Efficacy and safety of bisphosphonates on childhood osteoporosis secondary to chronic illness or its treatment: a meta-analysis

Huawei Zhao*, Yunfei Ding*, Jufei Yang, Yijun Luo, Zhenghao Xu (iD) **and Jing Miao**

Abstract

Background: Bisphosphonates are a type of medication that prevents the loss of bone density. Secondary childhood osteoporosis reduces bone strength and results in an increased risk of fragility fracture. This meta-analysis aims to explore the efficacy and safety of bisphosphonates on secondary childhood osteoporosis.

Methods: We performed a systematic search of PubMed, Cochrane library, and Web of Science databases up to 31 July 2022 to screen for random clinical trials (RCTs) on bisphosphonate treatment for childhood secondary osteoporosis. Data from selected studies, mainly changes in lumbar spine (LS) bone mineral density (BMD), changes in LS BMD Z-scores, fracture events, and adverse events (AEs), were extracted and analyzed.

Results: Nine RCTs ($n = 429$ in total) were included in our meta-analysis. The meta-analysis indicated that bisphosphonates improved the changes in LS BMD [mean difference (MD) = 0.04, 95% confidence intervals (CIs) = 0.01–0.07, $p < 0.01$] and LS BMD Z-scores [MD = 0.52, 95% CI = 0.23–0.81, $p < 0.01$]. Use of bisphosphonates did not increase the risk of AEs [odds ratio (OR) = 1.61, 95% CI = 0.87–2.99, $p = 0.13$]. Subgroup analysis showed that routes of administration, but not causes of secondary osteoporosis, might influence the efficacy of bisphosphonates. IV bisphosphonates close to significantly improved the incidence of fracture (OR = 0.34, 95% CI: 0.11–1.08, $p = 0.07$).

Conclusions: The use of bisphosphonates improves LS BMD without increasing AE rates, which supports the clinical use of bisphosphonates in secondary childhood osteoporosis. Further large RCTs are still warranted, especially for their long-term effects on fracture rates.

Keywords: bisphosphonate, bone mineral density, children, secondary osteoporosis

Correspondence to:
Zhenghao Xu
Laboratory of
Rheumatology & Institute
of TCM Clinical Basic
Medicine, College of
Basic Medical Science,
Zhejiang Chinese Medical
University, No. 548 Binwen
Road, Hangzhou 310053,
Zhejiang, China
xuzhenghao@zcmu.edu.cn

Jing Miao
Department of Pharmacy,
The Children's Hospital,
Zhejiang University School
of Medicine and National
Clinical Research Center
for Child Health, Hangzhou
310052, Zhejiang, China
miaojing@zju.edu.cn

Huawei Zhao
Jufei Yang
Jing Miao
Department of Pharmacy,
The Children's Hospital,
Zhejiang University
School of Medicine and
National Clinical Research
Center for Child Health,
Hangzhou, China

Yunfei Ding
Yijun Luo
Zhenghao Xu
Laboratory of
Rheumatology & Institute
of TCM Clinical Basic
Medicine, College of
Basic Medical Science,
Zhejiang Chinese Medical
University, Hangzhou,
China

*The first two authors
contributed equally to this
paper.

Introduction

Osteoporosis is a metabolic bone disease characterized by low bone mass and microarchitectural deterioration of bone tissue. Osteoporosis is generally divided into primary and secondary osteoporosis.[1] Osteoporosis in children is usually secondary osteoporosis, which is caused by chronic illness or its treatment, especially the use of steroids.[2] Secondary osteoporosis in childhood reduces bone strength and results in an increased risk of fragility fractures.

Bisphosphonates are a type of medication that prevents the loss of bone density, and hence are widely used to treat osteoporosis.[3] With regard to secondary osteoporosis in children, a previous Cochrane review in 2007[4] includes six random clinical trials (RCTs), two controlled clinical trials, and one prospective cohort, but the heterogeneity among these included studies precluded statistically combining the results. This Cochrane review[4] concludes that short-term (3 years or less) bisphosphonate use appears to be well-tolerated,

but its efficacy still needs further evaluation. Since then, an increased number of RCTs have been conducted to evaluate the efficacy and safety of bisphosphonate therapy for secondary osteoporosis in children. However, the evidence for bisphosphonate therapy in secondary childhood osteoporosis remains inadequate. Thus, here we conducted a meta-analysis to evaluate the efficacy and safety of bisphosphonate therapy in children with secondary osteoporosis.

Materials and methods

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. The protocol was registered in PROSPERO (registration number: CRD42022309845). Because the current research was based on the published data, no consent statement and ethical approval are required.

Searching strategy

Following the PRISMA guidelines, we searched the PubMed, Cochrane library, and Web of Science databases on 31 July 2022, using the following keywords: 'osteoporosis' AND ('bisphosphonate' OR 'bisphosphonates' OR 'alendronate' OR 'clodronate' OR 'etidronate' OR 'ibandronate' OR 'olpadronate' OR 'risedronate' OR 'tiludronate' OR 'zoledronate' OR 'phosphoric acid') AND (child OR child* OR pediatric OR adolescent OR juvenile). The detailed search strategy can be found in Supplementary Tables 1–3.

Inclusion and exclusion criteria

Inclusion criteria: (1) children or adolescents who suffered from osteoporosis secondary to chronic illness or its treatment; (2) treatment with bisphosphonates; (3) bone mineral density (BMD) should be measured by dual-energy X-ray absorptiometry (DEXA); (4) the study design should be RCT.

Exclusive criteria: (1) studies without controls or only self-control; (2) data were not available or were repeated; (3) reviews, editorials, single cases and case series, letters, and commentaries; (4) studies focused on primary osteoporosis; (5) studies focused on osteogenesis imperfecta.

Study selection

Two reviewers (H.Z. and Y.D.) independently reviewed studies to extract potentially eligible studies. Any disagreements regarding articles were resolved through discussion by all authors and resolved by consensus with the corresponding author (Z.X.).

Data extraction

The collected data included the author's name, publication year, countries, sample size, participant characteristics (age and sex), secondary cause, intervention (drug type, mode of administration, drug dose), follow-up duration, and outcomes. To assess the efficacy, we collected the changes in lumbar spine (LS) BMD and LS BMD *Z*-score as the main outcomes and the incidence of fracture as a secondary outcome. To assess the safety, we collected the adverse events (AEs).

Quality assessment

Study quality was assessed using Cochrane's Collaboration tool.[5] For each RCT, bias was estimated qualitatively by independent reviewers as low risk, unclear, or high risk, including items of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. In addition, to assess publication bias, funnel plots were performed.

Statistical analysis

The comprehensive meta-analysis was performed to calculate odds ratios (OR) or mean difference (MD) and their 95% confidence interval (CI) by RevMan 5. Statistical heterogeneity was assessed by Cochran's Q statistic and the I^2 statistic. I^2 values of 25%, 50%, and 75% represent low, moderate, and high degrees of heterogeneity, respectively. Similar to our previous study,[6] a random-effects model (Mantel–Haenszel method for dichotomous data or inverse-variance method for continuous data) was employed for the meta-analysis because the included studies in the analysis are not functionally identical (especially the use of different kinds of bisphosphonates). For the sensitivity analysis, included studies were excluded one by one. Subgroup analyses according to the route of bisphosphonate administration
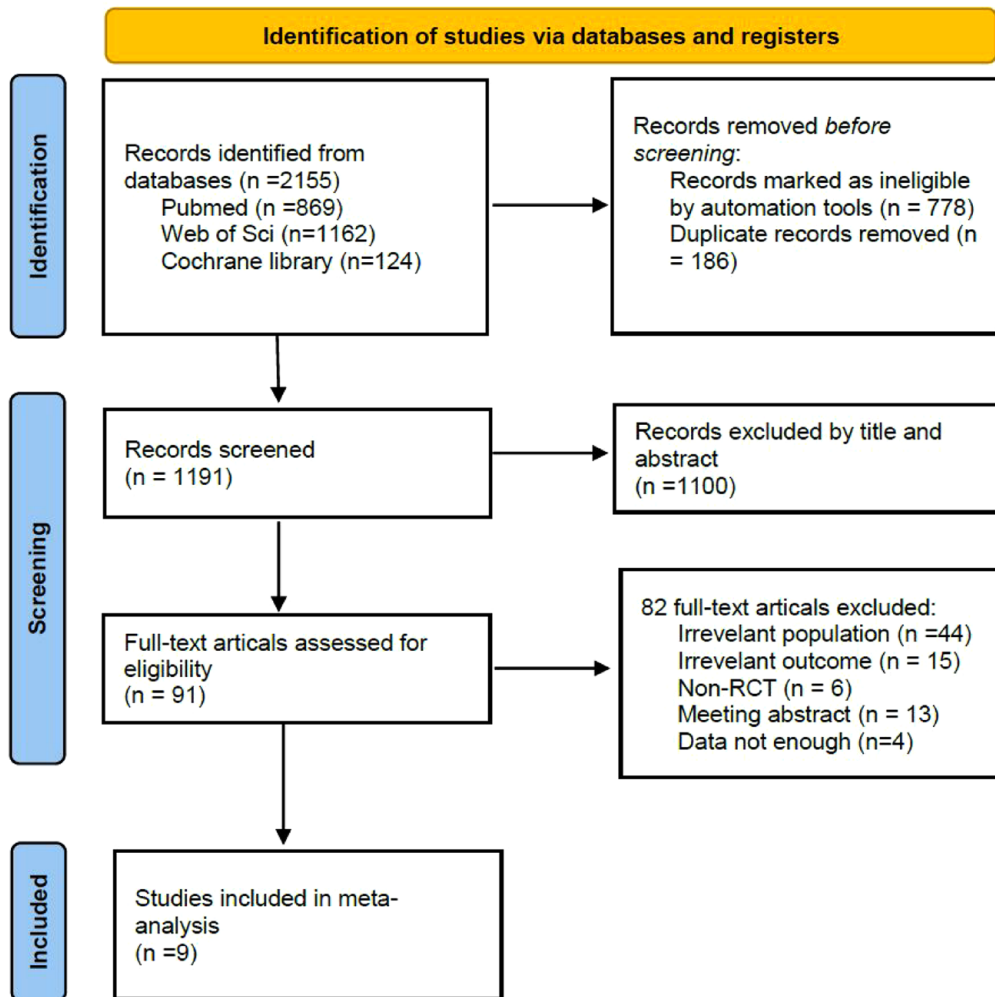
Identification of studies via databases and registers

Records identified from databases (n =2155)
  Pubmed (n =869)
  Web of Sci (n=1162)
  Cochrane library (n=124)

→ Records removed *before screening*:
  Records marked as ineligible by automation tools (n = 778)
  Duplicate records removed (n = 186)

Records screened (n = 1191)

→ Records excluded by title and abstract (n =1100)

Full-text articals assessed for eligibility (n = 91)

→ 82 full-text articals excluded:
  Irrevelant population (n =44)
  Irrevelant outcome (n = 15)
  Non-RCT (n = 6)
  Meeting abstract (n = 13)
  Data not enough (n=4)

Studies included in meta-analysis (n =9)

Identification / *Screening* / *Included*

Figure 1. Flow diagram of the study selection process.

[intravenous (IV) *versus* oral] and the cause of secondary osteoporosis (steroid-associated *versus* others) were also performed. *P* value <0.05 was revealed statistically significant.

Results

Study selection

The study selection process is depicted in Figure 1. Totally, 2155 potentially relevant articles were identified initially. Finally, nine RCTs ($n=429$ in total) were included in our meta-analysis.[7–15] Of note, we excluded three articles because of no available outcome data[16–18] and another one article because of data not consistent with other studies[19] when assessing the full articles. The details of included studies are shown in Table 1.

Among the nine included RCTs, six trials[8–13] used oral bisphosphonates, and the other three[7,14,15] trials used IV bisphosphonates. Placebo was used for the control group in two RCTs.[13,15] Calcium or calcium plus vitamin D were used in both control and bisphosphonate groups in eight RCTs.[7–12,14,15] The follow-up duration was 12 months in six RCTs,[8–10,12,13,15] 3 months in one RCT,[11] 18 months in one RCT,[7] and 24 months in the other one RCT.[14]

Quality assessment

All trials were generally considered to have high quality according to criteria, despite a bias in allocation concealment and blinding of participants and personnel in the trial of Zacharin *et al.*[14] (Figure 2).

Table 1. Details of included studies.

Studies	Country	Sample size		Secondary cause	Intervention		Follow-up	Outcome
		Control, *n* (F%), age (SD)	Bisphosphonates, *n* (F%), age (SD)		Control	Bisphosphonates		
Henderson et al.[7]	United States	6 [50.0%], 9.3 [3.8]	6 [33.3%], 9.3 [3.7]	Quadriplegic cerebral palsy	Calcium and VD	Pamidronate, iv. 1 mg/kg/day for 3 consecutive days at 0, 3, 6, 9, and 12 months	18 M	BMD, bone mineralization, fracture, serum N-telopeptide/calcium/albumin/25OHD
El-Husseini et al.[8]	Egypt	15 [26.7%], 14.6 [4.3]	15 [26.7%], 15.2 [3.5]	Live renal allotransplants	Calcium	Alendronate, po. 5 mg/day	12 M	BMD T-score, serum creatinine/calcium/phosphorus/albumin/ALP/osteocalcin, AEs
Golden et al.[9]	United States	15 [NA], 16.9 [2.2]	14 [NA], 16.9 [1.6]	Anorexia nervosa	Calcium and VD	Alendronate, po. 10 mg/day	12 M	BMD, BMC, AEs, serum hormones
Rudge et al.[13]	New Zealand	11 [63.6%], 8.0 [NA],	11 [54.5%], 8.7 [NA]	Long-term prednisone therapy	Placebo	Alendronate, po. 1–2 mg/kg /week	12 M	BMD, BMC, plasma calcium/phosphate/albumin/ALP/GGT/AST/ALT/calcidiol/parathyroid hormone/N-telopeptide, fracture, AEs
Kim and Cho[11]	Korea	22 [50.0%], 8.5 [2.39]	22 [22.7%], 8.5 [4.49]	Nephropathy receiving high doses of steroids	Calcium	Pamidronate, po. 125 mg/day	3 M	BMD, serum PTH/osteocalcin/urinary pyridinoline
Rooney et al.[12]	United Kingdom	77 [71.4%], 12.1 [3.5]	69 [76.8%], 12.0 [3.4]	Juvenile idiopathic arthritis, juvenile SLE, juvenile dermatomyositis, or vasculitis	Calcium and VD	Risedronate, po. 1 mg/kg/week if ≤30kg) or 35 mg/week if >30kg)	12 M	BMD, fracture, serum 25OHD/parathormone/ALP/osteocalcin/crosslaps, AEs
Jacobson et al.[10]	United States	18 [27.8%], 16.3 [NA]	32 [34.4%], 16.1 [NA]	Infected with HIV	Calcium and VD	Alendronate, po. 70 mg/week if >30 kg or 35 mg/week if ≤30kg	12 M	BMD, complete blood count, serum chemistries, AEs
Zacharin et al.[14]	Australia	31 [0%], 10.1 [2.6]	31 [0%], 10.1 [2.8]	Glucocorticoid-dependent Duchenne muscular dystrophy	Calcium and VD	Zoledronic acid, iv. 0.025 mg/kg/day at 0 and 3 months, 0.05 mg/kg at 6, 12 and 18 months	24 M	BMD, BMC, fracture, cortical thickness and cross-sectional area, serum calcium/25OHD/ALP/PTH, AEs
Ward et al.[15]	multinational	16 [31%], 12.3[3.4]	18 [33%], 13.0[3.5]	Nonmalignant conditions treated with systemic glucocorticoid	Calcium and VD + placebo	Zoledronic acid, iv. 0.05 mg/kg at 0 and 6 months	12 M	BMD, BMC, serum N-telopeptide/ALP/N-terminal propeptide of type I collagen/tartrate-resistant acid phosphatase isoform 5b, fracture, AEs

25OHD, 25-hydroxyvitamin D; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMC, bone mineral content; BMD, bone mineral density; GGT, gamma glutamyl transferase; HIV, human immunodeficiency virus; iv., intravenous; M, month; NA, not available; po., per os, means oral; PTH, parathyroid hormone; SLE, systemic lupus erythematosus; VD, vitamin D.

(a) **Risk of bias summary**
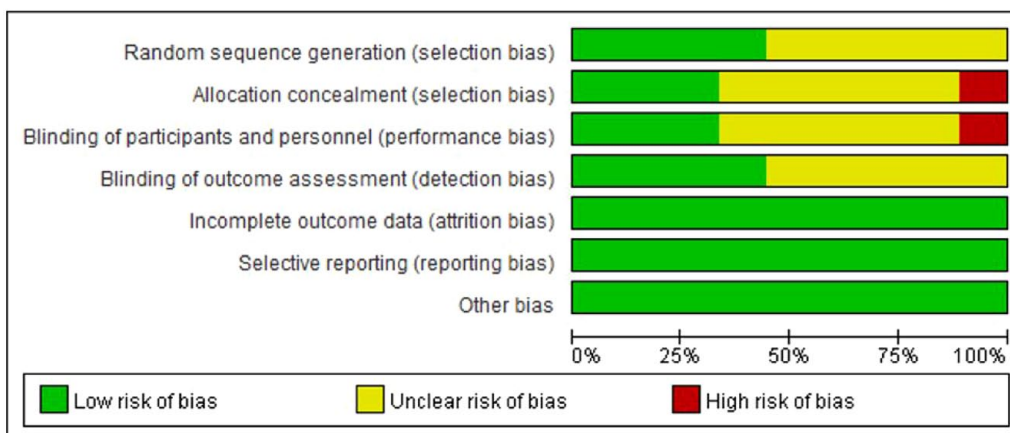

(b) **Risk of bias graph**

Figure 2. Risk of bias assessment: (a) assessments about each risk of bias item for each included study; (b) assessments about each risk of bias item were presented as percentages across all included studies.

Efficacy

Changes in LS BMD

Five included RCTs with a total of 303 individuals measured the changes in LS BMD.[9,11–14] Among them, four RCTs[9,11–13] used oral bisphosphonates and one RCT[14] used IV bisphosphonate. As shown in Figure 3, the meta-analysis showed that the changes in LS BMD in the bisphosphonate group were higher than those in the control group (MD = 0.04, 95% CI = 0.01–0.07, $p < 0.01$, $I^2 = 63\%$).

For the sensitivity analysis, five studies were excluded one by one (Supplementary Table 4). When the study of Rooney *et al.*[12] was excluded, the results became almost significant (MD = 0.05, 95% CI = 0.00–0.10, $p = 0.05$). When the rest of the studies were excluded by turns, the result remains significant. Of note, when the study of Zacharin *et al.*[14] (the only one RCT that used IV bisphosphonate) was removed, the I^2 changed from 63% to 0% (but the results remain significant, MD = 0.03, 95% CI: 0.02–0.05, $p < 0.0001$, $I^2 = 0\%$). When the rest of the studies were
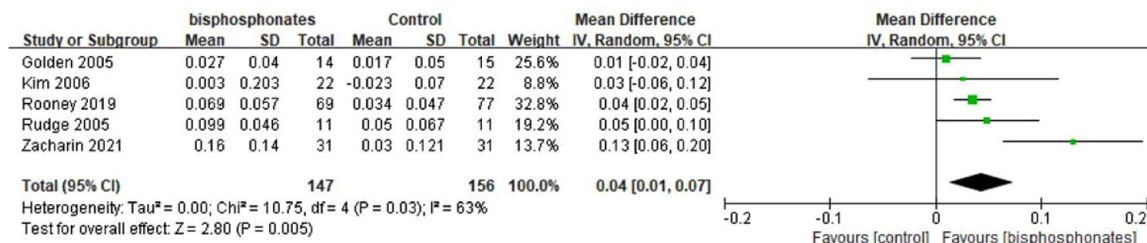
Figure 3. Forest plots indicating bisphosphonates improved the changes in LS BMD.
BMD, bone mineral density; 95% CI, 95% confidence interval; LS, lumbar spine; Weight%, weight coefficient.
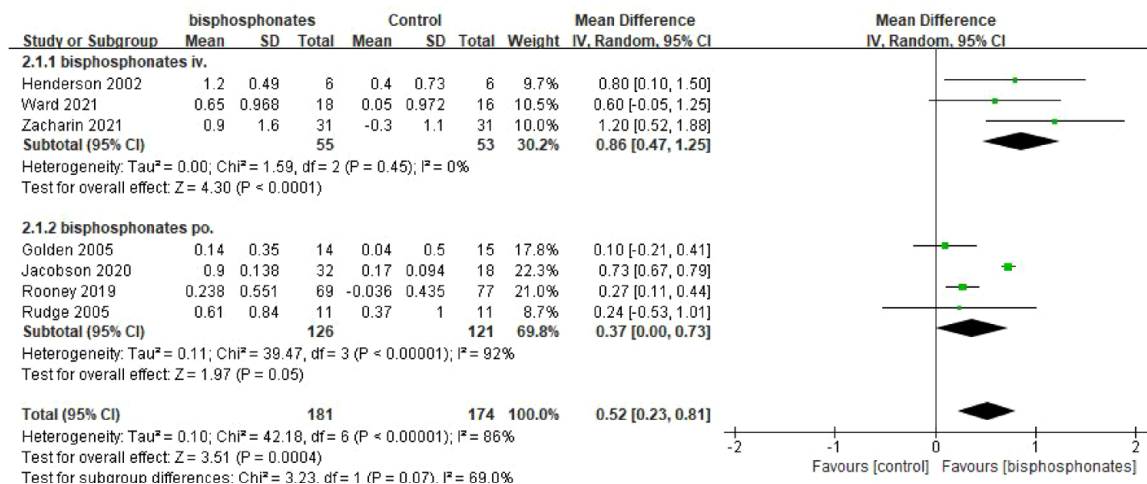

Figure 4. Forest plots indicating bisphosphonates with different administration routes improved the LS BMD *Z*-scores.
BMD, bone mineral density; 95% CI, 95% confidence interval; iv., intravenous; LS, lumbar spine; po., per os, means oral; Weight%, weight coefficient.

excluded by turns, the I^2 remains high (50–75%).

Changes in LS BMD Z-scores

Seven included RCTs with a total of 355 individuals that measured the changes in BMD Z-scores of the LS.[7,9,10,12–15] Among these included RCTs, three RCTs[7,14,15] used IV bisphosphonates and four RCTs[9,10,12,13] used oral bisphosphonates. As shown in Figure 4, the meta-analysis showed that the changes in LS BMD Z-scores in the bisphosphonate groups were higher than those in the control groups (MD = 0.52, 95% CI = 0.23–0.81, $p < 0.01$, $I^2 = 86\%$).

Subgroup analysis according to the route of bisphosphonate administration (IV *versus* oral) showed that (1) IV bisphosphonates significantly improved the BMD *Z*-scores (MD = 0.86, 95% CI = 0.47–1.25, $p < 0.001$, $I^2 = 0\%$), while oral bisphosphonates almost significantly improved the BMD *Z*-scores (MD = 0.37, 95% CI = 0.00–0.73, $p = 0.05$, $I^2 = 92\%$; Figure 4); (2) the efficacy of IV bisphosphonates was close to significantly better than oral bisphosphonates ($\chi^2 = 3.23$, $p = 0.07$, $I^2 = 69\%$; Figure 4).

Subgroup analysis according to the cause of secondary osteoporosis (steroid-associated *versus* others) showed that (1) bisphosphonates improved the BMD *Z*-scores in children with osteoporosis secondary to both causes (steroid-associated: MD = 0.52, 95% CI = 0.11–0.94, $p = 0.01$, $I^2 = 59\%$; others: MD = 0.52, 95% CI = 0.04–1.00, $p = 0.04$, $I^2 = 87\%$; Supplementary Figure 1); (2)
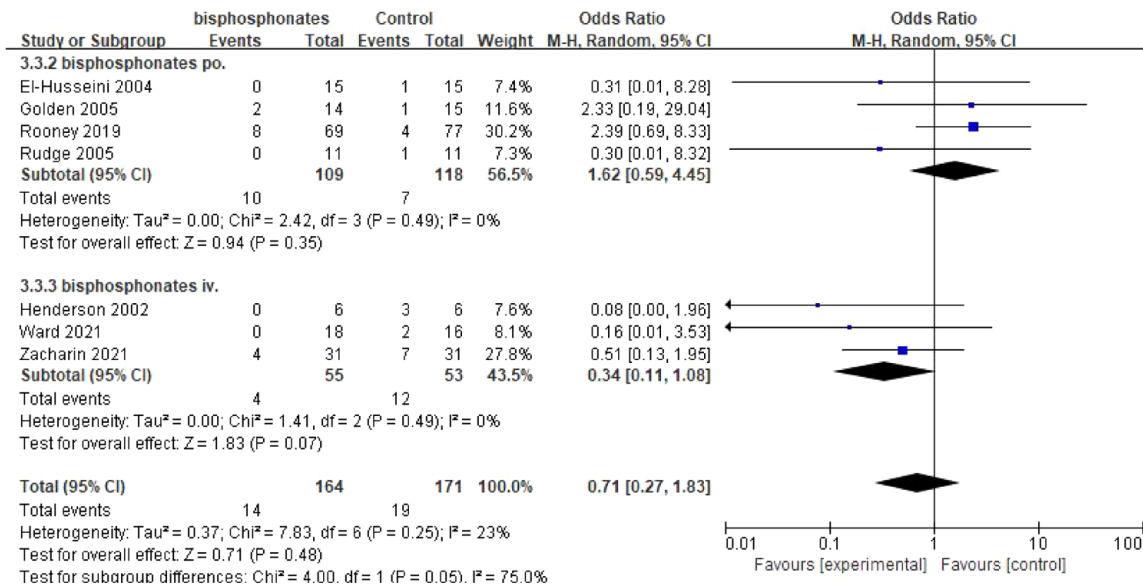
Figure 5. Forest plots of fracture.
95% CI, 95% confidence interval; iv., intravenous; po., per os, means oral; Weight%, weight coefficient.

the efficacy of bisphosphonates has no statistical difference between the two groups ($\chi^2 = 0.00$, $p = 0.99$, $I^2 = 0$).

For the sensitivity analysis, the result did not change significantly when studies were excluded one by one (Supplementary Table 4).

Fracture rate
Seven included RCTs with a total of 335 individuals measured fracture incidence.[7–9,12–15] As shown in Figure 5, the meta-analysis showed that bisphosphonates did not affect the incidence of fracture significantly (OR = 0.71, 95% CI: 0.27–1.83, $p = 0.48$, $I^2 = 23\%$).

Subgroup analysis according to the route of bisphosphonate administration (IV *versus* oral) further showed that (1) IV bisphosphonates close to significantly reduced the incidence of fracture (OR = 0.34, 95% CI: 0.11–1.08, $p = 0.07$, $I^2 = 0\%$; Figure 5); (2) the effect of IV bisphosphonates on reducing the incidence of fracture was almost significantly stronger than that of oral bisphosphonates ($\chi^2 = 4.00$, $p = 0.05$, $I^2 = 75\%$; Figure 5).

Subgroup analysis according to the cause of secondary osteoporosis (steroid-associated *versus* others) showed that bisphosphonates did not affect the incidence of fracture significantly in both groups (steroid-associated: OR = 0.76, 95% CI = 0.28–2.08, $p = 0.59$, $I^2 = 21\%$; others: OR = 0.49, 95% CI = 0.02–14.11, $p = 0.68$, $I^2 = 63\%$; Supplementary Figure 2).

For the sensitivity analysis, the result did not change significantly when studies were excluded one by one (Supplementary Table 4). The result also did not change significantly when the trial of Zacharin *et al.*[14] was removed (OR = 0.71, 95% CI: 0.20–2.47, $p = 0.59$, $I^2 = 30\%$).

Safety
Seven included trials reported AEs, and a total of 173 out of 363 patients experienced at least one kind of AE.[7–10,12,14,15] Among these included RCTs, four RCTs[8–10,12] used oral bisphosphonates and the other three RCTs[7,14,15] used IV bisphosphonates. As shown in Figure 6, the meta-analysis showed that bisphosphonates did not increase the total AE rate significantly (OR = 1.61, 95% CI: 0.87–2.99, $p = 0.13$, $I^2 = 0\%$).

Subgroup analysis showed the AE rate was not significantly affected by the routes of bisphosphonate administration (IV bisphosphonates: OR = 1.45, 95% CI = 0.71–2.96, $p = 0.31$, $I^2 = 0\%$; oral bisphosphonates: OR = 2.44, 95%
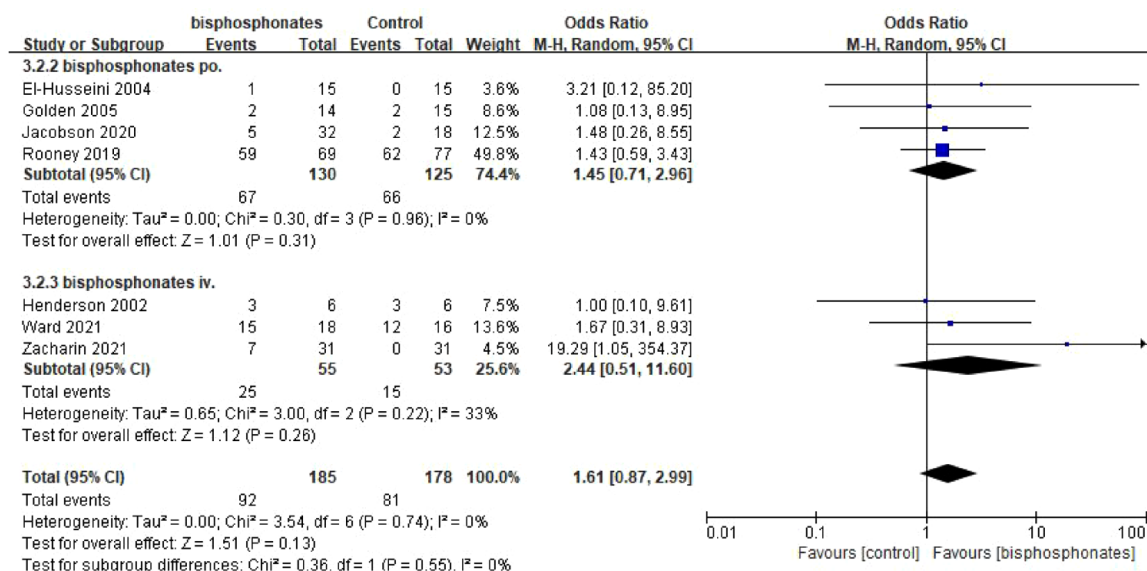
Figure 6. Forest plots indicating bisphosphonates did not increase the risk of AEs.
AEs, adverse events; 95% CI, 95% confidence interval; iv., intravenous; po., per os, means oral; Weight%, weight coefficient.

CI = 0.51–11.60, p = 0.26, I^2 = 33%; Figure 6) or the cause of secondary osteoporosis (steroid-associated: OR = 1.86, 95% CI = 0.85–4.11, p = 0.12, I^2 = 5%; others: OR = 1.22, 95% CI = 0.38–3.87, p = 0.74, I^2 = 0%; Supplementary Figure 3). The details of the AEs are described in Table 2.

For the sensitivity analysis, the result did not change significantly when studies were excluded one by one (Supplementary Table 4).

Publication bias

According to Figure 7, no significant publication bias was found among these included studies evaluating the LS BMD (Figure 7(a)), LS BMD Z-scores (Figure 7(b)), fracture rate (Figure 7(c)), and AE rate (Figure 7(d)).

Discussion

The incidence of secondary osteoporosis in children is on the rise due to the increased survival rate of chronically ill patients and the use of bone-damaging drugs.[20] Bisphosphonate therapy is a common treatment for osteoporosis.[21] However, safety concerns have to be considered because bisphosphonate may result in AEs in growing individuals with high bone metabolism.[22] These concerns are largely due to the lack of dependable efficacy and safety data in children with secondary osteoporosis. This meta-analysis evaluated

bisphosphonate therapy in secondary childhood osteoporosis, and the findings were as follows: (1) bisphosphonate treatment improved LS BMD and BMD Z-scores over 3–24 months of follow-up; (2) the efficacies of IV bisphosphonates on BMD Z-score and fracture rate were close to significantly better than oral bisphosphonates; (3) the efficacy of bisphosphonates may not be influenced by causes of secondary childhood osteoporosis (steroid-associated *versus* others); (4) bisphosphonates, either orally or intravenously, did not increase the risk of AEs. Thus, our results suggest bisphosphonates are efficacious and safe for the treatment of secondary childhood osteoporosis.

Because of the limited number of included studies and the existence of heterogeneity, the previous Cochrane review in 2007[4] indicates that the efficacy of bisphosphonates on secondary childhood osteoporosis still needs further evaluation. Compared with the Cochrane review of 2007,[4] here we collected and included four new RCTs[10,12,14,15] and did quantitative meta-analyses. We excluded one RCT[19] which was included in the Cochrane review 2007[4] because it reported bone mineral content (BMC) but not BMD. BMD measurement is one of the main bases for the diagnosis of secondary osteoporosis in children. The BMD in our included RCTs was all measured by dual-energy X-ray absorptiometry (DEXA), which is the gold standard for

Table 2. Details of adverse events.

AEs (*n*)	Henderson *et al.*[7]		El-Husseini *et al.*[8]		Golden *et al.*[9]		Jacobson *et al.*[10]		Rooney *et al.*[12,a]		Zacharin *et al.*[14]		Ward *et al.*[15,a]		Total
	C	B	C	B	C	B	C	B	C	B	C	B	C	B	
Number of patients	6	6	15	15	15	14	18	32	77	69	31	31	16	18	363
Patients with AEs	3	3	0	1	2	2	2	5	62	59	0	7	12	15	173
Abdominal pain	–	–	–	–	–	–	–	1	–	–	–	–	–	–	1
Abdominal bloating/ nausea	–	–	–	–	2	2	–	–	–	–	–	–	–	–	4
Bilirubin elevation	–	–	–	–	–	–	1	2	–	–	–	–	–	–	3
Hypocalcemia	–	–	–	1	–	–	–	–	–	–	–	4	–	–	5
Low phosphorus/ hypophosphatemia	–	–	–	–	–	–	–	1	–	–	–	3	–	–	4
Low platelet count	–	–	–	–	–	–	–	1	–	–	–	–	–	–	1
Weight loss/chest pain/ difficulty swallowing	–	–	–	–	–	–	1	–	–	–	–	–	–	–	1
Febrile response	3	3	–	–	–	–	–	–	–	–	–	–	–	–	6
Other AEs or unclear AEs	–	–	–	–	–	–	–	–	62	59	–	–	12	15	148

AEs, adverse events; B, bisphosphonate group; C, control group.
[a]Study that did not report detailed AEs.

determining BMD. Finally, all included studies used a relatively standardized approach to BMD reporting, which support us to do the quantitative meta-analyses. Based on five included RCTs and a total of 303 patients,[9,11–14] we reveal that bisphosphonates improved the change of LS BMD. Based on seven included RCTs and a total of 355 patients,[7,9,10,12–15] we reveal that bisphosphonates improved the change of LS BMD Z-scores. Besides, as suggested by the Cochrane review in 2007,[4] we additionally did a preliminary quantitative meta-analysis on the fracture rates, which partly represents the functional bone health outcomes. We found only IV bisphosphonates might slightly but not significantly improve the fracture rates (OR = 0.34, 95% CI: 0.11–1.08, $p = 0.07$, $I^2 = 0$%). Of note, the type of fracture varied from study to study, and all these included studies may be not powered to study the impact of bisphosphonates on fracture rates (such a trial might require several thousand participants for each kid of bisphosphonates). Thus, taken together, our study provides potentially more solid and comprehensive evidence supporting the use of bisphosphonates in secondary childhood osteoporosis than previous studies. Further RCTs are still warranted to investigate the effect of bisphosphonates on the fracture rates and other functional bone health outcomes in children with secondary osteoporosis.

Heterogeneity is high in the analyses for both LS BMD and BMD Z-scores. Sensitivity analysis shows that the study of Zacharin *et al.*[14] may be the source of heterogeneity in the analysis of LS BMD. The study of Zacharin *et al.*[14] is the only one included study that used IV bisphosphonates in the analysis of changes in LS BMD, suggesting drug delivery route may be an important interference factor. Thus, we further did the subgroup analysis according to the route of bisphosphonate administration (IV *versus* oral). We found the efficacy of IV bisphosphonates on BMD Z-scores was close to significantly better than oral bisphosphonates ($p = 0.07$ for IV *versus* oral). Similarly, the efficacy of IV bisphosphonates on fracture rates
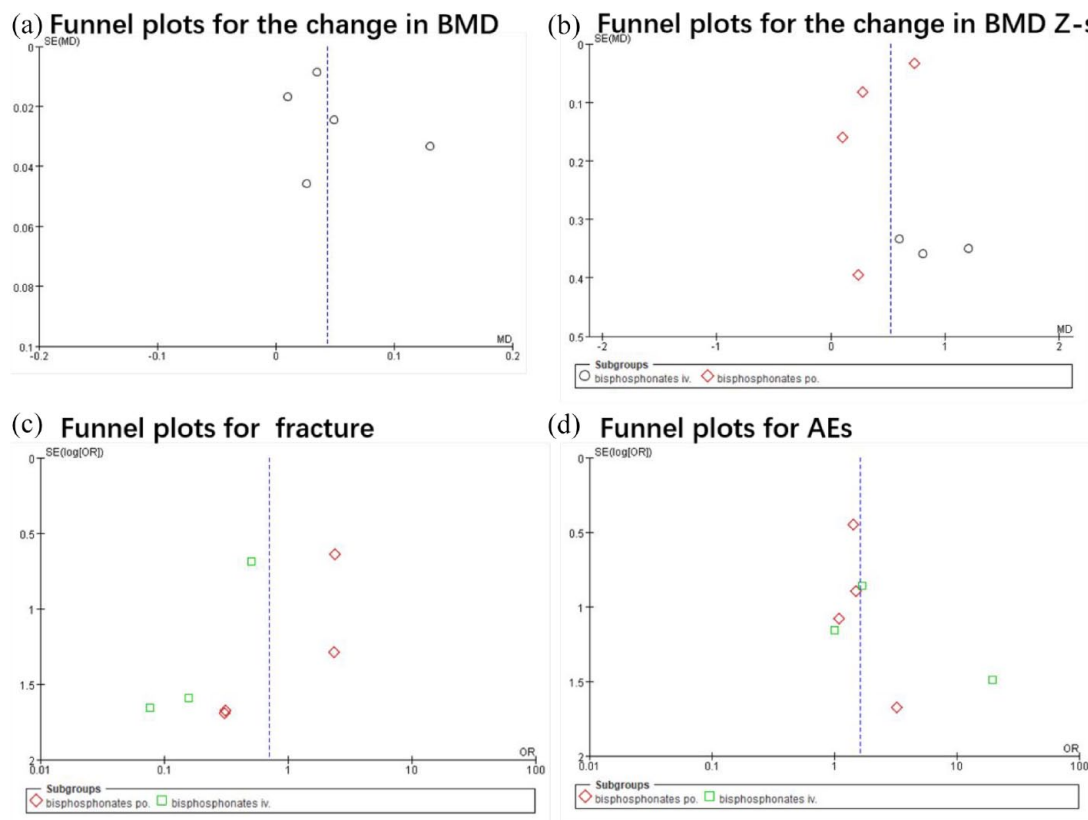
Figure 7. Funnel plots: (a) funnel plots for the changes in BMD of the LS; (b) funnel plots for the changes in BMD *Z*-scores of the LS; (c) funnel plots of fracture; (d) funnel plots of AEs.
AEs, adverse events; BMD, bone mineral density; iv., intravenous; LS, lumbar spine; po., per os, means oral.

was almost significantly better than oral bisphosphonates ($p = 0.05$ for IV *versus* oral). On the other hand, causes for secondary osteoporosis were also quite diverse among the nine included RCTs. Six of nine included RCTs[8,11–15] are mainly due to the use of steroids, while the other three[7,9,10] are probably caused by chronic diseases. We found bisphosphonate treatment improved the LS BMD or BMD *Z*-score in both conditions of secondary osteoporosis ($p = 0.99$ for steroid-associated *versus* others). In addition, because of the limited included studies, other interference factors, such as bisphosphonates types, drug delivery frequency, and follow-up duration, were not further analyzed here. Thus, our results suggest the efficacy of bisphosphonates might be influenced by the route of bisphosphonate administration (IV *versus* oral) rather than the cause of secondary osteoporosis (steroid-associated *versus* others). The efficacy of IV bisphosphonates may be slightly better than that of oral bisphosphonates for the treatment of secondary childhood osteoporosis. Further RCTs are still warranted to investigate the effect of specific types of bisphosphonates in secondary childhood osteoporosis.

Bisphosphonates may cause abdominal discomfort and abnormal blood tests, and other adverse events. Based on the included seven RCTs and a total of 363 patients,[7–10,12,14,15] our analysis interestingly showed that the use of bisphosphonates did not increase the risk of AEs compared with control. Subgroup analysis showed that (1) both IV and oral bisphosphonates are well-tolerated; (2) the causes for secondary osteoporosis also did not influence the safety of bisphosphonates. Thus, our results indicate that bisphosphonates are well-tolerated in children over 3–24 months of follow-up.

Several limitations in our meta-analysis should be considered. (1) Methodology limitations existed in some included RCTs, such as unclear randomization and inadequate allocation concealment. (2) The case number of most RCTs is low. This may be because of the rigorous standard to include the patient with secondary osteoporosis. For example,

86 out of 118 persons did not meet the criteria in the study of Golden *et al.*[9] Besides, the criterion for osteoporosis in children was not consistent among the included RCTs. (3) The follow-up duration in these included studies ranged from 3 to 24 months. The long-term efficacy and safety of bisphosphonates remain unclear. (4) the existence of unexplained high heterogeneity indicates that other interference factors may still exist (such as different kinds of bisphosphonate and different dosages). Causes for secondary osteoporosis were quite diverse among the studies, which may still contribute to heterogeneity and other bias. (5) As mentioned above, there are obvious limitations for analyzing the data of fracture. These included studies were underpowered to detect the effect of fracture and did not use a standardized approach to fracture reporting.

Conclusion

This meta-analysis suggests that bisphosphonates use is efficacious and safe for the treatment of secondary childhood osteoporosis. The use of bisphosphonates may improve the change in LS BMD and BMD *Z*-scores without affecting the risk of AEs over 3–24 months of follow-up, which supports the use of bisphosphonates for secondary childhood osteoporosis for clinicians. However, because of the existence of potential biases, high heterogeneity, and other interfering factors, high-quality RCTs are still required to assess the efficacy and safety of the bisphosphonate treatment for secondary osteoporosis in children. In addition to a standardized approach to BMD reporting, fracture and other functional bone health outcomes should be also measured with a uniform standard in future RCT trials. Besides, it still needs to be further confirmed whether the efficacy of IV bisphosphonates was better than that of oral bisphosphonates for the treatment of secondary childhood osteoporosis.

Declarations

Ethics approval and consent to participate
Because the current research was based on the published data, no consent statement and ethical approval are required.

Consent for publication
Not Applicable.

Author contributions
Huawei Zhao: Conceptualization; Data curation; Formal analysis; Methodology; Resources; Software.

Yunfei Ding: Data curation; Formal analysis; Methodology; Software.

Jufei Yang: Data curation; Validation.

Yijun Luo: Data curation; Validation.

Zhenghao Xu: Conceptualization; Writing – original draft; Writing – review & editing.

Jing Miao: Conceptualization; Writing – original draft; Writing – review & editing.

Competing interests
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials
The authors confirm that the data supporting the findings of this study are available within the article or its Supplementary Materials.

ORCID iD
Zhenghao Xu https://orcid.org/0000-0003-0033-525X

Supplemental material
Supplemental material for this article is available online.

References
1. Osteoporosis prevention diagnosis therapy. *JAMA* 2001; 285: 785–795.

2. Sakka SD and Cheung MS. Management of primary and secondary osteoporosis in children. *Ther Adv Musculoskelet Dis* 2020; 12: 69262.

3. Kanis JA, Cooper C, Rizzoli R, *et al*. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteop Int: J Estab Result Cooper Eur Found Osteop Natl Osteop Found USA* 2019; 30: 3–44.

4. Ward L, Tricco AC, Phuong P, *et al*. Bisphosphonate therapy for children and adolescents with secondary osteoporosis. *Cochrane Database Syst Rev* 2007; 2007: CD005324.

5. Higgins JP, Altman DG, Gotzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343: d5928.

6. Feng C, Chen R, Wang K, *et al*. Chinese traditional medicine (GuiZhi-ShaoYao-ZhiMu decoction) as an add-on medication to methotrexate for rheumatoid arthritis: a meta-analysis of randomized clinical trials. *Ther Adv Chronic Dis* 2021; 12: 993438.

7. Henderson RC, Lark RK, Kecskemethy HH, *et al*. Bisphosphonates to treat osteopenia in children with quadriplegic cerebral palsy: a randomized, placebo-controlled clinical trial. *J Pediatr* 2002; 141: 644–651.

8. El-Husseini AA, El-Agroudy AE, El-Sayed MF, *et al*. Treatment of osteopenia and osteoporosis in renal transplant children and adolescents. *Pediatr Transplant* 2004; 8: 357–361.

9. Golden NH, Iglesias EA, Jacobson MS, *et al*. Alendronate for the treatment of osteopenia in anorexia nervosa: a randomized, double-blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2005; 90: 3179–3185.

10. Jacobson DL, Lindsey JC, Gordon C, *et al*. Alendronate improves bone mineral density in children and adolescents perinatally infected with human immunodeficiency virus with low bone mineral density for age. *Clin Infect Dis* 2020; 71: 1281–1288.

11. Kim SD and Cho BS. Pamidronate therapy for preventing steroid-induced osteoporosis in children with nephropathy. *Nephron Clin Pract* 2006; 102: c81–c87.

12. Rooney M, Bishop N, Davidson J, *et al*. The prevention and treatment of glucocorticoid-induced osteopaenia in juvenile rheumatic disease: a randomised double-blind controlled trial. *Eclinicalmedicine* 2019; 12: 79–87.

13. Rudge S, Hailwood S, Horne A, *et al*. Effects of once-weekly oral alendronate on bone in children on glucocorticoid treatment. *Rheumatology* 2005; 44: 813–818.

14. Zacharin M, Lim A, Gryllakis J, *et al*. Randomized controlled trial evaluating the use of zoledronic acid in duchenne muscular dystrophy. *J Clin Endocrinol Metab* 2021; 106: 2328–2342.

15. Ward LM, Choudhury A, Alos N, *et al*. Zoledronic acid vs placebo in pediatric glucocorticoid-induced osteoporosis: a randomized, double-blind, phase 3 trial. *J Clin Endocrinol Metab* 2021; 106: e52225.

16. Iwasaki T, Nonoda Y and Ishii M. Long-term outcomes of children and adolescents who had cerebral palsy with secondary osteoporosis. *Curr Med Res Opin* 2012; 28: 737–747.

17. Iwasaki T, Takei K, Nakamura S, *et al*. Secondary osteoporosis in long-term bedridden patients with cerebral palsy. *Pediatr Int* 2008; 50: 269–275.

18. Hobby BD, Dominguez-Bartmess S and Szalay EA. Prevention of postoperative osteopenia using IV pamidronate: a pilot study, 2013, https://pubmed.ncbi.nlm.nih.gov/23872799/

19. Klein GL, Wimalawansa SJ, Kulkarni G, *et al*. The efficacy of acute administration of pamidronate on the conservation of bone mass following severe burn injury in children: a double-blind, randomized, controlled study. *Osteoporos Int* 2005; 16: 631–635.

20. Galindo-Zavala R, Bou-Torrent R, Magallares-López B, *et al*. Expert panel consensus recommendations for diagnosis and treatment of secondary osteoporosis in children. *Pediatr Rheumatol Online J* 2020; 18: 20.

21. Watts NB and Diab DL. Long-term use of bisphosphonates in osteoporosis. *J Clin Endocrinol Metab* 2010; 95: 1555–1565.

22. Marrani E, Giani T, Simonini G, *et al*. Pediatric osteoporosis: diagnosis and treatment considerations. *Drugs* 2017; 77: 679–695.