Review Article
Effect of denosumab, a fully human monoclonal antibody to RANKL, on bone mineral density and fractures: a meta-analysis

Yuanjin Zhang[1], Ling Zhang[1], Songbai Li[1], Farui Sun[1], Jun Li[1], Aihong Ke[1], Xiang Chen[1], Xin Zhang[1], Lijun Xu[1], Jun Duan[1], Guofu Zhang[1], Dongqing Li[1], Guozhen Ding[2], Lian Qin[1], Chengwei Wang[1]

[1]Department of Orthopedics, Huangshi Central Hospital, Affiliated Hospital of Hubei Polytechnic University, Huangshi 435000, Hubei, China; [2]Department of Otorhinolaryngological, Huangshi Central Hospital, Affiliated Hospital of Hubei Polytechnic University, Huangshi 435000, Hubei, China

Abstract: Receptor activator of nuclear factor κB ligand (RANKL) is the principal regulator of osteoclast differentiation, activity, and survival; denosumab, a fully human monoclonal antibody to RANKL, inhibits bone resorption and is approved for the treatment of women with postmenopausal osteoporosis at high risk of fractures. By searching the PubMed and Embase databases, we conducted a meta-analysis to examine the bone mineral density (BMD) and the fracture rate in osteoporosis patients being treated with denosumab. Studies were pooled, and mean difference (MD), the relative risk (RR) and its corresponding 95% confidence interval (CI) were calculated. Twelve relevant articles were included for this meta-analysis study. Compared to placebo, denosumab treatment significantly decreased the risk of fracture (RR = 0.42, 95% CI = 0.27-0.68, $P_{heterogeneity}$ = 0.005, I^2 = 73.1%) and increased the percent change in bone mineral density at the total hip (MD = 5.06%, 95% CI = 4.76-5.36, $P_{heterogeneity}$ < 0.001, I^2 = 99.7%) and lumbar spine (MD = 7.6%, 95% CI = 6.91-8.30, $P_{heterogeneity}$ < 0.001, I^2 = 99.9%). Compared to alendronate, denosumab treatment significantly increased the percent change in bone mineral density at the total hip (MD = 1.18%, 95% CI = 1.00-1.35, $P_{heterogeneity}$ < 0.001, I^2 = 98.1%) and lumbar spine (MD = 1.36%, 95% CI = 0.96-1.76, $P_{heterogeneity}$ < 0.001, I^2 = 99.3%), however, there was no significant difference in the incidence of fractures. In conclusion, these results indicate that denosumab can effectively prevent the resorption of bone and increase BMD compared with the placebo or alendronate group and there is a significant reduction in fractures risk in the denosumab compared with the placebo group.

Keywords: Denosumab, osteoporosis, meta-analysis, randomized controlled trials

Introduction

Osteoporosis is a common bone disease, which is characterized by low bone density (BMD) and poor bone quality, reduced bone strength and increased risk of fractures [1]. It is a global public health problem, affecting more than 75 million people in the United States, Europe and Japan, leading to more than 8.9 million fractures each year around the world [2]. In the United States, approximately 44 million people suffering from osteoporosis or low bone mass (osteopenia) increased risk of fracture [3]. With the aging of the population growing, China is experiencing an increasing the prevalence of osteoporosis. About a third of women aged

60-69 years and a half of over the age of 70 years have osteoporosis [4].

In the past few decades, osteoporosis treatment greatly expanded. Introducing a nitrogen-containing bisphosphonates, by inhibiting bone resorption, it has been an important step forward [5-8]. Parathyroid hormone (PTH) and teriparatide also help prevent fractures, but in general it is critically ill patients due to a variety of factors, including cost and inconvenience of daily injections [9]. Denosumab treatment program approved by the further expansion [10]. Denosumab, a human monoclonal antibodies, specific binding and receptor-activating factor nuclear factor Kappa B ligand (RANKL) and
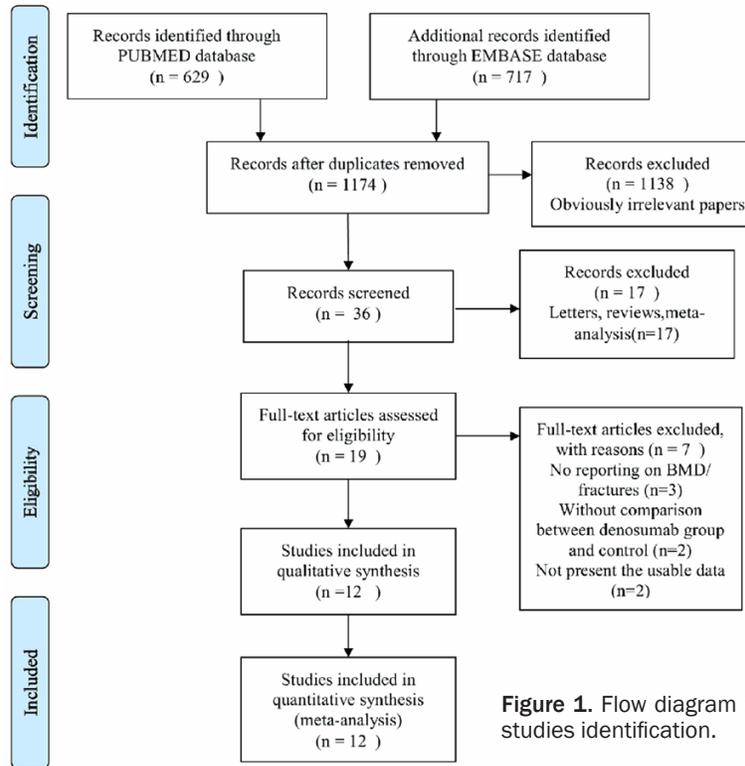
Figure 1. Flow diagram of studies identification.

of the following key words: Denosumab AND osteoporosis AND (bone mineral density OR fracture). The last search was updated on January 20 th, 2016. We also manually checked the reference list to identify additional publications. The published language was limited to English.

Selection criteria

The inclusion criteria included: 1) eligibility is limited to randomized controlled trials (RCT) in patients with osteoporosis; 2) study evaluated the BMD and the fracture rate in osteoporosis patients being treated with denosumab. We excluded clinical cases, literature reviews, commentaries, letters to the editor, and experimental studies.

Data extraction

All the available data were extracted from each study by two investigators independently according to the inclusion criteria listed above. The outcomes were: (1) BMD *T*-scores of lumbar spine; (2) BMD *T*-scores of total hip; (3) Fractures. If the data were not reported in the original article, we extrapolated them from the accompanying graphs.

Statistical analysis

We calculated the mean difference (MD) and 95% confidence intervals (CI) for the continuous data, and calculate the risk ratio (RR) and 95% confidence intervals for dichotomous data. Data was combined according to random effects (DerSimonian and Laird's method) or fixed effects model, depending on the significance of the I^2 statistic. If the heterogeneity was significant, random effects model was used; otherwise the fixed effects model was used. Publication bias was assessed with a visual inspection of funnel plots and with the Begg-Mazumdar Kendall's tau and Egger bias test ($P < 0.05$ was considered statistically significant). All results were summarized using STATA Software (version 12, StataCorp, College Station, TX).

thus reduce bone resorption, has launched for the treatment of postmenopausal osteoporosis. Use of either zoledronic acid administered once yearly as an iv infusion [11] or denosumab administered sc every 6 months [10] decreased bone turnover, increase bone mineral density (BMD), and reduce the risk of vertebral and non-vertebral and hip fractures.

In recent years, several randomized controlled trials (RCTs) have been conducted to evaluate the BMD and the fracture rate in osteoporosis patients being treated with denosumab [10, 12-22]. However, the results were not consistent. Therefore, the BMD and the fracture rate of denosumab therapy in patients with osteoporosis should be systematically evaluated. Here in this study, we performed a meta-analysis of eligible studies to assess the BMD and the fracture rate of denosumab therapy in patients with osteoporosis.

Materials and methods

Search strategy

A comprehensive literature searching of Pubmed and Embase database was conducted. The search strategy included the combinations

Table 1. Characteristics of randomised controlled trials included in this meta-analysis

Authors	Year of publication	Drug, dose and No randomised		Duration (months)	Evaluation criteria	Main outcomes
		Denosumab	Control			
McClung [12]	2006	60 mg (n = 46)	Placebo (N = 46) Alendronate 70 mg (N = 46)	12	BMDT-scores	Lumbar spine, total hip and incidence of fracture
Lewiecki [13]	2007	30 mg (n = 41)	Alendronate 70 mg (N = 47)	24	BMDT-scores	Lumbar spine and total hip
Bone [14]	2008	60 mg (n = 166)	Placebo (N = 166)	24	BMDT-scores	Lumbar spine and total hip
Cumings [10]	2009	60 mg (n = 3902)	Placebo (N = 3906)	36	BMDT-scores	Lumbar spine, total hip and incidence of fracture
Smith [15]	2009	60 mg (n = 734)	Placebo (N = 734)	36	BMDT-scores	Lumbar spine, total hip and incidence of fracture
Brown [16]	2009	60 mg (n = 594)	Alendronate 70 mg (N = 595)	12	BMDT-scores	Lumbar spine, total hip and incidence of fracture
Kendler [17]	2010	60 mg (n = 253)	Alendronate 70 mg (N = 251)	12	BMDT-scores	Lumbar spine, total hip and incidence of fracture
Bone [18]	2011	60 mg (n = 128)	Placebo (N = 128)	48	BMDT-scores	Lumbar spine and total hip
Jamal [19]	2011	60 mg (n = 423)	Placebo (N = 410)	36	NA	Incidence of fracture
Nakamura [20]	2012	60 mg (n = 54)	Placebo (N = 55)	12	BMDT-scores	Lumbar spine and total hip
Freemantle [21]	2012	60 mg (n = 106)	Alendronate 70 mg (N = 115)	12	NA	Incidence of fracture
Nakamura [22]	2014	60 mg (n = 472)	Placebo (N = 480) Alendronate 35 mg (N = 242)	24	BMDT-scores	Lumbar spine, total hip and incidence of fracture

BMD: Bone mineral density; NA: Not available.
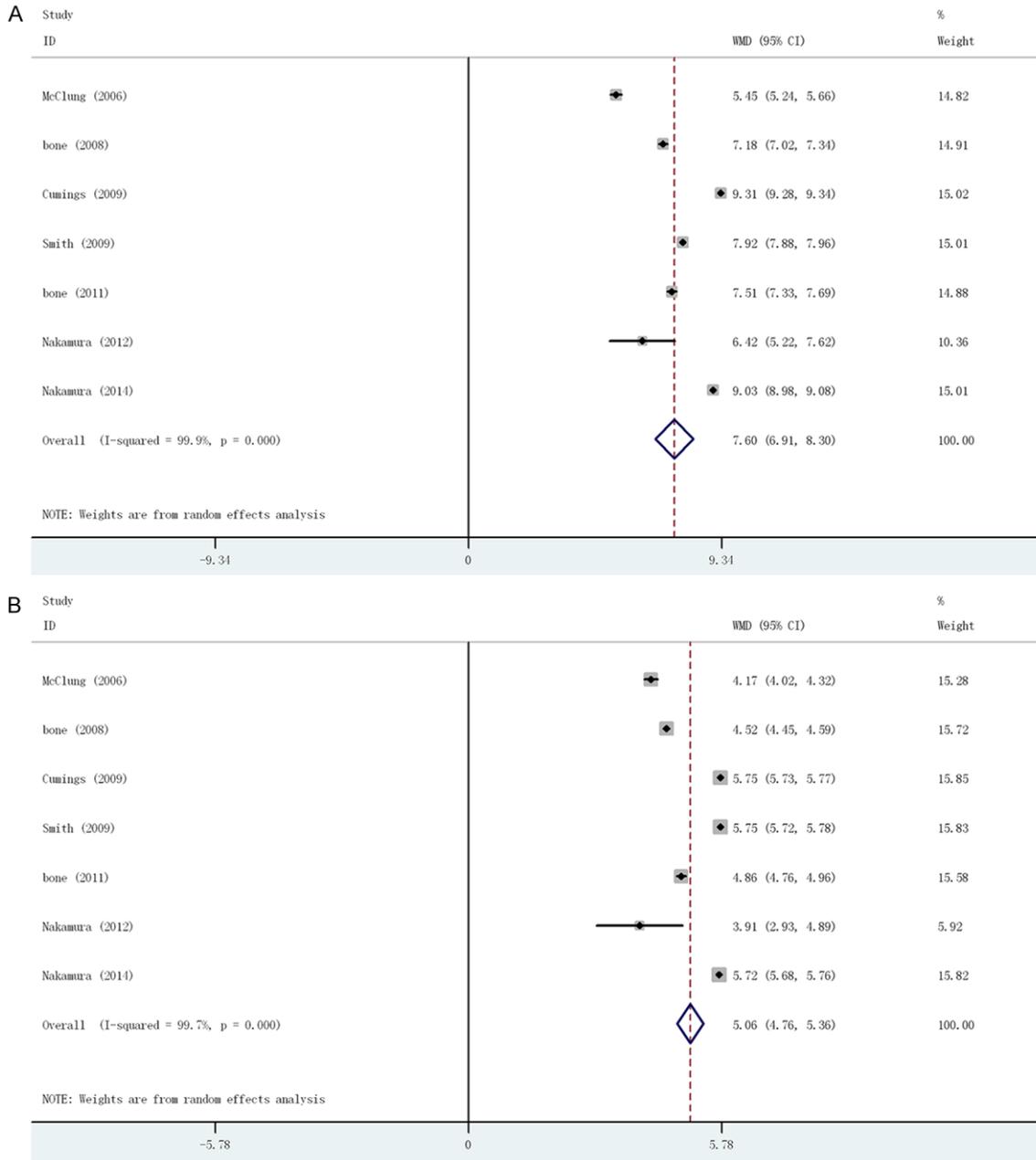
Figure 2. Efficacy outcomes of percentage change in BMD in randomised controlled trials of denosumab versus placebo. A. Lumbar spine; B. Total hip.

Results

Characteristics of the studies

The PRISMA flow diagram of studies is depicted in **Figure 1**. The last electronic search was conducted in January 20, 2016 and identified 626 relevant literatures in the Pubmed search and 717 sources through Embase. After removing repeat references and related articles, there are 36 records is restricted to full-text reading.

Nineteen publications meet the inclusion criteria, while others have no choice for various reasons (e.g., studies not reporting on BMD/fractures or without a control group). A total of 12 studies were included in the qualitative synthesis, and the data from these studies were included in the meta-analysis.

Table 1 Provides a summary of the studies included in the meta-analysis. There were 14,140 participants were included in this meta-
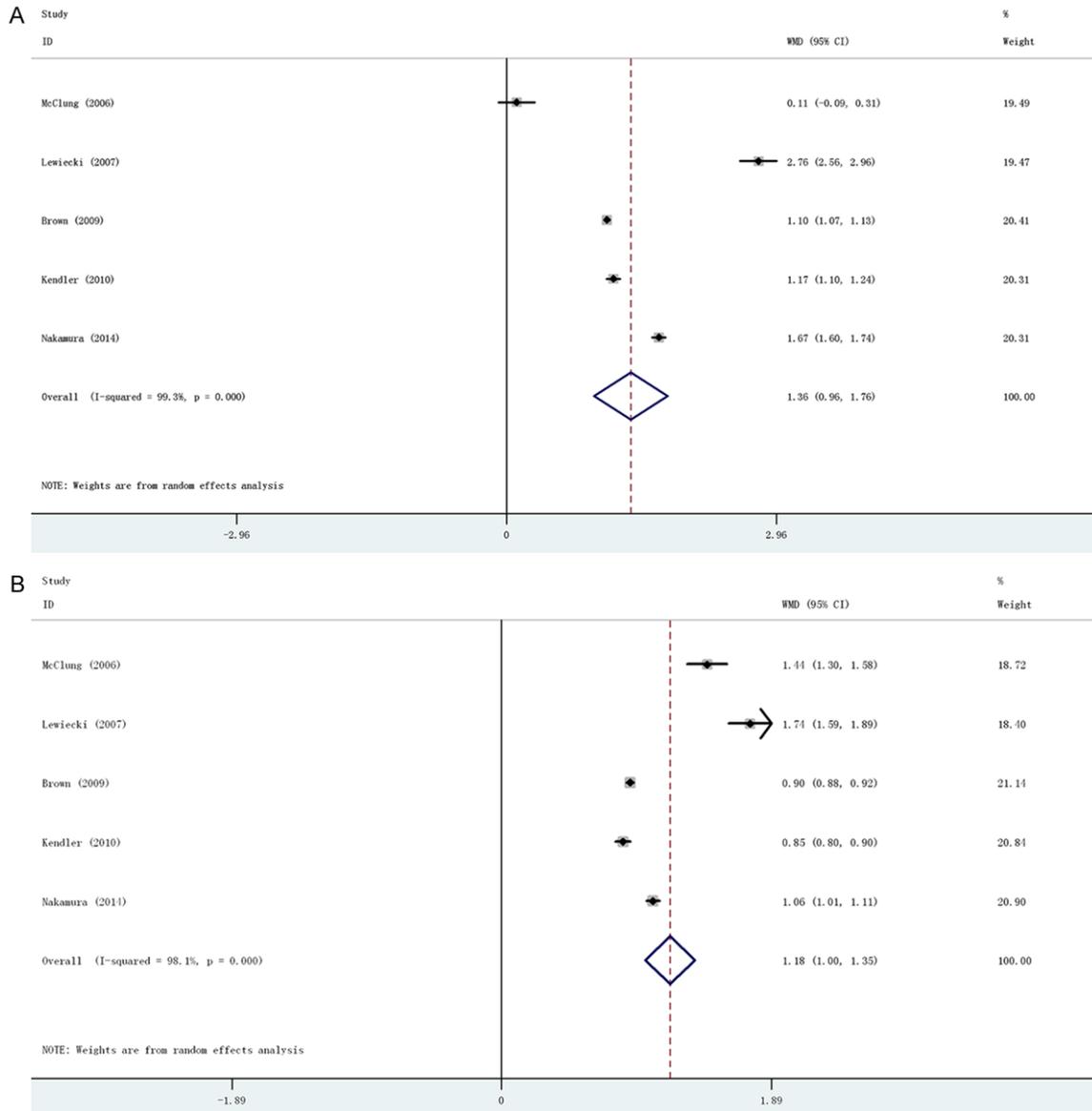
Figure 3. Efficacy outcomes of percentage change in BMD in randomised controlled trials of denosumab versus alendronate. A. Lumbar spine; B. Total hip.

analysis. Sample sizes ranged from 92 to 7808. These studies were published in 2006-2014.

Quantitative synthesis

The seven studies provided numerical data regarding the percent change in BMD of the lumbar spine from baseline between patients who received denosumab and placebo, and were included in the meta-analysis. There was evidence of heterogeneity among the 7 studies, therefore, a random-effects model of analysis was used. The pooled difference in means indicated that patients who received denosumab

(MD = 7.6%, 95% CI = 6.91-8.30, $P_{heterogeneity}$ < 0.001, I^2 = 99.9%) had significantly increased BMD of the lumbar spine compared with patients who received placebo (**Figure 2A**).

The 7 studies also provided total hip BMD data, and were included in the analysis. There was evidence of heterogeneity among the 7 studies, therefore, a random-effects model of analysis was used. The pooled difference in means indicated that patients who received denosumab (MD = 5.06%, 95% CI = 4.76-5.36, $P_{heterogeneity}$ < 0.001, I^2 = 99.7%) had significantly increased
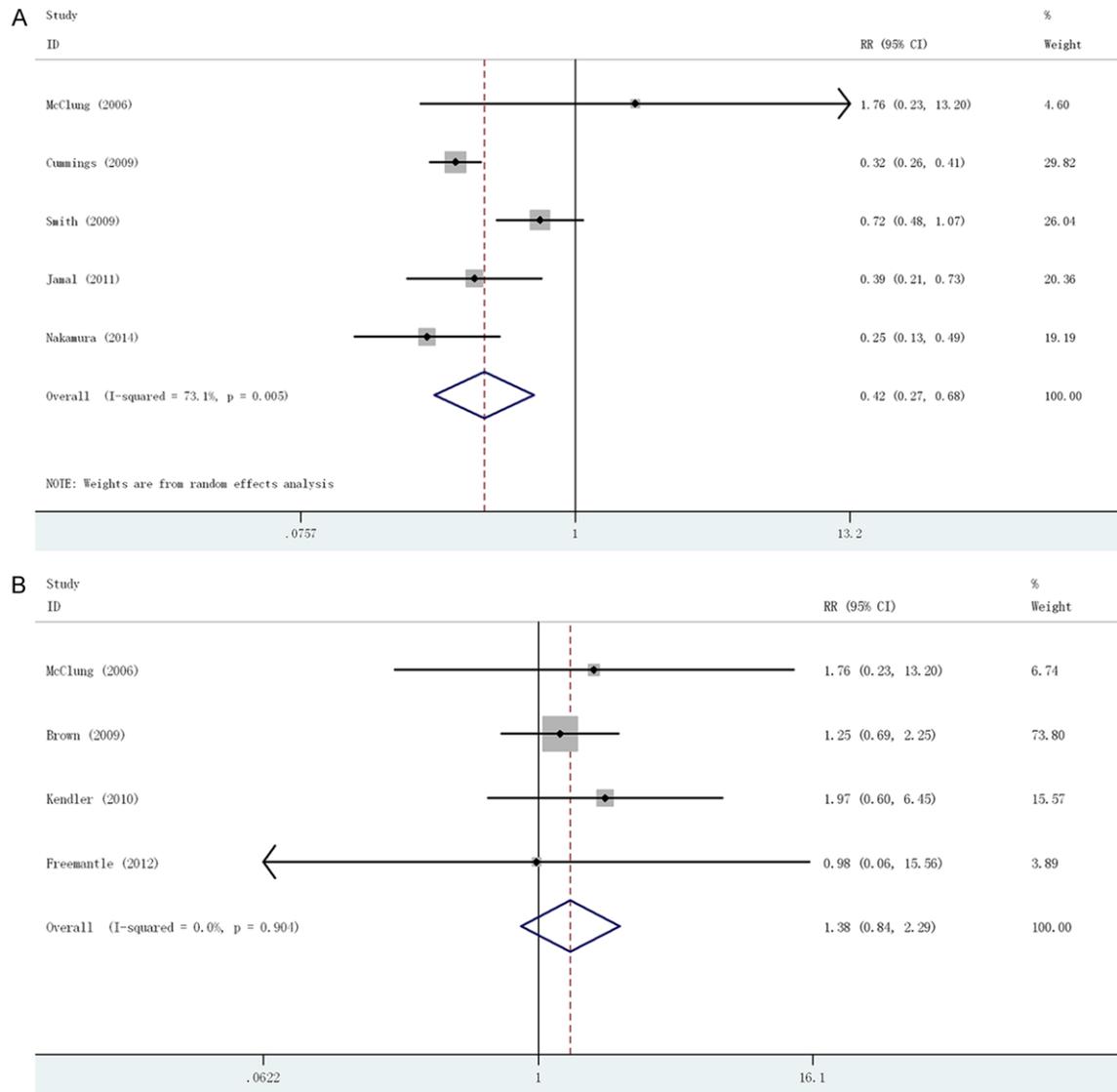
Figure 4. Meta-analysis of fracture risk in randomised controlled trials of denosumab versus placebo (A) or alendronate (B).

BMD of the total hip compared with patients who received placebo (**Figure 2B**).

The five studies provided numerical data regarding the percent change in BMD of the lumbar spine from baseline between patients who received denosumab and alendronate, and were included in the meta-analysis. There was evidence of heterogeneity among the 5 studies, therefore, a random-effects model of analysis was used. The pooled difference in means indicated that patients who received denosumab (MD = 1.36%, 95% CI = 0.96-1.76, $P_{heterogeneity} < 0.001$, $I^2 = 99.3\%$) had significantly

increased BMD of the lumbar spine compared with patients who received alendronate (**Figure 3A**).

The 5 studies also provided total hip BMD data, and were included in the analysis. There was evidence of heterogeneity among the 5 studies, therefore, a random-effects model of analysis was used. The pooled difference in means indicated that patients who received denosumab (MD = 1.18%, 95% CI = 1.00-1.35, $P_{heterogeneity} < 0.001$, $I^2 = 98.1\%$) had significantly increased BMD of the total hip compared with patients who received alendronate (**Figure 3B**).
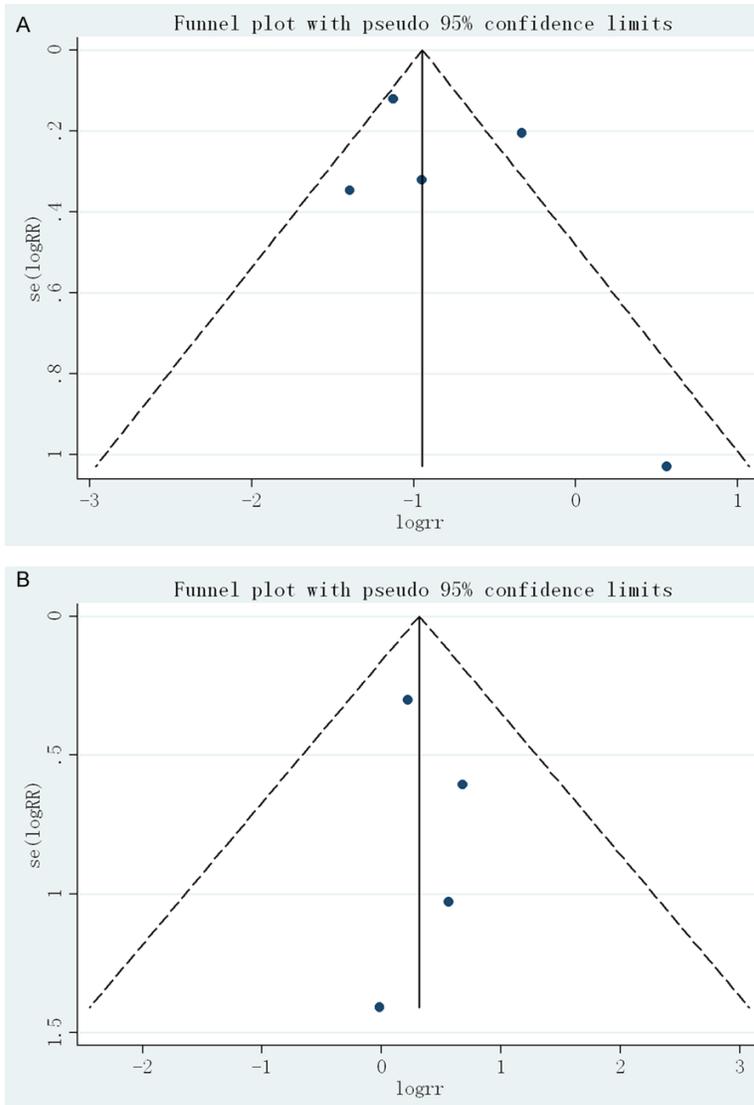
Figure 5. Begg's funnel plot for publication bias test. Each point represents a separate study for the indicated association. A. Incidence of fractures comparing denosumab to placebo; B. Incidence of fractures comparing denosumab to alendronate.

The five studies provided fracture data between patients who received denosumab and placebo, and were included in the meta-analysis. There was evidence of heterogeneity among the 5 studies, therefore, a random-effects model of analysis was used. The pooled difference indicated that patients who received denosumab (RR = 0.42, 95% CI = 0.27-0.68, $P_{heterogeneity}$ = 0.005, I^2 = 73.1%) had significant difference in the incidence of fractures compared with patients who received placebo (**Figure 4A**).

The four studies provided fracture data between patients who received denosumab and

alendronate, and were included in the meta-analysis. There was no evidence of heterogeneity among the 4 studies, therefore, a fixed-effects model of analysis was used. The pooled difference indicated that patients who received denosumab (RR = 1.38, 95% CI = 0.84-2.29, $P_{heterogeneity}$ = 0.904, I^2 = 0) had no significant difference in the incidence of fractures compared with patients who received alendronate (**Figure 4B**).

Publication bias

Finally, the Egger's regression test showed no evidence of asymmetrical distribution in the funnel plot in incidence of fractures comparing denosumab to placebo (Begg's test P = 0.806; Egger's test P = 0.538) and incidence of fractures comparing denosumab to alendronate (Begg's test P = 1.000; Egger's test P = 0.640) (**Figure 5A** and **5B**).

Discussion

Fractures are due to many factors, including factors increase the risk of bone fragility and risk of falling [23]. Bone fragility, the final approach is the degree and quality of bone metabolism and bone remodeling balance [24]. In most of the risk of bone fractures in women after menopause, bone remodeling, is expressed as the frequency of activation of the bone remodeling unit, and increased [25]. Therefore, bone resorption treatment resistance, reduce the rate of bone turnover has grown as the main way to prevent fractures.

Currently, the most commonly used antiresorptive drugs are bisphosphonates (BPs) and denosumab. Nitrogen-containing BPs bind to bone surface and inhibit the mevalonate pathway, leading to apoptosis of osteoclasts, inhibiting ceased effective BPs can last for a very long time, such as alendronate and zoledronic

acid sodium [26]. Denosumab is a fully human monoclonal antibody that specifically binds to the receptor activator of nuclear factor κB ligand (RANKL) and so inhibit the differentiation and activation of osteoclasts in six months, a suppression resolve one year after stopping [27]. The aim of this meta-analysis was to evaluate the bone mineral density (BMD) and the fracture rate in osteoporosis patients comparing denosumab to placebo or alendronate. Compared to placebo, denosumab treatment significantly decreased the risk of fracture and increased the percent change in bone mineral density at the total hip and lumbar spine. Compared to alendronate, denosumab treatment significantly increased the percent change in bone mineral density at the total hip and lumbar spine, however, there was no significant difference in the incidence of fractures. These results indicate that denosumab can effectively prevent the resorption of bone and increase BMD compared with the placebo or alendronate group and there is a significant reduction in relative fracture risk in the denosumab compared with the placebo group.

Denosumab is the first specific biotherapy authorized and reimbursed for the treatment of postmenopausal osteoporosis. In the FREEDOM study, patients with vertebral and non-vertebral fractures were significantly lower in the denosumab treatment group. At 12, 24 and 36 months the risk reduction was 61%, 71% and 68% for vertebral fractures and 20%, 21% and 16% for non-vertebral fractures, respectively. In three years, reduce the risk of hip fracture by 40% [10, 28]. Wrist fractures decreased risk and severity of osteoporosis [29]. The most important contribution of denosumab, it can be used for moderate or severe renal dysfunction in patients, because previously not reasonable treatment options [19]. The second advantage of denosumab is the effectiveness of subcutaneous administration. This means that responsibility for adherence passes from the patient alone to the physicianand patient together. The persistence of oral treatment for osteoporosis was poor, with all patients stopping at the first year and a half [30].

Several limitations in this meta-analysis should be addressed. First, although we do have a data extraction and repeated high reviewers agreement between the measured data, some information about deviations or measurement errors may occur, because in some trials dispersion measures extracted from the original publications in graphs. Secondly, evaluation of the data set was considered to be too small for visual or statistical examination of publication bias, and the potential existence of such bias could not be determined. Therefore, we assumed that publication bias was probably present. Third, even though we have clear inclusion and exclusion criteria, significant differences in research design, intervention and outcome measurements may have a certain impact on the results.

In conclusion, these results indicate that denosumab can effectively prevent the resorption of bone and increase BMD compared with the placebo or alendronate group and there is a significant reduction in relative fracture risk in the denosumab compared with the placebo group. Denosumab is a valuable new option for the treatment of osteoporosis and may be used as a first-line treatment in future. However, further studies are needed to verify the results of the present study due to the presence of an unstable factor.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ling Zhang, Department of Orthopedics, Huangshi Central Hospital, Affiliated Hospital of Hubei Polytechnic University, No.141 Tianjin Road, Huangshi 435000, Hubei, China. Tel: +86-714-6266755; Fax: +86-714-6266-755; E-mail: yjz_med@163.com

References

[1] Klibanski A, Adams-Campbell L, Bassford T, Blair SN, Boden SD, Dickersin K, Gifford DR, Glasse L, Goldring SR, Hruska K, Johnson SR, McCauley LK, Russell WE. Osteoporosis prevention, diagnosis, and therapy. JAMA 2001; 285: 785-795.

[2] Kanis JA. On behalf of the World Health Organization Scientific Group. Assessment of osteoporosis at the primary health-care level (World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK, 2008).

[3] National Osteoporosis Foundation. America's Bone Health: The State of Osteoporosis and Low Bone Mass in Our Nation (National Osteoporosis Foundation, Washington, DC, 2002).

[4] Zhang ZQ, Ho SC, Chen ZQ, Zhang CX, Chen YM. Reference values of bone mineral density and prevalence of osteoporosis in Chinese adults. Osteoporos Int 2014; 25: 497-507.

[5] Reid DM, Hosking D, Kendler D, Brandi ML, Wark JD, Weryha G, Marques-Neto JF, Gaines KA, Verbruggen N, Melton ME. Alendronic acid produces greater eff ects than risedronic acid on bone density and turnover in postmeno-pausal women with osteoporosis: results of FACTS- international. Clin Drug Invest 2006; 26: 63-74.

[6] Liberman UA, Weiss SR, Bröll J, Minne HW, Quan H, Bell NH, Rodriguez-Portales J, Downs RW Jr, Dequeker J, Favus M. Effect of oral alen-dronate on bone mineral density and the inci-dence of fractures in postmenopausal osteo-porosis. The alendronate phase III osteoporosis treatment study group. N Engl J Med 1995; 333: 1437-1443.

[7] Adami S, Felsenberg D, Christiansen C, Robin-son J, Lorenc RS, Mahoney P, Coutant K, Schimmer RC, Delmas PD. Efficacy and safety of ibandronate given by intravenous injection once every 3 months. Bone 2004; 34: 881-889.

[8] Reid IR, Brown JP, Burckhardt P, Horowitz Z, Richardson P, Trechsel U, Widmer A, Devoge-laer JP, Kaufman JM, Jaeger P, Body JJ, Brandi ML, Broell J, Di Micco R, Genazzani AR, Felsen-berg D, Happ J, Hooper MJ, Ittner J, Leb G, Mallmin H, Murray T, Ortolani S, Rubinacci A, Saaf M, Samsioe G, Verbruggen L, Meunier PJ. Intravenous zoledronic acid in postmenopaus-al women with low bone mineral density. N Engl J Med 2002; 346: 653-661.

[9] Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in post-menopausal women with osteoporosis. N Engl J Med 2001; 344: 1434–1441.

[10] Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, Delmas P, Zoog HB, Austin M, Wang A, Kutilek S, Adami S, Zanchet-ta J, Libanati C, Siddhanti S, Christiansen C; FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with os-teoporosis. N Engl J Med 2009; 361: 756-765.

[11] Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, Cosman F, Lakatos P, Leung PC, Man Z, Mautalen C, Mesenbrink P, Hu H, Caminis J, Tong K, Rosario-Jansen T, Krasnow J, Hue TF, Sellmeyer D, Eriksen EF, Cummings SR; HORIZON Pivotal Fracture Trial. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007; 356: 1809-1822.

[12] McClung MR, Lewiecki EM, Cohen SB, Bolog-nese MA, Woodson GC, Moffett AH, Peacock M, Miller PD, Lederman SN, Chesnut CH, Lain D, Kivitz AJ, Holloway DL, Zhang C, Peterson MC, Bekker PJ; AMG 162 Bone Loss Study Group. Denosumab in postmenopausal wom-en with low bonemineral density. N Engl J Med 2006; 354: 821-831.

[13] Lewiecki EM, Miller PD, McClung MR, Cohen SB, Bolognese MA, Liu Y, Wang A, Siddhanti S, Fitzpatrick LA; AMG 162 Bone Loss Study Group. Two-year treatment with denosumab (AMG 162) in a randomizedphase 2 study of postmenopausal women with low BMD. J Bone Miner Res 2007; 22: 1832-1841.

[14] Bone HG, Bolognese MA, Yuen CK, Kendler DL, Wang H, Liu Y, San Martin J. Effects of deno-sumab on bone mineral density and bone turn-over in post-menopausal women. J Clin Endo-crinol Metab 2008; 93: 2149-2157.

[15] Smith MR, Egerdie B, Hernández Toriz N, Feld-man R, Tammela TL, Saad F, Heracek J, Szwe-dowski M, Ke C, Kupic A, Leder BZ, Goessl C; Denosumab HALT Prostate Cancer Study Group.Denosumab in men receiving androgen-deprivation therapy for prostatecancer. N Engl J Med 2009; 36: 745-755.

[16] Brown JP, Prince RL, Deal C, Recker RR, Kiel DP, de Gregorio LH, Hadji P, Hofbauer LC, Alva-ro-Gracia JM, Wang H, Austin M, Wagman RB, Newmark R, Libanati C, San Martin J, Bone HG. Comparison of the effect of denosumab and alendronate on BMD andbiochemical markers of bone turnover in postmenopausal women withlow bone mass: a randomized, blinded, phase 3 trial. J Bone Miner Res 2009; 24: 153-161.

[17] Kendler DL, Roux C, Benhamou CL, Brown JP, Lillestol M, Siddhanti S, Man HS, San Martin J, Bone HG. Effects of denosumab on bone min-eral density and bone turnoverin postmeno-pausal women transitioning from alendronate therapy. J Bone Miner Res 2010; 25: 72-81.

[18] Bone HG, Bolognese MA, Yuen CK, Kendler DL, Miller PD, Yang YC, Grazette L, San Martin J, Gallagher JC. Effects of denosumab treatment and discontinuation on bone mineraldensity and bone turnover markers in postmenopaus-al women with lowbone mass. J Clin Endocrinol Metab 2011; 96: 972-980.

[19] Jamal SA, Ljunggren O, Stehman-Breen C, Cummings SR, McClung MR, Goemaere S, Eb-eling PR, Franek E, Yang YC, Egbuna OI, Boonen S, Miller PD. Effects of denosumab on fracture and bone min-eral density by level of kidney function. J Bone Miner Res 2011; 26: 1829-1835.

[20] Nakamura T, Matsumoto T, Sugimoto T, Shiraki M. Dose-responsestudy of denosumab on

bone mineral density and bone turnover markers in Japanese postmenopausal women with osteoporosis. Osteoporos Int 2012; 23: 1131-1140.

[21] Freemantle N, Satram-Hoang S, Tang ET, Kaur P, Macarios D, Siddhanti S, Borenstein J, Kendler DL; On behalf of the DAPS Investigators. Final results of the DAPS (Denosumab Adherence Prefer-ence Satisfaction) study: a 24-month, randomized, crossover comparisonwith alendronate in postmenopausal women. Osteoporos Int 2012; 23: 317-326.

[22] Nakamura T, Matsumoto T, Sugimoto T, Hosoi T, Miki T, Gorai I, Yoshikawa H, Tanaka Y, Tanaka S, Sone T, Nakano T, Ito M, Matsui S, Yoneda T, Takami H, Watanabe K, Osakabe T, Shiraki M, Fukunaga M. Fracture risk reduction with denosumab in Japanese postmenopausalwomen and men with osteoporosis: Denosumab fracture Intervention Ran-domized placebo Controlled Trial (DIRECT). J Clin Endocrinol Metab 2014; 99: 2599-2607.

[23] van den Bergh JP, van Geel TA, Geusens PP. Osteoporosis, frailty and fracture: implications for case finding and therapy. Nat Rev Rheumatol 2012; 8: 163-172.

[24] Seeman E, Delmas PD. Bone quality-the material and structural basis of bone strength and fragility. N Engl J Med 2006; 354: 2250-2261.

[25] Recker R, Lappe J, Davies KM, Heaney R. Bone remodeling increases substantially in the years after menopause and remains increased in older osteoporosis patients. J Bone Miner Res 2004; 19: 1628-1633.

[26] Grey A, Bolland M, Mihov B, Wong S, Horne A, Gamble G, Reid IR. Duration of antiresorptive effects of low-dose zoledronate in osteopenic postmenopausal women: a randomized, placebo-controlled trial. J Bone Miner Res 2014; 29: 166-172.

[27] Miller PD, Bolognese MA, Lewiecki EM, McClung MR, Ding B, Austin M, Liu Y, San Martin J; Amg Bone Loss Study Group. Amg Bone Loss Study Group. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. Bone 2008; 43: 222-229.

[28] Austin M, Yang YC, Vittinghoff E, Adami S, Boonen S, Bauer DC, Bianchi G, Bolognese MA, Christiansen C, Eastell R, Grauer A, Hawkins F, Kendler DL, Oliveri B, McClung MR, Reid IR, Siris ES, Zanchetta J, Zerbini CA, Libanati C, Cummings SR; FREEDOM Trial. Relationship between bone mineral density changes with denosumab treat-ment and risk reduction for vertebral and nonvertebral fractures. J Bone Miner Res 2012; 27: 687-693.

[29] Simon JA, Recknor C, Moffett AH Jr, Adachi JD, Franek E, Lewiecki EM, McClung MR, Mautalen CA, Ragi-Eis S, Nicholson GC, Muschitz C, Nuti R, Törring O, Wang A, Libanati C. Impact of denosumab on the peripheral skeleton of post-menopausalwomen with osteoporosis: bone density, mass, and strength of the radius,and wrist fracture. Menopause 2012; 20: 130-137.

[30] Huas D, Debiais F, Blotman F, Cortet B, Mercier F, Rousseaux C, Berger V, Gaudin AF, Cotté FE. Compliance and treatment satisfaction of post-menopausal women treatedfor osteoporosis. Compliance with osteoporosis treatment. BMC Woman Health 2010; 10: 1-8.