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META-ANALYSIS

Bisphosphonates for preventing bone disease in kidney transplant recipients: a meta-analysis of randomized controlled trials

Emmanuelle B. Versele,[1] Steven Van Laecke,[1] Annemieke W. Dhondt,[1] Francis Verbeke,[1] Raymond Vanholder,[1,2] Wim Van Biesen[1,2] and Evi V. Nagler[1,2]

1 Nephrology Section, Department of Internal Medicine, Ghent University Hospital, Ghent, Belgium
2 European Renal Best Practice (ERBP), guidance body of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA), Ghent, Belgium

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Correspondence
Evi V. Nagler, Nephrology Section, Ghent University Hospital, De Pintelaan 185, 9000 Gent, Belgium
Tel.: 0032/93324509;
fax: 0032/93324599;
e-mail: evi.nagler@ugent.be

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Summary

An estimated 60% of kidney transplant recipients have mineral bone disease and about 0.5% break their hip within the first year after transplantation. We conducted a systematic review of benefits and harms of bisphosphonates in kidney transplant recipients. We searched CENTRAL (Issue 5, 2015) for randomized controlled trials in all languages and screened the reference list of an earlier Cochrane review. One reviewer identified the trials, extracted all data, and assessed risk of bias. Meta-analysis used a random effects model, with results expressed as risk ratios (RR) or mean differences (MD) with 95% confidence intervals (CI). Bisphosphonates have uncertain effects on death (RR 0.45, CI 0.04–4.69) and vertebral fractures (RR 0.58, CI 0.24–1.43, I^2 0%). Bisphosphonates moderately to importantly reduce the loss of vertebral bone mineral density (MD 5.98%, CI 3.77–8.18% change from baseline in g calcium/cm² at 12 months, I^2 91%) and femoral bone mineral density (MD 5.57%, 3.12–8.01% change from baseline in g calcium/cm² at 12 months, I^2 69%). At this stage, insufficient evidence exists to support routine use of bisphosphonates to reduce fracture risk after kidney transplantation. Data on important health outcomes are lacking, surrogate outcomes poorly reflect bone quality in kidney transplant recipients, and serious adverse events are not studied and reported systematically.

Introduction

Mineral bone disease is common among people with chronic kidney disease and often persists after kidney transplantation. An estimated 60% of kidney transplant recipients have mineral bone disease and about 0.5% break their hip within the first year after transplantation [1]. In addition, the mineral and bone disorders seen after transplantation are thought to contribute to cardiovascular disease through extra skeletal calcification [2].

The pathogenesis of bone disease after transplantation is multifactorial. It includes enduring abnormalities in bone remodeling and mineralization caused by chronic kidney disease, resulting in high or low bone turnover or a combination of both. It also includes peri-transplant changes in the fibroblast growth factor 23-klotho-parathyroid hormone-vitamin D axis [3]. Finally, immunosuppressive agents, predominantly corticosteroids, reduce bone mass. They inhibit osteoblasts and stimulate osteoclasts, diminish gastrointestinal calcium absorption, increase renal calcium excretion, and increase secretion of parathyroid hormone [3].

Bisphosphonates are molecules that enter the bone and strongly bind to hydroxyapatite. Contact with bisphosphonate containing bone results in deactivation, destruction, or apoptosis of the osteoclasts, decreasing their numbers and activity. In addition, bisphosphonates reduce osteoclast proliferation. There are two molecular classes of bisphos-

phonates: non-nitrogen-containing (clodronate and etidronate) and more potent nitrogen-containing bisphosphates (alendronate, ibandronate, pamidronate, risedronate, and zolendronate) [4].

Bisphosphonates are administered to postmenopausal women with osteoporosis, with evidence that benefits (fewer vertebral and hip fractures) outweigh harms (osteonecrosis of the jaw, gastrointestinal disturbances) [4]. They are also administered to heart, lung, and liver transplant recipients with the intention to reduce the incidence of bone fractures [5]. It is unclear whether the risk–benefit balance is positive for kidney transplant recipients, although for several reasons this may not be true. First, approximately half of the absorbed bisphosphonate is excreted by the kidneys through active proximal tubular secretion [6]. Consequently, accumulation may occur with decreased clearance, which almost inevitably is present in most kidney graft recipients, and prolonged effects may induce or maintain adynamic bone disease, increasing rather than decreasing fracture risk [7]. Second, the wide variation in bone changes following kidney transplantation may alter response to treatment. Bone biopsy is the only appropriate tool to diagnose and monitor bone disease, but is invasive and most centers lack sufficient expertise for interpretation. As a consequence, differential diagnostic assessment is mostly suboptimal [3]. Bone mineral density is often used as a proxy, but does not adequately reflect the pathological bone changes observed after kidney transplantation [8].

A previous Cochrane review, published in 2007, indicated that treatment with bisphosphonates at any time after kidney transplantation had favorable effects on bone mineral density, but unclear downstream effects on fracture risk [9]. Since then, several new randomized trials have been completed. In this systematic review, we aimed to update previous analyses and to determine whether bisphosphonates reduce morbidity from bone disease in kidney transplant recipients, to characterize potential harms from such treatment, and to identify areas requiring further study. We focused on objective measures of change in the incidence of complications of bone disease, particularly the incidence of fractures. We also reported development of adynamic bone disease and other side effects of treatment, but we did not focus on cardiovascular disease.

Patients and methods

Criteria for considering studies for this review

Types of studies

We included all randomized controlled trials (RCTs) and quasi-RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth, or other accepted methods looking at treatment with bisphosphonates for bone disease following kidney transplantation.

Types of participants

Inclusion criteria: We only included trials conducted in kidney transplant recipients. We included trials with men and women, aged 18 and above, regardless of menopausal status. We did not restrict donor characteristics, dialysis vintage, or immunosuppressive regimens.

Exclusion criteria: We excluded studies accepting recipients of combined transplants including a kidney, or trials with recipients of a second or subsequent graft kidney.

We also excluded studies enrolling recipients who had been treated with corticosteroids before transplantation for a period of ≥ 12 months.

Types of interventions

We examined the effects of treatment with oral or parenteral bisphosphonates. We included all trials comparing bisphosphonates versus placebo or vitamin D as well as head-to-head comparisons of different bisphosphonates or different doses of the same bisphosphonate. Treatments could be started immediately before or up to two weeks after transplantation and continued for any length of time. Study participants could also be taking any form of calcium supplementation in addition to active treatment or placebo.

Types of outcome measures

The primary outcome measure was fracture after kidney transplantation, identified by radiographic examination, at any site, including vertebral compression fractures.

Other included outcome:

1. Important health outcomes:
   - **a.** Overall mortality
   - **b.** Acute graft rejection (clinically suspected or biopsy-proven)
   - **c.** Graft function
2. Surrogate end-points:
   - **a.** Changes in bone mineral density by dual-energy X-ray absorptiometry using *T*-scores or *Z*-scores at the lumbar spine, femoral neck, and radius, being the number of standard deviations away from the young normal reference mean or from average bone mineral density of their age, sex, and ethnicity.
   - **b.** Tissue or bone volume as measured by histomorphometry (presence of low bone turnover as defined by reduced bone formation rate as a function of either tissue volume or bone volume)
3. Side-effects from bisphosphonates:
   - **a.** Any gastrointestinal disorder: gastrointestinal ulcer, dysphagia, abdominal pain, nausea, diarrhea, constipation, ulcus ventriculi, duodenitis

b. Any musculoskeletal disorder: necrosis of the mandibula, myalgia, muscle cramps
c. Any neurological disorder: headache, vertigo
d. Hypersensitivity reactions
e. Hypocalcemia
f. Any hematological disorder: anemia, leucopenia, thrombocytopenia
g. Fever or shivering
h. Alopecia or pruritus
i. Peripheral edema

Search methods for identification of studies

We searched the Cochrane Central Register of Controlled Trials (CENTRAL in The Cochrane Library- Issue 5, 2015, http://community.cochrane.org/editorial-and-publishing-policy-resource/Cochrane-central-register-controlled-trials-central) for randomized trials using subject headings and text words for kidney transplantation and bisphosphonates. The full search is outlined in Supplement S1. We also screened the reference list of an earlier Cochrane review [9].

Data collection, extraction

The search strategy described was used to obtain titles and abstracts of studies possibly relevant to the review. One author (EV) screened all titles and abstracts and discarded studies that were not applicable; however, studies and reviews that possibly included relevant data or information on relevant studies were initially retained as well. One author assessed retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfied the inclusion criteria. EV extracted all data. Where more than one publication of one study existed, reports were grouped together and only the publication with the most complete data was used. In reporting, we tried to adhere to PRISMA reporting guideline (Supplement S2).

Assessment of risk of bias

To assess the risk of bias, we used the checklist as recommended by the Cochrane Handbook for Systematic Reviews of Interventions (Supplement S3) [10].

Statistical analysis

For dichotomous outcomes (death, fracture at any site after transplantation, the presence of adynamic bone disease on bone histomorphometry, and acute allograft rejection), results were expressed as a risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (e.g. changes in bone mineral density by dual-energy X-ray absorptiometry scanning), the mean difference (MD) was used. Data were pooled using the random effects model. Adverse effects were tabulated and assessed with descriptive techniques. Where possible, the risk difference for each adverse effect was calculated with 95% CI, either compared with no treatment or to another agent.

Heterogeneity was analyzed using a chi-square test on $N-1$ degrees of freedom, with an alpha of 0.05 used for statistical significance and with I^2 calculated to measure the proportion of total variation in the estimates of treatment effect that was due to heterogeneity beyond chance [11]. I^2 values of 25%, 50%, and 75% correspond to low, medium, and high levels of heterogeneity [11].

Results

Description of studies

Results of the search

In May 2015, we identified through an electronic search of CENTRAL 64 potentially relevant citations. After a first screening procedure, we reviewed 49 reports in detail, which ultimately led to the inclusion of 34 reports of 19 studies including 959 participants (Fig. 1) [12–30].

Included studies

Eighteen studies (providing data for 916 participants) compared a bisphosphonate versus placebo or no treatment [12–24,26–30]. One study [25] compared a bisphosphonate versus calcitonin. We found no study comparing different bisphosphonates or different doses of the same bisphosphonate. Bisphosphonate interventions included pamidronate [12,20,22,23,29,30]; ibandronate [17]; risedronate [13,27,28]; alendronate [14,15,18,19,21,24,26]; etidronate [25]; and clodronate [16]. In 13 studies, the bisphosphonate was given orally [13–16,18,19,21,22,24–28]; in six studies, it was administered intravenously [12,17,20,23,29,30]. Oral bisphosphonates were started immediately after transplantation and taken on a daily or weekly basis for up to 24 months. Parenteral bisphosphonates were started from 48 h before until 14 days after transplantation; and were continued for two to six doses on a one to three monthly basis. Follow-up varied from six months to three years after the start of administration.

In all save one study, all participants also received calcium [14,16–18,23], vitamin D [13], or a combination of the two [12,15,19–21,24–30].

Sample sizes varied and were generally small (median 51 participants; range 20 to 101); only one study included more than 100 participants [28]. All save two were single-center [28,29], and follow-up was mostly short (median 12 months, range 6 to 36 months). Data for at least one outcome of interest were available from

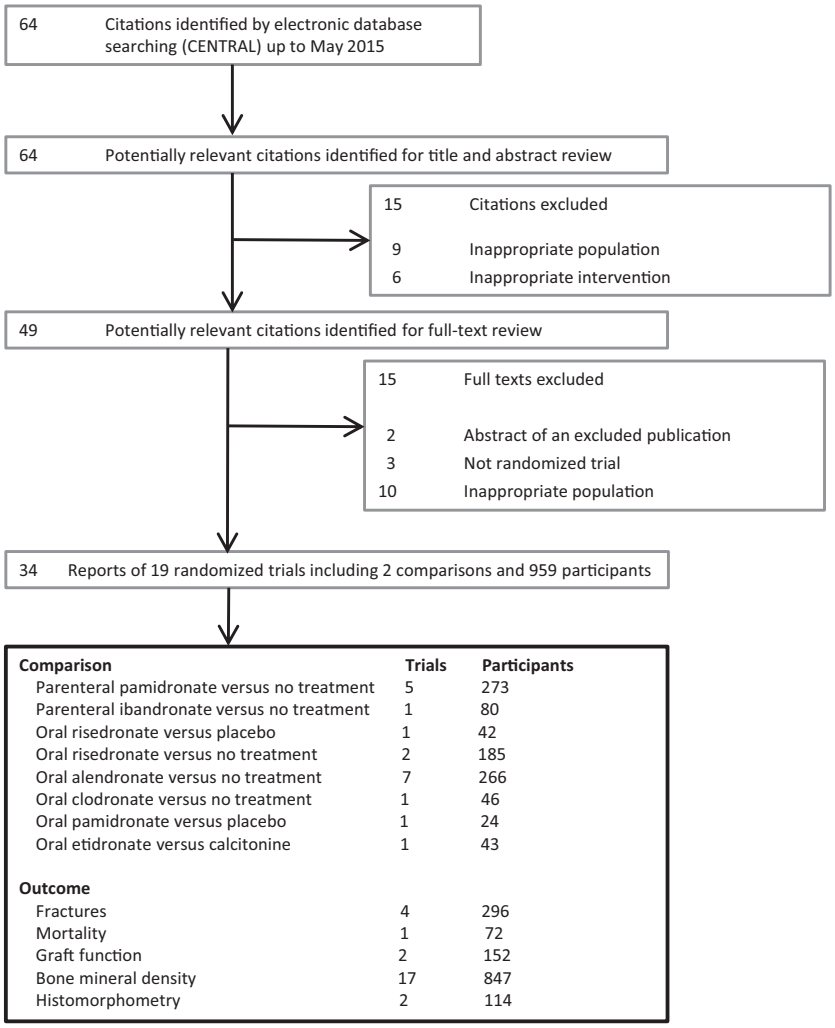

Figure 1 Flow chart of study identification and selection procedure.

17 studies and 959 participants, two studies reported no numerical data.

Excluded studies

We excluded 15 studies after full-text assessment; three were not randomized trials; eight included participants who had had previous kidney transplants; three were an abstract of an excluded publication and one included patients with long-term corticoid use before transplantation (Supplement S4).

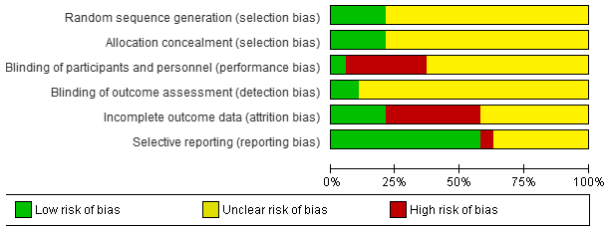

Figure 2 Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

Risk of bias in included studies

Methodological quality proved itself difficult to assess due to limitations in reporting. In general, trial quality was variable and reporting of trial method details unsatisfactory or incomplete for the majority of studies. Data in this regard are summarized in Fig. 2 and supplement S5.

Random sequence generation and allocation concealment

The randomization method, as well the random sequence generation as the allocation concealment, was adequate in four studies [12,14,16,28]. For the remaining studies, the authors provided insufficient information about the procedures to permit a judgment of the risk of bias.

Blinding
In three studies, the investigators attempted to blind participants [13,14,29], one also reported an attempt to blind the investigators [13]. One study explicitly reported blinding of outcome assessors [14]. In the 18 others, we judged blinding of outcome assessors would likely have occurred or measured outcomes were objective enough (death, hip fractures, bone mineral density) so that the risk of bias was probably low [12,13,15–30].

Incomplete outcome data
Attrition stayed below 20% with either well-documented reasons and/or limited opportunity for important bias in seven studies [12,14–17,20,30]. Four studies had attrition rates >20% [18,21,28,29], three of which with similar and well-documented reasons for all groups [18,28,29]. Eight studies did not report attrition rates [13,19,22–27].

Selective reporting
Five studies reported on fractures [12,27–30], one on death [20] and one on graft function [17]. The remaining studies only reported outcomes related to the surrogate end-point of bone mineral density and eight studies published mostly significant results [15,17–20,22–24].

Effects of intervention

Bisphosphonates versus placebo or no treatment

Important health outcomes: Bisphosphonates have uncertain effects on death (Table 1.1, 1 study, 57 participants, RR 0.45, 95% CI 0.04 to 4.69) and on the incidence of vertebral fractures (Fig. 3 and 4 studies, 283 participants, RR 0.58, 95% CI 0.24 to 1.43, I^2 0%). Only one study evaluated hip fractures, with no event in either group (Table 1.1, 1 study, 59 participants, RR not estimable).

Bisphosphonates moderately reduced the number of biopsy-proven acute rejections, but sample sizes were small and confidence intervals were wide (Fig. 4, 2 studies, 129 participants, RR 0.55, 95% CI 0.33 to 0.91, I^2 0%). No study reported on graft function.

Bone mineral density: Bone mineral density was measured at three different body sites (spine, femoral neck, and forearm) and expressed in fifteen different ways.

Vertebral spine: Bisphosphonates moderately to importantly reduced loss of vertebral bone mineral density at 12 months when expressed as percentage change from baseline in g calcium/cm² or in *T*-score (Fig. 5, 8 studies, 308 participants, MD 5.98%, 95% CI 3.77 to 8.18, I^2 91%; Table 1.1, 2 studies, 66 participants, MD 1.02%, 95% CI 0.43 to 1.62, I^2 0%). Although there was substantial heterogeneity among included studies as described by the I^2, individual point estimates all favored bisphosphonates within similar order of magnitude from a clinical perspective.

In absolute terms, the results were less impressive (Supplement S6, 10 studies, 327 participants, MD 0.04, 95% CI −0.01 to 0.09, I^2 50%; Supplement S7, 5 studies, 226 participants, MD 0.25, 95% CI −0.03 to 0.52, I^2 13%).

Femoral neck: Bisphosphonates also moderately to importantly reduced loss of bone mineral density at femoral neck when measured as a percentage change from baseline at 12 months in g calcium/cm² or in *T*-score (Fig. 6, 5 studies, 190 participants, MD 5.57%, 95% CI 3.12 to 8.01, I^2 69%; Table 1.1, 2 studies, 66 participants, MD 0.24%, 95% CI −0.23 to 0.72).

But again, when measured in absolute terms, results were less impressive and highly variable, with imprecise and widely varying effect estimates across individual studies (Supplement S8, 8 studies, 327 participants, MD 0.05 g

Table 1. Effects of intervention, outcomes reported only in one or two studies.

Comparison Outcome	Studies	Participants	Effect size [95% CI]
1 Bisphosphonates versus placebo or no treatment Death at 3 years	Lee 2004	57	RR 0.45 [0.04, 4.69]
Number of hip fractures after 12 months	Coco 2003	59	RR not estimable
BMD, vertebral, measured in *T*-score, expressed in %change from baseline at 12 months	Torregrosa 2003 Shahidi 2015	66	MD 1.02 [0.43, 1.62]
BMD, femoral neck, measured in *T*-score, expressed in %change from baseline at 12 months	Torregrosa 2003 Shahidi 2015	66	MD 0.24 [−0.23, 0.72]
2 Bisphosphonates versus Calcitonine BMD, vertebral, measured in g calcium/cm², expressed as absolute value at 12 months	Psimenou 2002	43	MD 0.03 [−0.04, 0.10]

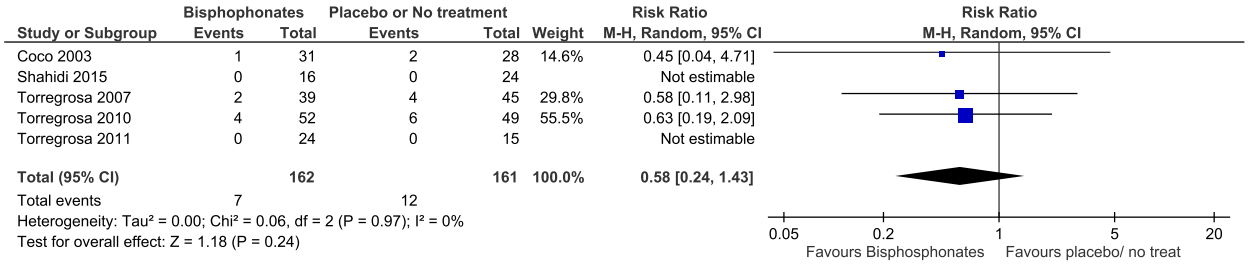

Figure 3 Bisphosphonates versus placebo or no treatment. Number of Fractures at vertebral spine after 12 months, diagnosed by X-ray.

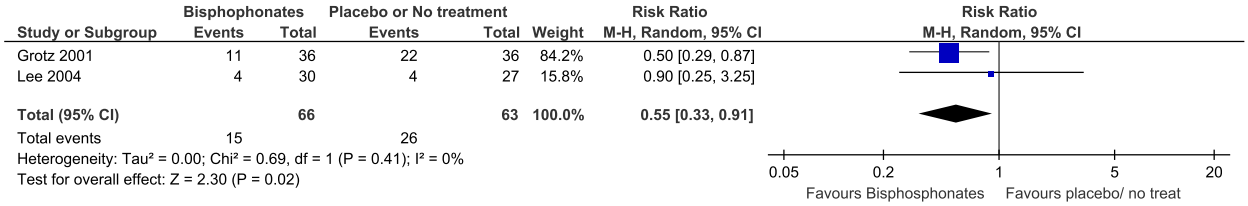

Figure 4 Bisphosphonates versus placebo or no treatment. Acute rejections at 12 months, clinically suspected, confirmed by biopsy.

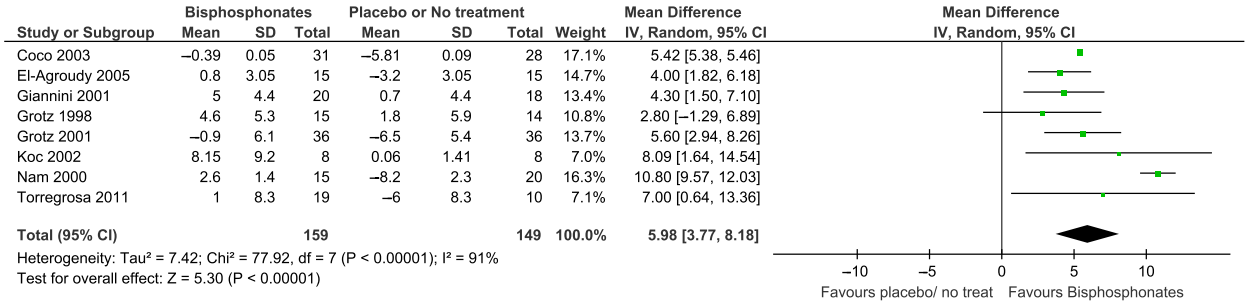

Figure 5 Bisphosphonates versus placebo or no treatment. Bone Mineral Density—vertebral, measured in g calcium/cm², expressed in % change from baseline at 12 months.

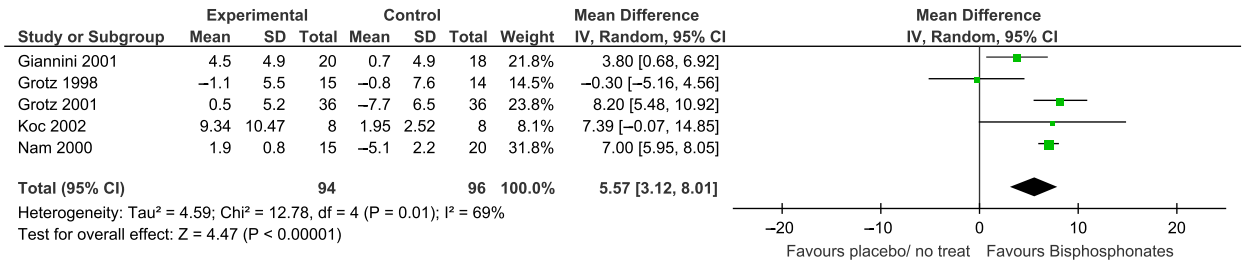

Figure 6 Bisphosphonates versus placebo or no treatment. Bone Mineral Density—femoral neck, measured in g calcium/cm², expressed in % change from baseline at 12 months.

calcium/cm², 95% CI −0.01 to 0.11, I^2 80%; Supplement S9, 5 studies, 226 participants, MD *T*-score 0.46, 95% CI 0.22 to 0.70, I^2 7%).

Forearm: Only two studies reported measurements at the forearm. The first included 42 persons showed a MD of −0.03 for the bone mineral density, expressed as absolute value at 12 months (95% CI −0.09 to 0.03) (Supplement S10). The second study of 30 persons found a MD of 0.30 for the bone mineral density, expressed as absolute value at 12 months (95% CI 0.26 to 0.34) (Supplement S10).

Bisphosphonates versus Calcitonin

One study compared bisphosphonates versus calcitonin and found no significant difference in vertebral bone

mineral density at 12 months (Table 1.2, 1 study, 43 participants, MD 0.03, 95% CI −0.04 to 0.10 g calcium/cm²).

None of the studies reported on adynamic bone disease, necrosis of the mandible, neurological disorders, hypersensitivity reactions, any hematological disorder, or alopecia. Two studies reported gastrointestinal adverse events, which occurred numerically more frequently in the treatment group [14,16]. The sample size was too small to draw any substantial conclusions.

Only one study reported on hypocalcemia, with numerically higher event rates in the treatment group, but sample size was too small to allow any conclusion [14]. Another study reported the number of adverse reactions in general, but failed to specify type [28].

Discussion

Summary of main results

Bisphosphonates had uncertain effects on death and fracture risk, with both outcomes insufficiently studied. Based on moderate-quality evidence from 18 randomized controlled trials involving 902 participants, bisphosphonates seemed to at best moderately reduce bone loss after transplantation. At 12 months, there was an average 6% difference in change from baseline when measured in g calcium/cm² both at the vertebral spine and femoral neck. In absolute differences, the results were even less impressive. At six to 12 months, kidney transplant recipients treated with bisphosphonates had a bone mineral density which was only 0.04 g calcium/cm² higher than of those treated with placebo at vertebral spine and 0.05 g calcium/cm² at femoral neck.

Compared with calcitonin, bisphosphonates showed no difference on bone mineral density.

Aside from mild gastrointestinal side effects, no study systematically studied and reported serious adverse events.

Overall completeness and applicability of evidence

A reduction of more than 5% in loss of bone mineral density at one year is generally considered an important effect. However, several factors challenged our confidence in the outcome. First, bone mineral density is known to poorly reflect bone quality in kidney transplant recipients because it does not adequately reflect the pathological bone changes observed after kidney transplantation. Second, regardless of its value as a measure for bone quality in kidney transplant recipients, it remains but a surrogate outcome with an uncertain association with the downstream end-points that truly matter to patients. Fractures, quality of life, and survival continue to be insufficiently studied. In addition, major adverse events are not studied or at least not systematically reported.

We found important differences in patient populations: some trials only included men, some excluded patients with diabetes, and some included only patients with reduced bone mineral density (Table 2). Most studies only included people with well functioning kidney grafts and this makes it difficult to generalize the results.

For a substantial number of outcomes, the results were mostly consistent, but the overall confidence intervals were very wide. This reduces the significance of the results.

Quality of evidence

Overall, data evaluating bone mineral density were considered of moderate quality because several of them were derived from studies at moderate risk of bias. However, the majority of remaining trials did not adequately report their method for the randomization procedure. How the allocation scheme was conceived; whether outcome assessors were blinded; and whether intention-to-treat analysis was used, remained concealed. In most of the trials, participants and personnel were not blinded and outcome data were incomplete. Small sample sizes and differences in outcome measurement as well as reporting further reduced the confidence of the present investigators in the results. Bone mineral density was measured in three different body areas (spine, femoral neck, and forearm) and expressed in fifteen different ways, which increased the risk that selective outcome reporting may have been at play. Bone mineral density can be measured in g calcium/cm², in *T*-score or in Z-score. Each of these measures can be expressed as an absolute value, as an absolute change from baseline or as a percentage change at a specific time point. Although we grouped the outcomes, it still resulted in five different sorts of outcomes for bone mineral density, increasing the risk of type 1 error.

We found no indications for industry funding, but most of the studies did not report information on this.

Potential biases in the review

First, studies were selected and data extracted by one author only. Although all procedures were meticulously conducted and all data carefully checked, lack of duplicate reviewing may have increased the risk of errors in data handling.

Second, although the review focused on bisphosphonates, it should not imply other treatments may not be effective. In most studies, participants received a co-intervention with calcium and/or vitamin D, but we did not examine whether those agents modified the effect of bisphosphonates on bone mineral density.

Table 2. Characteristics of included studies.

Author Year Reference	Methods Country Setting Time-frame Follow-up	Participants Inclusion criteria	N Age Sex (%male)	Interventions Treatment group – Intervention group	Co-intervention
Coco 2003 [12]	USA Single-1999–2000 1 year	Adult KTRs Hemodynamically stable perioperatively	72 44 ± 2.3 years 52%	IV Pamidronate 60 mg <48 h after KTX and 30 mg at months 1, 2, 3 and 6 – No treatment	PO calcitriol and calcium
Coco 2012 [13]	USA Single-center 2002–2006 1 year	Adult KTRs Living-donor KTX Able to give informed consent	42 45 ± 12 years 64%	PO Risedronate 35 mg weekly – Identical placebo	PO calcitriol 0.25 μg daily
El-Agroudy 2005 [14]	Egypt Single-center Not stated 1 year	Male, >20 years Living-donor KTX Not diabetic, no steroids before KTX Hemodialysis <2 years No previous fractures, no hypogonadism No suprarenal gland disease Creat <2 mg/dl	60 31.6 ± 9.4 years 100%	Group II: PO Alendronate 5 mg daily Group I: PO calcitriol 0.5 μg daily Group III: Intranasally calcitonine 100 μl every other day and stopped for 1 month every 3 month – No treatment (group IV)	PO calcium 500 mg daily
Giannini 2001 [15]	Italy Single-center Not stated 1 year	Cadaveric KTX >6 months after KTX No prior bisphosphonates No major upper gastrointestinal illness	40 56 ± 12 years 63%	PO Alendronate 10 mg daily 45 min < breakfast – No treatment	PO calcitriol 0.5 μg daily and calcium 500 mg daily
Grotz 2001 [17]	Germany Single-center Not stated 1 year	20–60 years No combined kidney- pancreas TX	80 43 ± 10 years 67%	IV Ibandronate 1 mg just before KTX and 2 mg at 3, 6 and 9 months – No treatment	PO calcium 500 mg daily
Grotz 1998 [16]	Germany Single-center Not stated 1 year	>6 months after KTX BMD < 1.5 SD of normal	46 44.5 ± 12 years 73%	Group I: PO Clodronate 800 mg daily during 14 days, followed by 75 days without Group II: Intranasally Calcitonin 100 IU in morning and 100 IU in evening – No treatment	PO calcium 500 mg daily
Koc 2002 [18]	Turkey Single-center Not stated 1 year	Not diabetic >12 months after KTX Creat < 2 mg/dl No increase in creat ≥ 20% in past year No changes in prednisolone dosage No hyperparathyroidism or PTX No gonadal insufficiency	24 35 ± 8.6 years 75%	Group I: PO Alendronate 10 mg daily Group II: Oral calcitriol 0.5 μg daily – No treatment	PO calcium 1 g daily

Table 2. continued

Author Year Reference	Methods Country Setting Time-frame Follow-up	Participants Inclusion criteria	N Age Sex (%male)	Interventions Treatment group – Intervention group	Co-intervention
Lan 2008 [19]	China Single-center Not stated 6 months	Creat < 2.5 mg/dl >12 months after KTX BMD < 1 SD of normal No diabetic, no liver disease No gastro-intestinal disease No intake of vitamin D post-KTX	46 39.8 ± 17.9 years NS	PO Alendronate 70 mg weekly – No treatment	PO calcitriol 0.25 μg daily and PO calcium 800 mg daily
Lee 2004 [20]	USA Single-center 1999–2000 3 years	Adult KTXs Hemodynamically stable perioperatively	72 44 ± 2.3 years NS	IV Pamidronate 60 mg <48 h after KTX and 30 mg at months 1, 2, 3 and 6 – No treatment	PO calcitriol and calcium
Lord 2001 [21]	Canada Single-center Not Stated 2 years	>18 years No previous KTX No severe hyperparathyroidism No osteoporosis	20 NS NS	PO Alendronate 5 mg daily – No treatment	PO calcium and vitamin D
Montilla 2001 [22]	Venezuela Single-center Not stated 1 year	Male patients Severe osteopenia or osteoporosis	24 39.8 ± 7.6 years 100%	PO Pamidronate 200 mg – Placebo	No
Nam 2000 [23]	South Korea Single-center Not stated 6 months	Cadaveric KTX	50 NS NS	Group I: IV Pamidronate 30 mg every 4 weeks Group II: Oral calcitriol 0.5 μg daily – No treatment	PO calcium 500 mg daily
Nayak 2007 [24]	India Single-center Not stated 6 months	No bone disease prior to renal failure No long-term immunosuppressive therapy prior	50 NS NS	PO Alendronate 35 mg weekly – No treatment	PO calcium 1 g daily and vitamin D
Psimenou 2002 [25]	Greece Single-center Not stated 12 months	Ca and P equilibrium	43 NS NS	PO Etidronate 200 mg daily for 15 days every 3 month – Intranasaly Calcitonin 200 IU daily periodically every 1.5 month	No
Shahidi 2015 [30]	Iran Single-center Not stated 6 months	>18 years Living donor KTX No PTX No corticosteroids > 3 months before KTX No bisphosphonates or calcitonin No persistent hypercalcemia post-KTX	40 45 ± 15.9 years 78%	IV Pamidronate 30 mg within 2 days of KTX and 3 months after KTX – No treatment	PO calcium 500 mg daily and calcitriol 0.25 μg daily

Table 2. continued

Author Year Reference	Methods Country Setting Time-frame Follow-up	Participants Inclusion criteria	 N Age Sex (%male)	Interventions Treatment group – Intervention group	 Co-intervention
Torregrosa 2010 [28]	Spain Multicenter Not stated 12 months	Between 18 and 75 years CKD patients on dialyses, resulting in KTX No hyperimmunized, No multiple organ TX No pregnant or breastfeeding women Therapy with steroids and Tacrolimus No PTX, PTH > 50 pg/mL, No diabetic No bisphosphonates or hormones In 6 months before KTX No anticonvulsants or calcitonin in 3 months before KTX No allergy to bisphosphonates No gastro-intestinal disease	101 49 ± 14.8 years 66%	PO Risedronate 35 mg weekly – No treatment	PO calcium 1.5 g daily and vitamin D
Torregrosa 2011 [29]	Spain Multicenter Not stated 12 months	Adults with CKD in dialysis and KTRs *T*-score ≤1 at transplantation, ≥18 years No corticosteroids, anticoagulants or anti-epileptica 3 month before No multiple organ transplant No allergy to bisphosphonates Creatinine clearance ≥ 30 ml/min	39 55.2 ± 14.5 years 67%	IV Pamidronate 30 mg between day 7 and 10 after KTX and 3 months post-KTX – No treatment	PO calcium 1 g daily and vitamin D
Torregrosa 2007 [27]	Spain Single-center Not stated 12 months	Between 18 and 70 years Creatinine < 2.5 mg/dl, PTH > 60 pg/ml BMD with a *T*-score <−1 No diabetic	84 56.5 ± 8.5 years 50%	PO Risedronate 35 mg weekly – No treatment	PO calcium 2.5 g daily and vitamin D
Torregrosa 2003 [26]	Spain Single-center Not stated 12 months	Between 18 and 70 years Creatinine < 2 mg/dl, PTH < 240 pg/ml BMD with a *T*-score <−2.5 No diabetic	26 NS 38%	PO Alendronate 10 mg daily – No treatment	PO calcium 10 mg daily and vitamin D

Creat, serum creatinine; IV, intravenously; KTRs, kidney transplant recipients; KTX, kidney transplant; *N,* number of participants; NS, not specified; PO, per oral; PTX, parathyroidectomy; TX, transplant.

Agreement and disagreement with other studies

Our findings agree with these of an earlier Cochrane review [9]. The latter review included 15 RCTs and 727 participants for the comparison of bisphosphonates, with inclusion as well of trials with recipients of a second or subsequent graft kidney and trials with kidney transplant recipients of all ages.

The review found bisphosphonates to significantly improve the percentage change in BMD at the lumbar spine and at the femoral neck (10 trials, 535 participants, MD 5.43%, 95% CI 2.50 to 8.36; 7 trials, 362 participants, MD 6.48%, 95% CI 5.27 to 7.69), but to have uncertain effects on fracture risk.

Furthermore, this previous review also found no significant effect of treatment with bisphosphonates on risk of low bone turnover, incidence of hypocalcemia, risk of gastro-esophageal disorder, or graft loss. The review finally also analyzed the combination of vitamin D, bisphosphonates, calcitonin, and calcium versus no treatment and found a relative risk reduction for fractures of 49% after 6 to 12 months in the treatment group.

Conclusion

At this stage, we believe there is insufficient evidence to support routine use of bisphosphonates to reduce fracture risk after kidney transplantation. Data on important health outcomes are lacking, surrogate outcomes poorly reflect bone quality in kidney transplant recipients and serious adverse events are not studied systematically and/or remain unreported.

An additional randomized controlled trial, including all degrees of graft function, comparing bisphosphonates versus placebo of adequate sample size and follow-up (36 to 60 months) is due. To inform decision-making, it would need to assess important health outcome such as fractures, mortality, and graft survival as well as serious adverse events (including avascular jaw necrosis and nephrotoxicity).

Authorship

EBV: designed and conducted the systematic review, selected and critically appraised the studies, collected the data, and wrote and revised the manuscript. SVL, AWD, FV, RV and WVB: wrote and revised the manuscript. EVN: designed and conducted the systematic review and wrote and revised the manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Supplement S1. Electronic search strategies.

Supplement S2. PRISMA guideline.

Supplement S3. The Cochrane Collaboration's tool for assessing risk of bias.

Supplement S4. Table of excluded studies.

Supplement S5. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

Supplement S6. Bisphosphonates versus placebo or no treatment. Bone Mineral Density – vertebral, measured in g calcium/cm², expressed as absolute value at 6 to 12 months.

Supplement S7. Bisphosphonates versus placebo or no treatment. Bone Mineral Density – vertebral, measured in *T*-score, expressed as absolute value at 12 months.

Supplement S8. Bisphosphonates versus placebo or no treatment. Bone Mineral Density – femoral neck, measured in g calcium/cm², expressed as absolute value at 6 to 12 months**.**

Supplement S9. Bisphosphonates versus placebo or no treatment. Bone Mineral Density – femoral neck, measured in *T*-score, expressed as absolute value at 12 months.

Supplement S10. Bisphosphonates versus placebo or no treatment. Bone Mineral Density – forearm, measured in g calcium/cm², expressed as absolute value at 12 months.

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