Kidney & Blood Pressure Research

Kidney Blood Press Res 2016;41:614-622
DOI: 10.1159/000447930
Published online: September 14, 2016
Accepted: July 1, 2016

Original Paper

Effect of Denosumab on Peripheral Compartmental Bone Density, Micro-architecture and Estimated Bone Strength in *De Novo* Kidney Transplant Recipients

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Key Words
Denosumab • Dual energy X-ray absorptiometry (DXA) • High-resolution peripheral quantitative computed tomography (HRpQCT) • Kidney transplantation • Osteoporosis

Abstract
Background/Aims: In a randomized controlled clinical trial in kidney transplant recipients (NCT01377467) we have recently shown that RANKL inhibition with denosumab significantly improved areal bone mineral density (aBMD) when given during the first year after transplantation. The effect of denosumab on skeletal microstructure and bone strength in kidney transplant recipients is not known. ***Methods:*** The purpose of the present bone microarchitecture ancillary study was to investigate high-resolution peripheral quantitative computed tomography (HRpQCT) data from the distal tibia and distal radius in 24 study patients that had been randomized to receive either two injections of denosumab 60 mg at baseline and after 6 months (n=10) or no treatment (n=14). ***Results:*** Consistent with the full trial findings, denosumab reduced biomarkers of bone turnover, and significantly increased aBMD at the lumbar spine (median difference of 4.7%; 95% confidence interval [CI] 2.6 – 7.8; p<0.001). Bone quality as assessed by total and cortical volumetric bone mineral density (Tot. vBMD, Ct.vBMD) and cortical thickness (Ct.Th) increased significantly at the tibia, while changes at the radius were less pronounced. The trabecular volumetric BMD (Tb.vBMD), thickness (Tb. Th), separation (Tb.Sp) and number (Tb.N) and the cortical porosity (Ct.Po) at the tibia and the radius did not significantly change in both treatment groups. Micro-finite element analysis (μFEA) showed that bone stiffness increased significantly at the tibia (median difference 5.6%; 95% CI 1.8% – 9.2%; p=0.002) but not at the radius (median difference 2.9%, 95% CI -3.7% – 9.1%; p=0.369). Likewise, failure load increased significantly at the tibia (median difference

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5.1%; 95% CI 2.1% – 8.1%; p=0.002) but not at the radius (median difference 2.4%, 95% CI -3.2% – 8.5%; p=0.336). ***Conclusions:*** These findings demonstrate that denosumab improves bone density and bone quality in first-year kidney transplant recipients at risk to develop osteoporosis.

Introduction

Kidney transplant recipients (KTR) are at high risk to loose bone mass, especially in the first year after transplantation, due to the immunosuppressive medication (glucocorticoids in particular) and other factors such as persistence of elevated PTH and FGF-23 levels and low vitamin D status [1]. Thus, KTR have a heightened risk to develop or to worsen osteoporosis and to suffer from fractures [2, 3]. Outcomes for KTR sustaining a fracture are significantly worse compared with the general population, with a 60% increased risk in mortality [4]. Preventing bone loss and reducing the risk of subsequent fractures among KTR is therefore of great clinical relevance [5, 6].

Therapeutic recommendations to prevent bone loss in first-year KTR include glucocorticoid minimization or avoidance, calcium and vitamin D supplementation, and bisphosphonates [7-10]. Recently we demonstrated in a randomized controlled clinical trial among 90 first-year KTR that denosumab effectively increased bone mineral density (BMD), with a therapeutic effect that appeared to surpass previously described treatments [11]. In the present bone quality ancillary study we examined whether treatment with denosumab also improved bone microarchitecture and estimated bone strength. Specifically, we assessed volumetric BMD, cortical thickness, cortical porosity, stiffness and failure load at the distal tibia and radius by HRpQCT analysis in a subgroup of 24 first-year KTR.

Materials and Methods

Subjects

Details of the "Prolia for Osteoporosis of Transplant Operated Patients" (POSTOP) study subjects have been reported previously [11]. In brief, we recruited a total of 90 KTR that had been transplanted less than 4 weeks ago to examine 1-year changes in aBMD at the lumbar spine and the hip by dual energy X-ray absorptiometry (DXA). A subset of 24 consecutive patients consented to have in addition two HRpQCT examinations of the distal tibia and radius at baseline and after 12 months.

Protocol

Male (n=16) and female (n=8) transplant recipients were randomly assigned (1:1) to open-label treatment with denosumab 60 mg subcutaneously at baseline and after 6 months (n=10), or no treatment (n=14). All patients were prescribed daily calcium (1000 mg) and vitamin D (800 IU). All participants gave their written informed consent. The study was designed and conducted to conform to the principles of the Declaration of Helsinki, was approved by the local Ethics Committee (IRB approval number 2011-0032), and was registered on ClinicalTrials.gov, number NCT01377467.

Patients were seen at defined study visits for assessment of transplant function (creatinine-based eGFR determination by CKD-EPI formula) and to measure biomarkers of bone metabolism (parathyroid hormone [PTH], 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D) and turnover (procollagen type I N-terminal propeptide [P1NP], bone-specific alkaline phosphatase [BSAP], β-form of C-terminal telopeptide of type I collagen [β-CTx] and urine deoxypyridinoline to creatinine ratio). All study patients underwent DXA (Hologic Discovery®, Marlborough, MA, USA) and HRpQCT (XtremeCT®, Scano Medical AG, Brüttisellen, Switzerland) measurements at baseline and after 12 months.

HRpQCT

At baseline and after 12 months, HRpQCT measurements were performed at the dominant radius and tibia according to the standard protocol which was provided by the manufacturer. The dominant side was chosen as most patients had a dialysis shunt at their non-dominant forearm which interfered with the positioning holder. With an isotropic voxel size of 82 microns, each scan included 110 slices representing a 9.02 mm region of interest. The final volume of interest for the standard analysis included the overlapping region from baseline and 12 months follow-up scans which was based on the manufacturer's 2D registration algorithm. Scan quality was graded according to Pialat et al. [12], with a five grade scheme ranging from grade 1 (no motion artifacts) to grade 5 (severe motion artifacts). Scans with insufficient quality (i.e. grade 4 or 5) were repeated. This was needed in 17 (35%) of the 48 radial scans and 6 (8%) of the 48 tibial scans.

The scans were evaluated using the standard patient evaluation protocol provided by the manufacturer [13]. First, cortical and trabecular regions were separated using a semi-automated contouring based on a threshold-based algorithm [14]. Voxels representing mineralized bone were then extracted using a Laplace-Hamming filter, followed by normalization and global thresholding to create segmented images. From the segmented images, the following parameters were calculated: volumetric bone mineral density (mg HA/cm^3) for the total (Tot.vBMD), cortical (Ct.vBMD) and trabecular regions (Tb.vBMD), micro-architectural parameters of the trabecular structure (trabecular thickness [Tb.Th, mm], trabecular separation [Tb.Sp, mm], trabecular number [Tb.N, mm^{-1}]) [15], and cortical thickness (Ct.Th, mm). Additionally, advanced cortical analysis was performed to calculate cortical porosity (Ct.Po, %) [16].

Micro-finite element analysis (μFEA) models were created from segmented images of all 110 slices of baseline and follow-up scans. Each voxel representing bone tissue was converted into a brick element of the same size with linear-elastic and isotropic material behavior, a Young's modulus of 10 GPa and a Poisson's ratio of 0.3 [17]. The μFEA model simulated a uniaxial "high friction" compression test where bone stiffness (kN/mm) and failure load (kN) were estimated. Failure load was defined based on the Pistoia criterion assuming that failure would occur when more than 2% of bone volume is loaded beyond a critical strain limit of 0.7%.

Statistical analysis

A complete case analysis was performed for all endpoints. The percentage change between baseline and 12 months was computed for lumbar spine aBMD and distal tibia and radius HRpQCT parameters and compared between the treatment groups with an exact Wilcoxon rank sum test. For lumbar spine T-score, the absolute change between baseline and 12 months was computed and compared between the treatment groups with an exact Wilcoxon rank sum test. One-year changes are described by the median and 95% confidence intervals (95% CI) based on quantiles of the binomial distribution. Hodges-Lehmann median differences with 95% CI were calculated to determine the differences between the treatment groups. Statistical analyses were done using IBM SPSS Statistics Version 20. The 95% CI were computed in R, Version 3.1.0.

Results

Characteristics of study subjects

The mean age of the 24 transplant recipients was 53.4 ± 10.9 years; two thirds were male and all were of white ethnicity; the baseline eGFR amounted to 52.5 ± 14.4 ml/min/1.73 m^2. All patients were treated with triple immunosuppression, including a calcineurin antagonist (tacrolimus 92%, cyclosporine 8%), mycophenolate mofetil (100%) and glucocorticosteroids (100%). Of all patients, 10 (42%) had osteopenia and another 3 (13%) had osteoporosis. Table 1 shows the baseline clinical characteristics of the 2 treatment groups. Patients in the denosumab group were older and more often male, with a higher total lumbar spine and total

hip aBMD. The baseline biochemical parameters of bone metabolism were balanced between the treatment groups. Thus patients had similar levels of PTH, 25-hydroxy- and 1,25-dihydroxyvitamin D, and biomarkers of bone formation (P1NP and BSAP) and bone resorption (β-CTx, urine deoxypyridinoline). Patients in the denosumab and control groups received similar amounts of supplementary daily calcium (average dose 929 ± 226 vs 867 ± 309 mg) and vitamin D (average dose 1597 ± 580 vs 1476 ± 1114 IU).

Table 1. Baseline Clinical Characteristics of Subjects

Characteristic	Control group (n = 14)	Denosumab group (n = 10)
Age (years)	49.0 ± 10.9	59.7 ± 7.8
Male sex (no, %)	8 (57%)	8 (80%)
Body mass index (kg/m^2)	24.0 ± 3.3	27.4 ± 2.3
Pre-transplant dialysis mode (no, %)		
Hemodialysis	7 (50%)	7 (70%)
Peritoneal dialysis	5 (36%)	2 (20%)
Pre-emptive transplantation	2 (14%)	1 (10%)
Living donor transplantation (no, %)	8 (57%)	3 (30%)
Repeated transplantation (no, %)	3 (21%)	1 (10%)
eGFR (mL/min/1.73 m^2)	56.3 ± 14.5	47.1 ± 13.2
PTH (ng/L)	135.2 ± 115.4	126.6 ± 40.9
25-hydroxyvitamin D (µg/L)	20.0 ± 9.1	19.3 ± 6.0
1,25-dihydroxyvitamin D (ng/L)	38.5 ± 26.3	24.3 ± 21.3
P1NP (µg/L)	74.8 ± 47.5	76.7 ± 54.3
BSAP (µg/L)	13.3 ± 5.0	10.3 ± 5.0
β-CTx (µg/L)	0.61 ± 0.22	0.58 ± 0.35
Urine deoxypyridinoline/creatinine ratio (nmol/mmol)	6.5 ± 1.2	6.2 ± 1.2
Total lumbar spine aBMD (g/cm^2)	0.933 ± 0.135	1.054 ± 0.137
Total hip aBMD (g/cm^2)	0.841 ± 0.076	0.978 ± 0.068
Osteopenic (no, %)	7 (50%)	3 (30%)
Osteoporotic (no, %)	3 (21%)	0 (0%)

BSAP = bone-specific alkaline phosphatase; β-CTx = C-terminal telopeptide of type I collagen; eGFR = estimated glomerular filtration rate as calculated by the CKD-EPI formula; P1NP = procollagen type 1 N-terminal propeptide. Values are mean ± SD, or no. (%).

Changes in eGFR and biochemical parameters of bone metabolism

Figure 1 depicts the course of the eGFR, and the changes of PTH, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D, as well as P1NP, BSAP, β-CTx and urine deoxypyridinoline to creatinine ratios from baseline to months 12 in the denosumab and control groups. Consistent with the full trial findings, the eGFR remained stable in both groups. PTH (mean ± SD) decreased similarly in both groups from baseline to 12 months (-21 ± 47 vs -42 ± 83 ng/l), although the decrease appeared to be slightly delayed in the denosumab group. 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D (mean ± SD) increased similarly in both groups (10.2 ± 9.6 vs. 13.5 ± 11.7 µg/l; and 29.7 ± 34.5 vs 14.0 ± 29.3 ng/l). The markers of bone formation (P1NP and BSAP) and bone resorption (β-CTx and urine deoxypyridinoline to creatinine ratios) decreased in the denosumab group and tended to increase in the control group.

Changes in areal BMD at total lumbar spine

DXA of the lumbar spine was performed in all study subjects at baseline and after 12 months to determine the changes in aBMD over the one year study period. Total lumbar spine aBMD of patients in the control group (n=14) showed a median percentage decrease of -1.6% (95% CI -4.7% – 0.8%), whereas patients in the denosumab group (n=10) showed a median increase of 2.4% (95% CI 2.2% – 4.3%) ($p < 0.001$ for median difference of 4.7%; 95% CI 2.6% – 7.8%). The corresponding T-score decreased by a median of -0.10 (95% CI -0.30 – 0.10) in the control group and increased by a median of 0.30 (95% CI 0.20 – 0.40) in the denosumab group ($p < 0.001$ for a median T-score difference of 0.45; 95% CI 0.30 – 0.70).

Changes in volumetric BMD and cortical thickness at distal tibia and radius

HRpQCT of the distal tibia and distal radius was performed in all study subjects at

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DOI: 10.1159/000447930
Published online: September 14, 2016

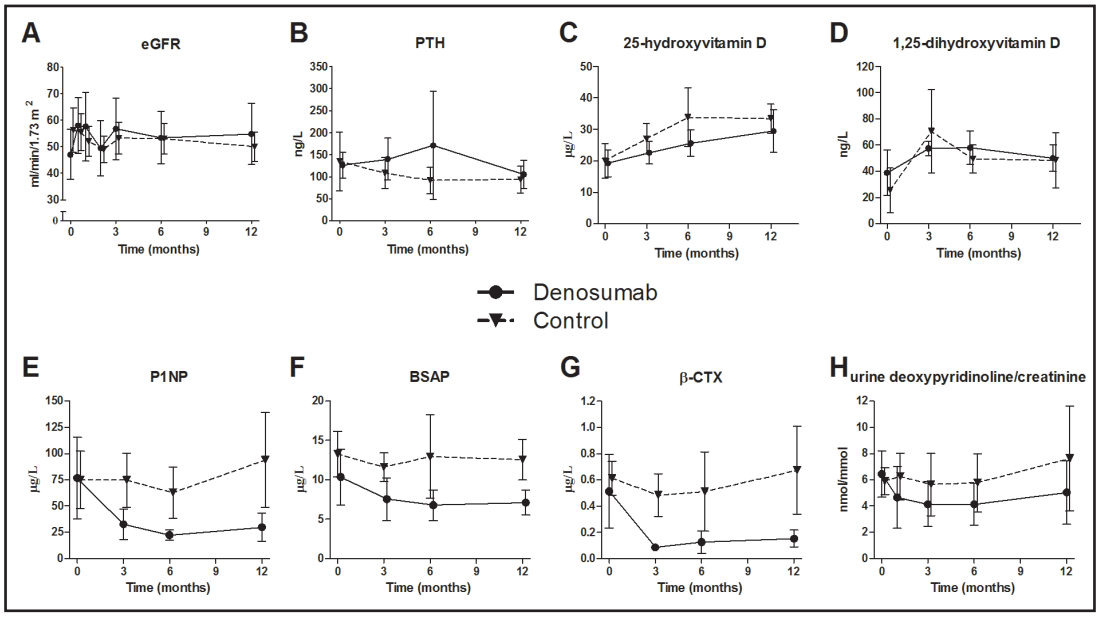

Fig. 1. A) Course of renal transplant function (eGFR, determined via creatinine-based CKD-EPI formula). B-D) Change in parameters of bone metabolism (PTH, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D). E-H) Change in biomarkers of bone turnover (P1NP, BSAP, β-CTx and urine deoxypyridinoline to creatinine ratio). Data are shown as mean and 95% confidence intervals.

Table 2. Baseline Values of HRpQCT Parameters of Study Subjects

Characteristic	Distal Radius		Distal Tibia	
	Control group (n = 14)	Denosumab group (n = 10)	Control group (n = 14)	Denosumab group (n = 10)
Tot.vBMD (mg HA/cm³)	297.6 ± 62.4	306.7 ± 92.5	243.0 ± 49.2	269.9 ± 65.7
Ct.vBMD (mg HA/cm³)	843.2 ± 100.8	837.7 ± 91.7	840.9 ± 56.1	814.3 ± 58.3
Tb.vBMD (mg HA/cm³)	152.5 ± 32.6	174.4 ± 54.7	136.6 ± 22.2	173.1 ± 47.8
Ct.Th (mm)	0.71 ± 0.24	0.78 ± 0.24	0.98 ± 0.26	1.06 ± 0.27
Tb.Th (mm)	0.065 ± 0.013	0.068 ± 0.017	0.065 ± 0.010	0.068 ± 0.019
Tb.Sp (mm)	0.45 ± 0.04	0.41 ± 0.07	0.51 ± 0.06	0.42 ± 0.12
Tb.N (mm⁻¹)	1.97 ± 0.14	2.14 ± 0.27	1.76 ± 0.21	2.14 ± 0.39
Ct.Po (%)	2.30 ± 1.04	4.02 ± 3.12	5.80 ± 1.94	9.15 ± 2.88
Stiffness (kN/mm)	83.3 ± 24.1	97.6 ± 25.9*	191.7 ± 32.8	242.1 ± 43.4
Failure load (kN)	4.22 ± 1.18	4.95 ± 1.18*	9.82 ± 1.69	12.45 ± 2.13

Tot.vBMD = total volumetric bone mineral density; Ct.vBMD = cortical vBMD; Tb.vBMD = trabecular vBMD; Ct.Th = cortical thickness; Tb.Th = trabecular thickness; Tb.Sp = trabecular separation; Tb.N = trabecular number; Ct.Po = cortical porosity.
Values are mean ± SD. *Values for one patient were missing.

baseline and after 12 months. The baseline HRpQCT parameters are shown in Table 2, and the median percentage changes from baseline to 12 months in vBMD and cortical thickness are shown in Figure 2. At the tibia, Tot.vBMD increased in the denosumab group by a median of 2.2% (95% CI 0.7% – 3.2%), whereas it decreased in the control group by 0.3% (-3.3% – 2.7%; p=0.019 for between-group difference). At the radius, Tot.vBMD increased in the denosumab group by 1.3% (-1.9% – 2.2%), whereas it decreased by -1.6% (-5.2% – 0.7%) in the control group (p=0.031). Denosumab significantly increased the Ct.vBMD at the tibia (0.1%; -0.5% – 1.4% vs. -0.5%; -2.0% – 0.1%; p = 0.042), but the difference was not significant at the radius (-0.1%; -1.8% – 1.3% vs. -0.9%; -2.7% – 0.4%; p=0.212). Denosumab did also

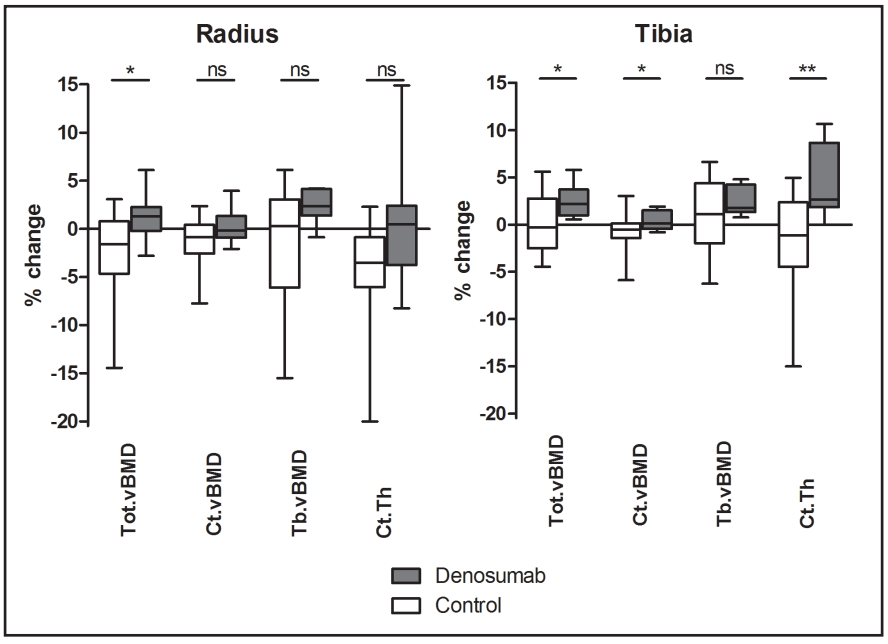

Fig. 2. Percentage change in vBMD and cortical thickness at the distal radius and tibia. Boxes show median and 1st and 3rd quartiles. Whiskers extend to minimum and maximum. * p < 0.05, ** p < 0.01, ns = not significant. Tot.vBMD = total volumetric bone mineral density; Ct.vBMD = cortical vBMD; Tb.vBMD = trabecular vBMD; Ct.Th = cortical thickness.

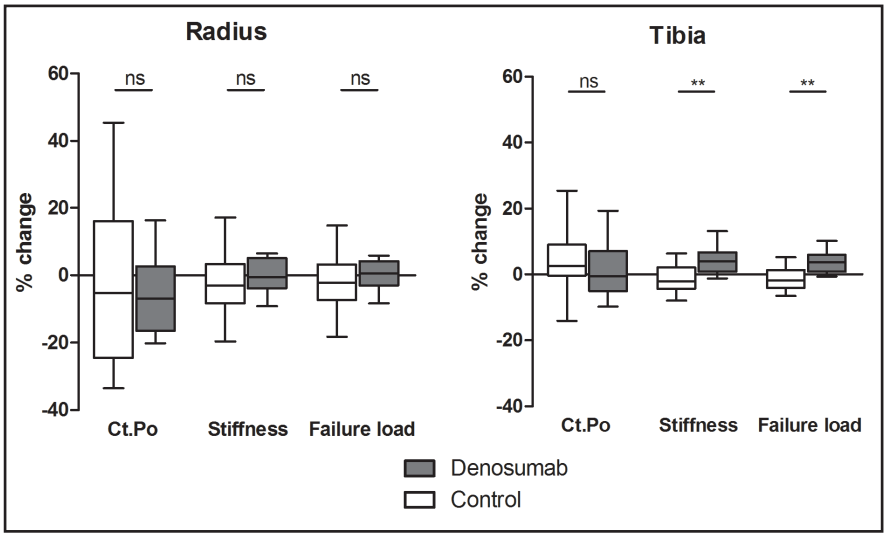

Fig. 3. Percentage change in cortical porosity, estimated stiffness and failure load at the distal radius and distal tibia. Boxes show median and 1st and 3rd quartiles. Whiskers extend to minimum and maximum. ** p < 0.01, ns = not significant. Ct.Po = cortical porosity.

not significantly change Tb.vBMD at the tibia (1.8%; 1.3% – 4.2% vs. 1.1%; -2.5% – 4.1%; p = 0.371) and the radius (2.4%; 1.1% – 4.1% vs. 0.2%; -9.4% – 3.1%; p=0.108). The Ct.Th increased significantly in the denosumab group at the tibia (2.6%; 0.9% – 8.5% vs. -1.1%; -5.9% – 2.2%; p=0.006) and also tended to increase at the radius (0.5%; -6.4% – 1.6% vs. -3.5%; -8.3% – -1.2%; p=0.058).

Changes in cortical microstructure and estimated bone strength

Using extended cortical analysis, changes in Ct.Po were then assessed in the two treatment groups. Furthermore, micro-finite element analysis (μFEA) was performed to assess changes in estimated stiffness and failure load. Data are shown in Figure 3.

At the tibia and the radius the Ct.Po was characterized by a large variability but did not appear to significantly change over the 12 months study period. Thus, in the denosumab vs the control group the median percentage change in Ct.Po amounted to -0.5% (-5.1% – 5.8%) vs. 2.5% (-0.2% – 10.8%) (p=0.371) at the tibia, and to -6.9% (-16.8% – 0.8%) vs.

Table 3. Median Percentage Change in Trabecular Microarchitecture from Baseline to 12 Months

Characteristic	Radius		Tibia	
	Control group (n = 14)	Denosumab group (n = 10)	Control group (n = 14)	Denosumab group (n = 10)
Tb.Th	0.3 (-13.0 – 5.2)	0.4 (-7.9 – 2.4)	-1.6 (-4.6 – 3.9)	-1.6 (-7.0 – 6.2)
Tb.Sp	0.8 (-7.6 – 6.6)	-2.2 (-9.9 – -0.3)	-0.8 (-7.0 – 1.7)	-4.1 (-11.5 – 4.2)
Tb.N	-0.4 (-8.6 – 8.0)	1.6 (0.0 – 10.1)	0.3 (-2.3 – 6.5)	4.1 (-10.6 – 9.3)

Values are median and 95% CI based on quantiles of the binomial distribution. Tb.Th = trabecular thickness; Tb.Sp = trabecular separation; Tb.N = trabecular number.

-5.2% (-23.7% – 28.6%) (p=0.977) at the radius. Likewise, the cortical pore diameter did not significantly change from baseline to 12 months at both sites (data not shown).

At the tibia, μFEA estimates of bone stiffness significantly increased in the denosumab group by a median of 3.9% (-0.8% – 6.6%) but decreased by a median of -2.1% (-3.9% – 2.7%) in the control group (p=0.002). At the radius however, changes in bone stiffness were not significantly different in the denosumab and control groups (-0.6%; -4.1% – 5.3% vs. -3.1%; -8.2% – 4.0%; p=0.369). Hodges-Lehmann estimates for group differences were 5.6% (1.8% – 9.2%; p=0.002) at the tibia and 2.9% (-3.7% – 9.1%; p=0.369) at the radius.

A similar pattern was seen for estimates of failure load which significantly increased at the tibia in the denosumab group by a median of 3.8% (-0.0% – 5.9%) but decreased by a median of -1.7% (-3.6% – 1.7%) in the control group (p=0.002). At the radius, changes in failure load were not significantly different in the denosumab and control groups (0.5%; -3.8% – 4.3% vs. -2.2%; -6.7% – 4.3%; p=0.336). Hodges-Lehmann estimates for group differences were 5.1% (2.1% – 8.1%; p=0.002) at the tibia and 2.4% (-3.2% – 8.5%; p=0.336) at the radius.

Changes in trabecular architecture

Changes in Tb.Th, Tb.Sp, Tb.N at tibia and radius did not significantly differ between the treatment groups (Table 3).

Discussion

In this bone microarchitecture ancillary study of the POSTOP trial, we show among 24 patients assessed with the additional measures of bone microarchitecture and estimated bone strength that denosumab had significant benefits on tibial bone microarchitecture and bone strength. A similar pattern – albeit to a lesser extent and not significant – was documented at the distal radius. In parallel with the increase of aBMD at the lumbar spine and a decrease of classical markers of bone turnover, denosumab significantly increased vBMD at the tibia and radius, and improved Ct.Th, stiffness and failure load at the tibia. Denosumab did not appear to change trabecular BMD and structure at both sites. Taken together and consistent with the full trial findings, denosumab appeared to have significant beneficial effects on bone health in *de novo* recipients of a renal transplant.

HRpQCT examination represents a valuable tool to examine various parameters of bone mineralization and structure at a three-dimensional level [18-20]. Due to the high resolution of the technique it is possible to obtain volumetric measurements of bone density (reflecting in large part the mineralization of the bone) at various skeletal sites and compartments (cortical vs trabecular). Furthermore, differential structural information on cortical and trabecular bone can be obtained. Using complex computer analyses (extended cortical analysis and so-called micro-finite element analysis; μFEA) it is furthermore possible to study changes in cortical porosity and biomechanical properties of the bone, including stiffness and failure load [20].

HRpQCT analyses have previously been performed in patients with chronic renal failure, including patients on hemo- and peritoneal dialysis [21-24]. These cross-sectional studies

provided useful baseline data for various HRpQCT parameters in patients with increasing levels of renal failure. KTR have also been examined by HRpQCT, and longitudinal analyses over the first 12 months after transplantation demonstrated that these patients have a decline of the radial and tibial cortical area, density and thickness, and an increase in cortical porosity, stiffness and failure load [25, 26]. At variance with these studies the more subtle changes which we documented in our control group transplant recipients may be explained by the consistent supplementation with vitamin D and calcium in our patients.

In different patient populations (mostly postmenopausal women) HRpQCT has been used to study the effect of several drugs on bone, including bisphosphonates, teriparatide and denosumab [27-29]. Our study is the first of its kind to use HRpQCT to examine the therapeutic effect of a drug in KTR, demonstrating beneficial effects of denosumab beyond those already shown by standard DXA in this patient population [11]. Our results are in large agreement with the results of the DATA-HRpQCT study, which also found stronger effects on bone mineralization and strength for denosumab in the tibia compared with the radius, and a lack of an effect on cortical porosity [29].

Conclusion

We conclude that denosumab had important short-term beneficial effects on bone mineralization, structure, microarchitecture and strength in first-year KTR. Whether these favorable changes will translate into long-term benefits such as a reduced incidence of fractures remains to be determined in adequately designed and powered clinical trials.

Disclosure Statement

All authors declare that they have no conflicts of interest. There was no commercial funding for this study.

Acknowledgments

We thank the study patients for their participation. This work was supported by the University Hospital Zürich and the University Zürich.

References

1 Cunningham J: Posttransplantation bone disease. Transplantation 2005;79:629-634.
2 Vautour LM, Melton LJ, 3rd, Clarke BL, Achenbach SJ, Oberg AL, McCarthy JT: Long-term fracture risk following renal transplantation: a population-based study. Osteoporos Int 2004;15:160-167.
3 Nikkel LE, Hollenbeak CS, Fox EJ, Uemura T, Ghahramani N: Risk of fractures after renal transplantation in the United States. Transplantation 2009;87:1846-1851.
4 Naylor KL, Li AH, Lam NN, Hodsman AB, Jamal SA, Garg AX: Fracture risk in kidney transplant recipients: a systematic review. Transplantation 2013;95:1461-1470.
5 Bouquegneau A, Salam S, Delanaye P, Eastell R, Khwaja A: Bone disease after kidney transplantation. Clin J Am Soc Nephrol 2016;11:1282-1296.
6 Molnar MZ, Naser MS, Rhee CM, Kalantar-Zadeh K, Bunnapradist S: Bone and mineral disorders after kidney transplantation: therapeutic strategies. Transplant Rev 2014;28:56-62.
7 Nikkel LE, Mohan S, Zhang A, McMahon DJ, Boutroy S, Dube G, Tanriover B, Cohen D, Ratner L, Hollenbeak CS, Leonard MB, Shane E, Nickolas TL: Reduced fracture risk with early corticosteroid withdrawal after kidney transplant. Am J Transplant 2012;12:649-659.
8 Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group: KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and

Bone Disorder (CKD-MBD). Kidney Int Suppl 2009;113:S1-130.
9 Palmer SC, McGregor DO, Strippoli GF: Interventions for preventing bone disease in kidney transplant recipients. Cochrane Database Syst Rev 2007;18:Cd005015.
10 Stein EM, Ortiz D, Jin Z, McMahon DJ, Shane E: Prevention of fractures after solid organ transplantation: a meta-analysis. J Clin Endocrinol Metab 2011;96:3457-3465.
11 Bonani M, Frey D, Brockmann J, Fehr T, Mueller TF, Saleh L, von Eckardstein A, Graf N, Wüthrich RP: Effect of twice-yearly denosumab on prevention of bone mineral density loss in de novo kidney transplant recipients: a randomized controlled trial. Am J Transplant 2016;16:1882-1891.
12 Pialat JB, Burghardt AJ, Sode M, Link TM, Majumdar S: Visual grading of motion induced image degradation in high resolution peripheral computed tomography: impact of image quality on measures of bone density and micro-architecture. Bone 2012;50:111-118.
13 Laib A, Hauselmann HJ, Ruegsegger P: In vivo high resolution 3D-QCT of the human forearm. Technol Health Care 1998;6:329-337.
14 Laib A, Ruegsegger P: Comparison of structure extraction methods for in vivo trabecular bone measurements. Comput Med Imaging Graph 1999;23:69-74.
15 Hildebrand T, Laib A, Muller R, Dequeker J, Ruegsegger P: Direct three-dimensional morphometric analysis of human cancellous bone: microstructural data from spine, femur, iliac crest, and calcaneus. J Bone Miner Res 1999;14:1167-1174.
16 Burghardt AJ, Buie HR, Laib A, Majumdar S, Boyd SK: Reproducibility of direct quantitative measures of cortical bone microarchitecture of the distal radius and tibia by HR-pQCT. Bone 2010;47:519-528.
17 Pistoia W, van Rietbergen B, Lochmuller EM, Lill CA, Eckstein F, Ruegsegger P: Estimation of distal radius failure load with micro-finite element analysis models based on three-dimensional peripheral quantitative computed tomography images. Bone 2002;30:842-848.
18 Nishiyama KK, Shane E: Clinical imaging of bone microarchitecture with HR-pQCT. Curr Osteoporos Rep 2013;11:147-155.
19 Jamal SA, Nickolas TL: Bone imaging and fracture risk assessment in kidney disease. Curr Osteoporos Rep 2015;13:166-172.
20 Geusens P, Chapurlat R, Schett G, Ghasem-Zadeh A, Seeman E, de Jong J, van den Bergh J: High-resolution in vivo imaging of bone and joints: a window to microarchitecture. Nat Rev Rheumatol 2014;10:304-313.
21 Bacchetta J, Boutroy S, Vilayphiou N, Juillard L, Guebre-Egziabher F, Rognant N, Sornay-Rendu E, Szulc P, Laville M, Delmas PD, Fouque D, Chapurlat R: Early impairment of trabecular microarchitecture assessed with HR-pQCT in patients with stage II-IV chronic kidney disease. J Bone Miner Res 2010;25:849-857.
22 Jamal S, Cheung AM, West S, Lok C: Bone mineral density by DXA and HR pQCT can discriminate fracture status in men and women with stages 3 to 5 chronic kidney disease. Osteoporos Int 2012;23:2805-2813.
23 Pelletier S, Vilayphiou N, Boutroy S, Bacchetta J, Sornay-Rendu E, Szulc P, Arkouche W, Guebre-Egziabher F, Fouque D, Chapurlat R: Bone microarchitecture is more severely affected in patients on hemodialysis than in those receiving peritoneal dialysis. Kidney Int 2012;82:581-588.
24 Trombetti A, Stoermann C, Chevalley T, Van Rietbergen B, Herrmann FR, Martin PY, Rizzoli R: Alterations of bone microstructure and strength in end-stage renal failure. Osteoporos Int 2013;24:1721-1732.
25 Nishiyama KK, Pauchard Y, Nikkel LE, Iyer S, Zhang C, McMahon DJ, Cohen D, Boyd SK, Shane E, Nickolas TL: Longitudinal HR-pQCT and image registration detects endocortical bone loss in kidney transplantation patients. J Bone Miner Res 2015;30:554-561.
26 Iyer SP, Nikkel LE, Nishiyama KK, Dworakowski E, Cremers S, Zhang C, McMahon DJ, Boutroy S, Liu XS, Ratner LE, Cohen DJ, Guo XE, Shane E, Nickolas TL: Kidney transplantation with early corticosteroid withdrawal: paradoxical effects at the central and peripheral skeleton. J Am Soc Nephrol 2014;25:1331-1341.
27 Seeman E, Delmas PD, Hanley DA, Sellmeyer D, Cheung AM, Shane E, Kearns A, Thomas T, Boyd SK, Boutroy S, Bogado C, Majumdar S, Fan M, Libanati C, Zanchetta J: Microarchitectural deterioration of cortical and trabecular bone: differing effects of denosumab and alendronate. J Bone Miner Res 2010;25:1886-1894.
28 Zebaze RM, Libanati C, Austin M, Ghasem-Zadeh A, Hanley DA, Zanchetta JR, Thomas T, Boutroy S, Bogado CE, Bilezikian JP, Seeman E: Differing effects of denosumab and alendronate on cortical and trabecular bone. Bone 2014;59:173-179.
29 Tsai JN, Uihlein AV, Burnett-Bowie SA, Neer RM, Zhu Y, Derrico N, Lee H, Bouxsein ML, Leder BZ: Comparative effects of teriparatide, denosumab, and combination therapy on peripheral compartmental bone density, microarchitecture, and estimated strength: the DATA-HRpQCT Study. J Bone Miner Res 2015;30:39-45.