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REVIEW

Bisphosphonates for prevention of osteopenia in kidney-transplant recipients: a systematic review of randomized controlled trials

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Abstract
Summary We conducted a systematic review of randomized controlled trials (RCTs) of bisphosphonates for the prevention of osteopenia in kidney-transplant recipients. Bisphosphonates improved bone mineral density at the lumbar spine and femoral neck after 12 months. However, additional well-designed RCTs are required to determine the optimal treatment strategy.

Osteopenic–osteoporotic syndrome is a bone complication of renal transplantation. Bisphosphonates, calcitonin, and vitamin D analogs may be used to prevent or treat osteoporosis or bone loss after renal transplantation. However, there is currently no widely recognized strategy for the prevention of corticosteroid-induced osteoporosis. This study aims to assess the available evidence to guide the targeted use of bisphosphonates for reducing osteoporosis and bone loss in renal-transplant recipients. We searched the Cochrane Central Register of Controlled Trials, PubMed, and EMBASE for randomized controlled trials of bisphosphonates for osteoporosis or bone loss after renal transplantation. A total of 352 abstracts were identified, of which 55 were considered for evaluation and 9 were included in the final analysis. The primary outcome measure was change in the bone mineral density (BMD) of the lumbar spine and femoral neck after 12 months. Data extraction was performed independently by two investigators. BMD at the lumbar spine was improved after treatment with bisphosphonates [9 trials; 418 patients; weighted mean difference (WMD), 0.61; 95 % confidence interval (CI), 0.16–1.06]. Eight trials (406 patients) that reported changes in BMD at the femoral neck also showed improved outcomes after treatment with bisphosphonates (WMD, 0.06; 95 % CI, 0.03–0.09). Bisphosphonates improve BMD at the lumbar spine and femoral neck after 12 months in renal-transplant recipients.

Keywords Bisphosphonates · Osteopenia · Renal transplantation · Osteoporosis

Introduction

Successful renal transplantation corrects many metabolic abnormalities associated with the development of renal osteodystrophy. However, osteopenia and osteoporosis remain prevalent, even in patients with well-functioning grafts. Increasing attention has focused on preventing late complications of transplantation and on patient quality of life by addressing factors affecting long-term morbidity, such as cardiovascular risk, post-transplantation diabetes mellitus, cancer, and bone disease [1–3].

Osteopenic–osteoporotic syndrome is a bone complication of renal transplantation. Although renal transplantation corrects abnormalities of calcium and phosphorus metabolism in patients with uremia, it may result in disturbances to bone metabolism, such as osteopenia, caused by treatment with glucocorticoids and cyclosporine. However, there is currently no widely recognized strategy for the prevention of corticosteroid-induced osteoporosis.

Bone mineral density (BMD) in the lumbar spine decreases by 5 % during the first year after engraftment [4], and

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longitudinal studies of stable renal-transplant recipients revealed an annual bone loss of 1.7 % in the lumbar spine [5]. Mineral and bone disorders are common following kidney transplantation and are characterized by loss of bone volume and mineralization abnormalities that may lead to low bone turnover [6].

BMD can be reduced by 6.8 and 8.8 % at 6 and 18 months, respectively, after successful renal transplantation [7]. Pre-existing osteopenia may deteriorate in kidney-graft recipients as a result of immunosuppressive therapy with calcineurin inhibitors [8] or corticosteroids [9]. Furthermore, immunosuppressive agents used in solid-organ transplantation can exert various effects on bone metabolism [10]. Changes in fracture rate and BMD are associated with secondary osteoporosis, though not as strongly as with primary osteoporosis.

Bisphosphonates such as pamidronate and ibandronate can prevent bone loss during the first year post-transplantation [11, 12]. Pamidronate is easy to administer and well-tolerated with no any serious adverse effects, and a recent meta-analysis suggested that it had a beneficial effect on bone loss, with no correlation with renal toxicity during the first year after renal transplantation [13].

In this review, we aimed to identify a rationale for the use of bisphosphonates for the prevention or treatment of osteoporosis or bone loss after renal transplantation.

Methods

Inclusion criteria

We conducted a review of randomized controlled trials (RCTs) that used bisphosphonates to treat osteopenia or osteoporosis in renal-transplant recipients. Trials that met the following criteria were included: (1) full-text original articles, (2) administration of bisphosphonates by any route (oral and parenteral), (3) intervention for the treatment of osteopenia or osteoporosis before or after transplantation, and (4) follow-up of patients for >12 months.

Trials involving transplantations other than renal transplantation, including kidney–pancreas transplants, were excluded. Trials that did not involve dual-energy X-ray absorptiometry (DXA) were also excluded. Trials including mixed populations were only included when data for patients receiving a kidney transplant were provided in the publication or were received from the authors on request.

Search strategy

Electronic searches were performed in PubMed (1966 to May 2014), EMBASE (1980 to May 2014), and the Cochrane Central Register of Controlled Trials using optimally sensitive search strategies for the identification of RCTs. We searched for the following medical subject headings and text words: kidney transplantation, osteopenia, osteoporosis, and RCT. The titles and abstracts of the identified studies were analyzed by two of the authors (JW and JHX) in consultation with a third author (XJC), according to the inclusion criteria. The reference lists of the identified articles were also searched. Trials reported in any language were considered.

Data extraction and quality assessment

Each trial was assessed by two independent authors (JW and JHX) who extracted data on study-sample characteristics, agent type and route of administration, trial method, and outcomes. The primary outcome measure was changes in BMD of the lumbar spine and femoral neck after 12 months. The risk of bias in the included RCTs was assessed using the risk of bias assessment tool from the Cochrane Collaboration [14]. Selection bias, performance bias, detection bias, attribution bias, and other biases in the included RCTs were assessed. Differences in and difficulties with data extraction were resolved by discussion among the authors. In the event of missing or incomplete data, the trial investigators were contacted for clarification. Three reviewers (JW, MY, JHX) independently assessed the qualities of the included studies and differences were resolved by discussion.

For trials reporting pre- and post-intervention values, mean changes were obtained by subtracting the pre-intervention from the post-intervention values and standard deviations were estimated using the following formula:

$$\text{ker}\ \sqrt{SD_{pre}^2 + SD_{pre}^2 - 2*r_{prepost}*SD_{pre}*SD_{post}}$$

in which the correlation between the pre- and post-intervention values ($r_{pre,post}$) was assumed to be 0.5.

Statistical analysis

Bisphosphonates, calcitonin, and vitamin D analogs were compared with controls according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [15]. Heterogeneity of treatment effects among the studies was tested using Q (heterogeneity χ^2) and I^2 statistics [16]. Values of $P<0.10$ and $I^2>50$ % were considered to indicate significant heterogeneity. Random-effect models were used when heterogeneity was present; otherwise, fixed-effect models were used. Summary estimators of treatment effects were calculated using relative risk or weighted mean difference (WMD) and 95 % confidence intervals (CI), as appropriate. Data were represented graphically using Forest plots. The main analysis was conducted using the random-effects model, as described by Der-Simonian and Laird [17].

Direct comparisons were performed using RevMan statistical software, version 5.1 (Nordic Cochrane Center) [18].

Results

Description of studies

The search strategy retrieved 352 potentially relevant records (Fig. 1), comprising 163 trials from PubMed, 121 from EMBASE, 65 from the Cochrane Central Register of Controlled Trials, and three from manual searches. Overall, 111 records were excluded by screening the titles and abstracts. The remaining 55 full-text articles were retrieved for additional scrutiny, among which 46 were ineligible because of nonuse of DXA, lack of primary outcome, unrelated to treatment for osteoporosis, or lack of full text. Nine RCTs met the eligibility criteria [11, 12, 19–25], all of which used bisphosphonates in relation to osteoporosis, included DXA examinations, and involved changes in BMD after 12 months as an outcome. The characteristics of the included RCTs are summarized in Table 1.

Methodological quality of RCTs

Figure 2 shows a graphical summary of the risk of bias assessments of the included studies based on the risk of bias domains. Based on the Cochrane criteria, three of the nine studies had low risks of selection bias, detection bias, and performance bias [11, 23, 24]. High risks of bias were identified as failure to describe or use appropriate allocation concealment (5/9) and lack of effective blinding procedures (observer, 6/9; patient, 5/9). Four studies [12, 20, 21, 25] included groups with equal distributions of clinical conditions. None of the studies had equal age and sex distributions. Four trials [11, 19, 21, 25] did not mention patient dropouts.

Bisphosphonates versus placebo or no treatment

Changes in lumbar spine BMD were reported in all nine trials, and improved after treatment with bisphosphonates (418 patients; WMD, 0.61; 95 % CI, 0.16–1.06), especially pamidronate. Eight trials (406 patients) also reported improved BMD at the femoral neck after treatment with bisphosphonates (WMD, 0.06; 95 % CI, 0.03–0.09), especially alendronate (Figs. 3 and 4). Levels of parathyroid hormone (PTH) were decreased in both the bisphosphonate-treated and placebo/untreated groups [11, 12, 21, 22, 24], with no significant difference between the two groups (WMD, 0.17; 95 % CI, −0.19–0.53). Four studies reported fracture rates [12, 22–24], but the positive effect of ibandronate on BMD was not accompanied by a reduction in fracture rate within the 12-month period [12, 24].

Discussion

This meta-analysis demonstrated that treatment with bisphosphonates had a beneficial effect on changes in BMD at both the lumbar spine and femoral neck. Current European Best Practice Guidelines recommend bisphosphonate treatment in potentially high-risk groups, including patients with pre-existing fractures and severe osteoporosis, patients with diabetes, recipients of kidney and pancreas transplants, and postmenopausal women [26]. Similarly, the Kidney Disease Outcomes Quality Initiative recommends limiting glucocorticoid therapy and measuring BMD at regular intervals to assess the presence or development of osteoporosis [27], and treatment with a parenteral bisphosphonate in the event of a BMD T-score <−2 standard deviations. The findings of the present study support the recommendation that bisphosphonates should be considered to improve BMD after renal transplantation. However, the trials demonstrated broad heterogeneity

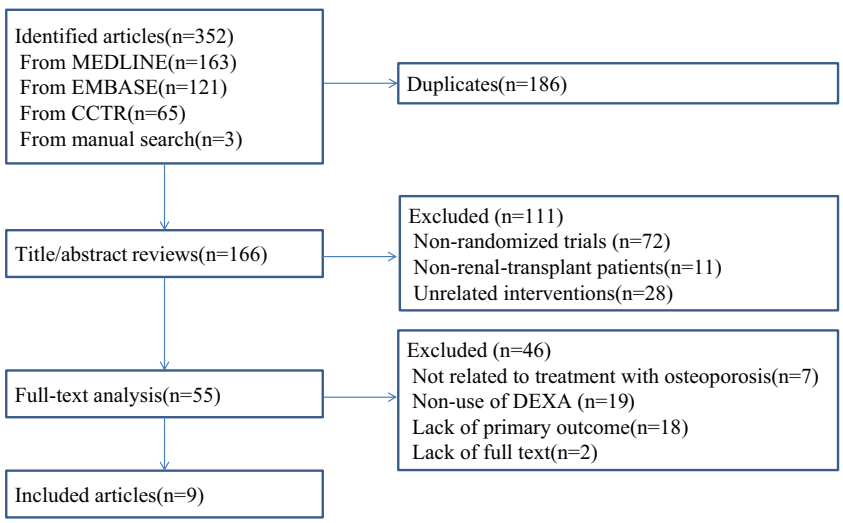

Fig. 1 Flow diagram of studies

Table 1 Characteristics of studies for the prevention of bone loss in recipients of renal transplant

Study	Participants	Male/female	Mean age (years) (SD or range)	Intervention		Follow-up (months)
				Treatment group	Control group	
Nam et al. 2000 [19]	Osteopenia after renal transplantation	50 patients (29/21)	44 (28–56)	Pamidronate (30 mg) i.v. every 4 week with calcium (0.5 g) oral each day for 6 months, beginning 2 weeks after transplantation	Calcitriol (0.5 g) and calcium (500 mg) oral daily supplementation alone for 6 months, beginning 2 weeks after transplantation	12
Fan et al. 2000 [11]	Osteopenia after renal transplantation	Pamidronate 14/0 Control 12/0	Pamidronate 53 (23–66) Control 50 (23–74)	Pamidronate (0.5 mg/kg) i.v. at the time of transplantation and again 1 month later	Placebo	12
Grotz et al. 2001 [12]	Osteopenia after renal transplantation	Ibandronate 25/11 Control 23/13	Ibandronate 42 (10) Control 44 (10)	Ibandronate, immediately before and at 3, 6, and 9 months after transplantation	No treatment	12
Koc et al. 2002 [20]	Osteopenia and osteoporosis after kidney transplantation	Alendronate 6/2 Calcitriol 5/3 Control 6/2	Alendronate 34.4 (8.9) Calcitriol 40.5 (8.1) Control 35.5 (8.4)	Alendronate (10 mg/day) plus elemental calcium (1000 mg/day) oral daily Calcitriol (0.5 g/day) plus elemental calcium (1000 mg/day) oral daily	Elemental calcium (1000 mg/day) oral daily	12
El-Agroudy et al. 2005 [21]	Osteopenia after kidney transplantation	Alfacalcidol 15/0 Alendronate 15/0 Calcitonin 15/0 Control 20/0	Alfacalcidol 31.4 (10.1) Alendronate 31.6 (8.6) Calcitonin 32.3 (7.9) Control 31.6 (10.1)	Alfacalcidol (0.5 μg) oral daily Alendronate (5 mg/day) oral daily Calcitonin (200 IU) intranasal every other day	No treatment	12
Walsh et al. 2009 [22]	Osteopenia after kidney transplantation	Pamidronate 35/11 Control 34/13	Pamidronate 46.1 (12.77) Control 46.1 (12.93)	Pamidronate (1 mg/kg) i.v. at baseline, then again at 1, 4, 8, and 12 months after transplantation	Received no bisphosphonates	24
Torregrosa et al. 2011 [23]	Osteopenia after kidney transplantation	Pamidronate 14/0 Control 12/0	Pamidronate 53.99 (13.79) Control 56.33 (15.48)	Two doses of 30 mg of disodium pamidronate	Placebo	12
Smerud et al. 2012 [24]	Osteopenia after kidney transplantation	Ibandronate 48/18 Control 51/12	Ibandronate 50.2 (13.5) Control 52.6 (14.0)	Ibandronate i.v. 3 mg every 3 months for 12 months	Placebo	12
Masanori Okamoto et al. 2014 [25]	Osteopenia after kidney transplantation	Alendronate 4/1 Control 4/3	Alendronate 52.8 (12.6) Control 52.9 (7.3)	Alendronate 35 mg/week for 24 months	Received no bisphosphonates	24

IU international unit, *i.v.* intravenous, *SD* standard deviation

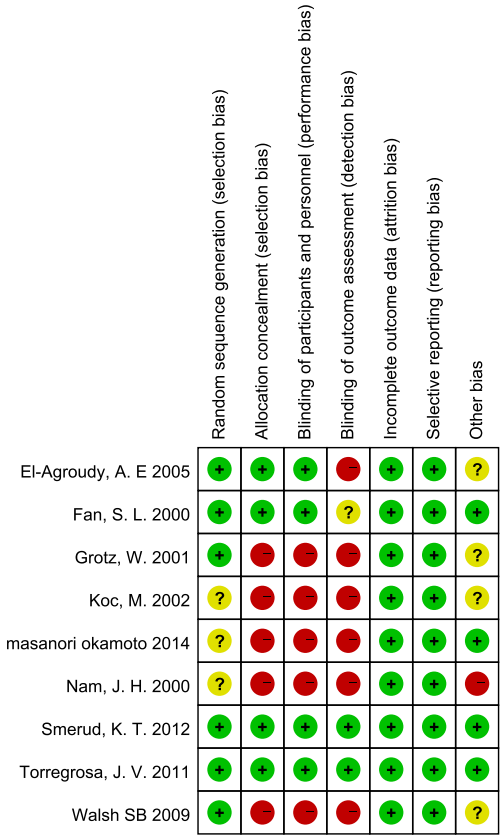

Fig. 2 Risk of bias summary: review authors' judgements about each risk of bias item for each included study

in terms of bisphosphonate use, with four studies using parenteral pamidronate, three using oral alendronate (5 and 10 mg), and two using intravenous injection of ibandronate.

Although treatment with bisphosphonates for 12 months is recommended when osteopenia is diagnosed, some studies [4, 19] also observed the effects after 6 months. However, although these results indicated non-inferior and effective changes in BMD of the lumbar spine and femoral neck with bisphosphonate treatment, their use for 6 months was less effective, and the 6-month results were therefore not analyzed in the current meta-analysis. The majority of RCTs recorded the outcomes after 12 months of treatment. However, long-term treatment is required after renal transplantation, and the timings of the BMD scans after transplantation varied from 6 months to several years after surgery.

A previous meta-analysis [28] reviewed interventions for the prevention of bone disease in renal-transplant recipients with a focus on osteoporotic fractures and other bone diseases, and concluded that bisphosphonates and vitamin D had beneficial effects on BMD at the lumbar spine and femoral neck [29]. Although the articles included in this previous meta-analysis were published over 10 years [28], to the best of our knowledge, there has been no significant increase in the quality or quantity of relevant RCTs for the interventional effects of bisphosphonates on osteoporosis after renal transplantation, and no large-scale studies are currently registered with clinicaltrials.gov.

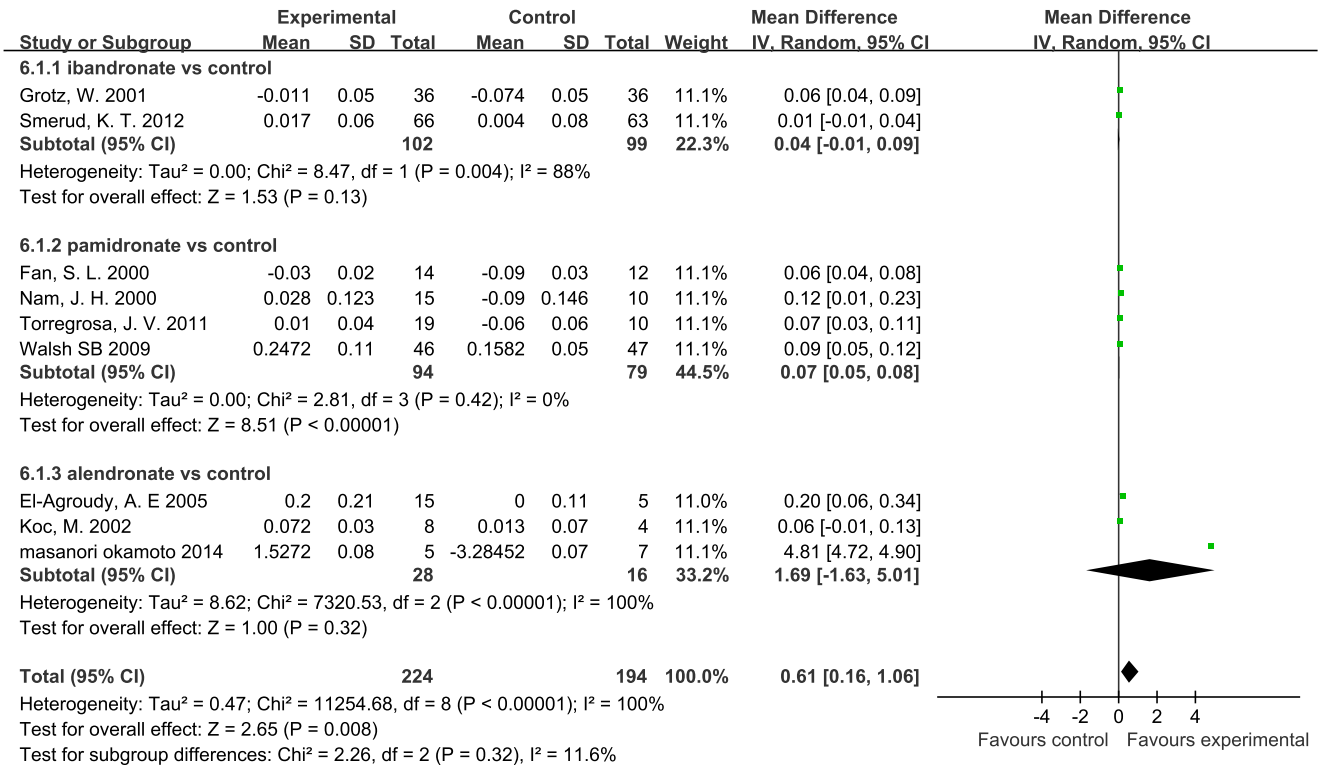

Fig. 3 Effect of bisphosphonates on change in BMD at the lumbar

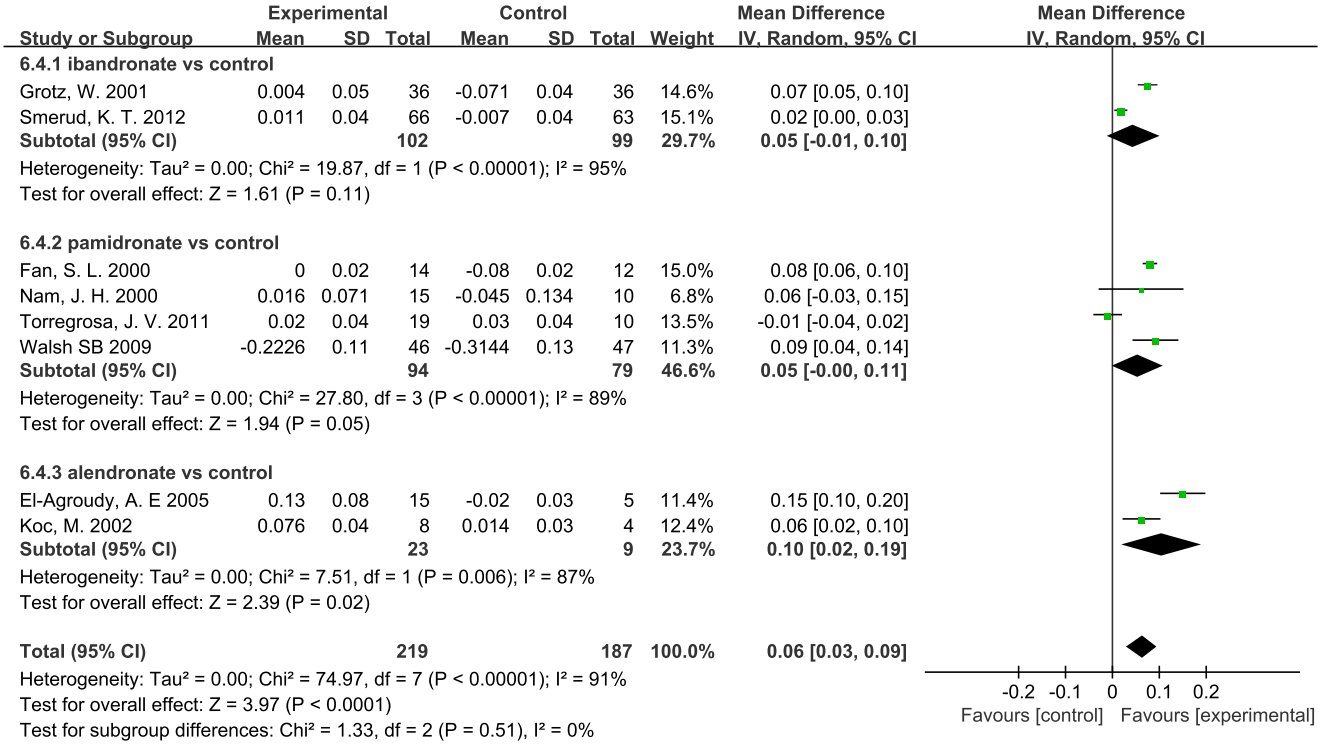

Fig. 4 Effect of bisphosphonates on change in BMD at the femoral

This review had several limitations. Fracture rate or fracture risk is the main consequence of osteoporosis, and efforts have been made to estimate these rather than relying solely on measurements of BMD. However, we were unable to draw any conclusions regarding these, because only four of the included studies evaluated the fracture rate [12, 22–24].

DXA provides no specific information on bone turnover, and BMD results should thus be interpreted together with clinical findings and bone-turnover biomarkers. The important biomarker PTH can exacerbate low bone turnover in renal-transplant recipients. Although PTH levels were decreased after renal transplantation in five studies [11, 12, 21, 22, 24], there was no significant difference between patients with and without bisphosphonate treatment, implying that bisphosphonates may not aggravate pre-existing hyperparathyroidism. Bone biopsies are required to demonstrate the course of events, but this is an invasive procedure and the subsequent analysis is time-consuming [30, 31]. However, bone-biopsy findings could help clinicians to decide on an appropriate therapeutic strategy and should thus be performed in patients with chronic kidney disease.

The patient populations varied among the included studies. Some trials excluded women to eliminate the confounding effects of menopausal status on outcomes, while other trials included both sexes. Only one trial clearly described the proportion of postmenopausal women, and the impact of this variable is thus unclear. The age distributions within the populations were also large, ranging from 20 to 70 years, which represented an important confounding factor. Furthermore, the small sample sizes in most studies (apart from one) reduced the strength of the conclusions that could be drawn from the data.

It was difficult to assess the included RCTs because of the omission of detailed information on the methods used in the trials. Most reports failed to include information on the method of allocation concealment, whether or not the outcome assessors were blinded, and whether an intention-to-treat analysis was used.

The current included trials also enrolled recipients from 0 to 24 months after transplantation. Future trials should consider randomizing enrollment before surgery and commencing interventions after graft function has been established [28].

Conclusions

This systematic review confirmed that treatment with bisphosphonates before and after renal transplantation had a favorable effect on BMD, with bisphosphonates, such as pamidronate and alendronate, being preferable to other treatments. Furthermore, the analyzed RCTs had small sample sizes, were of relatively poor quality, and had short follow-up periods, indicating the need for additional, well-designed RCTs to establish evidence-based recommendations regarding dosages, monitoring of interventions, adverse effects, and standardization of follow-up for BMD, to determine the optimal treatment for renal-transplant patients.

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Compliance with ethical standards

Conflicts of interest None.

Appendix 1. Search strategy of PubMed

Search ((((((((controlled clinical trial[Publication Type]) OR ((trial[Title]) OR randomly[Title/Abstract])) OR clinical trials as topic[MeSH Major Topic]) OR placebo[Title/Abstract]) OR randomized[Title/Abstract]) OR randomized controlled trial[Publication Type])) NOT ((animals[MeSH Terms]) NOT ("humans"[MeSH Terms] AND "animals"[MeSH Terms]))))) AND ((((((osteoporosis) OR bone mineral density) OR bone loss) OR osteopenia)) AND ((((kidney transplant) OR renal transplantation) OR kidney transplantation) OR renal transplant)).

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