Associations of Changes in Bone Turnover Markers with Change in Bone Mineral Density in Kidney Transplant Patients

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Abstract

Background Bone loss after kidney transplantation is highly variable. We investigated whether changes in bone turnover markers associate with bone loss during the first post-transplant year.

Methods Bone mineral density (BMD) was measured at 0 and 12 months, with biointact parathyroid hormone, bone-specific alkaline phosphatase (BALP), intact procollagen type I *N*-terminal propeptide (PINP), and tartrate-resistant acid phosphatase isoform 5b (TRAP5b) measured at 0, 3, and 12 months post-transplant ($N=209$). Paired transiliac bone biopsies were available in a subset ($n=49$). Between-group differences were evaluated by Student's t test, Wilcoxon signed-rank test, or Pearson's chi-squared test.

Results Changes in BMD varied from –22% to +17%/yr. Compared with patients with no change (±2.5%/yr), patients who gained BMD had higher levels of parathyroid hormone (236 versus 136 pg/ml), BALP (31.7 versus 18.8 μg/L), and Intact PINP (121.9 versus 70.4 μg/L) at time of transplantation; a greater decrease in BALP (−40% versus −21%) and Intact PINP (−43% versus −13%) by 3 months; and lower levels of Intact PINP (36.3 versus 60.0 μg/L) at 12 months post-transplant. Patients who lost BMD had a less marked decrease, or even increase, in Intact PINP (+22% versus −13%) and TRAP5b (−27% versus −43%) at 3 months and higher Intact PINP (83.7 versus 60.0 μg/L) and TRAP5b (3.89 versus 3.16 U/L) at 12 months compared with patients with no change. If none of the biomarkers decreased by the least significant change at 3 months, an almost two-fold (69% versus 36%) higher occurrence of bone loss was seen at 12 months post-transplant.

Conclusions Bone loss after kidney transplantation was highly variable. Resolution of high bone turnover, as reflected by decreasing bone turnover markers, associated with BMD gain, while increasing bone turnover markers associated with bone loss.

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Introduction

Fracture risk is higher in kidney transplant recipients,[1] particularly in the early post-transplant period.[2] Traditionally, substantial bone loss was expected after kidney transplantation,[3] but with the current steroid-sparing immunosuppressive protocols, the effect on the central skeleton seems overall neutral, with bone loss mainly at distal skeletal sites.[4] However, there is large interindividual variability in bone mineral density (BMD) changes post-transplant, with subsets of patients exhibiting BMD loss, stability, or even gain during the first post-transplant year.[4,5]

Ongoing disturbances of mineral metabolism and consequent effects on skeletal remodeling contribute to bone loss after kidney transplantation. Ongoing hyperparathyroidism post-transplant associate with deterioration of cortical bone by high-resolution imaging,[6] which could explain the significant BMD loss[4] and higher fracture risk[2] seen at the distal skeleton. Conversely, greater decreases in parathyroid hormone (PTH) levels associate with BMD gain during the first post-transplant year.[7] The normalization of skeletal remodeling brought on by the resolution of hyperparathyroidism is reflected by a reduction in circulating bone turnover markers.[4,8,9] These biomarkers are passively released from the bone during the process of skeletal remodeling and can be used as a noninvasive measure of overall skeletal bone turnover.[10]

In the realm of osteoporosis, bone turnover markers are used to assess treatment response and expected treatment benefits.[11,12] In a post-transplant setting, greater decreases in bone turnover markers associate with BMD gain,[4] but it is unknown whether changes in these biomarkers early in the post-transplant course may be able to predict later changes in BMD. This information could enable identification of patients at high risk of bone loss, who could benefit the most from early intervention.

To address this question, this study aimed to investigate how changes in bone turnover markers in the early post-transplant period would relate to later changes in BMD in contemporary kidney transplant recipients.

Methods

Cohort

This observational cohort study included adult kidney transplant recipients participating in prospective, ongoing cohort studies investigating skeletal health after kidney transplantation at the University Hospitals Leuven (NCT00547040 and NCT01886950). Patients were recruited between October 2006 and September 2016. Relevant demographic data, comorbidities, medical therapy, and routine biochemistry were extracted from electronic patient files. The cohort was restricted to patients with bone densitometry at time of transplantation and at 12 months post-transplant, who also had study visits with blood sampling at time of transplantation and 3 and 12 months post-transplant. Of 1343 patients prospectively enrolled at time of kidney transplantation, 333 patients had bone densitometry performed, and 235 of these had study visits at 3 and 12 months with blood samples available (Supplemental Figure 1). The only exclusion criterion was treatment with antiresorptive therapy at any time point during the first post-transplant year (n=26). Demographic data and markers of mineral metabolism were comparable between the selected patients and the overall cohort (Supplemental Table 1).

The study was approved by the local Research Ethical Committee (study IDs S52091 and S50111), and all patients provided written, informed consent for study participation. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

Immunosuppression

Patients received a standard immunosuppressive regimen consisting of a calcineurin inhibitor, an antimetabolite (mycophenolate mofetil), and glucocorticoids (methylprednisolone). Glucocorticoids were discontinued at the discretion of the treating physician, on the basis of immunological risk profile and the results of a protocoled kidney graft biopsy at 3 months post-transplant.

Biochemical Analyses

Nonfasting blood samples were collected at time of admission for kidney transplantation and at study visits 3 and 12 months post-transplant. Samples were kept for <2 hours at 5°C before being centrifuged at 3000 rpm for 10 minutes and then aliquoted and processed or stored at −80°C until later analyses. Plasma albumin, hemoglobin, creatinine, total calcium, phosphate, total bicarbonate, and total alkaline phosphatase were measured consecutively using standard laboratory techniques. Total alkaline phosphatase assays changed during the study period. Details of the

Table 1. Biochemistry and bone densitometry by time point in kidney transplant recipients

Variables	Missing	At Transplant (n=209)	At Month 3 (n=209)	At Month 12 (n=209)
Medications				
Calcium-containing phosphate binder or supplement	0	138 (66)	85 (41)	78 (37)
Non-calcium–containing phosphate binder	0	93 (45)	1 (0.5)	0 (0)
Vitamin D supplement	0	90 (43)	43 (21)	72 (34)
Active vitamin D	0	93 (45)	48 (23)	51 (24)
Calcimimetic	0	13 (6)	0 (0)	1 (0.5)
Biochemistry				
eGFR (CKD-EPI), ml/min per 1.73 m^2	7	NA	47±17	53±18
Hemoglobin g/dl	8	12.1±1.5	11.4±1.6	12.7±1.7
Albumin g/dl	45	4.4±0.4	4.4±0.4	4.4±0.4
CRP, mg/L	23	2.5 (1.1–5.7)	1.0 (0.8–2.7)	1.1 (0.6–2.9)
Bicarbonate, mmol/L	8	25±3	22±2	23±3
Total alkaline phosphatase, U/L	20	89 (70–121)	73 (56–96)	76 (56–98)
Biointact PTH, pg/ml	17	141 (81–254)	46 (26–75)	43 (27–78)
Phosphate, mg/dl	11	4.7±1.5	2.7±0.6	3.1±0.6
Total calcium, mg/dl	11	9.3±0.8	9.6±0.7	9.6±0.6
Magnesium, mg/dl	164	2.3±0.4	1.6±0.3	1.7±0.2
25-hydroxy vitamin D, ng/mL	35	38±17	30±13	35±16
BALP, μg/L	7	20.9 (14.9–31.5)	17.0 (11.2–25.1)	17.4 (11.5–25.8)
Intact PINP, μg/L	7	79.6 (51.7–130.6)	78.2 (47.7–120.0)	64.3 (32.0–107.6)
TRAP5b, U/L	7	5.11 (3.77–7.06)	3.14 (2.27–4.13)	3.27 (2.38–4.83)
Densitometry				
LS T-score	0	−1.2±1.5	N/A	−1.3±1.4
Total hip T-score	11	−1.1±1.1	N/A	−1.2±1.1
Femoral neck T-score	11	−1.6±1.0	N/A	−1.7±1.0
1/3 distal radius T-score	118	−1.3±1.5	N/A	−1.5±1.7
Ultradistal radius T-score	118	−1.9±1.3	N/A	−2.2±1.3

Data are mean±SD, median (interquartile range), or n (%). BALP, bone-specific alkaline phosphatase; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; LS, lumbar spine; NA, not available; N/A, not applicable; PINP, procollagen type I N-terminal propeptide; PTH, parathyroid hormone (1–84); TRAP5b, tartrate-resistant acid phosphatase isoform 5b.

conversions used are given in Supplemental Methods. GFR was estimated by the Chronic Kidney Disease Epidemiology Collaboration equation.[13] Biointact (1–84) PTH was measured by immunoradiometric assay (reference interval 3–40 ρg/ml).[14] 25-hydroxy vitamin D was measured by radioimmunoassay. Bone turnover markers were analyzed in batch after completion of the observational data collection. Bone-specific alkaline phosphatase (BALP), trimeric procollagen type I *N*-terminal propeptide (Intact PINP), and tartrate-resistant acid phosphatase isoform 5b (TRAP5b) were measured using the IDS-iSYS instrument (ImmunoDiagnosticSystems, Boldon, United Kingdom). Values above the assay upper limit of quantification (BALP: 75 μg/L, Intact PINP: 230 μg/L, TRAP5b: 14 U/L) were determined after sample dilution. The assay-specific reference values are given in Supplemental Methods.

Bone Densitometry

Bone densitometry was performed at the lumbar spine, proximal femur, and distal forearm by dual-energy x-ray absorptiometry (DXA) scan (QDR-4500A or Discovery; Hologic, Marlborough, MA) at time of transplantation and 1 year post-transplant (within ±1 month). The Hologic Spine Phantom was scanned regularly to monitor scanner performance and stability. A single, certified operator, blinded to study details, analyzed all DXA scans. Coefficients of variation for repeat patient scans were 0.58% at lumbar spine, 0.56% at total hip, 1.40% at femoral neck, 0.98% at the 1/3 distal radius, and 1.10% at the ultradistal radius.

Bone Histomorphometry

Transiliac bone biopsies were available for a subset of patients (n=49). A detailed report on these patients has been published previously.[9] In brief, these samples were retrieved using a trephine with an internal diameter of 3.55 mm (Biopsybell 8G, Mirandola, Italy). Bone cores were fixed in 70% ethanol and embedded in a methylmethacrylate resin. Five-μm undecalcified sections were stained by the Goldner method, and an image analysis software (AxioVision version 4.51, Zeiss Microscopy, Zeiss, Germany) running a customized program was used to determine static parameters. An experienced bone pathologist semiquantitatively assessed bone turnover (low, normal, high) and mineralization (normal, abnormal). All bone histomorphometric parameters are given in 2D using standardized nomenclature.[15]

Statistical Analyses

Continuous variables are given as mean with SD (±SD) if normally distributed or median with interquartile range if skewed. Missing data were not imputed, and patients with missing data did not contribute to statistical analyses for the parameter in question. Dichotomous and categorical variables are given as number and proportion (%). Between-group differences were evaluated by Student's t test, Wilcoxon signed-rank test, or Pearson's chi-squared test, respectively. We divided patients by whether they achieved a decrease in bone turnover marker levels greater than the least significant change of the biomarker at 3 months post-transplant. In stable hemodialysis patients, these are

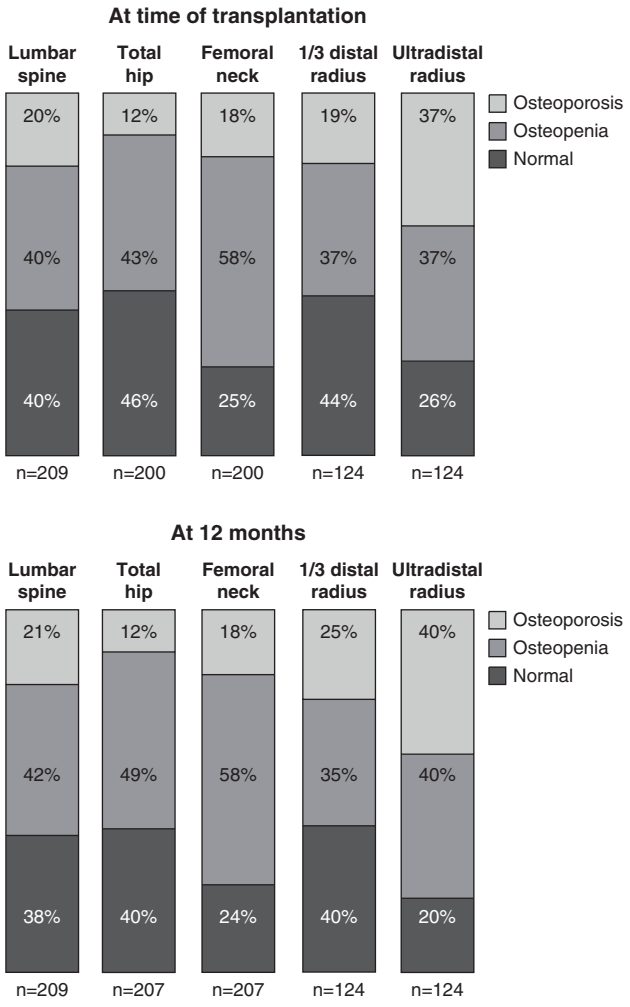

Figure 1. Prevalence of osteoporosis, defined as a DXA *T*-score <−2.5 at time of transplantation and at 12 months post-transplant. DXA, dual-energy x-ray absorptiometry.

reported to be 23% for BALP, 32% for Intact PINP, and 24% for TRAP5b.[16] A change in DXA BMD >2.5% per year was considered a clinically relevant change.[17] Multivariable logistic regression including potential confounders (age, sex, body mass index, eGFR at 12 months, cumulative steroid dose at 12 months, and levels of PTH at time of transplantation) was used to investigate whether changes in bone turnover markers were independently associated with later changes in BMD. All statistical analyses were performed using the statistical software solution STATA IC version 16.1 (StataCorp LP, College Station, TX).

Results

A total of 209 patients were included. Mean age was 53±12 years, 65% were men, and 15% had diabetes at time of transplantation. Cause of CKD was glomerulonephritis or vasculitis (25%), congenital disease (4%) or adult polycystic kidney disease (20%), chronic interstitial nephropathy (11%), diabetes mellitus type 1 or 2 (9%), hypertension or atherosclerosis (5%), other (4%), or unknown (21%). At time of transplantation, 144 (69%)

patients had been treated with long-term intermittent hemodialysis for 32 (19–52) months, and 55 (26%) had been treated with ambulatory peritoneal dialysis for 32 (20–45) months. The remaining ten patients (5%) were transplanted preemptively. A parathyroidectomy had been performed in 27 patients before transplantation.

Immunosuppression was maintained by a calcineurin inhibitor, with most patients receiving tacrolimus (85%), in combination with mycophenolate mofetil and prednisone. Steroids were discontinued in 26% of patients between months 3 and 12. The median cumulative steroid dose, including any treatment given for acute rejection, was 1.40 (1.22–1.71) g at 3 months and 2.37 (1.86–2.75) g at 12 months. Six patients underwent a subtotal parathyroidectomy in the first post-transplant year, all between months 3 and 12 (median, 172 days; range, 112–314). Five patients suffered a fragility fracture in the first post-transplant year; two of these were vertebral fractures, and three were foot or ankle fractures.

Changes in Bone Turnover Markers

Post-transplant biochemical measurements are shown in Table 1. Overall, median values of the bone turnover markers decreased by 3 months post-transplant. From 3 to 12 months, BALP levels remained stable, Intact PINP decreased further, while TRAP5b increased slightly. Bio-intact PTH and total alkaline phosphatase levels decreased by 3 months, with no further changes from 3 to 12 months.

Changes in BMD

At time of transplantation, the prevalence of osteoporosis (T-score ≤–2.5) was 18%–37% at different skeletal sites (Figure 1). A T-score ≤–2.5 at either spine or hip was seen in 30% of patients. Changes in BMD during the first post-transplant year ranged from –22% to +17% (Figure 2). A significant decrease in BMD was detected at the lumbar spine (–0.8%, [95% confidence interval, –1.5 to –0.04], $P = 0.04$), total hip (–1.2%, [–1.9 to –0.4], $P = 0.003$), femoral neck (–1.3%, [–2.0 to –0.5], $P = 0.001$), and ultradistal radius (–2.6%, [–3.6 to –1.6], $P < 0.001$), but not at the 1/3 distal radius (–0.5%, [–1.1 to 0.1], $P = 0.11$). A BMD decrease of 2.5% or more from baseline was seen in 37% of patients at the lumbar spine, 39% at the total hip, 37% at the femoral neck, 23% at 1/3 the distal radius, and 53% at the ultradistal radius.

There was a direct correlation between eGFR at 12 months and BMD change at the total hip (Spearman's *rho* 0.16, $P = 0.03$) and femoral neck (*rho* 0.20, $P = 0.004$), but not at the lumbar spine (*rho* 0.08, $P = 0.27$), indicating higher prevalence of bone loss in patients with suboptimal kidney graft function. There was a negative correlation between cumulative dose of steroids at 12 months and BMD change at the lumbar spine (*rho* –0.15, $P = 0.03$) and total hip (*rho* –0.19, $P = 0.009$), but not at the femoral neck (*rho* –0.09, $P = 0.22$), indicating a higher prevalence of bone loss with steroid exposure.

Relationship between Changes in Biomarkers and Bone Density

Figure 3 shows trajectories of PTH and bone turnover markers in patients who lost, remained stable, or gained BMD at the lumbar spine during the first post-transplant year, using a cutoff of 2.5%. Patients who gained BMD had higher levels of PTH and bone turnover markers at time of transplantation and a greater decrease in PTH and biomarkers by 3 months compared with patients with a stable BMD. For patients who lost BMD, bone turnover markers decreased less markedly, or even increased slightly at 3 months, while at 12 months, all three biomarkers were significantly higher compared with patients who were stable. Other markers of mineral metabolism did not differ according to BMD change (Table 2). The results were similar when considering BMD changes at

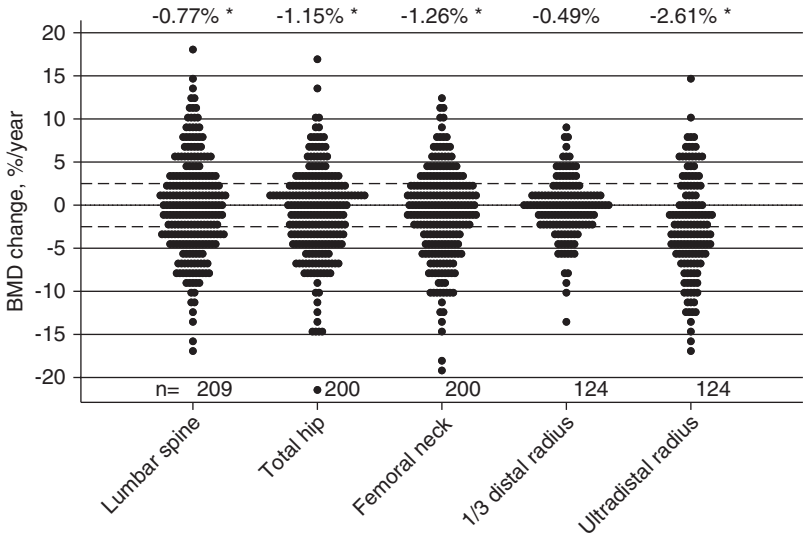

Figure 2. Changes in BMD from time of transplantation to 12 months post-transplant; number of patients and mean change in percentage from baseline given for each skeletal site. *$P < 0.05$. BMD, bone mineral density.

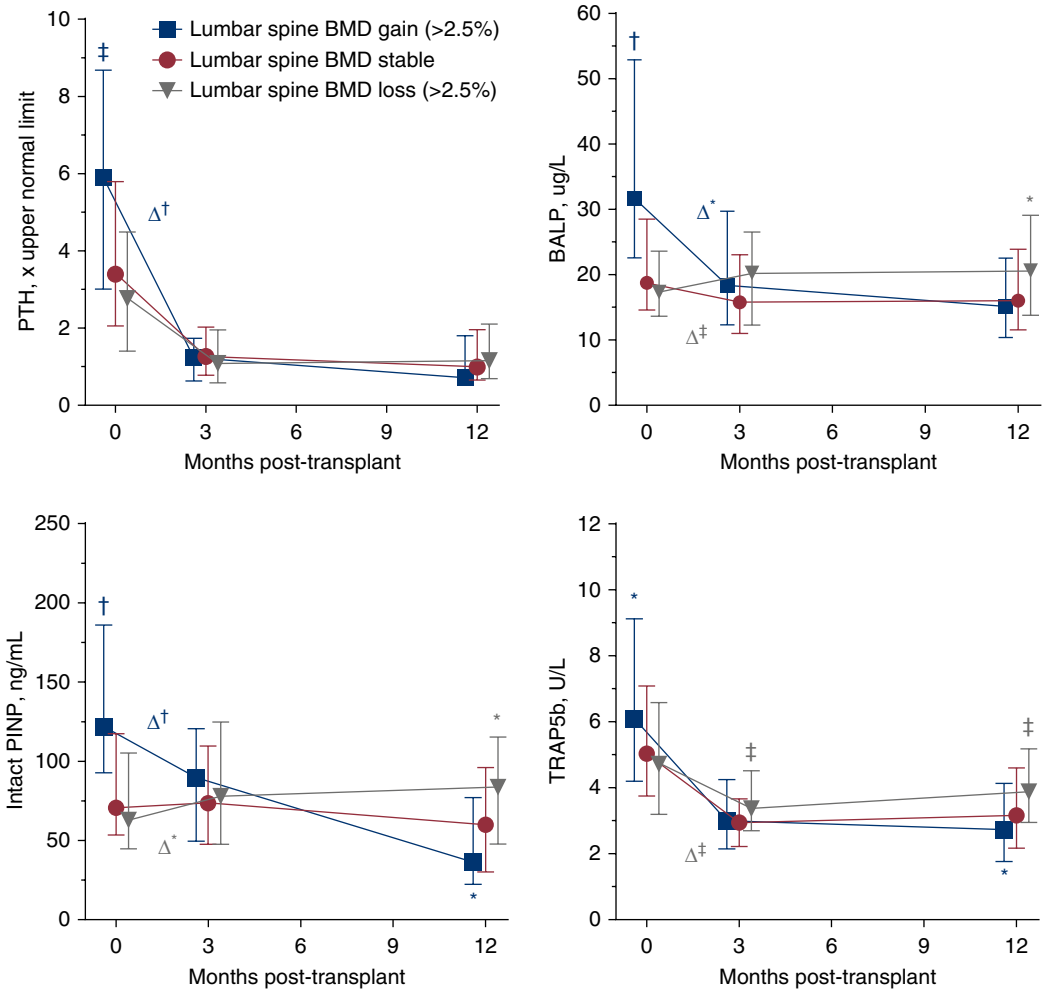

Figure 3. Trajectories of PTH in times upper normal limit and bone turnover markers in patients who lost, remained stable, or gained BMD at the lumbar spine in the first post-transplant year. Medians with IQR, $*P < 0.05$, $‡P < 0.01$, and $†P < 0.001$ compared with stable group. BALP, bone-specific alkaline phosphatase; IQR, interquartile range; PINP, procollagen type I *N*-terminal propeptide; PTH, parathyroid hormone; TRAP5b, tartrate-resistant acid phosphatase isoform 5b.

the proximal femur (Supplemental Figure 2). Trajectories of total alkaline phosphatase showed a pattern similar to, but less pronounced than, the bone turnover markers (Supplemental Figure 3).

Association between Early Change in Biomarkers and Later Bone Loss

To investigate the relationship between early changes in bone turnover markers and later bone loss, we dichotomized patients according to the decline in biomarkers at month 3 in descenders, showing a decline greater than the least significant change for the biomarker, and nondescenders, showing a decline less than the least significant change or even an increase. The occurrence of BMD loss was approximately twofold higher in nondescenders compared with descenders (Figure 4 and Supplemental Table 2). If *none* of the biomarkers decreased at 3 months (n=55), 69% of patients experienced bone loss at either spine or hip, while if all biomarkers decreased (n=53), this was true for 36% of patients (Pearson's chi-square P = 0.001).

A decrease in bone turnover markers greater than the least significant change at 3 months remained independently associated with a higher prevalence of bone loss at 12 months after adjusting for age, sex, kidney function, cumulative steroid dose, and PTH levels at time of transplantation (Table 3).

Bone Biopsy Findings

Paired transiliac bone biopsies at time of and 12 months after kidney transplantation were available for 49 patients. At time of transplantation, static parameters indicated a higher skeletal remodeling rate in patients who later gained BMD, while at 12 months post-transplant, these differences were no longer apparent. Patients who gained BMD exhibited greater amounts of osteoid at time of transplantation, with significant decreases in these parameters at 12 months post-transplant (Table 4).

Sensitivity Analyses

Similar results were found in sensitivity analyses excluding patients with lumbar spine osteoporosis at time of

Table 2. Demographic and biomarkers in kidney transplant recipients by lumbar spine bone mineral density change at 12 months post-transplant

Variables	Missing	BMD Loss (*n*=78)	BMD Stable (*n*=78)	BMD Gain (*n*=53)
Age, yr	0	53±13	54±11	54±11
Sex, male	0	44 (56)	53 (68)	38 (72)
Body mass index, kg/m^2	3	25±5	25±4	26±5
Diabetes mellitus, any type	0	10 (13)	13 (17)	9 (17)
Dialysis vintage, mo	0	32 (24–50)	29 (15–42)	37 (20–54)
eGFR, 3 mo, ml/min per 1.73 m^2	0	47±17	46±16	50±16
eGFR, 12 mo, ml/min per 1.73 m^2	5	53±18	52±20	56±14
Cumulative steroids 3 mo, g	1	1.41 (1.27–1.72)	1.36 (1.21–1.72)	1.43 (1.17–1.70)
Cumulative steroids 12 mo, g	1	2.48 (2.05–2.81)[a]	2.23 (1.80–2.52)	2.34 (1.86–2.75)
Bone densitometry				
LS BMD	0	1.023±0.169	0.962±0.146	0.886±0.169
LS *T*-score	0	−0.7±1.5	−1.3±1.3	−2.0±1.5
Total hip BMD	9	0.858±0.153	0.849±0.133	0.810±0.163
Total hip *T*-score	9	−1.0±1.1	−1.1±0.9	−1.4±1.2
Femoral neck BMD	9	0.708±0.135	0.704±0.112	0.663±0.137
Femoral neck *T*-score	9	−1.5±1.1	−1.6±0.9	−1.9±1.1
Phosphate, mg/dl				
At transplantation	2	4.8±1.4	4.6±1.7	4.6±1.4
At 3 mo	6	2.6±0.7	2.7±0.6	2.8±0.6
At 12 mo	5	3.1±0.7	3.0±0.6	3.1±0.6
% change at 3 mo	6	−38±31	−31±31	−30±39
% change at 12 mo	6	−30±30	−27±29	−25±34
Total calcium, mg/dl				
At transplantation	2	9.4±0.7	9.2±0.8	9.2±0.8
At 3 mo	6	9.7±0.7	9.6±0.6	9.6±0.7
At 12 mo	5	9.7±0.7	9.6±0.5	9.5±0.5
% change at 3 mo	6	2.9±8.4	5±9	6±11
% change at 12 mo	6	2.8±8.6	5±11	5±11
25-hydroxy vitamin D, ng/ml				
At transplantation	1	37±16	39±17	38±17
At 12 mo	14	38±17	34±16	34±14
Biointact PTH, pg/ml				
At transplantation	2	112 (57–183)	136 (82–235)	236 (115–348)[a]
At 3 mo	6	41 (22–76)	48 (31–79)	50 (25–70)
At 12 mo	11	47 (27–83)	39 (26–78)	39 (29–72)
% change at 3 mo	6	−56 (−75 to −20)	−64 (−75 to −47)	−79 (−87 to −59)[b]
% change at 12 mo	13	−59 (−75 to 1.3)[c]	−68 (−82 to −45)	−83 (−90 to −62)[a]
Total alkaline phosphatase, U/L				
At transplantation	12	82 (67–107)	90 (67–116)	108 (82–139)
At 3 mo	13	72 (52–94)	71 (55–92)	77 (60–103)
At 12 mo	18	82 (61–108)	76 (58–96)	63 (54–90)
% change at 3 mo	13	−16 (−30 to 5)	−20 (−33 to 3)	−31 (−44 to −5)
% change at 12 mo	18	−7 (−25 to 20)	−17 (−34 to 11)	−33 (−53 to −24)
BALP, μg/L				
At transplantation	0	17.4 (13.6–23.8)	18.8 (14.6–28.6)	31.7 (22.0–54.2)[a]
At 3 mo	0	20.2 (12.3–26.6)	15.8 (11.0–23.1)	18.9 (12.1–31.7)
At 12 mo	7	20.6 (13.8–29.2)	16.0 (11.6–23.9)	15.2 (10.4–22.5)
% change at 3 mo	0	−8 (−32 to 36)	−21 (−48 to 7)	−40 (−65 to −6)[c]
% change at 12 mo	7	−1 (−26 to 68)	−20 (−45 to 28)	−55 (−72 to −31)[b]
Intact PINP, μg/L				
At transplantation	0	62.8 (44.6–106.9)	70.4 (53.5–119.0)	121.9 (88.1–207.2)[b]
At 3 mo	0	78.1 (47.4–125.2)	73.7 (47.4–110.2)	89.8 (48.8–122.6)
At 12 mo	7	83.7 (47.3–115.9)[c]	60.0 (30.2–96.0)	36.3 (22.4–77.0)[c]
% change at 3 mo	0	22 (−29 to 83)[c]	−13 (−43 to 36)	−43 (−62 to −10)[b]
% change at 12 mo	7	13 (−26 to 75)[a]	−27 (−65 to 48)	−68 (−83 to −42)[b]
TRAP5b, U/L				
At transplantation	0	4.73 (3.17–6.58)	5.03 (3.73–7.10)	6.10 (4.08–9.47)
At 3 mo	0	3.37 (2.71–4.52)[a]	2.94 (2.22–3.67)	3.00 (2.14–4.25)
At 12 mo	7	3.89 (2.93–5.20)[a]	3.16 (2.17–4.60)	2.73 (1.76–4.13)
% change at 3 mo	0	−27 (−48 to 0.3)[a]	−43 (−59 to −19)	−52 (−66 to −29)
% change at 12 mo	7	−13 (−42 to 14)[a]	−37 (−56 to −17)	−54 (−67 to−43)[b]

Data are mean±SD or median (interquartile range). BALP, bone-specific alkaline phosphatase; BMD, bone mineral density; LS, lumbar spine; PINP, procollagen type I *N*-terminal propeptide; PTH, parathyroid hormone (1–84); TRAP5b, tartrate-resistant acid phosphatase isoform 5b.

[a]$P < 0.01$ by Student's *t* test or the Wilcoxon rank-sum test, compared with the stable group.

[b]$P < 0.001$ by Student's *t* test or the Wilcoxon rank-sum test, compared with the stable group.

[c]$P < 0.05$ by Student's *t* test or the Wilcoxon rank-sum test, compared with the stable group.

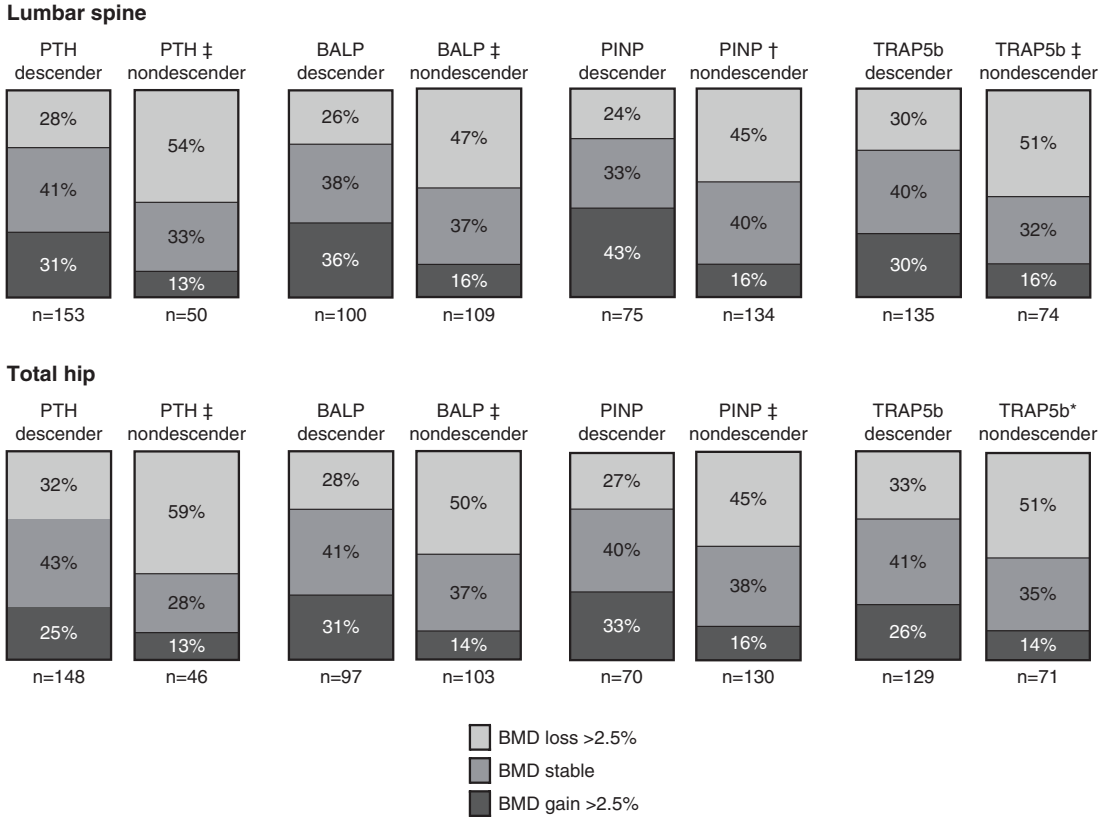

Figure 4. Risk of lumbar spine and total hip BMD loss at 12 months by whether biomarkers decreased by the least significant change at 3 months post-transplant (D+: descender, non-D; nondescender). *$P < 0.05$, ‡$P < 0.01$, and †$P < 0.001$ by Pearson's chi-squared test.

kidney transplantation (Supplemental Table 3), a parathyroidectomy performed either before or after transplantation (Supplemental Table 4), or normal lumbar spine BMD at time of transplantation (Supplemental Table 5).

Discussion

This study investigated the association between early changes in bone turnover markers and later changes in BMD after kidney transplantation. Our main findings were as follows: BMD changes in the first post-transplant year were highly variable, with 30%–40% of patients experiencing substantial bone loss, defined as a BMD decrease by at least 2.5%. Decreasing levels of PTH and bone turnover markers by 3 months post-transplant associated with less pronounced BMD loss, or even gain, while greater BMD losses were seen if bone resorption markers remained high throughout the first post-transplant year.

Decreases in BMD were seen at all skeletal sites in the first post-transplant year, except the 1/3 distal radius, with modest changes at spine and hip (approximately 1%) and a more pronounced decrease at the ultradistal radius (approximately 3%). Previous studies on the effect of kidney transplantation on skeletal health in patients receiving modern, steroid-sparing immunosuppressive therapy similarly demonstrated a limited bone loss at the central skeleton.[6,18] However, the changes in BMD post-transplant were highly variable, with subsets of patients losing, remaining stable, or even increasing in BMD during the first post-transplant year. This pattern of variability, with gainers and losers of BMD, seems to be a consistent finding demonstrated in several other cohorts.[5,7]

Patients who gained BMD during the first post-transplant year had higher levels of PTH and bone turnover markers at time of transplantation, with greater decreases in PTH and bone turnover markers at 3 months post-transplant. These findings indicate resolution of a high bone turnover state in BMD gainers, which was confirmed in the subset of patients with available paired transiliac bone biopsies. Furthermore, the histomorphometric analysis revealed that the amount of unmineralized bone (osteoid) was higher at time of transplantation and decreased at 1 year post-transplant in patients with BMD gain. This supports the hypothesis that the gain in BMD was caused by mineralization of preformed bone matrix, which accumulates in hyperparathyroid bone disease. This mechanism can be compared with what is seen after parathyroidectomy,[19] where rapid skeletal mineralization during the hungry bone syndrome can lead to impressive gains in BMD.[20]

Conversely, patients who experienced BMD loss during the first post-transplant year had lower levels of PTH at time of transplantation, with an increase in bone turnover markers during the first post-transplant year. At 12 months,

Table 3. Association between changes in biomarkers at 3 months and >2.5% decrease in bone mineral density at different skeletal sites at 12 months post-transplant

ΔBiomarker at 3 mo	Lumbar Spine (n=209)		Total Hip (n=200)		1/3 Distal Radius (n=124)		Ultradistal Radius (n=124)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Biointact PTH decrease by 43%	0.47	0.22 to 1.00	0.51	0.23 to 1.14	0.61	0.21 to 1.80	0.92	0.37 to 2.31
Alkaline phosphatase decrease by 16%	0.64	0.33 to 1.23	0.64	0.33 to 1.25	0.31	0.11 to 0.87	0.49	0.22 to 1.10
BALP decrease by 23%	0.39	0.21 to 0.73	0.33	0.17 to 0.64	0.44	0.17 to 1.17	0.53	0.24 to 1.16
PINP decrease by 32%	0.41	0.20 to 0.82	0.44	0.21 to 0.91	0.25	0.07 to 0.86	0.36	0.15 to 0.87
TRAP5b decrease by 24%	0.42	0.22 to 0.82	0.53	0.27 to 1.05	0.34	0.13 to 0.89	0.44	0.18 to 1.07

Multivariable logistic regression odds ratios with 95% confidence intervals after adjustment for age, sex, body mass index, parathyroid hormone at time of transplantation, eGFR at 12 months post-transplant, and cumulative steroid dose at 12 months post-transplant. BALP, bone-specific alkaline phosphatase; CI, confidence interval; OR, odds ratio; PINP, procollagen type I *N*-terminal propeptide; PTH, parathyroid hormone (1–84); TRAP5b, tartrate-resistant acid phosphatase isoform 5b.

the bone turnover markers were significantly higher in these patients. Thus, ongoing bone resorption signaled a greater prevalence of bone loss during the first post-transplant year.

Early (<3 months) changes in PTH and bone turnover markers associated with BMD changes at 1 year post-transplant. This was not the case for other markers of mineral metabolism, including phosphate, calcium, or 25-hydroxy vitamin D levels. Similar findings were seen in a *post hoc* analysis of a small trial of denosumab after kidney transplantation.[21] The correlation was only demonstrated in the control group, not in the active treatment arm, which is surprising considering results from other trials of denosumab in patients receiving dialysis.[22] None of the other bone biomarkers measured associated with BMD change[21]; however, these were all markers known to accumulate with reduced kidney function, making them less suitable in a CKD cohort.

In contrast to the bone turnover markers, PTH levels at 3 and 12 months were comparable across subgroups of BMD change in this study. Furthermore, changes in bone turnover markers remained independent determinants of BMD

Table 4. Bone histomorphometry by transiliac bone biopsy on the basis of change in bone mineral density at lumbar spine during the first year after kidney transplantation

Histomorphometric Variable	Missing	BMD Loss (n=15)	BMD Stable (n=17)	BMD Gain (n=17)
Time of transplantation, %				
Bone turnover, L/N/H	0	25/63/12	0/86/14	0/75/25
ObPm/BPm	0	1.6 (0.2–4.9)	1.4 (0.0–3.1)	7.7 (1.3–11.5)[a]
OcPm/BPm	0	0.4 (0.0–1.7)	0.4 (0.0–1.1)	1.0 (0.4–1.9)
EPm/BPm	0	4.7 (1.7–6.9)	3.7 (2.2–5.0)	5.1 (4.0–8.5)
OAr/BAr	0	1.6 (0.7–3.2)	1.7 (1.2–2.8)	5.8 (2.1–7.9)[a]
OPm/BPm	0	14.3 (7.6–26.5)	15.4 (12.4–20.3)	36.3 (26.2–40.8)[b]
12 mo post-transplant				
Bone turnover, L/N/H, %	0	12/88/0	10/90/0	33/58/8
BFR/TAr, $\mu m^2/mm^2$ per day	9	210 (92–312)	126 (69–221)	427 (134–493)
BFR/BS, $\mu m^3/\mu m^2$ per year	9	17 (9–32)	10 (5–23)	20 (7–40)
Mlt, d	9	44.3 (22.6–68.7)	36.0 (17.2–72.8)	22.6 (13.3–52.7)
ObPm/BPm, %	0	4.6 (0.9–8.3)	4.2 (0.0–10.2)	3.6 (1.3–7.2)
OcPm/BPm, %	0	0.7 (0.3–1.5)	0.4 (0.0–0.7)	0.6 (0.0–1.2)
EPm/BPm, %	0	3.5 (2.5–5.5)	2.7 (1.3–3.4)	2.7 (1.1—4.1)
OAr/BAr, %	0	3.4 (2.0–5.8)	3.0 (1.2–5.9)	2.0 (0.6–5.3)
OPm/BPm, %	0	23.1 (15.7–38.2)	25.2 (11.6–46.7)	17.1 (8.8–31.8)
Change at 12 mo, %				
ΔObPm/BPm	0	2.2±4.6	3.6±6.6	−0.6±6.6
ΔOcPm/BPm	0	0.1±0.7	−0.2±1.0	−0.6±1.4
ΔEPm/BPm	0	−1.3±3.9	−1.2±3.1	−3.0±3.5
ΔOAr/BAr	0	2.2±2.8	1.9±3.8	−1.7±4.3[c]
ΔOPm/BPm	0	9.0±15.6	10.5±22.8	−9.1±20.8[c]

Mean±SD or median (interquartile range), with P by Student's t test or the Wilcoxon rank-sum test for significance compared with the stable group. BAr, bone area; BFR, bone formation rate; BMD, bone mineral density; BPm, bone perimeter; BS, bone surface; EPm, eroded perimeter; Mlt, mineralization lag time; OAr, osteoid area; ObPm, osteoblast perimeter; OcPm, osteoclast perimeter; OPm, osteoid perimeter.

[a] $P < 0.01$.

[b] $P < 0.001$.

[c] $P < 0.05$.

change after adjustment for demographic factors, which was not the case for PTH. In other words, significant differences in bone turnover markers were seen despite similar PTH levels, which could indicate either competing factors affecting bone turnover or variability in the skeletal PTH responsiveness in kidney transplant recipients. The pathophysiology behind PTH hyporesponsiveness in CKD is unclear,[23] but the severity of hyperparathyroidism has been shown to be a main determinant, both in studies using the gold standard calcemic response after PTH infusion[24] and in others using bone turnover markers as surrogate measures.[25,26] Thus, a desensitization of the skeleton may take place in severe hyperparathyroidism, and such adaptive changes could still be in effect post-transplant, reducing the diagnostic accuracy of PTH levels in the evaluation of bone turnover.[27] In effect, it may be more helpful to evaluate the skeletal response to PTH using the bone turnover markers, rather than relying on PTH levels alone. These biomarkers passively reflect the process of skeletal remodeling and convey information on the current status of bone turnover regardless of any underlying causes (glucocorticoids, inflammation, PTH levels, *etc.*).[28]

Our findings indicate a usefulness of bone turnover markers in risk stratification post-transplant. BMD status is generally poor in kidney transplant recipients, with 20%–30% of patients having *T*-scores in the osteoporotic range and 35%–50% having *T*-scores in the osteopenic range at time of transplantation.[7,29,30] Considering that the risk of fractures is particularly high in the first post-transplant year,[2] timely intervention to minimize bone loss post-transplant could improve patient outcomes. Our findings indicate that an evaluation of bone turnover markers in the early post-transplant period could help identify patients at particularly high or low risk of BMD loss, which in turn could enable an individualized approach to preventing further bone loss.

Strengths of this study include a substantial cohort of contemporary kidney transplant recipients with extended biochemical evaluation at several time points post-transplant. We measured bone biomarkers known to be largely unaffected by kidney function, which is of importance when applied in cohorts of patients with kidney dysfunction. A modern, steroid-sparing immunosuppressive protocol was used, and the results should be generalizable to current day kidney transplant recipients. As limitations, we included patients with available study visits at 3 and 12 months after kidney transplantation, and the risk of selection bias should be considered. However, we found no marked differences in demography or mineral metabolism parameters in patients selected compared with the overall patient population. We excluded patients receiving antiresorptive therapy, which would be expected to amplify the associations demonstrated. Bone biomarkers were measured in the nonfasting state and randomly with regard to the last dialysis session before kidney transplantation. However, the effect of fasting and dialysis on these biomarkers are limited,[31–33] and any variability caused should be random with respect to the associations studied. Our results could be exaggerated by regression to the mean because patients with more severe hyperparathyroidism also had lower BMD at time of transplantation. Movement away from extreme values could thus be expected for both these parameters. We applied the principle of least significant change to both BMD and bone biomarker changes, which should help overcome analytical and biological variability. Furthermore, a sensitivity analysis excluding patients with osteoporosis at the lumbar spine at time of transplantation yielded identical results. We did not report on clinical outcomes (fractures), but BMD as a surrogate marker of bone strength. Low BMD has been shown to associate with risk of incident fractures in kidney transplant recipients.[29] Finally, the study cohort was exclusively White, with demographic data and mineral metabolism treatment targets reflective of Europe, and the results may not be fully applicable to other population groups or regions of the world.[34]

In conclusion, BMD changes after kidney transplantation were highly variable, and a subset of patients experienced substantial bone loss despite a steroid minimization protocol. Levels of bone turnover markers, and the changes in these markers, associated with BMD changes. Our findings indicate that bone turnover markers may be useful in identifying patients with ongoing bone resorption who are at a high risk of bone loss in the first post-transplant year, which could enable an individualized approach to improving skeletal health after kidney transplantation.

Disclosures

E. Cavalier reports consultancy for bioMerieux, DiaSorin, Fujirebio, IDS, Nittobo, Orifarm, Snibe, and Werfen. K. Claes reports consultancy for Astellas, Fresenius Kabi, GSK, and Sanofi; support from Alexion, Astellas, and AstraZeneca; advisory or leadership role for Alexion, Astellas, and Fresenius Kabi; and speaker's fee from AstraZeneca and Vifor Pharma. P. Evenepoel reports consultancy for Vifor CSL; research funding from Amgen, Sanofi, and Vifor CSL; and honoraria from Vifor CSL. H.S. Jørgensen reports other interests or relationships as a Steering Committee member of the European Renal Osteodystrophy initiative, under the CKD-MBD working group of the European Renal Association (ERA). D. Kuypers reports consultancy for Astellas Company, AZ, GSK, Hansa, Sangamo-Tx, and Takeda; honoraria from Astellas, AZ, GSK, Hansa, and Takeda; speakers bureau for Astellas and HIKMA; and advisory or leadership role as an Associate Editor for *Transplantation* and as an Editorial Board member of *Current Clinical Pharmacology*, *Therapeutic Drug Monitoring*, and *Transplantation Reviews*. M. Naesens reports consultancy for Agomab, Aiosyn, Argenx, and Hansa; research funding from CareDx; and honoraria from Argenx and Hansa. M. Naesens is inventor of two patents related to the FWO-SBO application: EP19152365.3: mRNA-based biomarkers for antibody-mediated transplant rejection. This biomarker was licensed in September 2020 to CareDx, a precision medicine solutions company focused on solutions for transplant patients; PCT/EP2018/097044: Biomarkers for typing allograft recipients (patent application submitted December 2018). All remaining authors have nothing to disclose.

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Data Sharing Statement

The data that support the findings of this study are available from the corresponding author on reasonable request.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/CJN/B839.

Supplemental Methods.

Supplemental Table 1. Demographic data and biochemical markers of mineral metabolism in patients included versus the overall cohort of kidney transplant recipients.

Supplemental Table 2. Change in bone mineral density (BMD) from baseline to 1 year in kidney transplant recipients, on the basis of whether they achieved a substantial decrease in biomarkers at 3 months post-transplant.

Supplemental Table 3. Sensitivity analysis excluding patients with lumbar spine osteoporosis at time of kidney transplantation.

Supplemental Table 4. Sensitivity analysis excluding patients with a parathyroidectomy before or after kidney transplantation.

Supplemental Table 5. Sensitivity analysis excluding patients with normal lumbar spine bone mineral density (BMD) at time of kidney transplantation.

Supplemental Figure 1. Flow chart of selection of patients for this study.

Supplemental Figure 2. Trajectories of parathyroid hormone (PTH) and bone turnover markers (median with IQR) in patients who lost, remained stable, or gained bone mineral density (BMD) at the femoral neck by a 2.5% cutoff.

Supplemental Figure 3. Trajectories of total alkaline phosphatase in patients who lost, remained stable, or gained bone mineral density (BMD) at lumbar spine and femoral neck by a 2.5% cutoff during the first post-transplant year.

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