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ORIGINAL ARTICLE

Comparison of the clinical effectiveness and safety between the use of denosumab vs bisphosphonates in renal transplant patients

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Abstract

Summary A retrospective chart review was conducted on 85 renal transplant patients aged 19–88 years, treated with denosumab or bisphosphonate therapy. Bone densitometry measures were compared between treatment groups at baseline; at years 1, 2, and 3; and at final follow-up (average of 3.4 years).

Both bisphosphonate and denosumab treatments increased lumbar spine bone density; however, the effect of denosumab was greater compared with that of bisphosphonate treatment. Denosumab treatment increased femoral neck BMD, whereas bisphosphonate treatment had a mean decrease in femoral neck BMD at final follow-up. Thus, our study provides evidence for the efficacy of denosumab treatment in renal transplant patients. Caution around hypocalcemia is warranted. We recommend more prospective studies to analyze the effects of long-term antiresorptive therapy in patients with a renal transplant.

Introduction To compare the clinical effectiveness and safety between the use of denosumab and bisphosphonates on bone density and incidence of adverse events in renal transplant patients.

Methods A retrospective chart review was conducted on 85 renal transplant patients aged 19–88 years, treated with denosumab or bisphosphonate therapy. Bone densitometry measures were compared between treatment groups at baseline; years 1, 2, and 3; and at final follow-up (average of 3.4 years).

Results Absolute change in lumbar spine and femoral neck BMD over the treatment period was 0.029 ± 0.075 g/cm^2 and -0.003 ± 0.064 g/cm^2, respectively, in the bisphosphonate group. Absolute change in lumbar spine and femoral neck BMD at final follow-up was 0.072 ± 0.094 g/cm^2 and 0.025 ± 0.063 g/cm^2, respectively, in the denosumab group. Denosumab resulted in significantly greater increases in lumbar spine BMD (0.045 g/cm^2 greater in the denosumab group). Similarly, the absolute change in BMD at the femoral neck was 0.022 g/cm^2 greater in the denosumab group as compared with the bisphosphonate group. The denosumab group had one event of severe hypocalcemia following first injection and one report of hospitalized pneumonia. No serious adverse events were reported in the bisphosphonate group.

Conclusions Both treatments increased lumbar spine BMD; however, the effect of denosumab was greater compared with that of bisphosphonate treatment. Our study provides evidence for the efficacy of denosumab treatment in renal transplant patients. Caution around hypocalcemia is warranted. We recommend more prospective studies to analyze the effects of long-term antiresorptive therapy in patients with a renal transplant.

Keywords Bisphosphonates · CKD · Denosumab · Osteoporosis · Renal transplant

Introduction

Osteoporosis is of particular interest in renal transplant recipients; however multiple disorders of bone metabolism can coexist including high and low bone turnover states. Vitamin D deficiency and continuing hyperparathyroidism also adds to the complexity of managing osteoporosis in these patients [1]. Multiple studies in renal transplant patients indicate that BMD declines by 4–10% in the first 6 months [2], with a further

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decrease of 0.4–4.5% in lumbar spine BMD between 6 and 12 months [3]. This rapid loss of bone mass begins in the early post-transplant period and often affects trabecular bone structures due to increased bone resorption on prednisone initiation and decreased bone formation as a result of long-term glucocorticoid (GC) therapy [4]. In the first 5 years after transplantation, approximately 22.5% of patients experience a fracture, an incidence rate four times greater than observed in the general population [5]. Fracture risk also remains significantly elevated at 10 years post-transplantation, suggesting that bone remains fragile for a prolonged period, despite improvement in parameters of mineral metabolism [6].

The progressive loss of BMD and increased fracture risk in renal transplant patients are modified by a variety of post-transplant factors, such as immunosuppressive medications, persistent hyperparathyroidism, ongoing vitamin D deficiency, and loss of kidney function over time. These factors all lead to changes in bone histomorphometry and architecture [7]. Impaired renal function contributes further to decreased BMD, evidenced by greater rates of bone loss [8, 9] and correlations between estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m^2 and hip fracture [10]. Exacerbation of physiological imbalances can give rise to a complex disorder termed CKD-mineral bone disorder (CKD-MBD) [11, 12]. CKD-MBD is associated with a variety of abnormalities in bone physiology including turnover (low or high), mineralization, volume, linear growth, or strength and/or vascular or other soft tissue calcification [13]. Many renal transplant patients have one, or several, of the aforementioned skeletal abnormalities, which lends to the difficulty in administering antiresorptive therapies that target increased bone fragility, without contributing to any existent skeletal or physiological imbalances.

Bisphosphonate therapy has been shown to be effective in reducing fracture risk in patients with osteoporosis, with a large body of evidence confirming its efficacy in preventing the development of vertebral, hip, and non-vertebral fractures, as well as in reducing fracture-related mortality among high-risk patients [14–16]. Nonetheless, clinical trials on bisphosphonate safety and efficacy have excluded patients based on prespecified renal measurement cutoffs (either serum creatinine or eGFR) [17]. The basis for these eGFR contraindications include the fact that bisphosphonates are cleared via glomerular filtration [18]. Thus, reduced renal function in renal transplant patients may result in excessive bisphosphonate retention in the skeletal matrix; whether this causes adverse effects remains unclear due to a lack of data in this patient population [19].

Denosumab (Prolia™), a fully humanized monoclonal antibody against RANKL, also presents an attractive option for increasing BMD in CKD patients, due to the lack of renal clearance, but there is limited clinical experience with this population. As a major regulator of osteoclast development and activity, denosumab is clinically approved for the treatment of osteoporosis and fracture risk reduction in postmenopausal women, and in men at a high risk of fracture [20–22]

This study aims to address the limited number of studies analyzing bisphosphonates and denosumab in renal transplant patients and the scarcity of literature surrounding the efficacy, safety, and optimal treatment protocols for these patients. Despite limitations in utilizing BMD in this patient population, it is the primary assessment tool utilized to guide standard osteoporosis therapies including the use of bisphosphonates and denosumab. Thus, using DXA BMD measures, this retrospective cohort study focuses on two osteoporosis treatments, bisphosphonates and denosumab, with the aim of providing greater insight into their efficacy and safety in renal transplant patients.

Materials and methods

Subjects

A total of 85 adult women and men seen in a tertiary care clinic were included in this retrospective chart review study. We identified renal transplant patients using electronic medical records (EMR) with the EMR query module "transplant.".We collected baseline demographics including age, family history, co-morbidities such as smoking, prednisone use, current medication use, past medication use, history of diabetes, cardiovascular disease, lung disease, and inflammatory bowel disease. We also collected information on vitamin D supplementation; daily calcium intake; and laboratory investigations including baseline (time of treatment initiation) and year 1 eGFR (1 year post-treatment), serum calcium concentration, parathyroid levels, alkaline phosphonate levels, 25-OH Vitamin D levels, and phosphate levels (Table 1). Any serious adverse events were noted, including but not limited to the following: osteonecrosis of the jaw (ONJ), atypical femoral fracture (AFF), and hypocalcemia over the post-transplant treatment period. Patients who switched osteoporosis medications during the treatment period or were inconsistent with treatment (did not adhere to treatment schedules) were categorized as "treatment failure," and data collection for that patient was halted on that date. We collected the first recorded DXA BMD measurement after commencement at both the femoral neck and lumbar spine (L1-L4) as baselines.

Inclusion criteria

The study population included adult patients, 18 or older, with a history of renal transplantation currently receiving medical care in our single site tertiary care medical practice in Ontario, Canada, between 01 Jan 2011 and 31 Dec 2015. Inclusion was further based on the following criteria: 1) a minimum of two

Table 1 Baseline demographic characteristics of patients taking bisphosphonate and denosumab

*Variables	Denosumab ($n = 46$) mean ± SD	Bisphosphonate ($n = 39$) mean ± SD
Medication type	Prolia $n = 46$	Alendronate $n = 8$, Risedronate $n = 31$
Age	60 ± 12	59 ± 13
Height (cm)	163 ± 9	160 ± 18
Weight (kg)	74 ± 15	76 ± 19
Baseline femoral neck BMD (g/cm^2)	0.634 ± 0.12	0.669 ± 0.10
Baseline lumbar spine BMD (g/cm^2)	0.928 ± 0.18	0.905 ± 0.12
Baseline estimated glomerular filtration rate (eGFR) Normal: > 90	52.04 ± 17.84	51.53 ± 20.03
Vitamin D intake (IU/day)	1846 ± 1146	2010 ± 734
Calcium intake (IU/day)	926 ± 1600	1019 ± 1245
Year 1 eGFR normal: > 90	54.50 ± 17.2	50.570 ± 20.2
Baseline serum calcium concentration normal: 8.5–10.2 mg/dL	9.66 ± 0.60	9.61 ± 0.93
Baseline parathyroid hormone (PTH) normal: 1.4–6.8 pmol/L	10.44 ± 37.4	15.23 ± 14.6
Baseline alkaline phosphonate (ALP) normal: 40–160 IU/L	78.40 ± 34.2	76.57 ± 37.8
Baseline 25-OH vitamin D (25(OH)D) normal: 20–100 ng/mL	25.45 ± 11.5	32.85 ± 20.1
Baseline phosphate normal: 1.0–1.5 mmol/L	1.09 ± 0.25	1.12 ± 0.49
Prednisone use (% yes)	87%	97%
Baseline prednisone dosage (mg/day)	5.51 ± 2.09	5.23 ± 1.83
Fracture history at baseline (yes/no)	$n = 15$	$n = 11$
Baseline FN T-score, normal: T-score > − 1.0	− 2.2 ± 1.05	− 1.95 ± 0.76
Baseline LS T-score, normal: T-score > − 1.0	− 1.26 ± 1.53	− 1.62 ± 1.05

*Statistical significance was set at the level of $p < 0.05$. No differences between groups were significant

*All "baseline" variables measured at treatment initiation

BMD measures, 2) the use of either denosumab (60 mg subcutaneously every 6 months), or bisphosphonate (alendronate 70 mg p.o. once weekly, or risedronate 35 mg once weekly) for at least 12 months (see Appendix).

Exclusion criteria

Additional patient exclusions were due to BMD measures over 3 years apart and therefore not accurately comparable, machine changes (location or Hologic to Lunar) at follow-ups, or only one BMD measure since transplant surgery (See Appendix Fig. 2).

Statistical analysis

Continuous variables were summarized as mean and standard deviation (SD) and categorical variables as the number (percent). Baseline comparisons between groups were performed by Student's *t* test for unpaired observations concerning continuous variables. Multivariable linear regression analyses were used to model differences at the last follow-up visit between groups in the absolute change in bone mineral density at the lumbar spine and femoral neck. Variables included in the analyses were treatment group, age, sex, BMI (< 18.5, 18.5 to 25, 25 to 30; 30 +), prior osteoporosis med use (yes, no), smoking status (current, past, never), alcohol consumption (yes, no), and follow-up duration (years). Parameter estimates and 95% confidence intervals are reported. All statistical analyses were performed using the SAS/STAT (version 9.3; SAS Institute Inc., Cary, North Carolina, USA) software package running on Windows.

Results

Baseline demographic parameters are presented in Table 1. There were no significant differences noted between treatment groups for baseline BMD serum levels of calcium, parathyroid hormone, alkaline phosphate, vitamin D, or phosphate. No significant difference between the two treatment groups was detected with respect to age, height, weight, year 1 eGFR, baseline eGFR, vitamin D dosage, calcium intake, GC dosage, T-score, or fracture history (Table 1). One patient switched medication, from Actonel to Prolia, due to declining BMD and was marked as treatment failure.

Absolute change in lumbar spine and femoral neck BMD over the total treatment period in the bisphosphonate group was 0.029 ± 0.075 g/cm^2 and − 0.003 ± 0.064 g/cm^2, respectively, and 0.072 ± 0.094 g/cm^2 and 0.025 ± 0.063 g/cm^2, respectively, in the denosumab group (Fig. 1).

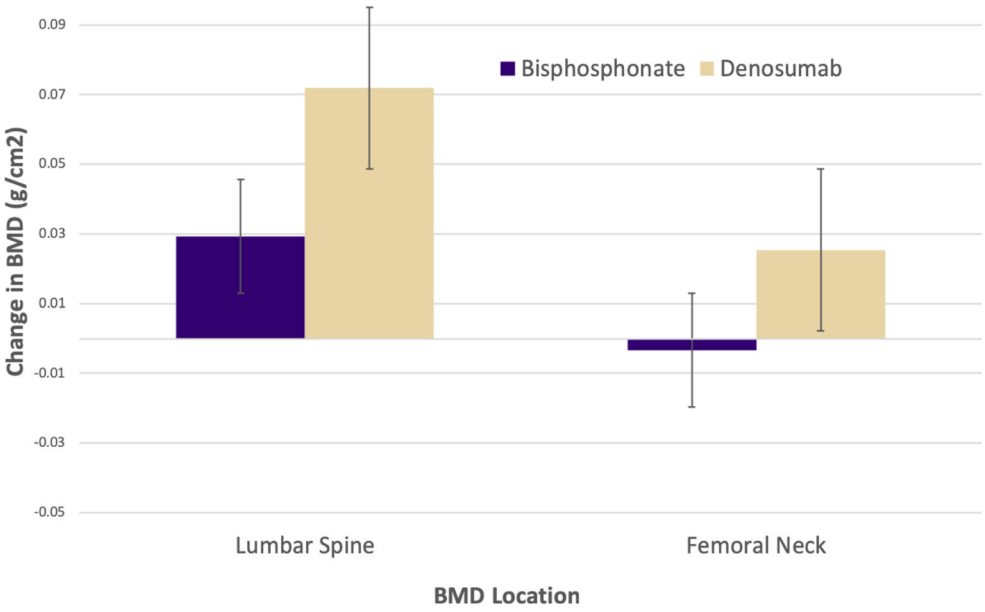

Fig. 1 Comparison of absolute changes in BMD at final follow-up between the treatment groups. Absolute change in bone mineral density (BMD) from baseline at the femoral neck and lumbar spine in the denosumab and bisphosphonate treatment groups. *Error bars represent standard deviation of each group BMD in g/cm^2

Absolute BMD changes from baseline to final follow-up (approximately 3.4 years) in the two treatment groups in the lumbar spine and femoral neck are presented in Table 2. At final follow-up, denosumab resulted in significantly greater increases in lumbar spine BMD (parameter estimate denosumab vs. bisphosphonate, 0.045 g/cm^2 (0.005, 0.085)) and increased femoral neck BMD (parameter estimate denosumab vs. bisphosphonate, 0.022 g/cm^2 (− 0.009, 0.53). Further, at year 1, year 2, and year 3, the denosumab group recorded higher absolute lumbar spine and femoral neck BMD (Table 3). No significant changes in femoral neck BMD at year 1, year 2, year 3, and final follow-up was observed in bisphosphonate patients (Table 3). At final follow-up, 67% of denosumab patients, compared with only 47% of bisphosphonate patients, recorded increases in femoral neck BMD. Similarly, 93% of denosumab patients, compared with 69% of bisphosphonate patients, recorded increases in lumbar spine BMD, at final follow-up.

For denosumab-treated patients, one serious adverse event of hospitalized hypocalcemia was reported after a denosumab injection (serum calcium levels pre- to post-injection; 2.25 mmol/L to 1.98 mmol/L, normal range 2.2–2.7 mmol/L). The patient, a 50-year-old post-menopausal diabetic woman on glucocorticoid therapy for 15 years post-transplant, was diagnosed with osteoporosis and secondary hyperparathyroidism. The patient was being supplemented with 2000 IU of 25-hydroxyvitamin D daily, pre- and post-injection. Another patient reported severe shoulder pain after the first denosumab injection, one patient was hospitalized due to pneumonia while on denosumab, and one patient had a thyroid adenoma while on treatment. No serious adverse events were reported for bisphosphonate-treated patients; however, 5 patients (13% of treatment group) reported gastro-intestinal (GI) complications (GERD, upset stomach, GI discomfort, GI pain), due to risedronate specifically for all reported events. None of the patients were on previous antiresorptive medications, and two patients discontinued bisphosphonate treatment and

Table 2 Absolute mean change in bone mineral density (BMD) in the two treatment groups at final follow-up. Parameter estimates of absolute change between treatment groups

Absolute change in BMD at final follow-up	Bisphosphonate ($n = 39$) mean ± SD	Denosumab ($n = 44$) mean ± SD	Parameter estimate*
Lumbar spine BMD (g/cm^2)	0.029 ± 0.0754	0.072 ± 0.095	0.045 (0.005, 0.085)
% Total increase in LS BMD	3.23%	8.06%	
Femoral neck BMD (g/cm^2)	− 0.003 ± 0.064	0.025 ± 0.063	0.022 (− 0.009, 0.53)
% Total increase in FN BMD	− 0.51%	4.49%	

*Denosumab group in reference to bisphosphonate group

Table 3 Mean change in bone mineral density (BMD) in both treatment groups at years 1, 2, and 3

Change in BMD from baseline (treatment initiation)		Denosumab ($n = 46$) mean ± SD	Bisphosphonate ($n = 39$) mean ± SD
Lumbar spine BMD (g/cm^2)	Year 1	0.029 ± 0.066	0.00048 ± 0.0303
	Year 2	0.059 ± 0.049	0.023 ± 0.047
	Year 3	0.071 ± 0.091	0.0236 ± 0.082
Femoral neck BMD (g/cm^2)	Year 1	0.0008 ± 0.063	− 0.0004 ± 0.036
	Year 2	0.028 ± 0.059	− 0.008 ± 0.049
	Year 3	0.018 ± 0.045	− 0.002 ± 0.072

switched to denosumab therapy, which was well tolerated. No significant events of osteonecrosis of the jaw or avascular necrosis were reported in either bisphosphonate or denosumab treatment groups.

Discussion

The present study provides evidence for the greater effects of denosumab treatment in increasing lumbar spine BMD compared with bisphosphonate treatment at final follow-up (average treatment period of 3.4 years). This has great implications for current treatment decisions on increasing BMD, where decreased eGFR in renal and CKD patients is an area of concern. In addition, our analysis revealed that BMD at the femoral neck is significantly improved by both denosumab and bisphosphonate treatments, yet the impact of denosumab is much more pronounced compared with bisphosphonates. These findings are important, as they provide novel insight into the efficacy of denosumab, compared with bisphosphonate therapy, over longer follow-up periods. The differences in BMD change observed at the lumbar spine compared with the femoral neck are also in correlation with the differences in trabecular bone mass between these bone areas and the greater effect of post-transplant factors on trabecular bone.

No changes in femoral neck BMD at year 1, year 2, year 3, and final follow-up were observed in bisphosphonate patients (Table 3). Further, not only was there a greater absolute increase in BMD under denosumab treatment at both the lumbar spine and femoral neck but also a much greater proportion of denosumab patients had increased BMD at both locations over the treatment period.

These findings are in accordance with those of other novel studies in non-transplant patients. Large randomized controlled trials and meta-analyses also show greater improvement of total hip BMD and reduced bone resorption with denosumab, compared with bisphosphonates, in a range of diverse patient populations [23–26]. Several mechanisms may justify the differential impact of denosumab on BMD compared with bisphosphonate treatment. Firstly, the inhibitory effect of denosumab on bone resorption, and thereby its anti-fracture efficacy, is more potent than bisphosphonates [27, 28]. Bisphosphonates target mature osteoclasts and must attach to bone and be resorbed by the functioning mature osteoclast, whereas denosumab prevents osteoclast maturation, activation, and survival, thereby decreasing resorption of cortical and trabecular bone more efficiently [21]. The impact of denosumab is also more pronounced on cortical bone, thereby affecting micro-architectural outcomes beyond BMD, as concluded by studies that employed hr-pQCT to assess bone parameters [23]. By also influencing micro-architectural changes, denosumab may provide a more complete inhibition of bone resorption and reduced fracture risk, compared with bisphosphonates.

Our study assessed the adverse effects of denosumab in post-transplant patients to address possible pharmacological concerns. Specifically, denosumab administration in hemodialysis patients has been associated with clinically significant hypocalcemia, which is a warranted concern in renal transplant patients [29]. Hypocalcemia is defined as a serum level of total calcium < 8.5 mg/dL (2.12 mmol/L). As denosumab is a "biologic," general immune suppression has also been a safety consideration, especially in GC-supplemented post-transplant patients. These cautions have resulted in a significant lack of data in this patient population. We reported one event of hypocalcemia that resulted in hospitalization. This finding is consistent with the literature, which suggests that denosumab may induce hypocalcemia through suppression of bone resorption, which can be amplified in renal transplant patients [30]. Following the initial injection, the patient's calcium levels dropped from 2.25 to 1.98 mmol/L (normal range 2.2–2.7 mmol/L). After hospitalization, calcium levels returned closer to baseline at 1-month follow up (2.12 mmol/L) and reached baseline at 2 months post-injection (2.22 mmol/L). At the time of injection, the patient reported an eGFR of 45 mL/min/1.73 m^2 which remained consistent post-injection. Serum calcium levels are reported to decrease shortly after an injection of denosumab, but to recover within 14 days [31]. To mitigate this physiological response, supplemental vitamin D (0.5 to 1.0 μg/day) has been cited to prevent hypocalcemia and support the efficacy of denosumab [30]. The patient was being supplemented with

2000 IU daily of vitamin D pre-injection. In general, denosumab pharmacokinetics or pharmacodynamics are not affected by impaired renal function [32]; however, extremely low eGFR may be a factor in the onset of hypocalcemia. Ideally, vitamin D and calcium supplementation should be initiated prior to treatment with denosumab and frequent surveillance of calcium levels are strongly recommended throughout the treatment period.

Our results clearly identify an important pharmacokinetic quality of denosumab, which is the complete reversibility of its effects, including reduced bone resorption and hypocalcemia, upon discontinuation of treatment. If therapy is discontinued, it would be imperative to take compensatory pharmacological measures to prevent rapid bone loss and return of fracture risk [33]. As denosumab is cleared by the reticuloendothelial system, and not through the kidneys, the half-life is relatively short, approximately 26 days [34]. This presents an attractive feature for denosumab in the case of adverse events.

Bisphosphonates also serve as potent inhibitors of osteoclastic bone resorption, which reduces calcium efflux from bone, causing a transient period of slight hypocalcemia [35, 36]. In post-transplant patients with renal dysfunction, the combination of excessive bisphosphonate retention and impaired intestinal calcium absorption could potentially increase the risk of developing hypocalcemia [35]. Our study did not report any serious adverse events associated with oral bisphosphonates, which is confirmed by studies that analyzed their safety and renal toxicity [37, 38]. Two *post-hoc* analyses from the pooled risedronate registration studies and the alendronate fracture intervention trials reported significant reductions in the incidence of vertebral and clinical fractures, over an average of 2.6-year duration, without any change in renal function in subjects with low eGFRs (15 to 30 mL/min/1.73 m^2) [37, 38]. Emerging reports of osteonecrosis of the jaw and atypical fractures present possible safety risks of bisphosphonate therapy longer than 10 years, although both are quite rare [39, 40]. The association of bisphosphonates with osteonecrosis of the jaw involved high-dose IV bisphosphonates in patients with cancer and patients undergoing major dental work [41]. Renal transplants generally last for up to 12 years, and thus patients who start bisphosphonate therapy early in the transplant period may require a "drug holiday," if they are at low to moderate risk of fracture after 3 to 5 years of use [41]. Higher-risk patients should begin a 1- to 2-year drug holiday after 10 years of therapy, and it is suggested that they be on a non-bisphosphonate treatment during that time [17].

Our study did record several reports of GI discomfort and/or pain in patients on bisphosphonate therapy. This is an expected outcome, as esophagitis and nonspecific GI symptoms are the most commonly cited reason for patient intolerance to oral bisphosphonates [42]. Nonetheless, studies have consistently shown that the incidence of dyspepsia, nausea, abdominal pain, and gastritis are not significantly different between alendronate [43], risedronate [44], and placebo. In our population, 26.0% of bisphosphonate patients, compared with 7.69% of denosumab patients, had a prevalent GI complaint.

This study has several limitations. The retrospective nature presents bias due to the effects of uncontrollable exposures or varied outcome assessments. Incomplete data and a limited sample size may further exacerbate potential bias. Limitations also exist in determining if absolute BMD or treatment type predicts fracture incidence in our patient population due to this retrospective design, thus we recommend future studies to identify fracture incidence as an important clinical outcome for transplant patients. Ultimately, further randomized clinical trials with longer follow-up periods and larger populations are suggested to identify whether long-term exposure to these medications is harmful to renal transplant patients.

Conclusion

Our study presents insight into the clinical and safety outcomes of denosumab and bisphosphonate therapies in renal transplant patients. We report that denosumab is an effective intervention for osteoporosis management in patients who have undergone renal transplantation, with greater increases in BMD at the lumbar spine and femoral neck at final follow-up, compared with bisphosphonate therapy. Severe hypocalcemia was reported in a patient after a single denosumab injection, supporting the need for adequate vitamin D and calcium supplementation pre- and post-injection. Overall, these findings have great implications for future treatment protocols and clinical decisions. We suggest further research into the long-term (> 5 years) outcomes of denosumab therapy in renal transplant and more severe CKD patients (eGFR of < 60 mL/min/1.73 m^2).

Compliance with ethical standards

Conflicts of interest None.

Ethical approval This study was approved by the Hamilton Integrated Research Ethics Board number 5091-C.

Appendix

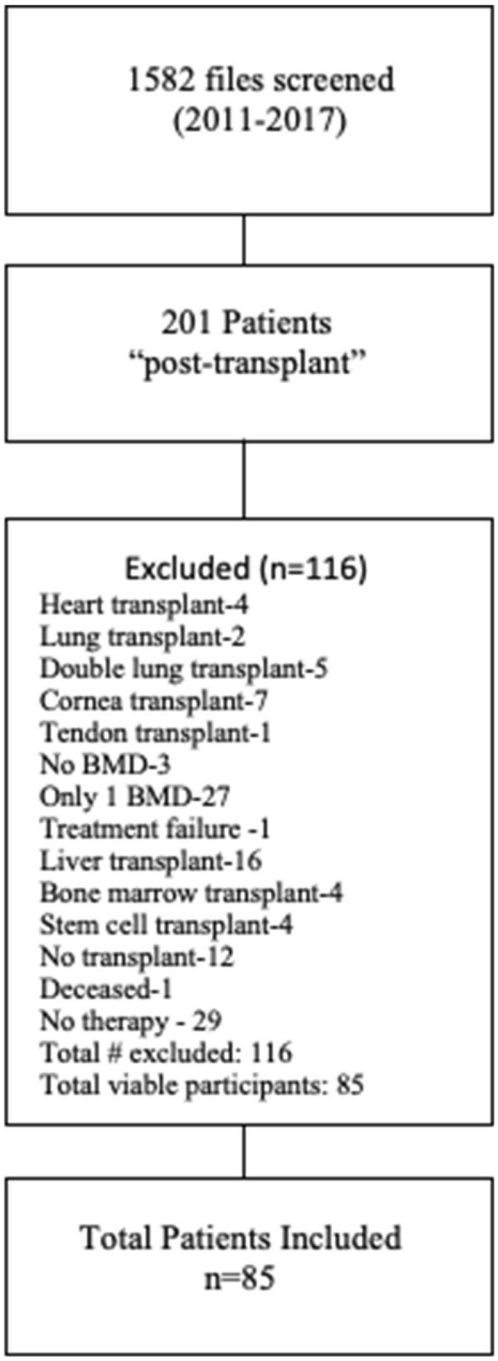

Fig. 2 Inclusion and exclusion criteria

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