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Bisphosphonates and bone mineral density in patients with end-stage kidney disease and renal transplants: A 15-year single-centre experience

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ABSTRACT

Chronic Kidney Disease Stage 5 (CKD-5) imparts a 4-fold increase in minimal trauma fracture with a substantial increase in mortality following hip fracture. Bone disease in CKD is complex, characterised by abnormal levels of PTH, calcium, phosphate, ALP, and vitamin D, manifesting as a condition known as CKD-Mineral and Bone Disorder (CKD-MBD). While bisphosphonates (BPs) are widely used in the management of osteoporosis, their therapeutic role when end-stage renal function and bone disease co-exist remains unclear. This 15-year retrospective cohort study examines the long-term use of BPs in CKD-4 and -5 patients receiving no renal replacement therapy, haemodialysis and renal transplant in a tertiary centre in Sydney, Australia. In multivariate regression adjusting for age, baseline bone mineral density (BMD) and history of fracture, BP use was associated with net gain in lumbar spine bone density in renal transplant recipients over a mean treatment period of 3.5 years (net annual BMD gain of 0.039 g/cm^2, $p = 0.005$). No such benefit was seen in hip BMD in CKD subjects. Regardless of transplant status, CKD patients treated with BPs had no improvement in hip BMD with a general decline in hip BMD across both groups during the study period (hip BMD: transplant recipients decline 0.024 ± 0.81 g/cm^2, non-transplant CKD patients decline 0.055 ± 0.84 g/cm^2). BP therapy did not result in significant changes in biochemical parameters (ALP, PTH, and phosphate) and no serious adverse effects were detected in association with BP use. In particular, kidney function was not affected by BPs post-transplant (eGFR = 43 ± 29 ml/min/1.73 m^2, $p = 0.80$). BPs preserved lumbar spine bone density in kidney transplant recipients but did not prevent declines in hip bone mineral density in either transplant patients or those with CKD-4 and -5.

Summary: There remains a lack of clarity of the risks vs. benefits of bone-sparing pharmacotherapy in chronic kidney disease Stages 4 and 5. This single-centre 15-year retrospective data analysis showed that bisphosphonates are not associated with any detectable serious adverse effects in CKD-4 and -5 and effective at mitigating lumbar spine bone loss in kidney transplant patients.

1. Introduction

Chronic kidney disease (CKD) is increasing globally with an annual incidence rate of 11 per 100,000 in Australia and contributing to 1.8 million hospitalisations per year (Welfare, 2017). Chronic Kidney Disease Stage 5D (CKD-5) is defined as an estimated glomerular filtration rate (eGFR) <15 ml/min/1.73 m^2 in patients requiring haemodialysis (Miller, 2014a), (Toussaint et al., 2009). In patients with CKD, compromised mineral homeostasis is common. Secondary hyperparathyroidism, interdependent hyperphosphatemia and vitamin D deficiency are hallmark abnormalities of CKD-Mineral and Bone Disorder (CKD-MBD) (Connelly et al., 2018). This condition can coexist with osteoporosis, further compounding the greater risk of fractures in CKD-5 (Toussaint et al., 2009; Connelly et al., 2018). Incidence of hip fracture in CKD-5 is 30 per 1000 and over double that in the general population (Alem et al., 2000), with vertebral fractures in up to 34% of patients

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with end-stage renal disease (Jansz et al., 2020; Jean et al., 2013). In addition, hip fractures in haemodialysis patients generally carry a 1-year morality rate of 50%, two times higher than those without kidney disease (Jean et al., 2013; Danese et al., 2006).

While bisphosphonates (BPs) are first-line agents for the treatment of postmenopausal osteoporosis, their use in patients with CKD-5 is contraindicated due to their unmetabolized renal excretion (Toussaint et al., 2009; Miller, 2014b; Wilson et al., 2017).

A subset of patients with CKD-5 receive BPs because they reduce the incidence of fractures in post-menopausal osteoporosis (Connelly et al., 2018; Ketteler et al., 2017; Nitta et al., 2017) but a clear evidence-base for their anti-fracture efficacy in CKD-4 and 5 is lacking (Toussaint et al., 2009; Miller, 2014b; Nitta et al., 2017; Schipper et al., 2015).

The theoretical concern that BPs may precipitate adynamic bone disease in CKD patients has restricted their use in this population but evidence for this is limited to small case series (Amerling, 2010) and a study examined bone turnover markers in CKD patients on alendronate (Chavassieux et al., 2014). However, animal data do not support this link (Allen and Aref, 2017), (Andress et al., 1986). Conversely, BPs may confer benefits in CKD-MBD, particularly in patients with high bone turnover and recurrent fractures, in whom a concurrent diagnosis of osteoporosis is possible (Toussaint et al., 2009; Bover et al., 2017; Liu, 2013; Moe et al., 2014; Ott, 2017). Due to complex biochemical dysregulation in CKD-MBD, making a specific diagnosis of osteoporosis in this patient population is often challenging (Miller, 2014a). However, recent updates to the KDIGO CKD-MBD guideline suggest regular DXA scans do affect treatment decisions and confer a net benefit (Ketteler et al., 2017). There is therefore clinical equipoise in the use of BPs in patients with CKD-MBD and a greater need to understand how bisphosphonates affect outcomes in this patient population, with key differences in the use of these treatments in patients receiving dialysis versus transplant recipients. Recent systematic studies and a Cochrane review, suggest a benefit of BPs in preserving BMD and preventing fracture in renal transplant recipients but call for more robust, real-world data to clarify the question (McKee et al., 2020; Palmer and Strippoli, 2020; Wang et al., 2016).

The Department of Renal Medicine at Royal North Shore Hospital in Sydney, Australia is a tertiary referral service with a patient load of over 400 end-stage kidney disease patients encompassing a catchment of over 1.1 million people. From 2014 to 2019, 273 patients were on dialysis, and, within the study period (2015–2020), 217 kidney transplants were performed, with an almost 5-fold increase in renal transplants per year in 2020 compared to 2005. Patients with CKD-MBD were concurrently managed in an adjoining Metabolic Bone Clinic at the same institution, within the Department of Endocrinology. This study presents the experience from this institution over 15 years on the use of BPs in a cohort of CKD patients to determine effects on bone outcomes including bone mineral density and biochemical markers of renal bone disease.

2. Methods

2.1. Study population

A two-fold method was used to select subjects for this study. First, the electronic database for Dual Energy X-ray Absorptiometry (DXA) scans at the Royal North Shore Hospital (RNSH) containing patient bone mineral density (BMD) data from 2005 to 2020 was accessed. Subjects were filtered by keyword search (renal, kidney, transplant, CKD, ESRF) and by referring physician (i.e., subjects referred from the renal department). A preliminary list of 273 subjects who met the initial criteria of transplant waiting list, kidney transplant recipient, chronic kidney disease, and/or haemodialysis was formed. Subjects in this study all had CKD-4 or 5 (eGFR <30 ml/min/1.73 m^2). This list was then cross-referenced with 3 electronic medical record databases used at RNSH to obtain individual data on anti-resorptive therapy, fracture incidence during the study period and fracture history prior to study period, type and length of renal replacement therapy, renal function (eGFR), underlying cause of renal failure, and biochemical parameters related to CKD-MBD (see below). Exclusion criteria included those with a DXA scan at only one time-point, all T-scores > -1.5 SD indicating the absence of bone densitometry criteria for osteoporosis, eGFR >30 ml/min/1.73m^2 or with limited data in corresponding eMR databases (Fig. 1).

The second part of the selection process consisted of cross-referencing the renal medicine transplant lists (the RNSH waiting list as of December 2020 and the completed kidney transplant list from 2005 to 2020) with eMR and DXA scan database. Subjects with at least two DXA BMD scans, T-scores < -1.5 SD in at least one timepoint, eGFR measurement <30 ml/min/1.73 m^2 in at least one time-point, the use of dialysis or kidney transplantation, and on bisphosphonate therapy were selected. Medical Record Numbers were then cross-referenced with the list generated from the DXA database (above) to remove duplicates (Fig. 1).

Subjects from this list were split into 1 of 4 groups according to their renal transplant status and history of anti-resorptive therapy: bisphosphonate transplant (BP-T), non-bisphosphonate transplant (nBP-T), bisphosphonate non-transplant (BP-nT), and non-bisphosphonate, non-transplant (nBP-nT). Non-transplant groups included subjects that were on haemodialysis and those that did not receive any form of renal replacement therapy. All patients in the transplant group had a functioning renal transplant without the need for resumption of renal replacement throughout the study period.

2.2. Demographic and biochemical factors

Age at completion of the study (2020) and age at time of first BMD DXA scan (i.e., baseline), and BMI were collected from the DXA scan database. The remaining data was obtained from patient eMR at RNSH including history of fracture (i.e., at or before baseline DXA scan), incident fractures (i.e., during study period), length and type of anti-resorptive pharmacotherapy, history of corticosteroid use, mean eGFR (at time of baseline BMD scan and the most recent measurement), length and type of renal replacement therapy (haemodialysis, peritoneal dialysis, and/or transplant), and underlying cause of renal failure. Several biochemical parameters related to chronic kidney disease-mineral bone disorder (CKD-MBD) (calcium, phosphate, magnesium, 25(OH)Vitamin D, parathyroid hormone (PTH), and alkaline phosphatase (ALP)) were collected at two time points that correlate to the DXA bone scan dates, designated ‘baseline’ and ‘most recent’.

2.3. Bone mineral density (DXA-BMD) assessment

Absolute values (g/cm^2) of bone mineral density (BMD) were collected for lumbar spine (reported as the average BMD at L1–L4) and total hip at the time of diagnosis (i.e., the first BMD available in the database, or baseline) and the most recent measurement. The time between scans was calculated for each patient and the mean time in each treatment group determined. A minimum of one single T-score < -1.5 SD at any location plus a minimum of two (2) scans at two (2) different points in time were required for the BMD data, and thus the subject, to be included. Net change in BMD (g/m^2) was calculated by taking the difference between the most recent measurement and that recorded at baseline. Annualised change in BMD was then calculated by dividing the net change by the time in years between each measurement (g/m^2/year).

2.4. Bisphosphonate therapy

The use of bisphosphonate (BP) therapy in these subjects was examined. Further evidence of BP therapy was cross-checked across three eMR database at RNSH: Written records were searched for evidence of prescriptions and New South Wales eHealth records containing

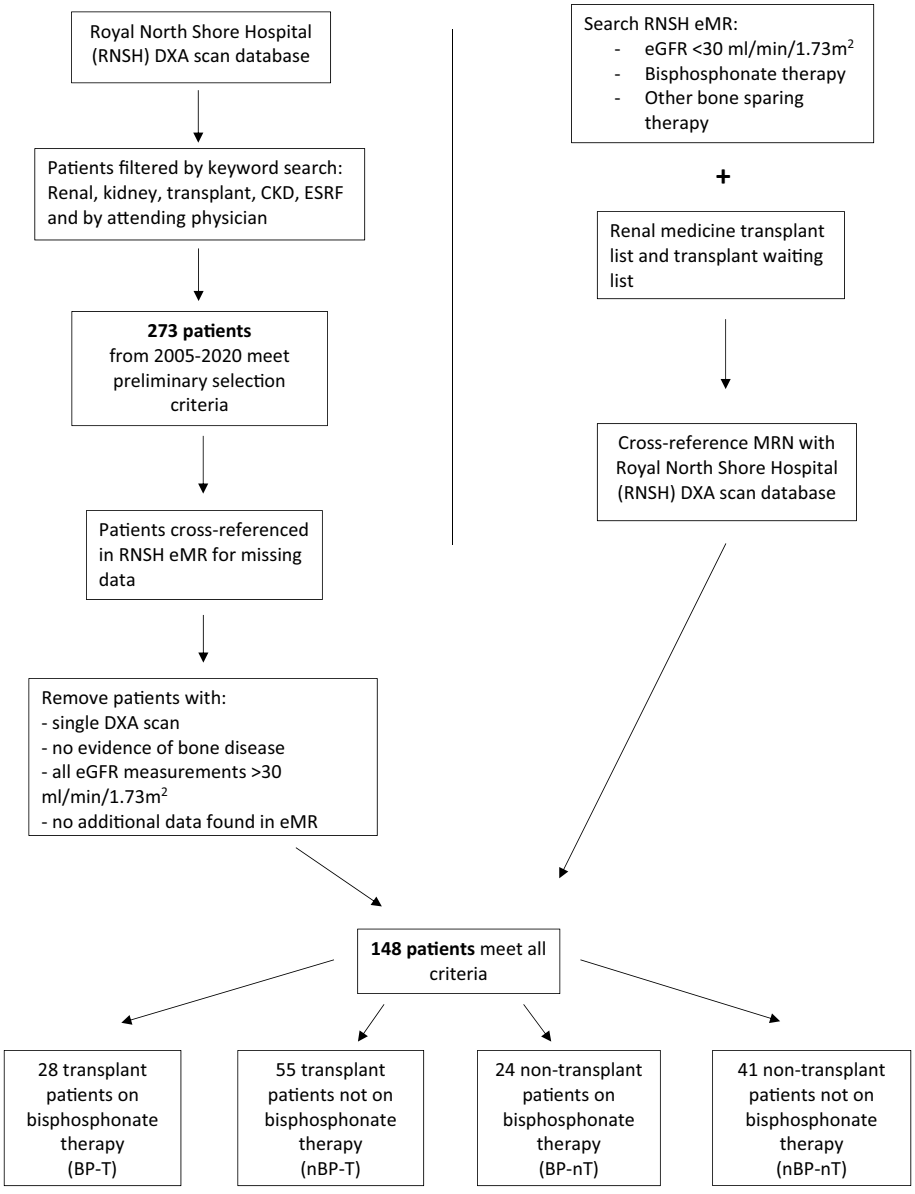

Fig. 1. Flow chart of data retrieval and selection of patients with CKD-MBD, Royal North Shore Hospital, Sydney, Australia.

medication data (a state-wide eMR database external to RNSH) were checked. In this group, the baseline bone density was at the initiation of bisphosphonate therapy. Ongoing use of BP throughout the study period and between the recorded BMD measurements was established for study subjects. Subjects prescribed denosumab, osteoanabolic agents or selective estrogen receptor modulators (SERMs) throughout the study period were excluded with the primary focus of this study on bisphosphonate therapy.

2.5. Statistical analysis

The annualised rate of change in BMD was calculated by subtracting the baseline from the most recent value and dividing by the number of years observed between the two measurements. Unadjusted analysis was first performed which compared the rate of change between the four groups (BP-T, nBP-T, BP-nT, nBP-nT) using ANOVA, with clinically relevant pairwise comparisons between groups performed using *t*-tests. Non-parametric tests including the Kruskall-Wallis test and the Wilcoxon rank-sum test were also performed as a sensitivity analysis. Adjusted analysis was performed using multivariable linear regression including covariates baseline BMD, baseline age and history of fracture. Adjusted least square means were calculated for rate of change by group. A subsidiary analysis was also done with net change (Fol-Base) as the outcome.

The correlation between the change in BMD and change in biochemistry measures was assessed using the Pearson or Spearman correlation coefficient depending on normality. This was assessed both overall and by group.

3. Results

3.1. Demographic factors

Of the 273 patients who met the preliminary inclusion criteria, 125 were removed due to missing or incomplete data. Retrospective data from 2005 to 2020 was collected for total of 148 patients. Eighty-three of these had received a kidney transplant at the time of the study (i.e., transplant group) and 65 had not (non-transplant). Within the transplant group, 28 subjects (11 males and 17 females) received bisphosphonates (BP transplant; BP-T) and 55 (33 males and 22 females)

did not (non-BP transplant; nBP-T). The non-transplant group was comprised of 24 subjects (9 male and 13 female) that received BPs (BP non-transplant; BP-nT) and 41 that did not receive BPs (non-BP non-transplant; nBP-nT; Table 1). Of the non-transplant patients, 42% ($n = 10$) of those receiving BPs were on dialysis with 78% ($n = 32$) in the non-BP receiving group.

Mean age at baseline was similar in renal transplant recipients who received BPs and those that did not (51.9 ± 12.2 years in BP-T compared 50.4 ± 13.4 for the nBP-T). Patients in the non-transplant groups were significantly older on BPs compared to not on BPs (65.4 ± 10.9 and 48.7 ± 11.3, respectively; $p < 0.001$; Table 1).

Mean body mass index (BMI) was similar all patients, with no significant differences between any of the groups (Table 1).

3.2. Bone mineral density at baseline

Transplant recipients prescribed BPs had a lower mean BMD compared to those not on BPs (Lumbar BMD 0.910 ± 0.156 g/cm^2 vs 1.033 ± 0.188 g/cm^2 not on BPs $p = 0.003$). The mean baseline lumbar T-score for transplant recipients prescribed BPs was −1.6 ± 1.4 SD compared to −1.1 ± 1.5 SD for those not on BPs. Similarly, non-transplant CKD patients on BPs had a trend for lower mean lumbar spine BMD at baseline (0.932 ± 0.134 versus 1.012 ± 0.196 g/cm^2 for nBP-nT group; $p = 0.07$) and significantly lower hip BMD (0.689 ± 0.140 g/cm^2; T-score = −1.9 ± 1.1, 0.814 ± 0.172 g/cm^2; $p < 0.008$; T-score = −0.9 ± 2.4; Table 1). No significant differences were found in either lumbar spine or hip baseline BMD between the transplant and non-transplant subjects on BPs ($p = 0.59$ and 0.46, respectively).

There were no significant differences in the average time between baseline and the most recent BMD measurements amongst study participants in each of the groups, indicating similar follow-up periods and allowing adequate longitudinal comparison of BP treatments (Table 1).

3.3. Bisphosphonate therapy

The average length of bisphosphonate therapy was 4.2 ± 3.1 years in the transplant group and 2.5 ± 1.8 years in the non-transplant group ($p = 0.12$) with a range from <1 year to 12 years. The most frequently prescribed BP was risedronate in both groups (46% and 63%, respectively), followed by pamidronate (32% and 17%), zoledronic acid (18% and 8%) and alendronate (14% and 17%; Table 1).

3.4. Fractures

A higher proportion of transplant recipients prescribed BPs had a fracture before or at the time of their baseline BMD measurements (11 of 28, 39.2%) compared to those not on BPs (2 of 55, 3.6%). Similarly, amongst non-transplant patients, 45.8% of those on BPs had previously experienced a fracture (11 of 24) as opposed to a lower proportion of non-transplant patients not on BPs (5 of 41, 12%) (Table 1). Fracture history was therefore incorporated in the regression model in examining BMD change by treatment. A small number of incident fractures occurred during the study period (three in each of the BP-receiving groups, 2 in nBP-T, and 3 in nBP-nT) and the study was underpowered to examine effects of BPs on fractures in this cohort. Adjusted and annualised BMD changes as a surrogate marker of fracture risk were examined.

3.5. Change in lumbar spine Bone Mineral Density

As there were significant differences in baseline age, BMD, and previous fractures between the treatment groups, multivariate analyses adjusted for these factors (Table 1). All values and statistical relationships assessing changes in BMD are least square means adjusted for baseline age, baseline BMD, and previous fracture.

A significant decline in lumbar spine BMD was seen in transplant patients that did not receive BPs (nBP-$T = -0.064 \pm 0.050$ g/cm^2) compared to the significant increase in BMD in the BP-receiving transplant group (0.054 ± 0.055 g/cm^2, $p = 0.001$). In contrast, amongst non-transplant CKD-4 and -5 subjects, BP use had no effect on BMD (−0.020 ± 0.054 g/cm^2 and 0.001 ± 0.063 g/cm^2 for nBP-nT and BP-nT, respectively; $p = 0.63$; Table 1; Fig. 2).

Annualised rates of change in bone density in the groups, adjusted for significant univariables, were also examined (Fig. 3). Renal transplant recipients treated with BPs had a mean net annual increase in lumbar spine BMD of 0.039 g/cm^2 compared to those not on BPs ($p = 0.005$). Fig. 3 illustrates the annual rate of change in lumbar spine BMD in the different groups.

3.6. Changes in hip bone mineral density

Adjusted for age, baseline BMD, and previous fracture, all groups had mean net losses in hip bone mineral density across the study period. Although BPs preserved hip BMD in transplant recipients, this effect was not significant at this site compared to transplant recipients not receiving BPs (Table 1; Fig. 4).

Further, annualised rates of change in hip BMD were not found to be significantly different between the groups. The lowest rate of decline, however, was observed in transplant recipients treated with BP (−0.003 ± 0.013 g/cm^2/year which was 0.01 g/cm^2/year less than nBP-T patients at −0.013 ± 0.001 g/cm^2/year, $p = 0.123$; Table 1; Fig. 5). Subjects not treated with BPs had similar annual reductions in hip BMD at −0.017 ± 0.014 and − 0.015 ± 0.010 g/cm^2/year, respectively for transplant and non-transplant groups ($p = 0.789$; Table 1; Fig. 5).

3.7. Bisphosphonate use and estimated Glomerular Filtration Rates (eGFR)

Mean estimated glomerular filtration rate at baseline in BP-T patients was 16 ± 16 ml/min/1.73 m^2 as measured at the time-point just prior to transplantation. This was similar to BP-nT patients that had a mean baseline eGFR of 13 ± 11 ml/min/1.73 m^2 ($p = 0.99$; Table 1). BP use in transplant recipients did not have an adverse effect on eGFR during the study period, with eGFR increasing in transplant recipients as expected, regardless of BP use (BP-T post-treatment eGFR = 43 ± 29 ml/min/1.73 m^2; nBP-T post-treatment eGFR = 46 ± 35 ml/min/1.73m^2; $p = 0.80$; Table 1).

3.8. Biochemical markers of CKD-MBD

There were no significant differences in alkaline phosphatase (ALP) or parathyroid hormone (PTH) between mean the baseline and most recent measurements in either group, regardless of treatment. Transplant recipients who were not receiving BPs demonstrated a significant reduction in serum phosphate across the study period (1.18 ± 0.53 vs 1.56 ± 0.45 mmol/l; $p = 0.0001$; Table 2).

Biochemical parameters of CKD-MBD did not change in association with BP use. In particular, Pearson and Spearman correlation coefficient revealed no correlation between change in ALP, PTH, or phosphate and change in BMD overall or within each group (Table 2).

4. Discussion

Chronic Kidney Disease-Mineral Bone Disorder CKD-MBD is a complex disease generally spanning many years of mineral and/or hormone dysregulation ultimately resulting in fractures and greater mortality. The clinical course and optimal management of CKD-MBD remain unclear with clinical equipoise in the use of anti-resorptive agents. The present study examines prescribing trends of bisphosphonates (BPs) in end-stage kidney disease at the Royal North Shore Hospital from 2005 to 2020 and identifies patient- and/or treatment-specific factors that may determine a benefit from osteoporosis therapy in the context of CKD-

Table 1
Demographic, bone mineral density, bone sparing pharmacotherapy, and renal parameters in kidney transplant and non-transplant patients with chronic kidney disease-mineral bone disorder (CKD-MBD), 2005–2020. Retrospective data was collected on patients with CKD Stage 4 and 5 (eGFR <30 ml/min/1.73 m^2) and concomitant BMD evidence of bone disease osteoporosis (t-score < −1.5 SD) from electronic medical records at the Royal North Shore Hospital, Sydney, Australia. Patients were first divided into transplant and non-transplant groups and subsequently split into those that received bisphosphonates and those that did not. The differences between the means of the various paramaters were statistically compared with analysis of variance (ANOVA).

	Transplant		Non-transplant		p-Values (ANOVA)[1]		
	BP	Non-BP	BP	Non-BP	BP-T vs nBP-T	BP-T vs BP-nT	BP-nT vs nBP-nT
Total number of patients	28	55	24	41	–	–	–
No. of male patients	11	33	9	17	–	–	–
No. of female patients	17	22	13	24	–	–	–
Mean age (years)							
At diagnosis	51.9 ± 12.2	50.4 ± 13.6	65.4 ± 10.9	48.7 ± 11.3	0.52	<0.001	<0.001
Current	61.1 ± 13.1	54.9 ± 13.9	71.5 ± 12.1	56.7 ± 11.4	0.10	0.008	<0.001
No. of deceased patients	3	3	2	3	–	–	–
Percent deceased (%)	11%	5%	8%	7%	–	–	–
Mean BMI (kg/cm^2)	25.7 ± 5.4	26.6 ± 3.6	26.1 ± 5.5	25.7 ± 5.7	0.64	0.87	0.84
Bone Mineral Density							
Mean baseline BMD (g/cm^2)							
Lumbar	0.910 ± 0.156	1.033 ± 0.188	0.932 ± 0.134	1.012 ± 0.196	0.003	0.59	0.07
Hip	0.724 ± 0.115	0.854 ± 0.154	0.689 ± 0.140	0.814 ± 0.172	<0.001	0.46	0.008
Mean baseline T-score							
Lumbar	−1.6 ± 1.4	−1.1 ± 1.5	−1.5 ± 2.1	−1.0 ± 1.4	0.03	0.46	0.33
Hip	−2.1 ± 0.9	−1.3 ± 1.7	−1.9 ± 1.1	−0.9 ± 2.4	<0.005	0.88	0.008
Mean time between baseline and most recent BMD measurement (years)	4.4 ± 2.4	3.8 ± 1.0	4.3 ± 2.3	4.2 ± 3.1	0.26	0.86	0.96
Mean net change in BMD (g/cm^2)							
Lumbar	0.068 ± 0.095	−0.072 ± 0.194	0.002 ± 0.092	−0.026 ± 0.099	<0.001	0.040	0.15
Hip	0.019 ± 0.086	−0.045 ± 0.070	−0.069 ± 0.109	−0.048 ± 0.069	<0.001	0.003	0.34
Mean annual rate of change in BMD (g•cm^{-2}•$year^{-1}$)							
Lumbar	0.020 ± 0.021	−0.024 ± 0.016	−0.007 ± 0.025	−0.005 ± 0.012	0.003	0.090	0.240
Hip	0.001 ± 0.032	−0.014 ± 0.027	−0.025 ± 0.043	−0.016 ± 0.022	<0.0005	0.001	0.250
Adjusted mean net change in BMD[2] (g/cm^2)							
Lumbar	0.054 ± 0.055	−0.064 ± 0.050	0.001 ± 0.063	−0.020 ± 0.054	0.001	0.210	0.63
Hip	−0.016 ± 0.030	−0.045 ± 0.026	−0.071 ± 0.032	−0.050 ± 0.027	0.145	0.012	0.34
Adjusted mean annual rate of change in BMD[2] (g•cm^{-2}•$year^{-1}$)							
Lumbar	0.016 ± 0.021	−0.023 ± 0.016	0.002 ± 0.025	−0.006 ± 0.012	0.005	0.420	0.620
Hip	−0.003 ± 0.013	−0.013 ± 0.001	−0.017 ± 0.014	−0.015 ± 0.010	0.123	0.230	0.789
Fracture history[3]							
Hip	3	2	5	3	–	–	–
Vertebral	4	–	1	–	–	–	–
Wrist	–	–	2	1	–	–	–
Other	4	–	3	1	–	–	–
Fracture incidence[4]					–	–	–
Hip	1	–	–	–	–	–	–
Vertebral	1	–	1	–	–	–	–
Wrist	–	1	1	1	–	–	–
Other	1	1	1	1	–	–	–
Pharmacotherapy							
Bisphosphonate (total number of patients)							
Risedronate	13	–	15	–	–	–	–
Pamidronate	9	–	4	–	–	–	–
Alendronate	5	–	2	–	–	–	–
Zoledronate	4	–	4	–	–	–	–
Average length of Therapy (years)	4.4	–	2.5	–	–	0.12	–
Range (years)	<1–12	–	<1–11	–	–	–	–
Corticosteroids	22	43	10	17			
Renal Parameters							
Mean eGFR (ml/min/1.73 m^2)							
At diagnosis	16 ± 16	13 ± 11	24 ± 17	18 ± 18	0.99	0.09	0.32
Most recent	43 ± 29	46 ± 25	17 ± 8	14 ± 17	0.80	<0.001	0.66
Renal replacement therapy (RRT)							
Total number on dialysis	23	39	10	32		–	

(continued on next page)

Table 1 (*continued*)

	Transplant		Non-transplant		p-Values (ANOVA)[1]		
	BP	Non-BP	BP	Non-BP	BP-T vs nBP-T	BP-T vs BP-nT	BP-nT vs nBP-nT
Mean time on dialysis (years)	4.2 ± 2.1	3.5 ± 2.9	4.8 ± 3.7	4.4 ± 3.4	0.87	0.50	0.73
Underlying cause of renal failure (number of patients)							
Type I diabetes mellitus	3	1	1	2	–	–	–
Type II diabetes mellitus	4	6	9	4	–	–	–
Hypertension	1	1	0	6	–	–	–
Glomerulonephritis	8	23	6	9	–	–	–
Acute kidney Injury	1	0	1	1	–	–	–
Polycystic kidney disease	2	7	9	3	–	–	–
Other or unknown	11	17	0	18	–	–	–

[1] Significant differences in the means were calculated with a of p-value <0.05.
[2] Least square means were adjusted for age, baseline BMD, and fracture incidence
BP-T = bisphosphonate transplant; nBP-T = non-bisphosphonate, transplant; BP-nT = bisphosphonate non-transplant; nBP-nT = non-bisphosphonate, non-transplant.
[3] Fracture history are fractures that occurred at or before the baseline BMD measurements and are included as a covariate in the regression model.
[4] Fracture incidence are those that occurred during the study period.

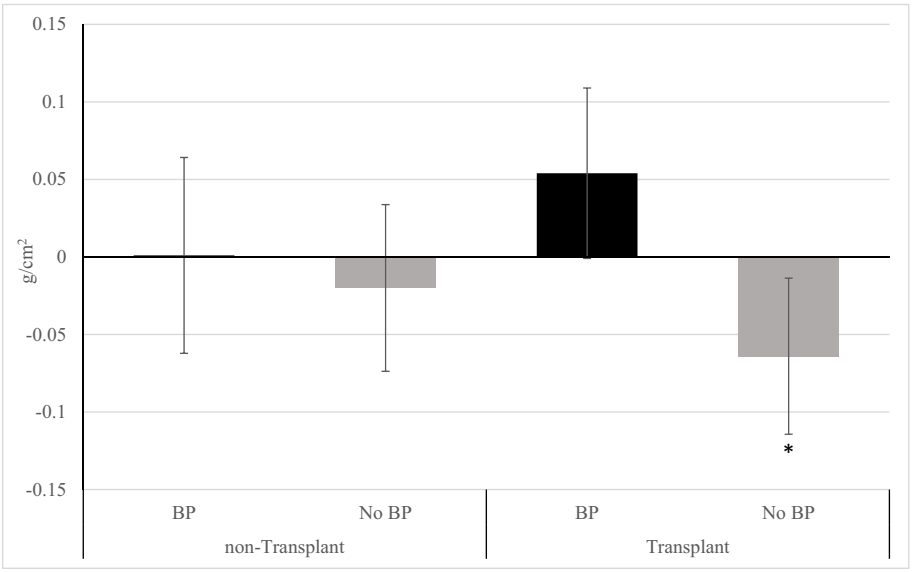

Fig. 2. Net change in lumbar spine bone mineral density (BMD; g/m^2) adjusted for age, baseline BMD, and fracture incidence. BMD was recorded in non-kidney transplant and kidney transplant patients and compared in those who received bisphosphonates (BPs) and those that did not.
Net change in BMD between the most recent measurements and those taken at time of diagnosis (i.e., baseline) was determined. Statistical differences were calculated by ANOVA and least square means adjusted for age, baseline BMD, and fracture incidence. Error bars indicate 95% confidence intervals.
* Indicates a significant difference (p = 0.001) between BP-receiving and non-BP receiving kidney transplant patients.
BP = bisphosphonate.

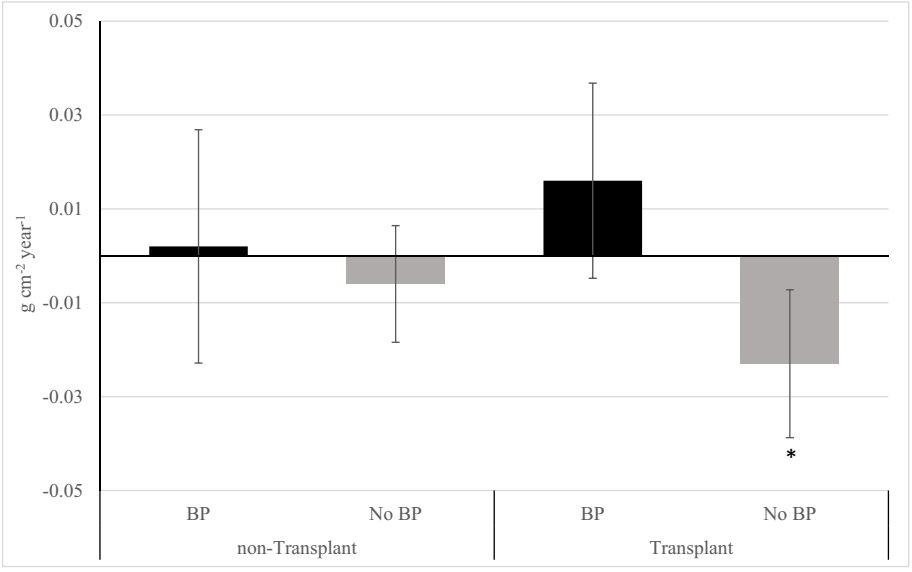

Fig. 3. Annual rate of change in lumbar spine bone mineral density (BMD; g•m^{-2}•year^{-1} adjusted for age, baseline BMD, and fracture incidence.
Lumbar spine BMD were recorded in non-kidney transplant and kidney transplant patients and compared in those who received bisphosphonates (BPs) and those that did not. Annual rate of change was calculated by dividing the net change in BMD between the most recent measurements and those taken at time of diagnosis by the number of years between measurements. Statistical differences were calculated by ANOVA and least square means adjusted for age, baseline BMD, and fracture incidence. Error bars indicate 95% confidence intervals.
*Indicates a significant difference (p = 0.005) between BP-receiving and non-BP receiving kidney transplant patients.
BP = bisphosphonate.

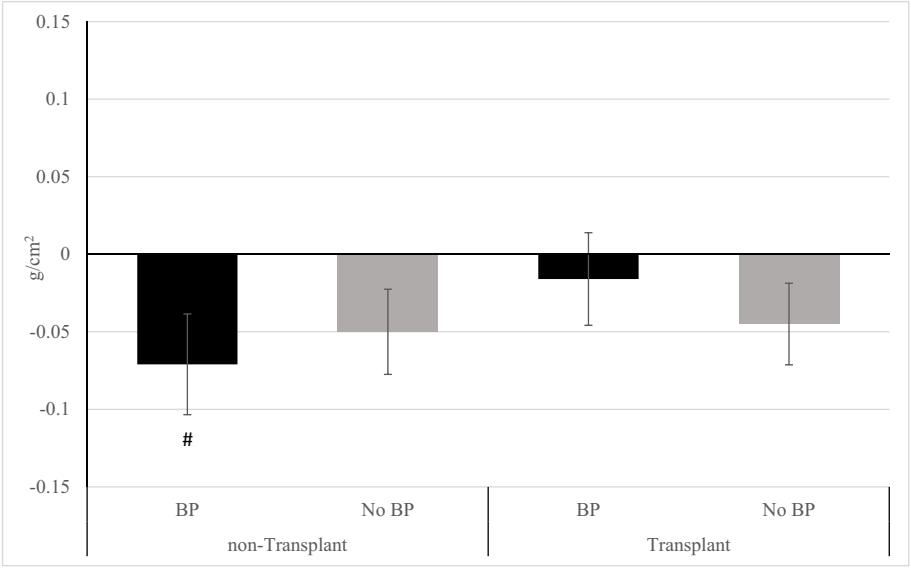

Fig. 4. Net change in hip bone mineral density (BMD; g/m^2) adjusted for age, baseline BMD, and fracture incidence.
BMD was recorded in pre-kidney transplant and post-kidney transplant patients and compared in those who received bisphosphonates (BPs) and those that did not. Net change in BMD between the most recent measurements and those taken at time of diagnosis was determined. Statistical differences were calculated by ANOVA and least square means adjusted for age, baseline BMD, and fracture incidence. Error bars indicate 95% confidence intervals.
# Indicates a significant difference ($p < 0.05$) between non-transplant and transplant patients who received BPs.
BP = bisphosphonate.

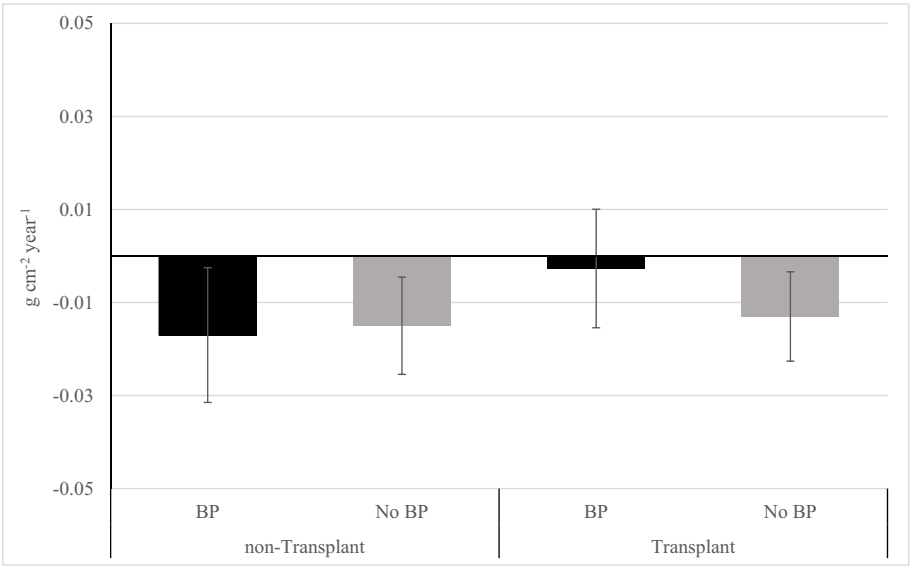

Fig. 5. Annual rate of change in hip bone mineral density (BMD; $g \bullet m^{-2} \bullet year^{-1}$) adjusted for age, baseline BMD, and fracture incidence.
Neck of femur BMD were recorded in non-kidney transplant and kidney transplant patients and compared in those who received bisphosphonates (BPs) and those that did not. Annual rate of change was calculated by dividing the net change in BMD between the most recent measurements and those taken at time of diagnosis by the number of years between measurements. Statistical differences were calculated by ANOVA and least square means adjusted for age, baseline BMD, and fracture incidence. Error bars indicate 95% confidence intervals.
BP = bisphosphonate.

MBD. Patients prescribed BPs were more likely to have a lower baseline bone density and previous fracture, consistent with mainstream indications for the use of these agents in patients with osteoporosis. Patients with biochemical evidence of higher bone turnover in this study were not preferentially treated with bisphosphonates.

Over the 15-year study period, BP use in CKD-4 and -5 patients did not result in significant changes in biochemical parameters and were not associated with detectable serious adverse events in either transplant recipients or non-transplant patients. Importantly, BPs had no effect on eGFR in transplant recipients. After adjustment for age, previous fractures and baseline bone density, BPs appeared to prevent a decline in lumbar bone density in transplant recipients. However, hip bone mineral density declined in CKD subjects, regardless of transplant status or bisphosphonate use. Across the study period, all groups demonstrated declines in hip bone density, regardless of BP use.

While previous studies support our conclusions (Ott, 2017), there have been inconsistencies in the evidence-base driven by heterogeneous patient populations (Coco et al., 2003), inclusion of various sub-types of renal failure and renal replacement regimens (Walsh et al., 2009), small patient cohorts and lack of longitudinal bone density data (Jamal et al., 2007). Experts have called for a greater number of longitudinal cohort studies to clarify the real-world use and efficacy of BPs in CKD-4 and- 5 (Palmer and Strippoli, 2020; Wang et al., 2016). The present study reflects 15 years of experience in the use of bisphosphonates in patients with CKD-MBD with serial bone density outcomes and clear differentiation of CKD patients by transplant status. Clear differences in biochemical factors in pre- versus post-renal transplant patients and the use of glucocorticoids and immune-suppressives in the latter would have significant differential effects on the skeleton, necessitating independent assessment of these groups.

BPs preserved bone in the peri- and post-transplant period in this study in lumbar spine, but by comparison, CKD-4 and 5 patients on dialysis or on no renal replacement continued to lose bone despite the use of BPs. Furthermore, hip bone density declined in both transplant and non-transplant CKD groups, possibly related to progressive loss of cortical bone not mitigated by BPs.. In addition, the deleterious effect of biochemical factors in CKD-4 and -5 including high bone turnover and electrolyte abnormalities may not be mitigated by BPs. This may relate

Table 2
Biochemical markers of bone health and mineralization measured at baseline (i.e., time of first BMD scan) and the most recent for the different treatment groups.

	Ca^{2+} (mmol/l)		Mg^{2+} (mmol/l)		PO^{4-} (mmol/l)		25(OH)Vitamin D (nmol/l)		PTH (pmol/l)		ALP (U/l)	
	Baseline	Most recent	Baseline	Most recent	Baseline	Most recent	Baseline	Most recent	Baseline	Most recent	Baseline	Most recent
Mean values												
BP-T	2.34 ± 0.19	2.37 ± 0.13	0.86 ± 0.13	0.76 ± 0.16	1.41 ± 0.55	1.13 ± 0.45	47.5 ± 37.9	76.5 ± 29.6	23.8 ± 31.5	13.6 ± 29.3	93 ± 47	94 ± 51
nBP-T	2.30 ± 0.19	2.40 ± 0.12	0.92 ± 0.18	0.80 ± 0.19	1.56 ± 0.45	1.18 ± 0.53	60.0 ± 29.5	66.2 ± 25.5	35.6 ± 35.5	33.3 ± 61.5	85 ± 56	91 ± 64
BP-nT	2.40 ± 0.93	2.36 ± 0.96	0.86 ± 0.33	0.88 ± 0.37	1.38 ± 0.49	1.34 ± 0.45	68.4 ± 26.2	75.3 ± 29.1	21.6 ± 12.8	30.3 ± 16.1	103 ± 41	112 ± 55
nBP-nT	2.31 ± 0.19	2.36 ± 0.20	0.89 ± 0.15	0.90 ± 0.12	1.55 ± 0.40	1.40 ± 0.42	55.6 ± 31.7	62.7 ± 27.0	37.2 ± 36.2	44.8 ± 32.5	90 ± 57	148 ± 246
p-Values[1]												
BP-T	0.998		0.001		0.181		0.052		0.488		0.858	
nBP-T	0.001		0.001		0.0001		0.256		0.818		0.624	
BP-nT	0.542		0.486		0.772		0.466		0.437		0.615	
nBP-nT	0.186		0.583		0.100		0.345		0.370		0.154	
Correlation to change in BMD[2]	Lumbar	Hip	Lumbar	Hip	Lumbar	Hip	Lumbar	Hip	Lumbar	Hip	Lumbar	Hip
BP-T												
r	0.096	−0.007	0.023	0.079	0.283	−0.153	0.591	0.156	0.042	0.209	0.210	0.337
p-Value	0.614	0.973	0.904	0.684	0.137	0.411	0.043	0.629	0.825	0.267	0.266	0.069
nBP-T												
r	−0.102	0.066	0.009	−0.031	−0.085	−0.120	−0.147	−0.139	0.056	0.088	−0.044	0.014
p-Value	0.482	0.652	0.955	0.837	0.558	0.410	0.326	0.364	0.709	0.560	0.763	0.926
BP-nT												
r	0.204	−0.049	0.128	0.134	−0.246	−0.133	0.591	0.156	0.303	−0.021	−0.123	0.455
p-Value	0.416	0.847	0.651	0.635	0.326	0.598	0.043	0.629	0.254	0.940	0.627	0.058
nBP-nT												
r	−0.264	0.060	0.192	0.152	0.086	0.138	0.176	−0.063	0.245	0.208	0.033	0.112
p-Value	0.125	0.724	0.285	0.384	0.624	0.414	0.391	0.755	0.191	0.260	0.852	0.509

BP-T = bisphosphonate transplant; nBP-T = non-bisphosphonate, transplant; BP-nT = bisphosphonate non-transplant; nBP-nT = non-bisphosphonate, non-transplant.
[1] p-values <0.05 inidicate a significant difference between baseline and the most recent measurement within each group, calculated by non-parametric *t*-test.
[2] r and *p*-values (<0.05) represent a correlation in the change of the different biochemical parameters to change in BMD at lumbar spine and hip determined by Pearson or Spearman correlation.

to predominant use of risedronate in our institution rather than parenteral forms, the latter possibly.

exerting a greater anti-resorptive effect in CKD. Due to the small number of fractures identified in this study, both prior to and during the study period, fractures were not a primary outcome measure of this study. Comparison of fracture rates between the groups was not possible due to lack of study power. However, previous fractures were significantly associated with BP use in this study and therefore included in the multivariate assessment of bone density changes.

Whether BPs are harmful in patients with CKD is a salient question. We found no evidence of biochemical changes in BP-receiving patients or deterioration of renal function in the 148 patients receiving these agents over the study period. However, in the absence of bone histomorphometry, this study could not report conclusively on the development of adynamic bone disease in BP-receiving patients. BP use in transplant recipients did not adversely affect renal function (Table 1), a reassuring finding as recent studies suggest potential deleterious effects of BPs in advanced stages of CKD (Wilson et al., 2017; Robinson et al., 2021).

Strengths of this study include the use of 3 independent eMRs to provide a real-world, albeit retrospective, picture on prescribing practices at a tertiary referral centre. Moreover, this study examined serial BMD over time on state-of-the-art densitometer using a surrogate marker of fracture, namely bone mineral density.

Limitations include the relatively small study population mainly due to incomplete data or the number of patients simply not meeting the criteria, and the inability to robustly assess fracture outcomes. There were no data on more specific markers of bone turnover such as bone-specific ALP or P1NP in this study. Furthermore, while several confounding factors were adjusted for in the statistical analyses (i.e., age, baseline BMD and previous fracture), other treatment biases exist that may have gone unaccounted. In CKD 4- and 5, lumbar spine BMD can be artefactually increased due to vascular calcification although these changes would be expected amongst the groups.

While there are limitations of this study, the conclusions drawn yield similar results from previous publications investigating bisphosphonate use in end-stage kidney disease (Coco et al., 2003; Walsh et al., 2009; Jamal et al., 2007). Importantly, a lack of strong evidence and clear clinical guidelines around the use of BPs in patients with declining kidney function is a reality, and many physicians are presented with a clinical equipoise when faced with this patient population. BP therapy, when safe and warranted, can provide life-saving bone-sparing therapy (Schipper et al., 2015; Ott, 2013). Conversely, worsening of any co-morbidity (e.g., adynamic bone disease or kidney function) in this frail population can have detrimental effects. Large, prospective, multi-centre studies may help to advance this field, clarify the clinical dilemma, and address the limitations of the present study. From our 15-year single-centre experience, BPs did not exacerbate biochemical changes of CKD-MBD and maintained lumbar spine bone mineral density in renal transplant recipients. Hip bone mineral density did not improve regardless of transplant status or BP use and specific strategies to promote cortical bone and hip bone density in CKD patients require further evaluation.

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CRediT authorship contribution statement

Dominic Hauck: Investigation, Data curation, Writing – original draft. **Liza Nery:** Resources. **Rachel O'Connell:** Formal analysis. **Roderick Clifton-Bligh:** Conceptualization. **Amanda Mather:** Resources, Supervision. **Christian M. Girgis:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

Dominic Hauck, Liza Nery, Rachel O'Connell, Roderick Clifton-Bligh, Amanda Mather, and Christian Girgis declare that they have no conflict of interest.

References

Alem, A.M., et al., 2000. Increased risk of hip fracture among patients with end-stage renal disease. Kidney Int. 58 (1), 396–399.

Allen, M.R., Aref, M.W., 2017. What animal models have taught us about the safety and efficacy of bisphosphonates in chronic kidney disease. Curr. Osteoporos. Rep. 15 (3), 171–177.

Amerling, R., 2010. Bisphosphonate use in chronic kidney disease: association with adynamic bone disease in a bone histology series. Blood Purif. 29, 293–299.

Andress, D.L., et al., 1986. Aluminum-associated bone disease in chronic renal failure: high prevalence in a long-term dialysis population. J. Bone Miner. Res. 1 (5), 391–398.

Bover, J.B.L., López-Báez, V., Benito, S., Ciceri, P., Galassi, A., Cozzolino, M., 2017. Osteoporosis, bone mineral density and CKD-MBD: treatment considerations. J. Nephrol. 30 (5), 677–687.

Chavassieux, P., et al., 2014. Bone histomorphometry of transiliac paired bone biopsies after 6 or 12 months of treatment with oral strontium ranelate in 387 osteoporotic women: randomized comparison to alendronate. J. Bone Miner. Res. 29 (3), 618–628.

Coco, M., et al., 2003. Prevention of bone loss in renal transplant recipients: a prospective, randomized trial of intravenous pamidronate. J. Am. Soc. Nephrol. 14 (10), 2669–2676.

<collab>Welfare, A.I.o.H.a.</collab>, 2017. Chronic Kidney Disease Compendium. Australian Government. WEB 108.

Connelly, K., Collister, D., Tangri, N., 2018. Fracture risk and treatment in chronic kidney disease. Curr. Opin. Nephrol. Hypertens. 27 (3), 221–225.

Danese, M.D., et al., 2006. PTH and the risks for hip, vertebral, and pelvic fractures among patients on dialysis. Am. J. Kidney Dis. 47 (1), 149–156.

Jamal, S.A., et al., 2007. Alendronate treatment in women with normal to severely impaired renal function: an analysis of the fracture intervention trial. J. Bone Miner. Res. 22 (4), 503–508.

Jansz, T.T., et al., 2020. The prevalence and incidence of vertebral fractures in end-stage renal disease and the role of parathyroid hormone. Osteoporos. Int. 31 (3), 515–524.

Jean, S., et al., 2013. Direct medical resource utilization associated with osteoporosis-related nonvertebral fractures in postmenopausal women. J. Bone Miner. Res. 28 (2), 360–371.

Ketteler, M., et al., 2017. Executive summary of the 2017 KDIGO chronic kidney disease-mineral and bone disorder (CKD-MBD) guideline update: what's changed and why it matters. Kidney Int. 92 (1), 26–36.

Liu, W., 2013. Bisphosphonates in CKD patients with low bone mineral density. Sci. World J. 2013, 1–11.

McKee, H., et al., 2020. Comparison of the clinical effectiveness and safety between the use of denosumab vs bisphosphonates in renal transplant patients. Osteoporos. Int. 31 (5), 973–980.

Miller, P.D., 2014. Chronic kidney disease and osteoporosis: evaluation and management. Bonekey Rep. 3, 542.

Miller, P.D., 2014. Bone disease in CKD: a focus on osteoporosis diagnosis and management. Am. J. Kidney Dis. 64 (2), 290–304.

Moe, S.M., et al., 2014. A comparison of calcium to zoledronic acid for improvement of cortical bone in an animal model of CKD. J. Bone Miner. Res. 29 (4), 902–910.

Nitta, K., Yajima, A., Tsuchiya, K., 2017. Management of osteoporosis in chronic kidney disease. Intern. Med. 56 (24), 3271–3276.

Ott, S.M., 2013. Therapy for patients with CKD and low bone mineral density. Nat. Rev. Nephrol. 9 (11), 681–692.

Ott, S.M., 2017. Review: osteoporosis drugs may improve BMD and reduce fractures in some patients with CKD. Ann. Intern. Med. 167 (4), JC19.

Palmer, S.C., Strippoli, G.F.M., 2020. Interventions for preventing bone disease in kidney transplant recipients: editorial summary of a Cochrane review. Am. J. Kidney Dis. 75 (5), 807–809.

Robinson, D.E., et al., 2021. Safety of oral bisphosphonates in moderate-to-severe chronic kidney disease: a binational cohort analysis. J. Bone Miner. Res. 36 (5), 820–832.

Schipper, L.G., et al., 2015. Treatment of osteoporosis in renal insufficiency. Clin. Rheumatol. 34 (8), 1341–1345.

Toussaint, N.D., Elder, G.J., Kerr, P.G., 2009. Bisphosphonates in chronic kidney disease; balancing potential benefits and adverse effects on bone and soft tissue. Clin. J. Am. Soc. Nephrol. 4 (1), 221–233.

Walsh, S.B., et al., 2009. Effect of pamidronate on bone loss after kidney transplantation: a randomized trial. Am. J. Kidney Dis. 53 (5), 856–865.

Wang, J., et al., 2016. Bisphosphonates for prevention of osteopenia in kidney-transplant recipients: a systematic review of randomized controlled trials. Osteoporos. Int. 27 (5), 1683–1690.

Wilson, L.M., et al., 2017. Benefits and harms of osteoporosis medications in patients with chronic kidney disease: a systematic review and meta-analysiseffect of osteoporosis medications in patients with CKD. Ann. Intern. Med. 166 (9), 649–658.