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Pulse Wave Velocity Is Inversely Related to Vertebral Bone Density in Hemodialysis Patients

Paolo Raggi, Antonio Bellasi, Emiliana Ferramosca, Geoffrey A. Block, Paul Muntner

Abstract—Abnormalities of bone mineral metabolism in patients with stage-5 chronic kidney disease may contribute to the high incidence of cardiovascular disease. Noninvasive imaging methods may help predict the simultaneous presence of vasculopathy and bone disease. Accordingly, we measured pulse wave velocity and bone mineral density (BMD), and T-scores (number of SDs below the BMD of a younger reference group) of the spine by both dual energy x-ray absorptiometry and quantitative computed tomography (QCT) in 110 maintenance hemodialysis patients. Older age, white race, diabetes mellitus, lower diastolic blood pressure, and lower albumin levels were associated with lower QCT-assessed T-scores (each $P < 0.05$). After age and multivariable adjustment, pulse wave velocity (PWV) increased as QCT BMD decreased (the prevalence of $PWV \geq 9$ m/s was 32.4%, 61.8%, and 76.5% for participants in the highest to the lowest tertile of QCT-assessed BMD; $P < 0.001$). In contrast, there was no relationship between spine dual energy x-ray absorptiometry-BMD and PWV. In unadjusted models, thoracic spine QCT-assessed T-scores correlated significantly, albeit weakly, with aorta calcification ($r = 0.22$; $P = 0.01$) but not with coronary calcification. The odds ratio of $PWV \geq 9$ m/s for patients taking vitamin D₃ or its analogs was 0.51 (95% CI: 0.19 to 1.39). In conclusion, low spine BMD is associated with increased PWV in stage-5 chronic kidney disease, supporting the notion of a close interaction of vascular and bone disease in this patient group. QCT and not dual energy x-ray absorptiometry should be used to assess spine BMD in dialysis patients. (*Hypertension*. 2007;49:1278-1284.)

Key Words: computed tomography ■ pulse wave velocity ■ bone density ■ vascular calcification ■ calcium ■ vascular stiffness

A large proportion of patients undergoing hemodialysis (stage-5 chronic kidney disease [CKD; CKD-5]) suffer from bone remodeling abnormalities caused by altered hormonal and metabolic pathways involving calcium, phosphate, vitamin D, and parathyroid hormone.¹ In addition, cardiovascular disease is common in CKD-5, with the majority of patients undergoing hemodialysis ultimately dying of cardiovascular complications.² Hence, in the context of CKD-5, vascular and bone disease may often coexist, and it has been suggested that they share common pathogenetic mechanisms.^{1,3-5} Interestingly, some investigators have noted a vascular-bone interaction in the general population as well.⁶⁻⁸

Patients with stage-5 CKD are affected by multiple cardiovascular risk factors and develop extensive vascular calcification.⁹ However, the latter is not solely because of severe atherosclerotic disease, as calcification of the muscular media of the vessel wall has also been described in these patients.⁵ The ensuing reduction in vascular compliance and increased stiffness is reflected in an increased pulse wave velocity (PWV).¹⁰ Of note, both increased PWV and bone demineralization have been associated with an increased mortality risk in patients with CKD-5.^{11,12} Therefore, we became interested in assessing the relationship of bone mineral density (BMD) and a noninvasive measure of cardiovascular risk, such as PWV, in CKD-5 patients. We performed both dual energy x-ray absorptiometry (DEXA) and quantitative computed tomography (QCT) to compare the reliability of these tools, because there appears to be a good rationale for considering DEXA less reliable in patients with CKD-5 than in the general population.¹³

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Methods

Patient Selection

Adult patients were recruited from 2 dialysis centers in the United States (Denver, Colo, and New Orleans, La). A total of 149 patients were selected based on a history of CKD-5 treated with maintenance hemodialysis and the ability to sign an informed consent. Patients were excluded if they were pregnant or planning a pregnancy within the next 6 months or if they had undergone previous coronary artery bypass surgery or coronary artery angioplasty and stent placement. Five participants were excluded from these analyses for not having undergone a PWV measurement, and 7 and 3 participants were

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excluded for having a PWV <5 m/s and >20 m/s, respectively, considered to be measurement errors. Finally, 24 participants were excluded from the current analysis for not having a QCT measurement of spine BMD. Participants with and without QCT measurements were similar with respect to PWV (10.0 and 10.4 m/s, respectively; $P=0.59$). After these exclusions, the final sample size for the current study included 110 participants.

BMD Measurements With DEXA and QCT

DEXA scans were performed on Hologic QDR-4500C in Denver and Lunar Prodigy DF +10357 in New Orleans. BMD was measured by DEXA in the lumbar spine. Although absolute values of BMD obtained may depend on the DEXA equipment used, the DEXA-derived BMD values were similar for the 2 study sites ($P>0.50$ comparing median absolute BMD values and T-scores for spine BMD across sites). Therefore, DEXA data were pooled across sites for all of the analyses.

Measurement of BMD by QCT was performed in the 2 lowest thoracic vertebrae, not showing deformities or fractures, with QCT Pro (Mindways). This software performs accurate BMD measurements of the trabecular bone of the vertebrae of interest. CT imaging was performed with electron beam C-150 scanners (GE-Imatron) both in Denver and New Orleans. Slice thickness was kept at 3 mm, and the z axis extended approximately from the fifth to the 12th thoracic vertebra while the patient laid on a calibration phantom positioned under the thorax. The thoracic vertebrae were used for QCT analysis, because the patients in this study were participating in a protocol that required the performance of a chest CT, as well as an abdominal plain x-ray for visualization of the abdominal aorta.¹⁴ The investigators, therefore, felt that there was no reason to expose the patients to additional radiation to perform CT imaging of the lumbar spine. Importantly, the thoracic spine is an appropriate site for investigation of BMD by QCT.^{15,16} In fact, carefully conducted studies showed a high correlation of thoracic and lumbar QCT measurements, although thoracic QCT BMD tended to be slightly higher.^{15,16} Furthermore, the thoracic spine is the site of frequent fractures in dialysis patients and, therefore, an appropriate target of BMD measurement. Absolute BMD was determined as the average of T11 and T12.

Calculation of Aorta and Coronary Artery Calcium Score

Electron beam tomography C-150 scanners (GE-Imatron) were used for this application. Contiguous tomographic sections (40 to 50 slices), 3-mm thick, were obtained starting at the bronchial carina and ending at the level of the diaphragm. The images were acquired in end expiration, during 1 breath hold period of ≈ 20 seconds, and at 60% of the R-to-R interval on a simultaneously recorded surface ECG. The calcium score of all of the areas of calcification seen along the coronary artery tree and the thoracic aorta was computed by means of the previously described Agatston score.¹⁷

Lateral Lumbar X-Ray

A lateral x-ray of the lumbar spine was obtained to assess the presence of abdominal aorta calcification. A detailed description of this methodology has been published elsewhere.¹⁸ Kauppila et al¹⁸ first introduced this scoring method to assess in a semiquantitative way the extent of aortic calcification. The score derived with this methodology ranges from 0 (no visible abdominal aorta calcium) to 24 (extensive abdominal aorta calcification) and has been shown to bear prognostic significance.¹⁹ The total radiation dose provided by the chest CT, DEXA, and abdominal aorta x-ray was ≈ 2.5 milli-Sieverts per patient (annual recommended patient limit in the United States: 5 milli-Sieverts).

Aortic PWV Measurement

PWV was assessed by applanation tonometry with the Sphygmocor Vx software (AtCor Medical). First, we measured the distance on the body surface between the sternal notch and the carotid artery pulse in centimeters. Next, we measured the distance between the sternal

notch and the femoral artery pulse, then subtracted the former from the latter measurement. This provides a close approximation of the distance between the heart and the femoral artery. With the use of a tonometer, we assessed the timing of the carotid and femoral artery pulse upstroke in relation to the R wave on a simultaneously acquired ECG. The time between the R wave and pressure upstroke at each arterial site was then computed by the Sphygmocor Vx software and eventually used in the calculation of velocity of conduction (velocity=distance between the heart and femoral artery/time difference between R wave and pressure upstroke at each site).

All of the imaging tests were sent to a central laboratory where an investigator was assigned an interpretation task according to his/her own area of expertise. All of the tests were evaluated in a blinded fashion by observers who were unaware of the patients' other test results.

Statistical Methods

Characteristics of the study population were calculated by tertile of T-score, obtained by QCT, as means for continuous variables and percentages for dichotomous variables. Trends across tertile were determined using regression analysis. Next, the age-standardized mean PWV and age-standardized prevalence and adjusted odds ratios of a PWV ≥ 9 m/s were calculated by tertile of QCT-derived absolute BMD and T-score, separately. Odds ratios were adjusted for age, race, sex, current smoking, body mass index, diabetes mellitus, and duration of dialysis. These analyses were repeated using absolute spine BMD and spine T-scores obtained using DEXA. We chose a PWV ≥ 9 m/s because it is an indication of increased arterial stiffness and has been associated with an adverse outcome in prospective studies.^{10,11} Also, we determined the age-standardized prevalence and multivariate adjusted odds ratio of PWV ≥ 9 m/s associated with intact parathyroid hormone (iPTH) ≥ 600 pg/mL (as a potential marker of high-turnover bone disease). Because only 9 patients had a very low iPTH value (<100 pg/mL), this precluded similar analyses for patients with probable adynamic bone disease. Next, we calculated a correlation coefficient between aorta calcium score, as well as coronary artery calcium scores, taken as continuous variables, and QCT BMD and T-scores. Finally, the multivariate adjusted odds ratio of coronary artery calcium score ≥ 1000 and aorta calcium score ≥ 3000 were calculated by tertile of QCT-derived T-score. All of the analyses were conducted using Stata software 8.1.

Results

Relationship of PWV and Bone Density on QCT

The demographic and clinical characteristics of patients categorized according to T-score tertiles are presented in Table 1. Older, white, and diabetic patients were more likely to have lower T-scores. In addition, lower diastolic blood pressure and serum albumin levels were present at lower T-scores.

After age standardization, persons with lower mean absolute BMD and T-scores had progressively higher PWV (Figure 1). Table 2 shows the age-standardized prevalence and multivariate adjusted odds ratios of PWV ≥ 9 m/s associated with tertile of BMD and T-scores. Consistent with the data in Figure 1, the age-standardized prevalence of PWV ≥ 9 m/s was higher at lower absolute BMD values and T-scores. Even after multivariate adjustment, participants with progressively lower absolute BMD and T-scores were more likely to have a PWV ≥ 9 (each P for trend <0.05).

Relationship of PWV and BMD on DEXA

There was no association between absolute BMD and T-scores of the spine assessed by DEXA and mean PWV or PWV ≥ 9 m/s before or after multivariate adjustment (Table 3).

TABLE 1. Characteristics of Study Participants by Spine Bone Mineral Density Tertile Measured by QCT (SD in Parentheses)

Characteristics	Tertile of Bone Mineral Density T-Score			P for Trend
	Tertile 1 (Less Than -1.75) (N=37)	Tertile 2 (-1.74 to 0.47) (N=38)	Tertile 3 (≥0.48) (N=35)	
Age, y, mean (SD)	64.8 (12.1)	56.3 (12.6)	46.7 (13.2)	<0.001
% Male	56.8	50.0	40.0	0.158
% Black	29.7	42.1	62.9	0.006
BMI, kg/m ² , mean (SD)	25.3 (4.8)	25.1 (4.3)	27.3 (5.9)	0.109
Current smoking, %	14.3	21.1	29.4	0.131
Sevelamer, %	52.8	47.4	51.4	0.906
Calcium-based phosphate binders, %	59.5	60.5	40.0	0.104
Statins, %	30.6	52.6	28.6	0.879
β-Blockers, %	41.7	52.6	45.7	0.727
ACE-I/ARB, %	46.0	47.4	57.1	0.347
Vitamin D supplements %	51.4	55.3	68.6	0.143
SBP, mm Hg, mean (SD)	144.6 (27.5)	146.4 (26.3)	149.2 (24.7)	0.454
DBP, mm Hg, mean (SD)	72.5 (15.6)	79.6 (13.9)	81.0 (13.1)	0.013
Pulse pressure, mm Hg, mean (SD)	72.0 (22.8)	66.7 (21.3)	68.2 (21.0)	0.448
Diabetes, %	67.6	57.9	22.9	0.001
Serum hemoglobin, mg/dL, mean (SD)	12.5 (1.3)	12.7 (1.3)	12.4 (1.4)	0.859
Serum albumin, mg/dL, mean (SD)	3.75 (0.34)	3.72 (0.34)	3.91 (0.25)	0.038
Total cholesterol, mg/dL, mean (SD)	145.3 (35.7)	156.9 (26.9)	152.7 (44.2)	0.382
HDL cholesterol, mg/dL, mean (SD)	48.4 (16.5)	45.3 (12.8)	44.3 (11.8)	0.213
Triglycerides, mg/dL*	146 (104 to 184)	161 (122 to 192)	133 (107 to 268)	0.378
Serum iPTH, pg/dL*	266 (182 to 443)	315 (200 to 673)	384 (211 to 1081)	0.211
Serum calcium, mg/dL, mean (SD)	9.1 (0.6)	9.1 (0.7)	8.9 (0.9)	0.485
Serum phosphorous, mg/dL, mean (SD)	4.8 (1.7)	4.8 (1.3)	5.4 (1.4)	0.066
CaxPi product, mean (SD)	43.4 (15.9)	43.4 (13.0)	48.3 (12.3)	0.140
History of ASCVD%	35.1	52.6	37.1	0.842
Dialysis duration ≥5 y, %	10.8	18.2	28.6	0.060

BMI indicates body mass index; ACE-I, angiotensin-converting enzyme inhibitor; ARB, adrenergic receptor blocker; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; CaxPi, calcium phosphate product; ASCVD, atherosclerotic cardiovascular disease.

*Presented as median (interquartile range) because of a skewed distribution.

The lack of an association between BMD, obtained by DEXA, and PWV may be due to the high prevalence of aortic calcification, a factor that could potentially impair the reliability of DEXA in CKD-5. To examine this further, we calculated the

correlation between QCT T-scores and DEXA T-scores for participants with and without calcification of the thoracic aorta on CT and with and without calcification of the abdominal aorta on a lateral lumbar x-ray film. In the

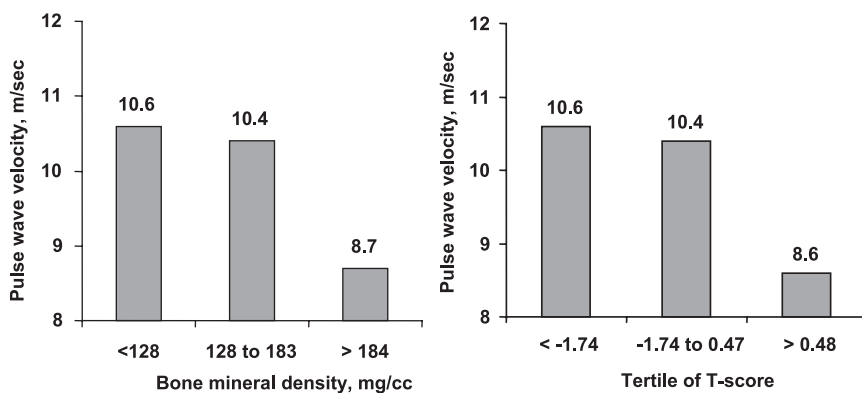


Figure 1. Age-standardized PWV by tertile of spine bone mineral density and T-score assessed by QCT.

*p-trend=0.027

*p-trend=0.030

TABLE 2. Age Standardized Prevalence and Adjusted Odds Ratios of PWV ≥ 9 m/s Associated With Tertile of BMD Measured by QCT

Characteristics	Average BMD, mg/cc			P
	<128	128 to 183	≥ 184	
% with PWV ≥ 9 m/s*	72.3%	59.2%	37.6%	<0.001
Adjusted odds ratio (95% CI)†	1.00 (ref)	0.38 (0.11 to 1.36)	0.22 (0.04 to 1.12)	0.048
Characteristics	T Scores			P
	Less than -1.74	-1.74 to 0.47	≥ 0.48	
% with PWV ≥ 9 m/s*	73.0%	59.2%	37.6%	<0.001
Adjusted odds ratio (95% CI)†	1.00 (ref)	0.39 (0.11 to 1.38)	0.21 (0.04 to 1.04)	0.040

ref indicates reference.

*Age standardized.

†Adjusted for age, race, sex, duration of dialysis, current smoking, body mass index, and diabetes mellitus.

presence of calcification of the aorta (either abdominal or thoracic), the correlation between the 2 techniques (QCT and DEXA) decreased substantially (Figure 2). This suggests that, in the presence of vascular calcification, a planar ("blind") imaging tool such as DEXA is not as reliable as QCT for spine BMD measurement.

Association of High iPTH Levels With BMD on QCT and PWV

After age standardization, the percentage of patients with iPTH ≥ 600 pg/mL in each tertile of QCT T-score (lowest to highest) was 8.1%, 35.1%, and 38.9% ($P=0.010$). In addition, 30% of participants with iPTH ≥ 600 pg/mL had a PWV ≥ 9 m/s, compared with 69% of the patients with iPTH between 100 and 599 pg/mL. After adjustment for age, sex, race, body mass index, diabetes mellitus, and dialysis vintage, the odds ratio of PWV ≥ 9 m/s associated with iPTH ≥ 600 pg/mL was 0.32 (95% CI: 0.10 to 1.04).

Relationship of BMD on QCT and Coronary Artery and Aorta Calcium on CT

There was a significant, albeit weak, correlation between aorta calcium score and thoracic spine QCT BMD and

T-scores ($r=0.20$; $P=0.02$ and $r=0.22$; $P=0.01$). Similar correlations did not exist between QCT-assessed BMD and T-scores and coronary artery calcium. After multivariate adjustment, the associations of coronary artery calcium score ≥ 1000 and aorta calcium score ≥ 3000 with tertile of QCT BMD or T-score were not significant (data not shown).

Use of Vitamin D₃ and Analogs and PWV

We did not obtain serum vitamin D levels. However, the multivariable-adjusted odds ratio of PWV ≥ 9 m/s associated with taking vitamin D₃ or its analogs was 0.51 (95% CI: 0.19 to 1.39). It would appear, therefore, that taking vitamin D products is associated with a $\approx 50\%$ lower risk of arterial stiffening.

Discussion

This study highlights several important points. There is an association between decreasing vertebral bone density measured by QCT and increasing vascular stiffness as measured by PWV. This observation is important for several reasons. The heavy vascular calcification that occurs in patients undergoing dialysis⁹ is likely responsible for a substantial

TABLE 3. Age-Standardized PWV and Prevalence and Odds Ratios of PWV ≥ 9 m/s by Tertile of Spine BMD and T Score on DEXA

Characteristics	Tertile of Spine BMD			P
	<0.96	0.96 to 1.10	≥ 1.11	
Mean PWV	10.0	10.2	10.0	0.986
PWV ≥ 9 m/s				
Prevalence*	56.1	61.3	54.3	0.885
Odds ratio†	1.00 (ref)	1.25 (0.36 to 4.39)	0.58 (0.14 to 2.40)	0.486
Characteristics	Tertile of Spine T Score			P
	Less than -1.18	-1.18 to 0.11	≥ 0.12	
Mean PWV	9.7	10.0	10.3	0.439
PWV ≥ 9 m/s				
Prevalence*	58.1	58.7	53.9	0.745
Odds ratio†	1.00 (ref)	1.18 (0.35 to 3.96)	0.56 (0.15 to 2.06)	0.403

ref indicates reference.

*Age standardized.

†Adjusted for age, race, sex, duration of dialysis, current smoking, body mass index, and diabetes mellitus.

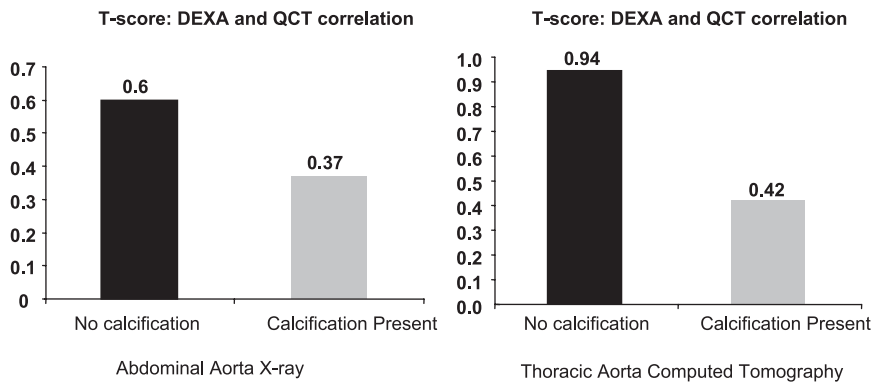


Figure 2. Correlation between T-scores measured by QCT and DEXA in the presence and absence of aortic calcification.

increase in vascular stiffness as measured by PWV.^{10,20} In turn, increased PWV is associated with an increased mortality in hemodialysis patients.¹¹ Hence, observational studies, such as that by Taal et al,¹² suggesting an increase in mortality proportional to bone demineralization in dialysis patients, may in fact be indicative of worsening vascular disease in the presence of worsening bone disease. Patients with CKD-5 frequently suffer from abnormalities of bone metabolism and remodeling predominantly in 2 forms: hyperdynamic and adynamic bone disease. In the former, excessive bone resorption causes rapid accrual and removal of calcium and phosphorus from the bone. In the adynamic state, the bone tissue rests in an indolent and inactive phase with very little ongoing remodeling and accrual of calcium. In both cases, poor bone mineralization and excessive calcium and phosphorus in the circulation likely favor deposition of hydroxyapatite crystals in soft tissues. Indeed, Braun et al²¹ described an inverse correlation between coronary artery calcium and vertebral

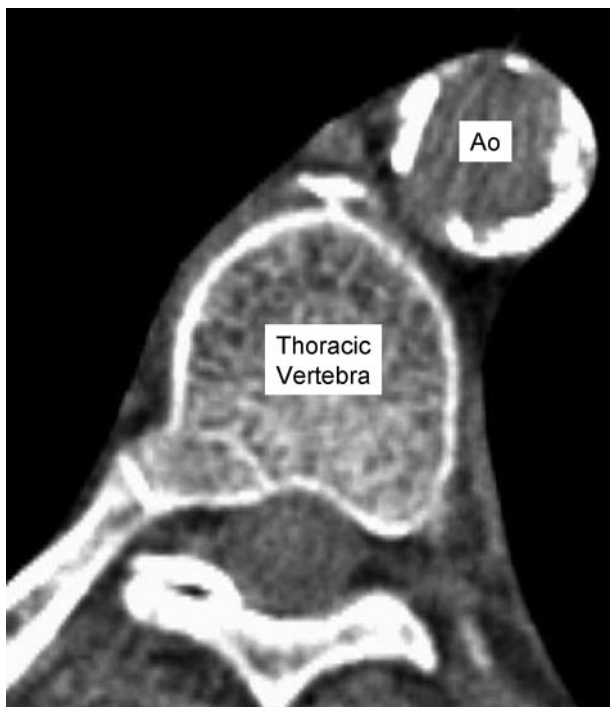


Figure 3. Example of an axial CT image showing dense calcification in the wall of the aorta next to the body of a thoracic vertebra.

BMD. We were not able to replicate such observation in our study, although we demonstrated a weak inverse correlation between QCT BMD and aorta calcium that disappeared after multivariable adjustments.

Serum levels of iPTH are often used as a surrogate marker of bone remodeling with very low levels (<100 pg/mL) suggesting the existence of an adynamic state and very high levels suggesting the presence of hyperdynamic remodeling.¹ However, the specificity of these concepts is quite low, because there is a fairly frequent discrepancy between serum iPTH levels and bone biopsy findings.^{1,22} In our study, high iPTH levels were more frequent at higher T-scores. In addition, a high PWV was noted more frequently at intermediate-to-high iPTH levels than with very high iPTH levels. The small patient numbers and the fact that iPTH is likely a weak marker of bone remodeling may have influenced the outcome and may limit the use of these analyses. Because of the uncertain value of iPTH as a marker of bone remodeling, the experts of the recent “Kidney Disease: Improving Global Outcomes” position statement suggested that, when bone biopsy is not available, physicians should refer to the many clinical biochemical and imaging abnormalities identified in renal failure as CKD-mineral bone disorder to avoid using the labels of adynamic or high bone turnover.¹

Calcification of the arterial system in patients with CKD-5 occurs both in the subintimal space (in the context of atherosclerosis) and in the media layer of the vessel wall.²³ The latter form of calcification, in particular, may be responsible for increased vessel stiffness. Both clinical and laboratory evidence reveal that mineral metabolism is closely interrelated with vascular calcification and stiffness in dialysis patients. In *in vitro* experiments, Jono et al²⁴ and Reynolds et al²⁵ demonstrated that both phosphorus and calcium can induce a transformation of smooth muscle cells into osteoblast-like cells capable of initiating and sustaining calcification of the interstitium. Guerin et al,²⁰ Goodman et al,²⁶ and Chertow et al²⁷ showed that development of arterial calcification is associated with the use of calcium containing phosphate binders and episodes of hypercalcemia. This illustrates the importance of mineral metabolism and alterations of bone remodeling as factors conditioning vascular health in dialysis patients. Of interest, our data reminisce those published recently by London et al²⁸ and suggest that active

vitamin D₃ and/or its analogs may have a protective effect on vasculopathic changes in CKD-5.

The presence of an interrelationship between vascular and bone disease has been reported in epidemiological and observational studies in the general population^{6–8} and in patients with CKD-5.^{3,4,21} Schulz et al⁸ described an association between rates of spinal bone loss and aortic calcification in postmenopausal women with osteoporosis and no evidence of renal dysfunction. Women with aortic calcification were 4.8 times more likely to have a spine fracture and 2.9 times more likely to have a hip fracture as compared with women without aortic calcification.⁸ London et al⁴ described a strong association among arterial calcification, assessed by ultrasonography, adynamic bone disease, and reduced bone remodeling on histological studies in hemodialysis patients. Finally, Raggi et al³ showed that progressive vascular calcification in patients treated with calcium containing phosphate binders is associated with demineralization of the spine.

A final important observation in our study is that DEXA is less reliable than QCT and is likely not appropriate for assessment of vertebral BMD in patients undergoing dialysis. The reason for such lack of reliability may lie in the fact that DEXA uses dual-energy x-ray beams projected blindly through the body and measures the relative absorption of such beams. As demonstrated in Figure 3, the x-ray beams could be absorbed by the densely calcified aorta rather than the spine, causing a falsely elevated BMD reading.

There are important differences between QCT and DEXA that should be mentioned. QCT is a volumetric method and provides an estimate of milligrams of hydroxyapatite per cubic centimeter of bone tissue, whereas DEXA is a planar technique providing an estimate of milligrams of hydroxyapatite per centimeter squared of bone surface. Furthermore, current QCT techniques allow only measurement of trabecular BMD, whereas DEXA-measured BMD is a composite of cortical and trabecular bone, as well as, potentially, other structures along the x-ray beam pathway, as discussed above.

There were a few limitations to this study. We performed QCT of the thoracic spine but DEXA of the lumbar spine. Because our primary objective was to verify whether there exists an interaction between PWV and BMD in patients undergoing hemodialysis, the 2 different locations for BMD measurement likely did not influence our results. Furthermore, thoracic spine QCT is as reliable as lumbar spine QCT.^{15,16} This was a cross-sectional analysis and, as such, we did not have any control over factors that could affect BMD and PWV assessment, such as use of antihypertensive agents, vitamin D analogs, and phosphate binders. However, no substantial differences in the use of these drugs across BMD scores were present.

Perspectives

There appears to be an association between bone mineralization status and vascular stiffness among hemodialysis patients. DEXA is not a reliable measure of spine BMD in these patients, and QCT should be used instead. In addition, iPTH levels may not predict the presence of abnormal vascular

function and decreased BMD. Finally, the use of vitamin D products is likely associated with a reduction in vascular stiffness, suggesting that this therapy may influence vascular function. These results highlight the importance of modern therapeutic efforts aimed at simultaneously improving bone and vascular health in dialysis patients.

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Disclosures

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