 studies were screened from the Pubmed, EMBASE, and Cochrane databases. After reviewing the titles and abstracts, 98 were reviews or not relevant studies. Five duplicates were removed, and 6 articles were not RCTs. Three articles were excluded because the type or the duration of medication were not meeting the requirements. Five other articles were excluded because of the inclusion criteria, not comparing the efficiency of bisphosphonate and teriparatide, one article was excluded for not elevating the BMD or bone fracture, one for re-analysis of the same trial, and one article was published in abstract form. Ten RCTs [12–21] were finally involved in this meta-analysis (▶ **Fig. 1**).

Characteristics of the included trials

A total of 1960 subjects with GIOP received > 5 mg equivalent PSL for at least 3 months, including postmenopausal, premenopausal women, and men in this meta-analysis. Those studies were intervened with bisphosphonate (eight studies with alendronate and two studies with risedronate) or teriparatide for at least 18 months, evaluated lumbar spinal, total hip and femoral neck BMD, vertebral and non-vertebral bone fracture incidence, bone formation marker and bone resorption marker, and adverse effects.

The mean age range was from 55.4–58.4 years old, 80 % of the subjects were women, 72.3 % were menopause women with osteoporosis, and two studies involved only men. The underlying disorders requiring glucocorticoid treatment included rheumatic disorders (rheumatoid arthritis, systemic lupus erythematosus, polymyalgia rheumatic, vasculitis), respiratory disorders, and inflammatory bowel diseases. The mean glucocorticoid dose ranged from 7.5–10 mg/d equivalent PSL, and the mean usage duration ranged from 1.3–6.4 years. A sum of 41.92 % of patients had previous bone fractures, and 12.1 % had prior anti-osteoporosis therapy with bisphosphonates. All patients received daily 1000 mg calcium and 800–1000 IU vitamin D supplement.

Risk of bias assessment

The risk of bias was assessed with the Cochrane risk-of-bias tool. There was a low risk of reporting bias in all the trials except for one study that had an unclear risk of selective reporting (▶ **Fig. 2**). Two studies had a relatively small sample size and only men participated in the studies (Gluer 2013 [20] and Farahmand 2013 [19]). In addition, these two studies used an open-label RCT design.

Change in BMD

The primary outcome analysis evaluated the change of BMD from baseline intervened by bisphosphonates or teriparatide for 18 months, involving six trials with a total of 1694 patients. Compared to bisphosphonates, the teriparatide therapy increased lumber spinal BMD by 3.96 % (95 % CI 3.01–4.9 %, p < 0.00001). The increase of BMD used teriparatide was greater by 1.23 % (95 % CI 0.36–2.1 %, p = 0.006) at total hip, and 1.45 % (95 % CI 0.31–2.58 %, p = 0.01) at femoral neck, respectively (▶ **Fig. 3**). These results showed that teriparatide increased greater BMD than bisphosphonate at all three positions. The extent of BMD increase by bisphosphonate or teriparatide differs from different positions.

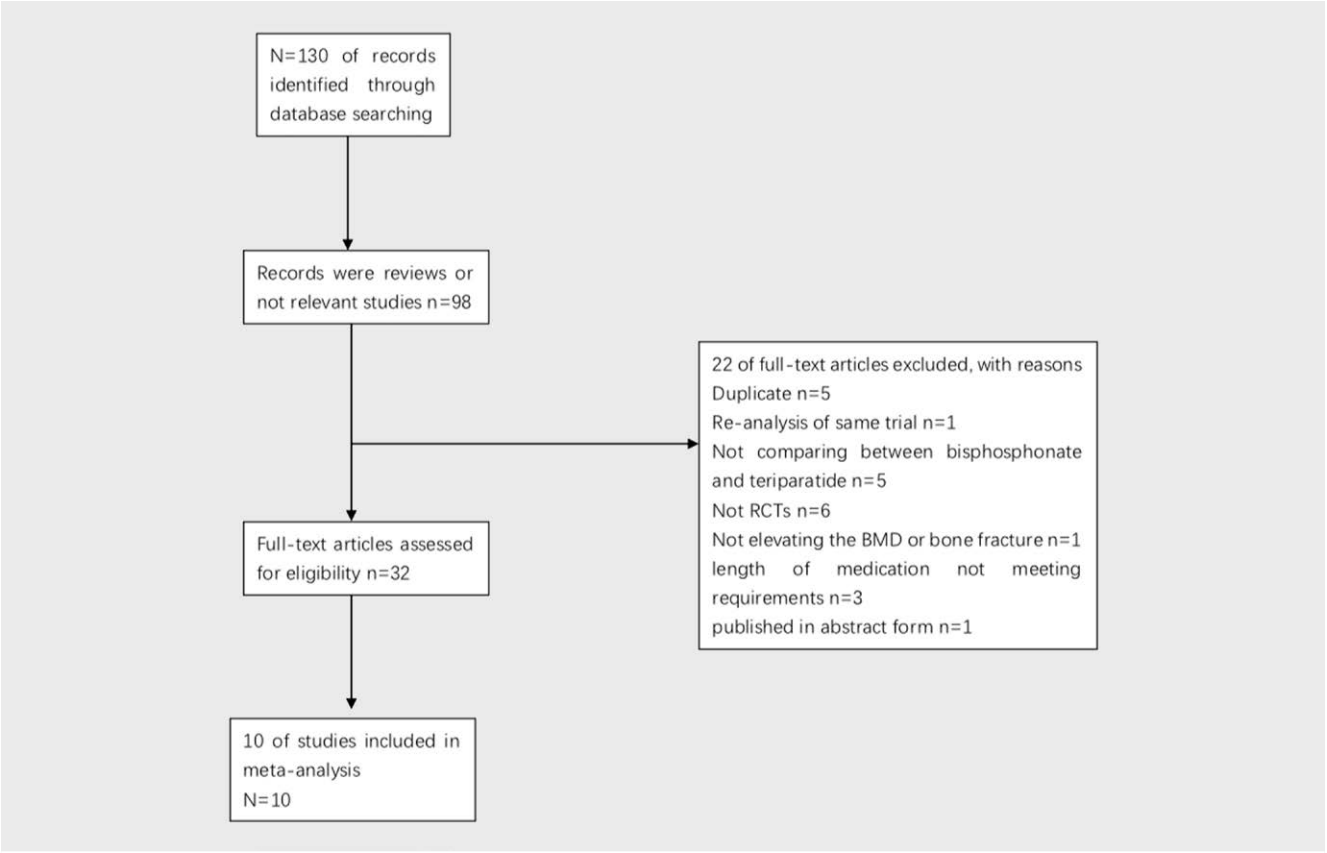
One trial (Saag 2009 [13]) prolonged continuation of the observational phase for another 18 months. At a total of 36 months, teriparatide group showed even greater mean increase of BMD from baseline than alendronate at the lumbar spine (ALN 5.3 % vs. TPTD 11.0 %, p < 0.001), at total hip (ALN 2.7 % vs. TPTD 5.2 %, p < 0.001), and at femoral neck (ALN 3.4 % vs. TPTD 6.3 %, p < 0.001), respectively [13]. The increasing extent at 36 months was significantly greater compared with that measured at 18-month time point. Thus, long-term treatment with teriparatide on GIOP may bring a more significant effect of increasing BMD showing a time-dependent tendency, and the extent of BMD enhancement was enlarged in the bisphosphonate therapy.

Bone fracture risk

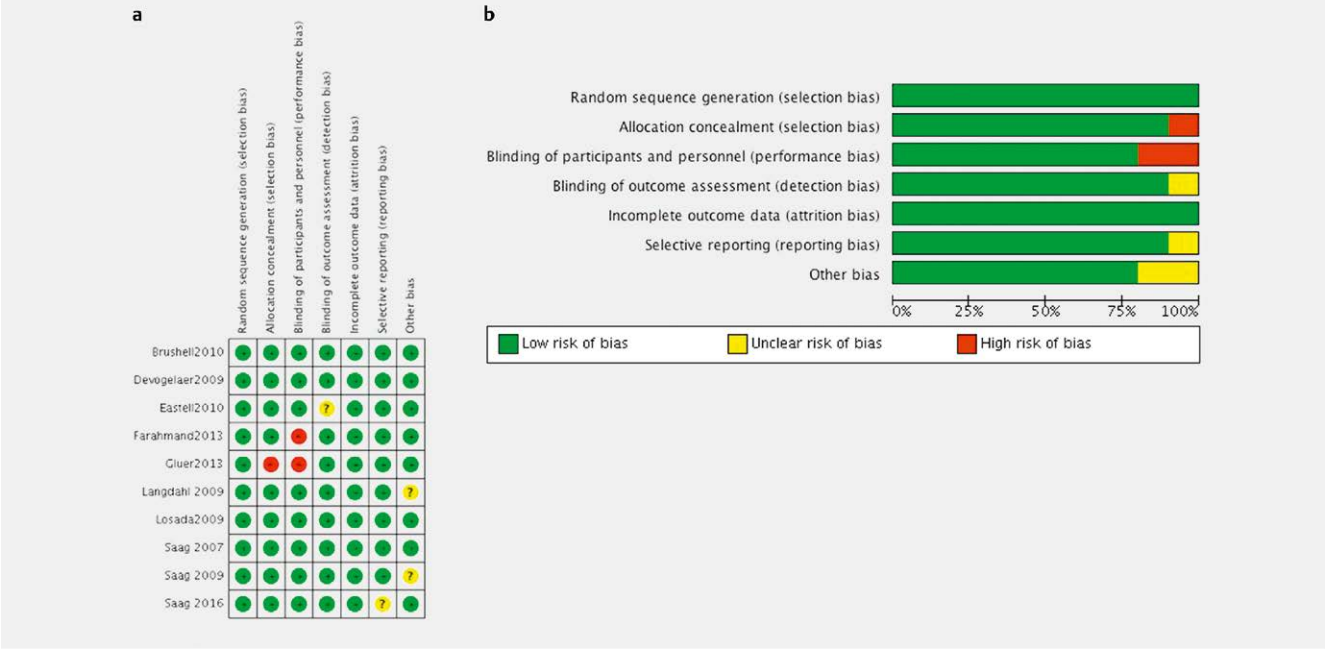
Three trials involved 1099 patients who reported the efficacy of bisphosphonate or teriparatide on vertebral bone fracture and 1191 patients on non-vertebral fracture during the observation phase. Teriparatide group showed significantly reduced incidence of vertebral bone fracture than bisphosphonates (p = 0.0001, RR 6.27, 95 % CI 2.44–16.07). However, teriparatide therapy showed no significant difference in reducing the risk of non-vertebral bone fracture (p = 0.93, RR 0.98, 95 % CI 0.62–1.55) (▶ **Fig. 4**). The effect on reducing bone fracture incidence differed from different positions. Teriparatide exhibited better performance than bisphosphonate in decreasing the risk of vertebral bone fracture, but not non-vertebral bones.

Bone biomarkers bone formation markers and bone resorption markers

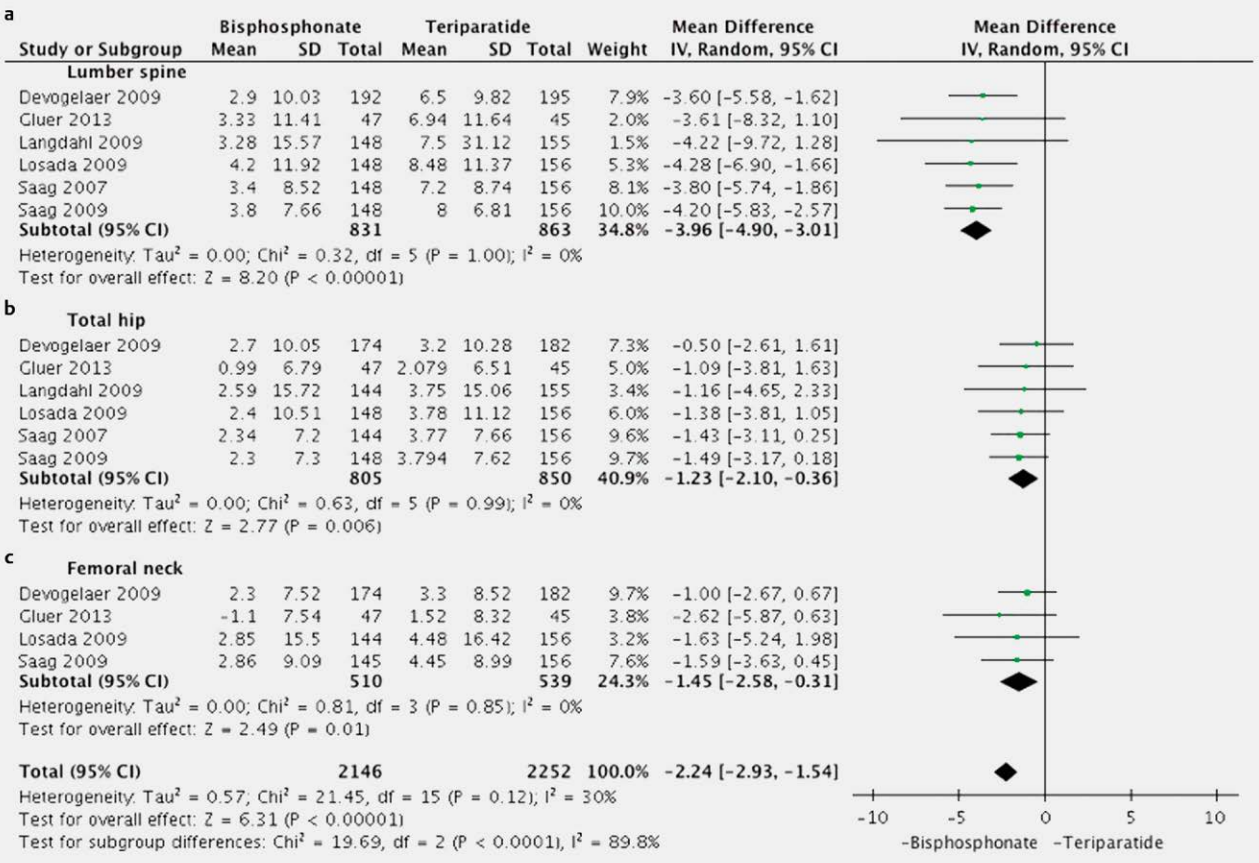
Five studies elevated bone turnover markers including bone formation marker PINP and bone resorption marker beta-CTX at 6-month and 18-month. Teriparatide therapy showed significantly increase in bone formation biomarker PINP changes from baseline (**Supplemental Fig. 1S**), as well as the bone resorption marker CTX (**Sup-**



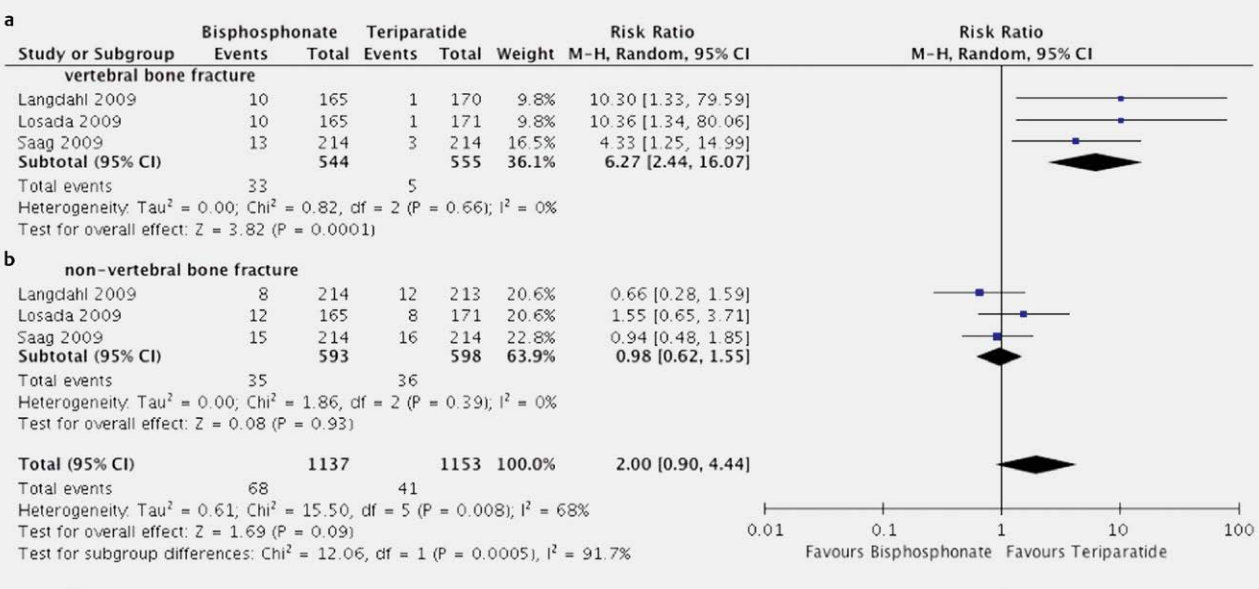
▶ **Fig. 1** Flow diagram of study selection.



▶ **Fig. 2** Quality assessment of the studies.



▶ **Fig. 3** Subgroup analysis of the efficiency of BMD change (%) by bisphosphonate and teriparatide for GIOP at lumbar spine (**a**), total hip (**b**), and femoral neck (**c**).



▶ **Fig. 4** Forest plot of the bone fracture risk by bisphosphonate and teriparatide treatment at vertebral (**a**) and non-vertebral (**b**) fracture at 18 months.

plemental Fig. 2S). In contrast, according to the mechanism of bisphosphonate, it showed reduced bone formation and bone resorption marker, suggesting its inhibitory effect on bone remodeling.

Adverse effects

Three studies reported adverse events and severe adverse events. Bisphosphonate did not show significant difference from teriparatide on the incidence of adverse effects (RR –0.01, 95 % CI –0.1–0.08, p = 0.77) or severe adverse effects (RR 1.27, 95 % CI 0.53–3.03, p = 0.59) reports (▶ **Fig. 5**). However, three trials in total of 411 patients provided data showed that the risk of withdraw due to AE was increased in the teriparatide group (RR 0.57, 95 % CI 0.33–1.00, p = 0.05) (▶ **Fig. 5**), with mild moderate heterogeneity (I^2 = 38 %). The common adverse events include peripheral edema, influenza, nausea, arthralgia, fall, or even death.

Publication bias

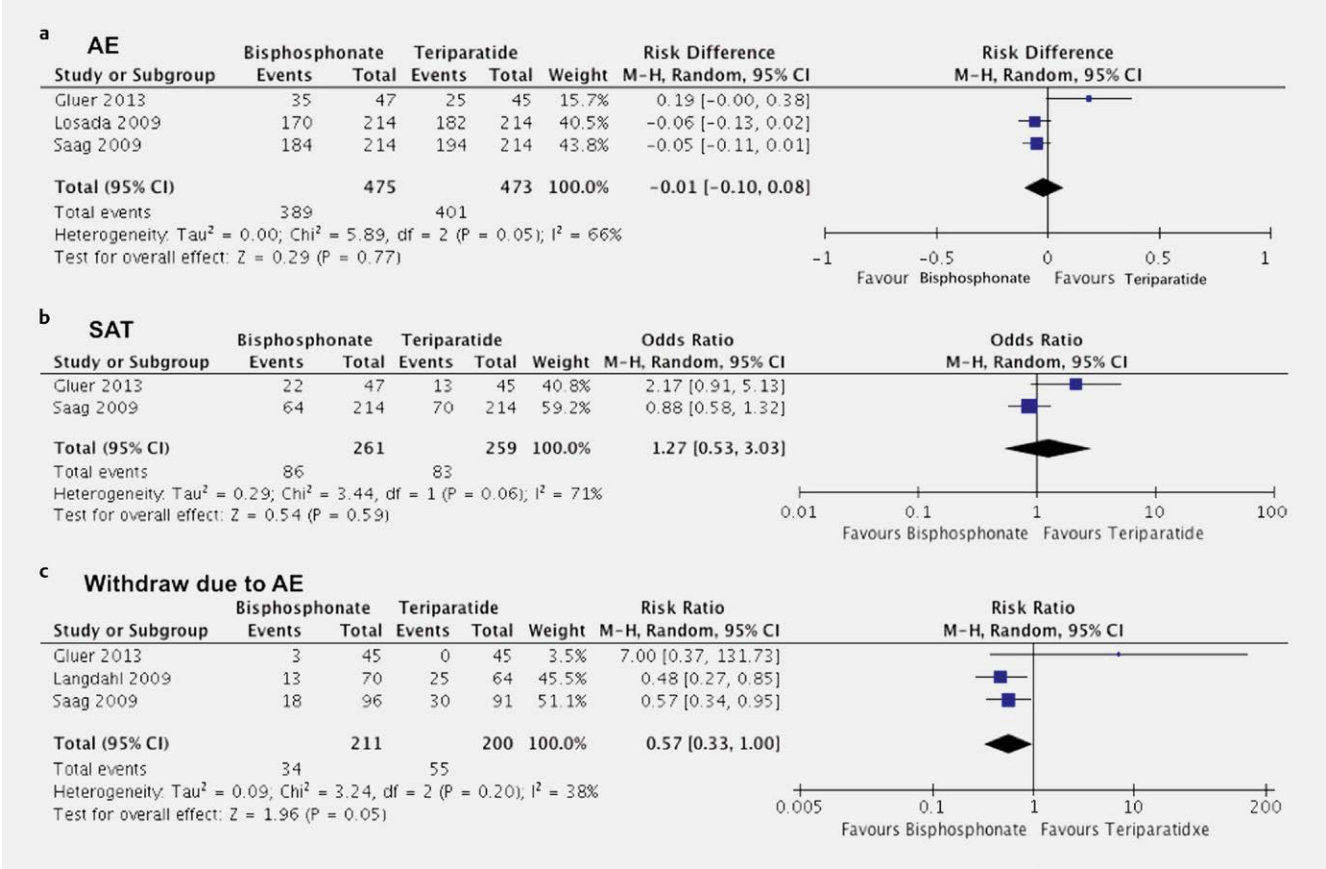
The publication bias of the primary outcomes of BMD at the spinal, total hip, and femoral neck was judged using funnel plots (**Supplemental Fig. 3S**) and Egger's weighted regression statistic. The publication bias of vertebral and non-vertebral bone fracture was judged using funnel plots (**Supplemental Fig. 4S**). The mean difference of BMD change from baseline at the lumbar spine, total hip, and femoral neck using Egger's test were p = 0.792, 0.137, 0.33, respectively. There was no significant publication bias.

Meta-regression analysis

Meta-regression analysis showed that factors including age, sex, menopausal status, steroid dosage, steroid duration, underlying diseases and previous rheumatic diseases, and previous bone fracture are not associated with the incidence of vertebral bone fracture (▶ **Table 1**), neither with the increasing extent of BMD at the lumbar spine, total hip and femoral neck (data not shown), using bisphosphonate or teriparatide.

Discussion

In this meta-analysis of RCTs, we compared the efficiency and safety of bisphosphonates and teriparitide on GIOP. We investigated the primary outcome of the BMD change from baseline at 18 months' therapeutic duration. We also compared the bone fracture risk of vertebral and non-vertebral bone, the change of bone formation marker PINP and bone resorption marker b-CTX, and the incidence of adverse events. Our study provided evidence that teriparatide is more effective than bisphosphonate in increasing BMD at the lumbar spine, total hip, and femoral neck at 18 months, especially in enhancing spinal BMD. In addition, bone fracture risk was reduced in the teriparatide treatment group on vertebral bone but not non-vertebral bone. Teriparatide significantly increased PINP and b-CTX level, however, based on the acting mechanism, bisphosphonate reduced bone turnover. The incidence of adverse events did not show a difference between two groups. Meta-



▶ **Fig. 5** Forest plot of adverse events at 18 months. Risk ratio of adverse events (**a**), severe adverse events (**b**), and withdraw due to adverse events (**c**).

▶ **Table 1** Meta-regression analysis of the demographic and clinical variables concerning the risk of vertebral bone fracture in GIOP.

Characteristics	Coefficient, 95 % CI	p-Value	Tau^2	Adj R-squared (%)
Age	1.395 (0.146–13.361)	0.671	1.436	−18.69
Female (%)	2.349 (0.062–88.767)	0.509	1.267	−4.74
Menopausal female	1.089 (0.658–1.803)	0.541	1.483	−11.24
Steroid dosage	2.356 (0.524–10.595)	0.167	0.599	50.42
Steroid duration	1.582 (0.472–5.299)	0.314	0.944	21.98
Underlying disease (previous rheumatic disease)	0.387 (0.00–25.483)	0.433	1.24	6.79
Previous fracture	1.342 (0.235–7.664)	0.543	1.487	−11.55
Previous vertebral fracture	1.348 (0.197–9.208)	0.655	1.431	−18.27

All are univariate meta-regression analyses, with the exception of teriparatide compared with bisphosphonate as a reference. Proportion between study variance was explained with Hartung–Knapp modification.

regression analysis showed that factors including age, gender, menopausal status, ethnic difference, previous bisphosphonate usage, steroid dosage and duration, underlying disease and previous rheumatic disease, and previous fracture, previous BMD are not associated with the increasing extent of BMD, neither the incidence of vertebral or non-vertebral bone fracture.

Persistent glucocorticoid usage disturbs bone metabolism. Glucocorticoids directly inhibit osteoblasts proliferation and differentiation by activating caspase 3, triggering the expression of Wnt signaling inhibitors sclerostin and dickkopf-1, and suppressing Wnt signaling to downregulate the expression of key osteogenic transcriptional factor Runx2, AP-1, and osteocalcin [22]. On the contrary, glucocorticoids increase receptor activator of nuclear factor-κB ligand (RANKL) and reduce osteoprotegerin (OPG) expression to imbalance the OPG/RANKL ratio, promote the maturation and function of osteoclasts, and transiently increase bone resorption [23]. Glucocorticoids also increase osteoblasts and osteocytes apoptosis [24]. Thus, the usage of glucocorticoids suppresses bone formation and enhances osteoclast-induced bone resorption. In addition, glucocorticoids suppress calcium absorption through intestine, increase renal calcium excretion, accelerate muscle wasting, and reduce sex-steroids [25]. Those mechanisms aggravate the decrease bone mass and bone strength. Moreover, the underlying conditions required glucocorticoid usage, such as rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, already have existed bone metabolic disorders [26, 27].

For the treatment of GIOP, bisphosphonates inhibit bone resorption and remodeling; they are recommended as first-line agents to prevent glucocorticoid-induced fractures [4, 28]. Randomized trials and clinical experience showed that bisphosphonate are generally safe and well tolerated. However, besides mild hypocalcemia, other severe rare adverse effects including osteonecrosis of the jaw and atypical femoral fractures have been observed [29, 30].

Teriparatide is an anabolic agent that mainly increase bone formation. The anabolic mechanism of PTH analogues relays on the rapid, transitory, and short-acting pulse. Therefore, teriparatide is administered by daily injection and is approved for up to two years of use. After the administration is discontinued, its benefits are quickly lost, so it should be followed by an antiresorptive agent [31]. In vitro study, PTH stimulates Wnt/beta-catenin signaling, upregulates the expression of key osteogenic factors including Osteocalcin, Runx2, promotes osteoblast differentiation and bone formation [32]. Those mechanisms directly inhibit glucocorticoid induced bone loss. However, the BMD cannot maintain and fracture risk increase after teriparatide is discontinued. Therefore, anti-resorptive agents such as bisphosphonate or denosumab are recommended to use after teriparatide administration.

Risk factors for glucocorticoid-induced bone fractures include age (>55 years), female sex, white race, menopause, previous fracture, and long-term use of daily doses of >7.5 mg equivalent prednisolone [4]. Cumulative glucocorticoid dose is an important factor that correlates with BMD reduction and fracture risk [33, 34]. Factors such as age, sex, body mass index (BMI), menopausal status, fracture history, exercise, smoking, alcohol consumption should be considered as the bone fracture risk, but have no direct correlation according to the study of Van Staa et al. [35]. According to our investigation on meta-regression comparing the efficiency of bisphosphonate and teriparatide, those factors including age, gender, menopausal status, ethnic difference, previous bisphosphonate usage, steroid dosage, steroid duration, underlying diseases, previous vertebral or non-vertebral bone fracture, previous BMD are not associated with the change of BMD, neither the incidence of vertebral or non-vertebral bone fracture using both bisphosphonate and teriparatide. Considering fracture risk increases with aging and dose-dependency of glucocorticoid usage, early prevention is important.

Findings

We performed the meta-analysis of ten RCTs, involving a total of 1960 GIOP patients, compared the effect of bisphosphonate and teriparatide on enhancing BMD at the spinal, total hip, and formal neck, decreasing bone fracture, the adverse effects, and tolerance. Compared to bisphosphonate, teriparatide treatment for GIOP

showed greater BMD change from baseline on vertebral spine, total hip, and femoral neck. Teriparatide exhibited a greater increasing extent on spinal BMD than other parts, suggesting the enhancement of BMD differ from different positions. In addition, the bone fracture incidence was lower in teriparatide treatment in the 18-month phase. Teriparatide also improved bone turnover by increasing bone formation maker PINP and bone resorption marker beta-CTX. On the contrary, bisphosphonate, based on its mechanism of action, reduced bone metabolic markers and suppressed bone turnover. Both of the agents showed good performance on safety, however, the incidence of adverse events leading to withdraw was increased in the teriparatide group. In addition, factors such as age, female, menopausal status, steroid dosage and duration, previous bone fracture are not associated with the efficiency and fracture risk in neither bisphosphonate nor teriparatide therapy.

Comparison with previous studies

Other meta-analyses have reported the comparison between bisphosphonate and teriparatide to treat osteoporosis [10, 36]. However, most of those reports are primary osteoporosis, including aging and menopausal associated osteoporosis, but not particularly in GIOP. According to the different mechanism, the anabolic agent teriparatide showed better performance in GIOP. Compared to the previous studies, we investigated the increasing extent of BMD and reducing fracture risk in different positions, and discussed the change of bone formation and resorption markers. These results may help advance the therapeutic strategy for osteoporosis induced by steroid.

Limitations

This study has limitations. 1) The number of involved RCTs and participants was small. It might result in the risk of bias in reporting and limit a quantitative analysis of the publication bias. 2) Due to the small number of studies and involved patients, there was limited ability to perform subgroup analysis. 3) Most of the included RCTs had the phase of 18 months, lacked the long-term observation.

Conclusions

Teriparatide significantly increased BMD at the lumber spine, total hip, and femoral neck than bisphosphonate with 18-month therapy for GIOP. Teriparatide also reduced bone fracture especially in vertebral bone, and improved bone remodeling by increasing bone formation and resorption marker levels. Teriparatide showed better performance over bisphosphonate in BMD enhancement, bone fracture reduction and bone remodeling improvement, without increasing the incidence of adverse effects.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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