

The effects of bisphosphonates on osteoporotic patients after lumbar fusion: a meta-analysis

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Purpose: We conducted a meta-analysis of controlled clinical trials to evaluate the efficacy of bisphosphonates in lumbar fusion.

Introduction: Bisphosphonates reduce bone resorption and remodeling by osteoclast activity inhibition, inactivation, and apoptosis. However, it remains controversial whether bisphosphonate therapy affects spinal fusion.

Methods: We searched MEDLINE, Cochrane CENTRAL, ScienceDirect, EMBASE, and Google Scholar to identify studies reporting the effects of bisphosphonates on osteoporotic patients after lumbar fusion. Secondary sources were identified from the references of the included literature. Pooled data were analyzed using RevMan 5.1.

Results: Seven studies met the inclusion criteria. There were significant differences in solid intervertebral fusion (RD=0.07, 95% CI: -0.00 to 0.15, $P=0.05$), subsequent VCFs (RD=-0.21, 95% CI: -0.30 to -0.12, $P<0.00001$), pedicle screw loosening (RD=-0.17, 95% CI: -0.28 to -0.05, $P=0.006$), and cage subsidence (RD=-0.25, 95% CI: -0.42 to -0.07, $P=0.005$) between two groups. No significant differences between two groups were found regarding implant fixation failure (RD=-0.06, 95% CI: -0.22 to 0.10, $P=0.48$).

Conclusion: This meta-analysis showed that bisphosphonates may increase solid intervertebral fusion and decrease subsequent VCFs, pedicle screw loosening, and cage subsidence.

Keywords: bisphosphonates, lumbar, fusion, meta-analysis

Introduction

Lumbar fusion surgery is a common treatment approach for patients suffering from lumbar instability, trauma, and deformity.¹ However, a previous study reported that these patients are more likely than other patients to have osteoporosis,² and an increased prevalence of bone mineral loss has been observed in patients who underwent lumbar fusion surgery.³ As osteoporosis can result in spinal fusion failure, implant fixation failure, and vertebral compression fractures (VCFs) around fusion sites,⁴ the application of anti-osteoporosis agents may improve outcomes in patients treated with spinal fusion and instrumentation.

Bisphosphonates, first-line anti-osteoporotic drugs that have been approved for bone loss prevention and increasing bone quality and density, act by inhibiting osteoclast-mediated bone resorption.⁵ However, extensive inhibition of bone resorption may lead to disruptions in the balance between osteoclastic and osteoblastic activities, with effects on bone graft healing.⁶ Previous animal studies have shown that bisphosphonates increase the size and density of fusion masses^{7,8} and enhance fusion rates⁹ and bone-screw interface fixation after pedicle screw placement in spinal fusion.¹⁰ Recently, several human clinical studies have reported treatment outcomes of bisphosphonates

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in lumbar fusion,^{11–16} though the results are contradictory. Moreover, methodological flaws in the published literature include poor study designs, small sample sizes, and variable outcomes. Therefore, we conducted a meta-analysis on the pooled results of randomized controlled trials (RCTs) and non-RCTs to evaluate the efficiency of bisphosphonates in lumbar fusion.

Methods

Search strategy

Electronic literature searches were performed in MEDLINE, Cochrane CENTRAL, ScienceDirect, EMBASE, and Google Scholar for articles published from 1966 to October 2017. Secondary sources were identified from studies cited in the references of retrieved articles. No studies were excluded based on language. The key search terms applied were “bisphosphonate”, “lumbar”, and “fusion” in combination with the Boolean operators AND or OR.

Selection criteria and quality assessment

The present meta-analysis included published RCTs and non-RCTs that compared a bisphosphonate with a control (placebo or null) in patients undergoing lumbar fusion. Two independent reviewers determined the suitability of the articles. A third reviewer resolved disagreements. Quality assessment for the RCTs was conducted according to a modification of the generic evaluation tool described in the Cochrane Handbook for Systematic Review of Interventions.¹⁷ The Methodological Index for Non-randomized Studies (MINORS) form was used to assess retrospective controlled trials.¹⁸

Data extraction

Data were extracted from the included studies by two independent researchers. In cases of incomplete data, the corresponding author of the study was contacted for additional information. The following information was extracted: the first author's name, publication year, interventions, outcome measures, sample size, and comparable baselines. Other relevant parameters were also extracted from the individual studies.

Data analysis and statistical methods

RevMan 5.1 (The Cochrane Collaboration, Oxford, UK) was used for analyzing pooled data. Heterogeneity was estimated by the *P*- and *I*²-values based on the standard chi-squared test. If significant heterogeneity was detected (*I*²>50%, *P*<0.1), a random-effects model was used for data analysis, whereas a fixed-effects model was used

when no significant heterogeneity was found (*I*²<50%, *P*>0.1). In cases of significant heterogeneity, subgroup analysis was performed to investigate the sources. Mean differences and 95% CI were determined for continuous outcomes. Dichotomous data were calculated by risk differences (RDs) and 95% CI.

Results

Search results

A total of 116 studies were identified as potentially relevant literature reports. By scanning the titles and abstracts, 109 reports were excluded according to the eligibility criteria. No additional studies were obtained after the reference review. Ultimately, three RCTs and four non-RCTs were eligible for data extraction and meta-analysis.^{11–16,19,20} The search process is shown in Figure 1.

Risk of bias assessment

RCT quality was assessed based on the Cochrane Handbook for Systematic Review of Interventions (Figure 2). RCTs stated the clear inclusion and exclusion criteria. Included RCTs employed an adequate method of randomization, concealment of allocation, blinding, and intent-to-treat analysis. No unclear bias due to incomplete outcome data or selective outcomes was reported. For non-RCTs, MINORS scores were 18–20 for retrospectively controlled trials. The methodological quality assessment process is illustrated in Table 1.

Study characteristics

Demographic characteristics and details concerning the types of literature of the included studies are summarized in Table 2. Statistically similar baseline characteristics were observed between the groups.

Outcomes of meta-analysis

Solid intervertebral fusion

Solid intervertebral fusion was involved in six studies.^{11,13–16,19} No significant heterogeneity was found, and a fixed-effects model was applied (*I*²=26%, *P*=0.24). Solid intervertebral fusion in the bisphosphonate group was significantly higher than that in the control group (RD=0.07, 95% CI: –0.00 to 0.15, *P*=0.05; Figure 3).

Subsequent VCFs

Subsequent VCFs were assessed in four studies.^{11,15,16,19} As no significant heterogeneity was found, a fixed-effects

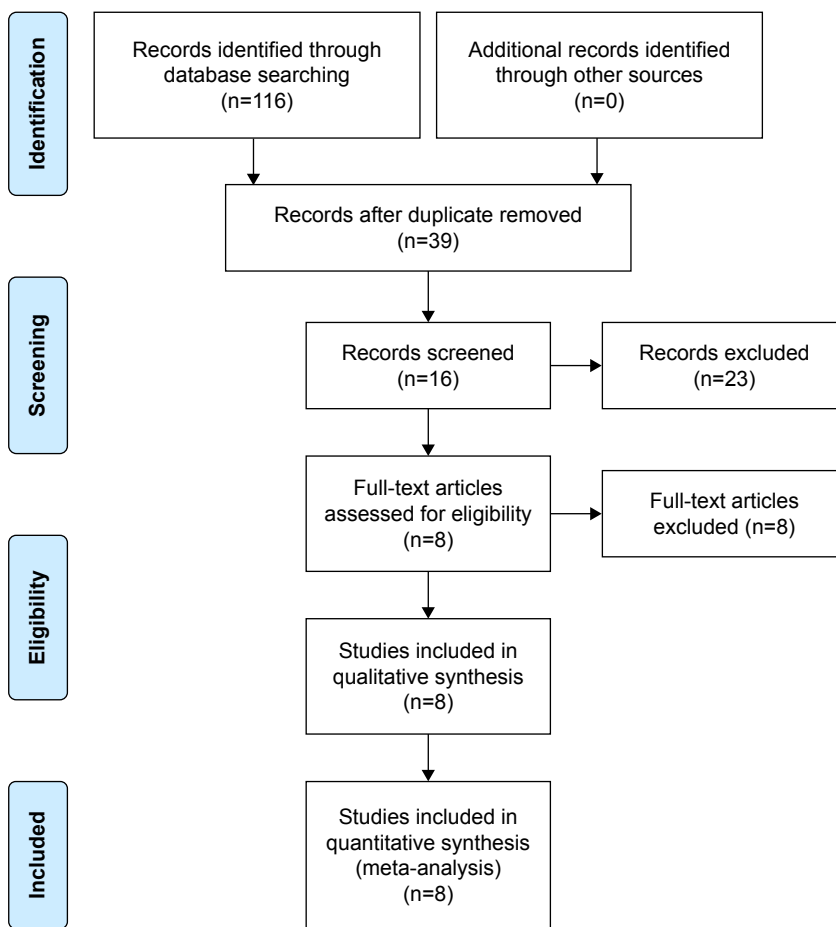


Figure 1 Flowchart of the study selection process.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chen et al, ¹¹ 2016	+	+	+	+	+	+	+
Li et al, ¹³ 2012	+	+	+	+	+	+	+
Nagahama et al, ¹⁴ 2011	+	+	+	+	+	+	+

Figure 2 Risk of bias summary. Note: green+ indicates low risk.

model was used ($I^2=0\%$, $P=0.51$). Subsequent VCFs in the bisphosphonate group were significantly lower than those in the control group (RD=-0.21, 95% CI: -0.30 to -0.12, $P<0.00001$; Figure 4).

Pedicle screw loosening

Data on pedicle screw loosening were available in three studies.^{16,19,20} A fixed-effects model was applied because no significant heterogeneity was found ($I^2=0\%$, $P=0.43$). Overall, the incidence of pedicle screw loosening in the bisphosphonate group was significantly lower than that in the control group (RD=-0.17, 95% CI: -0.28 to -0.05, $P=0.006$; Figure 5).

Implant fixation failure

Implant fixation failure was reported in two studies.^{11,15} No significant heterogeneity was found; thus, a fixed-effects model was utilized ($I^2=0\%$, $P=1.00$). There was no significant difference between the two groups regarding implant fixation failure (RD=0.00, 95% CI: -0.05 to 0.05, $P=1.00$; Figure 6).

Table 1 Quality assessment for non-randomized trials

Quality assessment for non-randomized trials	Ding et al, ¹⁹ 2017	Kim et al, ¹² 2014	Ohtori et al, ²⁰ 2013	Park et al, ¹⁵ 2013	Tu et al, ¹⁶ 2014
A clearly stated aim	2	2	2	2	2
Inclusion of consecutive patients	2	2	2	2	2
Prospective data collection	0	0	0	0	0
End points appropriate to the aim of the study	2	2	2	2	2
Unbiased assessment of the study end point	2	2	2	2	2
A follow-up period appropriate to the aims of study	2	2	2	2	2
Less than 5% loss to follow-up	0	2	2	0	2
Prospective calculation of the sample size	0	0	0	0	0
An adequate control group	2	2	2	2	2
Contemporary groups	2	2	2	2	2
Baseline equivalence of groups	2	1	2	2	2
Adequate statistical analyses	2	2	2	2	2
Total score	18	19	20	18	20

Cage subsidence

Two studies involved cage subsidence.^{14,16} Because no significant heterogeneity was found, a fixed-effects model was applied ($I^2=0\%$, $P=0.96$). The incidence of cage subsidence in the bisphosphonate group was significantly lower than that in the control group (RD=-0.25, 95% CI: -0.42 to -0.07, $P=0.005$; Figure 7).

Discussion

The most important finding of the present meta-analysis, including three RCTs and three non-RCTs, was that bisphosphonates promote lumbar intervertebral fusion and reduce subsequent VCFs, pedicle screw loosening, and cage

subsidence. To the best of our knowledge, our meta-analysis is the first quantitative study to evaluate the effects of bisphosphonates on human lumbar fusion.

Bisphosphonates reduce bone resorption and remodeling via inhibition of osteoclast activity, osteoclast inactivation, and osteoclast apoptosis.⁵ However, broad inhibition of bone resorption may reduce bone formation and lead to disruptions in the balance between osteoclastic and osteoblastic activities.⁶ Despite the controversy regarding whether bisphosphonate therapy affects spinal fusion, the present meta-analysis revealed that bisphosphonates improve the lumbar fusion rate (RD=0.03, $P=0.05$). This finding is consistent with those of three of the included studies.^{11,14,16} In a retrospective

Table 2 Characteristics of included studies

Study	Simple size (B/C)	Mean age (B/C)	Female (B/C)	Drug	Duration	Type of fusion	Assessment of fusion	Follow-up (months)
Chen et al, ¹¹ 2016	33/36	65/63	27/29	Zoledronic acid, 5 mg	One time infusion 3 days after surgery	PLIF	Rx, CT	12
Ding et al, ¹⁹ 2017	30/34	64/66	27/30	Zoledronic acid, 5 mg	One time infusion 3–5 days after surgery	TLIF	Rx, CT	24
Kim et al, ¹² 2014	44	64.7	35	Alendronate, 35 mg/week	NS	PLF	Rx	33.8
Li et al, ¹³ 2012	41/41	63/63	28/25	Zoledronic acid, 5 mg	One time infusion 3 days after surgery	TLIF	CT	12
Nagahama et al, ¹⁴ 2011	19/17	70/67	18/16	Alendronate, 35 mg/week	Started 1 week after surgery and continued for 12 months	PLIF	Rx, CT	12
Ohtori et al, ²⁰ 2013	20/22	75/77	20/22	Risedronate 2.5 mg/day	Started 2 months before and 10 months after surgery	Posterolateral lumbar fusion	Rx, CT	12
Park et al, ¹⁵ 2013	22/22	68/65	17/13	Zoledronic acid, 5 mg	Single dose	Posterolateral lumbar fusion	Rx, CT	6
Tu et al, ¹⁶ 2014	32/32	71/70	27/26	Zoledronic acid, 5 mg	3 days postoperative, then yearly	Lumbar interbody fusion	Rx	24

Abbreviations: B, bisphosphonate; C, control; CT, computed tomography; NS, not stated; PLF, posterior lumbar fusion; PLIF, posterior lumbar interbody fusion; Rx, X-ray; TLIF, transforaminal lumbar interbody fusion.

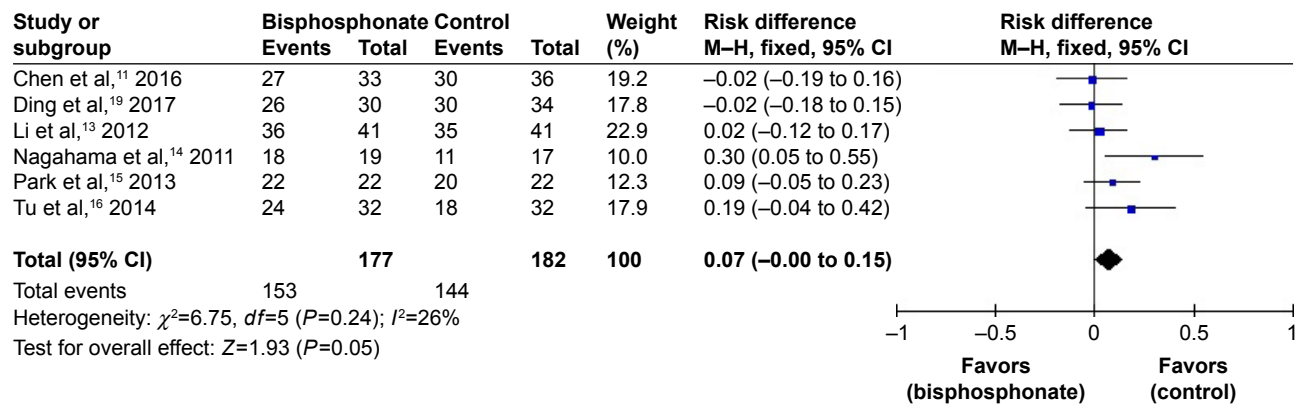


Figure 3 Forest plot of solid intervertebral fusion.

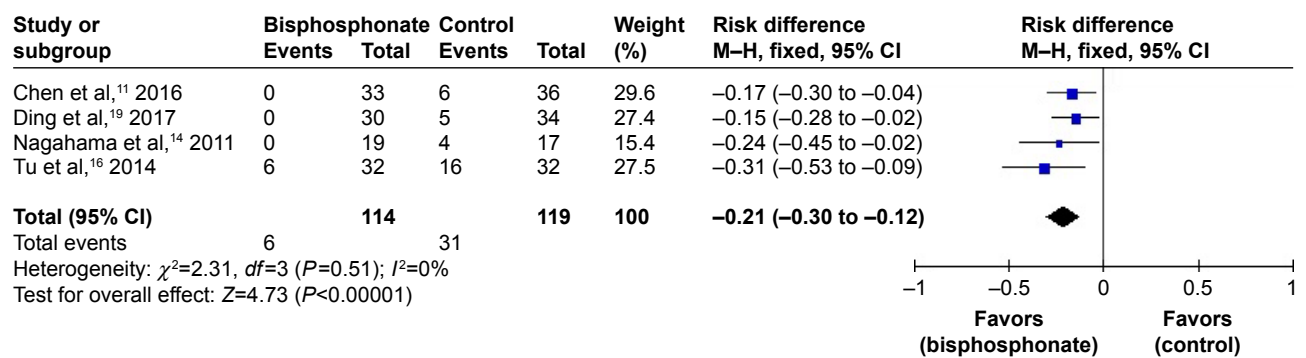


Figure 4 Forest plot of subsequent vertebral compression fractures.

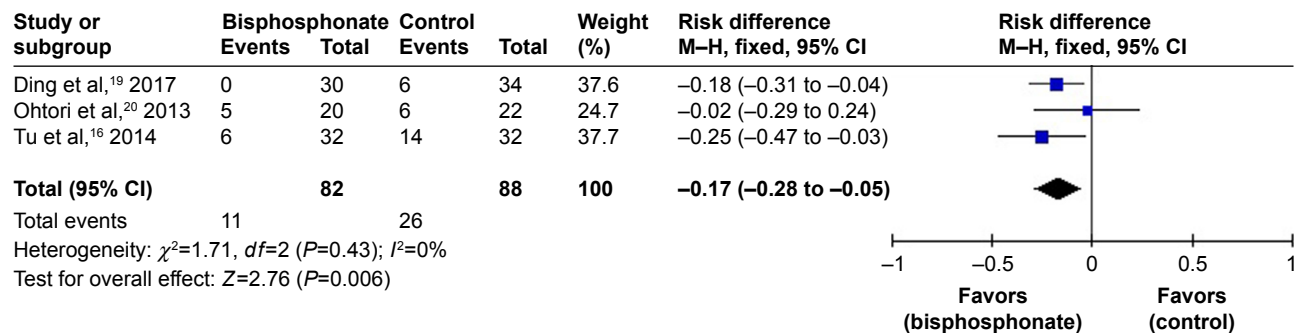


Figure 5 Forest plot of pedicle screw loosening.

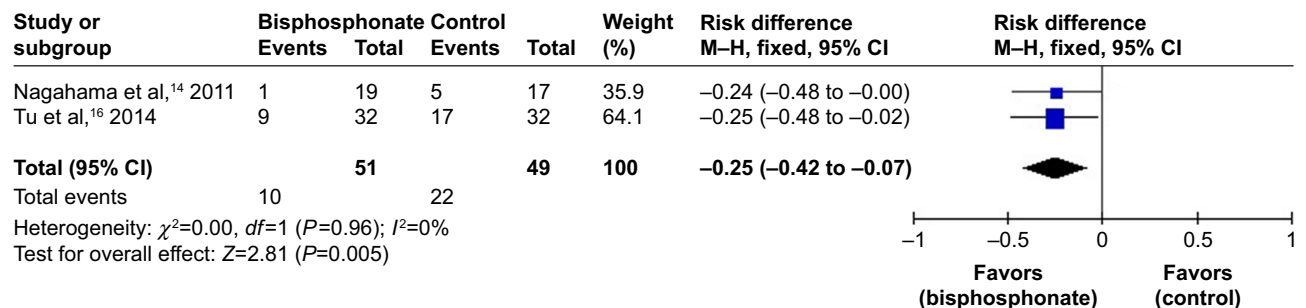


Figure 6 Forest plot of implant fixation failure.

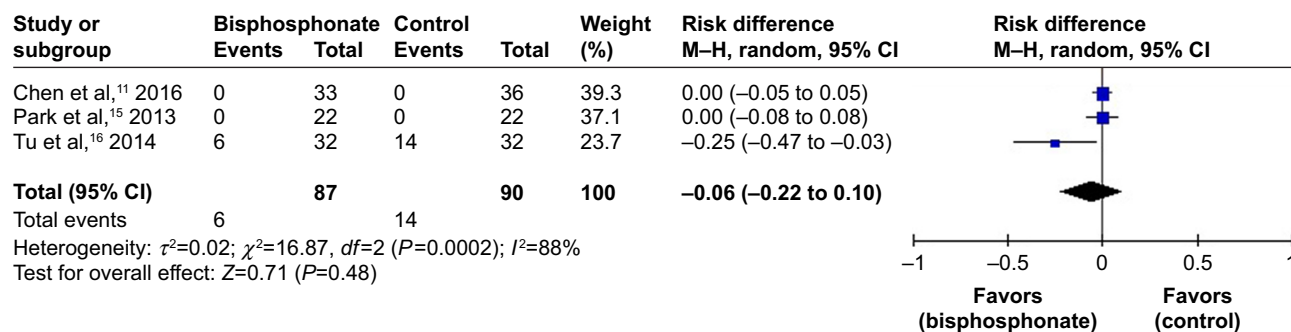


Figure 7 Forest plot of cage subsidence.

controlled study, Kim et al found that endplate degeneration decreases the fusion rate and that alendronate does not influence the fusion process.¹²

Three types of bisphosphonates were utilized among the included studies: zoledronic acid, alendronate, and risedronate in five, two, and one, respectively. Zoledronic acid was administered intravenously 5 mg once on the third to fifth days after surgery, and the other bisphosphonates were applied for 1 year after surgery. Previous studies have demonstrated that zoledronic acid has higher binding capacity for hydroxyapatite and stronger anti-bone resorption effects compared with other bisphosphonates.^{21,22} A recent meta-analysis also showed that zoledronic acid is highly effective at reducing fractures.²³ Regardless, there is no consensus on the timing of bisphosphonate application. Amanat et al found that in rat model, delayed single-dose infusion of zoledronic acid results in a larger and stronger callus than does immediate application at the time of the fracture.²⁴ Conversely, Colon-Emeric et al reported that zoledronic acid infusion has no clinically evident effect on fracture healing²⁵ and Einhorn concluded that fracture bone debris needs to be absorbed to allow space for new bone formation in compact bone.²⁶ In contrast, with a large enough environment for cancellous new bone formation, the bone remodeling suppressed by a reduction in resorption due to bisphosphonate is not an important element.²⁷

Failure of pedicle screw internal fixation is one of the crucial factors underlying nonunion after spinal fusion. Previous studies in animal models have found that bisphosphonates have an inhibitory effect on osteointegration around the implant.^{28,29} Xue et al used a porcine model to evaluate the influence of alendronate treatment on bone–pedicle screw interface fixation.¹⁰ These authors found that alendronate increased bone purchase of screw surfaces and can be an alternate approach for optimizing pedicle screw fixation. Previous clinical studies have also shown that bisphosphonates

can decrease pedicle screw loosening by inhibiting bone resorption on the surface of screws. Pooled results suggest a significant difference in the incidence of pedicle screw loosening between the two groups ($RD=-0.17$, $P=0.006$). Our results are consistent with these previous results.

Bisphosphonates have been found to significantly decrease the incidence of VCFs and to increase bone mineral density (BMD).³⁰ In osteoporotic patients, cortical bone becomes thin and porous; trabecular bone also becomes thin, with simultaneous reduction in the amount of bone. Both result in increased risk of microfracture. In addition, Li et al found that rigid fusion after posterior lumbar interbody fusion increases stress and leads to a greater risk of adjacent VCFs in osteoporotic patients.³¹ Pooled data demonstrated a significant difference in the incidence of subsequent VCFs ($RD=-0.24$, $P<0.001$): 7.1% in patients receiving a bisphosphonate and 30.6% in controls. Thus, bisphosphonates prevent subsequent VCFs in patients with lumbar fusion.

Moreover, cage subsidence, defined as >2 mm sinking of the cages, is a common complication of lumbar fusion surgery, and a higher rate of cage subsidence is more likely to be related to poor clinical outcomes.³² The present meta-analysis found that bisphosphonates decreased the incidence of cage subsidence ($RD=-0.25$, $P=0.005$). Several studies have shown that osteoporosis is a risk factor for cage subsidence.^{33,34} In addition, biomechanical studies have demonstrated that low BMD can weaken the endplate for load transfer and result in cage subsidence.^{35–37}

Some potential limitations were noted in the present meta-analysis: 1) only six studies were identified, and the sample size of each trial was relatively small; 2) a methodological weakness exists in non-RCTs and should be considered when interpreting the findings of the present meta-analysis; and 3) some of the data were incomplete, and we were unable to conduct a meta-analysis on outcomes, such as the volume of drainage and functional scores.

Conclusion

This meta-analysis of the current literature indicates that bisphosphonates can promote lumbar intervertebral fusion and reduce subsequent VCFs, pedicle screw loosening, and cage subsidence. Further high-quality studies are required to confirm our findings.

Author contributions

W-BL and F-JZ conducted the literature search and assessed the studies for exclusion or inclusion. W-BL and W-TZ extracted the data from the included studies, performed the meta-analysis, and drafted the manuscript. W-BL, PS, and F-JZ conceived the idea of the study, designed the study, and critically revised the manuscript for important intellectual content. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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