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

Sotomayor, Camilo G.; Benjamens, Stan; Gomes-Neto, António W.; Pol, Robert A.; Groothof, Dion; Velde-Keyzer, te, Charlotte; Chong, Guillermo; Glaudemans, Andor W. J. M.; Berger, Stefan P.; Bakker, Stephan J. L.

Published in:
Transplantation

DOI:
10.1097/tp.0000000000003226

Publication date:
2021

OPEN

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.

(*Transplantation* 2021;105: 231–239).

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

Received 4 December 2019. Revision received 25 February 2020.

Accepted 4 March 2020.

[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.

The authors declare no conflicts of interest.

C.A.t.V.-K. was supported by a personal grant from the Dutch Kidney Foundation (Kolff grant 17OKG02). C.G.S. was supported by a doctorate studies grant from CONICYT (F 72190118).

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantjournal.com).

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).

ISSN: 0041-1337/21/1051-231

DOI: 10.1097/TP.0000000000003226

<zdoi;10.1097/TP.0000000000003226>

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

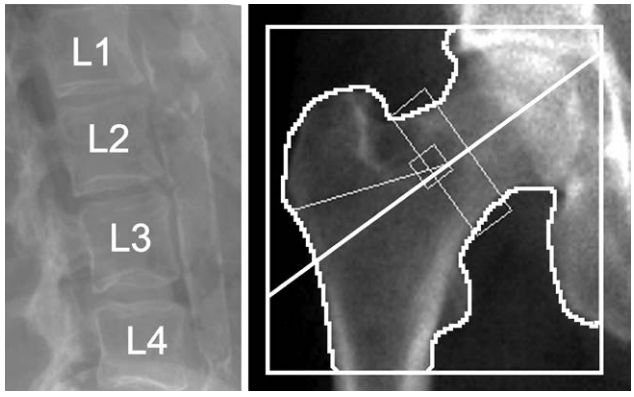

FIGURE 1. Example of a lateral single-energy image of the lumbar spine, with the lumbar vertebral bones L1– L4, and a proximal femur image for areal BMD assessment from dual-energy X-ray absorptiometry (DXA). BMD, bone mineral density.

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

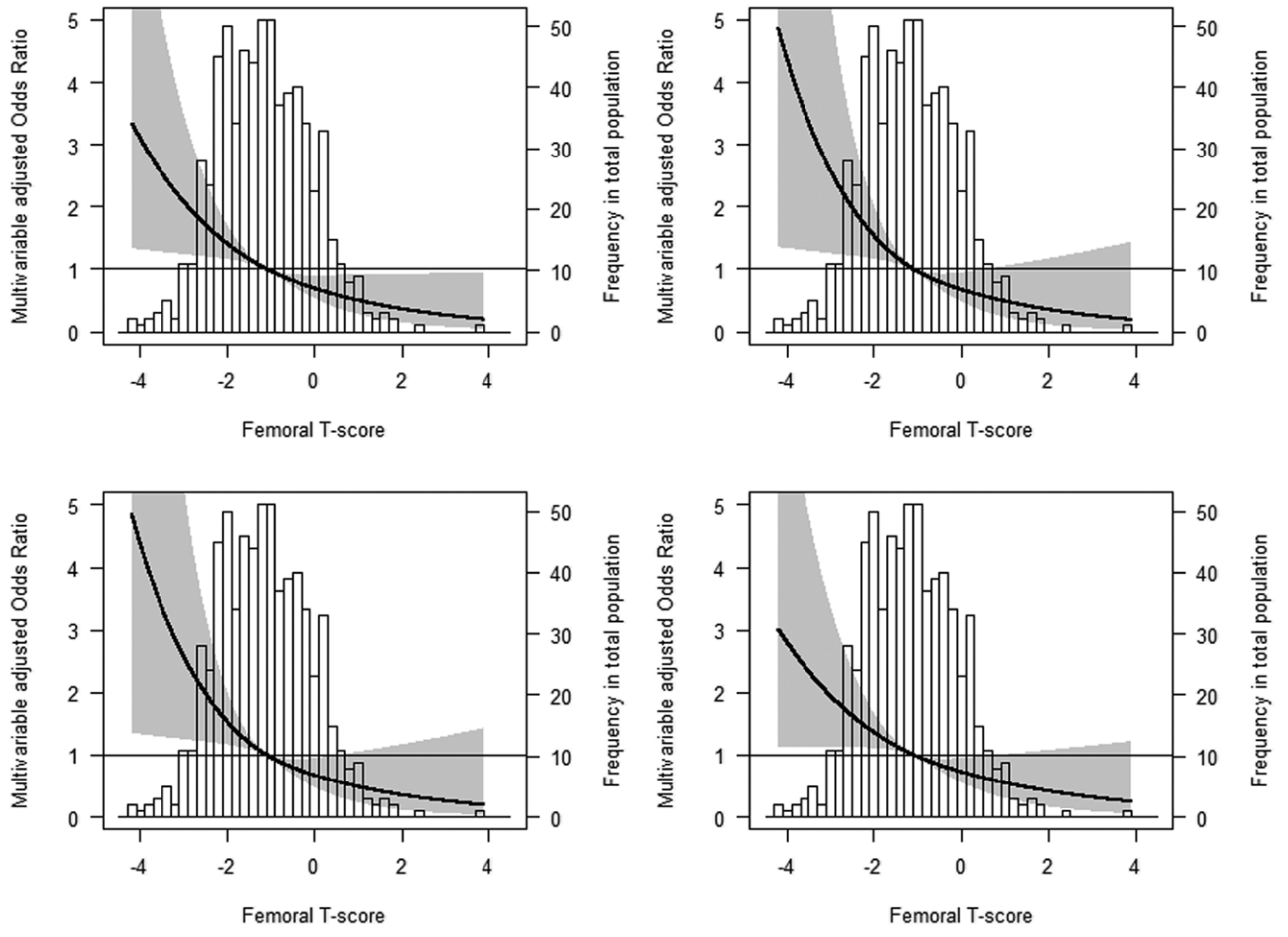

FIGURE 2. Association of femoral T-score with risk of AAC. Data were fitted by logistic regression using median femoral T-score as reference value and presented for the unadjusted outcomes (upper left), model 1 (upper right), model 2 (under left), and model 3 (under right). The black line represents 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.

ACKNOWLEDGMENTS

We thank Dr. José A. de Grazia for his kind collaboration providing helpful comments on the manuscript.

REFERENCES

1. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med.* 2004;351:1296–1305. doi:10.1056/NEJMoa041031
2. Jardine AG, Gaston RS, Fellstrom BC, et al. Prevention of cardiovascular disease in adult recipients of kidney transplants. *Lancet.* 2011;378:1419–1427. doi:10.1016/S0140-6736(11)61334-2

3. Lamb KE, Lodhi S, Meier-Kriesche HU. Long-term renal allograft survival in the United States: a critical reappraisal. *Am J Transplant.* 2011;11:450–462. doi:10.1111/j.1600-6143.2010.03283.x
4. DeLoach SS, Joffe MM, Mai X, et al. Aortic calcification predicts cardiovascular events and all-cause mortality in renal transplantation. *Nephrol Dial Transplant.* 2009;24:1314–1319. doi:10.1093/ndt/gfn753
5. Nguyen PT, Henrard S, Coche E, et al. Coronary artery calcification: a strong predictor of cardiovascular events in renal transplant recipients. *Nephrol Dial Transplant.* 2010;25:3773–3778. doi:10.1093/ndt/gfq268
6. Roe P, Wolfe M, Joffe M, et al. Inflammation, coronary artery calcification and cardiovascular events in incident renal transplant recipients. *Atherosclerosis.* 2010;212:589–594. doi:10.1016/j.atherosclerosis.2010.05.016
7. Claes KJ, Heye S, Bammens B, et al. Aortic calcifications and arterial stiffness as predictors of cardiovascular events in incident renal transplant recipients. *Transpl Int.* 2013;26:973–981. doi:10.1111/tri.12151
8. Davis B, Marin D, Hurwitz LM, et al. Application of a novel CT-based iliac artery calcification scoring system for predicting renal transplant outcomes. *AJR Am J Roentgenol.* 2016;206:436–441. doi:10.2214/AJR.15.14794
9. Benjamens S, Pol RA, Glaudemans AWJM, et al. A high abdominal aortic calcification score by dual X-ray absorptiometry is associated with cardiovascular events after kidney transplantation. *Nephrol Dial Transplant.* 2018;33:2253–2259. doi:10.1093/ndt/gfy158
10. Braun J, Oldendorf M, Moshage W, et al. Electron beam computed tomography in the evaluation of cardiac calcification in chronic dialysis patients. *Am J Kidney Dis.* 1996;27:394–401. doi:10.1016/s0272-6386(96)90363-7
11. Goodman WG, Goldin J, Kuizon BD, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med.* 2000;342:1478–1483. doi:10.1056/NEJM200005183422003
12. London GM, Marty C, Marchais SJ, et al. Arterial calcifications and bone histomorphometry in end-stage renal disease. *J Am Soc Nephrol.* 2004;15:1943–1951. doi:10.1097/01.asn.0000129337.50739.48
13. Moe SM. Vascular calcification and renal osteodystrophy relationship in chronic kidney disease. *Eur J Clin Invest.* 2006;36 (Suppl 2):51–62. doi:10.1111/j.1365-2362.2006.01665.x
14. Moe SM, Drüeke T, Lameire N, et al. Chronic kidney disease-mineral-bone disorder: a new paradigm. *Adv Chronic Kidney Dis.* 2007;14:3–12. doi:10.1053/j.ackd.2006.10.005
15. Seifert ME, Hruska KA. The kidney-vascular-bone axis in the chronic kidney disease-mineral bone disorder. *Transplantation.* 2016;100:497–505. doi:10.1097/TP.0000000000000903
16. Mizobuchi M, Towler D, Slatopolsky E. Vascular calcification: the killer of patients with chronic kidney disease. *J Am Soc Nephrol.* 2009;20:1453–1464. doi:10.1681/ASN.2008070692
17. Thompson B, Towler DA. Arterial calcification and bone physiology: role of the bone-vascular axis. *Nat Rev Endocrinol.* 2012;8:529–543. doi:10.1038/nrendo.2012.36
18. Perrin P, Caillard S, Javier RM, et al. Persistent hyperparathyroidism is a major risk factor for fractures in the five years after kidney transplantation. *Am J Transplant.* 2013;13:2653–2663. doi:10.1111/ajt.12425
19. Julian BA, Laskow DA, Dubovsky J, et al. Rapid loss of vertebral mineral density after renal transplantation. *N Engl J Med.* 1991;325:544–550. doi:10.1056/NEJM199108223250804
20. Monier-Faugere MC, Mawad H, Qi Q, et al. High prevalence of low bone turnover and occurrence of osteomalacia after kidney transplantation. *J Am Soc Nephrol.* 2000;11:1093–1099.
21. Bouquegneau A, Salam S, Delanaye P, et al. Bone disease after kidney transplantation. *Clin J Am Soc Nephrol.* 2016;11:1282–1296. doi:10.2215/CJN.11371015
22. Malluche HH, Monier-Faugere MC, Herberth J. Bone disease after renal transplantation. *Nat Rev Nephrol.* 2010;6:32–40. doi:10.1038/nrneph.2009.192
23. Drüeke TB, Evenepoel P. The bone after kidney transplantation. *Clin J Am Soc Nephrol.* 2019;14:795–797. doi:10.2215/CJN.04940419
24. Neves CL, dos Reis LM, Batista DG, et al. Persistence of bone and mineral disorders 2 years after successful kidney transplantation. *Transplantation.* 2013;96:290–296. doi:10.1097/TP.0b013e3182985468
25. Iyer SP, Nikkel LE, Nishiyama KK, et al. Kidney transplantation with early corticosteroid withdrawal: paradoxical effects at the central and peripheral skeleton. *J Am Soc Nephrol.* 2014;25:1331–1341. doi:10.1681/ASN.2013080851
26. Evenepoel P, D'Haese P, Bacchetta J, et al. ERA-EDTA Working Group on CKD-MBD. Bone biopsy practice patterns across Europe: the European renal osteodystrophy initiative-a position paper. *Nephrol Dial Transplant.* 2017;32:1608–1613. doi:10.1093/ndt/gfw468
27. Perrin P, Kiener C, Javier RM, et al. Recent changes in chronic kidney disease-mineral and bone disorders and associated fractures after kidney transplantation. *Transplantation.* 2017;101:1897–1905. doi:10.1097/TP.0000000000001449
28. Evenepoel P, Behets GJ, Viaene L, et al. Bone histomorphometry in de novo renal transplant recipients indicates a further decline in bone resorption 1 year posttransplantation. *Kidney Int.* 2017;91:469–476. doi:10.1016/j.kint.2016.10.008
29. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD-MBD). *Kidney Int Suppl*. 2017;7:1–59.
30. Marques IDB, Araújo MJCLN, Graciolli FG, et al. A randomized trial of zoledronic acid to prevent bone loss in the first year after kidney transplantation. *J Am Soc Nephrol.* 2019;30:355–365. doi:10.1681/ASN.2018060656
31. Keronen S, Martola L, Finne P, et al. Changes in bone histomorphometry after kidney transplantation. *Clin J Am Soc Nephrol.* 2019;14:894–903. doi:10.2215/CJN.09950818
32. Veit Barreto D, De F, Barreto C, et al. Association of changes in bone remodeling and coronary calcification in hemodialysis patients: a prospective study. *Am J Kidney Dis*. 2008;52:1139–1150. doi:10.1053/j.ajkd.2008.06.024
33. London GM, Marchais SJ, Guérin AP, et al. Association of bone activity, calcium load, aortic stiffness, and calcifications in ESRD. *J Am Soc Nephrol.* 2008;19:1827–1835. doi:10.1681/ASN.2007050622
34. Adragao T, Herberth J, Monier-Faugere MC, et al. Low bone volume–a risk factor for coronary calcifications in hemodialysis patients. *Clin J Am Soc Nephrol.* 2009;4:450–455. doi:10.2215/CJN.01870408
35. Asci G, Ok E, Savas R, et al. The link between bone and coronary calcifications in CKD-5 patients on haemodialysis. *Nephrol Dial Transplant.* 2011;26:1010–1015. doi:10.1093/ndt/gfq491
36. Gomes-Neto AW, Osté MCJ, Sotomayor CG, et al. Fruit and vegetable intake and risk of posttransplantation diabetes in renal transplant recipients. *Diabetes Care.* 2019;42:1645–1652. doi:10.2337/dc19-0224
37. Sotomayor CG, Gomes-Neto AW, Eisenga MF, et al. Consumption of fruits and vegetables and cardiovascular mortality in renal transplant recipients: a prospective cohort study. *Nephrol Dial Transplant.* 2020;35:357–365. doi:10.1093/ndt/gfy248
38. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2003;26(Suppl 1):S5–S20. doi:10.2337/diacare.26.2007.s5
39. Piepoli MF, Hoes AW, Agewall S, et al; ESC Scientific Document Group. 2016 European guidelines on cardiovascular disease prevention in clinical practice: the sixth joint task force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts)developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J.* 2016;37:2315–2381. doi:10.2337/diacare.26.2007.s5
40. Levey AS, Stevens LA, Schmid CH, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150:604–612. doi:10.7326/0003-4819-150-9-200905050-00006
41. Schousboe JT, Wilson KE, Kiel DP. Detection of abdominal aortic calcification with lateral spine imaging using DXA. *J Clin Densitom.* 2006;9:302–308. doi:10.1016/j.jocd.2006.05.007
42. Marcén R, Caballero C, Uriol O, et al. Prevalence of osteoporosis, osteopenia, and vertebral fractures in long-term renal transplant recipients. *Transplant Proc.* 2007;39:2256–2258. doi:10.1016/j.transproceed.2007.07.073
43. Durieux S, Mercadal L, Orcel P, et al. Bone mineral density and fracture prevalence in long-term kidney graft recipients. *Transplantation.* 2002;74:496–500. doi:10.1097/00007890-200208270-00011
44. Mazzaferro S, Diacinti D, Proietti E, et al. Morphometric X-ray absorptiometry in the assessment of vertebral fractures in renal transplant

patients. *Nephrol Dial Transplant.* 2006;21:466–471. doi:10.1093/ndt/gfi206
45. Hutchison AJ, Whitehouse RW, Boulton HF, et al. Correlation of bone histology with parathyroid hormone, vitamin D3, and radiology in end-stage renal disease. *Kidney Int.* 1993;44:1071–1077. doi:10.1038/ki.1993.350
46. Giachelli CM. Vascular calcification mechanisms. *J Am Soc Nephrol.* 2004;15:2959–2964. doi:10.1097/01.ASN.0000145894.57533.C4
47. Ducy P, Karsenty G. The family of bone morphogenetic proteins. *Kidney Int.* 2000;57:2207–2214. doi:10.1046/j.1523-1755.2000.00081.x
48. Moe SM, O'Neill KD, Duan D, et al. Medial artery calcification in ESRD patients is associated with deposition of bone matrix proteins. *Kidney Int.* 2002;61:638–647. doi:10.1046/j.1523-1755.2002.00170.x
49. Cheng SL, Shao JS, Charlton-Kachigian N, et al. MSX2 promotes osteogenesis and suppresses adipogenic differentiation of multipotent mesenchymal progenitors. *J Biol Chem.* 2003;278:45969–45977. doi:10.1074/jbc.M306972200
50. Moe SM, Chen NX. Pathophysiology of vascular calcification in chronic kidney disease. *Circ Res.* 2004;95:560–567. doi:10.1161/01.RES.0000141775.67189.98
51. Price PA, Faus SA, Williamson MK. Bisphosphonates alendronate and ibandronate inhibit artery calcification at doses comparable to those that inhibit bone resorption. *Arterioscler Thromb Vasc Biol.* 2001;21:817–824. doi:10.1161/01.atv.21.5.817
52. Price PA, June HH, Buckley JR, et al. Osteoprotegerin inhibits artery calcification induced by warfarin and by vitamin D. *Arterioscler Thromb Vasc Biol.* 2001;21:1610–1616. doi:10.1161/hq1001.097102
53. Price PA, Caputo JM, Williamson MK. Bone origin of the serum complex of calcium, phosphate, fetuin, and matrix Gla protein: biochemical evidence for the cancellous bone-remodeling compartment. *J Bone Miner Res.* 2002;17:1171–1179. doi:10.1359/jbmr.2002.17.7.1171
54. Price PA, Buckley JR, Williamson MK. The amino bisphosphonate ibandronate prevents vitamin D toxicity and inhibits vitamin D-induced calcification of arteries, cartilage, lungs and kidneys in rats. *J Nutr.* 2001;131:2910–2915. doi:10.1093/jn/131.11.2910
55. Price PA, June HH, Buckley JR, et al. SB 242784, a selective inhibitor of the osteoclastic V-H+atpase, inhibits arterial calcification in the rat. *Circ Res.* 2002;91:547–552. doi:10.1161/01.res.0000033987.22436.50
56. Nitta K, Akiba T, Suzuki K, et al. Effects of cyclic intermittent etidronate therapy on coronary artery calcification in patients receiving long-term hemodialysis. *Am J Kidney Dis.* 2004;44:680–688.
57. Song S, Huh K, Choi H, et al. Bisphosphonates effectively improve the long term renal transplant outcomes; a single center retrospective study [abstract]. *Am J Transplant*. 2019;19(Suppl 3) 317
58. Ritter C, Miller B, Coyne DW, et al. Paricalcitol and cinacalcet have disparate actions on parathyroid oxyphil cell content in patients with chronic kidney disease. *Kidney Int.* 2017;92:1217–1222. doi:10.1016/j.kint.2017.05.003
59. Evenepoel P, Cooper K, Holdaas H, et al. A randomized study evaluating cinacalcet to treat hypercalcemia in renal transplant recipients with persistent hyperparathyroidism. *Am J Transplant.* 2014;14:2545–2555. doi:10.1111/ajt.12911
60. Gal-Moscovici A, Sprague SM. Bone health in chronic kidney disease-mineral and bone disease. *Adv Chronic Kidney Dis.* 2007;14:27–36. doi:10.1053/j.ackd.2006.10.010
61. Ribot C, Tremollieres F, Pouilles JM, et al. Obesity and postmenopausal bone loss: the influence of obesity on vertebral density and bone turnover in postmenopausal women. *Bone.* 1987;8:327–331. doi:10.1016/8756-3282(87)90062-7
62. Siris ES, Miller PD, Barrett-Connor E, et al. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: results from the National Osteoporosis Risk Assessment. *JAMA.* 2001;286:2815–2822. doi:10.1001/jama.286.22.2815
63. Dequeker J. Osteoporotic fractures, ageing, and the bone density T-score. *Clin Rheumatol.* 2000;19:171–173. doi:10.1007/s100670050150
64. Adragão T, Frazão JM. Cardiovascular risk in dialysis patients: an X-ray vision on vascular calcifications. *Kidney Int.* 2008;74:1505–1507. doi:10.1038/ki.2008.503