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Effect of Bisphosphonates on Bone Health in Adult Renal Transplant Patients: Beyond the First Year Posttransplant—A Systematic Review and Meta-Analysis

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Abstract

Background: Bone mineral density (BMD) decreases postrenal transplantation. Evidence demonstrating the effects of bisphosphonates on BMD and fracture risk beyond 1-year posttransplant is sparse in existing literature, but remains essential to enhance clinical outcomes in this population.

Objective: Our study aimed to systematically review and meta-analyze the current literature on the use of any bisphosphonate in the adult renal transplant population beyond the first year of renal transplant to determine its effect on BMD and fracture incidence.

Design: We conducted a systematic review and meta-analysis of primary research literature that included full-text, English-language, original randomized clinical trials (RCTs) and observational studies.

Setting: Patient data were primarily captured in an outpatient setting across various studies.

Patients: Our population of interest was patients older than 18 years who received deceased/living donor kidney transplantation and any bisphosphonate with a follow-up greater than 12 months posttransplantation.

Measurements: The primary outcome was change in BMD from baseline. Secondary outcomes were the incidence of fractures and effects of other confounders on bone health.

Methods: We included RCTs and observational studies that satisfied our inclusion criteria. Each study was analyzed for risk of bias and data were extrapolated to analyze for overall statistical significance accounting for heterogeneity of studies.

Results: Sixteen studies (N = 1762) were analyzed. The follow-up ranged from 12 to 98 months. There was a nonsignificant improvement in BMD with bisphosphonate treatment persisting into the second and third years posttransplant at the lumbar spine. The calculated standardized mean BMD difference was −0.29 (−0.75 to 0.17), $P = .22$. Only 5 studies reported a total of 43 new fractures. Prednisone ($P < .01$), low body weight ($P < .001$), low body mass index ($P < .01$), and male gender ($P < .05$) correlated with reduced lumbar and femoral BMD.

Limitations: Limitations of this review include the use of BMD as a surrogate outcome, the bias of the included studies, and the incomplete reporting data in numerous analyzed studies.

Conclusions: We demonstrate no statistically significant benefit of bisphosphonate treatment on BMD beyond the first year postrenal transplantation. Despite heterogeneity of treatment, a differential nonsignificant improvement in lumbar spine BMD was consistent and may be clinically relevant.

Trial Registration: PROSPERO CRD42019125593

Abrégé

Contexte: La densité minérale osseuse (DMO) décroit à la suite d'une greffe rénale. Les données probantes faisant état des effets des bisphosphonates sur la DMO et le risque de fracture au-delà d'un an post-greffe sont rares dans la littérature, mais demeurent essentielles pour améliorer les résultats cliniques pour cette population.

Objectif: L'étude actuelle visait à réaliser une revue systématique et une méta-analyse de la littérature faisant état de l'usage des bisphosphonates dans une population de greffés rénaux adultes, au-delà de la première année post-greffe, afin de connaître les effets de cette médication sur la DMO et sur l'incidence de fractures.

Type d'étude: Une revue systématique et une méta-analyse de la littérature ont été réalisées à partir d'articles rédigés en anglais, présentant les résultats d'essais cliniques et d'études observationnelles.

Cadre: Dans les différentes études, les données provenaient principalement de patients suivis sur une base externe.
Sujets: Notre population d'intérêt était constituée de patients adultes ayant subi une greffe rénale provenant d'un donneur décédé ou vivant, ayant reçu un traitement par un bisphosphonate et ayant été suivis pendant plus de douze mois post-transplantation.
Mesures: L'issue principale était une variation de la DMO par rapport à la valeur initiale. L'incidence de fractures et les effets des autres facteurs de confusion sur la santé osseuse constituaient les issues secondaires.
Méthodologie: Ont été inclus les essais cliniques et les études observationnelles qui répondaient à nos critères d'inclusion. Chaque étude a fait l'objet d'une analyse des risques de biais et les données ont été extrapolées pour analyser la signification statistique de l'ensemble en tenant compte de l'hétérogénéité des études.
Résultats: Seize études (n=1762) ont été analysées. La période de suivi variait de 12 à 98 mois. Une amélioration non significative de la DMO du rachis lombaire ayant persisté dans la deuxième et la troisième année post-greffe a été observée à la suite d'un traitement par un bisphosphonate. La moyenne normalisée calculée des variations de la DMO s'établissait à -0,29 (-0,75 à 0,17; p=0,22). Seules cinq études ont rapporté de nouvelles fractures, pour un total de 43 fractures. La prise de prednisone ($p<0,01$), un faible poids ($p<0, 001$), un faible IMC ($p<0,01$) et le fait d'être un homme ($p<0,05$) ont corrélé avec une DMO lombaire ou fémorale réduite.
Limites: Le recours à la DMO comme issue intermédiaire, les biais contenus dans les études incluses et le fait que plusieurs des études analysées comportaient des données incomplètes constituent les limites de l'étude.
Conclusion: Nous n'avons pu démontrer un avantage statistiquement significatif sur la DMO à poursuivre un traitement par les bisphosphonates au-delà de la première année suivant une greffe rénale. Malgré l'hétérogénéité du traitement, une amélioration non significative de la DMO lombaire a été observée et pourrait s'avérer pertinente sur le plan clinique.

Keywords
renal transplantation, osteodystrophy, bisphosphonate

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What was known before

Rapid bone loss occurs in the first year postrenal transplantation but is a chronic disease. Existing systematic reviews identify a benefit of bisphosphonates in reducing bone mineral density (BMD) loss in the first 12 months posttransplant.

What this adds

This current review adds there is no statistically significant benefit to bisphosphonate treatment on BMD beyond 1 year postrenal transplantation.

Introduction

End-stage renal disease (ESRD) is associated with renal osteodystrophy (osteitis fibrosa, adynamic bone disease, and osteomalacia).[1-4] A well-functioning renal allograft ameliorates many metabolic abnormalities associated with the development of mineral and bone disorders (MBDs) of ESRD. However, renal transplant recipients are particularly susceptible to bone damage due to a multitude of factors including preexisting bone disorders, immunosuppression, and alteration in the renal-bone metabolism axis.[5,6]

Bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DEXA) has been shown to decrease below 2 standard deviations (SDs) posttransplantation,[7] with estimated 3%-7% loss in the lumbar spine in the first year.[8-11] Ongoing vertebral bone loss (approximately 2%/yr) has been demonstrated in longitudinal evaluation of BMD in 70 renal transplant recipients.[12]

There are few studies demonstrating that low BMD predicts fractures in renal recipients. Akaberi et al[13] showed that low hip BMD predicted fractures in 238 renal recipients. The prevalence of fractures in the posttransplant population is up to 4-fold greater than pretransplant statistics, ranging widely between 5% and 44%, likely due to variations in observation time, definitions of fractures included, and the presence of diabetes.[14-17]

There is currently no established strategy for the prevention of posttransplant osteopenia and osteoporosis. Bisphosphonates, which inhibit osteoclast activity, are widely accepted as a treatment for osteopenia and osteoporosis in the

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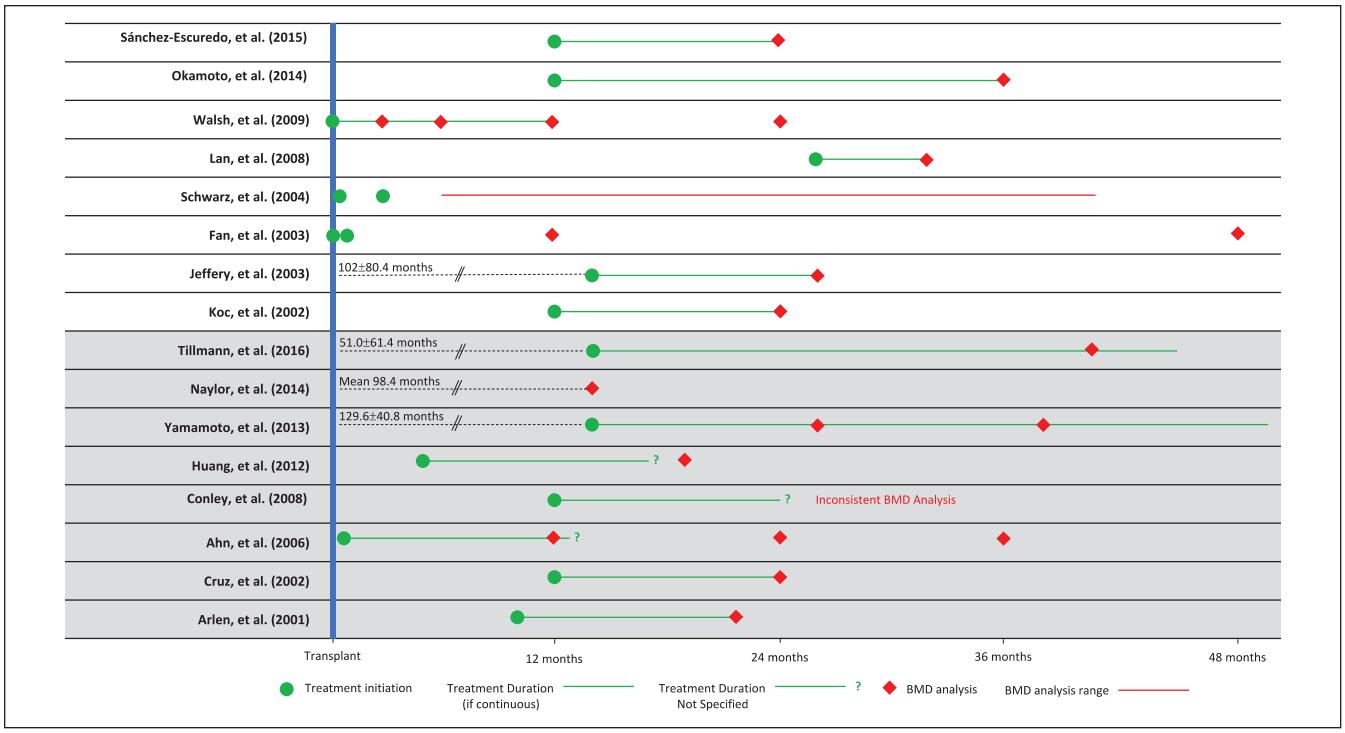

Figure 1. Summary of study timelines in postrenal transplant patients on bisphosphonate therapy.
Note. BMD = bone mineral density.

general population.[18] They have also been shown to protect against bone loss in the renal transplant recipients,[1,7,19,20] although a specific risk is the potential to exacerbate a baseline low-turnover adynamic state.[1,21,22]

The currently available research on bisphosphonate use in the renal transplant population is limited to analysis of randomized clinical trial (RCTs) within the first year posttransplant[18,23-25] The first year posttransplant is wrought with confounding factors including the physiologic adjustments in metabolism, the uremic effects of ESRD, the fluctuant nature of the posttransplant course, and aggressive immunosuppression.

Our study aimed to systematically review and meta-analyze the current literature on the use of any bisphosphonate in the adult renal transplant population beyond the first year of renal transplant to determine its effect on BMD and fracture incidence.

Methods

Eligibility Criteria

We conducted a systematic review and meta-analysis of primary research literature that included full-text, English-language, original RCTs and observational studies. Our population of interest was patients older than 18 years who received deceased/living donor kidney transplantation and any bisphosphonate with a follow-up greater than 12 months posttransplantation (Figure 1). Supplemental Table S1 summarizes the inclusion and exclusion criteria of our review.

Search Strategy

Electronic searches were performed in MEDLINE, EMBASE, and the Cochrane Register of Controlled Trials (CENTRAL) between 1946 and 2017 (Figure 2). A sample search strategy is outlined in Supplemental Figure 1.

Data Extraction and Outcome Measures

Each included study was assessed in conjunction by 2 authors (A.L. and A.W.) for data extraction (Tables 1-4). The primary outcome was the change in BMD from baseline. The secondary outcomes were the incidence of fractures and the effects of other confounders that may modify the risk of osteoporosis and fractures.

Bias Assessment

Articles were independently assessed by each reviewer (A.L. and A.W.), and dichotomized to low/high risk of bias based on standardized scoring systems. An RCT was considered low risk if it satisfied a score of 8 or more based on the Cochrane Risk of Bias Tool Criteria (Supplemental Table S2).[43] An observational trial was considered low risk if it

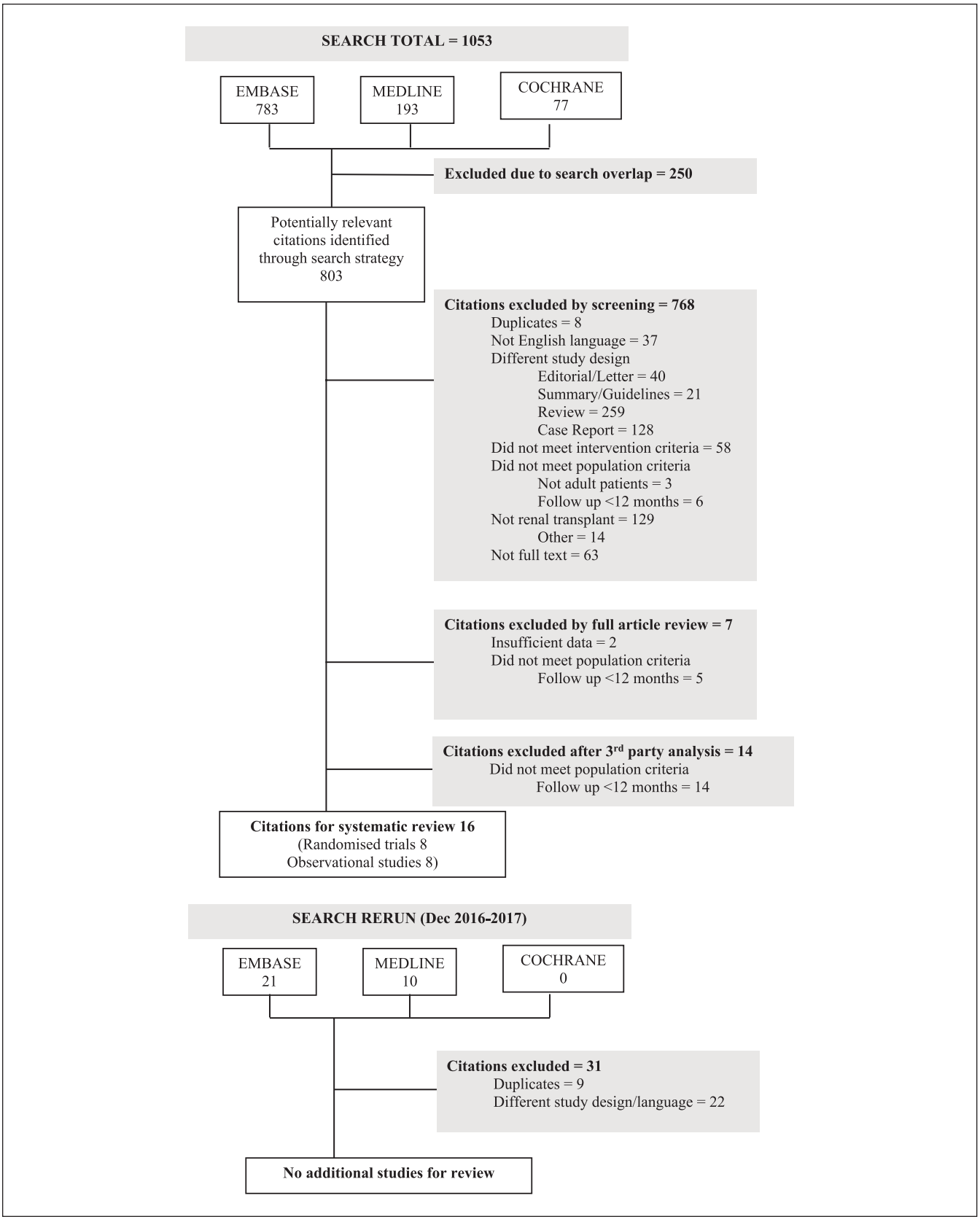

Figure 2. Schema of literature search.

Table 1. Duration of Bisphosphonate Therapy and Follow-up in Postrenal Transplant Patients.

Study	Treatment	Concomitant treatment	Treatment start date	Treatment duration	Time of outcome analysis from treatment initiation
Sánchez-Escuredo et al[26]	Oral ibandronate 150 mg monthly (n = 35) Control: Oral risedronate 35 mg weekly (n = 34)	$CaCO_3$ 2500 mg Vitamin D 800 IU	At least 12 months posttransplant	12 months	12 months
Okamoto et al[27]	Oral alendronate 35 mg per week (n = 5) Control: no bisphosphonates (n = 7)	Not specified	At least 12 months posttransplant	24 months	24 months
Walsh et al[28]	IV pamidronate 1 mg/kg within 14 days of transplant and 1, 4, 8, and 12 months after transplant (n = 46) Control: no intervention (n = 47)	Calcium $CaCO_3$ 500 mg Cholecalciferol 400 IU	At transplantation	12 months	3, 6, 12, and 24 months
Lan et al[29]	Alendronate 70 mg/wk for 6 months (n = 23) Control: no intervention (n = 23)	$CaCO_3$ 800 mg Calcitriol 0.25 µg for 6 months	Treatment: 25.9 ± 10.6 months Control: 27.1 ± 12.4 months	6 months	6 months
Schwarz et al[30]	IV zoledronic acid 4 mg at 2 weeks and 3 months (n = 9) Control: placebo (n = 10)	Calcium citrate 1000 mg daily for first 6 months	At time of transplantation	2 doses—at 2 weeks and 3 months posttransplant	6 to 36 months
Fan et al[31]	IV pamidronate 0.5 mg/kg at the time of transplant and 1 month later (n = 9) Control: 500 mL NS (n = 8)	Not specified	At the time of transplantation	2 doses—at the time of transplant and 1 month later	12 and 48 months
Jeffery et al[32]	Alendronate 10 mg/d open label (n = 57; 46 completed 1 year) Control: Calcitriol 0.25 µg/d (n = 60; 51 completed 1 year)	Calcium 500 mg/d	102 ± 80.4 months (8.5 ± 6.7 years) posttransplantation	12 months	12 months
Koc et al[33]	1: Alendronate 10 mg/d (n = 8) 2: Calcitriol 0.5 µg/d (n = 8) Control: no intervention (n = 8)	Calcium 1000 mg/d	Minimum duration of renal transplant was 12 months	Study period: 12 months	12 months
Tillmann et al[34]	IV ibandronate 3 mg every 3 months (average dose 12.0 ± 6.7 g) (n = 30) Control: No intervention (n = 30)	Not specified	51.0 ± 61.4 months after transplant First BMD measured at minimum 14 months posttransplant	Average 19.3 ± 11 months	26.8 ± 12.1 months after first measurement

(continued)

Table 1. (continued)

Study	Treatment	Concomitant treatment	Treatment start date	Treatment duration	Time of outcome analysis from treatment initiation
Naylor et al[35]	Unspecified bisphosphonate, grouped into "osteoporosis treatment"—includes >90% bisphosphonate, nasal calcitonin, raloxifene, systemic estrogen (n = 329) No comparator	—	—	—	Mean 98.4 months (8.2 years) follow-up from study start
Yamamoto et al[36]	Oral alendronate 35 mg/wk (n = 24) No control group	Not specified	129.6 ± 40.8 months (10.8 ± 3.4 years) posttransplant	36 months treatment period	12 and 24 months
Huang et al[37]	Alendronate 70 mg/wk (n = 41) Control: no intervention (n = 35)	Not specified	At least 5 months posttransplantation	Duration of treatment unclear	14 ± 1.6 months
Conley et al[38]	Bisphosphonate as prescribed by treating physician (n = 315) Control: no intervention (n = 239)	Intervention: Calcium = 170 (71.1%) Vitamin D = 35 (14.6%) Active vitamin D = 11 (4.6%) Control: Calcium = 220 (69.8%) Vitamin D = 83 (26.3%) Active vitamin D = 39 (12.4%)	12 months posttransplant	Treatment duration not specified	Not consistent
Ahn et al[39]	Oral alendronate sodium or risedronate sodium (dose not specified) Control: alfacalcidol (dose not specified) (n = 294, total)	Calcium (dose not specified)	In study group, within 1 month of transplant	Treatment duration not specified	12, 24, and 36 months posttransplant
Cruz et al[40]	Oral alendronate 10 mg/d (n = 29, high risk) Control: no intervention (n = 28, low risk)	None	12 months posttransplant	Study period: 12 months	12 months
Arlen et al[41]	Oral etidronate disodium 400 mg for 2 weeks of every 12 weeks (n = 25) Control: no intervention (n = 24)	Calcium replacement and Vitamin D at the discretion of the treating physicians Patients held medication during the 2 weeks of treatment Intervention: $CaCO_3$ (n = 3) Calcitriol (n = 4) Control: $CaCO_3$ (n = 3) Calcitriol (n = 8)	Treatment: 10.4 ± 5.3 months after transplant Control: 10.7 ± 4.5 months	Study period: 12 months	12 months

Note. IU = international unit; IV = intravenous; NS = normal saline; BMD = bone mineral density. White is RCT, Grey shaded region is Observational trials.

Table 2. Baseline Characteristics of Included Studies.

Study	Year	Population (male/female)	Mean age (mean ± SD)	Time after transplant	Intervention	Comparator	Funding support
Randomized control trials							
Sánchez-Escuredo et al	2015	77 (19/58)	Ibandronate: 63 ± 12 Risedronate: 64 ± 10	Ibandronate: 20 ± 8 months Risedronate: 18 ± 7 months	Ibandronate 150 mg/month Vitamin D 800 IU $CaCO_3$ 2500 mg (n = 38)	Risedronate 35 mg/wk Vitamin D 800 IU $CaCO_3$ 2500 mg (n = 39)	NA
Okamoto et al	2014	12 (8/4)	Alendronate: 52.8 ± 12.6 Control: 52.9 ± 7.3	Alendronate: 59.6 ± 59.5 months Control: 45.3 ± 42.3 months	Alendronate 35 mg/wk for 24 months (n = 5)	No intervention (n = 7)	MSD K.K.
Walsh et al	2009	93 (69/24)	Treatment: 46.1 ± 12.77 Control: 46.1 ± 12.93	0	Pamidronate IV 1 mg/kg peri-op, 1, 4, 8 and 12 months $CaCO_3$ 500 mg Cholecalciferol 400 units (n = 46)	$CaCO_3$ 500 mg Cholecalciferol 400 units (n = 47)	Novartis
Lan et al	2008	46 (19/27)	Treatment: 40.2 ± 18.5 Control: 39.4 ± 17.3	Treatment: 25.9 ± 10.6 months Control: 27.1 ± 12.4 months	Alendronate 70 mg/wk $CaCO_3$ 800 mg/d Calcitriol 0.25 µg/d (n = 23)	$CaCO_3$ 800 mg/d Calcitriol 0.25 µg/d (n = 23)	Not reported
Schwartz et al	2004	19 (not reported)	Not reported	0	Two infusions of 4 mg zoledronic acid at 2 weeks and 3 months posttransplant (n = 9)	Placebo (n = 10)	Not reported
Fan et al	2003	126 (26/0)	Treatment: 46.2 (21.1-67.1) Control: 41.5 (21.3-65) Mean age calculated with only patients with BMD measurements at 4 years	Not reported	Pamidronate IV 0.5 mg/kg in 500 mL NS peri-op and at 1 month (n = 14)	500 mL NS (n = 12)	Not reported
Jeffrey et al	2003	117 (97 completed treatment) (71/26)	Treatment: 44.8 ± 11.6 Control: 45.9 ± 10.8 Mean age documented is at the time of transplant and calculated with only patients who completed treatment	Treatment: 85.2 ± 62.4 months Control: 115.2 ± 81.6 months Mean duration calculated with only patients who completed treatment	Alendronate 10 mg/d open label Calcium (*unspecified dose*) (n = 60) 46 completed treatment	Calcitriol 0.25 µg/d Calcium (*unspecified dose*) (n = 57) 51 completed treatment	Not reported
Koc et al	2002	24 (17/7)	Alendronate: 34.3 ± 8.9 Calcitriol: 40.5 ± 8.1 Control: 35.5 ± 8.4	Alendronate: 48.7 ± 50.1 months Calcitriol: 47.4 ± 46.4 months Control: 41.5 ± 37.1 months	11: Alendronate 10 mg/d Calcium 1000 mg/d (n = 8) 12: Calcitriol 0.5 µg/d Calcium 1000 mg/d (n = 8)	Calcium 1000 mg/d (n = 8)	Not reported

(continued)

Table 2. (continued)

Study	Year	Population (male/female)	Mean age (mean ± SD)	Time after transplant	Intervention	Comparator	Funding support
Observational studies							
Naylor et al	2014	326 (199/27)	46.1 ± 12	6.12 (2.4-24) months	>90% bisphosphonates, nasal calcitonin, raloxifene, systemic estrogen	No control group	NA
Yamamoto et al	2013	24 (12/12)	52 ± 7.8	129.6 ± 40.8 months	Alendronate 35 mg/d	No control group	NA
Huang et al	2012	76 (36/40)	Treatment: Male: −51.9 ± 9.0 Female: −53.3 ± 8.8 Control: Male: −48 ± 10.4 Female: −49.7 ± 7.6	Treatment: Male: −103.7 ± 59.4 Female: −53.3 ± 8.8 Control: Male: −92 ± 68.1 Female: −61.4 ± 39.6	Alendronate 70 mg/wk (n = 34)	No intervention (n = 42)	NA
Conley et al	2008	554 (320/234)	Treatment: 45.9 ± 0.7 Control: 46.9 ± 0.2	Not reported	Bisphosphonate, type not described Calcium = 170 (71.1), Vitamin D = 35 (14.6), Active vitamin D = 11 (4.6) (n = 315)	Calcium = 220 (69.8) (NS) Vitamin D = 83 (26.3) (*P* = .001) Active vitamin D = 39 (12.4) (*P* = .003) (n = 239)	Not reported
Ahn et al	2006	294	Not reported	Within 1 month	Calcium Alfacalcidol or bisphosphonate (alendronate or risendronate)	No intervention	Not reported
Cruz et al	2002	58 (39/19)	Treatment: 48.6 ± 2.0 Control: 46.2 ± 2.0	Treatment: 97.2 ± 8.4 months Control: 84 ± 10.8 months	Alendronate 10 mg/d (n = 29)	No intervention (n = 29)	NCRR grant, National Kidney Foundation of Connecticut, NIH
Arlen et al	2001	49 (29/20)	Treatment: 41 ± 13 Control: 42 ± 12	Treatment: 10.4 ± 5.2 months Control: 10.8 ± 4.5 months	Etidronate disodium 400 mg for 2 weeks out of every 12 $CaCO_3$ (n = 3) Calcitriol (n = 4) (n = 25)	No intervention $CaCO_3$ (n = 3) Calcitriol (n = 8, *P* < .03) (n = 24)	Not reported
Tillmann et al	2001	60 (24/36)	Treatment: 47.9 ± 13.4 Control: 45.7 ± 11.4 Mean age documented is at the time of transplant	Treatment: 51 ± 61.4 months Control 59.6 ± 59.7 months	Ibandronate 3 mg IV Q3 months (n = 30)	No intervention (n = 30)	None

Note. IU = international unit; NA = not applicable; IV = intravenous; BMD = bone mineral density; NS = normal saline; NCRR = National Center for Research Resources; NIH = National Institutes of Health.

Table 3. Change in Bone Mineral Density in Postrenal Transplant Patients Between Bisphosphonate and Control Groups.

	BMD		
Study	Lumbar	Femoral neck	Other
Sánchez-Escuredo et al[26] I1: n = 35 I2: n = 34	T-score at pretreatment/12 months I1: −1.7 ± 0.8/−1.4 ± 0.6 I2 −1.9 ± 0.8/−1.5 ± 0.8	T-score at pretreatment/12 months I1: −2.1 ± 0.7/−1.8 ± 0.9 I2: −2.2 ± 0.6/−1.8 ± 0.8	
Okamoto et al[27] I: n = 5 C: n = 7	NA	NA	Total BMD: % change from baseline I: 1.86% ± 0.85%, $P < .05$ *No other raw data provided*
Walsh et al[28] I: n = 46 C: n = 47	% change in BMD at 12 months from baseline AMTD: 7.78%, 95% CI: 5.15-10.41, $P < .001$ Significant difference between groups at 24 months *No raw data*	% change in BMD at 12 months from baseline AMTD: 2.51%, 95% CI: −0.33 to 5.35, $P = .08$ No significant difference between groups at 24 months *No raw data*	Ward's area: Significant increase in I vs C at both 12 and 24 months AMTD: 5.83%, 95% CI: 2.19-9.45, $P < .01$ Total hip: Significant increase in I vs C at both 12 and 24 months AMTD: 2.79%, 95% CI: 0.92-4.67, $P < .01$
Lan et al[29] I: n = 23 C: n = 23	Mean g/cm^2 at pretreatment/6 months I: (L1) 0.781 ± 0.117/0.820 ± 0.114, NS C: (L1) 0.760 ± 0.062/0.771 ± 0.069, NS	Mean g/cm^2 at pretreatment/6 months I: 0.650 ± 0.107/0.731 ± 0.109, $P < .05$ C: 0.657 ± 0.061/0.676 ± 0.060, NS Significant difference between groups at 6 months posttreatment,$P < .05$	Trochanter: Mean g/cm^2 at pretreatment/6 months I: 0.524 ± 0.093/ 0.572 ± 0.103, NS C: 0.54 ± 0.082/ 0.561 ± 0.079, NS
Schwarz et al[30] I: n = 9 C: n = 10	Z-score at 6 months to 32 months posttreatment I: No difference C: No difference NS between groups No raw data	Z-score at 6 months to 32 months posttreatment I: −1.6 (2.9) to −1.2 (1.9), $P < .05$ between groups, $P < .05$ C: −1.3 (2.6) to −0.2 (3.6), $P < .05$ between groups, $P < .05$ median and range	
Fan et al[31] I: n = 9 C: n = 8	Mean g/cm^2 at baseline/1 year/4 years I: 1.15 ± 0.07/(1 year) 1.11 ± 0.05, NS/(4 years) 1.10 ± 0.04, NS C: 1.27 ± 0.07/(1 year) 1.2 ± 0.5, $P < .05$/(4 years) 1.21 ± 0.08, NS	Mean g/cm^2 at baseline/1 year/4 years I: 0.93 ± 0.05/(1 year) 0.94 ± 0.04, NS/(4 years) 0.88 ± 0.04, NS C: 1.08 ± 0.07/ (1 year) 0.98 ± 0.06, $P < .05$/(4 years) 0.94 ± 0.06, $P < .01$	

(continued)

Table 3. (continued)

Study	BMD		
	Lumbar	Femoral neck	Other
Jeffery et al[32] I: n = 57 C: n = 60	Mean g/cm^2 at pretreatment/12 months I: 0.984 ± 0.149/1.025 ± 0.143, $P < .001$ C: 1.014 ± 0.15/1.034 ± 0.146, $P < .01$ NS between groups at 12 months ($P = .082$)	Mean g/cm^2 at pretreatment/12 months I: 0.809 ± 0.092/0.836 ± 0.107, $P < .001$ C: 0.830 ± 0.144/0.857 ± 0.125, $P < .05$ NS between groups at 12 months ($P = .96$)	
Koc et al[33] I1: n = 8 I2: n = 8 C: n = 8	Mean g/cm^2 at 12 months/pretreatment I1: 1.050 ± 0.086/1.122 ± 0.094, $P < .01$ I2: 0.963 ± 0.142/ 1.034 ± 0.119, $P < .05$ C: 1.082 ± 0.187/1.095 ± 0.142, NS % change of BMD I1: 8.15% ± 9.2% I2: 6.89% ± 4.03% C: 0.06% ± 1.41% $P < .05$ compared with control	Mean g/cm^2 at 12 months/pretreatment I1: 0.826 ± 0.121/ 0.902 ± 0.092, $P < .05$ I2: 0.816 ± 0.121/0.902 ± 0.092, NS C: 0.933 ± 0.082/0.947 ± 0.082, NS % change of BMD I1: 9.34 ± 10.47% I2: 8.51 ± 13.8% C: 1.92 ± 2.52% NS compared with control	
Tillmann et al[34] I: n = 30 C: n = 30	Z-score at pre-treatment/26.8 ± 12.1 months I: −2.25 ± 1.11/−1.78 ± 1.30, $P < .05$ C: −0.52 ± 1.52/−0.28 ± 1.55, $P < .05$ Change in BMD I: 0.055 ± 0.066 C: 0.033 ± 0.079 NS between groups, $P = .217$	Z-score at pretreatment/26.8 ± 12.1 months I: −1.97 ± 0.85/−1.73 ± 0.71, $P < .05$ C: −0.69 ± 1.31/−0.55 ± 1.12, $P < .05$ Change in BMD I: 0.025 ± 0.077 C: 0.013 ± 0.106 NS between groups, $P = .647$	
Naylor et al[35] n = 329	Z-score −0.4 ± 1.6 At median 6 months (baseline) −0.2 ± 1.6, $P < .001$ vs baseline At mean 2.7 years +0.5 ± 1.5, $P < .001$ vs baseline At mean 8.2 years	Z-score −0.7 ± 1.1 At median 6 months (baseline) −0.6 ± 1, $P < .01$ vs baseline At mean 2.7 years +0.1 ± 1.5, $P < .001$ vs baseline At mean 8.2 years	Hip Z-score −0.7 ± 1.1 At median 6 months (baseline) −0.6 ± 1.1, $P < .01$ vs baseline At mean 2.7 years −0.5 ± 1.1, $P < .001$ vs baseline At mean 8.2 years
Yamamoto et al[36] n = 24	Mean g/cm^2 pretreatment/12 months/24 months (Baseline) 0.80 ± 0.11/(12-month) 0.78 ± 0.12, NS/ (24-month) 0.79 ± 0.15, NS		

(continued)

Table 3. (continued)

Study	BMD		
	Lumbar	Femoral neck	Other
Huang et al[37] I: n = 34 C: n = 42	For 76 included patients T-score at pretreatment/14 ± 1.6 months −1.53 ± 1.24/−1.32 ± 1.26, $P < .001$ BMD: Mean g/cm^2 at pretreatment/14 ± 1.6 months 0.90 ± 0.14/0.92 ± 0.14, $P = .001$	T-score at pretreatment/14 ± 1.6 months −2.45 ± 0.96/−2.42 ± 1.02, NS BMD: Mean g/cm^2 at pretreatment/14 ± 1.6 months 0.68 ± 0.12/ 0.69 ± 0.13, NS	Hip: T-score at pretreatment/14 ± 1.6 months −1.76 ± 0.97/−1.68 ± 1.07, NS BMD: Mean g/cm^2 at pretreatment/14 ± 1.6 months 0.81 ± 0.14/0.81 ± 0.14, NS
Conley et al[38] I: n = 315 C: n = 239	T-score at mean 1.2 ± 0.05 years posttransplant/2.5 ± 0.05 years posttransplant I: −1.4 ± 1.3/−1.0 ± 1.3 C: 1.3 ± 0.5/0 ± 1.4 $P < .001$ between groups	T-score at mean 1.2 ± 0.05 years posttransplant/2.5 ± 0.05 years posttransplant I: −1.9 ± 1/−1.7 ± 1 C: 1.0 ± 0/−1.0 ± 1.0 $P < .001$ between groups	
Ahn et al[39] n = 294	Mean different in T-score at 12, 24, and 36 months compared with baseline 1 year C/I: −0.51 ± 0.66/−0.13 ± 0.73, $P < .05$ (n = 275/19) 2 year C/I: −0.76 ± 0.74/−0.4 ± 0.79, $P < .05$ (n = 151/45) 3 year C/I: −0.83 ± 0.83/−0.5 ± 0.8, $P = .10$ (n = 74/32)	Mean different in T-score at 12, 24 and 36 months compared with baseline 1 year C/I: −0.22 ± 0.69/0.13 ± 0.55, $P < .05$ (n = 273/19) 2 year C/I: −0.38 ± 0.82/−0.1 ± 0.77, $P = .20$ (n = 150/44) 3 year C/I: −0.43 ± 0.85/0.20 ± 0.94, $P = .21$ (n = 75/31)	
Cruz et al[40] I: n = 29 C: n = 28	T-score at pretreatment/12 months I: −1.71 ± 0.19/*no raw data* result (change in T-score: + 3.4% ± 0.6%, $P < .001$) C: −0.70 ± 0.24/*no raw data result*	T-score at pretreatment/12 months I: −1.43 ± 0.13/−1.34 ± 0.14($P < .01$) (change in T-score +1.6 ± 0.6%, $P < .001$) C: −1.10 ± 0.15/*no raw data result*	Total femur: T-score at pretreatment/12 months I: −1.43 ± 0.13/−1.34 ± 0.14 ($P < .01$) (change in T-score: +1.6 ± 0.6%, $P < .001$) C: −0.67 ± 0.16/*no raw data result*
Arlen et al[41] I: n = 25 C: n = 24	Mean g/cm^2 at pretreatment/23.3 ± 6.6 months I: 0.981 ± 0.138/1.021 ± 0.140 C: 1.134 ± 0.168/1.143 ± 0.175 Change in % BMD (I vs C) 4.3% ± 6.1% vs 0.55 ± 5.3%, $P < .05$	Mean g/cm^2 at pretreatment/23.3 ± 6.6 months (change in % BMD) I: 0.784 ± 0.102/ 0.810 ± 0.110 C: 0.867 ± 0.137/ 0.893 ± 0.147 Change in % BMD (I vs C) 3.4 ± 6.5% vs 3.2 ± 6.4% NS	Trochanter: Mean g/cm^2 at pretreatment/23.3 ± 6.6 months (change in % BMD) I: 0.619 ± 0.094/0.683 ± 0.126 C: 0.725 ± 0.116/ 0.738 ± 0.109 Change in % BMD (I vs C) 10.3 ± 11.9% vs 2.2 ± 5.7%, $P < .05$

Note. BMD = bone mineral density; I = intervention; C = control; n = number; AMTD = adjusted mean treatment difference; CI = confidence interval. White is RCT, Grey shaded region is Observational trials.

Table 4. Fracture Incidence in Postrenal Transplant Patients Between Bisphosphonate and Control Groups.

Study	Protocol	Baseline fractures	New fracture incidence		Findings
Walsh et al[28]	Spine radiographs at baseline, 12, 24 months Blinded interpretation using Genant et al[42] scale	N = 23/93 total 12/46 in intervention group (1 axial) 11/47 in control group	At 12 months I (n = 46): 2 C (n = 47): 4	At 24 months 2 (3.3%/yr) 6 (6.4%/yr)	4.2% (−7.3 to 16.6) difference between groups at 12 months (P = .7) 8.4% (−3.7 to 22.2) between groups at 24 months (P = .3)
Schwarz et al[30]	Not formally assessed as endpoint	Not assessed	Between 6 months and 3 years: I (n = 9): 2 vertebral fractures C (n = 10): 2 vertebral fractures		No analysis done
Yamamoto et al[36]	Nontraumatic (low energy) fractures Assessed via personal interviews and medical records	N = 7/24 (4 wrist, 2 rib, 1 leg, 1 cuboidal)	4 patients with 5 fractures during 3-year period (2 leg, 1 lumbar spine, 1 hip, 1 humeral)		New fractures correlated with higher intact PTH levels (pg/mL) at baseline: Fracture (−) = 116.0 ± 52.6 Fracture (−) = 255.0 ± 3.0 (P < .0001)
Conley et al[38]	Self-reported Counted if occurring between BMD1 and BMD2 (both occurring >1 year posttransplant)	I: 56/315 C: 16/239 Significantly more patients with fracture in intervention group (P = .0002)	I: 16 C: 7 (P < .05) Increase in bone density between BMD1 and BMD2 did not prevent late fractures		Treatment associated with decreased probability of fracture-free survival (HR = 0.40; 95% CI = 0.29-0.73, P = .001) No association found between rate of bone loss and fractures, regardless of the bisphosphonate therapy
Arlen et al[41]	Not formally assessed as endpoint	Not assessed	I (n = 25): n = 2 C (n = 24): n = 1		All patients who sustained fractures were from high-risk treatment group (BMD lower than mean baseline of control group)

Note. I = intervention; C = control; BMD = bone mineral density; PTH = parathyroid hormone; HR = hazard ratio; CI = confidence interval. White is RCT, Grey shaded region is Observational trials.

satisfied a score of 3 or more based on the Newcastle-Ottawa Criteria (Supplemental Table S3).[44]

Statistical Analysis

A standardized mean difference (SMD) and its 95% confidence interval (CI) were calculated to account for heterogeneity of different units of pre- and posttransplant measurements.[45] Using the 95% CIs, the SDs were then derived.[46] Subsequently, forest/funnel plots were created using the Cochrane Collaboration RevMan v5.3 software.[46] A random effects model was used to account for clinical heterogeneity of the meta-analyzed studies. Values of I^2 >50% and P < .10 were considered to indicate significant heterogeneity.

Results

Description of the Search

The search strategy yielded 1084 articles between 1946 and 2017. All titles and abstracts were reviewed independently by 2 authors (A.L. and A.W.) in accordance with inclusion criteria (Figure 2). Thirty-five articles were fully reviewed. Fourteen articles were differentially categorized between reviewers. These were independently reviewed and resolved by a third author (D.T.W.) to ascertain eligibility.

Description of Studies

Sixteen studies met full inclusion criteria (Table 1), including 8 randomized trials[26-33] and 8 observational studies.[34-41] Two RCTs[28,30] and 7 observational studies,[34-36,38-41] were considered to have low risk of bias (Supplemental Figures S2 and S3).

The total sample size was 1762 patients; 683 patients were treated with bisphosphonates while the remaining were allocated to various comparison groups. Bisphosphonates used included alendronate, alendronate/risedronate, pamidronate, zolendronate, ibandronate, and etidronate. Comparators included no therapy, calcium and/or vitamin D, calcitriol, placebo, an alternative bisphosphonate, and no control group. Baseline characteristic data of each study are summarized in Table 2.

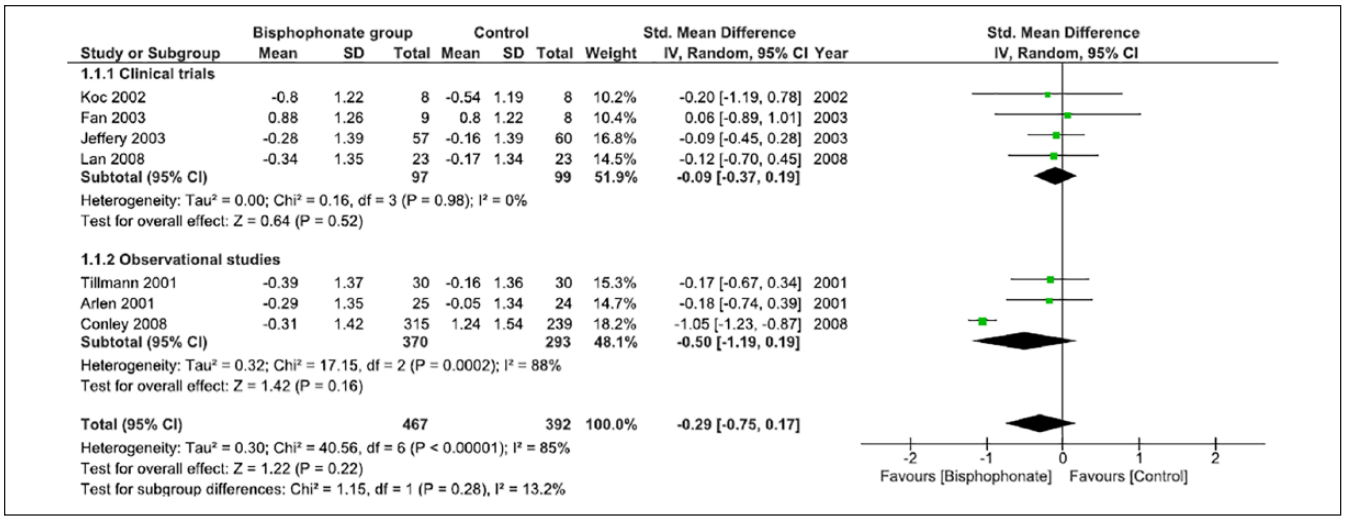

Figure 3. Change in bone mineral density at the lumbar spine in postrenal transplant patients between bisphosphonate and control groups.
Note. CI = confidence interval.

From the RCTs, 226 patients were prescribed a bisphosphonate with a concomitant treatment with Ca and/or vitamin D in 212 patients. Bisphosphonate-treatment duration ranged from 1 to 24 months, with a follow-up duration of 12 to 24 months (Table 1). From the observational studies, 457 patients were prescribed a bisphosphonate. Of these patients, 223 had a concomitant treatment with Ca and/or vitamin D. Precise treatment was not clearly specified in an additional 624 patients. The range for bisphosphonate treatment was 12 to 36 months with a follow-up duration of 12 to 98.4 months (Table 1).

BMD measurement was performed using DEXA in all studies, with results most often expressed as T-scores representing the number of SDs that the measurement falls from the mean of a young population. A T-score of −1 to −2.5 describes osteopenia and less than −2.5 is diagnostic of osteoporosis.[47] Results were also reported as bone mineral content or Z-scores that describe the number of SDs from the mean value of gender and age-matched adults (Z-score less than or equal to −2 suggests abnormal bone loss).

Change in BMD

One year posttransplant. Thirteen studies demonstrated at least one site of improvement in BMD, while the other 3 studies[30,32,36] showed nonsignificant changes. However, only 2 studies[28,39] were able to capture patient data from the immediate peri-transplant period. At 12 months posttransplant, Walsh et al[28] identified a significant change in BMD in the intervention group vs control group, at the lumbar spine, +2.3% vs −5.7%, adjusted mean treatment difference (AMTD) 7.78%, $P < .001$. T-scores were also significantly different in the intervention vs control group at both the lumbar spine (−0.13 ± 0.73 vs −0.51 ± 0.66, $P < .05$) and the femoral neck (0.13 ± 0.55 vs −0.22 ± 0.69, $P < .05$) at 12 months.[39] Both intervention groups showed significant improvement with bisphosphonate persisting into the second[28,39] and the third year[39] posttransplantation at the lumbar spine, with no significant difference at the femoral neck (Table 3).

One year postinitiation of bisphosphonate. Thirteen studies captured BMD data at least 12 months postinitiation of bisphosphonate treatment. Only 2 of these studies did not exhibit a significant increase in BMD[32] or Z-score[30] in the intervention vs control group in the lumbar spine at 12 and 32 months posttreatment.[32]

Unlike the lumbar spine, all studies showed minimal change in BMD measurements at the femoral neck except for 3 studies[31,33,39] that showed a significant change (Table 3). Result interpretation of the significantly different Z-scores between groups posttreatment was inconclusive in the study by Tillmann et al[34] as pretreatment measurements were also different. Cruz et al[40] also found different T-scores at the femoral neck posttreatment (change in T-score +1.6% ± 0.6%, $P < .001$), but did not provide raw data of the control group to allow for comparison.

Using the calculated SMD between the intervention (bisphosphonate) and control groups, Figures 3 and 4 summarize the study findings that include pre and postbisphosphonate treatment information on BMD, at the lumbar spine and femoral neck, respectively. Data from 4 RCTs[29,31-33] and 3 observational studies[34,38,41] were included in analysis. There is a nonsignificant improvement in BMD favoring the use of bisphosphonates, as evidenced at both the lumbar spine and femoral neck. There was no statistical heterogeneity noted when a random effects model was used. The funnel plot demonstrates reasonable dispersion (Supplemental Figure S4).

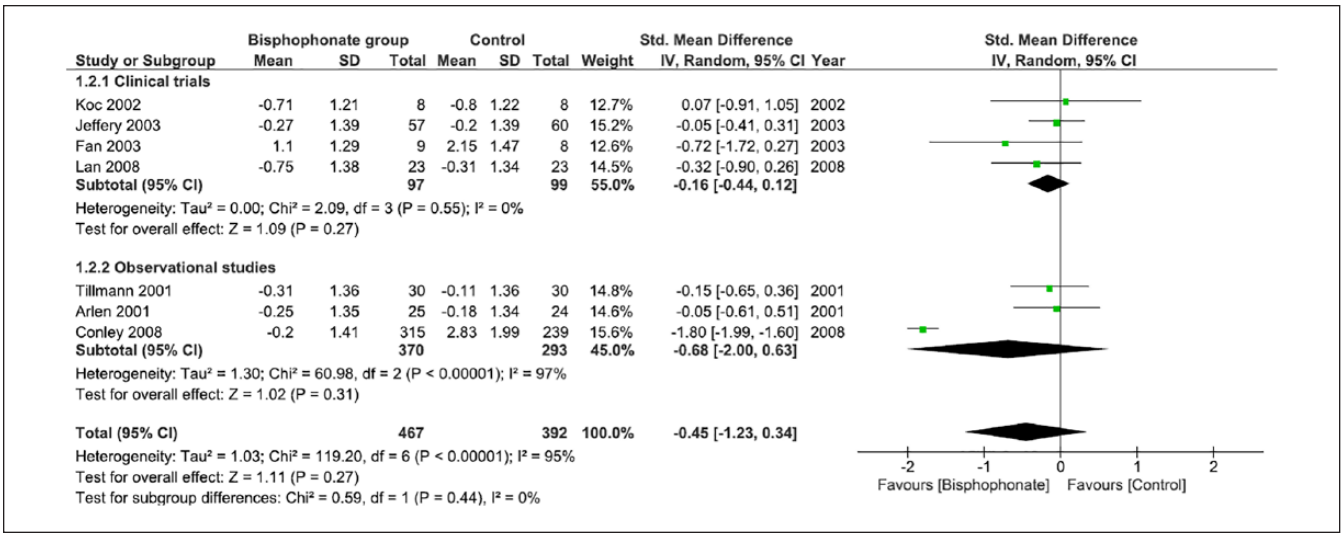

Figure 4. Change in bone mineral density at the femoral neck in postrenal transplant patients between bisphosphonate and control groups.
Note. CI = confidence interval.

Fracture Incidence

Fracture incidence was low but only reported in 5 studies[28,30,36,38,41] with a total of 43 new fractures. Conley et al[38] reported benefit from bisphosphate treatment and decreased fracture rates (hazard ratio [HR] = 6.7, 95% CI = 6-6284, $P < .01$), despite only a small subset of patients (n = 3) with baseline osteoporosis at the femoral neck. Conley et al[38] noted that bisphosphonate treatment was associated with decreased probability of fracture-free survival (HR = 0.40, 95% CI = 0.29-0.73, $P = .001$) in the initial analysis, even though treatment was associated with significant reduction in bone loss at the femoral neck (HR = 1.56, 95% CI = 1.21-2.06, $P < .001$) and lumbar spine (HR = 1.48, 95% CI = 1.13-1.98, $P < .01$). However, after adjusted analysis, no association was identified between bone loss and fractures regardless of the bisphosphonate treatment.[38]

Confounding Factors Affecting BMD

Immunosuppression. Four studies[32,35,37,39] examined the effects of steroids on bone health. At baseline, patients with osteoporosis received a greater cumulative steroid dose than patients with osteopenia (1326.5 mg vs 724.5 mg; $P < .01$).[37] In a univariate analysis, prednisolone use was associated with osteoporosis (odds ratio [OR] = 5.18; 95% CI = 1.6-16.4, $P < .01$).[37] Jeffery et al[32] described prednisone as an independent predictor of low BMD (multivariate, $P < .01$). Alternatively, Naylor et al[35] found greater glucocorticoid exposure was not associated with a significant change in BMD at the lumbar spine, total hip, and femoral neck ($P > .05$), regardless of whether the patient had received osteoporosis treatment before. Similarly, no BMD differences were observed, 1 year posttransplant, in recipients receiving steroids.[39] The effects of cyclosporine on BMD were examined in 2 studies[37,39] and demonstrated no effects up to 1 year posttransplant.

Body mass index. Three studies[32,35,39] found that low body weight ($P < .001$) and body mass index (BMI) ($P < .01$) were correlated with reduced lumbar and femoral BMD in a univariate analysis.[32] Greater BMI was associated with a better BMD.[35,39]

Gender. Five studies[32,34,35,37,39] examined the role of gender in BMD posttransplantation. Only one study[32] identified a baseline association between female gender and reduced lumbar and overall BMD ($P < .05$). The other studies found no significant difference in gender with respect to change in BMD, although bone density may change differentially depending on site in males and females.[35,37] Alendronate increased the BMD at the lumbar spine and the hipbone in males ($P < .05$), but only at the lumbar spine in females ($P < .05$).[37] Male gender was also associated with a greater improvement in lumbar spine BMD in patients receiving osteoporosis treatment ($P < .01$).[35]

Diabetes. Three studies[32,37,39] examined the role of diabetes in bone loss, but none investigated the duration or control of diabetes pretransplantation. One study[32] identified pretransplantation diabetes as an independent risk factor for low BMD ($P < .001$), while the other 2 found a greater reduction in T-score at the lumbar spine in nondiabetic recipients (-0.52 ± 0.67 vs -0.15 ± 0.50, $P < .01$).[39] Consequently, diabetes was not a significant predictive factor in BMD (OR = 0.6).[37]

Hemodialysis (HD) pretransplant. Only one study examined the impact of pretransplant HD duration on BMD.[39] The mean change reduction in T-score at the lumbar spine in the first year posttransplant was significantly greater in recipients who had been on HD for ≥12 months compared with those who had experienced dialysis <12 months (−0.67 ± 0.79 vs −0.39 ± 0.57, $P = .001$).[39]

Smoking. In a multivariate analysis,[37] smoking was not a risk factor of BMD change posttransplantation (see Supplemental Table S2).

Discussion

This systematic review and meta-analysis is the first to investigate the bisphosphonate effects on increasing BMD and fracture prevention beyond the first year postkidney transplantation. A recently published meta-analysis by Wang et al[25] demonstrated that bisphosphonate treatment in general had a beneficial effect on BMD changes at both the lumbar spine and femoral neck, which is congruent with previous studies and established practice guidelines.[48] Although prior studies have shown that the most rapid decrease in lumbar spine BMD occurs within the first year posttransplantation (estimated at 3%-7%), we recognize declining BMD to be a problem of longer chronicity, often confounded by several factors unique to the immediate posttransplant period.[8-11,25]

In our study, we demonstrate no statistically significant benefit of bisphosphonate treatment on BMD beyond the first year posttransplant. There was heterogeneity in studies' treatment choice and duration, but a nonsignificant improvement in lumbar spine BMD was consistently seen, while the effect appeared inconsistent in the femoral neck. Two studies[28,39] captured peri-transplant patients' data providing a baseline comparison, and both groups showed significant improvement with bisphosphonate treatment at the lumbar spine and femoral neck beyond 1 year posttransplant, when treatment was initiated at the time of transplantation and lasted for at least 1 year. This significant improvement persisted into the second[28,39] and third year[39] at the lumbar spine but not at the femoral neck.

As bone loss progresses beyond the first year posttransplantation,[9,12] we also analyzed the effects of bisphosphonates on BMD at least 12 months posttreatment initiation, regardless of the time from initial transplantation. Although bisphosphonate protocols varied widely across studies, 11 studies[26-28,31,33,34,36,37,39-41] identified a significant increase in BMD at 12 months posttreatment as compared with baseline.

This review demonstrated no statistically significant change in BMD beyond 1 year with bisphosphonates. Thus, the benefit of bisphosphonates may be only evident within 1 year of transplant. This is an important observation, as the protective effect may be limited to the time with highest corticosteroid dosing, and other pre- and posttransplant factors such as inflammation or bone disease. This likely indicated that there is no benefit to bisphosphonate use in renal transplant recipients beyond 1 year posttransplantation.

Despite the significant changes found with the bisphosphonate treatment at the lumbar vertebral levels, only 3 studies[31,33,39] displayed improvement at the femoral neck level. Although this does not translate directly to a lower fracture risk, this may extrapolate into ongoing hip fracture risks with greater protective effect at the lumbar spines in this population. This is a clinical consideration when risk-stratifying patients based on their BMD and fracture risks posttransplant. A significant limitation is that none of the studies captured fracture incidence as the sole primary outcome, likely given the paucity of fracture events.

Only one study[38] was able to interpret fracture results beyond reporting incidence and found no difference (HR = 0.40; 95% CI = 0.29-0.73, $P = .001$) in fracture rate after bisphosphonate treatment in their adjusted analysis.[38] Thus, the clinical significance of bisphosphonate therapy on patient morbidity with fracture prevention remains to be established.

Steroid use in both the early and long-term posttransplant periods has been shown to cause increased bone loss.[37] Specifically, prednisone doses of >7.5 mg/d results in trabecular bone loss in most patients.[41] Calcineurin inhibitors have also been implicated in bone loss in animal models.[37] While all studies that examined steroid use reaffirmed their deleterious impact on bone health, the effect of bisphosphonates in patient populations that had received higher cumulative steroid doses was not congruent. Only Huang et al[37] was able to demonstrate that bisphosphonates resulted in a greater improvement in BMD at the lumbar spine in those with osteoporosis at baseline versus osteopenic patients.

Previous systematic reviews on a similar population highlighted limitations of few studies and small sample sizes. Thus, the wide scope of literature analyzed in this study sought to address this by including both observational and randomized control trials with appropriate bias analysis. A second strength of this study is our focus on long-term effectiveness of bisphosphonate treatment. It is important to recognize that the predominant population to which these data apply is well beyond the initial 12-month posttransplant and that these are the patients who carry the burden of bone disease. Our findings on bisphosphonate treatment in BMD preservation beyond 12 months posttransplant highlight limited evidence supporting the use of bisphosphonates on renal osteodystrophy.

Limitations of this review include the use of BMD as a surrogate outcome, the bias of the included studies, and the incomplete reporting data in numerous analyzed studies. The most clinically relevant outcome is the incidence of fractures. Our review assessed BMD as the primary outcome, acknowledging that BMD is not an accurate indicator of clinically meaningful patient outcomes and quality of life. Other indicators, such as bone biopsy, should be

considered as a surrogate outcome in the future, keeping in mind that biopsy is expensive, invasive, and biopsy-based treatment guidelines are not yet available. We had limited information on the bone turnover state of patients to identify patients who would potentially benefit from anti-resorptive therapy. Last, we recognize that high risk of bias was identified in 44% of our included studies. We elected to include these studies given the limited sample size of the renal transplant population. The conclusions drawn from this review, however, did not change based on this bias assessment.

In conclusion, our review finds no statistical evidence for improvement in BMD in renal transplant patients beyond the first year posttransplantation with the use of bisphosphonates. We detected a differential improvement in BMD favoring the lumbar spine more so than the femoral neck, which may have clinical implications despite nonsignificance. However, the limitations of this review highlight the need for randomized control trials in patients with quantified bone turnover status evaluating fracture risk. Also quantifying other surrogate outcomes such as bone biopsy is necessary to provide more definitive evidence for the use of bisphosphates for current practice guidelines. In our future work, we plan to explore the evidence on the safety profile of bisphosphonates in this unique population with a focus on graft function. Finally, anti-resorptive and anabolic therapies are alternatives to bisphosphonates in bone mineral diseases in the general population and investigation into the use of these therapies in the renal transplant population is an avenue to further treatment options.

List of Abbreviations

AMTD, adjusted mean treatment difference; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; DEXA, dual energy X-ray absorptiometry; ESRD, end-stage renal disease; MBD, mineral and bone disorders; RCT, randomized control trial; SD, standard deviation.

Ethics Approval and Consent to Participate

No ethics was required as our study reviewed existing literature.

Consent for Publication

AL and AW independent screened and reviewed all articles. AL and AW are the primary authors of this manuscript. MKS, BT, and DTW provided supervision and clinical expertise. All authors have consented for publication.

Availability of Data and Materials

All data is provided in the article and supplementary tables. Primary data can be obtained directly from the original articles.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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