

# Bone Mass and Microarchitecture in CKD Patients with Fracture

Thomas L. Nickolas,\* Emily Stein,\* Adi Cohen,\* Valerie Thomas,\* Ronald B. Staron,<sup>†</sup> Donald J. McMahon,\* Mary B. Leonard,<sup>‡</sup> and Elizabeth Shane\*

Departments of \*Medicine and <sup>†</sup>Radiology, Columbia University Medical Center, New York, New York; and

<sup>‡</sup>Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

## ABSTRACT

Patients with predialysis chronic kidney disease (CKD) have increased risk for fracture, but the structural mechanisms underlying this increased skeletal fragility are unknown. We measured areal bone mineral density (aBMD) by dual-energy x-ray absorptiometry at the spine, hip, and radius, and we measured volumetric BMD (vBMD), geometry, and microarchitecture by high-resolution peripheral quantitative computed tomography (HR-pQCT) at the radius and tibia in patients with CKD: 32 with fracture and 59 without fracture. Patients with fracture had lower aBMD at the spine, total hip, femoral neck, and the ultradistal radius, the last having the strongest association with fracture. By HR-pQCT of the radius, patients with fracture had lower cortical area and thickness, total and trabecular vBMD, and trabecular number and greater trabecular separation and network heterogeneity. At the tibia, patients with fracture had significantly lower cortical area, thickness, and total and cortical density. Total vBMD at both radius and tibia most strongly associated with fracture. By receiver operator characteristic curve analysis, patients with longer duration of CKD had area under the curve of >0.75 for aBMD at both hip sites and the ultradistal radius, vBMD and geometry at the radius and tibia, and microarchitecture at the tibia. In summary, patients with predialysis CKD and fractures have lower aBMD by dual-energy x-ray absorptiometry and lower vBMD, thinner cortices, and trabecular loss by HR-pQCT. These density and structural differences may underlie the increased susceptibility to fracture among patients with CKD.

*J Am Soc Nephrol* 21: 1371–1380, 2010. doi: 10.1681/ASN.2009121208

Fracture rates in patients with ESRD are elevated,<sup>1</sup> as high as individuals who have normal kidney function and are older by 10 to 20 years.<sup>2</sup> Recently, there has been increasing recognition that patients with predialysis chronic kidney disease (CKD) also experience an increased fracture burden.<sup>2–5</sup> In 2006, we reported that participants who were older than 50 years in the Third National Health and Nutrition Examination Survey (NHANES III) and had an estimated GFR (eGFR) between 15 and 59 ml/min (stages 3 and 4 CKD) had a two-fold higher risk for hip fracture than individuals without CKD.<sup>6</sup> Subsequent studies confirmed our findings and also demonstrated that fracture risk increases as kidney function declines.<sup>3–5</sup> In one study, hip fracture risk was as high in patients with stage 4 CKD as in patients with ESRD.<sup>4</sup> Given the rapid expansion of the

population of individuals who are older than 65 years worldwide and the high prevalence of CKD in the elderly,<sup>7</sup> it is highly important to improve our understanding of the structural and biologic mechanisms that contribute to increased fracture rates in patients with CKD so that we can develop strategies to identify those who are at risk for fracture.

In patients with ESRD, relationships between areal

Received December 2, 2009. Accepted February 15, 2010.

Published online ahead of print. Publication date available at [www.jasn.org](http://www.jasn.org).

**Correspondence:** Dr. Thomas L. Nickolas, Columbia University Medical Center, 622 West 168th Street, PH 4 Stem, Room 124, New York, NY 10032. Phone: 212-305-5020; Fax: 212-305-6692; E-mail: [tl2001@columbia.edu](mailto:tl2001@columbia.edu)

Copyright © 2010 by the American Society of Nephrology

bone mineral density (aBMD) measured by dual-energy x-ray absorptiometry (DXA) and prevalent fractures are inconsistent; some studies detected no difference in aBMD,<sup>8–11</sup> whereas others, including a meta-analysis, found lower aBMD in those with prevalent spine and nonspine fractures<sup>8,11,12</sup>; therefore, recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for the diagnosis and management of CKD-mineral and bone disorder (CKD-MBD) do not recommend routine measurement of aBMD by DXA in patients with ESRD or in those with late stages 3 through 5 CKD, because more severe CKD is commonly associated with renal osteodystrophy.<sup>13</sup> In contrast, however, KDIGO guidelines recommend DXA to assess fracture risk in patients with stage 1 through early stage 3 CKD, as long as biochemical testing does not suggest CKD-MBD.

Fractures occur when bone strength is not sufficient to withstand an applied force. Bone strength is determined both by the density of bone present and by the quality of that bone. Whereas bone density is measured by DXA, other factors that contribute to bone quality, such as cortical and trabecular microarchitecture, are not. Chronic parathyroid hormone excess, a common biochemical feature of CKD, is generally associated with trabecularization of endocortical bone, cortical thinning, and increased cortical porosity.<sup>14–16</sup> Whereas effects of hyperparathyroidism on trabecular bone are less consistent, trabecular structure and connectivity are generally maintained.<sup>14</sup> The resolution of DXA is too low to distinguish between cortical and trabecular bone, both of which influence resistance to fracture; this may account for its inconsistent utility in discriminating fracture status in patients with ESRD.

Bone biopsy studies have demonstrated that histomorphometric abnormalities of renal osteodystrophy may begin early in the development of CKD<sup>17</sup>; therefore, DXA may also have limited utility in patients with predialysis kidney disease. Recently, Bacchetta *et al.*<sup>18</sup> used high-resolution peripheral quantitative computed tomography (HR-pQCT; voxel size 82  $\mu\text{m}$ ) to demonstrate that both cortical and trabecular microarchitecture are abnormal in patients with early CKD compared with healthy control subjects. In addition, they reported thinner cortices and abnormal trabecular microarchitecture in a small number of patients with CKD and with fractures; however, they did not measure aBMD by DXA. In this study, we measured aBMD by DXA and volumetric BMD (vBMD) and bone microarchitecture by HR-pQCT in patients with predialysis CKD (stages 2 through 5), with and without prevalent fracture. On the basis of results in postmenopausal women with normal kidney function reported by Boutroy *et al.*<sup>19</sup> and by our group,<sup>20</sup> we hypothesized that HR-pQCT would detect abnormalities of vBMD and bone geometry and microstructure in patients with CKD and a history of fracture, whereas measurement of aBMD by DXA would not.

## RESULTS

### Characteristics of Study Participants

Of 91 patients, 32 had a total of 49 fractures. Eighteen patients had 22 vertebral fractures, 14 of which were mild and eight of

which were moderate. Twenty patients had 27 nonvertebral fractures (eight wrist, four ankle, three rib, two humerus, two femur, three tibia/fibula, four metatarsal, and two at other sites). Six patients had both prevalent vertebral and nonvertebral fracture.

Groups with and without fracture (Table 1) were balanced for age, race, weight, height, use of tobacco and alcohol, cause and duration of CKD, and laboratory parameters (serum calcium and phosphorus) associated with secondary hyperparathyroidism (SHPT) and metabolic acidosis ( $\text{CO}_2$ ). Although more women were present in the fracture group, the difference was not statistically significant ( $P = 0.1$ ). The proportion of patients who were taking phosphate binders and calcium and vitamin D supplements did not differ.

### DXA and HR-pQCT Measurements by Fracture Status

In patients with a history of fracture, absolute aBMD ( $\text{g}/\text{cm}^2$ ) by DXA was 7 to 10% lower (Table 2) at the lumbar spine (LS), femoral neck (FN), total hip (TH), ultradistal radius (UDR) but not one-third radius (1/3R). More patients with fracture had osteoporosis (T score  $\leq -2.5$ ) at the TH (16 *versus* 3%;  $P < 0.05$ ) and UDR (38 *versus* 16%;  $P < 0.05$ ) than patients without fracture (Figure 1); however, the majority of patients with fracture had T scores  $> -2.5$  (all sites 48%, LS 81%, TH 81%, FN 75%, 1/3R 72%, and UDR 63%). Low aBMD at the LS, both hip sites, and the UDR but not 1/3R was associated with increased odds of fracture (Table 2). For each SD decrease in LS, TH, and FN aBMD, there was a 93, 65, and 86% increased odds of fracture, respectively. Notably, low UDR aBMD was associated with the highest risk, with greater than two-fold increased odds of fracture.

Figure 2 shows representative HR-pQCT images of the radius and tibia (Figure 2A), from a healthy, postmenopausal white woman (Figure 2B), a woman with CKD and without fracture (Figure 2C), and a woman with CKD and with fracture (Figure 2D). At the radius, HR-pQCT measurements of bone geometry, density, and microarchitecture demonstrated that cortical area (CtArea) and thickness (CtTh), total density (Dtot) and trabecular density (Dtrab), and trabecular number (TbN) were lower and trabecular separation (TbSp) and network heterogeneity (TbSpSD) higher in the fracture group (Table 2). For each SD decrease in CtArea and CtTh, there was an 85 and 78% increased odds of fracture, respectively (Table 2). Similarly, each SD decrease in Dtot and Dtrab was associated with more than a two-fold increased odds of fracture. Trabecular microarchitectural parameters associated with fracture included TbN, TbSp, and TbSpSD; each SD decrease in TbN increased odds of fracture by 79%, whereas each SD increase in TbSp and TbSpSD increased odds of fracture by 71 and 76%, respectively.

At the weight-bearing tibia, CtArea, CtTh, and both Dtot and cortical density (Dcort) were lower in the fracture group, but trabecular vBMD (Dtrab) and microarchitecture did not differ. Similarly, cortical parameters were associated with fracture, whereas trabecular parameters were not. Both CtArea and

**Table 1.** Characteristics of study participants

Characteristic	Fracture (n = 32)	No Fracture (n = 59)
eGFR (ml/min; median [range])	33 (7 to 68)	30 (7 to 76)
Women (n [%])	19 (59)	24 (41)
Age (years; mean ± SD)	72 ± 9	70 ± 9
Race (n [%])		
white	15 (47)	22 (37)
black	4 (12)	4 (7)
Hispanic	13 (41)	33 (56)
Weight (kg; mean ± SD)	76 ± 17	81 ± 14
Height (cm; mean ± SD)	165 ± 10	165 ± 9
BMI (mean ± SD)	28 ± 5	29 ± 6
Duration of kidney failure (years; median [range])	3.7 (0.2 to 26.0)	5.1 (0.1 to 20.2)
Cause of kidney failure (n [%])		
diabetes or hypertension	23 (72)	42 (71)
nephritis/nephrosis	2 (6)	4 (7)
other	7 (22)	13 (22)
Laboratory parameters		
serum calcium (mg/dl; mean ± SD)	9.5 ± 0.6	9.4 ± 0.5
serum phosphorus (mg/dl; mean ± SD)	4.0 ± 1.0	3.8 ± 0.7
serum bicarbonate (mM/L; mean ± SD)	23.8 ± 3.6	23.0 ± 3.1
Current alcohol consumption (n [%])	3 (9)	7 (12)
Current smoking (n [%])	4 (12)	9 (15)
Using a vitamin D supplement (n [%])	20 (74)	36 (61)
Using a calcium supplement (n [%])	8 (27)	12 (21)
Using phosphate binder (n [%])	5 (17)	10 (17)

*P* < 0.05. BMI, body mass index.

CtTh were associated with increased odds of fracture by 73 and 82%, respectively. Each SD decrease in Dtot and Dcort was associated with an 85 and 70% increased odds of fracture, respectively. Between groups, differences (3 to 19%) were generally smaller at the tibia than at the radius. In general, percentage differences between groups with and without fracture (3 to 44%) were larger by HR-pQCT than by DXA.

Correlations between measures of aBMD and vBMD by DXA and HR-pQCT, respectively, were weakest between TH BMD and radius Dcort ( $r = 0.22$ ,  $P = 0.03$ ) and strongest between UDR BMD and radius Dcort ( $r = 0.81$ ;  $P < 0.0001$ ).

Receiver operating characteristic (ROC) analyses of the whole cohort demonstrated that no DXA or HR-pQCT measurement yielded an area under the curve (AUC) of >0.75 (Table 2); however, stratification by tertile of CKD duration (Table 3) improved fracture discrimination by both DXA and HR-pQCT. For patients in the lowest tertile, no DXA or HR-pQCT parameter discriminated fracture status. For patients in the middle tertile, HR-pQCT measures of density (Dtot), geometry (CtArea and CtTh), and trabecular microarchitecture (TbN, TbSp, and TbSpSD) at the tibia had high discrimination for fracture; Dtot, TbN, and TbSp had highest discrimination (AUC 0.86 and 0.81, respectively). In contrast, for patients in the highest tertile, HR-pQCT measures of density (Dtot and Dcort) and geometry (CtArea and CtTh) at the radius and tibia had higher discrimination for fracture, whereas trabecular microarchitecture did not. The AUC was 0.86, 0.82, and 0.81 for radius

Dtot, Dcort, and CtTh, respectively, and 0.80 and 0.78 for tibia Dcort and CtArea, respectively. For DXA, UDR and FN aBMD performed with highest discrimination in patients with the longest CKD duration (AUC 0.84 and 0.78, respectively; Figure 3). Patients who had had CKD for ≥6.9 years had more severe CKD than those with CKD for <6.9 years (mean eGFR 24 ± 11 versus 38 ± 17 ml/min;  $P < 0.0001$ ). Age, body mass index, gender, race, calcium, phosphorus, or CO<sub>2</sub> did not differ by CKD duration (data not shown).

## DISCUSSION

To our knowledge, this is the first study to investigate and compare the utility of DXA and HR-pQCT to assess fracture status in patients with predialysis CKD. Our results indicate an array of parameters measured by both techniques differ between patients with and without fracture. With regard to measures of density, aBMD by DXA of the LS, TH, FN, and UDR were associated with fracture. By HR-pQCT, Dtrab at the radius but not the tibia and Dcort at the tibia but not the radius were associated with fracture. With regard to bone geometry and microarchitecture, CtArea and CtTh of both radius and tibia and TbN and TbSpSD at the radius only were associated with fracture. From a mechanistic perspective, HR-pQCT imaging suggested that lower cortical density, thinner cortices, and trabecular loss distinguish patients with CKD and with fracture. Despite marked differences in all of these parameters in the group as a whole, no DXA or HR-pQCT measurement

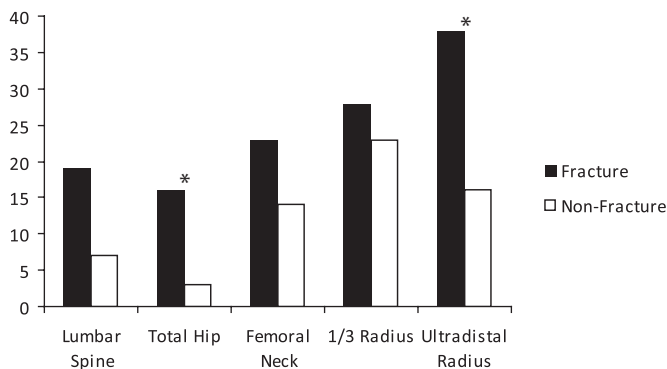
**Table 2.** Comparison of imaging parameters for patients with CKD and with and without fractures

Parameter	Fracture (mean ± SD)	No Fracture (mean ± SD)	% Difference	OR (95% CI)	AUC (95% CI)
<b>DXA</b>					
total LS BMD (g/cm <sup>2</sup> )	0.957 ± 0.173	1.069 ± 0.203 <sup>a</sup>	-10	1.93 (1.15 to 3.25)	0.66 (0.54 to 0.78)
total LS T score	-1.1 ± 1.5	-0.1 ± 1.8 <sup>a</sup>		1.91 (1.15 to 3.17)	0.67 (0.55 to 0.78)
TH BMD (g/cm <sup>2</sup> )	0.840 ± 0.171	0.923 ± 0.176 <sup>b</sup>	-9	1.65 (1.02 to 2.67)	0.63 (0.50 to 0.75)
TH T score	-1.2 ± 1.1	-0.7 ± 1.1		1.60 (0.98 to 2.58)	0.61 (0.49 to 0.73)
FN BMD (g/cm <sup>2</sup> )	0.677 ± 0.127	0.755 ± 0.154 <sup>b</sup>	-10	1.86 (1.10 to 3.14)	0.66 (0.55 to 0.78)
FN T score	-1.9 ± 0.9	-1.4 ± 1.1 <sup>b</sup>		1.76 (1.05 to 2.99)	0.62 (0.50 to 0.75)
1/3R BMD (g/cm <sup>2</sup> )	0.652 ± 0.107	0.697 ± 0.117	-7	1.51 (0.96 to 2.37)	0.60 (0.48 to 0.72)
1/3R T score	-1.6 ± 1.8	-1.2 ± 1.4		1.30 (0.84 to 2.02)	0.52 (0.39 to 0.65)
UDR BMD (g/cm <sup>2</sup> )	0.363 ± 0.084	0.430 ± 0.093 <sup>a</sup>	-16	2.29 (1.34 to 3.89)	0.68 (0.57 to 0.80)
UDR T score	-2.1 ± 1.4	-1.3 ± 1.2 <sup>c</sup>		1.94 (1.17 to 3.21)	0.62 (0.50 to 0.75)
<b>HRpQCT, radius</b>					
total area (mm <sup>2</sup> )	274 ± 59	293 ± 73	-6	1.33 (0.85 to 2.08)	0.56 (0.44 to 0.69)
CtArea (mm <sup>2</sup> )	45 ± 15	55 ± 19 <sup>a</sup>	-18	1.85 (1.12 to 3.08)	0.63 (0.51 to 0.75)
trabecular area (mm <sup>2</sup> )	228 ± 53	237 ± 69	-4	1.15 (0.74 to 1.79)	0.52 (0.40 to 0.65)
Dtot (mg HA/cm <sup>3</sup> )	255 ± 63	300 ± 71 <sup>a</sup>	-15	2.11 (1.24 to 3.57)	0.66 (0.54 to 0.77)
Dcort (mg HA/cm <sup>3</sup> )	801 ± 82	825 ± 81	-3	1.35 (0.87 to 2.10)	0.56 (0.43 to 0.68)
Dtrab (mg HA/cm <sup>3</sup> )	122 ± 43	151 ± 48 <sup>a</sup>	-19	2.01 (1.21 to 3.34)	0.65 (0.53 to 0.77)
BV/TV (%)	10.2 ± 3.6	12.6 ± 4.0 <sup>a</sup>	-19	2.01 (1.21 to 3.35)	0.65 (0.53 to 0.76)
CtTh (μm)	626 ± 179	743 ± 241 <sup>b</sup>	-16	1.78 (1.09 to 2.91)	0.61 (0.49 to 0.73)
TbN (1/mm)	1.7 ± 0.5	2.0 ± 0.4 <sup>b</sup>	-12	1.79 (1.13 to 2.83)	0.64 (0.52 to 0.77)
trabecular thickness (μm)	59 ± 13	64 ± 13	-8	1.62 (0.98 to 2.70)	0.58 (0.45 to 0.71)
TbSp (μm)	574 ± 206	477 ± 164 <sup>b</sup>	20	1.71 (1.07 to 2.74)	0.65 (0.53 to 0.78)
TbSpSD (1/μm)	315 ± 214	218 ± 146 <sup>a</sup>	44	1.76 (1.07 to 2.91)	0.65 (0.53 to 0.78)
<b>HRpQCT, tibia</b>					
total area (mm <sup>2</sup> )	769 ± 139	771 ± 147	-0.3	1.02 (0.66 to 1.57)	0.50 (0.37 to 0.63)
CtArea (mm <sup>2</sup> )	90 ± 46	110 ± 38 <sup>b</sup>	-18	1.73 (1.04 to 2.88)	0.67 (0.55 to 0.79)
trabecular area (mm <sup>2</sup> )	679 ± 133	662 ± 143	3	0.88 (0.57 to 1.36)	0.55 (0.42 to 0.67)
Dtot (mg HA/cm <sup>3</sup> )	226 ± 56	259 ± 63 <sup>b</sup>	-13	1.85 (1.11 to 3.09)	0.65 (0.53 to 0.76)
Dcort (mg HA/cm <sup>3</sup> )	744 ± 87	786 ± 77 <sup>b</sup>	-5	1.70 (1.07 to 2.68)	0.62 (0.50 to 0.74)
Dtrab (mg HA/cm <sup>3</sup> )	142 ± 37	158 ± 48	-10	1.48 (0.92 to 2.37)	0.57 (0.45 to 0.70)
BV/TV (%)	11.8 ± 3.1	13.2 ± 4.0	-10	1.48 (0.92 to 2.38)	0.58 (0.45 to 0.70)
CtTh (μm)	793 ± 374	979 ± 338 <sup>b</sup>	-19	1.82 (1.09 to 3.02)	0.68 (0.56 to 0.80)
TbN (1/mm)	1.7 ± 0.4	1.9 ± 0.5	-8	1.44 (0.92 to 2.25)	0.58 (0.46 to 0.70)
trabecular thickness (μm)	68 ± 12	69 ± 10	-2	1.11 (0.71 to 1.72)	0.56 (0.43 to 0.68)
TbSp (μm)	542 ± 189	494 ± 179	10	1.29 (0.84 to 1.98)	0.58 (0.46 to 0.70)
TbSpSD (1/μm)	292 ± 232	248 ± 163	18	1.25 (0.82 to 1.92)	0.56 (0.44 to 0.68)

<sup>a</sup>P < 0.01.

<sup>b</sup>P < 0.05.

<sup>c</sup>P < 0.001.

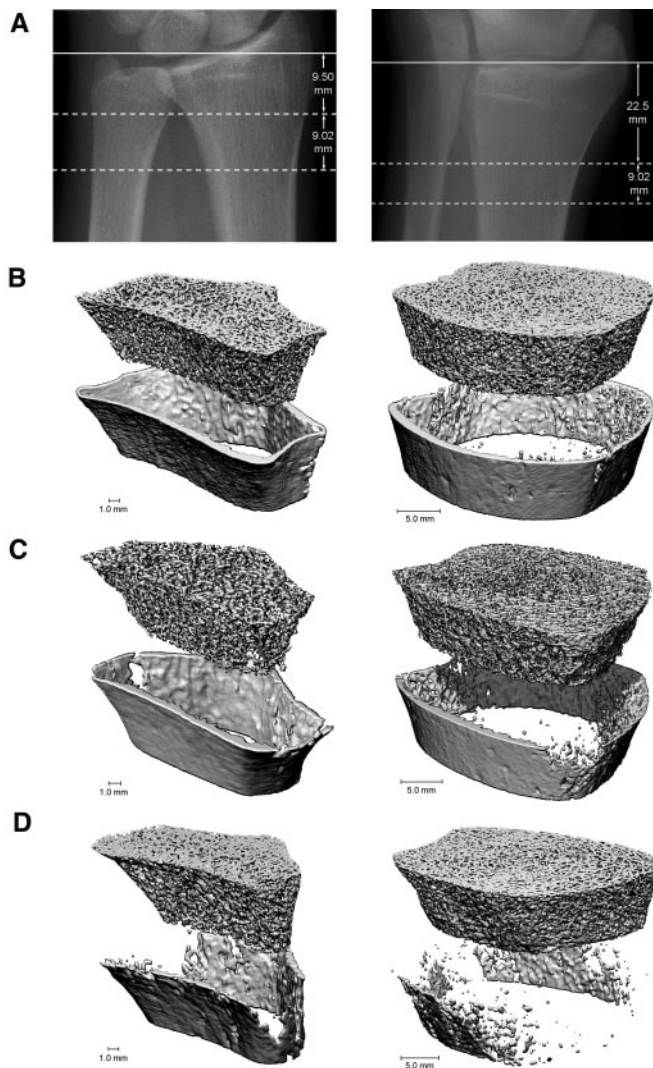


**Figure 1.** Osteoporosis is significantly more common at the total hip and ultradistal radius in CKD patients with fracture. (\*P < 0.05).

discriminated fracture status by ROC analysis; however, diagnostic test characteristics of several DXA and HR-pQCT measurements were better in patients with longer CKD duration. Although KDIGO guidelines do not recommend measurement of BMD by DXA in patients with late stages 3 through 5 CKD, our data suggest diagnostic test characteristics for DXA are superior in patients with longer duration and more severe CKD than in those with less severe CKD.

Although several studies have shown that aBMD by DXA is lower in patients with predialysis CKD than without CKD,<sup>6,21,22</sup> only two have assessed relationships between fracture and aBMD.<sup>5,6</sup> In an analysis of NHANES III participants with stages 3 and 4 CKD, we observed that FN BMD was lower than that in matched control subjects without CKD but was





**Figure 2.** HR-pQCT provides detailed images of bone geometry and microarchitecture at the radius (left) and tibia (right). (A) Scout view represents the reference line position (solid line) and the measurement site (dotted line). (B) Images from a healthy, postmenopausal white woman. (C) Images from a predialysis female patient with CKD and without fracture. (D) Images from a predialysis female patient with CKD and with prevalent fracture.

not associated with hip fracture.<sup>6</sup> In contrast, a *post hoc* analysis of postmenopausal women who had moderate to severe CKD and participated in the Study of Osteoporotic Fractures (SOF)<sup>5</sup> found that FN BMD contributed independently to risk for both hip and vertebral fracture. Our finding that decreased aBMD was associated with fracture is consistent with those reported for the SOF; however, it is noteworthy that half of fractures occurred in patients with CKD, with aBMD measurements above World Health Organization diagnostic threshold for osteoporosis (T score  $\leq -2.5$ ), similar to reports of women with postmenopausal osteoporosis.<sup>23</sup> By HR-pQCT, decreased Dcort at the weight-bearing tibia and Dtrab at the non-weight-bearing radius were associated with fracture. Interestingly and

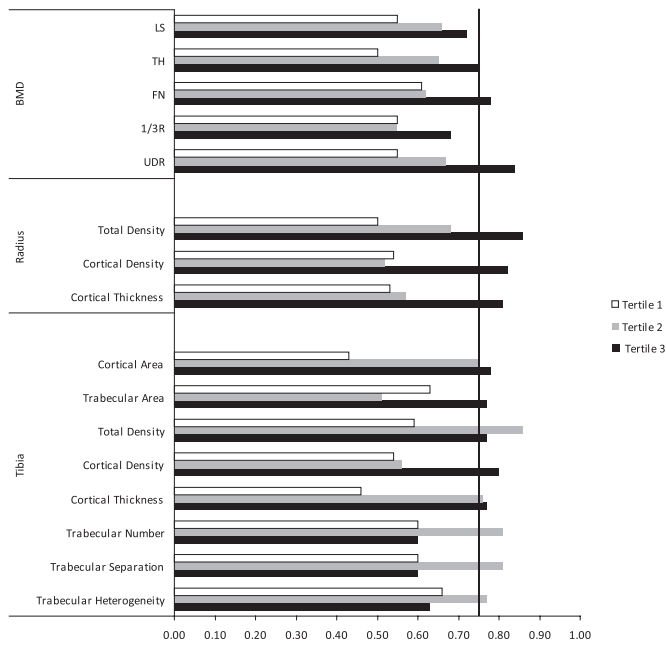
**Table 3.** AUC for the ability of imaging modalities to discriminate fracture status stratified by duration of CKD

Parameter	Tertile 1	Tertile 2	Tertile 3
DXA			
total LS BMD (g/cm <sup>2</sup> )	0.55	0.66	0.72
TH BMD (g/cm <sup>2</sup> )	0.50	0.65	0.75
FN BMD (g/cm <sup>2</sup> )	0.61	0.62	0.78
1/3R BMD (g/cm <sup>2</sup> )	0.55	0.55	0.68
UDR BMD (g/cm <sup>2</sup> )	0.55	0.67	0.84
HRpQCT, radius			
total area (mm <sup>2</sup> )	0.60	0.67	0.55
CtArea (mm <sup>2</sup> )	0.52	0.61	0.74
trabecular area (mm <sup>2</sup> )	0.61	0.60	0.65
Dtot (mg HA/cm <sup>3</sup> )	0.50	0.68	0.86
Dcort (mg HA/cm <sup>3</sup> )	0.54	0.52	0.82
Dtrab (mg HA/cm <sup>3</sup> )	0.54	0.67	0.71
BV/TV (%)	0.54	0.67	0.71
CtTh ( $\mu$ m)	0.53	0.57	0.81
TbN (1/mm)	0.55	0.63	0.71
trabecular thickness ( $\mu$ m)	0.47	0.63	0.58
TbSp ( $\mu$ m)	0.56	0.66	0.72
TbSpSD (1/ $\mu$ m)	0.53	0.70	0.73
HRpQCT, tibia			
total area (mm <sup>2</sup> )	0.59	0.61	0.67
CtArea (mm <sup>2</sup> )	0.43	0.75	0.78
trabecular area (mm <sup>2</sup> )	0.63	0.51	0.77
Dtot (mg HA/cm <sup>3</sup> )	0.59	0.86	0.77
Dcort (mg HA/cm <sup>3</sup> )	0.54	0.56	0.80
Dtrab (mg HA/cm <sup>3</sup> )	0.58	0.73	0.64
BV/TV (%)	0.58	0.73	0.64
CtTh ( $\mu$ m)	0.46	0.76	0.77
TbN (1/mm)	0.60	0.81	0.60
trabecular thickness ( $\mu$ m)	0.53	0.47	0.63
TbSp ( $\mu$ m)	0.60	0.81	0.60
TbSpSD (1/ $\mu$ m)	0.66	0.77	0.63

Tertile 1,  $\leq 2.7$  years; tertile 2, 2.7 to 6.9 years; tertile 3,  $\geq 6.9$  years.

contrary to our hypothesis, aBMD and vBMD by DXA and HR-pQCT, respectively, were equivalently associated with fracture (odds ratios 1.65 to 2.29). These findings are consistent both with the moderate to strong correlations between aBMD and vBMD and with studies of postmenopausal women without CKD,<sup>24–26</sup> in which decreased aBMD measured at any site was similarly associated with osteoporotic fracture.

There are few studies with which to compare our microarchitectural findings. Bacchetta *et al.*<sup>18</sup> compared HR-pQCT of the radius and tibia in white patients with CKD with healthy matched control subjects. The 13 patients with fractures (traumatic and fragility combined) had significantly lower total vBMD, CtTh, and TbN at both radius and tibia. In contrast, we did not find significant differences in trabecular microarchitecture at the tibia. Bacchetta *et al.* did not evaluate the ability of HR-pQCT to discriminate fracture status and did not measure BMD by DXA in patients with CKD. In a study of 52 patients who were on long-term hemodialysis (HD; 27 with prevalent fracture), Jamal *et al.*<sup>9</sup> evaluated conventional pQCT of the distal radius and found that cortical parameters were



**Figure 3.** Longer kidney disease duration associates with improved fracture discrimination by DXA and HR-pQCT. Tertile 1,  $\leq 2.7$  years; tertile 2, 2.7 to 6.9 years; tertile 3,  $\geq 6.9$  years; black, vertical line corresponds to AUC 0.75.

strongly associated with fracture, with an approximate 16- and three-fold increased odds of fracture, respectively, for each SD decrease in Dcort and CtTh. Dcort highly discriminated fracture status (AUC 0.89; 95% confidence interval 0.90 to 0.99). In contrast, neither Dtrab measured by pQCT nor hip and LS BMD measured by DXA was associated with fracture. Of note, resolution of conventional pQCT (approximately 300  $\mu\text{m}$ ) used in that study was too low to assess trabecular microarchitecture.<sup>9</sup>

Our finding that diagnostic accuracy of both DXA and HR-pQCT was better in patients with longer duration and more severe CKD deserves further exploration, because KDIGO guidelines do not recommend routine BMD testing for patients with stages 3 through 5D CKD. This finding is consistent with data that fracture risk increases with increasing time on HD.<sup>11,11</sup> Although no studies have directly demonstrated improved fracture risk assessment by DXA after adjustment for CKD duration, several studies suggested this may be true.<sup>11,27</sup> In a study of patients with ESRD, Urena *et al.*<sup>11</sup> demonstrated that fracture risk was associated both with lower total body z scores and longer HD duration. Another study that used central QCT to evaluate determinants of vertebral fracture in 72 patients with ESRD reported a strong association between fracture and cortical vBMD and a modest inverse association between HD duration and decreased cortical vBMD ( $r = -0.38$ ,  $P < 0.001$ )<sup>27</sup>; however, resolution of central QCT is too low to measure reliably the thin rim of cortical bone encompassing the vertebral body.<sup>28</sup> It is also interesting to note that the AUCs we calculated for radius Dtot and Dcort in patients with the longest duration of and most severe CKD are similar to the AUC of Dcort reported in patients with ESRD by Jamal *et al.*<sup>9</sup>

Although their study did not evaluate relationships between diagnostic accuracy of pQCT for fracture and CKD duration, patients had been on HD for  $> 1$  year and median HD duration was approximately 40 months.

Our study found that diagnostic accuracy of both DXA and HR-pQCT for fracture in patients with short-term duration of CKD is poor and similar to that reported for patients with normal kidney function.<sup>19,29,30</sup> AUCs reported in our study are consistent with those recently reported by Melton *et al.*,<sup>29</sup> in which diagnostic test characteristics of DXA and HR-pQCT for fracture were evaluated in 100 postmenopausal women with prevalent Colles fracture and 105 matched control subjects without fracture. Strong associations were detected between fracture and parameters measured by DXA and HR-pQCT (odds ratios 1.4 to 2.0), but fracture discrimination by both DXA and HR-pQCT was equivalent and AUCs were  $< 0.75$  (0.48 to 0.68).<sup>29</sup> Although HR-pQCT did detect microstructural differences that have been associated with fragility fractures in other studies,<sup>19,31–35</sup> in our cross-sectional investigation, these microstructural differences did not predict fractures. Several *post hoc* analyses of the major registry osteoporosis clinical trials suggested that measurement of BMD by DXA may be useful to assess incident fracture risk in patients with stages 1 through 4 CKD and without biochemical evidence of CKD-MBD.<sup>21,36,37</sup> Prospective studies are needed to determine whether measurement of microstructure by HR-pQCT, application of finite element analysis (a computational method to evaluate bone strength) to HR-pQCT data sets, or evaluation of bone turnover markers improves fracture discrimination by HRpQCT. In this regard, it is possible that no imaging technique will predict fracture adequately, because a major component of fracture risk is related to fall risk, a risk that cannot be assessed by either DXA or HR-pQCT.

This study has several limitations. Our sample size was relatively small. The cross-sectional design did not permit either the assessment of fracture prediction or the evaluation of longitudinal effects of CKD and its associated metabolic and hormonal abnormalities on bone structure. We used CKD duration as a surrogate for longer exposure to metabolic and hormonal abnormalities associated with CKD. Although our data suggest that effects are progressive over time, possibly related to metabolic and hormonal alterations that accompany progressive kidney failure (*e.g.*, SHPT, metabolic acidosis, hypogonadism) and may adversely affect bone density, geometry, and microarchitecture, our method to quantify CKD duration was limited by our ability to obtain historical information on kidney function. Measurements of vitamin D metabolites, parathyroid hormone, and biochemical markers of bone turnover, particularly bone-specific alkaline phosphatase, which could provide additional information regarding potential biochemical mechanisms, are not yet available. Finally, we did not include a control group without CKD; however, because the hypotheses of this investigation were comparisons by fracture status, the absence of a control group without CKD is reasonable.

Technical limitations of HR-pQCT must be considered. HR-pQCT voxel size (82  $\mu\text{m}$ ) is at the threshold of trabecular dimensions and is also greater than cortical pore size. Thus, partial volume effects limit assessment of trabecular microarchitecture and cortical density.<sup>38</sup> The algorithm for measurement of CtTh assumes density of fully mineralized bone is 1.2 g hydroxyapatite (HA)/ $\text{cm}^3$ . Cortex segmentation is then based on a threshold algorithm whereby voxels with a mean density greater than one-third apparent cortical bone value are considered to belong to the cortical region.<sup>39</sup> CtTh is then derived from the formula (cortical volume/circumference). These assumptions may not apply to patients with SHPT or to those with osteomalacia; however, excellent correlations have been demonstrated between HR-pQCT and microCT measures of CtTh ( $R = 0.98$ ).<sup>40</sup>

In conclusion, in patients with predialysis CKD, an array of parameters measured by DXA and HR-pQCT were associated with fracture history. Diagnostic test characteristics for DXA and HR-pQCT were better for patients with longer duration of and more severe CKD. Both cortical and trabecular abnormalities may contribute to fracture susceptibility early in the course of CKD, whereas cortical deficits seem to underlie propensity for fracture in patients with CKD of longer duration. Although HR-pQCT provides novel information regarding the structural mechanisms that may cause bone fragility in patients with CKD, neither imaging tool demonstrated an AUC >0.75. Longitudinal studies are required to investigate further the microstructural and biochemical pathogenesis of fracture and to determine whether DXA and HR-pQCT predict incident fracture in patients with predialysis CKD.

## CONCISE METHODS

### Patients

For this analysis, all predialysis patients who had CKD with and without a history of fracture and were enrolled in an ongoing longitudinal study of relationships between kidney function and bone structure and strength were included in this analysis ( $n = 91$ ). Participants were recruited from the general medicine and nephrology clinics of Columbia University Medical Center (CUMC) between August 2006 and September 2009. eGFR was determined by the Modification of Diet in Renal Disease (MDRD) short formula.<sup>41</sup> Patients included in this analysis had eGFR <90 ml/min. Patients with a history of kidney transplantation or malignancy and those who were taking bisphosphonates, gonadal steroids, aromatase inhibitors, and anticonvulsants that induce hepatic cytochrome P450 enzymes were excluded. Two patients had a remote history of glucocorticoid use (>1 year before the study visit) for treatment of IgA nephropathy and idiopathic FSGS. The CUMC institutional review board approved the study, and all patients provided written informed consent.

### Laboratory Measurements

Laboratory parameters were measured by Quest Diagnostics. Serum creatinine was determined by the Jaffe reaction, and serum calcium, phosphorus, and bicarbonate were measured by spectrophotometry.

## Assessment of CKD, Fracture Status, and Factors Associated with BMD

CKD duration was estimated for all patients by review of medical records and previous measurements of serum creatinine. The online medical records system at CUMC contains clinical and demographic data dating to 1990, and this system was used to determine date of CKD duration for patients who were seen within the CUMC system (approximately 95% of this cohort). The onset of CKD was determined from the earliest serum creatinine levels that consistently corresponded to an eGFR <90 ml/min and would be in compliance with Kidney Disease Outcomes Quality Initiative Guidelines (KDOQI).<sup>42</sup> For patients lacking historical information (seven [8%] patients), duration of kidney function was based on the date of first presentation to a nephrologist. In cases of inadequate historical clinical data, the serum creatinine at nephrology presentation was uniformly abnormal. In cases when the earliest serum creatinine was abnormal and no normal-range serum creatinine levels were available, duration of CKD was based on the date of abnormal serum creatinine. Cause of kidney disease was grouped into three categories: (1) Diabetic and hypertensive kidney disease; (2) glomerular causes of CKD (nephritis or nephrosis); and (3) other causes of CKD (polycystic kidney disease, tubulointerstitial, or unknown).

Fragility fracture was defined as a fracture associated with trauma equivalent to or less than a fall from a standing height; fractures associated with major trauma, such as motor vehicle accidents, and skull and digit fractures were excluded. Both vertebral and nonvertebral fragility fractures were included. Nonvertebral fractures were ascertained by self-reported history during our standardized interview and confirmed by review of radiographs or radiology reports. Twenty patients had 27 nonvertebral fractures; 10 of these were confirmed by radiographs, whereas 17 were confirmed only by patient report. Vertebral fractures were identified by an expert skeletal radiologist (R.B.S.) and graded by the semi-quantitative method on spine radiographs performed according to the protocol of the SOF.<sup>43</sup> All study patients underwent lateral spine x-rays. Because all vertebral fractures were identified at the study visit, it was not possible to determine their occurrence in relationship to the duration of CKD.

Current alcohol consumption was defined as one or more drinks daily. Current tobacco use was reported as having smoked tobacco in the 5 years before the study visit. Vitamin D supplementation was defined as any use of ergocalciferol ( $n = 22$ ), cholecalciferol ( $n = 27$ ), paricalcitol ( $n = 17$ ), doxercalciferol ( $n = 6$ ), or calcitriol ( $n = 5$ ). Phosphate binders included calcium acetate ( $n = 1$ ) or sevelamer ( $n = 14$ ). No patient was taking cinacalcet, lanthanum carbonate, or aluminum-containing phosphate binding agents.

### Measurement of aBMD by DXA

aBMD by DXA was measured at the total LS (L1 through L4), TH, FN, and nondominant 1/3R and UDR using a Hologic QDR 4500 densitometer (Hologic, Inc, Waltham, MA) in the array (fan beam) mode. In our laboratory, short-term *in vivo* precision is 0.68% for the spine, 1.36% for the FN, and 0.70% for the radius. T scores compared patients with young-normal populations of the same race and gender



provided by the manufacturer (spine and forearm) and by NHANES III (TH and FN).

### HR-pQCT Imaging of the Radius and Tibia

HR-pQCT (XtremeCT; SCANCO Medical AG, Bassersdorf, Switzerland) of the nondominant forearm and leg was performed by a dedicated research densitometry technologist as described previously<sup>19</sup> and performed in our laboratory (Figure 2).<sup>39,44</sup> HR-pQCT of the dominant limb was performed when there was a previous fracture or an arteriovenous fistula or graft in the nondominant limb. The arm or leg was positioned in the scanner, and the region of interest was defined on a scout film by manual placement of a reference line at the endplate of the radius or tibia, with the first slice 9.5 and 22.5 mm proximal to the reference line at the radius and tibia, respectively. A stack of 110 parallel CT slices was acquired at the distal end of both sites using an effective energy of 40 keV, slice thickness of 82  $\mu\text{m}$ , image matrix size 1024  $\times$  1024, and a nominal voxel size of 82  $\mu\text{m}$ . This provided a three-dimensional image of approximately 9 mm in the axial direction. Attenuation data were converted to equivalent HA densities. The European Forearm Phantom was scanned daily for quality control.

The analysis methods have been described,<sup>39,44,45</sup> validated *ex vivo* against the gold standard  $\mu\text{-CT}$  at the radius<sup>40</sup> and tibia,<sup>35</sup> and applied in several clinical studies.<sup>18,30,33–35,46,47</sup> Image processing and calculation of numerical values were performed using Scanco software. Briefly, the volume of interest is automatically separated into cortical and trabecular regions using a threshold-based algorithm set to one third the apparent cortical bone density. Mean CtTh is defined as the mean cortical volume divided by the outer bone surface. Trabecular bone density is defined as the average bone density within the trabecular volume of interest; BV/TV (%) is derived from Dtrab, assuming the density of fully mineralized bone was 1.2 g HA/cm<sup>3</sup> (BV/TV = 100  $\times$  Dtrab/1200 mg HA/cm<sup>3</sup>). Because measurements of trabecular microstructure are limited by the resolution of the XtremeCT, which approximates the width of individual trabeculae, trabecular structure is assessed using a semiderived algorithm.<sup>44,48</sup> Trabeculae are identified by a mid-axis transformation method, and the distance between them is assessed by the distance-transform method.<sup>49</sup> TbN is defined as the inverse of the mean spacing of the mid-axes. Trabecular thickness and TbSp are derived from BV/TV and TbN using formulas from traditional quantitative histomorphometry: Trabecular thickness = (BV/TV)/TbN, and TbSp = (1 – BV/TV)/TbN. The intraindividual distribution of separation ( $\mu\text{m}$ ), a parameter that reflects the heterogeneity of the trabecular network, is also calculated.

### Statistical Analysis

Statistical analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC). Categorical data were compared using  $\chi^2$  test. All continuous data were log-transformed before statistical testing, and group differences were determined by *t* test for unequal variances. No adjustments for age; gender; race; duration of kidney failure; or serum levels of calcium, phosphorus, or bicarbonate were performed because of the homogeneous distribution of these variables between the two popu-

lations (Table 1). Univariate logistic regression was performed to determine univariate relationships between fracture and measures of bone density and microarchitecture determined by DXA and HR-pQCT, respectively. Standard ROC curve analysis was performed to determine the ability of DXA and HR-pQCT to discriminate fracture status. In this type of analysis, an AUC  $>0.75$  is considered compelling evidence for the ability to discriminate an outcome.<sup>50,51</sup> A diagnostic test with an AUC of 0.5 is considered to perform no better than chance. ROC analysis was also performed on groups of patients stratified by duration of kidney failure. Stratification was determined on the basis of tertiles of CKD duration. These categories were  $\leq 2.7$ , 2.7 to 6.9, and  $\geq 6.9$  years.

### ACKNOWLEDGMENTS

This research was supported by grants from the National Institutes of Health (K23 DK080139 [T.L.N.], K24 DK076808 [M.B.L.], and K24 AR052665 [E.S.]), Amgen (Young Investigator Award [T.L.N.]), and the International Society for Clinical Densitometry (Special Projects Award [T.L.N.]). We would like to thank X. Sherry Liu for assistance with HR-pQCT imaging.

### DISCLOSURES

None.

### REFERENCES

1. Alem AM, Sherrard DJ, Gillen DL, Weiss NS, Beresford SA, Heckerbert SR, Wong C, Stehman-Breen C: Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int* 58: 396–399, 2000
2. Nickolas TL, Leonard MB, Shane E: Chronic kidney disease and bone fracture: A growing concern. *Kidney Int* 74: 721–731, 2008
3. Fried LF, Biggs ML, Shlipak MG, Seliger S, Kestenbaum B, Stehman-Breen C, Sarnak M, Siscovick D, Harris T, Cauley J, Newman AB, Robbins J: Association of kidney function with incident hip fracture in older adults. *J Am Soc Nephrol* 18: 282–286, 2007
4. Dooley AC, Weiss NS, Kestenbaum B: Increased risk of hip fracture among men with CKD. *Am J Kidney Dis* 51: 38–44, 2008
5. Ensrud KE, Lui LY, Taylor BC, Ishani A, Shlipak MG, Stone KL, Cauley JA, Jamal SA, Antonucci DM, Cummings SR: Renal function and risk of hip and vertebral fractures in older women. *Arch Intern Med* 167: 133–139, 2007
6. Nickolas TL, McMahon DJ, Shane E: Relationship between moderate to severe kidney disease and hip fracture in the United States. *J Am Soc Nephrol* 17: 3223–3232, 2006
7. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS: Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 41: 1–12, 2003
8. Yamaguchi T, Kanno E, Tsubota J, Shiomi T, Nakai M, Hattori S: Retrospective study on the usefulness of radius and lumbar bone density in the separation of hemodialysis patients with fractures from those without fractures. *Bone* 19: 549–555, 1996
9. Jamal SA, Gilbert J, Gordon C, Bauer DC: Cortical pQCT measures



- are associated with fractures in dialysis patients. *J Bone Miner Res* 21: 543–548, 2006
10. Jamal SA, Chase C, Goh YI, Richardson R, Hawker GA: Bone density and heel ultrasound testing do not identify patients with dialysis-dependent renal failure who have had fractures. *Am J Kidney Dis* 39: 843–849, 2002
  11. Urena P, Bernard-Poenaru O, Ostertag A, Baudoin C, Cohen-Solal M, Cantor T, De Vernejoul MC: Bone mineral density, biochemical markers and skeletal fractures in haemodialysis patients. *Nephrol Dial Transplant* 18: 2325–2331, 2003
  12. Jamal SA, Hayden JA, Beyene J: Low bone mineral density and fractures in long-term hemodialysis patients: a meta-analysis. *Am J Kidney Dis* 49: 674–681, 2007
  13. Moe S, Drueke T, Cunningham J, Goodman W, Martin K, Olgaard K, Ott S, Sprague S, Lameire N, Eknoyan G: Definition, evaluation, and classification of renal osteodystrophy: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 69: 1945–1953, 2006
  14. Parisien M, Silverberg SJ, Shane E, de la Cruz L, Lindsay R, Bilezikian JP, Dempster DW: The histomorphometry of bone in primary hyperparathyroidism: Preservation of cancellous bone structure. *J Clin Endocrinol Metab* 70: 930–938, 1990
  15. Slatopolsky E, Delmez J: Renal osteodystrophy. In: *Disorders of Bone and Mineral Metabolism*, edited by Coe FL, Favus MJ, New York, Raven Press, 1992, pp 905–934
  16. Parfitt AM: Hormonal influences on bone remodeling and bone loss: Application to the management of primary hyperparathyroidism. *Ann Intern Med* 125: 413–415, 1996
  17. Hamdy NA, Kanis JA, Beneton MN, Brown CB, Juttmann JR, Jordans JG, Josse S, Meyrier A, Lins RL, Fairey IT: Effect of alfacalcidol on natural course of renal bone disease in mild to moderate renal failure. *BMJ* 310: 358–363, 1995
  18. Bacchetta J, Boutroy S, Vilayphiou N, Juillard L, Guebre-Egziabher F, Rognant N, Sornay-Rendu E, Szulc P, Laville M, Delmas PD, Fouque D, Chapurlat R: Early impairment of trabecular microarchitecture assessed with HR-pQCT in patients with stage II-IV chronic kidney disease. *J Bone Miner Res* September 23, 2009 [epub ahead of print]
  19. Boutroy S, Bouxsein ML, Munoz F, Delmas PD: *In vivo* assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. *J Clin Endocrinol Metab* 90: 6508–6515, 2005
  20. Stein EM, Nickolas T, Cohen A, Thomas V, Rogers H, Cosman F, Nieves G, McMahon D, Shane E: *High Resolution Peripheral Quantitative Computed Tomography (HRpQCT) Measurements Predict Central and Peripheral Fragility Fractures in Postmenopausal Women*, Denver, American Society of Bone and Mineral Research, 2009
  21. Jamal SA, Bauer DC, Ensrud KE, Cauley JA, Hochberg M, Ishani A, Cummings SR: Alendronate treatment in women with normal to severely impaired renal function: An analysis of the fracture intervention trial. *J Bone Miner Res* 22: 503–508, 2007
  22. Dukas L, Schacht E, Mazor Z, Stahelin HB: Treatment with alfacalcidol in elderly people significantly decreases the high risk of falls associated with a low creatinine clearance of <65 ml/min. *Osteoporos Int* 16: 198–203, 2005
  23. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy: Osteoporosis prevention, diagnosis, and therapy. *JAMA* 285: 785–795, 2001
  24. Cummings SR, Black DM, Nevitt MC, Browner W, Cauley J, Ensrud K, Genant HK, Palermo L, Scott J, Vogt TM: Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. *Lancet* 341: 72–75, 1993
  25. Black DM, Cummings SR, Genant HK, Nevitt MC, Palermo L, Browner W: Axial and appendicular bone density predict fractures in older women. *J Bone Miner Res* 7: 633–638, 1992
  26. Melton LJ 3rd, Atkinson EJ, O'Fallon WM, Wahner HW, Riggs BL: Long-term fracture prediction by bone mineral assessed at different skeletal sites. *J Bone Miner Res* 8: 1227–1233, 1993
  27. Mares J, Ohlidalova K, Opatrna S, Ferda J: Determinants of prevalent vertebral fractures and progressive bone loss in long-term hemodialysis patients. *J Bone Miner Metab* 27: 217–223, 2009
  28. Augat P, Gordon CL, Lang TF, Iida H, Genant HK: Accuracy of cortical and trabecular bone measurements with peripheral quantitative computed tomography (pQCT). *Phys Med Biol* 43: 2873–2883, 1998
  29. Melton LJ 3rd, Christen D, Riggs BL, Achenbach SJ, Muller R, van Lenthe GH, Amin S, Atkinson EJ, Khosla S: Assessing forearm fracture risk in postmenopausal women. *Osteoporos Int* August 28, 2009 [epub ahead of print]
  30. Vico L, Zouch M, Amirouche A, Frere D, Laroche N, Koller B, Laib A, Thomas T, Alexandre C: High-resolution pQCT analysis at the distal radius and tibia discriminates patients with recent wrist and femoral neck fractures. *J Bone Miner Res* 23: 1741–1750, 2008
  31. Boutroy S, Van Rietbergen B, Sornay-Rendu E, Munoz F, Bouxsein ML, Delmas PD: Finite element analysis based on *in vivo* HR-pQCT images of the distal radius is associated with wrist fracture in postmenopausal women. *J Bone Miner Res* 23: 392–399, 2008
  32. Sornay-Rendu E, Cabrera-Bravo JL, Boutroy S, Munoz F, Delmas PD: Severity of vertebral fractures is associated with alterations of cortical architecture in postmenopausal women. *J Bone Miner Res* 24: 737–743, 2009
  33. Cohen A, Dempster DW, Muller R, Guo XE, Nickolas TL, Liu XS, Zhang XH, Wirth AJ, van Lenthe GH, Kohler T, McMahon DJ, Zhou H, Rubin MR, Bilezikian JP, Lappe JM, Recker RR, Shane E: Assessment of trabecular and cortical architecture and mechanical competence of bone by high-resolution peripheral computed tomography: Comparison with transiliac bone biopsy. *Osteoporos Int* 21: 263–273, 2010
  34. Cohen A, Liu XS, Stein EM, McMahon DJ, Rogers HF, Lemaster J, Recker RR, Lappe JM, Guo XE, Shane E: Bone microarchitecture and stiffness in premenopausal women with idiopathic osteoporosis. *J Clin Endocrinol Metab* 94: 4351–4360, 2009
  35. Liu XS, ZX, Sekhon KK, Adam MF, McMahon DJ, Bilezikian JP, Shane E, Guo XE: High-resolution peripheral quantitative computed tomography can assess microstructural and mechanical properties of human distal tibial bone. *J Bone Miner Res* September 23, 2009 [epub ahead of print]
  36. Miller PD, Roux C, Boonen S, Barton IP, Dunlap LE, Burgio DE: Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: A pooled analysis of nine clinical trials. *J Bone Miner Res* 20: 2105–2115, 2005
  37. Miller PD, Schwartz EN, Chen P, Misurski DA, Kregge JH: Teriparatide in postmenopausal women with osteoporosis and mild or moderate renal impairment. *Osteoporos Int* 18: 59–68, 2007
  38. Cooper D, Turinsky A, Sensen C, Hallgrímsson B: Effect of voxel size on 3D micro-CT analysis of cortical bone porosity. *Calcif Tissue Int* 80: 211–219, 2007
  39. Laib A, Hauselmann HJ, Rueggsegger P: *In vivo* high resolution 3D-QCT of the human forearm. *Technol Health Care* 6: 329–337, 1998
  40. MacNeil JA, Boyd SK: Accuracy of high-resolution peripheral quantitative computed tomography for measurement of bone quality. *Med Eng Phys* 29: 1096–1105, 2007
  41. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D: A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 130: 461–470, 1999
  42. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis* 39: S1–S266, 2002
  43. Black DM, Palermo L, Nevitt MC, Genant HK, Epstein R, San VR, Cummings SR: Comparison of methods for defining prevalent vertebral deformities: The Study of Osteoporotic Fractures. *J Bone Miner Res* 10: 890–902, 1995
  44. Laib A, Rueggsegger P: Calibration of trabecular bone structure mea-

- surements of *in vivo* three-dimensional peripheral quantitative computed tomography with 28-microm-resolution microcomputed tomography. *Bone* 24: 35–39, 1999
45. Hildebrand T, Laib A, Muller R, Dequeker J, Ruegsegger P: Direct three-dimensional morphometric analysis of human cancellous bone: Microstructural data from spine, femur, iliac crest, and calcaneus. *J Bone Miner Res* 14: 1167–1174, 1999
  46. Melton LJ 3rd, Riggs BL, van Lenthe GH, Achenbach SJ, Muller R, Bouxsein ML, Amin S, Atkinson EJ, Khosla S: Contribution of *in vivo* structural measurements and load/strength ratios to the determination of forearm fracture risk in postmenopausal women. *J Bone Miner Res* 22: 1442–1448, 2007
  47. Walker MD, McMahon DJ, Udesky J, Liu G, Bilezikian JP: Application of high-resolution skeletal imaging to measurements of volumetric BMD and skeletal microarchitecture in Chinese-American and white women: Explanation of a paradox. *J Bone Miner Res* 24: 1953–1959, 2009
  48. Laib A, Ruegsegger P: Comparison of structure extraction methods for *in vivo* trabecular bone measurements. *Comput Med Imaging Graph* 23: 69–74, 1999
  49. Hildebrand T, Ruegsegger P: Quantification of bone microarchitecture with the structure model index. *Comput Methods Biomech Biomed Engin* 1: 15–23, 1997
  50. Swets JA: Measuring the accuracy of diagnostic systems. *Science* 240: 1285–1293, 1988
  51. Fischer JE, Bachmann LM, Jaeschke R: A readers' guide to the interpretation of diagnostic test properties: Clinical example of sepsis. *Intensive Care Med* 29: 1043–1051, 2003