Bone Imaging and Chronic Kidney Disease: Will High-Resolution Peripheral Tomography Improve Bone Evaluation and Therapeutic Management?

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Bone damage because of chronic kidney disease (CKD) represents a daily challenge for nephrologists. The impact of CKD on bone health may be immediate (serum phosphocalcic disturbances) or delayed (bone fractures and vascular calcifications). Histomorphometry remains the gold standard to evaluate bone, but it is rarely performed in clinical practice. Areal measurement of bone mineral density by dual x-ray absorptiometry is routinely performed to evaluate bone mass. However, this technique presents some limitations. In 2000, the United States National Institutes of Health defined new “quality” criteria for the diagnosis of osteoporosis in addition to decreased bone mass. Bone strength actually integrates two concepts: bone quantity and bone quality (i.e., microarchitectural organization, bone turnover, bone material properties such as mineralization, collagen traits, and microdamage) that cannot be evaluated by dual x-ray absorptiometry. New three-dimensional, noninvasive bone-imaging techniques have thus been developed, e.g., high-resolution peripheral quantitative computed tomography. High-resolution peripheral quantitative computed tomography allows evaluation of both volumetric density and microarchitecture in different compartments of bone, at the distal radius and tibia. High-resolution peripheral quantitative computed tomography may be useful in predicting fractures and assessing bone preventive or therapeutic strategies in CKD patients. It should be evaluated in long-term, longitudinal follow-ups.

Bone damage in patients with chronic kidney disease (CKD) represents a daily challenge for nephrologists.1 The deleterious effects of CKD on bone result from a combination of factors, e.g., vitamin D deficiency, hyperparathyroidism, hypogonadism, malnutrition, resistance to growth hormone, and drug toxicity (e.g., corticosteroids or calcineurin inhibitors).2-3 Traditional risk factors for fractures, such as aging, female gender, postmenopausal status, low body weight, chronic inflammation, immobilization, and exposure to benzodiazepines, alcohol, and tobacco, may apply in CKD as well.4-5 However, specific risks may also be identified, particularly in terms of duration of renal replacement therapy and history of renal transplantation.5 Chronic kidney disease mineral and bone disorders (MBD) occurs as soon as the glomerular filtration rate (GFR) falls below 60 mL/min per 1.73 m².1 The impact of CKD on bone and mineral status may be immediate (serum phosphocalcic dysequilibrium) or delayed (fractures or vascular calcifications). In hemodialysis patients, there is a fourfold increased risk of hip fracture,6 whereas there is a twofold increased risk of hip fracture in predialysis patients.7 Histomorphometry remains the gold standard for evaluating bone.8,9 A transiliac crest
Bone biopsy allows for dynamic analysis, with tetracycline labeling of bone-forming sites and a two-dimensional static analysis of bone, for assessment of bone microarchitecture (e.g., bone volume/tissue volume, trabecular number, trabecular thickness, and trabecular separation). However, bone biopsy is an invasive technique and is rarely performed in daily practice. Moreover, bone biopsy provides limited information about three-dimensional trabecular connectivity and orientation.

Areal measurement of bone mineral density (aBMD) by dual x-ray absorptiometry (DXA) is routinely performed to evaluate bone mass. However, this technique presents some limitations. In 2000, the United States National Institutes of Health defined new “quality” criteria for the diagnosis of osteoporosis in addition to decreased bone mass. Bone strength is influenced not only by the amount of bone, but also by its spatial distribution, cortical and trabecular microarchitecture, bone turnover, and material properties such as matrix mineralization, collagen traits, and microdamage. These “quality” criteria cannot be evaluated by DXA. Thus, new bone-imaging techniques were developed, leading to an improvement in bone evaluation. These techniques are particularly challenging in CKD, especially for evaluating bone and improving the management of CKD MBD and fracture-risk prediction.

Bone Turnover Markers and CKD in Daily Practice

Bone turnover is characterized by bone formation by osteoblasts and bone resorption by osteoclasts. Bone turnover markers (BTMs) are divided into two groups: bone formation markers (e.g., total and bone alkaline phosphatase, tAP and bAP; osteocalcin, OC; and procollagen type I N-propeptides and C-propeptides, PINP and PICP) and bone-resorption markers (e.g., N-terminal cross-linking telopeptides of type I collagen, CTX; and tartrate-resistant acid phosphatase type 5b, TRACP). These markers cannot, however, discriminate between bone-turnover changes in cortical or trabecular compartments. During CKD, there is an accumulation of most BTMs, except for tAP, bAP, and TRACP, as recently described by Yamada et al. in predialysis patients.

Table 1 illustrates the correlation between BTM and GFR. These data confirm the accumulation of CTX and fibroblast growth factor (FGF)-23 during CKD, thus introducing a bias for the use of these BTMs. There is a trend toward an accumulation of OC when GFR decreases. In contrast, neither tAP nor bAP is influenced by GFR, and thus can be used reliably in CKD.

Dual X-Ray Absorptiometry and CKD in Daily Practice

Dual x-ray absorptiometry is a noninvasive and inexpensive tool for the diagnosis of osteoporosis, with low radiation exposure (1 to 5 μSv). Dual x-ray absorptiometry is based on a two-dimensional projection of a three-dimensional structure. It allows for the quantification of bone mineral content (BMC, in grams) and aBMD (in grams per square centimeters). Two sites are mainly studied in adults: the lumbar spine (from the L1 to L4 vertebral bodies) and proximal femur. Peripheral sites (e.g., the forearm) may also be used. Precision is excellent, with a reproducibility of about 1% for the lumbar spine, and 1% to 2% for the proximal femur. Scanning times are short (about 2 minutes for the spine). A World Health Organization consensus proposed a limit of −2.5 standard deviations below the mean obtained in the same gender-matched young healthy controls as the main criterion for osteoporosis, corresponding to the T-score. There is an inverse relationship between incidence of osteoporotic fractures and aBMD. However, up to 50% of fractures occur among individuals who would not be classified as osteoporotic, based on DXA alone. The assessment of microarchitecture parameters in addition to aBMD may improve fracture-risk prediction.

Dual x-ray absorptiometry has technical limitations that should be taken into account when

| Table 1. Bone Biomarker Accumulation in Patients With CKD Stages II to IV |
|-----------------|------------------|--------|
| Correlation     | With GFR         | P Value|
| Cross-laps (CTX)| −0.373           | .004   |
| NMID-OC         | −0.239           | .068   |
| Total alkaline phosphatase | 0.235 | NS     |
| Bone alkaline phosphatase | 0.1   | NS     |
| Parathyroid hormone | −0.518 | <.001 |
| FGF-23          | −0.338           | .022   |

CKD, chronic kidney disease; GFR, glomerular filtration rate; FGF, fibroblast growth factor; NS, not significant; NMID-OC, N-terminal midfragment of osteocalcin.
interpreting results. Because measurements are two-dimensional, larger bones may have higher BMD values than smaller bones, in the absence of differences in absolute bone density. This fact is of particular importance during growth in children. Moreover, artifacts may occur because of orthopedic hardware, movements during study, and aortic calcifications. These calcifications and the endplate osteosclerosis of vertebral bodies represent strong technical limitations to lumbar-spine DXA in CKD patients. The radius thus seems to be an promising site for DXA in CKD.1 Another limitation of DXA is its inability to distinguish trabecular from cortical bone, whereas hyperparathyroidism preferentially affects cortical bone and corticosteroids rather than trabecular bone. The last important limitation of DXA is its inability to assess bone microarchitecture.

In CKD patients, aBMD values can be low, normal, or high in the two main forms of renal bone

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>N</th>
<th>CKD Stage</th>
<th>Site</th>
<th>Other Imaging Techniques</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Russo et al.22</td>
<td>1998</td>
<td>39 patients</td>
<td>Hemodialysis</td>
<td>Radius</td>
<td>No</td>
<td>Decreased cortical vBMD in patients. Cortical vBMD inversely correlated with age, dialysis duration, and PTH. No difference for trabecular vBMD.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ 67 controls</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Hasegawa et al.23</td>
<td>2004</td>
<td>83 controls</td>
<td>Hemodialysis</td>
<td>Radius</td>
<td>No</td>
<td>Decreased cortical vBMD and thickness in patients. No difference for trabecular vBMD.</td>
</tr>
<tr>
<td>Tsuchida et al.24</td>
<td>2005</td>
<td>85</td>
<td>Predialysis</td>
<td>Radius</td>
<td>No</td>
<td>Negative correlation between trabecular vBMD and biomarkers of bone formation. No correlation between vBMD and biomarkers of bone resorption.</td>
</tr>
<tr>
<td>Negri et al.25</td>
<td>2006</td>
<td>22 + 27 controls</td>
<td>Peritoneal dialysis</td>
<td>Radius</td>
<td>DXA (spine, hip)</td>
<td>Decreased cortical vBMD and thickness. No correlation between pQCT cortical parameters and aBMD measured by DXA.</td>
</tr>
<tr>
<td>Jamal et al.26</td>
<td>2006</td>
<td>52</td>
<td>Hemodialysis</td>
<td>Radius</td>
<td>DXA (spine, hip)</td>
<td>Association between onset of fractures and decreased cortical vBMD and thickness. No association between onset of fractures and neither trabecular vBMD nor aBMD measured by DXA. Longitudinal studies are warranted to confirm these results.</td>
</tr>
<tr>
<td>Obatake et al.27</td>
<td>2007</td>
<td>53</td>
<td>Predialysis</td>
<td>Radius</td>
<td>No</td>
<td>After 1 year of follow-up, both total cortical and trabecular vBMDs decreased. Positive correlation between 25 OH vitamin D$_2$ level and vBMD (total and trabecular).</td>
</tr>
</tbody>
</table>

pQCT, peripheral quantitative computed tomography; CKD, chronic kidney disease; DXA, dual x-ray absorptiometry; BMD, bone mineral density (a, areal; v, volumetric); PTH, parathyroid hormone.
disease, i.e., hyperparathyroidism and adynamic bone disease. Moreover, a study of 20 children undergoing dialysis revealed abnormal histomorphometric analyses (for both dynamic and static parameters) in all cases, whereas only 25% of the children had an abnormal aBMD value. Data about DXA, CKD, and fracture risk are conflicting, but two conclusions can be drawn: in patients with CKD, aBMD appears to be decreased, but DXA cannot provide a detailed fracture-risk prediction. Moreover, decreased aBMD is associated with increased vascular calcification, and is an independent risk factor of mortality in hemodialysis patients.

Techniques Derived From Tomography and CKD in Research Studies

Quantitative Computed Tomography

Based on standard body computed tomography scanners, this three-dimensional technique separately measures trabecular and cortical volumetric BMD (vBMD) at central sites (the lumbar spine and hip). Quantitative computed tomography (QCT) also permits the evaluation of bone size and geometry. However, this technique induces higher radiation than DXA (about 50 mSv) and is rarely available in daily practice, and reference values are limited.

Peripheral Quantitative Computed Tomography (pQCT)

Also based on x-rays but with less radiation exposure than QCT, this technique separately measures trabecular and cortical density at peripheral sites. It allows for the assessment of parameters of bone strength, such as polar moment of inertia, section modulus, and cortical thickness. This technique is rarely available in clinical practice. Table 2 summarizes the results of clinical studies with peripheral quantitative computed tomography (pQCT) in CKD patients.

High-Resolution Peripheral Quantitative Computed Tomography (HR-pQCT)

This system corresponds to a technical improvement of pQCT, with a decreased voxel resolution from 350 to 82 μm. High-resolution peripheral quantitative computed tomography (HR-pQCT) allows the measurement of both volumetric density and microarchitecture parameters in total, cortical, and trabecular bone at the distal radius and distal tibia, as summarized in Table 3. It induces low radiation exposure (effective dose of 3 μSv per measurement), and has excellent precision for both density (0.7% to 1.5%) and trabecular microarchitecture (1.5% to 4.4%). At each acquisition site, 110 bone slices are obtained, leading to a three-dimensional representation of approximately 9 mm in the axial direction, for an acquisition time of 3 minutes. However, HR-pQCT requires a specialized device, and measurements are limited to peripheral skeletal

Table 3. Evaluation of Different Bone Parameters With HR-pQCT

<table>
<thead>
<tr>
<th>Density Parameters</th>
<th>Microarchitecture Parameters</th>
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<tbody>
<tr>
<td>Volumetric bone mineral density</td>
<td>Cortical parameters: cortical thickness</td>
</tr>
<tr>
<td>Total</td>
<td>Trabecular parameters: trabecular number, trabecular thickness, trabecular separation, intra-individual distribution of separation</td>
</tr>
<tr>
<td>Cortical</td>
<td>Geometric parameters: cross-sectional, cortical, and trabecular area; periosteal circumference</td>
</tr>
<tr>
<td>Trabecular</td>
<td></td>
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</table>

Figure 1. Three-dimensional reconstruction, using HR-pQCT, of a tibia in a CKD patient. HR-pQCT, high-resolution peripheral quantitative computed tomography, CKD, chronic kidney disease.
In the context of CKD, bone-remodeling damage such as osteomalacia cannot be assessed with this technique, because it evaluates only mineralized bone. Figure 1 represents a three-dimensional tibia reconstruction from a 74-year-old woman with CKD stage IV and receiving corticosteroids.

**HR-pQCT: Qualitative Analysis in CKD Patients and Perspectives**

A preliminary study was performed in 60 patients with CKD stages II to IV. As shown in Figure 2, qualitative analysis of HR-pQCT tibia slices revealed that cortical bone varied from homogenous cortical bone (patient 1) to heterogeneous destructured cortical bone (patient 2). Patients with vascular or diabetic nephropathy seem to experience more qualitative cortical damage. In this prospective study, patients with CKD stages II to IV did not experience severe hyperparathyroidism (mean serum parathyroid hormone level of 106 ± 68 pg/mL in 40 men, and 84 ± 60 pg/mL in 20 women [results are mean ± SD]; Roche Elecsys [Roche Diagnostics, Mannheim, Germany]). However, they often presented with a vitamin D deficiency (85% of patients with 25 OH vitamin D3 serum levels below 30 ng/L).

**Conclusion**

In addition to DXA and techniques derived from tomography, other bone-imaging techniques may be used to evaluate bone microarchitecture, e.g., magnetic resonance imaging and ultrasound. These new bone-imaging techniques, currently limited to research studies, more accurately assess BMD, bone microarchitecture, and ultimately bone strength. Although HR-pQCT may be a useful tool for fracture-risk prediction, it still needs to be validated in further longitudinal studies. Because the proportion of elderly subjects at risk for both CKD and osteoporosis is increasing in the general population and because CKD patients are often excluded from clinical trials evaluating bone protective therapies (e.g., bisphosphonates, teriparatide, and strontium ranelate), there is an urgent need for randomized, controlled trials of otherwise validated preventive strategies. In such clinical trials, the use of HR-pQCT may be of great interest.

**References**