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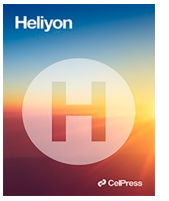

Research article

Efficacy and safety of zoledronic acid in the treatment of osteoporosis: A meta-analysis of randomized controlled trials

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ABSTRACT

Purpose: Zoledronic acid can inhibit the activity of osteoclasts, and thus, may slow or inhibit bone loss. The purpose of this study was to systematically evaluate the efficacy and safety of zoledronic acid in the treatment of osteoporosis.

Methods: Four databases, PubMed, Embase, Cochrane Library, and Web of Science, were systematically searched up to December 26, 2022. The primary outcomes included bone mineral density (BMD), carboxy-terminal cross-linked telopeptide of type 1 collagen (CTX), bone-specific alkaline phosphatase (BSAP), procollagen type 1 N-terminal prope-ptide (P1NP), adverse events, and fracture. Secondary outcomes included serum sclerostin level, Visual Analogue Scale (VAS) score, and Oswestry Disability Index (ODI).

Results: A total of 22 randomized controlled trials were included in this meta-analysis. Meta-analysis results showed that zoledronic acid was effective in increasing BMD of the lumbar spine,

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femoral neck, trochanter and serum sclerostin level; and reduced CTX, BSAP, P1NP, VAS score, and ODI in patients with osteoporosis. Regarding safety, zoledronic acid could reduce the incidence of fractures but had relatively more adverse events.
Conclusion: Zoledronic acid can significantly improve BMD of the lumbar spine, femoral neck and trochanter, and effectively reduce incidence of fracture in patients with osteoporosis, thereby significantly improving patients' quality of life. However, the incidence of adverse events was higher than that of patients treated with placebo.

1. Background

Osteoporosis is a prevalent skeletal disorder characterized by decreased bone mass and degraded bone tissue microarchitecture, leading to increased bone fragility and consequently to an increased risk of fracture [1]. In 2019, it was estimated that 32 million people over 50 years of age across Europe (EU, Switzerland, and UK) had osteoporosis, including approximately 25.5 million female patients and 6.5 million male patients [2]. Osteoporosis causes more than 8.9 million fractures per year, with an osteoporotic fracture every 3 s worldwide [3]. By 2050, the global incidence of hip fractures is expected to increase by 310 % in men and 240 % in women compared to 1990 [4]. Among older adults, osteoporosis-related fractures result in physical disability, reduced quality of life, and an increased risk of subsequent fractures, and are also associated with higher mortality rates and high healthcare costs [5–7]. Thus, osteoporosis is an important global public health problem that significantly impacts society and the economy.

For the treatment of osteoporosis, the common treatments are bisphosphonates (BPs), menopausal hormone replacement therapy, denosumab and anabolics [8]. BPs are synthetic compounds with common phosphorus-carbon-phosphorus bonds and have a high affinity for calcium hydroxyapatite of bone. Among them, nitrogen-containing BPs are highly effective in inhibiting bone resorption. They inhibit the farnesyl diphosphate synthase (FPPS) osteoclast enzyme, reducing its activity [9]. Although oral BPs are effective in the treatment of osteoporosis, compliance with the drug is very low in patients taking it orally, with more than half of patients not complying after 1 year [10]. Poor compliance reduces the efficacy of treatment and increases healthcare costs [11]. Zoledronic acid, a nitrogenous BP that can be administered intravenously, is administered at long intervals and has the potential to improve patient compliance with BPs therapy, thereby improving patient prognosis. Infusion of the intravenous formulation of zoledronic acid reduces bone turnover and improves bone mineral density (BMD) within at least 12 months [12]. However, the available evidence indicates that the safety and efficacy of zoledronic acid in the treatment of osteoporosis are inconsistent [13–15].

Therefore, we conducted a meta-analysis of published randomized controlled trials (RCTs) to investigate the efficacy and safety of zoledronic acid in the treatment of osteoporosis.

2. Materials and methods

The meta-analysis followed methodological guidelines according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement 2020 (**S1 File)** [16]. This systematic review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO; ref. no. CRD42023411779).

2.1. Literature search

A comprehensive search was conducted in PubMed, Embase, the Cochrane Library, and Web of Science using the keywords "zoledronic acid" and "osteoporosis" from the date of establishment to December 26, 2022. The search utilized a combination of subject and free-text terms in order to encompass all relevant studies. The search strategy is shown in **S2 File**.

2.2. Inclusion and exclusion criteria

The study inclusion criteria were as follows: (1) patients diagnosed with osteoporosis; (2) patients in the intervention group given zoledronic acid, while patients in the control group given placebo treatment; (3) outcome: BMD, carboxy-terminal cross-linked telopeptide of type 1 collagen (CTX), bone-specific alkaline phosphatase (BSAP), procollagen type 1 N-terminal prope-ptide (P1NP), serum sclerostin level, Visual Analogue Scale (VAS) score, Oswestry Disability Index (ODI), incidence of fracture and adverse events; (4) RCTs. The study exclusion criteria were as follows: (1) non-English studies; (2) interventions or populations that did not meet the criteria; (3) incomplete outcome data; (4) the full text was not available.

2.3. Literature screening

Two investigators (JS and WX) independently screened the retrieved literature to determine which relevant literature to include in the present study. Final eligibility for inclusion of the retrieved full-text articles was evaluated separately by the two investigators. Any disagreements were resolved through discussion with the third reviewer (MR). For study selection, the two investigators conducted an initial evaluation of RCTs. Additionally, the two investigators independently examined the abstracts of all articles that had undergone preliminary screening and evaluated them to determine their suitability for inclusion. Furthermore, the two investigators thoroughly

examined the complete texts of initially eligible articles to eliminate those that lacked complete data, populations, or interventions that did not meet the criteria set for the study.

2.4. Data extraction

Two investigators (JS and WX) independently extracted all relevant information related to the study characteristics. The resolution of disputes was entrusted to a third investigator (MR). In order to ascertain the integrity and dependability of the study results, two researchers employed a standardized form to obtain data from the included literature. The primary features of data extraction comprised first author, publication year, author country, sample size, gender, diagnosis, mean age, interventions, duration of follow-up, and outcomes.

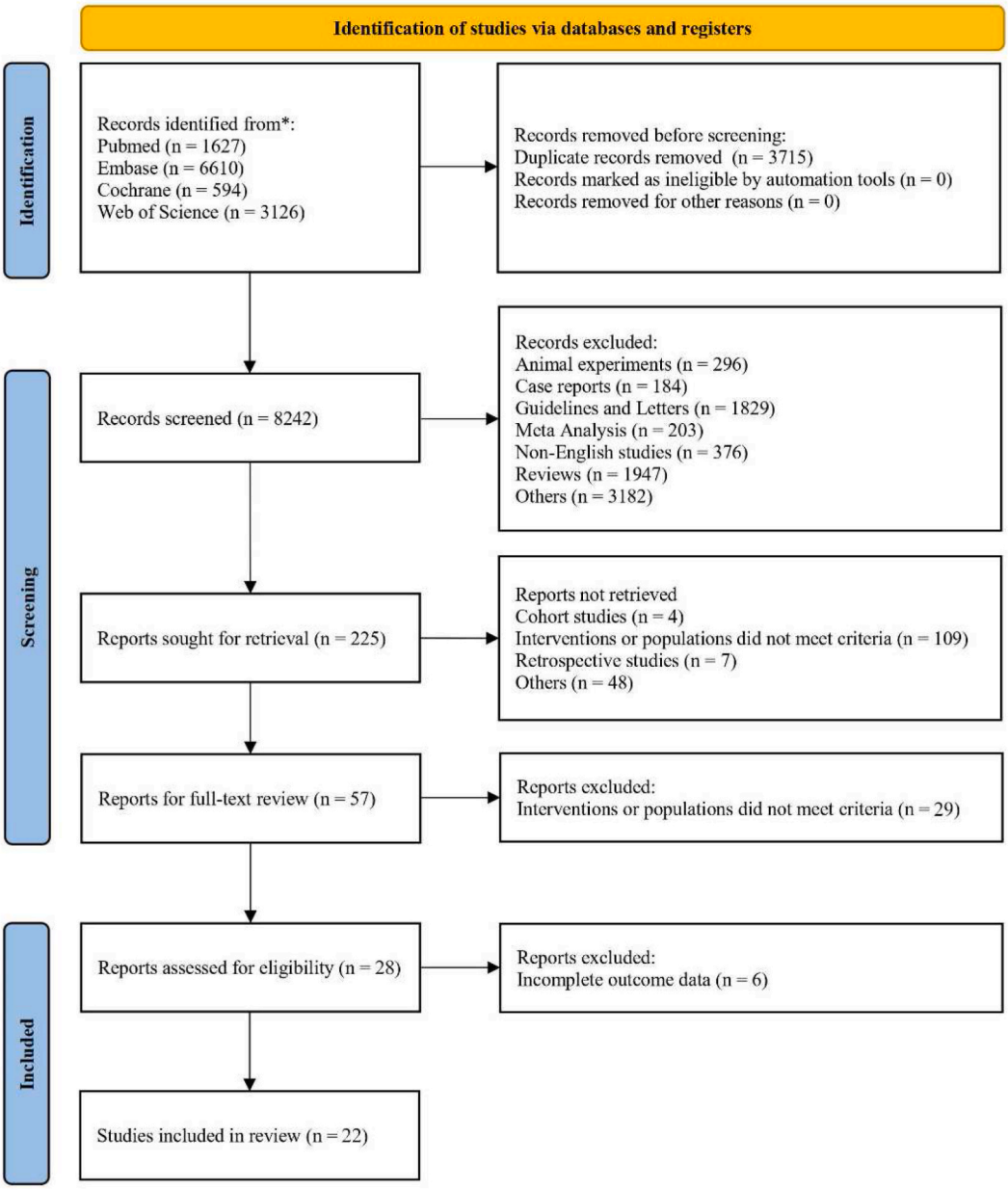

Fig. 1. PRISMA flow diagram for the quantitative analysis of zoledronic acid in the treatment of osteoporosis.

Table 1
General information about included studies.

Study	Year	Country	Sample size		Gender (M/F)	Mean age		Intervention		Outcome	Follow-up
			EG	CG		EG	CG	EG	CG		
Antonino Catalano [18]	2013	Italy	20	20	0/40	62.75	62.45	zoledronic acid 5 mg, intravenous infusion, once a year	placebo	Sclerostin, CTX, BSAP	12 m
Beifang Weng [34]	2022	China	30	30	–	–	–	zoledronic acid 5 mg, intravenous infusion, once a day	calcium Erqi D	P1NP, VAS, Fracture	3 m
Bin Liu [29]	2017	China	52	52	31/73	67.7	70.9	PKP + zoledronic acid, intravenous infusion, once a year	PKP	CTX, VAS, ODI	12 m
Bin Liu [28]	2019	China	21	22	21/22	67.0	66.2	zoledronic acid 5 mg, intravenous infusion, once a year	placebo	BMD, CTX, P1NP	12 m
Davide Gatti [22]	2014	Italy	18	20	0/38	68	69	zoledronic acid 5 mg, intravenous infusion, once a year	placebo	Sclerostin, CTX, P1NP	12 m
Dennis M. Black [19]	2007	USA	3875	3861	0/7718	73.0	73.1	zoledronic acid 5 mg, intravenous infusion, once a year	placebo	BSAP, Adverse events, Fracture	36 m
E M Ryhänen [32]	2021	Finland	27	27	7/47	69.0	67.9	zoledronic acid, intravenous infusion, once a year	placebo	BMD, Sclerostin, CTX, BSAP, P1NP	24 m
Fei Chen [21]	2015	China	33	36	13/56	65	63	zoledronic acid 5 mg, intravenous infusion, once a year	placebo	BMD, CTX, P1NP	12 m
Hua Bai [17]	2013	China	242	241	0/483	56.50	57.15	zoledronic acid 5 mg, intravenous infusion, once a year	placebo	BMD, Fracture	24 m
Jawl-Shan Hwang [25]	2010	Taiwan	163	160	0/323	72.5	73.3	zoledronic acid 5 mg, intravenous infusion, once a year	placebo	Adverse events, Fracture	36 m
Jiting Zhang [36]	2020	China	54	48	54/48	74.07	73.23	zoledronic acid 5 mg, intravenous infusion, once a year	placebo	CTX, VAS	12 m
Kan Liu [38]	2022	China	119	119	109/129	70.73	72.00	PKP + zoledronic acid 5 mg, intravenous infusion, once a year	PKP	BMD, CTX, P1NP, VAS, ODI	12 m
Ke Lu [30]	2021	China	78	76	30/124	68.69	70.80	zoledronic acid 5 mg, intravenous infusion, once a year	placebo	VAS, ODI, Fracture	36 m
Leanne M. Ward [33]	2021	Canada	18	16	23/11	13.0	12.3	zoledronic acid 0.05 mg/kg, intravenous infusion, twice a year	placebo	BMD, Adverse events	12 m
Li Kong [26]	2020	China	53	53	55/51	69.46	70.02	zoledronic acid 5 mg, intravenous infusion, once a day	–	BMD, VAS	6 m
Qingchang Hu [24]	2022	China	30	30	33/27	62.59	62.31	calcitriol + zoledronic acid 5 mg, intravenous infusion, once a year	calcitriol	BMD, P1NP, VAS, Fracture	12 m
Shiela M. Varghese [37]	2016	India	12	13	22/3	37.92	38.69	zoledronic acid 4 mg, intravenous infusion, once a year	placebo	BMD	12 m
Steven Boonen [20]	2012	Belgium	588	611	1199/0	66	66	zoledronic acid 5 mg, intravenous infusion, once a year	placebo	Fracture	24 m
Susan L. Greenspan [23]	2015	USA	89	92	0/181	85.4	85.5	zoledronic acid 5 mg, intravenous infusion	placebo	CTX, P1NP, Adverse events, Fracture	24 m
T. Nakamura [31]	2016	Japan	330	331	40/621	74.0	74.3	zoledronic acid 5 mg, intravenous infusion, once a year	placebo	CTX, BSAP, Fracture	24 m
Yi Yang [35]	2015	China	50	50	0/100	61.4	59.7	zoledronic acid 5 mg, intravenous infusion, once a year	placebo	BMD, CTX, BSAP	12 m
Yong Li [27]	2016	China	30	30	24/36	74.99	73.96	zoledronic acid 5 mg, intravenous infusion, once a year	–	BMD, VAS	12 m

EG, experimental group; CG, control group; TPTD, Teriparatide; PKP, percutaneous kyphoplasty; CTX, carboxy-terminal cross-linked telopeptide of type 1 collagen; BSAP, bone-specific alkaline phosphatase; P1NP, procollagen type 1 N-terminal prope-ptide; VAS, Visual Analogue Scale; ODI, Oswestry disability index; BMD, bone mineral density.

2.5. Quality evaluation

The quality of the literature was assessed using the Cochrane Risk of Bias Tool. Two investigators completed the process independently. Any disagreements were resolved through consultation with a third investigator. Quality assessment includes seven aspects: generation of random sequences, allocation concealment, blinding of patients and trial investigators, blinding of outcome assessors, incomplete outcome data, selective reporting, and other bias. The studies were evaluated and classified as "low risk", "high risk", or "unclear risk" according to the aforementioned criteria. Review Manager (version 5.4.1) was utilized to evaluate the quality and potential bias of the studies included in the analysis, which helped to visually represent the risk of bias in the included studies.

2.6. Statistical analysis

Data were analyzed using Stata 15.1 software. We performed this meta-analysis with Mantel-Haenszel statistical analysis to assess the efficacy and safety of zoledronic acid as a therapeutic intervention for osteoporosis. Odds ratio (OR) was used to express dichotomous outcomes, while standardized mean difference (SMD) was used to express continuous outcomes. The I^2 statistic was used to estimate the heterogeneity between the statistics. A fixed effects model was used for $I^2<50$ % to determine a difference between trial and control groups. For $I^2\geq50$ %, a random effects model was used, with $P < 0.05$ indicating a statistically significant difference. Upon detecting substantial heterogeneity, a sensitivity analysis by excluding a trial at one time would be conducted to identify the specific trials that potentially introduced bias into the results. Publication bias was assessed using the Egger test.

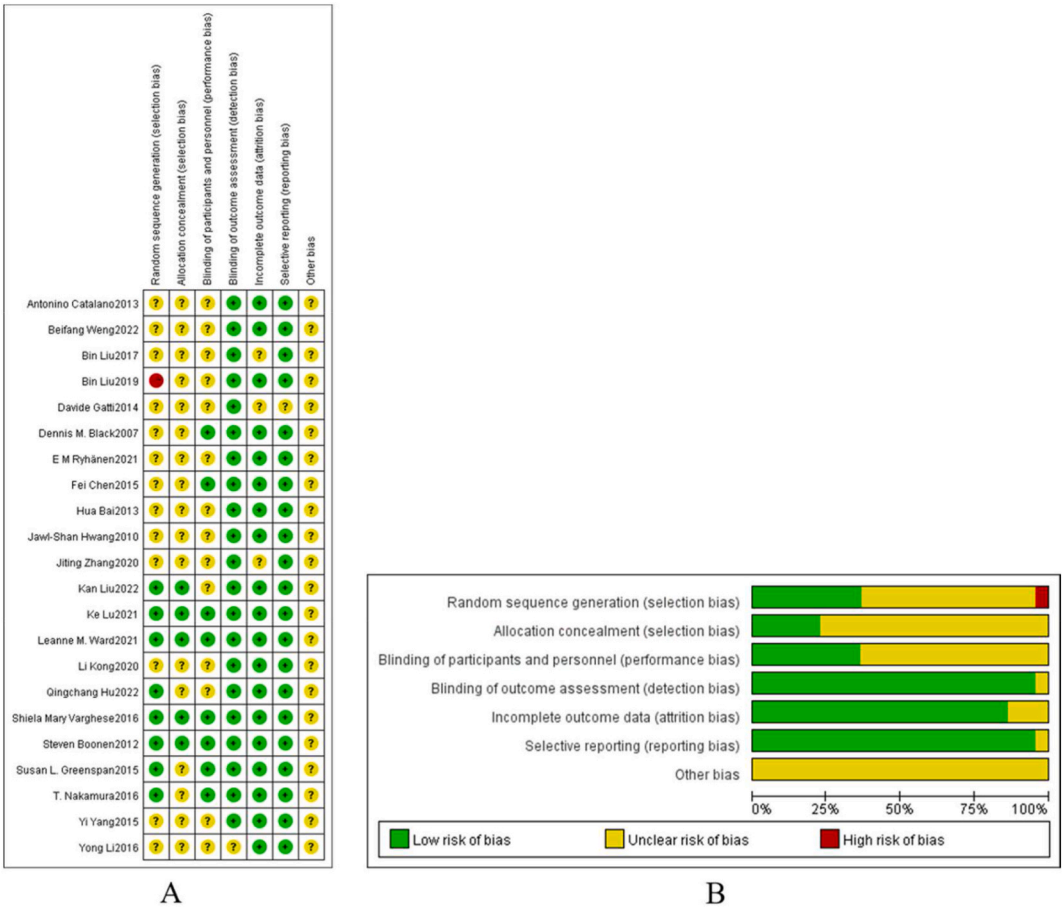

Fig. 2. The quality assessment of the included studies. A. Risk of bias summary: Independent reviewers' judgments about each risk of bias item for each included study. B. Risk of bias: Independent reviewers' judgments about each risk of bias item are presented as percentages across all included studies.

3. Results

3.1. Literature search

A comprehensive and systematic search of the literature on zoledronic acid for the treatment of osteoporosis was conducted in the following databases: PubMed (n = 1627), Embase (n = 6610), Cochrane (n = 594), and Web of Science (n = 3126). A total of 11,957 literature records were retrieved. Retrieved studies were screened in strict accordance with inclusion and exclusion criteria to ensure that the findings were based on the best available evidence. After the preliminary screening, 57 studies were selected for further evaluation by full-text review, where 29 studies were excluded for reasons such as ineligible study population or study design. Data extraction was performed for the remaining 28 studies, and 6 studies were subsequently excluded due to incomplete outcome data. Ultimately, 22 studies were considered eligible for the quantitative analysis. The literature screening process is shown in Fig. 1.

3.2. General characteristics of the included studies

The general information of the included studies is shown in Table 1. The 22 studies [17–38] had a total of 11,852 participants. The sample size of the studies ranged from 23 to 7718. The duration of follow-up ranged from 3 to 36 months. The studies were conducted in different countries, including China (13 studies), USA (2 studies), Italy (2 studies), India (1 study), Japan (1 study), Belgium (1 study), Canada (1 study), and Finland (1 study).

3.3. Risk of bias evaluation

The Cochrane Risk of Bias Tool was applied to assess the quality of the included studies, and the results are shown in Fig. 2. Fig. 2A summarizes the investigators' assessment of the individual risk of bias for all studies. Some of the included studies did not provide clear reporting of relevant information in their method section and were therefore assessed as having an unclear risk of bias in random sequence generation, allocation concealment, and blinding of patients and trial investigators. Only 1 of the 22 studies was assessed as high risk in random sequence generation. Most of the included studies exhibited excellent study design and fully reported outcome data with low risk of detection bias, attrition bias and reporting bias. In addition, the risk of other bias in all included studies was unclear. As shown in Fig. 2B, each risk of bias of the included studies was expressed as percentages. Moreover, the results of sensitivity analyses revealed no sign of any particular study accounting for a large proportion of heterogeneity (**S3 File**).

The one study eliminated method was used for sensitivity analysis to evaluate summary estimates and identify studies that contributed significantly to heterogeneity.

3.4. Meta-analysis results

3.4.1. Effect of zoledronic acid on BMD

Seven studies [17,26–28,32,33,35] reported data on BMD of lumbar spine. There was statistically significant heterogeneity among the studies (I^2 = 64.1 %, P = 0.010). The meta-analysis using a random effects model showed that zoledronic acid contributed to a significant increase in lumbar spine BMD in patients compared to placebo, with a statistically significant difference [SMD = 0.53, 95 % CI (0.26, 0.81), P = 0] (Fig. 3A).

Ten studies [17,21,24,26–28,32,35,37,38] reported data on femoral neck BMD. Since there was statistical heterogeneity among them (I^2 = 97.6 %, P = 0), a random effects model was used for data analysis. The meta-analysis showed that zoledronic acid was

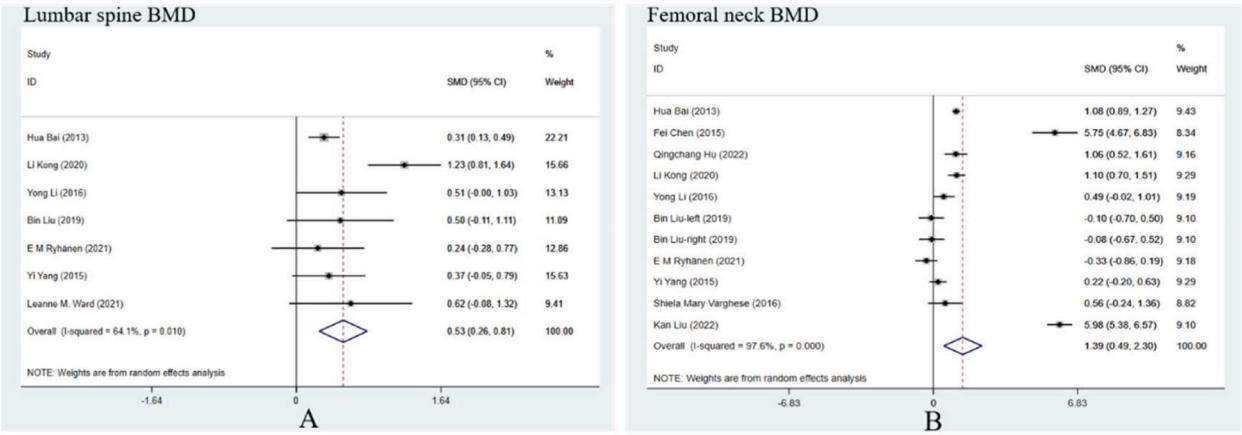

Fig. 3. Forest plot showing the effect of zoledronic acid on the lumbar spine BMD and femoral neck BMD. A. lumbar spine BMD. B. femoral neck BMD.

associated with a significant increase in femoral neck BMD in patients compared to placebo, with a statistically significant difference [SMD = 1.39, 95 % CI (0.49, 2.30) P = 0.003] (Fig. 3B).

Three studies [17,24,27] reported data on trochanter BMD. Since there was statistical heterogeneity among them (I^2 = 87.3 %, P = 0), the random effects model was used. The meta-analysis showed that zoledronic acid was correlated with a significant increase in trochanter BMD compared to placebo, with a statistically significant difference [SMD = 0.93, 95 % CI (0.26, 1.59), P = 0.006] (Fig. 4A).

Four studies [17,32,35,37] reported data on BMD of the total hip joint. Since there was statistical heterogeneity among them (I^2 = 82.7 %, P = 0.001), a random effects model was employed. The meta-analysis showed no statistically significant difference in the BMD of the total hip joint [SMD = 0.42, 95 % CI (−0.09, 0.93), P = 0.105] (Fig. 4B).

3.4.2. Effect of zoledronic acid on serum sclerostin level

Three studies [18,22,32] reported data on serum sclerostin. Since there was no statistical heterogeneity among them (I^2 = 0 %, P = 0.676), a fixed effects model was adopted. The meta-analysis showed that zoledronic acid was associated with a significant increase in serum sclerostin compared to placebo, with a statistically significant difference [SMD = 0.35, 95 % CI (0.01, 0.70), P = 0.046] **(S4 File)**.

3.4.3. Effect of zoledronic acid on CTX, BSAP, and P1NP

Twelve studies [18,21–24,28,29,31,32,35,36,38] reported data on CTX. Since there was statistical heterogeneity among them (I^2 = 96.6 %, P = 0), a random effects model was employed. The meta-analysis showed that zoledronic acid administration contributed to a significant reduction in CTX compared to placebo, with a statistically significant difference [SMD = −2.24, 95 % CI (−2.94, −1.54), P = 0] **(S5 File)**. Due to the high heterogeneity among the studies (I^2 > 50 %), a sensitivity analysis was performed to explore potential sources of heterogeneity.

Five studies [18,19,31,32,35] reported data on BSAP. Since there was statistical heterogeneity among them (I^2 = 91.0 %, P = 0), a random effects model was used for data analysis. The meta-analysis showed that zoledronic acid was correlated with a significant reduction in BSAP compared to placebo, and the difference was statistically significant [SMD = −0.75, 95 % CI (−1.24, −0.27), P = 0.002] **(S6 File)**.

Eight studies [21–24,28,32,34,38] reported data on P1NP. Since there was statistical heterogeneity among them (I^2 = 93.1 %, P = 0), a random effects model was used. The meta-analysis showed that zoledronic acid was associated with a significant reduction in P1NP compared to placebo, with a statistically significant difference [SMD = −2.60, 95 % CI (−3.37, −1.82), P = 0] **(S7 File)**.

3.4.4. Effect of zoledronic acid on VAS score

Eight studies [24,26,27,29,30,34,36,38] reported data on VAS. Since there was statistical heterogeneity among them (I^2 = 96.4 %, P = 0), a random effects model was used. The meta-analysis showed that zoledronic acid correlated with a significant reduction in VAS score compared to placebo, with a statistically significant difference [SMD = −2.21, 95 % CI (−3.05, −1.36), P = 0] **(S8 File)**.

3.4.5. Effect of zoledronic acid on ODI

Three studies [29,30,38] reported data on ODI. Due to statistical heterogeneity among them (I^2 = 79.3 %, P = 0.008), a random effects model was adopted. The meta-analysis showed that zoledronic acid had a correlation with a significant reduction in ODI compared to placebo, and there was a statistically significant difference [SMD = −0.83, 95 % CI (−1.25, −0.41), P = 0] **(S9 File)**.

3.4.6. Effect of zoledronic acid on adverse events

Five studies [19,23,25,31,33] reported data on adverse events. Most of the adverse events were pyrexia, myalgia, influenza-like symptoms, headache and arthralgia. Serious adverse events include osteonecrosis of the jaw, atypical femoral fractures, atrial

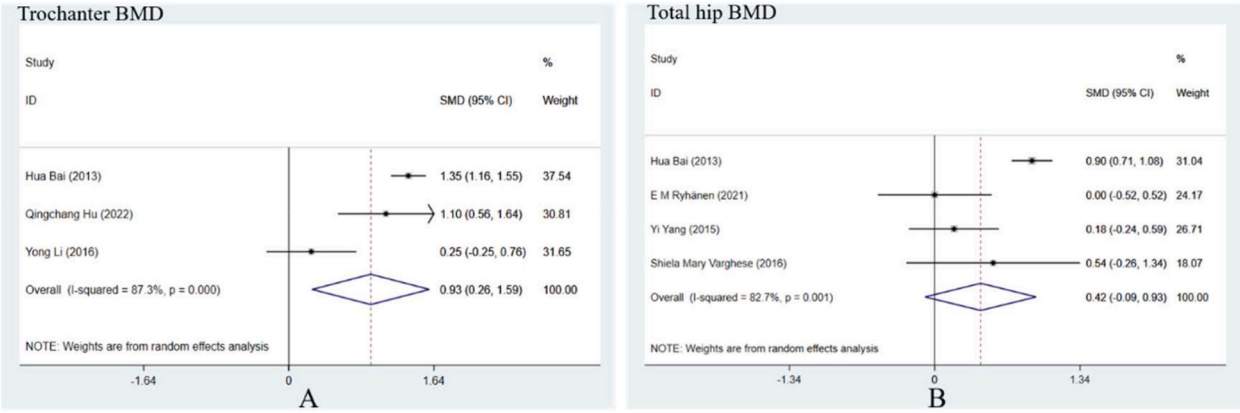

Fig. 4. Forest plot showing the effect of zoledronic acid on the trochanter BMD and total hip BMD. A. trochanter BMD. B. total hip BMD.

fibrillation, renal impairment, and hypocalcemia. With no statistical heterogeneity among them (I^2 = 0 %, P = 0.944), a fixed effects model was employed. The meta-analysis showed that the incidence of adverse events was higher in patients treated with zoledronic acid than in those treated with placebo, and the difference was statistically significant [RR = 1.02, 95 % CI (1.01, 1.03), P = 0] (Fig. 5A). However, the incidence of serious adverse events showed no statistically significant difference between the two groups [RR = 1.00, 95 % CI (0.81, 1.25), P = 0.965] (Fig. 5B).

3.4.7. *Effect of zoledronic acid on fractures*

Nine studies [17,19,20,23–25,30,31,34] reported data on fractures. Since there was no statistical heterogeneity among them (I^2 = 37.7 %, P = 0.118), a fixed effects model was adopted. The meta-analysis showed that the incidence of fractures was significantly lower in patients treated with zoledronic acid than in those treated with placebo, and there was a statistically significant difference [RR = 0.35, 95 % CI (0.30, 0.41), P = 0] (**S10 File**).

3.5. *Evaluation of publication bias*

We applied the Egger test to assess publication bias. The results showed no publication bias for the trials in the study group with respect to lumbar spine BMD (Egger test, p = 0.339), femoral neck BMD (Egger test, p = 0.603), trochanter BMD (Egger test, p = 0.418), serum sclerostin level (Egger test, p = 0.43), BSAP (Egger test, p = 0.189), ODI (Egger test, p = 0.12) and incidence of fracture (Egger test, p = 0.917). In contrast, there was potential publication bias for the trials in the study group with respect to CTX (Egger test, p = 0), P1NP (Egger test, p = 0.008), and VAS score (Egger test, p = 0.002) (**S11 File**).

4. Discussion

With an aging global population, the prevalence of osteoporosis is increasing [2]. In Europe, the incidence of osteoporosis-induced disability exceeds that of cancer-induced disability (except lung cancer). Moreover, it is comparable to or greater than that caused by various chronic noncommunicable diseases, causing significant personal and economic costs [3,39]. BPs are currently the most widely used drugs for the treatment of osteoporosis.

The strengths of this study are evident in its comprehensive inclusion of substantial studies and its innovative assessment of zoledronic acid's efficacy, which for the first time combines bone turnover markers and functional scores with BMD. Furthermore, the evaluation of zoledronic acid's safety profile enhances the evidence supporting its clinical application.

This meta-analysis offers a thorough assessment of the clinical efficacy and safety of zoledronic acid in osteoporosis patients, encompassing an integration of BMD, bone turnover markers, functional scores, fracture risk, and adverse events. The results demonstrate that patients with osteoporosis who receive zoledronic acid treatment show a significant increase in BMD compared to those in the control group, reinforcing the drug's effectiveness in augmenting BMD. Apart from two studies, the findings of this analysis align with the bulk of the included research, underscoring the consistency of our results. Liu et al. [28] reported a marginal enhancement in the BMD of the femoral neck among patients in the zoledronic acid group; however, this difference was not statistically significant (p = 0.485 > 0.05). Similarly, Ryhänen et al. [32] observed an increase in total hip joint BMD in the zoledronic acid group, yet the difference was also not statistically significant (p = 0.88, >0.05). It is important to consider that the sample sizes of these respective trials were relatively small, with 43 and 54 participants. The lack of significant differences between the zoledronic acid and control groups in these studies could potentially be attributed to the limited sample sizes, which may not have been adequate to detect a statistically meaningful effect.

In this study, the assessment of bone turnover markers, specifically CTX, BSAP, and P1NP, within the zoledronic acid group revealed a notable decrease in bone turnover markers when contrasted with the control group. These results are in line with the

Fig. 5. Forest plot showing the effect of zoledronic acid on any adverse events and serious adverse events. A. adverse events. B. serious adverse events.

outcomes of previous research [19,23]. Assessed via CTX, bone resorption in the zoledronic acid group was found to decrease at 12 and 24 months (0.095 and 0.087 nmol/L) ($P < 0.05$), while it increased in the placebo group at 12 and 24 months (0.068 and 0.070 nmol/L) ($P < 0.05$). The bone formation marker P1NP showed a respective decrease of 21.9 and 20.4 μg/L in the treatment group at 12 and 24 months ($P < 0.01$) [23]. In a similar large-scale randomized controlled trial conducted in parallel, Black et al. [19] also observed a significant reduction in all three biochemical markers of bone turnover in the zoledronic acid group. At the 12-month assessment point, the levels of CTX, BSAP, and P1NP in the zoledronic acid group had decreased by 59 % (95 % CI, 55 to 63), 30 % (95 % CI, 27 to 32), and 58 % (95 % CI, 55 to 60) respectively. CTX serves as a marker for bone resorption, while BSAP and P1NP are indicators of bone formation [40]. The study's findings suggest that the reduction in bone remodeling associated with zoledronic acid can enhance bone strength without adversely affecting the capacity for bone remodeling.

The present study demonstrated that patients treated with zoledronic acid had a higher incidence of any adverse events than those treated with placebo, but their incidence of serious adverse events was similar to that of patients receiving placebo. This is in agreement with previous studies by Black et al. [19]. The researchers observed a notably higher incidence of adverse events in the zoledronic acid group (95.5 %) compared to the placebo group (93.9 %), primarily due to a greater number of post-treatment symptoms. Similarly, Nakamura et al. [31] reported an adverse event rate of 94.6 % in the zoledronic acid group, compared to 92.2 % in the placebo group. In fact, the most common adverse reaction in patients in the zoledronic acid group was an acute phase reaction to the first dose. Symptoms included fever, muscle pain, arthralgia, headache, chills, and flu-like symptoms. Therefore, it is essential for clinicians to not only inform patients about these common adverse reactions but also to prepare and implement appropriate preventive measures when administering the first injection of zoledronic acid. This study has some limitations that should be noted. Firstly, only a limited number of high-quality RCTs were included, and some studies were excluded from the analysis due to incomplete data, which may have limited the scope of our findings. Secondly, there was a high degree of heterogeneity among the included studies. Although sensitivity analyses were performed to explore potential sources of heterogeneity, no significant information was found. Lastly, the follow-up periods among the included studies varied considerably, ranging from 12 months to 36 months. As a result, the clinical outcomes differed significantly depending on the duration of follow-up. Therefore, we should conduct a subgroup analysis to evaluate the efficacy of zoledronic acid across different time points.

5. Conclusion

Based on the current evidence, the application of zoledronic acid for the treatment of osteoporosis may improve BMD, reduce fracture risks and bone turnover, and thus significantly improve older adults' quality of life. However, the incidence of adverse events was higher than that of patients treated with placebo, necessitating vigilance and preventive measures against such events in clinical settings.

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Ethics approval and consent to participate

Ethical approval was not needed because this is a meta-analysis.

Data availability statement

The data used to support the findings of this study are included in the article.

CRediT authorship contribution statement

Jianfeng Sun: Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Masoud Rahmati:** Software, Methodology, Formal analysis, Conceptualization. **Wenqing Xie:** Software, Data curation. **Guang Yang:** Software, Formal analysis. **Bingzhou Ji:** Software, Formal analysis. **Dong Keon Yon:** Writing – review & editing, Software, Investigation. **Seung Won Lee:** Writing – review & editing, Supervision, Software. **Razak M. Gyasi:** Writing – review & editing, Software. **Guillermo F. López Sánchez:** Writing – review & editing. **Pinar Soysal:** Writing – review & editing. **Ai Koyanagi:** Writing – review & editing. **Lee Smith:** Writing – review & editing. **Jae Il Shin:** Writing – review & editing. **Yusheng Li:** Writing – review & editing, Visualization, Validation, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

influence the work reported in this paper.

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