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# Bone Mineral Density and Aortic Calcification: Evidence for a Bone-vascular Axis After Kidney Transplantation

Camilo G. Sotomayor, MD,[1,2] Stan Benjamens, BSc,[3,4] António W. Gomes-Neto, MD,[1] Robert A. Pol, MD, PhD,[3] Dion Groothof, BSc,[1] Charlotte A. te Velde-Keyzer, MD, PhD,[1] Guillermo Chong, MD,[5] Andor W.J.M. Glaudemans, MD, PhD,[4] Stefan P. Berger, MD, PhD,[1] Stephan J.L. Bakker, MD, PhD,[1] and Riemer H.J.A. Slart, MD, PhD[4,6]



**Background.** Chronic kidney disease mineral and bone disorders (CKD-MBD) and vascular calcification are often seen in kidney transplantation recipients (KTR). This study focused on the bone–vascular axis hypothesis, the pathophysiological mechanisms driving both bone loss and vascular calcification, supported by an association between lower bone mineral density (BMD) and higher risk of vascular calcification. **Methods.** KTR referred for a dual-energy X-ray absorptiometry procedure within 6 mo after transplantation were included in a cross-sectional study (2004–2014). Areal BMD was measured at the proximal femur, and abdominal aortic calcification (AAC) was quantified (8-points score) from lateral single-energy images of the lumbar spine. Patients were divided into 3 AAC categories (negative-AAC: AAC 0; low-AAC: AAC 1–3; and high-AAC: AAC 4–8). Multivariable-adjusted multinomial logistic regression models were performed to study the association between BMD and AAC. **Results.** We included 678 KTR (51 ± 13 y old, 58% males), 366 (54%) had BMD disorders, and 266 (39%) had detectable calcification. High-AAC was observed in 9%, 11%, and 25% of KTR with normal BMD, osteopenia, and osteoporosis, respectively ($P < 0.001$). Higher BMD (T-score, continuous) was associated with a lower risk of high-AAC (odds ratio 0.61, 95% confidence interval 0.42-0.88; $P = 0.008$), independent of age, sex, body mass index, estimated glomerular filtration rate, and immunosuppressive therapy. KTR with normal BMD were less likely to have high-AAC (odds ratio 0.24, 95% confidence interval 0.08-0.72; $P = 0.01$). **Conclusions.** BMD disorders are highly prevalent in KTR. The independent inverse association between BMD and AAC may provide evidence to point toward the existence, while highlighting the clinical and epidemiological relevance, of a bone–vascular axis after kidney transplantation.

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## INTRODUCTION

Chronic kidney disease (CKD) is an independent risk factor for cardiovascular disease. Cardiovascular disease, in turn, leads the burden of morbidity and premature mortality in patients with CKD and end-stage renal disease.[1] Although kidney transplantation is the gold-standard treatment for

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*[1] Division of Nephrology, Department of Internal Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.*

*[2] Department of Radiology, Clinical Hospital of the University of Chile, University of Chile, Santiago, Chile.*

*[3] Division of Transplant Surgery, Department of Surgery, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.*

*[4] Medical Imaging Center, Department of Nuclear and Molecular Imaging, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.*

*[5] Department of Radiology, Clínica Alemana De Santiago, Universidad del Desarrollo, Santiago, Chile.*

*[6] Department of Biomedical Photonic Imaging, University of Twente, Enschede, The Netherlands.*

*C.G.S. and S.B. contributed equally to this work. C.G.S. and S.B. were involved in research design, acquired the data, and were involved in data analysis and interpretation and writing the manuscript. A.W.G.-N. was involved in data analysis and contributed to the final adjustments to the manuscript after revising it critically for intellectual content. R.A.P. was involved in research design and contributed to the final adjustments to the manuscript after revising it critically for intellectual content. D.G. acquired the data and contributed to the final adjustments to the manuscript after revising it critically for intellectual content. C.A.t.V.-K., G.C., A.W.J.M.G., and S.P.B. contributed to the final adjustments to the manuscript after revising it critically for intellectual content. S.J.L.B. and R.H.J.A.S. initiated the study, were involved in research design and data interpretation, and contributed to the final adjustments to the manuscript after revising it critically for intellectual content.*

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*Correspondence: Dr. Camilo G. Sotomayor, MD, Division of Nephrology, Department of Internal Medicine, University Medical Center Groningen, Hanzeplein 1, P.O. Box 30.001, 9713 GZ Groningen, The Netherlands. (c.g.sotomayor.campos@umcg.nl).*



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end-stage renal disease, cardiovascular disease continues to portray the major risk after kidney transplantation, which continues to challenge improvement of long-term survival after kidney transplant.[2,3]

A large body of evidence underscores the relevance of vascular calcification as being independently associated with major adverse cardiovascular events and mortality due to cardiovascular disease in kidney transplant recipients (KTR).[4-9] Linking vascular disease with bone disease, CKD mineral and bone disorders (CKD-MBDs) constitute a syndrome codified by the Kidney Disease Improving Global Outcomes (KDIGO) more than a decade ago, in which vascular calcification is associated with CKD due to disruption of the complex systems biology encompassing the kidney, skeleton, and cardiovascular system.[10-17]

Kidney transplantation aims to restore renal function, as well as mineral regulating hormones and overall homeostasis of mineral metabolites. However, disturbed bone and mineral metabolism persists after kidney transplantation.[18] Upon pretransplant renal osteodystrophy and persistent metabolic bone disorders, maintenance immunosuppressive therapy appends an additional transplant-specific hazard for altered bone turnover, mineralization, and volume.[19,20] Indeed, posttransplant bone disease is considered significantly different to that observed within the context of pretransplant CKD-MBD.[21] The substantial epidemiological relevance of posttransplant bone disease is being ever-increasingly acknowledged and, accordingly, actively addressed among clinicians.[21-31] Recommendations of bone mineral density (BMD) testing after transplantation have been formally incorporated in the KDIGO 2017 clinical practice guidelines.[29] Noninvasive, relatively accurate and cost-effective, dual-energy X-ray absorptiometry (DXA) is the imaging method of choice for bone mass screening early after kidney transplantation.[29]

While the link between bone disease and vascular calcification arising from primary disturbance of calcium phosphate homeostasis has long been acknowledged in native CKD, there is in contrast a paucity of studies devoted to investigate the postulated independent association between bone disease and risk of vascular calcification in the posttransplant setting.[10,12,15-17,32-35] We hypothesized that, in KTR, BMD is independently and inversely associated with the risk of vascular calcification. Evidence of this association would further support the existence of a bone–vascular axis, it would provide data to evaluate its epidemiological relevance after transplantation, and would point toward otherwise overlooked therapeutic opportunities to potentially decrease the high cardiovascular burden in KTR.

In a large cohort of KTR, we aimed to investigate BMD disorders as assessed by a DXA scan, in line with the KDIGO guidelines, and study the potential independent association between BMD and the risk of abdominal aortic calcification (AAC) after kidney transplantation.

## MATERIALS AND METHODS

### Study Design

We performed a single-center cross-sectional cohort study in a university setting (University Medical Center Groningen, Groningen, The Netherlands) (**Table S1, SDC,** http://links.lww.com/TP/B906). All adult patients referred for a DXA scan within 6 mo after the first kidney transplantation between 2004 and 2014 were considered eligible. The study protocol regarding patient data processing and storage for medical research involving human subjects was approved by the Institutional Review Board (Medical Ethical Committee 2017/457) and conducted in accordance with declarations of Helsinki and Istanbul.

Medical history, including transplant characteristics, and medication use were extracted from patients' medical records. As described elsewhere,[36] standard immunosuppression consisted of the following: cyclosporine (target trough levels 175–200 mg/L in the first 3 mo, 100 mg/L thereafter), prednisolone (starting with 20 mg/d and tapering to 10 mg/d) and mycophenolate mofetil (2 g/d), and for KTR with no complications, cyclosporine was slowly withdrawn from 1 y after transplantation onward. In 2012, cyclosporine was replaced by tacrolimus, and KTR continued triple-immunosuppressive therapy with prednisolone (20 mg/d, tapering to 5 mg/d), tacrolimus (target trough levels 8–12 mg/L in the first 3 mo, 6–10 mg/L until month 6, and 4–6 mg/L from 6 mo onward), and mycophenolate mofetil (starting with 2 g/d, tapering to 1 g/d).

We investigated and documented clinical data as following. Pretransplant hypertension was defined as blood pressure >140/90 mm Hg or current antihypertensive medication. Pretransplant hypercholesterolemia was defined as total cholesterol levels >200 mg/dL or current use of lipid-lowering agents. Following the World Health Organization (WHO) guidelines—*International statistical classification of diseases and related health problems*—cardiovascular events were defined as the occurrence of a myocardial infarction (International Statistical Classification of Diseases and Related Health Problems ([ICD]-10: I21), both ST-elevation myocardial infarction and non-ST-elevation myocardial infarction, instable angina pectoris (ICD-10: I20), a cerebrovascular accident (ICD-10: I60-I66), or a transient ischemic attack (ICD-10: G45). Information with regard to the definition used to prospectively collect data on cardiovascular events posttransplant in this patient cohort, and the analyses on the association between AAC and the risk of cardiovascular events can be found elsewhere.[9] As described elsewhere,[37] pretransplant diabetes mellitus was defined according to the guidelines of the American Diabetes Association, when at least 1 of the following criteria was met: symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/dL (11.1 mmol/L), or fasting plasma glucose ≥126 mg/dL (7.0 mmol/L), or 2-h postload glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test; or the use of antidiabetic medication.[38] Smoking status was considered active if patients were current smokers at the time of transplant waitlisting admission.[39] Cardiovascular disease history was considered positive if patients had a myocardial infarction, cerebrovascular accidents, or transient ischemic attack. Either history of hyperparathyroidism or use of cinacalcet was used to indicate pretransplant hyperparathyroidism. Estimated glomerular filtration rate (eGFR) was calculated applying the serum creatinine–based CKD Epidemiology Collaboration equation.[40]

### DXA Scan, BMD, and AAC Scoring

Lateral single-energy images of the lumbar spine were obtained on a Discovery DXA System (Hologic, Bedford, MA). DXA images were analyzed by 2 blinded independent

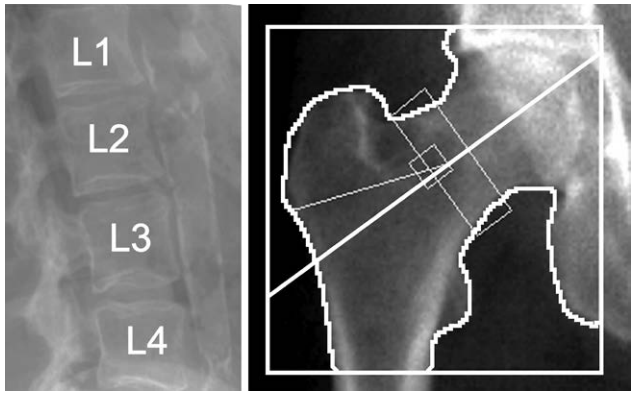


**FIGURE 1.** Example of a lateral single-energy image of the lumbar spine, with the lumbar vertebral bones L1– L4, and a proximal femur image for areal BMD assessment from dual-energy X-ray absorptiometry (DXA). BMD, bone mineral density.

imaging specialists. Areal BMD was measured at the proximal femur and expressed as a T-score (Figure 1). In keeping with the WHO, BMD was then classified into osteoporosis with a T-score of –2.5 or less; osteopenia with a T-score between –2.5 and –1.0; or normal BMD with a T-score >–1.0. AAC was quantified by means of a visual 8-point scale, as previously described by Schousboe et al.[41] This scale reflects the total length of calcification on the anterior and posterior aortic walls between L1 and L4 vertebral bones. The scale system assigns 1 point for a single-sided calcification with an aggregate length up to the height of 1 vertebra. Additional scoring points are given when calcifications reached the level of the 3 other vertebrae. The total score was the summation of anterior and posterior calcification scores and ranged from 0 to 8, as described before.[9] Based on AAC scoring, patients were stratified into 3 AAC categories: (1) negative finding; (2) low AAC; and (3) high ACC, according to AAC scores 0, 1–3, and 4–8, respectively.

### Statistical Analyses

Data were analyzed using IBM SPSS software version 23.0 (SPSS Inc., Chicago, IL), STATA 14.1 (STATA Corp., College Station, TX), and R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria). Data are expressed as mean ± SD for normally distributed variables, and as median (interquartile range) for skewed variables. Categorical data are expressed as n (percentage). The percentage of missing data was 0.003% for immunosuppressive therapy, and 32% and 38% for risk-of-fracture and dialysis vintage, respectively. Differences in baseline characteristics among categories of BMD were evaluated by using the Kruskal–Wallis test for skewed variables, the ANOVA for normally distributed variables, and Chi-squared test for categorical data. In all analyses, a 2-sided $P$ value <0.05 was considered significant.

To study the association of BMD with the risk of low and high AAC, multinomial logistic models were fitted to the data, with adjustment for age, sex, body mass index, eGFR, and immunosuppressive therapy (model 1); history of hyperparathyroidism, history of parathyroidectomy, use of calcium supplements, use of vitamin D supplements, use of cinacalcet pretransplantation and posttransplantation, and use of biphosphonates (model 2); and calcium, phosphate, aspartate aminotransferase, gamma glutamyl transpeptidase, and alkaline phosphatase (model 3). To comprehensively study these associations, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with BMD as a continuous variable and as a categorical variable according to clinical categories (normal BMD and osteopenia, with osteoporosis as reference). Potential heterogeneity on the association of BMD with AAC by age, sex, body mass index, eGFR, diabetes, smoking history, cardiovascular history, hyperparathyroidism, use of cinacalcet pretransplantation and posttransplantation, and immunosuppressive therapy was tested by fitting models containing both main effects and their cross-product terms. The $P_{interaction}$ value <0.05 was considered to indicate significant heterogeneity.

## RESULTS

We included 678 KTR (51 ± 13 y old, 58% males, eGFR 51 ± 15 mL/min/1.73 $m^2$, and proximal femur T-score –1.1 ± 1.1), of whom 366 (54%) had BMD disorders, that is, 301 (44%) had osteopenia and 65 (10%) had osteoporosis. In turn, 266 (39%) had detectable aortic calcification (AAC score ≥1). Additional baseline characteristics, overall and by categories of BMD, are shown in Table 1. Distribution of AAC categories was significantly different across subgroups of KTR according to BMD ($P$ < 0.001), with, for example, high AAC observed in 9%, 11%, and 25% of KTR with normal BMD, osteopenia, and osteoporosis, respectively. Patients with osteoporosis were older, mostly women, and had lower body mass index, higher general and hip-specific risk of fracture, higher aspartate aminotransferase, gamma glutamyl transpeptidase, and alkaline phosphatase.

In unadjusted logistic regression analyses, we found that relatively higher BMD (T-score, continuous) was consistently associated with lower risk of low AAC (OR 0.71, 95% CI 0.60-0.84; $P$ < 0.001) or high AAC (OR 0.66, 95% CI 0.52-0.84; $P$ = 0.001). When we analyzed BMD as a categorical variable, we found that in comparison to KTR with osteoporosis, those with normal BMD (OR 0.26, 95% CI 0.12-0.52; $P$ < 0.001) or osteopenia (OR 0.39, 95% CI 0.19-0.79; $P$ = 0.01) were less likely to have high AAC. These findings remained materially unaltered in further models with, for example, adjustment for a history hyperparthyroidism, history of parathyroidectomy, use of calcium and vitamin D supplements, use of cinacalcet, and use of biphosphonates (model 2; Table 2). We observed no heterogeneity for the association of BMD and AAC by age, sex, body mass index, eGFR, diabetes, smoking history, cardiovascular history, hyperparathyroidism, use of cinacalcet, and immunosuppressive therapy ($P_{interaction}$ > 0.05 for all). Figure 2 represents the association of femoral T-score with risk of AAC, and data were fitted by logistic regression using median femoral T-score as a reference value.

## DISCUSSION

Our study shows an independent inverse association between BMD and the risk of AAC, which supports the hypothesis of the existence of a bone–vascular axis after kidney transplantation. These findings underscore a nontraditional and modifiable—yet rather underestimated—risk factor for excess cardiovascular disease and premature cardiovascular mortality of KTR.

**TABLE 1.**

**Baseline characteristics, overall, and by BMD categories according to T-score measured by DXA at the proximal femur**

| Baseline characteristics | Total | BMD, categories | | | P |
|---|---|---|---|---|---|
| | | Normal | Osteopenia | Osteoporosis | |
| | 678 (100) | 312 (46) | 301 (44) | 65 (10) | – |
| Demographics | | | | | |
| Age, y, mean (SD) | 51 (13) | 50 (13) | 52 (13) | 54 (12) | 0.02 |
| Gender, male, n (%) | 394 (58) | 199 (64) | 171 (57) | 24 (37) | <0.001 |
| Body mass index, kg/m$^2$, mean (SD) | 25.5 (4.2) | 26.6 (4.2) | 24.7 (3.9) | 23.6 (4.3) | <0.001 |
| eGFR, mL/min/1.73 m$^2$, mean (SD) | 51 (15) | 52 (15) | 52 (15) | 46 (15) | 0.07 |
| Hypertension, n (%) | 547 (81) | 259 (83) | 237 (79) | 51 (79) | 0.36 |
| Hypercholesterolemia, n (%) | 291 (43) | 131 (42) | 130 (43) | 30 (46) | 0.82 |
| Diabetes mellitus, n (%) | 92 (14) | 42 (14) | 36 (12) | 14 (22) | 0.12 |
| Smoking history, n (%) | 142 (21) | 62 (20) | 63 (21) | 17 (26) | 0.53 |
| Cardiovascular history, n (%) | 112 (17) | 55 (18) | 44 (15) | 13 (20) | 0.44 |
| Hyperparathyroidism, n (%) | 144 (21) | 67 (22) | 60 (20) | 17 (26) | 0.59 |
| Postparathyroidectomy, n (%) | 38 (6) | 22 (7) | 12 (4) | 4 (6) | 0.28 |
| Dual-energy X-ray absorptiometry | | | | | |
| General risk-of-fracture, median (IQR)[a] | 5.8 (3.6–10.0) | 4.2 (2.4–6.5) | 7.0 (4.5–10.0) | 17.0 (11.0–23.8) | <0.001 |
| Hip risk-of-fracture, median (IQR)[a] | 1.1 (0.3–2.8) | 0.3 (0.1-0.9) | 1.9 (0.8–3.8) | 8.1 (3.6–15.0) | <0.001 |
| Vertebral fractures, n (%) | 122 (18) | 49 (16) | 58 (19) | 15 (23) | 0.28 |
| Thoracic, n (%) | 65 (10) | 28 (9) | 28 (10) | 7 (11) | 0.90 |
| Lumbar, n (%) | 26 (4) | 15 (5) | 8 (3) | 3 (5) | 0.39 |
| Thoracic and lumbar, n (%) | 10 (2) | 6 (2) | 3 (1) | 1 (2) | 0.66 |
| AAC-score, median (IQR) | 0 (0–2) | 0 (0–1) | 0 (0–2) | 1 (0–4) | 0.001 |
| AAC-score, categories | | | | | <0.001 |
| No calcification, n (%) | 412 (61) | 212 (68) | 168 (56) | 32 (49) | |
| Low AAC score (1–3), n (%) | 190 (28) | 73 (23) | 100 (33) | 17 (26) | |
| High AAC score (4–8), n (%) | 76 (11) | 27 (9) | 33 (11) | 16 (25) | |
| Kidney transplant and immunosuppressive therapy | | | | | |
| Dialysis vintage (mo), median (IQR)[b] | 39 (21–55) | 39 (19–53) | 35 (22–56) | 46 (27–65) | 0.06 |
| Immunosuppressive therapy | | | | | |
| Use of corticosteroids, n (%)[c] | 661 (98) | 302 (97) | 295 (98) | 64 (99) | 0.82 |
| Corticosteroids dose, mg/d, median (IQR) | 17.5 (10.0–20.0) | 17.5 (10.0–20.0) | 17.5 (10.0–19.4) | 17.5 (15.0–20.0) | 0.81 |
| Calcineurin inhibitors | | | | | |
| Use of cyclosporine, n (%)[c] | 309 (46) | 146 (47) | 124 (41) | 39 (60) | 0.02 |
| Use of tacrolimus, n (%)[c] | 186 (27) | 87 (28) | 86 (29) | 13 (20) | 0.36 |
| Proliferation inhibitors | | | | | |
| Use of azathioprione, n (%)[c] | 14 (2) | 3 (1) | 9 (3) | 2 (3) | 0.18 |
| Use of myfortic, n (%)d | 237 (35) | 103 (33) | 115 (38) | 19 (29) | 0.26 |
| Combined immunosuppressive therapy[c] | | | | | |
| Cyclosporine+MMF+corticosteroids, n (%) | 307 (45) | 145 (47) | 123 (41) | 39 (60) | 0.02 |
| Tacrolimus+MMF+corticosteroids, n (%) | 332 (49) | 150 (48) | 160 (53) | 22 (34) | 0.02 |
| Others, n (%) | 37 (6) | 15 (5) | 18 (6) | 4 (6) | 0.80 |
| Medication | | | | | |
| Use of calcium supplements, n (%) | 87 (13) | 35 (11) | 43 (15) | 8 (12) | 0.45 |
| Use of vitamin D supplements, n (%) | 97 (14) | 50 (16) | 38 (13) | 9 (14) | 0.55 |
| Use of biphosphonates, n (%) | 16 (2) | 4 (1) | 7 (2) | 3 (5) | 0.09 |
| Use of cinacalcet pretransplantation, n (%) | 60 (9) | 27 (9) | 22 (7) | 11 (17) | 0.05 |
| Use of cinacalcet posttransplantation, n (%) | 26 (4) | 10 (3) | 13 (4) | 3 (5) | 0.73 |
| Laboratory measurements | | | | | |
| Hemoglobin, mmol/L, mean (SD) | 7.7 (1.1) | 7.7 (1.1) | 7.6 (1.1) | 7.7 (1.1) | 0.43 |
| Leukocyte count, $\times 10^9$/L, mean (SD) | 7.5 (3.2) | 7.6 (3.4) | 7.5 (3.4) | 7.2 (3.0) | 0.69 |
| Total cholesterol, mmol/L, mean (SD) | 5.4 (1.3) | 5.4 (1.2) | 5.5 (1.3) | 5.7 (1.1) | 0.18 |
| Low-density lipoprotein cholesterol, mmol/L, mean (SD) | 226 (74) | 228 (72) | 226 (78) | 216 (69) | 0.53 |
| Calcium, mmol/L, mean (SD) | 2.4 (0.2) | 2.4 (0.2) | 2.4 (0.2) | 2.5 (0.1) | 0.13 |
| Phosphate, mg/dL, mean (SD) | 0.9 (0.2) | 0.9 (0.2) | 0.9 (0.2) | 0.9 (0.2) | 0.92 |

*Continued next page*

**TABLE 1. (Continued)**

| Baseline characteristics | Total | BMD, categories | | | P |
|---|---|---|---|---|---|
| | | Normal | Osteopenia | Osteoporosis | |
| ASAT, U/L, mean (SD) | 23 (10) | 22 (7) | 23 (11) | 26 (16) | 0.02 |
| ALAT, U/L, median (IQR) | 19 (15–26) | 20 (15–26) | 19 (14–26) | 19 (17–28) | 0.70 |
| Gamma glutamyl transpeptidase, U/L, median (IQR) | 30 (21–50) | 20 (28–46) | 31 (21–55) | 38 (26–56) | 0.01 |
| Alkaline phophatase, U/L, median (IQR) | 81 (63–109) | 78 (60–98) | 82 (64–116) | 89 (69–138) | 0.004 |

Differences in baseline characteristics among categories of BMD were evaluated by using the Kruskal-Wallis test for skewed variables, the ANOVA for normally distributed continuous variables, and Chi-squared test for categorical data.
Data available in
[a]455,
[b]420,
[c]676, and patients.
AAC, abdominal aortic calcification; ALAT, alanine-aminotransferase; ASAT, aspartato-aminotransferase; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MMF, mycophenolate mofetil.

**TABLE 2.**

**Association between BMD by DXA scan and risk of low and high AAC**

| BMD | Categories of AAC | | | | | |
|---|---|---|---|---|---|---|
| | Low calcification | | | High calcification | | |
| | OR | (95% CI) | P | OR | (95% CI) | P |
| Unadjusted | | | | | | |
| T-score, continuous | 0.71 | 0.60-0.84 | <0.001 | 0.66 | 0.52-0.84 | 0.001 |
| Categories | | | | | | |
| Normal BMD | 0.65 | 0.34-1.24 | 0.19 | 0.26 | 0.12-0.52 | <0.001 |
| Osteopenia | 1.13 | 0.59-2.13 | 0.72 | 0.39 | 0.19-0.79 | 0.01 |
| Osteoporosis | Ref. | | | Ref. | | |
| Model 1[a] | | | | | | |
| T-score, continuous | 0.67 | 0.53-0.84 | 0.001 | 0.61 | 0.42-0.88 | 0.008 |
| Categories | | | | | | |
| Normal BMD | 0.55 | 0.24-1.27 | 0.16 | 0.24 | 0.08-0.72 | 0.01 |
| Osteopenia | 0.92 | 0.41-2.10 | 0.85 | 0.44 | 0.16-1.23 | 0.12 |
| Osteoporosis | Ref. | | | Ref. | | |
| Model 2[b] | | | | | | |
| T-score, continuous | 0.71 | 0.60-0.84 | <0.001 | 0.67 | 0.52-0.85 | 0.001 |
| Categories | | | | | | |
| Normal BMD | 0.62 | 0.32-1.20 | 0.16 | 0.26 | 0.13-0.55 | <0.001 |
| Osteopenia | 1.09 | 0.57-2.09 | 0.79 | 0.42 | 0.20-0.87 | 0.02 |
| Osteoporosis | Ref. | | | Ref. | | |
| Model 3[c] | | | | | | |
| T-score, continuous | 0.72 | 0.60-0.86 | <0.001 | 0.73 | 0.57-0.94 | 0.02 |
| Categories | | | | | | |
| Normal BMD | 0.65 | 0.33-1.29 | 0.22 | 0.31 | 0.15-0.67 | 0.003 |
| Osteopenia | 1.12 | 0.58-2.19 | 0.73 | 0.42 | 0.20-0.90 | 0.03 |
| Osteoporosis | Ref. | | | Ref. | | |

Unadjusted and multivariable-adjusted multinomial logistic regression analyses.
[a]Model 1 was adjusted for age, sex, body mass index, estimated glomerular filtration rate, and immunosuppressive therapy.
[b]Model 2 was adjusted for history of hyperparthyroidism, history of parathyroidectomy, use of calcium and vitamin D supplements, use of cinacalcet pretransplantation and posttransplantation, and use of biphosphonates.
[c]Model 3 was adjusted for calcium, phosphate, aspartato aminotransferase, gamma glutamyl transpeptidase, and alkaline phosphatase.
ORs and 95% CIs were calculated with BMD (T-score) as a continuous variable and as a categorical variable according to clinical categories (normal BMD and osteopenia, with osteoporosis as reference).
AAC, abdominal aortic calcification; BMD, bone mineral density; CI, confidence interval; DXA, dual-energy X-ray absorptiometry; OR, odds ratio.

The presented data underline that BMD disorders are substantially prevalent after kidney transplantation, with a ratio higher than 1 out of 2 KTR, as assessed by a DXA scan within 6 mo after kidney transplantation. This is in line with recently published studies and international guidelines focusing on posttransplant bone disease.[21-31] As soon as 6 mo after kidney transplantation, BMD declines 4–10%, with a prevalence of BMD disorders of at least 50% within the first year after transplantation.[22,42-44] Recently, Keronen et al[31] provided valuable DXA scan data to show that in comparison to a baseline pretransplant examination, femoral neck T-score was significantly lower 2 y postkidney transplantation. In addition, although the rate of abnormal mineralization of patients that remained in dialysis decreased after 2 y of follow-up, patients who underwent kidney transplantation depicted a relative

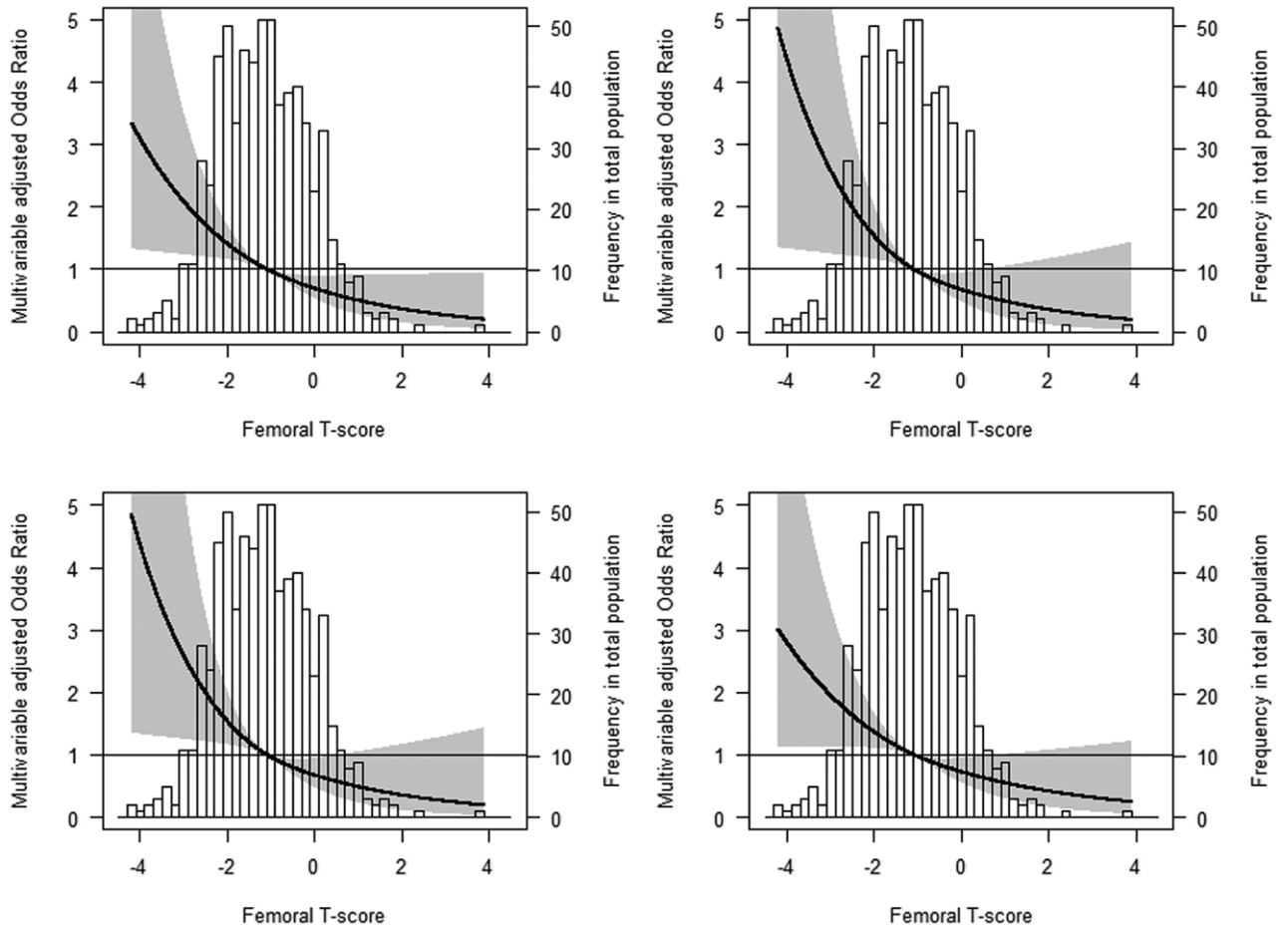


**FIGURE 2.** Association of femoral T-score with risk of AAC. Data were fitted by logistic regression using median femoral T-score as reference value and presented for the unadjusted outcomes (upper left), model 1 (upper right), model 2 (under left), and model 3 (under right). The black line represents the odds ratio and the gray area represents the 95% confidence interval. AAC, abdominal aortic calcification.

increase in abnormal mineralization rates during the same follow-up period.[31] It is relevant to note that low bone turnover increases by 100% within 2 y posttransplant.[31,45] Two major recent studies further support that bone turnover tends to decline after kidney transplantation.[28,30] These findings underscore that transplantation itself is a hallmark for additional hazards for bone health. The latter partly explains that posttransplant bone disease is considered significantly different to that observed within the context of pretransplant CKD-MBD.[21]

The most widely studied clinical consequence hereof is the posttransplant risk of fracture. In the US Renal Data System, 22.5% of KTR showed to have a fracture within 5 y after transplantation (n = 68 814 KTR). However, despite a large body of evidence accounting for the relationship between bone mineralization and calcium deposition in the vascular wall of native CKD patients,[10-14,17,46] bone disease in KTR as a risk factor for an increased risk of vascular calcification is underrepresented in the literature.

Vascular calcification is an active cell-mediated process that resembles developmental osteogenesis, and it is made worse by disturbances in calcium phosphate metabolism with involvement of mediators of bone mineralization.[16,47-49] Bone demineralization and abnormal bone remodeling seen in CKD promote vascular calcification via multiple mechanisms (reviewed in detail in Refs. 14-17,47). By leading to release of circulating nucleational complexes, bone turnover plays a key pathophysiological role linking BMD disorders with vascular calcification.[51-53] Although low-turnover bone disease appears to account for the greatest vascular calcification risk,[12,45] severe high-turnover bone disease has also been linked with vascular calcification.[25,51,52,54,55] Bisphosphonates, aiming at reduction of bone resorption, have been reported to prevent vascular calcification in hemodialysis patients, although the exact mechanism of inhibition remains unclear.[56] In KTR, an inverse association was recently shown between the use of bisphosphonates and hard endpoints after kidney transplantation such as graft and patient survival.[57] Regrettably, however, the data collected by Song et al[57] do not allow to evaluate the potential explanatory involvement of the bone–vascular axis for such findings. As first observed by Malluche et al,[22] and recently emphasized by Seifert and Hruska,[15] in the posttransplant setting, there is no evidence encompassing relation of bone disease with vascular calcification. Yet, vascular calcification is associated with adverse cardiovascular outcomes, which, in turn, leads the burden of premature mortality of KTR.[2,3,9] By underscoring the substantial prevalence of osteoporosis and osteopenia in KTR, and describing its independent association with AAC, we emphasize the multifold nature

of clinical hazards derived from bone disease, particularly after kidney transplantation.

Because a previous study showed that treatment of hyperparathyroidism with cinacalcet—a calcimimetic agent that activates the calcium-sensing receptors in parathyroid glands—may negatively impact thyroid function,[58] we aimed to study whether cinacalcet use pretransplantation and posttransplant may interact with the association between BMD and AAC. In agreement with observations of a large and double-blind randomized study, in which no beneficial impact of cinacalcet on BMD was shown,[59] we found that there is no significant interaction of cinacalcet use pre or posttransplant on the association of BMD with an increased risk of AAC.

Assessment of bone health by means of a DXA scan is a limitation of the current study on the basis that quantitative histomorphometric analysis of a bone biopsy with use of the turnover, mineralization, and volume system is the gold standard for evaluation of bone alterations.[31,60] DXA scans, among other imaging techniques such as magnetic resonance imaging, high-resolution peripheral quantitative computed tomography (CT), and 18F-sodiumfluoride positron emission tomography, are meaningful help to noninvasively assess bone health, yet it is unlikely that these techniques may thoroughly substitute bone biopsies.[26] Nevertheless, it should be realized that in daily clinical practice, bone biopsies are not part of routine diagnostic tools nor used for long-term follow-up of patients, being only exceptionally performed in specific cases.[26] Furthermore, bone biopsy studies in KTR, beyond being logistically hampered by the invasive nature of the procedure, have long delivered limited conclusions due to small sample sizes that lack statistical power to comprehensively study clinical impacts of bone disease. The latter explains the fact that KDIGO bone biopsy recommendations are not graded.[29] Future combined efforts to collaboratively perform adequately powered studies are warranted.[23,26,31] The routine use of DXA scans after kidney transplantation, on the contrary, is supported by KDIGO guidelines. The current study, performed in a large cohort of KTR, provides data derived from DXA scans, a routinely accessible imaging technique for the assessment of bone alterations early post–kidney transplantation. This large dataset allowed us to study the independent association of BMD disorders with the risk of vascular calcification in KTR, which was robust to adjustment for several potential confounders including body mass index,[61,62] eGFR, and immunosuppressive therapy. This observation is particularly relevant by taking into account that patients under the aforementioned regimen indeed showed a significantly lower prevalence of osteoporosis, whereas an alternative regimen (corticosteroids + mycophenolate mofetil + cyclosporine) seemed to relate with a significantly higher prevalence of osteoporosis; yet, the increased risk of AAC observed in relation to a relatively lower BMD was not modified by the use of either immunosuppressive regimen. Taken together, these data may suggest that underlying mechanisms linking vascular disease with bone disease may persist posttransplant. The latter is concerning when contrasting the relatively scant attention given to bone disease in this particular clinical setting in current international guidelines on CKD-MBD (eg, KDIGO[29]), in spite of the opportunity it may offer to aid on managing vascular calcification-associated risk for cardiovascular events after kidney transplantation.[4-9] These findings point toward a rather underestimated, yet epidemiologically relevant and potentially modifiable, nontraditional cardiovascular risk factor after kidney transplantation, which urges collaborative clinical and scientific attention.

Although electron beam CT and multislice CT are considered the gold-standard imaging techniques for quantitative evaluation of vascular calcifications, DXA-based quantification showed to be associated with cardiovascular endpoints in several studies. Studies using improved sensitivity of imaging modalities may be of particular interest to study the progression of vascular calcifications longitudinally. Although studies focusing on CT quantification usually are of limited clinical extrapolation due to cost-effectiveness constraints and lead to a significant radiation burden, DXA-based screening is inexpensive, a single combined procedure of BDM and AAC assessment, and easy to interpret by the attending nephrologist or physician and associates a low radiation burden.[63,64]

The cross-sectional design of the current study should be considered as its main limitation, hampering hard conclusions about the temporal nature of the bone-vascular axis. Achieving further understanding of whether it is bone loss driving vascular calcification, or vascular calcification driving bone loss through impaired blood and nutrient supply to the bones, or rather a vicious circle of these pathophysiological mechanisms occurring concurrently, warrants future studies. Considering that we measured BMD at a single site, the proximal femur, and that we were limited in differentiation of pretransplant from posttransplant bone–vascular disease, comprehensive longitudinal assessments starting from pretransplant stages are essential. Given the potential therapeutic opportunity that the bone–vascular axis may point toward strategies for managing vascular calcification-associated cardiovascular risk after kidney transplantation, which is the leading individual cause of long-term mortality in this population, the current findings hold the plea for future studies in which such analyses are performed.

In conclusion, BMD disorders are highly prevalent in KTR, and BMD assessed by DXA scan is inversely and independently associated with the risk of AAC. These findings point toward the existence of a bone–vascular axis, evidenced, for the first time, after kidney transplantation. Our findings are in line with previous studies, which have separately emphasized the posttransplant milieu as an additional hazard for the complex biology system enclosed by the kidney, skeleton, and cardiovascular system. Further studies are warranted to evaluate whether focused preventive management of CKD-MBD early after kidney transplantation may represent a material therapeutic target to reduce the high cardiovascular burden after kidney transplantation.

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