

# Efficacy of risedronate in improving bone mineral density in patients undergoing total hip arthroplasty

## A meta-analysis of randomized controlled trials

Jing Su, MD<sup>a</sup>, Yi Wei, MD<sup>a</sup>, Xiao Ming Li, MD<sup>b</sup>, Yan-Ping Diao, MD<sup>c</sup>, Huai-Gang Liu, MD<sup>d</sup>, Liang Zhang, MD<sup>e,\*</sup>

### Abstract

**Background:** Risedronate is widely used in the therapy of osteoporosis and other metabolic bone diseases. This meta-analysis was aimed to assess whether administration risedronate could increase the bone mineral density (BMD) in patients undergoing primary total hip arthroplasty (THA).

**Methods:** Electronic databases: PubMed, EMBASE, Web of Science, Cochrane Library, and Chinese Wanfang database were searched for all relevant studies. Inclusion criterion was that patients prepared for THA and use risedronate as intervention group and placebo as control group. BMD change in Gruen zone 1 and 7 were primary outcomes. Meta-analysis was performed using Stata 12.0 software.

**Results:** Six RCTs were finally included in this meta-analysis. Compared with control group, risedronate has a beneficial role in increasing BMD in Gruen 1, 2, 6, and 7 at 3 months ( $P < .05$ ). Oral risedronate has a beneficial role in preservation of BMD in all of the Gruen zones at 6 and 12 months ( $P < .05$ ). Moreover, oral risedronate could significantly increase the Harris hip scores and bone alkaline phosphatase than control group ( $P < .05$ ).

**Conclusion:** Oral risedronate has an effect on the preservation of periprosthetic BMD in proximal regions (Gruen zone 1, 2, 3, and 7) at 3 months and all of the regions at 6 and 12 months after THA.

**Abbreviations:** BAP = bone alkaline phosphatase, BMD = bone mineral density, CI = confidence interval, HR = hazard ratio, NTX-I = N-telopeptide of type I collagen, RCT = randomized controlled trials, THA = total hip arthroplasty, WMD = weighted mean difference.

**Keywords:** bone loss, meta-analysis, risedronate, total hip arthroplasty

## 1. Introduction

Total hip arthroplasty (THA) is currently 1 of the most reliable treatments to relieve the pain for the patients with end-stage osteoarthritis (OA) and rheumatoid arthritis (RA).<sup>[1]</sup> It was estimated that THAs are projected to grow by 137% between 2005 and 2030.<sup>[2]</sup> However, prosthesis loosening and periprosthetic fracture was the major concern for the administration of

THA.<sup>[3]</sup> After the implantation of the femoral component, the stress that would normally be borne by the bone alone is reduced, which leads to proximal femoral bone resorption.<sup>[4,5]</sup> If an ideal drug suppressing the bone resorption after THA was found, the service life of prosthesis would be much prolonged.<sup>[6,7]</sup>

Currently, bisphosphonates are antiresorptive agents which promote bone mineralization and inhibit the biological effect of osteoclasts.<sup>[8]</sup> Many randomized controlled trials (RCTs) have demonstrated that bisphosphonates have a beneficial role in preserving periprosthetic bone in THA patients.<sup>[9,10]</sup> Risedronate is a new generation of bisphosphonate drug and has a role of inhibiting the action of mevalonate metabolic pathway.<sup>[11,12]</sup> It could promote the apoptosis of the osteoclast and inhibit the osteoclast formation.<sup>[13]</sup>

Based on the potential positive effects, risedronate has been recommended to be used in THA as routine. Currently, the use of risedronate for preventing periprosthetic bone loss in THA was seldom published. Therefore, there is a lack of scientific evidence.

Thus, the purpose of this meta-analysis from RCTs was to evaluate whether oral risedronate could reduce the femoral periprosthetic BMD loss and increase the hip function in patients undergoing primary THA.

## 2. Methods

This meta-analysis was reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses

Editor: Danny Chu.

The authors declare that they have no competing interests.

Supplemental Digital Content is available for this article.

<sup>a</sup> Department of Hematology, <sup>b</sup> Department of Respiratory Medicine, <sup>c</sup> Department of Gastrointestinal Surgery, <sup>d</sup> Department of Anesthesiology, Shandong Province Jinan City Zhangqiu District People's Hospital, Jinan, Shandong, <sup>e</sup> Department of Sports Medicine, Hong Hui Hospital, Xi'an Jiaotong University College of Medicine, Xi'an, Shaanxi Province, China.

\* Correspondence: Liang Zhang, Department of Sports Medicine, Hong Hui Hospital, Xi'an Jiaotong University College of Medicine, No. 555 YouYi Road, Xi'an, Shaanxi Province 710054, China (e-mail: sciaoren2017@163.com).

Copyright © 2018 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Medicine (2018) 97:51(e13346)

Received: 4 November 2017 / Accepted: 30 October 2018

<http://dx.doi.org/10.1097/MD.0000000000013346>

guidelines. All analyses were based on previous published studies; thus no ethical approval and patient consent are required.

### 2.1. Search strategy

We searched PubMed, EMBASE, Web of Science, Cochrane Library, and Chinese Wanfang database from 1966 to October, 2018 to identify studies reporting the effects of risedronate on BMD after THA. Key words and corresponding Mesh items was listed in Supplement file 1 (<http://links.lww.com/MD/C647>). There were no language restrictions. Reference lists of all the selected RCTs were hand-searched for any additional studies. First author and corresponding authors were contacted when possible to obtain missing data or information.

### 2.2. Inclusion and exclusion criteria

Inclusion criteria were as follows:

- (1) Participants: The patients underwent unilateral THA.
- (2) Interventions: The study involved the comparison of oral risedronate to placebo group or no treatment at all.
- (3) Outcomes: Change in bone mineral density (BMD) in Gruen zones<sup>[14]</sup> Harris hip scores, serum bone alkaline phosphatase (BAP), and urinary N-telopeptide of type I collagen (NTX-I).
- (4) Study design: the trial was RCT.

Exclusion criteria were as follows:

- (1) Revision THA or bilateral THA.
- (2) Non-RCTs.
- (3) Compared with other medication.

### 2.3. Selection criteria

Two authors according to inclusion criteria independently scanned the title and abstracts of the potential articles. Meanwhile, authors excluded the studies that did not meet the inclusion criteria obviously. Any divergences were resolved by discussion with a senior reviewer.

### 2.4. Data extraction

Two authors independently extracted data and record in an Excel spreadsheet. We extracted the following data: patients general characteristic (first author name, age and sex of patients, dose of risedronate), outcomes, and follow-up duration.

### 2.5. Outcome measures and statistical analyses

The main outcomes were the change in BMD in Gruen zones and the Harris hip scores. Continuous outcomes (change in BMD in Gruen zones, Harris hip scores, serum BAP, and NTX-I) were expressed as the weighted mean difference (WMD) and 95% confidence interval (CI). Statistical significance was set at  $P < .05$  across the trials. Stata 12.0 (Stata Corp., College Station, TX) was used for meta-analysis. Statistical heterogeneity was tested using  $I^2$  statistic. The Mantel-Haenszel (M-H) method was used to combine the studies. If there were significant heterogeneity ( $P < .1$  and  $I^2 > 50\%$ ), a random-effect model was used; if not, a fixed-effect model was used. Publication bias was not tested because the number of included studies was less than 10.<sup>[15]</sup>

## 3. Results

### 3.1. Search results

The course of study selection is demonstrated in the Fig. 1. Initially, we identified 335 relevant studies, of which 33 were excluded because of duplicates. Then, 296 studies did not meet the eligibility criteria at the title and abstract level. Finally, 6 RCTs involving 259 patients (risedronate group 127, control group 132) were finally included in this meta-analysis.<sup>[9–11,16–18]</sup>

### 3.2. General characteristic and quality assessment

Table 1 outlined the general information of the included RCTs. All of the included studies were published between the year of 2005 and 2015. Four RCTs used 35 mg risedronate as intervention group, 1 RCT used 2.5 mg/d, and the rest study used 5 mg/d as intervention groups. Three studies were originated from Sweden, 1 from Bulgaria, 1 from China, and 1 from Japan. All of the included THAs used uncemented prosthesis.

### 3.3. Risk of bias summary and graph

Risk of bias summary and risk of bias graph can be seen in Figs. 2 and 3, respectively. We classify 1 study as low risk of bias, 3 studies as unclear risk of bias, and the rest 2 studies as high risk of bias. Kappa value between reviewers was 0.739.

### 3.4. Effects of risedronate for preservation of BMD in different Gruen zones at 3 months, 6 months, and 12 months in THA

Effects of risedronate for preservation of BMD in different Gruen zones in THA are listed in Table 2. Compared with control group, risedronate had a beneficial role in increasing BMD in Gruen zones 1, 2, 6, and 7 at 3 months ( $P < .05$ ). There was no significant difference between the risedronate and control groups in terms of the BMD in Gruen zones 3, 4, and 5 ( $P > .05$ ) at 3 months.

Oral risedronate had a beneficial role in preservation of BMD in all of the Gruen zones at 6 and 12 months ( $P < .05$ ; Table 2).

### 3.5. Harris hip scores at final follow-up

A total of 5 studies totaling 245 THAs (risedronate group 121, control group 245) reported Harris hip scores at final follow-up. Harris hip scores in risedronate group was significantly higher than that in control group (WMD=4.60, 95% CI 2.04–7.15,  $P = .000$ ,  $I^2 = 54.3\%$ ; Fig. 4).

### 3.6. Serum BAP

Five trials including 161 THAs compared risedronate with placebo on serum BAP. BAP in the risedronate group was significantly higher than that in the control group (WMD=5.57, 95% CI 2.69–8.44,  $P = .000$ ,  $I^2 = 64.0\%$ ; Fig. 5).

### 3.7. NTX-I

Three trials including 127 THAs compared risedronate with placebo on NTX-I. NTX-I in the risedronate group was significantly lower than that in the control group (WMD=−15.60, 95% CI −26.37 to −4.83,  $P = .005$ ,  $I^2 = 47.0\%$ , Fig. 6).

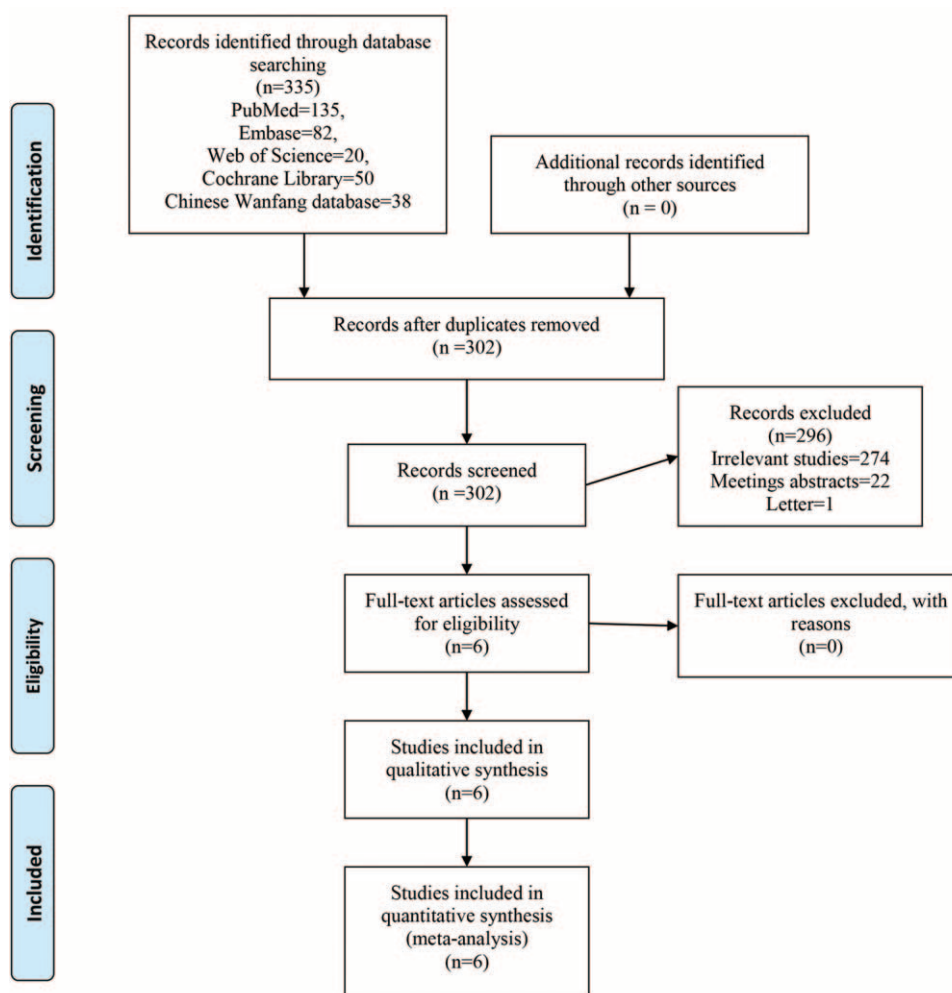


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart of retrieved studies.

## 4. Discussion

### 4.1. Main findings

Our meta-analysis comprehensively and systematically reviewed the current available literature and found that oral risedronate can significantly increase the BMD around uncemented femoral stem (Gruen zones 1, 2, 3, and 7) at 3 months; oral risedronate can significantly increase the BMD at all of the Gruen zones at 6 and 12 months; oral risedronate could increase the Harris hip scores in THA patients; and oral

risedronate significantly increases serum BAP and decreases NTX-I.

### 4.2. Comparison with other meta-analyses

Two relevant meta-analysis about this topic have been published.<sup>[19,20]</sup> Main finding of our meta-analysis between ours was not consistent. Another difference between ours and the previous ones should be noted. First, previous meta-analyses mixed different follow-ups for analyses and thus heterogeneity

**Table 1**  
The general characteristic of the included studies.

First author, y	Country	Type of THA	Participant (E/C)	Mean age (y, E/C)	Male/female (% E/C)	Intervention	Control	Follow-up	Study
Kinov, 2005 <sup>[10]</sup>	Bulgaria	Uncemented	12/12	NS	NS	35 mg risedronate	Placebo	6 mos	RCTs
Yamasaki, 2007 <sup>[17]</sup>	Japan	Uncemented	19/21	66.8/66.6	23.2/23.9	2.5 mg/d risedronate	Placebo	6 mos	RCTs
Sköldenberg, 2011 <sup>[10]</sup>	Sweden	Uncemented	36/37	61/60	55/55	35 mg risedronate	Placebo	12 mos	RCTs
Sköldenberg, 2011 <sup>[10]</sup>	Sweden	Uncemented	30/31	60/61	59/61	35 mg risedronate	Placebo	1 y	RCTs
Muren, 2015 <sup>[6]</sup>	Sweden	Uncemented	30/31	62/60	52/54	35 mg risedronate	Placebo	4 y	RCTs
Yin, 2013 <sup>[18]</sup>	China	Uncemented	13/13	59/62	49/48	5 mg/d risedronate	Placebo	6 mos	RCTs

C=control group, E=risedronate group, RCT=randomized controlled trials, THA=total hip arthroplasty.

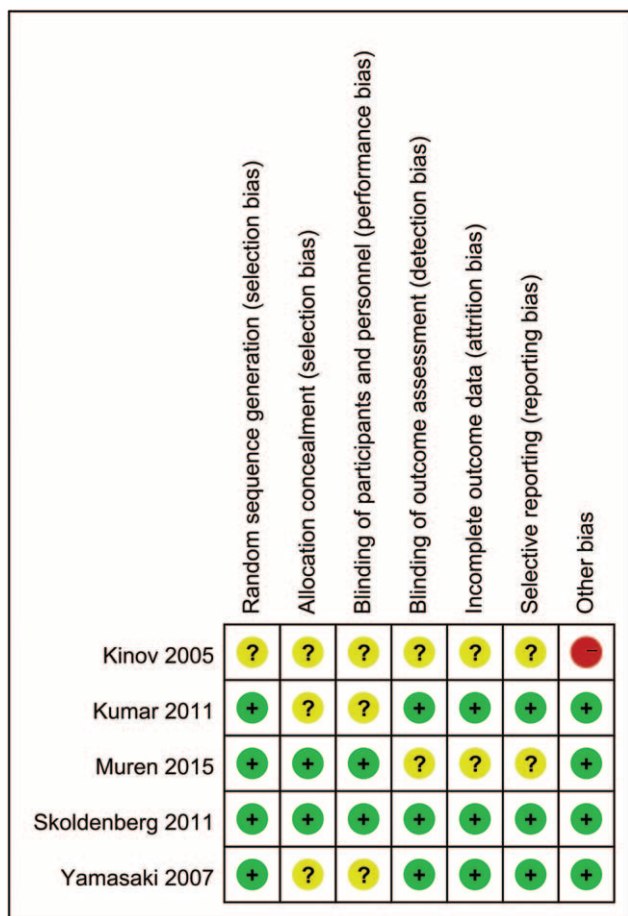


Figure 2. Risk of bias summary.

was large. Second, these previous meta-analyses included no more than 4 trials and 200 patients. In comparison, we included 6 RCTs and further enhanced earlier results of previous meta-analyses.

Firstly, we found that risedronate is more effective on the preservation of BMD in proximal regions (Gruen zones 1, 2, 3, and 7). Shi et al<sup>[21]</sup> included 25 RCTs about bisphosphonates for BMD after THA and total knee arthroplasty. Results showed that

Table 2

Comparison of the effects of risedronate in preservation of BMD in different Gruen zones in THA patients.

ROI	3 mos WMD (95% CI)	6 mos WMD (95% CI)	12 mos WMD (95% CI)
1	0.15 (0.11, 0.19) <i>P</i> < .05	0.06 (0.03, 0.09) <i>P</i> < .05	0.08 (0.06, 0.11) <i>P</i> < .05
2	0.07 (0.02, 0.13) <i>P</i> < .05	0.07 (0.04, 0.12) <i>P</i> < .05	0.09 (0.04, 0.12) <i>P</i> < .05
3	0.71 (−0.02, 0.13) <i>P</i> > .05	0.08 (0.04, 0.15) <i>P</i> < .05	0.11 (0.05, 0.16) <i>P</i> < .05
4	0.07 (0.00, 0.14) <i>P</i> > .05	0.06 (0.03, 0.13) <i>P</i> < .05	0.12 (0.07, 0.17) <i>P</i> < .05
5	0.06 (−0.03, 0.12) <i>P</i> > .05	0.04 (0.03, 0.13) <i>P</i> < .05	0.13 (0.08, 0.17) <i>P</i> < .05
6	0.07 (0.04, 0.11) <i>P</i> < .05	0.09 (0.06, 0.11) <i>P</i> < .05	0.15 (0.07, 0.18) <i>P</i> < .05
7	0.12 (0.05, 0.17) <i>P</i> < .05	0.10 (0.06, 0.12) <i>P</i> < .05	0.13 (0.08, 0.21) <i>P</i> < .05

C = control group, CI = confidence interval, E = risedronate group, RCT = randomized controlled trials, ROI = region of interest, THA = total hip arthroplasty, WMD = weighted mean difference.

bisphosphonates are more effective on the preservation of BMD in proximal regions. Their major conclusion was similar with our results. Another meta-analysis also found that bisphosphonates could increase BMD around prosthesis after THA.<sup>[22]</sup> Previous studies showed that aseptic loosening was associated with poor bone quality.<sup>[23,24]</sup> Risedronate belonged to the G3 bisphosphonates, which found to be up to 1000 times more potent with respect to antiresorptive activity than G1 or G2 bisphosphonates.<sup>[25]</sup> More important, G3 bisphosphonates had less effects on the bone formation than G1 or G2 bisphosphonates.<sup>[26]</sup>

Results showed that oral risedronate significantly increased the Harris hip scores at final follow-up. This is the first meta-analysis that compared the efficacy of risedronate for hip function. Yin et al<sup>[18]</sup> conducted a RCT and followed up these patients for at least 1 year. Results found that Harris hip scores in risedronate groups were higher than that in control group. Chen et al<sup>[27]</sup> assessed alendronate for clinical outcome and Harris hip scores at final follow-up. Results showed that alendronate has no benefit on the Harris hip scores.

A major strength of current meta-analysis was that we assessed the serum BAP and NTX-I level between risedronate and control groups. Oral risedronate could increase the level of serum BAP, which is a symbol of bone formation. Nagashima et al<sup>[28]</sup> found that G3 bisphosphonates had inhibitory effects on terminal differentiation of osteoblasts for bone remodeling, consequently leading to a delay in bone healing. Meanwhile, oral risedronate could reduce the level of NTX-I. Chailurkit et al<sup>[29]</sup> revealed that alendronate could lower the level of NTX-I in postmenopausal osteoporosis patients.

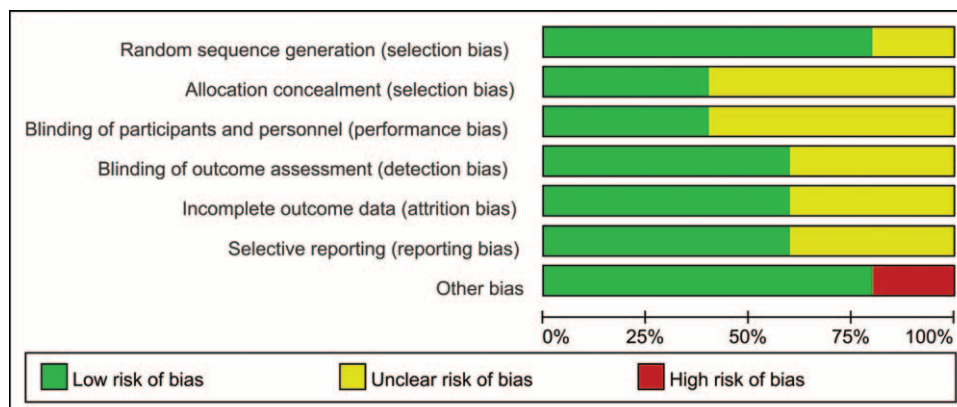


Figure 3. Risk of bias graph.

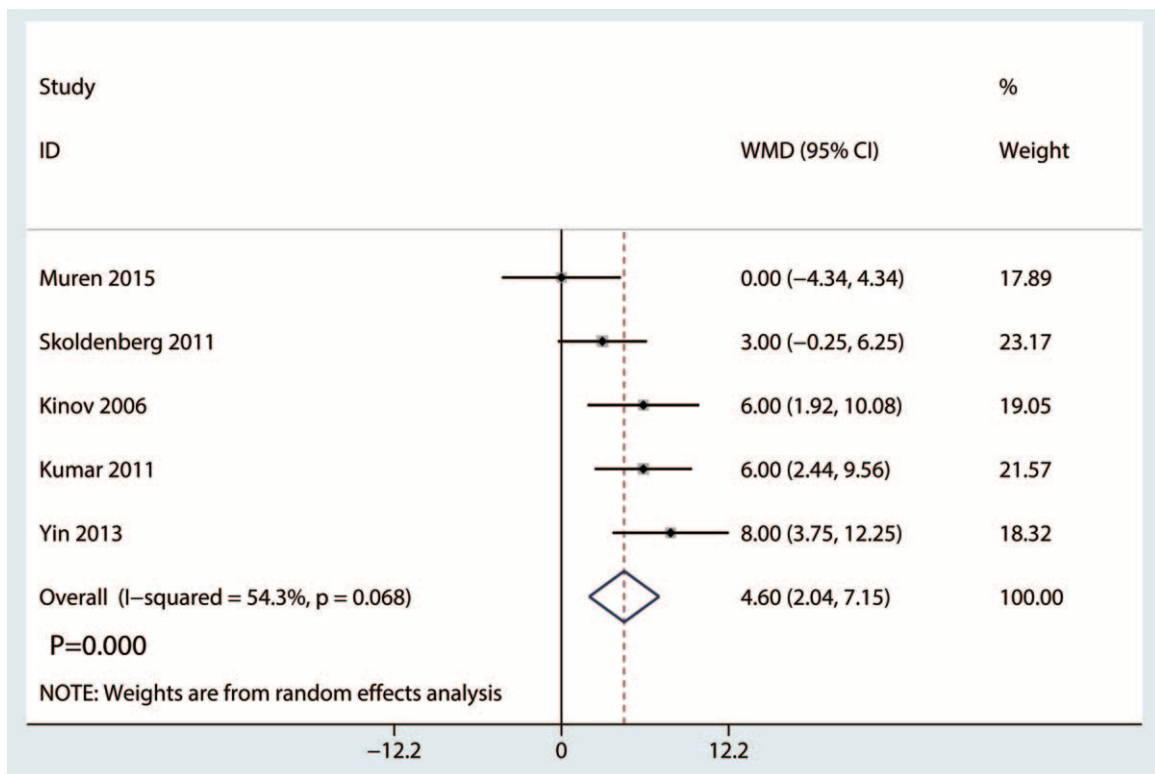


Figure 4. Forest plot comparing the Harris hip scores between the 2 groups.

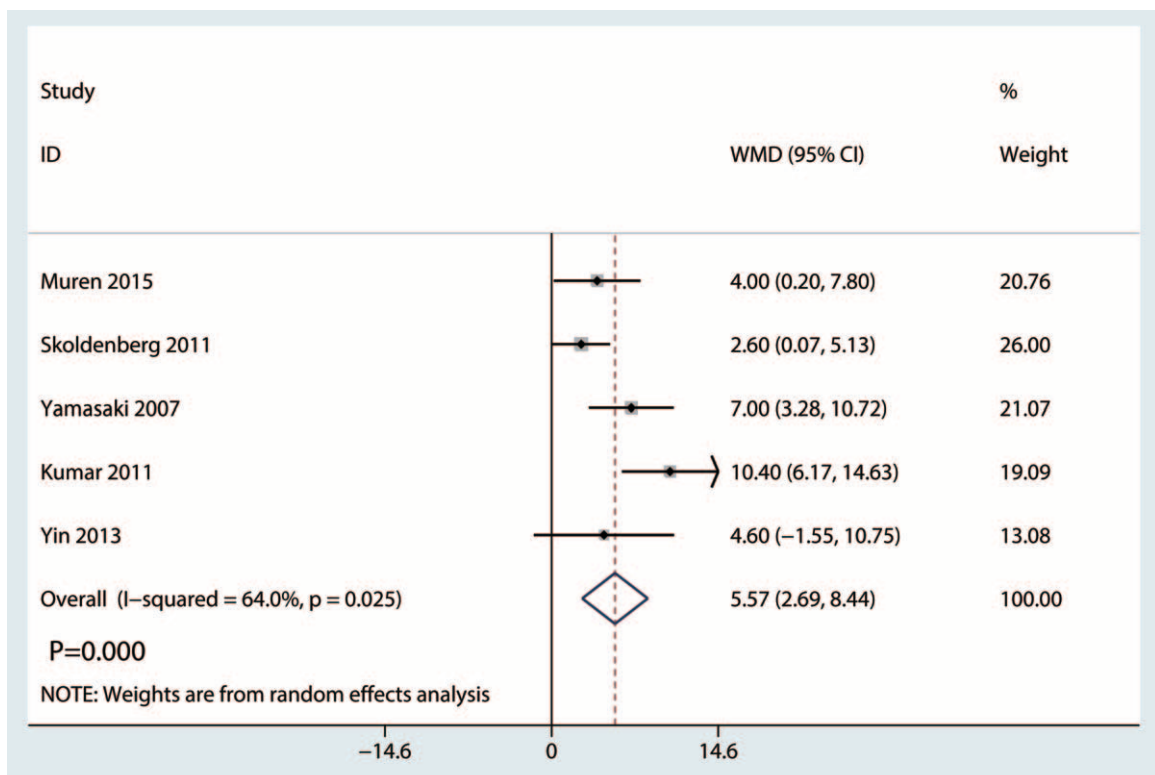
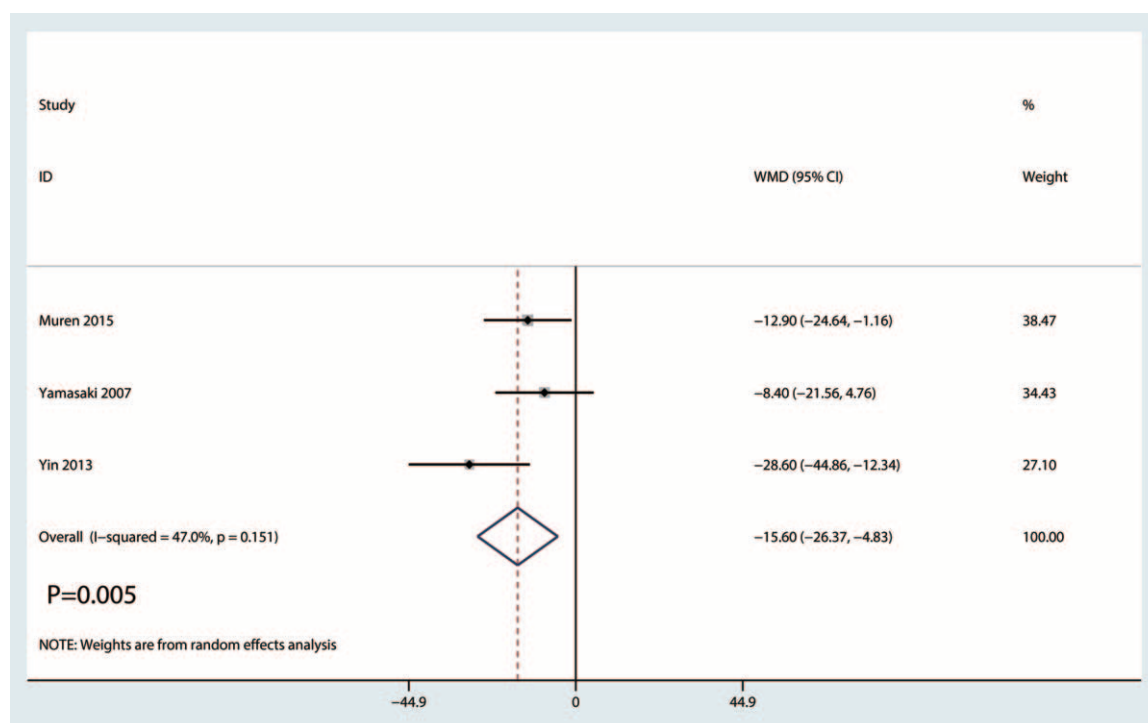


Figure 5. Forest plot comparing the Serum BAP between the 2 groups. BAP=bone alkaline phosphatase.



**Figure 6.** Forest plot comparing the serum NTX-I between risedronate group and control group. NTX-I=N-telopeptide of type I collagen.

The limitations of our study include the following:

- (1) The number of the included RCTs of risedronate for preventing bone loss after THA was limited. Most of RCTs focused on G1 or G2 bisphosphonates for preventing bone loss after THA. Future studies should be focused on the comparison between G1/G2 bisphosphonates versus G3 bisphosphonates for THA patients.
- (2) The follow-up of the included RCTs ranged from 6 months to 4 years, and more studies should be focused on long-term efficacy of risedronate for bone loss in THA patients.
- (3) Type of prosthesis was not unanimous in all of the included RCTs; more studies should be addressed subgroup analysis risedronate for different type of prosthesis of THA.
- (4) Dose of risedronate was different between the included studies, so more studies should be given available data about the optimal dose of risedronate for preventing bone loss after THA.

## 5. Conclusions

In conclusion, oral risedronate has an effect on the preservation of periprosthetic BMD in proximal regions (Gruen zones 1, 2, 3, and 7) at 3 months after THA. Meanwhile, oral risedronate has a beneficial role on the preservation of periprosthetic BMD in all of the regions at 6 and 12 months after THA. Due to the limited included studies and shortcoming of this meta-analysis, more high-quality RCTs were still needed to identify the efficacy of risedronate for bone loss in THA.

## Author contributions

**Data curation:** Jing Su.

**Methodology:** Yi Wei.

**Software:** Xiao Ming Li.

**Supervision:** Xiao Ming Li, Yan-Ping Diao, Huai-Gang Liu.

**Validation:** Yan-Ping Diao, Huai-Gang Liu.

**Visualization:** Liang Zhang.

**Writing – original draft:** Jing Su, Yi Wei.

**Writing – review & editing:** Liang Zhang.

## References

- [1] Zhao X, Hu D, Qin J, et al. Effect of bisphosphonates in preventing femoral periprosthetic bone resorption after primary cementless total hip arthroplasty: a meta-analysis. *J Orthop Surg Res* 2015;10:65.
- [2] Kurtz S, Ong K, Lau E, et al. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am* 2007;89:780–5.
- [3] Furnes O, Lie SA, Espehaug B, et al. Hip disease and the prognosis of total hip replacements. A review of 53,698 primary total hip replacements reported to the Norwegian Arthroplasty Register 1987–99. *J Bone Joint Surg Br* 2001;83:579–86.
- [4] Lin T, Yan SG, Cai XZ, et al. Bisphosphonates for periprosthetic bone loss after joint arthroplasty: a meta-analysis of 14 randomized controlled trials. *Osteoporos Int* 2012;23:1823–34.
- [5] Prieto-Alhambra D, Javaid MK, Judge A, et al. Association between bisphosphonate use and implant survival after primary total arthroplasty of the knee or hip: population based retrospective cohort study. *BMJ* 2011;343:d7222.
- [6] Canales Cortes V, Panisello Sebastiá JJ, Herrera Rodríguez A, et al. Ten-year follow-up of an anatomical hydroxyapatite-coated total hip prosthesis. *Int Orthop* 2006;30:84–90.
- [7] Gallo J, Landor I, Cechová I, et al. Comparison of hydroxyapatite-coated stems in total hip arthroplasty after a minimum 10-years follow-up. *Acta Chir Orthop Traumatol Cech* 2008;75:339–46.
- [8] Bhandari M, Bajammal S, Guyatt GH, et al. Effect of bisphosphonates on periprosthetic bone mineral density after total joint arthroplasty. A meta-analysis. *J Bone Joint Surg Am* 2005;87:293–301.
- [9] Kinov P, Tivchev P, Doukova P, et al. Effect of risedronate on bone metabolism after total hip arthroplasty: a prospective randomised study. *Acta Orthop Belg* 2006;72:44–50.
- [10] Sköldenberg OG, Salemyr MO, Bodén HS, et al. The effect of weekly risedronate on periprosthetic bone resorption following total hip

- arthroplasty. A randomized, double-blind, placebo-controlled trial. *J Bone Joint Surg Am* 2011;93:1857–64.
- [11] Sköldenberg OG, Salemyr MO, Bodén HS, et al. The effect of weekly risedronate on periprosthetic bone resorption following total hip arthroplasty: a randomized, double-blind, placebo-controlled trial. *J Bone Joint Surg Am* 2011;93:1857–64.
- [12] Malouf-Sierra J, Tarantino U, García-Hernández 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.
- [13] 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.
- [14] Gruen TA, McNeice GM, Amstutz HC. Modes of failure” of cemented stem-type femoral components: a radiographic analysis of loosening. *Clin Orthop Relat Res* 1979;141:17–27.
- [15] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
- [16] Muren O, Akbarian E, Salemyr M, et al. No effect of risedronate on femoral periprosthetic bone loss following total hip arthroplasty. A 4-year follow-up of 61 patients in a double-blind, randomized placebo-controlled trial. *Acta Orthop* 2015;86:569–74.
- [17] Yamasaki S, Masuhara K, Yamaguchi K, et al. Risedronate reduces postoperative bone resorption after cementless total hip arthroplasty. *Osteoporos Int* 2007;18:1009–15.
- [18] Yin P, Yao Y, Cui LH, et al. Effect of risedronate on early postoperative periprosthetic bone mineral density of the proximal femur after cementless total hip arthroplasty. *Chin J Osteoporosis* 2013;19:732–6.
- [19] Li Q, Xu B. Oral risedronate increases Gruen zone bone mineral density after primary total hip arthroplasty: a meta-analysis. *J Orthop Surg Res* 2018;13:144.
- [20] Ren L, Wang W. Effect of risedronate on femoral periprosthetic bone loss following total hip replacement: a systematic review and meta-analysis. *Medicine (Baltimore)* 2018;97:e0379.
- [21] Shi M, Chen L, Xin Z, et al. Bisphosphonates for the preservation of periprosthetic bone mineral density after total joint arthroplasty: a meta-analysis of 25 randomized controlled trials. *Osteoporos Int* 2018;29:1525–37.
- [22] Shi J, Liang G, Huang R, et al. Effects of bisphosphonates in preventing periprosthetic bone loss following total hip arthroplasty: a systematic review and meta-analysis. *J Orthop Surg Res* 2018;13:225.
- [23] Nixon M, Taylor G, Sheldon P, et al. Does bone quality predict loosening of cemented total hip replacements? *J Bone Joint Surg Br* 2007;89:1303–8.
- [24] Behairy YM, Harris WH. Mode of loosening of matt-finished femoral stems in primary total hip replacement. *Saudi Med J* 2002;23:1187–94.
- [25] Morris CD, Einhorn TA. Bisphosphonates in orthopaedic surgery. *J Bone Joint Surg Am* 2005;87:1609–18.
- [26] Eriksen EF, Diez-Perez A, Boonen S. Update on long-term treatment with bisphosphonates for postmenopausal osteoporosis: a systematic review. *Bone* 2014;58:126–35.
- [27] Chen CH, Chang JK, Lai KA, et al. Alendronate in the prevention of collapse of the femoral head in nontraumatic osteonecrosis: a two-year multicenter, prospective, randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2012;64:1572–8.
- [28] Nagashima M, Sakai A, Uchida S, et al. Bisphosphonate (YM529) delays the repair of cortical bone defect after drill-hole injury by reducing terminal differentiation of osteoblasts in the mouse femur. *Bone* 2005;36:502–11.
- [29] Chailurkit LO, Jongjaroenprasert W, Rungbunnapun S, et al. Effect of alendronate on bone mineral density and bone turnover in Thai postmenopausal osteoporosis. *J Bone Miner Metab* 2003;21:421–7.