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A Structural Approach to Skeletal Fragility in Chronic Kidney Disease

Mary B. Leonard, MD, MSCE

Associate Professor of Pediatrics and Epidemiology, The Children's Hospital of Philadelphia, The Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine

Abstract

Renal osteodystrophy is a multifactorial disorder of bone metabolism in chronic kidney disease (CKD). As CKD progresses, ensuing abnormalities in mineral metabolism result in distortions in trabecular microarchitecture, thinning of the cortical shell, and increased cortical porosity. Recent studies have demonstrated significantly increased hip fracture rates in CKD stages 3 and 4, in dialysis patients, and in transplant recipients. The majority of studies of bone loss in CKD relied on dual energy x-ray absorptiometry (DXA) measures of bone mineral density (BMD). However, DXA summarizes the total bone mass within the projected bone area, concealing distinct structural alterations in trabecular and cortical bone. Recent data have confirmed that peripheral quantitative computed tomography (pQCT) measures of cortical density and thickness provide substantially better fracture discrimination in dialysis patients, compared with hip or spine DXA. The following review summarizes the growing evidence for bone fragility in CKD stages 3 through 5, considers the effects of CKD on trabecular and cortical bone structure as relates to fracture risk, and details the potential advantages and disadvantages of DXA and alternative measures of bone density, geometry, and microarchitecture, including pQCT, high resolution pQCT, and micro-magnetic resonance imaging for fracture risk assessment in CKD.

Keywords

chronic kidney disease; renal osteodystrophy; fracture; DXA; bone mineral density

Introduction

Renal osteodystrophy is a multifactorial and universal disorder of bone metabolism in advanced chronic kidney disease (CKD). As renal failure progresses, ensuing abnormalities in vitamin D metabolism and parathyroid hormone (PTH) secretion result in distortions in trabecular microarchitecture, thinning of the cortical shell, and increased cortical porosity.(1) As detailed below, hip fracture rates are significantly increased in CKD stages 3 and 4, in dialysis patients, and in transplant recipients. The majority of studies of bone loss in CKD relied on dual energy x-ray absorptiometry (DXA) measures of bone mineral density (BMD). However, DXA summarizes the total bone mass within the projected bone area (g/cm^2), concealing the distinct structural alterations in trabecular and cortical bone density and architecture that contribute to

Mary B. Leonard, MD, MSCE, The Children's Hospital of Philadelphia, 34th St. and Civic Center Blvd, CHOP North, Room 1564, Philadelphia, PA 19104, Telephone: 215-590-0874, Fax: 215-590-0604, E-mail: leonard@email.chop.edu.

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skeletal fragility in CKD. Newer imaging modalities, such as peripheral quantitative computed tomography (pQCT), high resolution pQCT (HRpQCT) and micro-magnetic resonance imaging (micro-MRI) techniques may provide greater fracture discrimination in CKD and may prove useful as surrogate measures of bone strength for clinical trials of bone therapies.

Fracture Epidemiology in Chronic Kidney Disease

In 2000, Alem, et al. examined hip fracture rates in over 300,000 maintenance dialysis patients, demonstrating an overall four-fold increase in fracture rates in male and female dialysis patients compared with population-based controls.(2) Dialysis was associated with a greater than 80-fold increased risk of fracture in young adults (age less than 45 years), but the greatest population burden was observed in older adults where the risk was increased more than two fold over the high rate observed in the general elderly population. For example, the magnitude of the added risk of hip fracture in women ranged from approximately three per 1000 person-years in young adults to 18 per 1000 person-years in those 75 years and older. The risk of hip fracture escalated with increasing duration since dialysis initiation across all age groups for men and women.

Subsequent studies identified multiple risk factors for fracture in dialysis patients. These included the following traditional risk factors for hip fracture that have been observed in the general population: older age, female sex, Caucasian race (compared with black race), lower BMI and cigarette smoking,(3) as well as impaired physical functioning (e.g. 6-minute walk, functional reach, and timed up and go).(4) Among dialysis patients, additional risk factors for fracture included peripheral vascular disease,(3) and either low or high parathyroid hormone (PTH) levels.(5,6) In one study, the lowest risk of hip fracture was observed at a PTH level of 300 pg/mL(5) and in another study, parathyroidectomy in dialysis patients was associated with a significantly lower risk of fracture.(7) Population based studies of the associations between either diabetes or cardiovascular disease with fracture risk have generated conflicting results, reporting either no associations with hip fracture risk(3) or significantly greater risk of long-bone fractures among diabetics and among patients with cardiovascular disease(6) in multivariate models.

Although one study reported that the risk of hip fracture was comparable among dialysis patients and renal transplant recipients,(2) this study was likely subject to selection bias since less-healthy dialysis patients that were not eligible for transplantation were included. Accordingly, these investigators subsequently conducted a study including only those patients on the waiting list for renal transplantation, resulting in a cohort of relatively more uniform health status.(8) Immediately following renal transplantation, the relative risk of hip fracture was 34% greater in transplant recipients compared with those patients that continued to undergo hemodialysis. However, over the ensuing months, the relative risk of fracture decreased until approximately 630 days after transplantation when rates were comparable between transplant recipients and dialysis patients (adjusted for interval since placement on the waiting list). The greater fracture risk observed soon after transplantation was attributed to high doses of glucocorticoids and post-operative immobility.

More recently, greater fracture rates have been also been reported in adults with moderate chronic kidney disease in population based databases,(9,10) and in secondary analyses of existing observational studies.(11-13) In the first population based study of the relationship between moderate to severe CKD and hip fracture, Nickolas, et al. utilized the National Health and Nutrition Examination Survey to assess hip fracture rates in adults (> 50 years of age) with an estimated glomerular filtration rate (eGFR) between 15 and 60 ml/min compared with those with an eGFR > 60 ml/min.(9) An eGFR < 60 ml/min was independently associated with an odds ratio of reported hip fracture of 2.12, and in multivariate logistic regression analysis, only

the presence of CKD, a reported history of osteoporosis, and low physical activity levels were associated with a history of hip fracture. A subsequent study conducted in men greater than 50 years of age at eight Veterans Affairs Medical Centers demonstrated that, compared with an eGFR > 60 ml/min/1.73m², stage 3 CKD (eGFR 30 to 59 ml/min/1.73m²) and stage 4 CKD (eGFR 15 to 29 ml/min/1.73m²) were associated with relative risks of fracture of 1.28 and 3.98, respectively.(10)

Similar studies within the Women's Health Initiative Observational Health Study,(13) the Study of Osteoporotic Fractures (SOF),(11) and the Cardiovascular Health Study(12) confirmed a significant association between hip fracture and CKD. Importantly, in the two studies that included DXA scans,(9,11) the associations between CKD and hip fracture were independent of BMD, suggesting that CKD impairs bone quality in a way that is not fully captured by DXA BMD. Finally, unlike the other studies, the analysis within SOF participants included assessment of vertebral fractures,(11) and did not demonstrate an independent association between vertebral fracture risk and stage 3 or 4 CKD, compared with an eGFR > 60 ml/min/1.73m². This may implicate secondary hyperparathyroidism in the greater hip fracture rates in CKD, as detailed below, since elevated PTH levels result in predominantly cortical bone loss that might preferentially increase the risk of femoral neck fractures.

Structural Determinants of Bone Strength

In 2000, the National Institutes of Health Osteoporosis Consensus Statement concluded that bone strength reflects the integration of two main features: bone density and bone quality. (14) Bone quality refers to cortical and trabecular bone architecture, turnover, damage accumulation (e.g., micro-fractures), and mineralization. CKD likely has adverse effects on each of these determinants of bone strength.

Cortical bone comprises over 80% of skeletal mass and fulfills a predominantly mechanical function. Cortical bone strength depends on bone geometry, bone density, and the location and direction of applied loads.(15) The long bones are tubular structures that are loaded mainly in bending. The resistance of long bones in bending (i.e. bone strength) is represented by the cross-sectional moment of inertia (CSMI) which is a function of the periosteal radius (R_p) and the endosteal radius (R_e): $CSMI = \pi/4 (R_p^4 - R_e^4)$.(16) These power relationships indicate that small decreases in cortical R_p or increases in R_e markedly decrease bone bending strength. In addition, cortical volumetric BMD (g/cm³) also contributes to bone strength. Ferretti et al., demonstrated that the bone strength index (a measure of CSMI weighted for cortical volumetric BMD) explained 94% of the variability in fracture load in rat femurs.(17) Cadaver studies in human bones showed that the CSMI at the radius correlates well with the fracture load at the femoral neck ($r = 0.85$). (18) Bone biomechanics studies demonstrated that fractures of predominantly trabecular sites, such as vertebral and femur fractures, propagated from defects in cortical bone.(19,20) As trabecular bone is lost, the thin shell of cortical bone takes up the load. As detailed below, loss of cortical density and dimensions are important determinants of fracture rates in CKD.

The strength of trabecular bone and its resistance to fracture traditionally have been associated with bone quantity, e.g. bone volume/total volume (BV/TV; or bone volume fraction [BVF]) or apparent density (g/cm² or g/cm³). However, trabecular micro-architectural parameters, such as trabecular thickness, number, spacing, orientation (i.e. anisotropy), and connectivity, and the ratio of plate- and rod-like structures all contribute to bone strength.(21) Age-related and postmenopausal bone loss proceeds via inhomogeneous thinning of trabecular plates leading to fenestration of plates and conversion to rods.(22) These rods may become disconnected and eventually resorbed entirely. Loss of bone mass is accompanied by a decline in the trabecular bone network's structural integrity. A meta-analysis indicates that up to 50%

of the variation in bone strength is caused by structural alterations in trabecular bone, independent of bone volume.(23) Of note, a three-dimensional analysis of the spine in autopsy cases in dialysis patients demonstrated normal to increased trabecular BV/TV but abnormal connectivity with frequent and severe trabecular perforations and microcallus formation.(24) Spinal deformities were observed despite normal BV/TV, and were attributed to the abnormal trabecular microarchitecture.

The Effect of Hyperparathyroidism on Bone Structure

PTH is anabolic in trabecular bone and catabolic in cortical bone.(25) The catabolic effect of increased PTH on cortical bone structure, whether due to primary hyperparathyroidism or secondary to renal failure, depends on its severity. If mild, bone turnover is increased approximately two to three-fold, amplifying changes due to aging or menopause:(1) cortical porosity and endocortical resorption are increased, and cortical thickness declines. Traditionally, assessment of renal osteodystrophy has focused on trabecular morphology, to the exclusion of cortical bone. However, a study of full-thickness bone biopsies in dialysis patients demonstrated a 45% reduction in cortical bone volume in both high-turnover and low-turnover disease.(26) Most of the cortical deficit was due to cortical thinning. A small case series suggested that loss of cortical bone dimensions in CKD was irreversible.(27)

The anabolic effect of hyperparathyroidism on trabecular bone also depends on its severity. If mild, age-related losses in trabecular bone are minimized, with fewer perforations and greater preservation of three-dimensional connectivity. Dempster, et al. used microcomputed tomography (micro-CT) scans of bone biopsy specimens to show that post-menopausal women with primary hyperparathyroidism had greater BV/TV and trabecular connectivity compared with post-menopausal controls.(28) If the hyperparathyroidism is severe, osteitis fibrosis develops with progression to dissecting intra-trabecular resorption and loss of bone volume. The trabecular manifestations of CKD are well-described in iliac crest bone biopsies.(29) The increased remodeling rate in high-turnover disease initially results in thickened, irregularly shaped trabeculae, with increased bone volume.(26) Increased bone volume is not necessarily equated with greater bone strength because the irregular trabeculae may lose their proper three dimensional architecture and connectivity. As disease progresses, resorption cavities dissect trabeculae and bone volume decreases.

Radiographic Assessment of Bone Mineral Density and Structure

DXA is safe, rapid, and - by far - the most widely used technique for measuring bone mass and BMD. However, DXA is a projectional technique in which three dimensional objects are analyzed as two dimensional. Bone is presented as the combined sum of cortical and trabecular BMC within the projected bone area, concealing the distinct structural characteristics. DXA provides an estimate of BMC expressed as grams per anatomical region (e.g., individual vertebrae or hip). Dividing the BMC (g) by the projected area of the bone (cm^2) then derives "areal-BMD" (g/cm^2). This is not a measure of volumetric density (g/cm^3).

In contrast, computed tomography (CT) provides a cross-sectional image unobscured by overlying structures.(30) The CT attenuation of different tissues provides quantitative information, referred to as quantitative CT (QCT). In contrast to DXA, this technique describes authentic volumetric BMD (g/cm^3), accurately measures bone dimensions, and distinguishes between cortical and trabecular bone. In order to minimize radiation exposure, special high-resolution scanners were developed for the peripheral skeleton (pQCT). These pQCT measures of cortical dimensions predicted fracture load in the radius and femoral neck in the absence of renal disease ($R \geq 0.91$). (31)

The mechanical competence of trabecular bone is largely determined by BV/TV and microarchitecture. Recently, advanced imaging techniques, such as micro-MRI and ultra high resolution pQCT (HRpQCT) have been developed for the assessment of trabecular microarchitecture. These techniques provide morphologic parameters synonymous to standard histomorphometry [e.g. BV/TV, trabecular separation (Tb.Sp), trabecular thickness (Tb.Th) and trabecular number (Tb.N)], as well as estimates of trabecular connectivity.(22,32) These measures are associated with fractures independent of DXA BMD, and are sensitive to structure changes induced by testosterone replacement in hypogonadal men,(33) and hormone replacement therapy in women.(34)

Bone Imaging and Fracture Discrimination in CKD

DXA and pQCT in CKD

DXA has been used extensively to evaluate patients with CKD. However, since trabecular and cortical bone behave differently in response to increased parathyroid activity (increase and decrease, respectively), and DXA does not distinguish between CKD effects on these two types of bone, DXA may be of limited value in CKD. The conflicting data on DXA-derived measures of BMD in CKD are consistent with these limitations: DXA results have been variable with mean BMD values that are higher than, the same as, or lower than control subjects (reviewed by AM Parfitt (1)).

A study in adults with primary hyperparathyroidism illustrates the limitations of DXA in the setting of increased PTH.(35) The two-dimensional posterior-anterior DXA projection of the spine captures the largely trabecular vertebral body, as well as the superimposed cortical spinous processes. However, the lateral projection allows one to distinguish between the vertebral body and posterior elements. Spine BMD on the posterior-anterior projection was normal; however, the lateral scan revealed increased BMD in the predominantly trabecular vertebral body, and decreased BMD in the cortical spinous processes. The greater trabecular BMD effectively masked the cortical bone loss on the PA projection. Consistent with the cortical bone loss in patients with primary hyperparathyroidism, the International Society of Clinical Densitometry (<http://www.iscd.org>) recommends that DXA scans should be performed in the distal one third of the radius (an entirely cortical site) in patients with hyperparathyroidism, rather than in the predominantly trabecular lumbar spine or femoral neck.

In 2007, Jamal et al reported the results of a meta-analysis conducted to determine whether DXA measures of BMD at the femoral neck, spine, and radius were associated with spine and/or non-spine fractures in dialysis patients.(36) Based on six studies totaling 683 subjects, the authors reported that subjects with fractures had significantly lower BMD at all sites except for the femoral neck. However, there was important heterogeneity across the six studies and the analysis may have suffered publication bias. Although BMD levels may be lower in CKD patients with a history of fracture, there is considerable overlap in BMD levels such that BMD provides poor fracture discrimination in individuals.

Spine QCT data in CKD confirmed biopsy histomorphometric data: trabecular volumetric BMD was increased in high-turnover disease (+ 1.6 SD) and decreased in low-turnover disease (-1.2 SD), relative to age-matched controls.(37) A recent pQCT study in 12 adult transplant recipients demonstrated a significantly greater endosteal circumference and lower cortical thickness, compared with controls.(38) Total time on dialysis prior to renal transplantation correlated negatively with cortical thickness ($r = 0.62$; $p < 0.01$). A pQCT study in children illustrated the opposing effects of renal osteodystrophy on cortical and trabecular volumetric BMD.(39) PQCT scans and bone biopsies were obtained in 21 children and adolescents treated with maintenance peritoneal dialysis. Trabecular volumetric BMD was significantly greater in CKD subjects compared with controls ($p < 0.0001$), whereas cortical volumetric BMD was

significantly lower in CKD subjects compared with controls ($p < 0.001$). Trabecular volumetric BMD was lower in patients with adynamic bone, compared with those with high-turnover lesions ($p < 0.001$). In contrast, cortical volumetric BMD was higher in patients with adynamic bone compared with those with high-turnover lesions ($p < 0.05$). Data on cortical thickness or dimensions were not provided. Finally, Figure 1 illustrates significant cortical bone loss in the midshaft of the tibia in an adult with CKD stage 4, compared with an age and gender matched control. The reductions in cortical bone mineral content are due to loss of cortical thickness on the endocortical surface and reductions in cortical volumetric BMD.

Although pQCT discriminates between trabecular and cortical bone, and provides details regarding cortical density and geometry, pQCT is not of sufficient resolution to provide detailed micro-architectural information in the trabecular sites. This limitation is illustrated in the study below relating pQCT trabecular BMD to fracture risk.

DXA and pQCT Receiver Operating Characteristic Curves in CKD

The diagnostic test characteristics of the varied imaging modalities in discriminating fracture risk is best assessed using receiver-operating characteristic (ROC) curves. (40,41) In order to assess the discriminative ability of the varied tests, ROC curves can be constructed for each scan outcome; e.g. DXA areal-BMD, pQCT cortical thickness, or pQCT trabecular volumetric BMD. ROC curves plot the sensitivity on the y-axis versus $1 - \text{specificity}$ on the x-axis. A variable that has excellent predictive power for fracture will tend, at all possible cut-off values, to have greater sensitivity (and hence be farther “up”) and greater specificity (and hence be farther to the left), than a test with worse predictive value. The predictive power is assessed by computing the area under the ROC curve, or the AUC; as the AUC approaches 1.0, the greater the predictive power of the test. To compare measures directly (e.g. to test the hypothesis that pQCT measures of cortical volumetric BMD provide better fracture discrimination than DXA areal-BMD), one can test the equality of the AUC values using a χ^2 test.

A recent cross-sectional ROC study in 52 adults on maintenance hemodialysis demonstrated that reductions in pQCT measures of cortical bone in the radius were strongly predictive of vertebral and fragility fractures while pQCT trabecular volumetric BMD and DXA areal-BMD were not. (42) Table 1 illustrates the marked differences in the odds of fracture and area under the ROC curve at each site. For example, the AUC for DXA areal-BMD in the hip was only 0.56 while the AUC for pQCT cortical volumetric BMD was 0.89; this difference was significant as illustrated in Figure 2. The clinical significance of these marked differences is highlighted by the odds ratio in Table 1. Of note, this study did not include DXA measures in the radius. Therefore, it is not known if DXA measures in the cortical midshaft of the radius will improve fracture discrimination. Finally, the failure of pQCT trabecular volumetric BMD to discriminate fractures in dialysis patients is not surprising given that pQCT does not have sufficient resolution to detect the unique effects of renal osteodystrophy on trabecular microarchitecture, independent of bone quantity. Recall that a three-dimensional analysis of the spine in autopsy cases in dialysis patients demonstrated that abnormal connectivity was associated with vertebral deformities, despite normal to increased BV/TV. (24)

Research Applications: Micro-CT and Micro-MRI

The newest generation of high resolution CT and MRI scanners can be used to evaluate bone microarchitecture. For example, the resolution of conventional pQCT is $< 350 \mu\text{m}$, compared to $< 100 \mu\text{m}$ for HRpQCT and $8 \mu\text{m}$ for in vitro micro-CT machines. We recently used micro-CT to assess the structure effects of severe high turnover renal osteodystrophy on trabecular and cortical architecture in growing rats. Renal osteodystrophy resulted in irregular trabecular thickening and loss of trabecular connectivity in the femoral neck and greater endocortical

porosity in the femoral shaft, compared with controls (Figure 3).(43) Of note, scan acquisition required greater than 3 hours; therefore, this technique is limited to in vitro applications.

We recently completed a pilot study of micro-MRI in 17 young adults on maintenance hemodialysis, compared with healthy controls.(44) Figure 4 illustrates the cortical thinning and disruption of trabecular architecture in a young adult male with severe uncontrolled renal osteodystrophy of many years duration, ultimately resulting in parathyroidectomy. BV/TV did not differ significantly in this small sample of hemodialysis patients compared with controls; however, the pattern of lower surface and greater curve voxels suggested deterioration of the trabecular network. These studies were recently extended to include MRI measures of cortical porosity.(45) In vivo, bone water in post-menopausal women was 65% greater than in pre-menopausal women, and in dialysis patients was 43% greater than the post-menopausal women; DXA BMD showed much smaller group differences. Because the majority of bone water is in the pore system of cortical bone, this parameter provides a surrogate measure for cortical porosity.

Two cross-sectional studies have used high-resolution CT(46) or MRI(47) to evaluate trabecular architecture in renal transplant recipients; patients were evaluated months to years after transplantation. Grotz, et al reported that vertebral deformities were associated with lower trabecular area, lower trabecular diameter and increased intertrabecular spacing in transplant recipients, compared to transplant recipients without vertebral deformities.(46) Link, et al reported that transplant recipients had significantly lower MRI measures of BV/TV, Tb.Sp, Tb.Th and Tb.N compared with controls; (47) however, spine QCT trabecular BMD, and DXA hip and spine BMD did not differ between transplant recipients and controls. The MRI and QCT measures differed between fracture and non-fracture ESRD patients; the DXA measures did not.

Summary

The 2003 *National Kidney Foundation Clinical Practice Guidelines for Bone Metabolism and Disease in CKD* recommended the following for all adult patients with CKD:(48) “Bone mineral density should be measured by dual energy x-ray absorptiometry in patients with fractures and in those with known risk factors for osteoporosis”. More recently, the *Kidney Disease: Improving Global Outcomes* working group published a position paper on the evaluation of renal osteodystrophy.(49) The report concluded that the value of DXA BMD measurement in the evaluation of CKD metabolic bone disease is not well established, and concluded that the radius is the preferred site of measurement in CKD patients, consistent with the recommendations of International Society of Clinical Densitometry for patients with primary hyperparathyroidism, as detailed above. The working group also recommended that bone biopsy results in CKD should be categorized according to bone turnover, mineralization and volume (TMV). Unfortunately, non-invasive measures of bone turnover have poor diagnostic accuracy in CKD; however, positron emission tomography may prove useful for the differentiation of low turnover from high turnover lesions in CKD and may provide quantitative estimates of bone cell activity that correlate with histomorphometric data.(50) In vivo measures of bone mineralization are not yet available. However, MRI and CT techniques can be used to assess trabecular bone volume fraction, as well as trabecular micro-architecture, cortical volumetric BMD, porosity, and dimensions.

The assessment of the effects of CKD and its potential therapies on fracture risk requires novel imaging techniques to characterize accurately the effects on trabecular and cortical bone. Recent data suggest that DXA has minimal, if any, utility in predicating fractures in advanced CKD. Validation of surrogate measures of fracture risk (e.g. QCT measures of cortical volumetric BMD and dimensions, or micro-MRI or HRpQCT measures of trabecular connectivity) is required for future clinical trials of therapeutic agents. Ongoing research in

this field will guide future studies to improve bone strength and decrease fracture rates in a population that will continue to require renal replacement therapies throughout their lifetime.

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Figure 1. PQCT Scans in the Mid-shaft of the Tibia in (A) a 64 year old male with stage 4 CKD, and (B) a 62 year old male with normal renal function

This figure illustrates the bone loss on the endosteal surface and the reduced endocortical volumetric BMD. (From Nickolas TL, Leonard MB, Shane E 2008 Chronic kidney disease and bone fracture: a growing concern. *Kidney Int* **74**(6):721-31)

Figure 2. ROC Curves for DXA areal BMD in the Hip and pQCT cortical vBMD in the midshaft of the radius in Dialysis Patients

(From Jamal SA, Gilbert J, Gordon C, Bauer DC 2006 Cortical pQCT measures are associated with fractures in dialysis patients. *J Bone Miner Res* **21**(4):543-8.)

Controls**Renal Osteodystrophy** **Femoral neck** **Femoral Shaft**

Figure 3. Axial μ CT images (8.2 micron resolution) in the femoral neck illustrate the effects of renal osteodystrophy on trabecular microarchitecture in rats
(adapted from Hopper TA, et al. 2007 Quantitative microcomputed tomography assessment of intratrabecular, intertrabecular, and cortical bone architecture in a rat model of severe renal osteodystrophy. *J Comput Assist Tomogr* **31**(2):320-8.)

Figure 4. Tibia μ MRI illustrates severe cortical thinning and loss of trabecular connectivity and bone volume in a hemodialysis patient, compared with a healthy, age and gender matched control (adapted from Wehrli FW, Leonard MB, Saha PK, Gomberg BR 2004 Quantitative high-resolution magnetic resonance imaging reveals structural implications of renal osteodystrophy on trabecular and cortical bone. *J Magn Reson Imaging* **20**(1):83-9)

Table 1
Association Between Fractures and pQCT or DXA Measures in Adult Hemodialysis Patients(42)

Predictor	Odds of Fracture (95% CI) per SD decrease	Area under ROC curve
pQCT		
Trabecular volumetric BMD	1.18 (0.60, 2.33)	0.52 (0.34, 0.39)
Cortical volumetric BMD	16.67 (2.94, 83.3)	0.89 (0.90, 0.99)
Cortical Thickness	3.26 (1.36, 7.87)	0.78 (0.63, 0.93)
DXA		
Spine areal BMD	0.53 (0.27, 1.06)	0.63 (0.48, 0.78)
Femoral neck areal BMD	0.69 (0.36, 1.30)	0.42 (0.23, 0.57)
Total hip areal BMD	1.10 (0.85, 2.08)	0.56 (0.30, 0.63)