Review Article
Denosumab versus bisphosphonates for treatment of postmenopausal osteoporosis: a meta-analysis

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Abstract: Bisphosphonate is a first-line treatment for osteoporosis. Denosumab is a monoclonal antibody against human IgG-2 that has become common for the treatment of osteoporosis in postmenopausal women. Their efficacy is in controversy. We thus performed a systematic review and meta-analysis to compare the efficacy and safety of denosumab with bisphosphonates to treat osteoporosis. EMBase, PubMed, CNKI and Cochrane Clinical Controlled Experiment Center databases were searched from inception to March 2019. Randomized controlled trials (RCTs) comparing denosumab with bisphosphonates to treat osteoporosis were included. Both random-effect/fixed effect models were used for meta-analysis. Revman 5.3 was used for meta-analysis. Twelve studies depicting 11 RCTs with a total of 6392 patients were collected in the final meta-analysis. As for changes in bone mineral density (BMD) of the lumbar spine, total hip and femoral neck, the pooled outcomes all favored Denosumab (P < 0.00001). In terms of adverse events and severe adverse events, no significant difference was observed. Similar outcomes were detected in the incidences of fractures and mortality, and the pooled RRs were 1.06 (95% CI: 0.81, 1.39; I2 = 0%, P = 0.68) and 0.64 (95% CI: 0.20, 2.06; I2 = 0%, P = 0.45), respectively. Conclusions: This meta-analysis suggests that compared with bisphosphonates, denosumab can significantly increase BMD of hip, lumbar vertebra, femoral neck and other places in postmenopausal osteoporotic women; and the safety of the two drugs is similar, with no significant difference.

Keywords: Bisphosphonates, denosumab, postmenopausal osteoporosis

Introduction

Osteoporosis is a metabolic bone disease characterized by a decrease in bone mass per unit volume. In most cases, the decrease of bone tissue is mainly due to the increase of bone absorption, accompanied by bone pain and easy fracture. According to current statistics, when adults are older than 50 years old, about half of them suffer from osteoporosis of varying degrees, of which 70% are postmenopausal women [1-4]. In Europe and America, an average of 2,300,000 fractures occurs every year due to osteoporosis [5, 6]. Once the fracture occurs; the quality of life of patients will be seriously affected, wasting unnecessary medical expenses, and even leading to death. With the progress of society and the extension of life expectancy, osteoporosis has become a global public health problem. Therefore, active prevention and treatment of osteoporosis has become an urgent task.

At present, the clinical anti-osteoporosis drugs are mainly divided into three kinds; parathyroid hormone as the representative of bone formation drugs, bisphosphonates as the representative of anti-bone resorption drugs, and calcium and vitamin D and its analogues as the representative of the basic supplements [7-9]. Bisphosphonate is a first-line treatment for osteoporosis. Bisphosphonates can be classified into two broad categories based on their structural and functional mechanisms. The first includes pyrophosphates like bisphosphonates, such as etidronates and chlorophosphonates, which are metabolically bound to nonhydrolytic adenosine triphosphate (ATP) analogues as ATP dependent enzyme inhibitors. The second group is nitrogen-containing bisphosphonates,
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which are the latest and most effective drugs, such as ibandronate, pamidronate, alendronate, risedronate and zoledronic acid [10]. Denosumab is a monoclonal antibody against human IgG-2, targeting osteoclast-regulating factor. It has high specificity and affinity for human nuclear factor-κB receptor-activated ligand (RANKL). Its binding to RANKL can significantly reduce bone resorption and thus improve bone density and reduce fractures. This opens up new ideas for the treatment of osteoporosis [11]. In 2009, the Food and Drug Administration officially approved denosumab for the treatment of osteoporosis in postmenopausal women. Similarly, the American Society of Clinical Endocrinologists listed denosumab as a first-line drug in the osteoporosis guidelines for postmenopausal women in 2010 [12, 13]. Although denosumab and bisphosphonates have different mechanisms of action, the indications are very similar. To further compare the efficacy and safety of the two drugs, international scholars have conducted a number of multicenter randomized controlled trials (RCTs) in recent years. The purpose of this article is to analyze the efficacy and safety of the two drugs in the treatment of postmenopausal women with osteoporosis by meta-analysis, and to provide references for clinical treatment.

Methods

Literature retrieval strategy

The retrieval method was formulated according to the requirements of Cochrane collaboration system evaluation. Search in the following databases: EMBase, PubMed, CNKI and Cochrane Clinical Controlled Experiment Center databases. Retrieve “osteoporosis, bone mineral density, bisphosphonates, and denosumab” and so on. The retrieval time period was from inception to March 2019. In order to ensure that the included studies were fully searched, a manual retrieval approach was adopted.

Literature inclusion and exclusion criteria

Inclusive criteria: (1) Literature on postmenopausal osteopenia or osteoporosis has been reported, with bisphosphonates group and denosumab group included in the literature. (2) The main outcome measures were the elevation of bone mineral density relative to baseline and the presence of fracture at follow-up. (3) Follow-up time was more than 1 years. (4) Sample size exceeds 50 cases. Exclusion criteria: (1) Articles with identical data or samples are used in cross references. (2) Literature on nonstandard randomized controlled design and errors in diagnosis or efficacy evaluation. (3) Patients with metastatic bone disease in the past.

Data extraction and study quality evaluation

Two researchers independently searched the literature and selected data according to relevant criteria. The main contents of the collected literature included topics, research groups, first authors, publication time, sample size, controlled trials, follow-up time, statistical characteristics of the subjects, changes in bone mineral density (BMD), intervention and control methods, fractures and adverse reactions. If the literature data is incomplete or there is no original data, the author of the literature was contacted to obtain relevant information, or the literature charts. The quality of the included literature was assessed using the “Cochrane collaboration bias assessment criteria”, such as randomization, allocation concealment, implementation of blindness, measurement blindness, and completeness of results, with the 0-2/3-5/5-7 score as low/medium/high quality, respectively. In case of disagreement, two researchers discussed and resolved the matter, and if no decision was reached, they sought the advice of a third-party senior expert [14, 15].

Data analysis

Meta-analysis was carried out by RevMan 5.3 Software [16]. We explored heterogeneity by utilizing the chi-square ($\chi^2$) test, with significance set at $p$ value less than 0.100. For the quantification, we used the $I^2$ test, with the significant values of less than 25% indicating low heterogeneity, less than 50% indicating moderate heterogeneity, and greater than 50% indicating substantial heterogeneity. If the heterogeneity was significant, we selected a random effect model (DerSimonian and Laird method) [15] and a subgroup analysis was performed for the used literature to minimize the influence of heterogeneity on the results. Sensitivity analysis was performed to evaluate the stabili-
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Results

Literature review and quality evaluation

844 related literatures were retrieved initially in the databases (Figure 1). After preliminary screening, 813 articles were excluded, and the remaining 31 were retrieved for full-text reading. Finally, 12 studies depicting 11 RCTs with a total of 6392 patients were collected in the final meta-analysis [17-28].

Characteristics of the included studies

Table 1 lists the baseline clinicopathological characteristics for the included studies. Nine studies were compared between denosumab and alendronate [18, 21-28], one between denosumab and Ibandronate [20], one between risedronate [19] and the other zoledronate acid.

Changes in BMD of lumbar spine, total hip and femoral neck

In the validity analysis for denosumab, BMD elevations in the lumbar spine, hip and femoral neck were compared with bisphosphonates after 1 year of treatment. The intervention in the denosumab group was subcutaneous injection of 60 mg per 6 months. Figure 3A, shows nine RCTs reporting the degree of BMD elevation in the lumbar spine after 12 months of treatment. A total of 5009 patients were enrolled. The results of the heterogeneity examination included statistical values: $I^2 = 78\%$, $P < 0.0001$. It is suggested that there was heterogeneity in the 9 studies, and the random effects model is used for analysis. The results showed that BMD increased by 1.33% (95% CI: 0.86%-1.81%) in the denosumab group, $P < 0.01$. After subgroup analysis with different treatment regimens, intra-group heterogeneity was significantly reduced ($I^2 = 0\%$), suggesting that the heterogeneity originated from different
Table 1. Baseline characteristics of the included studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design</th>
<th>Study location</th>
<th>Primary outcomes</th>
<th>Comparisons</th>
<th>No. of patients</th>
<th>Mean age (years)</th>
<th>BMD (T-score): lumbar spine/hip/femoral neck</th>
<th>Medication</th>
<th>Duration of treatment</th>
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</thead>
<tbody>
<tr>
<td>Miller et al [17]/(2016)</td>
<td>RCT</td>
<td>United States</td>
<td>1, 2, 3, 4, 5, 6, 7, 8</td>
<td>Denosumab</td>
<td>321</td>
<td>68.5 (7.1)</td>
<td>-2.74/-1.93/NA</td>
<td>60 mg, q6m, sc</td>
<td>12 m</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Zoledronic acid</td>
<td>322</td>
<td>69.5 (7.7)</td>
<td>-2.64/-1.93/NA</td>
<td>5 mg, qy, iv</td>
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<td>Nakamura et al [18]/(2014)</td>
<td>RCT</td>
<td>Japan</td>
<td>1, 2, 3, 4, 5, 6, 7</td>
<td>Denosumab</td>
<td>472</td>
<td>69.9 (7.4)</td>
<td>-2.78/-2.01/-2.38</td>
<td>60 mg, q6m, sc</td>
<td>24 m</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>242</td>
<td>70.2 (7.3)</td>
<td>-2.69/-1.96/-2.29</td>
<td>35 mg, q1w, po</td>
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<td>Roux et al [19]/(2014)</td>
<td>RCT</td>
<td>France</td>
<td>1, 2, 3, 4, 5, 6, 7, 8</td>
<td>Denosumab</td>
<td>480</td>
<td>69.0 (7.7)</td>
<td>-2.73/-1.95/-2.29</td>
<td>60 mg, q6m, sc</td>
<td>12 m</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>402</td>
<td>69.0 (7.7)</td>
<td>-2.73/-1.95/-2.29</td>
<td>60 mg, q6m, sc</td>
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<td>Recknor et al [20]/(2013)</td>
<td>RCT</td>
<td>United States</td>
<td>1, 2, 3, 4, 5, 6, 7, 8</td>
<td>Denosumab</td>
<td>417</td>
<td>67.2 (8.1)</td>
<td>-1.80/-2.10/-2.50</td>
<td>60 mg, q6m, sc</td>
<td>12 m</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>416</td>
<td>66.2 (7.8)</td>
<td>-1.80/-2.10/-2.50</td>
<td>150 mg, qm, po</td>
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<tr>
<td>Freemantle et al [21]/(2012)</td>
<td>RCT</td>
<td>United Kingdom</td>
<td>1, 2, 3, 4, 5, 6, 7</td>
<td>Denosumab</td>
<td>126</td>
<td>65.1 (7.6)</td>
<td>-2.04/-1.60/-2.01</td>
<td>60 mg, q6m, sc</td>
<td>24 m</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Alendronate</td>
<td>124</td>
<td>65.3 (7.7)</td>
<td>-1.89/-1.60/-2.03</td>
<td>70 mg, q1w, po</td>
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<td>Kendler et al [22]/(2010)</td>
<td>RCT</td>
<td>Canada</td>
<td>1, 2, 3, 4, 5, 6, 7, 8</td>
<td>Denosumab</td>
<td>253</td>
<td>66.9 (7.8)</td>
<td>-2.64/-1.79/NA</td>
<td>60 mg, q6m, sc</td>
<td>12 m</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>251</td>
<td>68.2 (7.7)</td>
<td>-2.62/-1.81/NA</td>
<td>70 mg, qw, po</td>
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<tr>
<td>Seeman et al [23]/(2010)</td>
<td>RCT</td>
<td>Australia</td>
<td>4, 5, 6</td>
<td>Denosumab</td>
<td>83</td>
<td>60.3 (5.9)</td>
<td>-2.40/-1.40/NA</td>
<td>60 mg, q6m, sc</td>
<td>12 m</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>82</td>
<td>60.7 (5.2)</td>
<td>-2.50/-1.40/NA</td>
<td>70 mg, q1w, po</td>
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<td>Brown et al [24]/(2009)</td>
<td>RCT</td>
<td>Spain</td>
<td>1, 2, 3, 4, 5, 6, 7, 8</td>
<td>Denosumab</td>
<td>594</td>
<td>64.1 (8.6)</td>
<td>-2.57/-1.75/NA</td>
<td>60 mg, q6m, sc</td>
<td>12 m</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Alendronate</td>
<td>595</td>
<td>64.6 (8.3)</td>
<td>-2.57/-1.69/NA</td>
<td>70 mg, q1w, po</td>
<td></td>
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<tr>
<td>Beck et al [25]/(2008)</td>
<td>RCT</td>
<td>United States</td>
<td>1, 3</td>
<td>Denosumab</td>
<td>39</td>
<td>63.0 (8.0)</td>
<td>NA/-1.42/NA</td>
<td>60 mg, q6m, sc</td>
<td>24 m</td>
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<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>38</td>
<td>63.0 (8.0)</td>
<td>NA/-1.46/NA</td>
<td>70 mg, q1w, po</td>
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<tr>
<td>Lewiecki et al [26]/(2008)</td>
<td>RCT</td>
<td>United States</td>
<td>1, 2, 4, 5, 6, 7, 8</td>
<td>Denosumab</td>
<td>314</td>
<td>62.3 (8.0)</td>
<td>-2.20/-1.40/-1.90</td>
<td>60 mg, q6m, sc</td>
<td>24 m</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>46</td>
<td>62.8 (8.2)</td>
<td>-2.20/-1.60/-1.90</td>
<td>70 mg, q1w, po</td>
<td></td>
</tr>
<tr>
<td>McClung et al [27]/(2006)</td>
<td>RCT</td>
<td>United States</td>
<td>1, 2</td>
<td>Denosumab</td>
<td>47</td>
<td>62.8 (8.2)</td>
<td>-2.00/-1.50/-2.00</td>
<td>60 mg, q6m, sc</td>
<td>12 m</td>
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<td>Placebo</td>
<td>47</td>
<td>63.1 (8.1)</td>
<td>-2.00/-1.60/-1.90</td>
<td>70 mg, qw, po</td>
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</table>

Values were in means and standard deviations. Abbreviations: RCT, randomized controlled trials; BMD, bone mineral density; AE, adverse events; NA, not available. *Primary outcomes: 1, change in lumbar spine BMD; 2, change in total hip BMD; 3, change in femoral neck BMD; 4, AEs; 5, severe AEs; 6, withdrawn due to AEs; 7, risk of fracture; 8, mortality. †A total of 412 women from 29 study centers in the United States, were randomly assigned to receive Denosumab (314 patients) given subcutaneously either every three months (at a dose of 6, 14, or 30 mg) or every six months (at a dose of 14, 60, 100, or 210 mg), open-label alendronate (at a dose of 70 mg) given orally once weekly, or placebo.*Enrolled patients were the same with Kendler et al’s RCT (2011) [28].
treatment regimens in the bisphosphonates group. In detail, compared with bisphosphonates of alendronate, denosumab for osteoporosis patients further increased the change in lumbar for spine BMD (WMD = 0.97%; 95% CI: 0.70% to 1.25%; P < 0.00001, I² = 0%). Compared with other bisphosphonates such as zoledronic acid, risedronate and ibandronate, the results also favored the denosumab group (all P < 0.00001). We performed a sensitivity analysis by leaving out one study in turn and results showed that the overall effect size was not changeable, indicating a robustness of the results.

As for the total hip and femoral neck, BMDs of the denosumab group were 1.11% and 1.01% higher than that in the bisphosphonates group, respectively (95% CI: 0.97%-1.26%, P < 0.00001; and 95% CI: 0.81%-1.22%, P < 0.00001), as shown in Figure 3B and 3C.

**Adverse events**

In the safety analysis, the adverse events, severe adverse events, fractures, withdrawal and death caused by adverse events occurring within one year after the start of the trial were studied by meta-analysis. Severe adverse events refer to major complications of tumors, infections, comorbidities from digestive, respiratory or circulatory systems. The RR of adverse events was 0.99 (95% CI: 0.96, 1.02), P = 0.62 (Figure 4A) of denosumab versus bisphosphonates. In terms of severe adverse events, no significant difference was observed between the two groups (RR = 1.03, 95% CI: 0.85, 1.24; P = 0.76, I² = 0%) (Figure 4B). The withdrawal rate of patients with adverse events in the denosumab group was lower than that in bisphosphonates group, and the difference was statistically significant (RR = 0.53, 95% CI: 0.37, 0.76; P = 0.0006, I² = 0%) (Figure 4C).
Fractures and mortality

Figure 5A and 5B show no significant differences were observed between denosumab and bisphosphonates in the pooled estimates, and the pooled RRs were 1.06 (95% CI: 0.80, 1.39; P = 0.68, I² = 0%) and 0.64 (95% CI: 0.20, 2.06; P = 0.45, I² = 0%) respectively.

Publication bias

Begg’s funnel plot was employed to assess the publication bias. As shown in Figure 6, the funnel plots failed to reveal any obvious asymmetry except in the change in total lumbar spine BMD, and in the withdrawn due to adverse events of denosumab versus bisphosphonates.

Discussion

Based on the current available literature, the present systematic review and meta-analysis has confirmed that denosumab, a fully human monoclonal antibody against the RANKL, could potently reduce bone resorption with an accom-
panying increase in BMD. Compared with the traditional bisphosphonates for bone loss in postmenopausal osteoporosis patients, denosumab significantly increased changes in lumbar spine, total hip and femoral neck BMD. The results were robust as confirmed by the sensitivity analysis. As for the safety concern, both the adverse events and severe adverse events were comparable between the two groups, as well as the rates of withdraw due to adverse events. Moreover, compared with bisphosphonates, denosumab has no benefit in reducing...
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the risk of fracture. The pooled results also showed similarly in terms of mortality outcomes.

As an antiresorptive mechanism, the direct combination of the RANKL and the inhibiting effect for the osteoclasts’ survival and differentiation simultaneously makes denosumab a more powerful drug than bisphosphonates, in theory. In fact, we did observe a significant difference between denosumab and bisphosphonates for clinical outcomes that were changes in the skeletal BMD. It might be reasonable that BMD increasing leads to a reduced fracture rate for postmenopausal osteoporosis patients. However, no significant changes in fracture occurrence were detected in the present study. In a network meta-analysis the different pharmaceutical agents in reducing the risk of fragility fractures were investigated. Although both denosumab and bisphosphonates were most effective in reducing the risk of fragility fractures, the differences in denosumab, zoledronate, risedronate, ibandronate, and alendronate were not statistically significant [29]. We speculate that the reason may be that the occurrence of fracture is the outcome of multiple factors, and the increase of BMD in a short time is not enough to reduce the risk of fracture.

Previous meta-analyses on this topic were associated several limitations. The differences between the current work and the previous ones should be highlighted. Lin et al conducted a head-to-head comparison of efficacy and safety profiles between 60 mg denosumab subcutaneously per 6 months and 70 mg alendronate orally per week for postmenopausal women with low BMD [30]. Of note was the observation that only four heterogeneous RCTs were included. The included studies were small and newly published ones have been published in recent years. Our meta-analysis added a statistical power of 11 RCTs with a total of 6392 patients being collected. Another systematic

Figure 5. Forest plots depicting the incidence of bone fractures (A) and mortality (B) of denosumab versus bisphosphonates.
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In this study, meta-analysis of BMD elevation at different sites revealed some heterogeneity, possibly due to differences in basic characteristics and treatment options among the study groups. First, the baseline BMD of subjects in each study group was different (Table 1). There have been studies reporting that when the patient’s baseline BMD is low, the use of bisphosphonates would lead to BMD increasing more significantly [32, 33]. Second, in ethnicity considerations, the subjects of Nakamura et al.'s, were of different race and the control group was given alendronate 35 mg per week [18]. Third, different postmenopausal osteoporosis diagnostic criteria were applied for patients from different countries, and the dose

review and meta-analysis of denosumab compared to other treatments to prevent or treat osteoporosis in individuals at risk of fracture, had nine studies including a total of 4890 postmenopausal women being identified [31]. However, the real effects of denosumab for postmenopausal osteoporosis could not be accurately assessed as they included patients that were prescribed daily or weekly bisphosphonates therapy for more than 1 month. What’s more, both the above meta-analyses were conducted to compare the efficacy and safety of denosumab over other pharmacological treatments for osteoporosis, except for bisphosphonates, thus a larger heterogeneity was unavoidable.

In this study, meta-analysis of BMD elevation at different sites revealed some heterogeneity, possibly due to differences in basic characteristics and treatment options among the study groups. First, the baseline BMD of subjects in each study group was different (Table 1). There have been studies reporting that when the patient’s baseline BMD is low, the use of bisphosphonates would lead to BMD increasing more significantly [32, 33]. Second, in ethnicity considerations, the subjects of Nakamura et al.’s, were of different race and the control group was given alendronate 35 mg per week [18]. Third, different postmenopausal osteoporosis diagnostic criteria were applied for patients from different countries, and the dose

Figure 6. Funnel plots depicting the change in total lumbar spine, hip and femoral neck BMD (A-C); AEs (D), severe AEs (E) and withdrawn due to AEs (F), fractures (G) and mortality (H) of denosumab versus bisphosphonates. Abbreviations: BMD, bone mineral density; AE, adverse event.
and duration of the medication were not consistent; as in the Recknor et al’s and Roux et al’s studies, all patients were treated with alendronate for more than 30 days prior to intervention [19, 20]. These differences might have contributed some effects on the heterogeneity, but in the sensitive analysis when removing these studies, the pooled results were similar. Moreover, severe complications might have been underestimated due to the relatively short follow-up duration of the included studies.

There are also some shortcomings in this study: (1) Most of the subjects are white, which may lead to distribution bias and selection bias, and affect the meta-analysis results. (2) Publication bias, including the reported literature, the results of negative unreporting was not statistically analyzed. (3) BMD changes in different parts of the body (lumbar spine, total hip and femoral neck BMD) before and after treatment were taken as the main observation index in all studies. The occurrence of fracture was only described as a secondary observation index in adverse reactions, and there was insufficient evidence to reflect the effectiveness of treatment. (4) Follow-up time was short, and only the data from 60 mg/6 months of subcutaneous injection of denosumab were analyzed. Its long-term effectiveness and safety need to be further studied. Nevertheless, in our study, strict inclusion and exclusion criteria were established, all of which were from RCTs. Most of the literature quality scores were medium to high level, and the reliability of the conclusion is strong.

Conclusion

In conclusion, compared with bisphosphonates, denosumab can significantly increase bone mineral density of the hip, lumbar vertebra, femoral neck and other places in postmenopausal osteoporotic women, and the safety of the two drugs is similar.

Disclosure of conflict of interest

None.

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