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REVIEW ARTICLE

Effects of denosumab on bone metabolism and bone mineral density in kidney transplant patients: a systematic review and meta-analysis

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Abstract

Objective The use of immunosuppressive agents, especially glucocorticoids, are associated with increased risks of bone loss in kidney transplant patients. Denosumab, a potent antiresorptive agent, has been shown to increase bone mineral density (BMD) in patients with CKD. However, its effects on bone metabolism and BMD in kidney transplant patients remain unclear.

Methods A literature search was conducted using MEDLINE, EMBASE, and Cochrane Database from inception through April 2018 to identify studies evaluating denosumab's effect on changes in bone metabolism and BMD from baseline to post-treatment course in kidney transplant patients. Study results were pooled and analyzed utilizing random-effects model. The protocol for this systematic review is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42018095055).

Results Five studies (a clinical trial and four cohort studies) with a total of 162 kidney transplant patients were identified. The majority of patients had a baseline eGFR ≥ 30 mL/min/1.73 m^2. After treatment (≥ 6 to 12 months), there were significant increases in BMD with standardized mean differences (SMDs) of 3.26 (95% CI 0.88–5.64) and 1.83 (95% CI 0.43 to 3.22) for lumbar spine and femoral neck, respectively. There were also significant increases in *T* scores with SMDs of 0.92 (95% CI 0.58 to 1.25) and 1.14 (95% CI 0.17 to 2.10) for lumbar spine and femoral neck, respectively. After treatment, there were no significant changes in serum calcium (Ca) or parathyroid hormone (PTH) from baseline to post-treatment course (≥ 6 months) with mean differences (MDs) of 0.52 (95% CI, − 0.13 to 1.16) mmol/L and − 13.24 (95% CI, − 43.85 to 17.37) ng/L, respectively. The clinical trial data demonstrated more asymptomatic hypocalcemia in the denosumab (12 episodes in 39 patients) than in the control (1 episode in 42 patients) group. From the cohort studies, the pooled incidence of hypocalcemia following denosumab treatment was 1.7% (95% CI 0.4 to 6.6%). All reported hypocalcemic episodes were mild and asymptomatic, but the majority of patients required Ca and vitamin D supplements.

Conclusion Among kidney transplant patients with good allograft function, denosumab effectively increases BMD and *T* scores in the lumbar spine and femur neck. From baseline to post-treatment, there are no differences in serum Ca and PTH. However, mild hypocalcemia can occur following denosumab treatment, requiring monitoring and titration of Ca and vitamin D supplements.

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Introduction

Kidney transplantation (KTx) is the renal replacement therapy of choice for the majority of patients with end-stage renal disease (ESRD) as it improves survival and quality of life [1]. Patients with chronic kidney disease (CKD) and ESRD have substantially increased risk of developing mineral bone disorders (MBDs), largely due to alterations in calcium, phosphorus, vitamin D, parathyroid hormone, and fibroblast growth factor 23 [2, 3]. However, despite successful KTx, recipients can experience persistent abnormalities in MBD parameters, modification of osteoblast-osteoclast activity by the immunosuppressants, and accelerated age-related bone loss [4–13]. Fracture risk among KTx patients is up to 34% in the first 2 years post-transplant, and the incidence is up to 22.5% over 5 years [14, 15]. Correspondingly, higher rates of hospitalization, increased health care costs, and mortality rates up to 60% after a fracture were observed in KTx patients in comparison with the general population [8, 16, 17].

Denosumab is a fully humanized monoclonal antibody against the receptor activator of nuclear factor kappa-B ligand (RANKL), an osteoclast differentiating factor. It inhibits osteoclast formation and decreases bone resorption, increases bone mineral density, and reduces the risk of vertebral, non-vertebral, and hip fractures in patients with osteoporosis [18–21]. Overall, denosumab therapy provides an antiresorptive effect with a significant improvement in BMD. While its efficacy in the general population has been well studied [18, 22], denosumab's impacts on MBD parameters and bone mineral density remain unclear [23–28] in kidney transplant recipients. In addition, despite safe renal profiles, hypocalcemia has been reported in 10–29% among CKD patients and 42% among ESRD patients following denosumab treatment [29–35]. Although ESRD patients have significant improvement in renal functions after successful KTx, transplant recipients remain at risk as their estimated glomerular filtration rate (eGFR) commonly range between 30 and 60 mL/min/1.73 m^2 [36, 37].

This systematic review and meta-analysis aimed to assess denosumab's (1) effects on bone metabolism and bone mineral density changes and (2) the incidence of associated hypocalcemia among KTx patients.

Methods

Information sources and search strategy

The protocol for this systematic review is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42018095055). A systematic literature search was conducted utilizing Ovid MEDLINE, EMBASE, and Cochrane Database from inception through April 2018 to identify all original studies that evaluated the effects of denosumab on changes in bone metabolism and BMD from baseline to post-treatment course in KTx patients. The systematic literature review was individually conducted by two investigators (C.T. and W.C.) using the search strategy as demonstrated in Online Supplementary Data 1. A manual search for additional potentially relevant studies using references of the included articles was also performed. No language limitation was applied. Any differing decisions were resolved by mutual consensus. This systematic review was conducted in agreement with the STROBE (reporting epidemiological studies) [38] and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement [39] as described in Online Supplementary Data 2.

Selection criteria

Eligible studies included (1) controlled clinical trials or observational studies such as case-control, cross-sectional, or cohort studies that evaluated denosumab's effects on bone metabolism and BMD changes from baseline to post-treatment course in KTx patients, (2) studies that presented data to calculate mean differences (MDs), standardized mean differences (SMDs), hazard ratios, or relative risks with 95% confidence intervals (CIs), and/or (3) studies that evaluated changes in serum calcium, PTH, and BMD with denosumab treatment when compared with a control group composed of KTx patients who did not receive denosumab. Inclusion was not restricted by study size. The quality of included each study was quantified via the Cochrane risk of bias tool [40]. The quality of each included study was evaluated by the investigators using Jadad quality assessment scale [41] and the validated methodological index for non-randomized studies (minors) quality score [42], as demonstrated in Table 1.

Data abstraction

A structured data collection report was adopted to derive the following information from included studies: study title, publication year, year of the study, first author name, demographic data, number of patients, data on calcium, phosphate, PTH, *T* score (when osteoporosis was defined as *T* score of − 2.5 or lower), BMD, and dosing regimen of denosumab. To increase precision, this data extraction process was independently performed by three investigators (C.T., W.C., and P.A.).

Table 1 Characteristics of included studies [24–28]

Study	Bonani et al. [28]	Doddoli et al. [24]	Yoshino et al. [25] and Nakayama et al. [26]	Brunova et al. [27]
Year	2016	2017	2017	2018
Study design	Randomized controlled trial	Cohort study	Cohort study	Cohort study
Study sample	Kidney transplant patients	Kidney transplant patients	Kidney transplant patients	Kidney transplant patients with osteoporosis
Number	90 (46 denosumab)	37	38 (30 denosumab)	49 (15 pancreas and kidney transplant, 34 kidney transplant)
Age (years)	50.0 ± 14.0	60.5	51 ± 21	N/A
Male	35/46 (76.1%)	15/37 (40.5)	30/38 (78.9%)	N/A
Calcium level	2.31 ± 0.16 mmol/L	2.33 mmol/L	N/A	Pancreas and kidney 2.42 ± 0.1 mmol/L Kidney 2.4 ± 0.1 mmol/L
Phosphate	0.58 ± 0.23 mmol/L	N/A	N/A	N/A
PTH	163.1 ± 157.9 ng/L	95 ng/L	N/A	Pancreas and kidney 10.1 ± 4.4 pmol/L Kidney 14.8 ± 8.9 pmol/L
L-spine BMD (g/cm^2)	1.002 ± 0.139	N/A	0.95 ± 0.15	N/A
L-spine *T* score	− 0.67 ± 1.25	− 2.04	N/A	Pancreas and kidney − 1.8 ± 1.7 Kidney − 2.9 ± 0.7
Hip/femoral neck BMD (g/cm^2)	0.925 ± 0.132	0.676	0.64 ± 0.11	N/A
Hip/femoral neck *T* score	− 0.59 ± 0.97	− 2.7	N/A	Pancreas and kidney − 3.2 ± 0.5 Kidney − 2.4 ± 1.1
Osteoporosis/osteopenia	Osteopenia 16/46 (34.8%) Osteoporosis 3/46 (6.5%)	Osteopenia 13/37 (35.1%) Osteoporosis 24/37 (64.9%)	N/A	Osteoporosis 49/49 (100%)
Immunosuppression	Cyclosporine/tacrolumus, mycophenolate, steroid	Steroid (≥ 5 mg/day). Not specified other immunosuppression	Not specified	Cyclosporine/tacrolimus, mycophenolate, sirolimus, steroid
Control	Yes	No	Yes	No
Denosumab	60 mg subcutaneous at baseline and at 6 months	60 mg subcutaneous	60 mg subcutaneous two times during the first year after transplant	60 subcutaneous every 6 months; minimum treatment duration 1 years
Supplement	Calcium (1000 mg/day), vitamin D (≥ 800 IU/day)	Calcium and vitamin D	Alfacalcidol (0.25–1.0 mg/day) or cholecalciferol (400 IU/day)	Calcium (500–1000 mg/day), vitamin D (800–1000 IU/day) and 1,25(OH)$_2$ vitamin D3 (calcitriol or paricalcitol 0.25–0.50 μg/day)
Follow-up	1 year	1 year	1 year	1.65 ± 0.7 years
Quality assessment scores	Jadad score 4	MINOR score 14/16	MINOR score 21/24	MINOR score 14/16

BMD bone mineral density, *N/A* not available, *PTH* parathyroid hormone

Statistical analysis

Data analysis was performed using the Comprehensive Meta-Analysis (version 3; Biostat Inc.). The incidence rate and 95% CIs of hypocalcemia were reported using a DerSimonian–Laird random-effects model, which allowed the weight of each study in the pooled analysis based on its variance [43]. The summary statistics for each outcome were the mean change from baseline

and standard deviations (SD) of the mean change. The mean change in each group was obtained by subtracting the final mean from the baseline mean. The MDs were preferred when all studies use the same continuous outcome and unit of measure. Otherwise, SMDs and 95% CIs were calculated for the summary effect of continuous data. The SD of mean change was computed assuming a conservative correlation coefficient of 0.5 [44]. Effects size of 0.2 were interpreted as small, those of 0.5 as moderate and of 0.8 as large [45]. Given high likelihood of between-study variance, we used random-effects model rather than a fixed-effect model. Cochran's Q test and I^2 statistic were utilized to evaluate the between-study heterogeneity. A value of I^2 of 0–25% represents insignificant heterogeneity, 26–50% represents low heterogeneity, 51–75% represents moderate heterogeneity, and more than 75% represents high heterogeneity [46]. Egger regression symmetry test was used to assess for publication bias. The p value < 0.05 was considered statistically significant for all analyses. Raw data for this review are publicly available, through the Open Science Framework (https://osf.io/wb5vc/?view_only=3970813f26ab4603b8149c879a91d209).

Results

Our search strategy retrieved 112 potentially relevant articles. After exclusion of 87 articles based on title and abstract not fulfilling inclusion criteria and 11 articles due to being duplicates, 14 articles underwent full-length review (Fig. 1). An additional nine articles were excluded for failing to meet criteria: six articles did not report the outcome of interest, and three articles were not observational studies. Kappa coefficient of agreement for the investigators was 0.91.

Five studies (a clinical trial and four cohort studies) [24–28] with a total of 162 KTx patients met the eligibility criteria and were enrolled in our meta-analysis. The majority of patients had a baseline eGFR ≥ 30 mL/min/1.73 m^2. The literature retrieval, review, and selection process are shown in Fig. 1. The characteristics of included studies and quality assessment of the studies included in this meta-analysis are shown in Table 1. Extracted data from included studies are provided in Table 2.

Changes in bone metabolism and BMD from baseline to post-treatment course

After denosumab treatment (≥ 6 to 12 months), there were significant increases in BMD (g/cm^2) with SMDs of 3.26 (95% CI 0.88–5.64, I^2 = 94%) and 1.83 (95% CI 0.43 to 3.22, I^2 = 54%) for lumbar spine and femoral neck, respectively. There were also significant increases in T scores with SMDs of 0.92 (95% CI 0.58 to 1.25, I^2 = 0%) and 1.14 (95% CI 0.17 to 2.10, I^2 = 82%) for lumbar spine and femoral neck, respectively (Fig. 2).

After denosumab treatment, there were no significant changes in serum Ca or PTH from baseline to post-treatment course (≥ 6 months) with MDs of 0.52 (95% CI, − 0.13 to 1.16) mmol/L and − 13.24 (95% CI, − 43.85 to 17.37) ng/L, respectively.

Incidence of hypocalcemia in KTx patients during denosumab treatment

Data from the clinical trial demonstrated that asymptomatic hypocalcemia occurred more often in the denosumab (12 episodes in 39 patients) than in control (1 episode in 42 patients) group. From the cohort studies, the pooled incidence of hypocalcemia following denosumab (within 6 to 12 months) treatment was 1.7% (95% CI 0.4 to 6.6%, I^2 = 0%) (Fig. 2). All reported hypocalcemic episodes were mild and asymptomatic, but the majority of all patients required Ca and vit D supplements (Tables 1 and 2).

Reported adverse side effects of denosumab treatment in KTx patients

Reported adverse side effects of denosumab treatment in KTx patients are shown in Table 3. Urinary tract infection and diarrhea were commonly observed among KTx patients receiving denosumab (Table 3). Bonani et al. [28] found significantly higher incidence of urinary tract infection (52% vs 25%) and diarrhea (50% vs 29.5%) among KTx patients who received denosumab than those who did not receive denosumab (p < 0.05). However, there were no differences in allograft renal function, rates of allograft rejection, and opportunistic infections among denosumab and control groups.

Evaluation for publication bias

Funnel plots (Supplementary Fig. 1–6) and Egger's regression asymmetry tests were performed to evaluate for publication bias in the incidence of hypocalcemia during denosumab treatment and changes in serum calcium, PTH, T scores, and BMD from baseline to post-treatment course of denosumab in KTx patients. There was no significant publication bias (p > 0.05 for all outcomes of interest).

Discussion

In this systematic review, we demonstrated that denosumab treatment among kidney transplant patients effectively increased BMD and T scores for lumbar spine and femoral neck. The overall incidence of denosumab-associated hypocalcemia in the KTx population was 1.7%.

Among KTx patients, the use of immunosuppressant agents such as glucocorticoids and calcineurin inhibitors play an

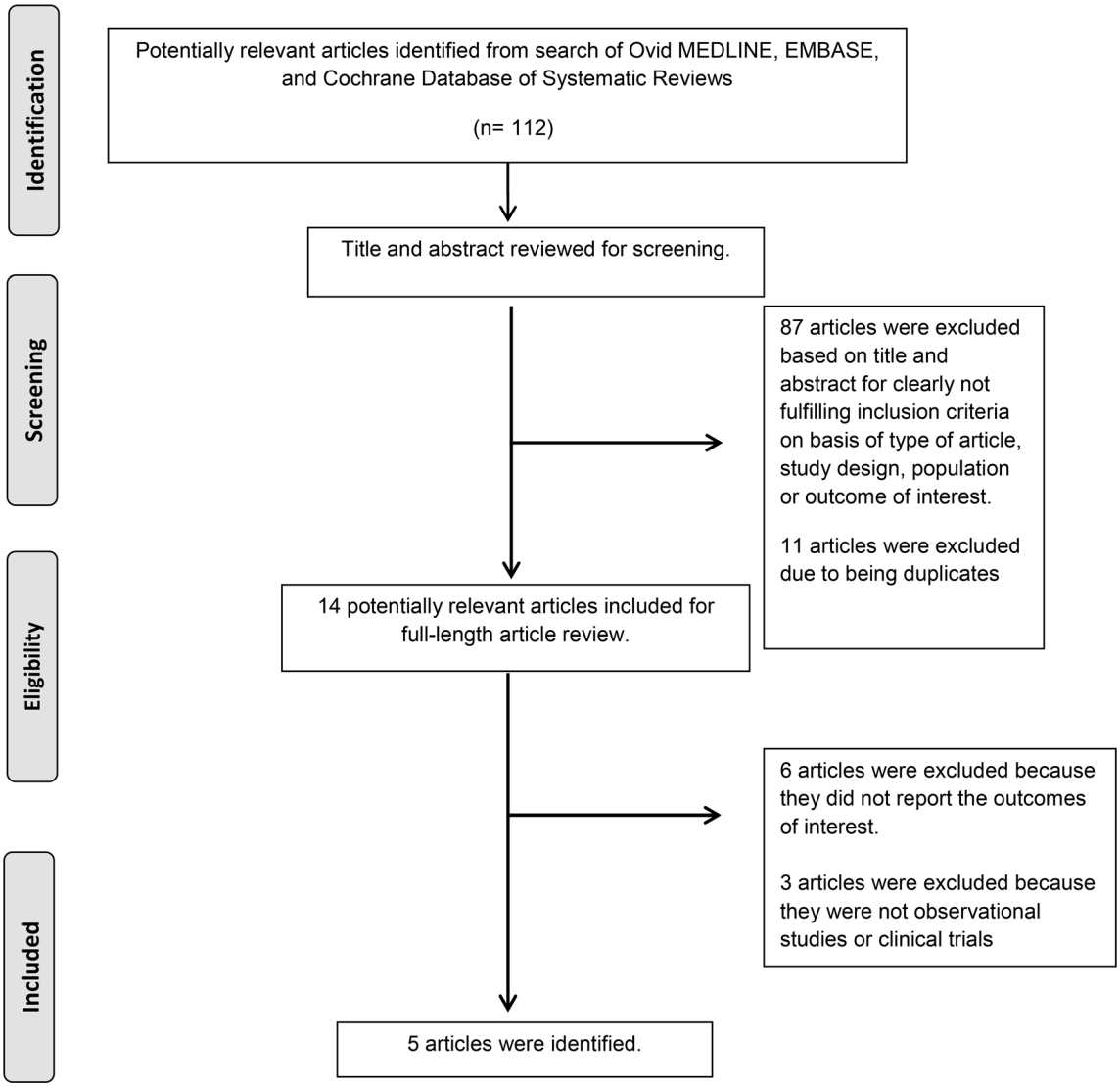


Fig. 1 Literature review process

important role in the development of post-transplant osteoporosis [13, 47–50], which is associated with increased morbidity and mortality [51]. Glucocorticoids can decrease osteoblast production, induce osteoblast apoptosis, and promote osteoclastogenesis via the RANKL system [12]. Glucocorticoids can also lead to reduced intestinal calcium absorption, enhanced renal calcium wasting, and decreased gonadal function, which all can contribute to bone loss [12, 13, 52]. The actual impact of calcineurin inhibitors on human bone density is unclear because the majority of KTx patients also commonly use glucocorticoids in a multidrug combination immunosuppressive regimen [12, 13, 52–55]. In animal models, however, the use of calcineurin inhibitors (especially cyclosporine) can reduce serum testosterone levels and subsequently lead to significant bone loss [56–59]. Furthermore, in addition to lifelong immunosuppression therapy, KTx patients also commonly have vitamin D deficiency, malnutrition, and secondary hyperparathyroidism [12]. Consequently, osteoporosis is more frequent in KTx patients than the general population [4–10].

While bisphosphonates are effective medications to improve BMD among KTx patients [60–66], certain patients cannot tolerate bisphosphonate and many KTx patients are given recommendations to avoid bisphosphonates due to serum creatinine > 2 mg/dL or CrCl < 30–35 mL/min [67, 68], since bisphosphonates are eliminated by the kidneys [12, 68]. Furthermore, osteonecrosis of the jaw, avascular osteonecrosis of the hip, and atypical fractures have also been reported among KTx patients who received bisphosphonate therapy [69–74]. Among non-KTx patients, zoledronate-induced acute tubular necrosis and pamidronate-associated collapsing focal segmental glomerulosclerosis [75–78] raise concerns about their use in the KTx population. Additionally, a case of acute granulomatous interstitial nephritis related to zoledronate use in a KTx patient with subsequent acute cellular rejection was recently reported

Table 2 Data on changes in bone metabolism and BMD from baseline to post-treatment course of denosumab in kidney transplant patients

Study	Marker	No. of denosumab	Before denosumab	After denosumab	No. of control	Control
Bonani et al. [23]	eGFR (mL/min/1.73 m^2)	44	53.5 ± 15.4	3 months 56.0 ± 17.2 6 months 54.2 ± 17.9 12 months 56.4 ± 17.4	44	3 months 52.9 ± 15.1 6 months 55.0 ± 15.3 12 months 55.2 ± 20.7
	Calcium (mmol/L)	39	2.31 ± 0.16	3 months 2.40 ± 0.21 6 months 2.46 ± 0.15 12 months 2.47 ± 0.15	42	3 months 2.47 ± 0.19 6 months 2.47 ± 0.17 12 months 2.52 ± 0.16
	Phosphate (mmol/L)	40	0.58 ± 0.23	3 months 0.78 ± 0.33 6 months 0.82 ± 0.28 12 months 0.85 ± 0.37	41	3 months 0.76 ± 0.16 6 months 0.83 ± 0.19 12 months 0.89 ± 0.18
	25(OH) vitamin D (μg/L)	41	17.4 ± 8.3	3 months 21.6 ± 5.9 6 months 24.4 ± 7.1 12 months 28.5 ± 8.2	40	3 months 22.9 ± 7.1 6 months 26.7 ± 11.6 12 months 28.4 ± 8.9
	1,25(OH) vitamin D (ng/L)	36	29.6 ± 21.0	3 months 60.5 ± 29.7 6 months 54.2 ± 21.4 12 months 47.2 ± 23.7	34	3 months 55.3 ± 14.5 6 months 58.1 ± 22.5 12 months 51.5 ± 20.0
	PTH (ng/L)	40	163.1 ± 157.9	3 months 173.6 ± 175.5 6 months 157.0 ± 167.4 12 months 106.7 ± 69.7	40	3 months 111.6 ± 85.4 6 months 99.4 ± 64.7 12 months 100.7 ± 67.3
	Change from baseline in total lumbar spine aBMD (g/cm^2)	46	N/A	6 months 3.0 (1.9–4.1) 12 months 4.6 (3.3–5.9)	44	6 months − 1.6 (− 2.7 to − 0.5) 12 months − 0.5 (− 1.8 to 0.9)
	Change from baseline in total lumbar spine *T* score	46	N/A	6 months 0.25 (0.16–0.35) 12 months 0.40 (0.28–0.52) 0.40 ± 2 (0.06)	44	6 months − 0.13 (− 0.23 to − 0.03) 12 months − 0.02 (− 0.14 to 0.10)
	Change from baseline in total hip a BMD (g/cm^2)	46	N/A	6 months 1.4 (0.5–2.3) 12 months 2.3 (1.1–3.5)	44	6 months − 0.3 (− 1.2 to 0.6) 12 months 0.4 (− 0.8 to 1.7)
	Change from baseline in total hip *T* score	46	N/A	6 months 0.09 (0.03–0.15) 12 months 0.14 (0.07–0.22)	44	6 months − 0.01 (− 0.07 to 0.05) 12 months 0.04 (− 0.03 to 0.12)
	Change from baseline in femoral neck aBMD (g/cm^2)	46	N/A	6 months 1.1 (− 0.3 to 2.6) 12 months 1.5 (− 0.1 to 3.1)	44	6 months − 0.9 (− 2.4 to 0.6) 12 months 0.4 (− 1.2 to 2.1)
	Change from baseline in femoral neck *T* score	46	N/A	6 months 0.05 (− 0.04 to 0.14) 12 months 0.05 (− 0.05 to 0.15)	44	6 months − 0.05 (− 0.14 to 0.05) 12 months 0.03 (− 0.07 to 0.13)
	Change in average vBMD of distal tibia	10	N/A	2.2 (0.7–3.2)	14	− 0.3 (− 3.3 to 2.7)

Table 2 (continued)

Study	Marker	No. of denosumab	Before denosumab	After denosumab	No. of control	Control
	Change in cortical vBMD of distal tibia	10	N/A	0.1 (− 0.5 to 1.4)	14	− 0.5 (− 2.0 to 0.1)
	Change in trabecular vBMD of distal tibia	10	N/A	1.8 (1.3 to 4.2)	14	1.1 (− 2.5 to 4.1)
	Cortical thickness of distal tibia	10	N/A	2.8 (1.4 to 8.0)	14	− 0.9 (− 5.9 to 1.6)
	Change in average vBMD of distal radius	10	N/A	1.3 (− 1.9 to 2.2)	14	− 1.6 (− 5.2 to 0.7)
	Change in cortical vBMD of distal radius	10	N/A	− 0.1 (− 1.8 to 1.3)	14	− 0.9 (− 2.7 to 0.4)
	Change in trabecular vBMD of distal radius	10	N/A	2.4 (1.1 to 4.1)	14	0.2 (− 9.4 to 3.1)
	Cortical thickness of distal radius	10	N/A	0.9 (− 6.0 to 2.0)	14	− 3.6 (− 7.7 to − 1.3)
	Fracture	46	N/A	0/46 (0%)	44	1/44 (2.3%)
	Graft loss	46	N/A	1/46 (2.2%)	44	0/44 (0%)
	Acute rejection	46	N/A	5/46 (10.9%)	44	3/44 (6.8%)
	UTI	46	N/A	24/46 (52.2%)	44	11/44 (25%)
	Transplant pyelonephritis	46	N/A	3/46 (6.5%)	44	5/44 (11.4%)
	CMV viremia	46	N/A	20/46 (43.5%)	44	18/44 (40.9%)
	BK viremia	46	N/A	12/46 (26.1%)	44	11/44 (25%)
Brunova et al. [27]	Creatinine (μmol/L)	Pancreas and kidney 15 Kidney 34	Pancreas and kidney 197.1 ± 114.8 Kidney 192.8 ± 90.3	Pancreas and kidney 197.2 ± 116.3 Kidney 208.3 ± 104.9	N/A	N/A
	Calcium (mmol/L)	Pancreas and kidney 15 Kidney 34	Pancreas and kidney 2.42 ± 0.1 Kidney 2.4 ± 0.1	Pancreas and kidney 2.4 ± 0.1 Kidney 2.46 ± 0.1	N/A	N/A
	PTH (pmol/L)	Pancreas and kidney 15 Kidney 34	Pancreas and kidney 10.1 ± 4.4 95.243 ± 41.4920 Kidney 14.8 ± 8.9 139.564 ± 83.927	Pancreas and kidney 10.8 ± 7.3 101.844 ± 68.839 Kidney 14.2 ± 0.4 133.906 ± 3.772	N/A	N/A
	L-spine *T* score	Pancreas and kidney 15 Kidney 34	Pancreas and kidney − 1.8 ± 1.7 Kidney − 2.9 ± 0.7	Pancreas and kidney − 0.6 ± 1.8 Kidney − 2.2 ± 0.7	N/A	N/A
	Proximal femur *T* score	Pancreas and kidney 15 Kidney 34	Pancreas and kidney − 3.2 ± 0.5 Kidney − 2.4 ± 1.1	Pancreas and kidney − 2.2 ± 0.5 Kidney − 2.1 ± 0.8	N/A	N/A
	Forearm *T* score	Pancreas and kidney 15 Kidney 34	Pancreas and kidney − 3.1 ± 1.9 Kidney − 3.0 ± 1.7	Pancreas and kidney − 2.9 ± 1.7 Kidney − 2.8 ± 1.7	N/A	N/A
	Change in L-spine BMD (%)	Pancreas and kidney		Pancreas and kidney	N/A	N/A

Table 2 (continued)

Study	Marker	No. of denosumab	Before denosumab	After denosumab	No. of control	Control
		15 (OP = 5) Kidney 34 (OP = 28)		OP 14.0 ± 6.9 All 9.6 ± 6.0 Kidney OP 10.9 ± 5.6 All 10.1 ± 5.9		
	Change in proximal femur BMD (%)	Pancreas and kidney 15 (OP = 14) Kidney 34 (OP = 17)		Pancreas and kidney OP 7.8 ± 3.52 All 7.5 ± 3.3 Kidney OP 10.4 ± 8.3 All 8.0 ± 6.7	N/A	N/A
	Change in forearm BMD (%)	Pancreas and kidney 15 (OP = 9) Kidney 34 (OP = 24)		Pancreas and kidney OP − 1.0 ± 5.3 All 0.6 ± 5.5 Kidney OP 5.0 ± 11.6 All 3.0 ± 10.2	N/A	N/A
	Prevalence of osteoporosis of L-spine	Pancreas and kidney 15 Kidney 34	Pancreas and kidney 5/15 (33.3%) Kidney 28/34 (82.3%)	Pancreas and kidney 1/15 (6.7%) Kidney 12/34 (35.3%)	N/A	N/A
	Prevalence of osteoporosis of proximal femur	Pancreas and kidney 15 Kidney 34	Pancreas and kidney 14/15 (93.3%) Kidney 17/34 (50%)	Pancreas and kidney 10/15 (66.6%) Kidney 11/34 (32.3%)	N/A	N/A
	Prevalence of osteoporosis of forearm	Pancreas and kidney 15 Kidney 34	Pancreas and kidney 9/15 (60%) Kidney 24/34 (70.5%)	Pancreas and kidney 7/15 (46.7%) Kidney 19/34 (55.8%)	N/A	N/A
Yoshino et al. [25]	Bone fracture	30	N/A	2/30 (6.7%)	8	1/8 (12.5%)
	Hypocalcemia	30	N/A	0/30 (0%)	N/A	N/A
Nakayama et al. [26]	BMD of L-spine (g/cm^2)	30	0.95 ± 0.15	6 months 0.96 ± 0.15	N/A	N/A

Table 2 (continued)

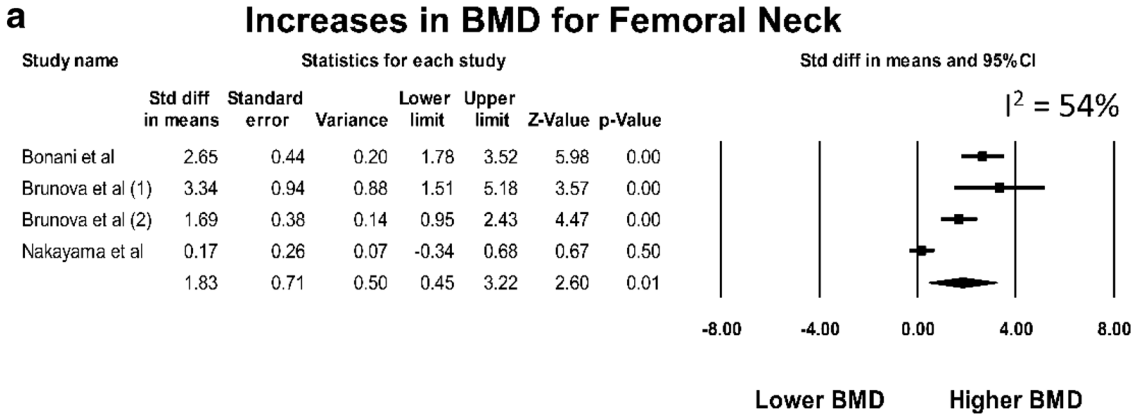
Study	Marker	No. of denosumab	Before denosumab	After denosumab	No. of control	Control
				12 months		
				0.98 ± 0.16		
	BMD of femoral neck (g/cm^2)	30	0.64 ± 0.11	6 months	N/A	N/A
				0.65 ± 0.11		
				12 months		
				0.66 ± 0.12		
	Trabecular bone score	30	1.33 ± 0.07	6 months	N/A	N/A
				1.33 ± 0.08		
				12 months		
				1.33 ± 0.07		
Doddoli et al. [24]	Fracture	37	N/A	0/37 (0%)	N/A	N/A
	Hypocalcemia	37	N/A	0/37 (0%)	N/A	N/A
	Graft failure	37	N/A	0/37 (0%)	N/A	N/A
	Death	37	N/A	0/37 (0%)	N/A	N/A

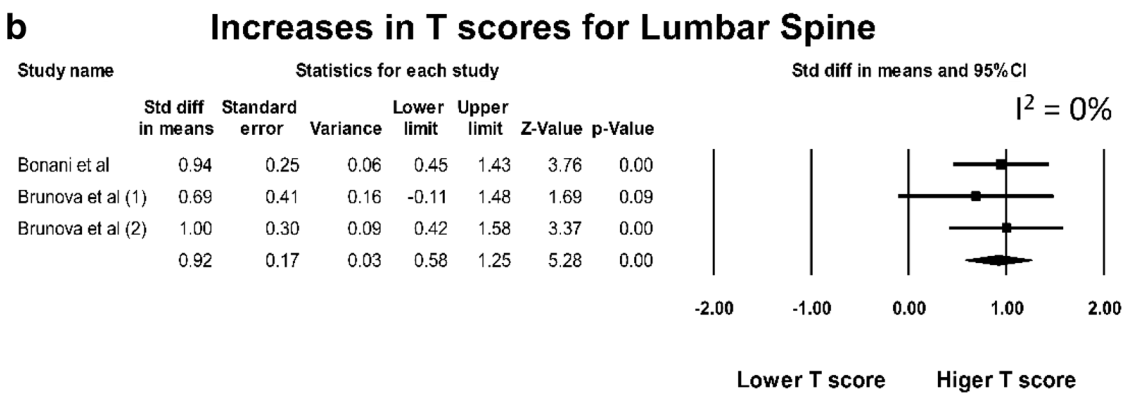
BMD bone mineral density, *N/A* not available, *PTH* parathyroid hormone

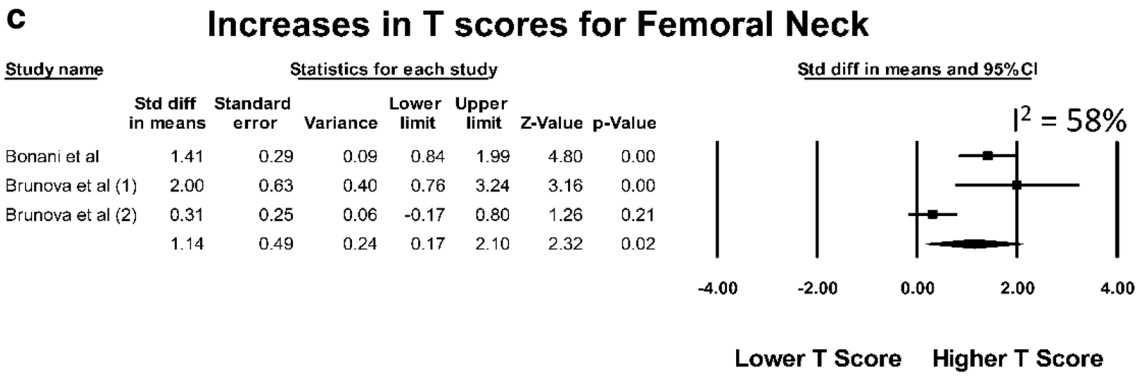
[79]. Alternative treatment options are thus in dire need for this at-risk population. When compared with alendronate, teriparatide has shown to more effectively increase BMD in patients with glucocorticoid-induced osteoporosis. However, its effectiveness and safety have not been well studied in the KTx population [80]. Consequently, denosumab, a non-nephrotoxic agent, has been increasingly suggested as an alternative treatment agent for osteoporosis among KTx patients [23–27]. In this meta-analysis, we confirmed that denosumab could effectively increase BMD and *T* scores for lumbar spine and femoral neck among KTx patients.

One of the important adverse reactions reported with denosumab treatment, especially in patients with reduced kidney function, is hypocalcemia [32]. The use of denosumab in ESRD patients can lead to significant hypocalcemia with an incidence of 42% [35]. Although ESRD patients have an improvement in kidney function after successful KTx, the majority of recipients still have a GFR in CKD stage 3 (eGFR 30–60 mL/min/1.73 m^2) [36, 37]. Furthermore, vitamin D deficiency is common among KTx patients [12, 81, 82], which may potentiate the risk of hypocalcemia during denosumab treatment [35]. In our meta-analysis, we demonstrated an overall incidence of denosumab-associated hypocalcemia in the KTx transplant population of 1.7%. With calcium and vitamin D supplementation, our study showed no differences in serum calcium and PTH levels from baseline to post-treatment course. Previous studies for treatment of osteoporosis with denosumab (in patients without advanced CKD) have demonstrated a significant increase in PTH levels, especially following the first administration of denosumab. This effect could conceivably be due to the effects following inhibition of bone resorption [83, 84]. However, in our study, we found no significant increase in PTH after 1 year of denosumab treatment among KTx patients, likely due to the effects of proactive calcium and vitamin supplementation on PTH [85, 86].

To our knowledge, this is the first meta-analysis performed on the use of denosumab in the KTx population; however, this study faced several limitations. First, there was statistical heterogeneity present in the final analysis for denosumab's effects on changes in BMD of lumbar spine and *T* score of femoral neck in KTx patients. The possible source of this heterogeneity includes the differences in testing methodology in each study. Thus, we used random-effects model and summarized the statistics for these outcomes with SMDs and 95% CIs. Second, although we demonstrated the beneficial effect of denosumab on BMD while having a low incidence of denosumab-associated hypocalcemia among KTx patients, the majority of KTx patients in the included studies have an eGFR ≥ 30 mL/min/1. 73 m^2 whereas previous reported denosumab-associated hypocalcemia were in KTx patients with reduced allograft function [87, 88]. Additionally, a recently published post hoc analysis of a clinical trial by Bonani et al. showed an association between urinary tract infections and the use of denosumab among KTx patients [67]; thus, future studies assessing the safety of denosumab in KTx patients







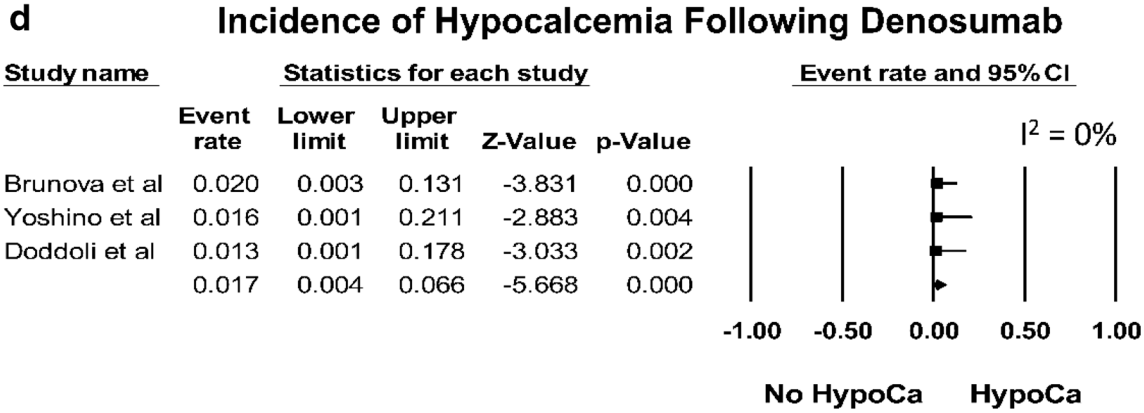


Fig. 2 Forest plot of all included studies evaluating denosumab's effect on **a** changes in BMD for femoral neck, **b** changes in *T* scores for lumbar spine, **c** changes in *T* scores for femoral neck, and **d** incidence of hypocalcemia. A value of I^2 of 0–25% represents insignificant heterogeneity, 26–50% represents low heterogeneity, 51–75% represents moderate heterogeneity, and more than 75% represents high heterogeneity

Table 3 Data on reported adverse side effects of denosumab treatment in kidney transplant patients

Study	Adverse side effects	*N* (%)
Bonani et al. [28]	Urinary tract infection*	24/46 (52%)
	Transplant pyelonephritis	3/46 (6.5%)
	Diarrhea*	23/46 (50%)
	CMV viremia	20/46 (43.5%)
	Cough	7/46 (15.2%)
	Leg pain	9/46 (19.6%)
	Flu-like disease	11/46 (23.9%)
	Polyoma viremia	12/46 (26.1%)
	Abdominal pain	9/46 (19.6%)
	Leg edema	9/46 (19.6%)
	lymphocele	7/46 (15.2%)
	Herpes labialis	5/46 (10.9%)
	Acute rejection	5/46 (10.9%)
	fracture	0/46 (0%)
	Loss of graft function	1/46 (2.2%)
Doddoli et al. [24]	Recurrent cutaneous abscess	1/37 (2.7%)

CMV cytomegalovirus

*, significantly higher than control group (p <0.05)

are needed. Lastly, this is a meta-analysis of observational studies, not randomized controlled trials. Therefore, future high-quality studies and large randomized controlled trials in the field are needed to confirm the findings from our meta-analysis.

In conclusion, our meta-analysis suggests the effectiveness of denosumab in the improvement of BMD among KTx. The estimated incidence of denosumab-associated hypocalcemia in KTx patients with adequate kidney function (with eGFR $\geq$ 30 mL/min/1.73 m^2) is low with calcium and vitamin D supplementation.

Authors' contributions All authors had access to the data and a role in writing the manuscript.

Compliance with ethical standards

Conflict of interest None.

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