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REVIEW

Prevention and treatment of bone loss and fractures in patients undergoing a hematopoietic stem cell transplant: a systematic review and meta-analysis

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The most effective method to prevent and treat bone loss following hematopoietic stem cell transplantation (HSCT) remains uncertain. We conducted a comprehensive search in four electronic databases until August 2015. We retrieved articles describing patients with bone loss or fractures who received HSCT. Controlled trials, with a follow-up period of at least 12 months, were included. Twelve studies (19 publications) met our inclusion criteria. A total of 643 participants underwent HSCT (85.7% allogeneic HSCT). There was a statistically significant lower mean bone mineral density (g/cm^2) percentage change of the lumbar spine (mean difference (MD) 7.8, 95% confidence interval (CI) 5.6–10.0) and femoral neck (MD 6.7, 95% CI 5.6–7.9) in the bisphosphonate therapy group compared with the control group with no bisphosphonate therapy at 12 months. In a subgroup analysis, seven different comparison groups were evaluated. The rate of fractures or X-ray findings of subclinical vertebral fractures was similar between groups. Bisphosphonates are promising in the prevention and treatment of bone loss following HSCT. Additional research is required to determine whether they reduce long-term fracture risk.

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INTRODUCTION

With advances in transplantation techniques and post-transplant care, the number of long-term survivors following hematopoietic stem cell transplantation (HSCT) is growing.[1,2] As patients survive long term, their risk of developing late complications such as bone loss also increase. Bone mineral density (BMD) loss can lead to increased bone fragility and fractures that can cause substantial morbidity and mortality and impair the quality of life during the survivorship period.[3]

Bone remodeling in the context of HSCT is complex and multiple factors are involved in post-transplantation bone loss. Pretransplantation chemotherapy, conditioning regimens, GvHD prophylaxis, glucocorticoid use and several endocrine factors have been implicated in post HSCT bone disease.[3,4] Other known risk factors for bone loss such as older age, immobilization, low body mass index, genetic factors and improper nutrition may also potentially contribute to bone loss following HSCT.[3,5]

A few studies have suggested that most of the bone loss in this setting occurs within the first year following transplantation with variable recovery thereafter.[6–8] Our previous research also shows that the incidence of fractures is significantly higher following HSCT compared with the general US population.[9] Most patients do not return to normal BMD levels, possibly because of prolonged risk exposure. General preventive measures with calcium (Ca) and vitamin D (VitD) supplementation have not been shown to prevent bone loss in this patient population.[10] In recent times a few studies have also been conducted to assess the efficacy of antiresorptive medications in preventing bone loss following HSCT.

To the best of our knowledge, there have been only two summaries of the literature to assess bone loss management strategies in this patient population.[2,11] These summaries did not make any conclusive recommendations. Controversies as to the best modality of prevention and treatment of bone loss and fractures following HSCT still remain. This is the first systematic review and meta-analysis to comprehensively evaluate the evidence and systematically analyze the treatments currently available to treat or prevent bone loss following HSCT.

MATERIALS AND METHODS

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement for reporting methods.[12,13]

Search and information sources

We searched on Medline, EMBASE, Cochrane Library and Web of Science from inception to August 2015 without any restrictions. Appendix A shows the search terms used in Medline. In addition, the reference lists from the identified clinical trials and the Clinicaltrials.gov registry were searched for possible references not otherwise found. Retrieved citations were exported into reference manager software and duplicates were removed.

Eligibility criteria and study selection

Our review encompassed a two-step screening process. In the first step, the titles and abstracts of the unique citations were independently screened by two reviewers (HIC and GSP). We included studies evaluating the effects of any antiresorptive

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medication or supplement to prevent or treat bone loss in patients receiving HSCT. We excluded studies reporting on young children (<15 years old), case reports, reviews or not original research articles. In the second step, full-text articles were acquired for the relevant citations. Studies were included if they were controlled trials (randomized or not), with a follow-up period of at least 12 months, and reported separate data on BMD and bone turnover markers for each intervention. Studies were excluded if the control group did not receive HSCT (that is, healthy individuals). A consensus was established at both steps and, when not reached, a third reviewer (MES-A) solved the disagreement.

Data collection process and data items

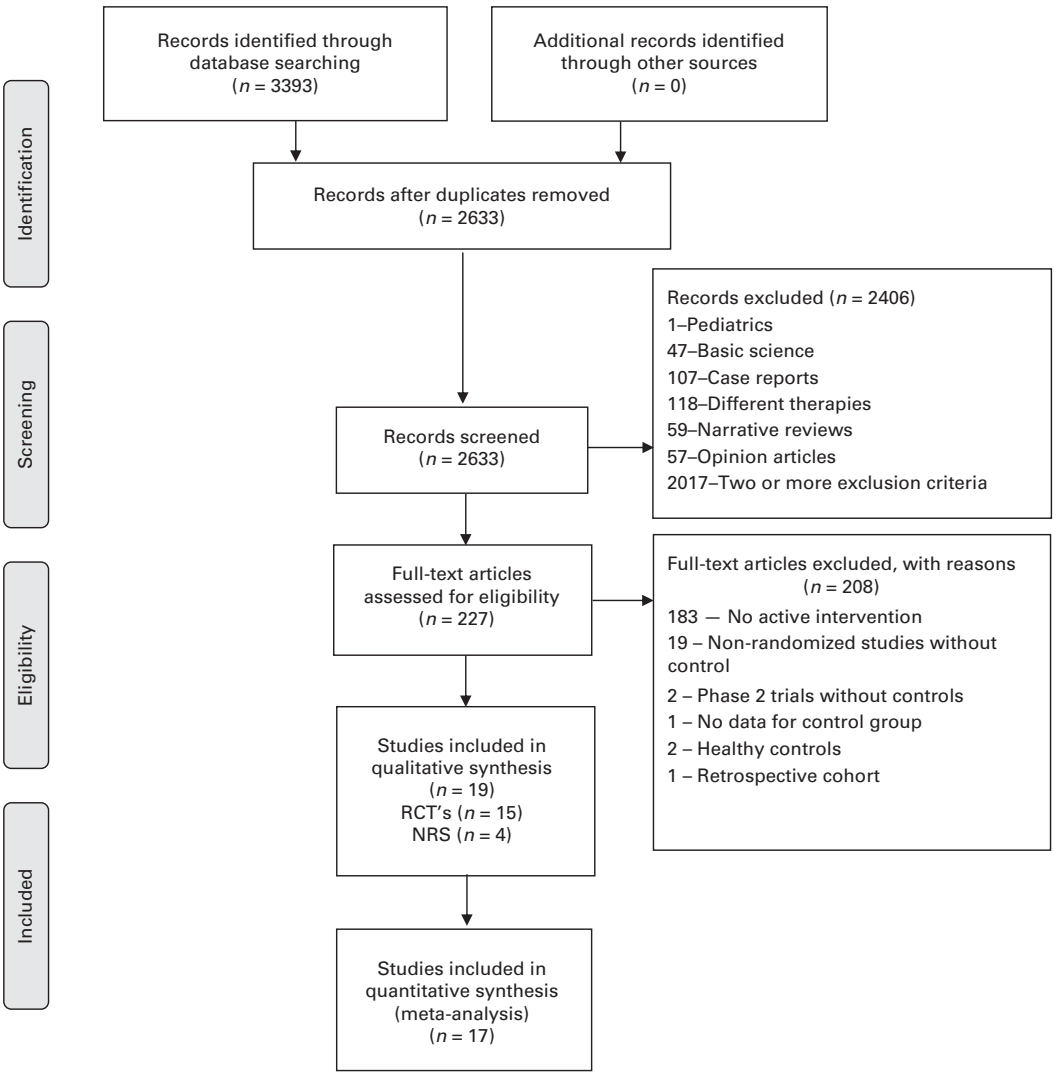
Data were independently extracted by two reviewers (HIC and GSP). Collected information included: (1) study design and general information, (2) details of treatment and control groups (age, gender, dosage and route of drug administration, duration of treatment and follow-up) and (3) outcome measures. Data were extracted from text, tables or graphs. In addition, we extracted sources of funding and other support such as intervention supply and the role of the funders.

Outcome measures

Our primary end points were bone loss measured by BMD (g/cm^2) at either the lumbar spine or femoral neck. We also evaluated the following secondary outcomes: fractures, bone turnover markers (for example, osteocalcin, carboxy-terminal collagen crosslinks, bone-specific alkaline phosphatase and so on), hormonal changes (for example, estradiol, parathyroid hormone, testosterone and so on) and adverse events (for example, avascular necrosis, osteonecrosis of the jaw, toxicity, infections, fever, flu-like symptoms, myalgia and so on).

Risk of bias across studies

The quality of the studies was evaluated independently by two reviewers (HIC and GSP). Details on methods used to assess the risk of bias can be found in the Supplementary Information section. Evaluation of publication bias through funnel plot



RTC's = Randomized controlled trials; NRS = Non-randomized studies; PRISMA = Preferred reporting Items for systematic reviews and meta-analyses

Figure 1. Flow diagram of the study selection process following PRISMA recommendations. A full color version of this figure is available at the *Bone Marrow Transplantation* journal online.

Table 1. Study characteristics of the included studies

No	Study	Design	Center	Follow-up (months)	Sample size	Funding	Overall risk of bias score[a]
1	Hari *et al.*[22–24]	RCT	Multicenter	24	61	Novartis Pharmaceuticals Corporation and Janie Lymphoma Fund (LJB.)	5
2	Tauchmanova *et al.*[16]	RCT	Single	12	60	Ministero dell'Universita` e della Ricerca Scientifica e Tecnologica (MURST), from Regione Campania and from Associazione Italiana Leucemie Linfomi (AIL) Salerno	7
3	Arabi *et al.*[17]	RCT	Single	12	8	Novartis	5
4	Tauchmanova *et al.*[14]	RCT	Single	12	34	Not mentioned	6
5	Jang *et al.*[25,26]	RCT	Single	12	73	Sanofi-Aventis Korea	9
6	Kananen *et al.*[27,28]	RCT	Not mentioned	12	72	Jalmari and Rauha Ahokas Foundation, Research Foundation of Orion Corporation, and Lilly Foundation and by research funding from Helsinki University Central Hospital (Erityisvaltionosuus)	5
7	Grigg *et al.*[19–21]	RCT	Multicenter	24	116	Novartis	7
8	Valimaki *et al.*[32]	RCT	Single	12	44	Sandoz Ltd, Basel, Switzerland	5
9	Pundole *et al.*[33]	RCT	Single	12	78	Not mentioned	5
10	Tauchmanova *et al.*[29,30]	Prospective cohort	Single	12	30	Ministero dell'Universita` e della Ricerca Scientifica e Tecnologica (MURST), from Regione Campania and from Associazione Italiana Leucemie Linfomi (AIL) Salerno	8
11	Chae *et al.*[18]	Prospective cohort	Single	24	53	Not mentioned	7
12	Wang *et al.*[31]	Prospective cohort	Single	24	12	Not mentioned	5

Abbreviations: BMD = bone mineral density; RCT = randomized controlled trial. [a]We generated an overall risk of bias score for any given randomized control trial by assigning scores to each of the domains assessed. For each domain there were three response options offered: low risk of bias (score 2), high risk of bias (score 0) or unclear risk of bias (score 1). For the nonrandomized studies we used the summary of the start system utilized by the Newcastle–Ottawa Scale (0 to 9 stars) for generating the overall score of risk of bias. More details by each domain for any given study and the methods used can be found in the Supplementary Information section.

asymmetry was planned if >10 studies were included to assess the primary outcome (power for tests is too low when <10 studies are included).

Synthesis of results and additional analysis

We performed a direct comparison meta-analysis using RevMan v5.3.[15] Dichotomous data were analyzed as relative risk (RR) and use 95% confidence intervals (CIs). Continuous data were analyzed as mean difference (MD) with corresponding 95% CI. Missing data was handled in two ways: (1) computing from other statistics (for example, s.e. to s.d.), extrapolating from graphs or other similar studies in the meta-analysis; and (2) exploring the impact of excluding such studies by a sensitivity analysis (dropping studies one by one from each comparison group for those that had missing data and evaluating the effect on the mean change). Fixed-effect model was used, but when heterogeneity was present, we used random-effects model. Heterogeneity was assessed by observing study characteristics, visually inspecting the forest plots to assess for obvious differences in result between the studies, and using the I^2 test. An I^2 value of $>40\%$ was considered substantial heterogeneity. We compared any bisphosphonate with no bisphosphonates for our primary outcome change in BMD at either the lumbar spine or femoral neck. A subgroup analysis was performed to compare therapies with different bisphosphonates separately to those not receiving bisphosphonates.

RESULTS

Study selection

Our search resulted in 3393 citations. We included 12 studies[14,16–33] in the qualitative synthesis and, of these, 10 studies were included in the quantitative synthesis.[14,16,18–32] Results from our stepwise selection process are shown in Figure 1. Eight studies were randomized open-label trials,[14,16,17,19–24,27,28,32,33] one was a randomized, double-blind trial[25,26] and three studies were nonrandomized and nonblinded trials.[18,29–31]

Study characteristics

Study characteristics are shown in Table 1. Two studies were multicenter.[19–24] One study did not specify the number of centers.[27,28] The rest of the studies were conducted in one center. The sample sizes ranged from 8 persons[17] to 116 persons.[19–21] The major outcome measured in 11 of the 12 studies was percent change in BMD (expressed in g/cm^2, *T*- and/or *Z*-score) of the lumbar spine (L1–L4) and femoral neck measured by dual-energy X-ray absorptiometry before HSCT, and 3, 6, 12, 24 or 36 months after HSCT.[14,16,18–33] Some studies analyzed BMD in other anatomical sites such as total hip[14,17,19–21,25–28,33] and trochanter.[17,27,28] One study evaluated changes in BMD under influences of glucocorticoid and cyclosporin therapy 12 months after HSCT.[19–21] Details on common secondary outcomes and bone turnover markers are listed in Supplementary Table 1. Bone turnover markers were reported in most studies except in three studies.[17,25,26,33] Six studies were funded by only pharmaceutical companies or pharmaceutical companies and private organizations.[17–28,32] Three studies did not disclose the source of funding.[14,31,33] Two studies were supported only by private foundations or organizations.[16,29,30]

Participant characteristics

A total of 643 participants were included. Of these, 562 (87.4%) underwent allogeneic HSCT,[14,16,18–24,27–33] 8 (1.2%) underwent autologous HSCT[17] and 73 (11.4%)[25,26] did not report the type of transplant. Table 2 shows participants' age and percent of females, eligibility criteria and interventions. Information on type of donor, source of stem cells, race, primary disease for

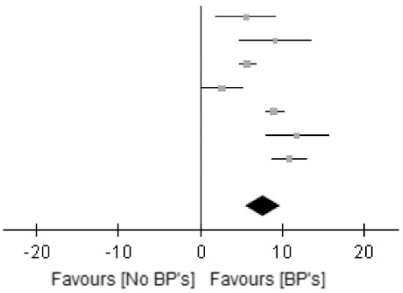
Table 2. Participants' characteristics

No	Study	Groups	Dose	Initiation and length of therapy	Inclusion criteria	Exclusion criteria	Age	Female	Type of HSCT
1	Hari *et al.*[22–24]	Ca/VitD vs Ca/VitD/ZA	Ca 1000 mg daily orally; 400 to 500 IU VitD daily orally; ZA 4 mg IV	Before HSCT and at 3 and 6 months after HSCT	>18 Years of age, *T*-score between −1 s.d. and −2.5 s.d. at either LS, proximal femur or both	Multiple myeloma, renal dysfunction or concomitant dental or endocrine problems	22 to 70	36%	Allogeneic
2	Tauchmanova *et al.*[16]	Ca/VitD vs Ca/VitD/HRT vs Ca/VitD/Ris vs Ca/VitD/ZA	Ca 1000 mg daily orally; 800 IU VitD daily orally; estradiol 2 mg daily and dihydroprogesterone 10 mg for 14 days a month for 12 consecutive cycles; Ris 35 mg weekly orally; ZA 4 mg IV	Median 4 months after HSCT; ZA every 28 days for 3 consecutive months	Allo-SCT, persistent amenorrhea	Not mentioned	17 to 36	100%	Allogeneic
3	Arabi *et al.*[17]	Ca/VitD/placebo vs Ca/VitD/ZA	Ca 1000 mg daily orally; 800 IU VitD daily orally; ZA 4 mg IV	Unclear start date; ZA 4 mg IV every 3 months for 1 year	Auto-SCT	Not mentioned	Not mentioned	Unknown	Autologous
4	Tauchmanova *et al.*[14]	Ca/VitD vs Ca/VitD/Ris	Ca 1000 mg daily orally; 800 IU VitD daily orally; Ris 5 mg orally once daily	Start 6 months after allo-SCT and continue for 6 months	Allo-SCT; T-score < −1.5 s.d. at LS and/or FN	GvHD and osteoporosis receiving ZA	20 to 51	53%	Allogeneic
5	Jang *et al.*[25,26]	Ca/VitD/placebo vs Ca/VitD/Ris	Ca 1 tab b.i.d.; Ris 35 mg per week (VitD dose not mentioned)	Not mentioned	HSCT	Not mentioned	Not mentioned	Not mentioned	Not mentioned
6	Kananen *et al.*[27,28]	Ca/VitD/HRT vs Ca/VitD/HRT/Pam	Ca 1000 mg daily orally; 800 IU VitD daily orally; 2 weeks after HSCT HRT[a]; Pam 6 IV infusions of 60 mg	Ca/VitD started after HSCT; HRT started 2 weeks after HSCT; pamidronate for 6 infusions with first just before and then 1, 2, 3, 6 and 9 months after HSCT	Allo-SCT for hematological malignancy	Multiple myeloma and diseases affecting bone, serum creatinine above reference limit	28 to 54	50%	Allogeneic
7	Grigg *et al.*[19–21]	Ca/VitD/HRT vs Ca/VitD/HRT/Pam	Ca 1000 mg daily orally; Calcitriol 0.25 μg daily orally; Pam 90 mg IV; all females received oral estrogen-containing preparation and progestogen in the majority; testosterone supplementation was not routine	Ca and VitD for 24 months; Pam started 1 week before pre transplant chemotherapy	Allo-SCT irrespective of donor source, stem cell type or intensity of conditioning regimen and had >20% expected long-term survival	Multiple myeloma	16 to 65	45%	Allogeneic
8	Valimaki *et al.*[32]	Ca/calcitonin vs Ca alone vs no intervention	Ca 1000 mg twice daily orally; Calcitonin intranasal 400 IU/day for first month and 200 IU/day for next 11 months	Ca and calcitonin for 12 months	Allo-SCT	Not mentioned	29 to 53	52%	Allogeneic
9	Pundole *et al.*[33]	Ca/VitD vs Ca/VitD/Ibandronate	Ca 500 mg twice daily orally; VitD 400 IU twice daily orally; Ibandronate iv 3 mg infusion (4 total doses)	First dose within 45 days of allo-SCT and at 3, 6 and 12 months; Ca and VitD for 12 months	Adult recipients of allo-SCT	Not mentioned	Adult patients	Not mentioned	Allogeneic
10	Tauchmanova *et al.*[29,30]	Ca/VitD vs Ca/VitD/ZA	Ca 500 mg daily orally; VitD 400 IU orally daily; ZA 4 mg IV over 15 min infusion every 28 days for 3 months	Ca/VitD started immediately after allo-SCT and continued for study period; ZA started at median 12.5 months post transplant	Allo-SCT; osteoporosis or rapidly progressing osteopenia (bone loss >5%/year) at median 12.5 month evaluation post allo-SCT	Not mentioned	19 to 44	47%	Allogeneic
11	Chae *et al.*[18]	Ca/VitD vs Ca/VitD/ZA (VitD and HRT not routinely administered)	Ca 1000 mg daily orally; VitD and HRT not routinely; ZA 4 mg IV infusion	Ca from discharge to 2 years; ZA starting at 2 months post allo-SCT and every 3 months until 2 years	Allo-SCT agreeing to use ZA	Renal failure, hyperparathyroidism, thyroid disorders	15 to 68	45%	Allogeneic
12	Wang *et al.*[31]	HRT vs no intervention	Not mentioned	Not mentioned	Allo-SCT; menopausal	Not mentioned	Not mentioned	100%	Allogeneic

Abbreviations: Allo-SCT = allogeneic stem cell transplantation; Ca = calcium; FN = femoral neck; HRT = hormone replacement therapy; HSCT = hematopoietic stem cell transplantation; LS = lumbar spine; Pam = Pamidronate; Ris = risedronate; VitD = vitamin D; ZA = zoledronic acid. [a]Female patients on estrogen patches releasing 50 μg estradiol per 24 h and 10 mg oral hydroxyprogesterone acetate; male patients on testosterone replacement therapy using patches that release 2.5 or 5 mg testosterone per 24 h dose adjusted based on serum testosterone level.

Table 3a. Mean differences comparing bisphosphonate with no bisphosphonate therapy for bone mineral density of the lumbar spine at 12 months

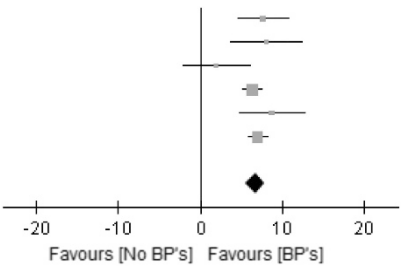
	Bisphosphonates			*No bisphosphonates*				*Mean difference*	*Mean difference*
Study or subgroup	*Mean*	*s.d.*	*Total*	*Mean*	*s.d.*	*Total*	*Weight*	*IV, Random, 95% CI*	*IV, Random, 95% CI*
Grigg *et al.*[19]	2.3	8	49	−3.3	8	30	12.2%	5.60 (1.97, 9.23)	
Hari *et al.*[23]	4.1	7	11	−5.14	3	19	10.7%	9.24 (4.89, 13.59)	
Jang *et al.*[25]	−0.7	1.7	16	−6.46	1.4	20	17.5%	5.76 (4.73, 6.79)	
Kananen *et al.*[27]	−0.25	1.5511	33	−2.9	7.3826	33	14.6%	2.65 (0.08, 5.22)	
Tauchmanova *et al.*[14]	5.7	1.7	15	−3.4	1.4	16	17.4%	9.10 (8.00, 10.20)	
Tauchmanova *et al.*[29]	9.8	7	15	−2.1	3	15	11.7%	11.90 (8.05, 15.75)	
Tauchmanova *et al.*[16]	7.2	5.2737	30	−3.7	1.9678	30	15.8%	10.90 (8.89, 12.91)	
Total (95% CI)			169			163	100.0%	7.77 (5.56, 9.98)	



Abbreviation: CI = confidence interval. Test for overall effect: $Z = 6.90$ ($P < 0.00001$). Heterogeneity: $Tau^2 = 6.97$; $\chi^2 = 50.24$, d.f. = 6 ($P < 0.00001$); $I^2 = 88\%$.

Table 3b. Mean differences comparing bisphosphonate with no bisphosphonate therapy for bone mineral density of the femoral neck at 12 months

	Bisphosphonates			*No bisphosphonates*				*Mean difference*	*Mean difference*
Study or subgroup	*Mean*	*s.d.*	*Total*	*Mean*	*s.d.*	*Total*	*Weight*	*IV, Random, 95% CI*	*IV, Random, 95% CI*
Grigg *et al.*[19]	−2.8	6.9	49	−10.5	6.6	30	10.8%	7.70 (4.65, 10.75)	
Hari *et al.*[23]	2	7	11	−6.1	3.5	19	5.7%	8.10 (3.67, 12.53)	
Kananen *et al.*[27]	−4.2	6.6616	33	−6.2	9.8339	33	6.7%	2.00 (−2.05, 6.05)	
Tauchmanova *et al.*[14]	1.3	1.2	15	−5.1	2	16	34.7%	6.40 (5.25, 7.55)	
Tauchmanova *et al.*[29]	6.47	7	15	−2.3	3.5	15	7.0%	8.77 (4.81, 12.73)	
Tauchmanova *et al.*[16]	3.3	2.7557	30	−3.75	1.5911	30	35.0%	7.05 (5.91, 8.19)	
Total (95% CI)			153			143	100.0%	6.74 (5.62, 7.86)	



Abbreviation: CI = confidence interval. Heterogeneity: $Tau^2 = 0.59$; $\chi^2 = 7.63$, d.f. = 5 ($P = 0.18$); $I^2 = 34\%$. Test for overall effect: $Z = 11.79$ ($P < 0.00001$).

undergoing a transplant and smoking status can be found in the Supplementary Information section.

Treatment was triggered by an abnormal baseline BMD in 3 of the 12 studies included in the analysis.[14,23,29] In one study, although treatment was not triggered by an abnormal BMD, all groups evaluated had osteopenia,[16] and in another study, 39% of patients had osteopenia at the lumbar spine and 25% had osteopenia at the femoral neck.[32] In contrast, majority of the patients in other studies had normal BMD levels.[18,19,27] Four of the studies were abstracts and did not provide sufficient information to evaluate baseline BMD status.[17,25,31,33]

Risk of bias

A summary of judgments about each risk of bias item is presented in Supplementary Figures 1a and b as percentages across all included studies. Several studies have attempted to provide a numerical score of risk of bias for a given study for simplicity.[34–36] However, use of an overall score for the risk of bias (that is, summarizing risk of bias across several outcomes for a given study) is strongly discouraged by the Cochrane workgroup.[37] We used the scoring used by Ferreira *et al.*[34] and a summary overall score of risk of bias is presented in Table 1 for each study.

Efficacy of the interventions

We compared changes in BMD at the lumbar spine and femoral neck between studies comparing bisphosphonate therapy with no bisphosphonate therapy. Seven studies reported change in BMD of the lumbar spine at 12 months. There was a statistically significant lower mean BMD (g/cm^2) percentage change of the lumbar spine in the bisphosphonate therapy group compared with the control group with no bisphosphonate therapy (MD 7.8, 95% CI 5.6–10.0; Table 3a). Similarly, six studies reported change in BMD of the femoral neck at 12 months. There was a statistically significant increase in mean BMD (g/cm^2) percentage change of the femoral neck in the bisphosphonate therapy group compared with the control group with no bisphosphonate therapy (MD 6.7, 95% CI 5.6–7.9; Table 3b).

One randomized controlled trial evaluating the role of ibandronate did not have sufficient information and was not included in the quantitative analysis.[33] Seven comparisons were evaluated in a subgroup analysis. We observed a statistically significant lower mean BMD (g/cm^2) percentage change in a majority of the comparisons that included a bisphosphonate in the treatment arm at most locations and time points assessed (Table 4). A detailed description of the subgroup analysis can be found in the Supplementary Information section. Findings of all other outcomes are shown in Supplementary Table 1.

Fractures. No statistically significant differences were observed in spontaneous fractures, X-ray findings of subclinical fractures and osteonecrosis of the jaw between any of the comparison groups (Supplementary Table 1).

Table 4. Subgroup analysis

	Follow-up (months)	*No. of studies*	*Sample size*	*MD (95% CI)*
Zoledronic acid+Ca/VitD versus Ca/VitD				
BMD lumbar spine	12	3	90	**11.5 (9.3, 13.8)**[a]
BMD femoral neck	12	3	90	**9.4 (8.2, 10.7)**[a]
T-score lumbar spine	12	1	30	**142.9 (141.5, 144.3)**
T-score femoral neck	12	1	30	**50.0 (49.5, 50.5)**
Z-score lumbar spine	12	1	30	**119.5 (118.7, 120.3)**
Z-score femoral neck	12	1	30	**83.7 (83.2, 84.2)**
Pamidronate+Ca/VitD+HRT versus Ca/VitD+HRT				
BMD lumbar spine	3	1	86	2.1 (−1.0, 5.2)
	6	2	150	**3.1 (1.2, 4.9)**
	12	2	145	**3.6 (1.5, 5.7)**
	24	1	63	2.9 (−1.4, 7.2)
BMD femoral neck	3	1	86	**3.0 (0.62, 5.4)**
	6	2	150	**3.5 (1.6, 5.4)**
	12	2	145	7.7 (−3.3, 18.8)[b]
	24	1	63	3.4 (−0.79, 7.6)
BMD total hip	3	1	86	**3.6 (1.4, 5.8)**
	6	2	150	**5.0 (3.1, 7.0)**[b]
	12	2	145	**4.3 (1.8, 6.8)**[b]
	24	1	63	**3.9 (0.28, 7.5)**
BMD trochanter	6	1	72	**5.1 (0.1, 10.2)**
	12	1	66	4.9 (−1.5, 11.3)
Risedronate+Ca/VitD versus Ca/VitD				
BMD lumbar spine	6	1	34	**8.7 (7.7, 9.7)**
	12	3	97	**8.2 (5.6, 10.9)**[b,c]
BMD femoral neck	6	1	34	**5.5 (4.4, 6.7)**
	12	2	61	**5.5 (4.7, 6.3)**
BMD total hip	6	1	34	**5.3 (4.4, 6.2)**
	12	1	31	**5.5 (4.5, 6.4)**
T-score lumbar spine	12	1	31	**29.9 (29.3, 30.6)**
T-score femoral neck	12	1	31	**26.5 (25.9, 27.2)**
T-score total hip	12	1	31	**22.2 (21.7, 22.7)**
Zoledronic acid+Ca versus Ca alone[d]				
Z-score lumbar spine	6	1	53	**1.2 (0.78, 1.6)**
	12	1	53	**1.5 (1.3, 1.7)**
	24	1	53	**1.9 (1.3, 2.5)**
Z-score femoral neck	6	1	53	**0.54 (0.28, 0.80)**
	12	1	53	**0.36 (0.21, 0.51)**
	24	1	53	**0.72 (0.04, 1.4)**
Ca/VitD+HRT versus Ca/VitD				
BMD lumbar spine	12	1	30	1.2 (−0.16, 2.6)
BMD femoral neck	12	1	30	0.90 (−0.21, 2.0)
Ca+Calcitonin versus no intervention				
BMD lumbar spine	6	1	32	1.0 (−2.4, 4.4)
	12	1	31	0.10 (−3.6, 3.8)
BMD femoral neck	6	1	32	1.3 (−4.9, 7.5)
	12	1	31	0.70 (−9.4, 10.8)
BMD trochanter	6	1	32	0.80 (−6.4, 8.0)
	12	1	31	−2.2 (−11.1, 6.7)
BMD Ward's triangle	6	1	32	2.2 (−5.4, 9.8)
	12	1	31	−1.6 (−9.1, 5.9)
Ca alone versus no intervention				
BMD lumbar spine	6	1	34	1.6 (−2.4, 5.6)
	12	1	30	2.6 (−1.5, 6.7)
BMD femoral neck	6	1	32	1.5 (−2.3, 5.3)
	12	1	31	0.00 (−3.9, 3.9)
BMD trochanter	6	1	32	2.1 (−3.9, 8.1)
	12	1	31	3.3 (−3.0, 9.6)
BMD Ward's triangle	6	1	32	4.0 (−8.1, 16.1)
	12	1	31	3.4 (−5.3, 12.1)

Abbreviations: BMD = bone mineral density; Ca = calcium; CI = confidence interval; HRT = hormone replacement therapy; MD = mean difference; VitD = vitamin D. All BMD measurements, *T*-scores and *Z*-scores expressed as percentage changes at 3, 6, 12 and 24 months from baseline. [a]For one study s.d. imputed from Tauchmanova *et al.*[29] [b]Random-effects model. [c]The s.d. imputed from Tauchmanova *et al.*[29] [d]Values expressed as differences in mean change. Entries in bold indicate statistically significant results.

Adverse events. In the zoledronic acid combined with Ca/VitD versus Ca/VitD alone subgroup, flu-like symptoms (that is, myalgia, nausea and increase in body temperature) were more common in patients in the zoledronic acid group compared with the control group (RR 25.0, 95% CI 1.6–387.4). Participants with at least one serious adverse event were more common in the zoledronic acid group compared with the control group (RR 2.4, 95% CI 1.3–4.5). Death rates at 12 months and overall mortality at 24 months were also increased in the zoledronic acid group compared with the control group (RR 2.3, 95% CI 1.0–5.0; and RR 2.3, 95% CI 1.1–4.8, respectively) (Supplementary Table 1). No statistically significant differences were observed in any of the reported adverse events in any of the other comparison groups (Supplementary Table 1).

Sensitivity analysis and publication bias. To handle missing data we conducted a sensitivity analysis. We did not observe any differences, and the inclusion of these studies did not impact the overall conclusion. As we had < 10 studies, publication bias could not be investigated.

DISCUSSION

Bone loss following HSCT occurs early following transplantation and is a multifactorial process.[11,22] The main goal of our study was to evaluate the available evidence on efficacy and safety of bisphosphonates and/or general preventive strategies in the prevention and treatment of post-transplant bone loss. Results of this systematic review and meta-analysis showed that patients receiving any bisphosphonate therapy showed an increase in BMD of the lumbar spine and femoral neck, or a lesser decrease in BMD, from baseline to 12 months compared with those not receiving any bisphosphonates.

Subgroup analysis of the different bisphosphonates used showed that zoledronic acid in combination with Ca/VitD supplementation prevented bone loss of lumbar spine and femoral neck at 1 year. Furthermore, evaluation of *Z*-scores of zoledronic acid in combination with Ca alone was effective in preventing lumbar spine and femoral neck bone loss at 6, 12 and 24 months following transplant. Similarly, risedronate in combination with Ca/VitD prevented bone loss of the lumbar spine, femoral neck and the total hip at 6 and 12 months.

Pamidronate in combination with Ca/VitD and hormone replacement therapy showed varying results; it prevented bone loss in the lumbar spine and trochanter at 6 and 12 months, but failed to do so at 3 and 24 months in the lumbar spine. In addition, this combination also prevented femoral neck bone loss at 3 and 6 months but failed to do so at 12 and 24 months. It also prevented bone loss of the total hip at 3, 6, 12 and 24 months. In contrast, Ca/VitD in combination with hormone replacement therapy did not prevent bone loss following transplantation in comparison with Ca/VitD. Similarly, Ca and calcitonin did not prevent bone loss following transplantation in comparison with no intervention. Ca alone also did not prevent bone loss following transplantation in comparison with no intervention.

Although bisphosphonates are commonly used in the post-transplant setting, they do have some side effects. A previous study found that patients taking zoledronic acid in combination with Ca/VitD had a greater number of deaths at 1 and 2 years. The authors of the primary study concluded that the increased mortality observed in the zoledronic acid group was not related to the adverse events related to bisphosphonates. They speculated that although they had well matched patients in terms of disease- and transplantation-related variables, there was considerable disparity in pretransplantation comorbidity scores and this was likely the explanation for the increased mortality observed. Furthermore, those taking zoledronic acid in combination with Ca/VitD had increased flu-like symptoms and greater number of patients affected with a serious adverse event than those only taking Ca/VitD.[23]

The risk of fractures or X-ray findings of subclinical vertebral fractures was not increased in any of the comparison groups, but this is likely as the studies were not sufficiently powered or of sufficient duration. Fracture development is an important outcome associated with increased morbidity and financial burden and future studies evaluating the efficacy of bisphosphonates should be designed to evaluate fracture occurrence outcomes. Our study shows that bisphosphonates are the most optimal pharmacological agents currently available to prevent bone loss following HSCT.

Our study is limited in that only different therapeutic groups were compared. The optimal dose, duration of therapy and when to start patients on preventive therapies could not be assessed. Additional questions for future studies include the frequency and timing of screening, the population that would benefit from bisphosphonate and other therapies, effects of treatment on fracture prevention and cost effectiveness of various approaches.

Another limitation of our review is that the included studies started treatment with bisphosphonates before, at the time of or right after the HSCT. Evaluating the role of bisphosphonates in long-term survivors was not comprehensively assessed in this systematic review. However, one randomized study evaluating the role of bisphosphonates in long-term survivors conducted by Tauchmanova *et al*.[14] was included in which risedronate treatment was started 17 to 24 months following grafting and they observed that lumbar spine BMD significantly improved within 12 months; it also prevented further femoral neck bone loss.

CONCLUSION

Bisphosphonates are promising in the prevention and treatment of bone loss following HSCT. In particular, zoledronic acid was effective in preventing bone loss of the lumbar spine and femoral neck; risedronate was effective in preventing bone loss of the lumbar spine and femoral neck and total hip; and pamidronate was variably effective in preventing lumbar spine, femoral neck, trochanter and total hip bone loss following HSCT.

Before more information is available, we propose that every patient undergoing HSCT should have their bone status evaluated. A dual-energy X-ray absorptiometry scan should be obtained and secondary causes of bone loss should be looked for. Bisphosphonates are the most commonly evaluated pharmacotherapy in this population and have shown to prevent bone loss in the early post-transplant period. However, because of the lack of information on fracture risk and the potential adverse effects of bisphosphonates, all patients on bisphosphonates should be monitored closely in order to assess improvement in bone strength and identify adverse events early on and manage them effectively. We believe that it is reasonable to start bisphosphonates and continue them at least for the first year post HSCT. Future studies directly comparing different bisphosphonate agents, dosing regimens and duration of treatment are imperative.

CONFLICT OF INTEREST

Dr Lopez-Olivo reports grants from Rheumatology Research Foundation, outside the submitted work. Dr Suarez-Almazor reports advisory/consulting role for Ardea Biosciences and a Pfizer Aspire Grant, outside the submitted work.

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AUTHOR CONTRIBUTIONS

Dr Suarez-Almazor had full access to all of the data in the study and takes responsibility for the integrity and the accuracy of the data analysis. Study concept and design: Suarez-Almazor and Lu; search strategy: Pratt; selection of the studies: Cheema, Sanchez Petitto, Pundole and Lopez-Olivo; quality appraisal and data extraction: Cheema, Sanchez Petitto, Pundole and Lopez-Olivo; analysis and interpretation of data: Cheema, Sanchez Petitto, Pundole, Lopez-Olivo, Lu and Suarez-Almazor; drafting of the manuscript: Cheema, Pundole, Lu and Lopez-Olivo; critical revision of the manuscript for important intellectual content: Cheema, Sanchez Petitto, Pundole, Lopez-Olivo, Lu and Suarez-Almazor; administrative, technical or material support: Suarez-Almazor; study supervision: Suarez-Almazor.

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