

Commentary

Evolving Role of Imaging in the Evaluation of Bone Structure

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A top priority in osteoporosis research is the identification of the structural parameters that contribute to variations in the strength of bone and the risk of fragility fractures. For the past two decades, DXA has been used to diagnose osteoporosis based on measurements of BMC and areal BMD. Whereas DXA has become the most commonly used technique worldwide to predict fracture risk and assess response to therapy, it is based on a 2D interpretation of the 3D skeleton and provides limited information on the structural properties of bone. Other imaging modalities such as CT and MR offer considerably greater characterization of bone architecture, but their cost and inaccessibility have precluded them from becoming widely adopted clinically. Recent advances, however, have led to the introduction of more manageable CT and MR techniques that provide 3D assessments of the appendicular skeleton. In this issue of the *Journal*, two studies by Wang et al.⁽¹⁾ and Walker et al.⁽²⁾ highlight how progress in analyzing variations in bone structure among humans comes from the use of these techniques in comparative studies to identify the skeletal differences between persons who are susceptible to fractures and those who are not.

Using high-resolution peripheral QCT (HR-pQCT), Wang et al. and Walker et al. examined the differences in macro- and microarchitecture of the peripheral skeleton between young white and Chinese women. Available data indicate that Asian women have a lower incidence of hip and forearm fractures despite consistently being reported to have lower areal BMD values as measured by DXA compared with white women and other racial groups.^(1,2) With the detailed analysis of cancellous and cortical bone in the distal radius and tibia that HR-pQCT provides, these two studies arrived at strikingly similar explanations for this paradox. Both Wang et al. and Walker et al. found Asian women to have significantly greater cortical thickness and density, as well as greater trabecular thickness at both sites. Trabecular number was also greater in the distal tibia but not in the radius in both studies. The authors reasonably suggest that these anatomical differences are

likely contributors to the lower risk for fractures in the appendicular skeleton of Chinese women. In contrast, the study by Walker et al. found the areal BMD by DXA of the axial and appendicular skeleton did not differ between races.

It is remarkable that such comparable results were obtained in both studies with relatively small cohorts of white and Chinese women from two different continents with different environmental conditions. This consistency underscores the power of 3D techniques and the generalizability of the results. It is also likely a reflection of the young age of the participants in both studies, because the magnitude of the genetic effect on bone mass and bone architecture is higher in young premenopausal women.⁽³⁾ As indicated by these two studies, advances in our understanding of the great variations in bone structure in the appendicular skeleton among humans will likely come from improved 3D imaging technology, much like prior studies using CT had done for our knowledge of the axial skeleton.

Conventional CT advanced our understanding of the relationships between vertebral size and fracture risk beyond the knowledge that could be provided by using DXA. The use of CT indicated that men have larger vertebrae than women, even after adjusting for differences in body size, and that the lower vertebral mass of women compared with men resulted from early sex differences in the size of bone rather than differences in bone densities.⁽⁴⁾ 3D techniques also helped establish vertebral size as an important determinant of vertebral fracture risk.⁽⁵⁾ Additionally, the ability of 3D techniques to assess BMD without soft tissue errors was key to establishing that peak BMD in the axial skeleton, a major contributor to osteoporosis in the elderly, is achieved soon after sexual maturity and not in the third, fourth, or fifth decades as indicated by DXA.⁽⁶⁾

CT and pQCT have the advantages of allowing for the segmentation of trabecular and cortical bone, as well as for measurements of bone geometry, cortical density, and the apparent density of trabecular bone. Further advances, as reported by Wang et al. and Walker et al., came from the introduction of HR-pQCT equipment with the ability to

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acquire multiple slices in the peripheral skeleton with considerably greater resolution than was previously available. Although the current resolution of 82 μm does not permit direct measurement of microstructural parameters given a trabecular thickness around 40 μm , methods have been developed to estimate these parameters from the 3D grayscale images.⁽⁷⁾ Even though these parameters are a gross estimation of the true microarchitecture,⁽⁸⁾ they may be extremely useful and promising to our understanding of bone changes among humans, as shown by the two comparative studies reported in this issue of the *Journal*.

There are other technical limitations with HR-pQCT that have to be considered as well. In contrast to DXA, which is precise but not accurate, pQCT has greater accuracy but its precision is less well established. The reported reproducibility of the density measurements is good, with a CV of <1%. However, the reproducibility of the architectural parameters is much more variable, with CVs up to 7.4%.^(1,2) Moreover, the great variability in the anatomy of the metaphysis among individuals further complicates HR-pQCT measurements. Differences in long bone metaphyseal morphology, with gradients of trabecular BMD ranging from twice that of the vertebrae at sites close to the physal plate to zero in the diaphyseal medullary canal, make accurate positioning critical for the acquisition of comparable data. Indeed, in a previous study using CT in the proximal tibia, we observed that the cancellous density changed at a rate between 9% and 38% for a 1-mm offset in slice positioning.⁽⁹⁾ Significant variability is therefore introduced by the current lack of standardization in defining the reference line and starting location of pQCT scans. Such standardization would be a first step toward obtaining consistent measurements between HR-pQCT studies.

In addition, because of the great variability in metaphyseal morphology among individuals and within the same individual during growth, even with exact short-term positioning of the scan, different anatomical sites may be examined. This limitation is acknowledged by Wang et al., who noted that the Chinese women had an ~ 1 cm shorter radius and 2 cm shorter tibia than the white women. Hence, even though both groups were measured for 9 mm starting at a fixed location relative to the physal plate, this location may not be equivalent because one group has a shorter metaphysis than the other. The 9-mm multislice scan length used by Walker et al. and Wang et al. is a great improvement over single-slice imaging, but it still covers only a portion of the metaphysis. It is likely that the entire metaphysis needs to be studied to gain a full understanding of how metaphyseal morphology influences the bone properties measured by pQCT.

The ultimate goal of bone imaging measurements is to provide the strongest possible predictors of fracture risk. Unfortunately, one half of the incident fractures occur in women with DXA BMD values above the World Health Organization–defined diagnostic for osteoporosis.⁽⁷⁾ Whereas DXA, a projection technique, is unable to determine a threshold for fracture risk, this may be possible in the appendicular skeleton through the use of HR-pQCT.

Indeed, recent data suggested that changes in cortical and trabecular structure measured by HR-pQCT are associated with fragility fractures.^(1,2,10) In the axial skeleton, CT established that vertebral fragility fractures are unlikely to occur when trabecular vertebral BMD is greater than ~ 100 mg/cm³, which corresponds to 2.5 SDs below peak BMD.⁽⁴⁾ Defining whether a similar threshold or combination of bone and muscle parameters applies to fragility fractures in the appendicular skeleton would be extremely useful in the identification of those individuals toward whom preventative strategies should be geared.⁽¹¹⁾ Granted, determining such a threshold in the appendicular skeleton may be more difficult because factors beyond bone strength, such as load magnitude and load distribution, are key determinants of Colles and hip fractures in the elderly.

The development of HR-pQCT methods, as evidenced by the studies of Wang et al. and Walker, allows for the independent assessment of cancellous and cortical bone, 3D assessments of bone morphology, and estimates of bone microstructural parameters. Such a tool has a great potential to facilitate the study of age-, disease-, and treatment-related changes in bone structure at peripheral skeletal sites. As an evolving technology, standardization is still needed, as well as a greater understanding of how to deal with the large variability of the metaphyseal regions of the long bones. Studies are necessary to establish acquisition and analysis methods that could provide more representative measures of the entire metaphyseal bone structure. Most importantly, prospective studies are also badly needed to determine the ability of HR-pQCT to predict fracture risk.

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