Noninvasive Imaging of Bone Microarchitecture in Patients Receiving Renal Transplant: Can it Replace Histology?

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It is important to the general nephrology community to find noninvasive methods to diagnose metabolic bone disease, whether in patients receiving dialysis or renal transplant. Undiagnosed renal bone disease can lead to debilitating fractures that are many times more common than in the general population (1–3). Renal transplant recipients have underlying renal osteodystrophy that develops pretransplantation and is mainly due to loss of control of bone and mineral metabolism. Diagnosis of renal osteodystrophy relies on an understanding of the normal and pathologic microarchitecture of bone. Mineralized histology of bone biopsies is the gold standard for determination of microarchitecture. The diagnostic spectrum obtained from it spans from low turnover (adynamic) to high turnover (hyperparathyroid) bone disease. In addition to adynamic bone where cellular activity is essentially at a standstill, low turnover disease may include mineralization defect, where bone is replaced with excess unmineralized osteoid. High turnover histology typically shows an exuberance of cellular activity with increased osteoblasts, osteoclasts, and peritrabecular fibrosis. The bone biopsy can give static information on trabecular number, thickness, microfractures, spatial configuration, and connectivity—all parameters that speak to bone strength and metabolic capacity. In addition, the bone biopsy can give information on dynamic parameters such as bone formation rate, a measure of new bone made, the rate at which the new bone is mineralized, and the activation frequency or estimate of bone remodeling (4,5). However, bone histology has fallen out of favor in part because of its invasiveness and technical difficulty in acquisition, processing, and interpretation.

Noninvasive imaging methods have largely replaced mineralized bone histology and have made clinical assessment of bone status a universal standard of practice. In addition to offering a more global view of the physical status of bone than the small sample in a biopsy, these methods can also yield some of the information obtained from mineralized bone histology. The two techniques currently best suited to be partial surrogates for mineralized bone histology are dual-energy x-ray absorptiometry (DXA) and quantitative computed tomography in its various forms (central, peripheral, high-resolution, and micro computed tomography). However, these methods have their limitations. Even in their most advanced forms, they cannot give critical measurements obtained from histology.

DXA measures bone mineral density and has been validated across women in the general nonrenal population to predict fracture risk and to generate treatment paradigms on the basis of the derived T-score (6). In general, a T-score of −2.5 (SD from normal in the normal 30-year-old woman) is considered osteoporotic and is associated with increased fracture risk. However, bone mineral density as measured by DXA, important in the diagnosis of osteoporosis, cannot distinguish between underlying high or low turnover bone disease: it only measures mineral content. This is not surprising because DXA contains little of the spatial or cellular information detected by bone histology. DXA does not correlate with bone histology or histomorphometric analysis of bone activity. In fact, the Kidney Disease Outcomes Quality Initiative does not recommend its routine use in patients who are prerenal transplant (7).

The shortcomings of DXA compared with mineralized histology in the diagnosis of renal bone disease are best illustrated in studies of patients receiving renal transplant. Here, osteodystrophy takes on more and different significance because bone architecture is altered beyond what is already present in renal failure by the added stressors of transplantation. These include the addition of antirejection medications (calcineurin inhibitors and steroids especially), changes in mineral metabolism (because electrolytes are in constant flux as allograft function stabilizes), and normal age-related changes. In the days before steroid minimization for prevention of allograft rejection, it was not unusual to see a significant decrease in bone mineral density (BMD) in the first 6 months post-transplant (8).

Few studies have compared BMD with histomorphometry. A cross-sectional study of bone histomorphometry in women receiving transplant with normal renal function reported high and low bone turnover, with BMD T-scores in the osteoporotic range. Hip BMD but not vertebral BMD correlated with cortical and trabecular histomorphometry (9). Bone histomorphometry done in a cross-sectional study of renal transplant recipients, both men and women, who were postrenal transplant...
for a varying number of years, showed mainly low bone turnover and low bone volume; however, no BMD data were presented (10). In a study on the use of the intravenous bisphosphonate pamidronate to prevent bone loss, we showed that vertebral BMD decreased significantly in the control group as compared with the treated group, whereas most of the patients in both groups developed adynamic bone disease. However, this study did not compare bone histology with BMD readings (11).

In a subsequent study on men and women receiving transplant, on steroid minimization, and randomized for use of the popular oral bisphosphonate risedronate, we found that baseline BMD was in the healthy or osteopenic range of T-scores and that it did not change over the course of the 12-month study in either group. Bone histomorphometry showed lowered bone turnover with osteomalacia in the treated men and preserved trabecular thickness in the treated women. Of interest, neither T-scores nor BMD at any site correlated with any histomorphometric measures, and BMD could not predict bone disease (12). This may imply that we cannot reliably diagnose transplant bone disease on the basis of BMD alone.

High resolution peripheral quantitative computed tomography (HR-pQCT) scanning is a new and still experimental imaging technique that yields more detailed information than any previous noninvasive technique. It is derived from clinically used quantitative computed tomography methods and improves resolution of bone trabecular structure and volume, but only on thin or small specimens or parts of the body. It has very low resolution compared with microscopy (82 μm as compared with <1 μm for light microscopy) and does not give cellular, biochemical, or compositional information. Nonetheless, it has yielded useful information on bone microarchitecture.

Trabecular bone score (TBS) is a new, clinically applicable approach to bone evaluation that can generate a measure of the potential to fracture in trabecular bone by recalculating DXA images (16). This is the first technique to directly add a clinical component to an otherwise purely structural evaluation. Whereas DXA measures total mineral content and derives a score (T-score) from this, TBS extracts spatial information from DXA images using grayscale textural analysis and thereby quantifies trabecular microarchitecture. There have been studies that show improved fracture prediction by TBS over DXA T-scores alone in the general population (17), and other retrospective studies that suggest that TBS scores predict fractures in renal transplant recipients (18). A recent cross-sectional study examined transiliac bone biopsy specimens from patients with idiopathic osteoporosis and fractures. It compared TBS obtained by spinal DXA to trabecular parameters of the bone biopsies as assessed by micro computed tomography. A significant correlation was found between TBS and the micro computed tomography images. However, TBS was not compared with the actual histomorphometry of the bone biopsy specimen (19).

In the study published in this issue of the Clinical Journal of the American Society of Nephrology, Luckman et al. compared morphometric parameters derived from HR-pQCT with TBS parameters derived from DXA (20). A series of renal transplant recipients had been studied over the years with serial HR-pQCT and DXA (14,15). In a post hoc analysis, TBS was applied and correlated with DXA and HR-pQCT. Most of the patients had healthy DXA T-scores (>−1.0) pre- and post-transplant, which would imply a lower fracture risk over time. TBS analysis redefined fracture risk with at least 50% risk at any time point. TBS correlated with BMD, as expected because both are derived from DXA. TBS also correlated with HR-pQCT with respect to trabecular measurements of thickness, density, stiffness, and failure load. However, there were no incident or prevalent fractures reported during the study period, so the actual significance of the TBS prediction remains uncertain.

At this time, it is still unclear whether the TBS can be useful as a noninvasive tool in the management of bone disease in patients receiving renal transplant. TBS may correlate with other imaging methods but it has not been validated with underlying bone histology and activity so that treatment decisions remain empirical. We are still looking, after many years of new methodology, laboratory tests, and examinations, for that noninvasive way to diagnose renal bone disease on which to base our treatments. For now, the bone biopsy remains the gold standard.

Disclosures
None.

References


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