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NEWS

Noninvasive evaluation of bone microarchitecture and strength: better than DXA?

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New imaging approaches, the focus of a recent *IBMS BoneKEy* webinar, provide invaluable research tools, but lag behind in predicting who will fracture

Historically, bone mineral density (BMD), as assessed by dual X-ray absorptiometry (DXA), has been the physician's primary diagnostic tool to evaluate patients at risk for osteoporosis. The bone field has long recognized, however, that BMD is of circumscribed value when trying to understand the skeleton. Strikingly, most postmenopausal women who experience osteoporotic fractures do not even have osteoporosis as defined by the BMD T score. Furthermore, in clinical trials of oral bisphosphonates, changes in BMD do not actually explain most of the fracture risk reduction benefit seen with those antiresorptive agents. In fact, the recognition that BMD is of limited explanatory power was one of the driving factors behind FRAX, the World Health Organization fracture risk assessment tool that estimates the 10-year probability of fracture. In addition to BMD, FRAX integrates a host of clinical risk factors into its algorithm, such as age, use of glucocorticoids, consumption of alcohol and the presence of rheumatoid arthritis. Finally, to think only of BMD is to ignore other risk factors such as falls—most fractures result from spills, after all—as well as genetic variations such as single-nucleotide polymorphisms that have been linked to fracture.

Consequently, fracture experts have sought to move beyond the narrow focus on BMD to a much broader look at skeletal characteristics, such as bone microarchitecture and strength, which are thought to underlie fracture risk. Noninvasive imaging techniques, including quantitative computed tomography (QCT), high-resolution peripheral QCT (HRpQCT) and magnetic resonance imaging (MRI) allow for the assessment of such features, and these methods were the focus of 'Noninvasive Evaluation of Bone Microarchitecture and Strength' (http://www.nature.com/bonekey/webinars/index.html?key=webinar12), a recent *IBMS BoneKEy* webinar presented by Sundeep Khosla (Mayo Clinic, USA). Professor Khosla concentrated on the potential clinical utility of these techniques to enhance understanding of the skeletal changes that occur during growth and aging, differences between male and female skeletons, the assessment of the response to drug therapies and the identification of patients at risk of fracture. At least in those first three areas, the newfangled imaging systems appear poised to serve as invaluable research tools that ultimately may offer an understanding of fracture mechanisms far beyond what DXA can provide. However, the message from Professor Khosla, and from a distinguished panel discussion moderated by Serge Ferrari, *BoneKEy* editor-in-chief, was that they are unlikely to supplant DXA any time soon in the realm of fracture risk prediction.

What Noninvasive Imaging of Bone Microarchitecture and Strength Can Do…

Professor Khosla first discussed the role of HRpQCT in illuminating the skeletal alterations that occur during growth. He focused on a 2009 study he conducted with colleagues of 140 healthy girls and boys from 6 to 21 years of age, whom the study divided into five groups based on skeletal maturity, as defined by wrist X-rays.[1] HRpQCT allows for an examination of both trabecular and cortical bone. With regard to the former, the study revealed that by late puberty, boys exhibited significant increases in parameters such as the bone volume to trabecular volume ratio, trabecular number and trabecular thickness and decreases in trabecular spacing in the distal radius, compared with girls who showed fewer changes in those measures. Concerning the latter, both girls and boys displayed a similar pattern of a temporary decrease in cortical thickness and volumetric BMD at mid puberty, followed by a large increase at late puberty. Increases in periosteal circumference were also seen in boys but not girls, but as endosteal circumference also went up in boys, both genders had similar net cortical thickness.

Cataloging skeletal changes in this way is valuable, but the study also addressed a loftier question: can techniques such as HRpQCT provide a mechanistic explanation of well-known facts, such as why the incidence of fractures peaks when it does both in girls (early-mid puberty) and in boys (mid-late puberty)? Thus the investigation also analyzed the HRpQCT scans using finite element analysis (FEA), a computational tool that can assess the biomechanical behavior of bone, in order to compare bone strength at the different stages of growth. It turned out that total bone strength increased in both girls and boys during their peak fracture periods. Other indicators that

might account for peak fracture incidence, such as falls force and the load-to-strength ratio (factor of risk), also could not do so. However, the research did document decreases in the load carried by cortical bone, which reflects the relative strength of the cortical bone compartment, in both girls and boys at the time of peak fracture incidence. 'This was the first variable we encountered that was actually behaving in some way that might explain or correspond to the increase in adolescent forearm fractures,' said Professor Khosla, who also noted that other cortical indicators, including changes in the cortical to trabecular bone volume ratio, and the cortical porosity index, also correlated with the peak in fractures. He also emphasized that all of these changes in cortical bone mirror the incidence of forearm fractures seen in adolescent populations examined in other studies.

Approaches such as HRpQCT can also provide insight into the skeletal transformations that occur during aging. Age is a highly important determinant of skeletal health, and one that is independent of areal BMD as assessed by DXA, yet heretofore vague notions of bone 'quality' have yet to clearly illustrate why. So Professor Khosla described another study he conducted with colleagues.[2] This study matched, by DXA areal BMD, 44 women with a mean age of 41 years to 44 women with a mean age of 63 years, and used HRpQCT to study the ultradistal radius. A total of 57 younger (mean age of 41 years) men were also matched to 57 older (mean age of 68 years) men.

To their surprise, the group found that, although the younger and the older women had the same areal BMD, there was no difference in the trabecular microarchitecture, with similar values between younger and older women seen for the bone volume to total volume ratio, trabecular number and trabecular thickness; similar results were seen in men. 'We expected microarchitectural deterioration for the same DXA value, but DXA seemed to have captured this in whatever way it had,' Professor Khosla said. Meanwhile, other than a small decrease in cortical volumetric BMD in the older women, the researchers found no other differences between younger and older women, nor did they see differences between younger and older men, in cortical parameters including cortical thickness, periosteal circumference and endocortical circumference. When they looked at a number of cortical porosity parameters, however, a different story emerged: both older women, and older men, exhibited increases in cortical porosity, cortical pore volume, cortical pore diameter and cortical pore diameter distribution, compared with their younger counterparts, and similar findings came from an examination of the tibia. 'At least for appendicular sites represented by the radius and tibia, the major effect of age independent of areal BMD is on cortical porosity,' Professor Khosla said. 'More studies are needed to define the extent to which this deterioration in cortical microstructure contributes to the areal BMD-independent effect of age on bone fragility and fracture risk at the radius, as well as other sites of osteoporotic fractures, such as the spine and hip.'

The imaging techniques that Professor Khosla described have also been used to understand gender differences in bone. Epidemiological evidence suggests that absolute areal BMD, as assessed by DXA, predicts a similar fracture risk in both genders. So Professor Khosla described a recent *Osteoporosis International* study from his group that considered the relationship between femoral neck areal BMD and volumetric BMD, bone size and femoral strength in 114 men and 114 women matched for femoral neck areal BMD, hoping to understand why these individuals had the same score on that measure.[3] This QCT study revealed that while the men had bigger bones, as indicated by a higher femoral neck cross-sectional area, compared with the women, they also exhibited lower volumetric bone density. These two effects offset one another, and so the result is a similar areal BMD.

With regard to bone strength, FEA revealed that while the men had higher fall loads (because they are bigger), there was little difference between genders in bone strength or the load-to-strength ratio. 'This provides a biomechanical basis for using areal BMD independent of gender in trying to assess fracture risk,' Professor Khosla explained. 'While more work is needed looking at other sites, like the spine, in general these biomechanical findings fit with the growing epidemiological data suggesting that DXA works regardless of gender, in part because it's so influenced by bone size', he said.

Bone microarchitecture and strength imaging approaches have also been used to reveal how bone responds to drug treatment. Here, Professor Khosla pointed to a 2007 study by panelist Tony Keaveny and colleagues (University of California, Berkeley, USA).[4] The researchers were able to use FEA of QCT scans to show the effects of alendronate and teriparatide on vertebral strength in patients from the Forteo Alendronate Comparator Trial. However, using such techniques to assess the treatment response will require careful thought as great variation in that response is seen within any particular bone. The 2005 QUEST MRI study, which examined the effect of salmon calcitonin on trabecular microarchitecture in postmenopausal osteoporotic women, is a perfect example.[5] 'What was really striking was that there were large differences in the effects of treatment versus placebo, even within the small region of the measurement at the radius,' Professor Ferrari (Geneva University Hospital, Switzerland) said. 'How do we know, then, what is best representative of what happens elsewhere in the skeleton?' he asked. Panelist Sharmila Majumdar (University of California, San Francisco, USA), a bone imaging expert and author on the QUEST study, noted that the radius is a particularly tricky site in which to gauge drug responses as the microarchitecture differs the further away one moves from the joint line. 'The radius has very marked linear variation in terms of trabecular and cortical bone structure. Similar differences probably exist even in the hip,' she said. When investigating drug effects, it is also important not to be seduced by the sheen of the technology. For instance, HRpQCT has much higher resolution than QCT, but assesses only peripheral skeletal sites that may be far away from actual fractures. 'I think you have to include the spine and the hip' when assessing pharmacological responses, said panelist Claus-C Glüer (Universitätsklinikum Schleswig-Holstein, Germany). 'In the setting of looking at the effects of new agents and approving them, if we look for surrogate markers in the periphery, there are clear, fundamental limitations,' he said.

...and What It Cannot

Understanding how the skeleton responds to antiresorptive and anabolic drugs is important, but identifying those at risk for fracture, to prevent the need for a drug in the first place, is what bone experts are really after. Unfortunately, results thus far suggest that the noninvasive approaches that assess bone

microarchitecture and strength are not any better than the bone field's old standby.

Indeed, Professor Khosla described another of his studies comparing a control group of 90 postmenopausal women with no vertebral deformities to 142 women with 1 or more mild vertebral deformities and to 51 women with any moderate/severe deformities.[6] On the one hand, the study found that differences between cases and controls, particularly for those cases with moderate/severe vertebral deformities, were greater when using HRpQCT and QCT/FEA than when using DXA. For example, in those with moderate/severe deformities, femoral neck and spine areal BMD were lower by 10% and 7%, respectively, compared with controls. But the moderate/severe deformity cases displayed, for instance, 25% lower bone volume to total volume, and 27% higher trabecular spacing, compared with controls, when HRpQCT was used. As another example, they also exhibited 21% lower lumbar spine trabecular volumetric BMD, and 50% higher load/strength.

Yet, when the researchers looked at area under the curve data—which in the study indicated the sensitivity and specificity of the imaging techniques to assess the risk of vertebral deformities—HRpQCT and QCT/FEA performed only modestly better than DXA. Professor Khosla noted that this may change as the imaging techniques are honed, and also perhaps if the techniques are applied to subjects at earlier stages of bone loss. But, as it stands now, the newer imaging approaches are disappointing in their ability to discriminate those who will fracture from those who will not.

'These techniques can tell us a lot about the mechanisms of bone growth and deterioration, and also about how drugs work, but I don't know, practically speaking, whether they will ever supplant something like DXA,' said panelist Elizabeth Shane (Columbia University Medical Center, USA). As an expert clinician, Professor Shane agreed that the imaging approaches could potentially be useful for patients with osteopenia, a group for whom there are little data to guide clinical decision making—to treat or not to treat?—but, right now, clinical translation remains elusive.

Exactly how much better do the techniques, and the strength and microarchitecture measures they provide, need to be? That is precisely the question that Professor Keaveny said the bone field must consider, if the requirements of regulatory authorities are ever to be satisfied. 'If these studies aren't done with the FDA (US Food and Drug Administration) in mind, I think ultimately we might hit a wall in terms of the clinical impact of these measures,' he said.

The imaging studies that Professor Khosla described are cross-sectional studies, but researchers also want to follow subjects over time. One weakness to current approaches, particularly CT, for conducting longitudinal investigations is that results will be hard to interpret unless the same imaging machine is used throughout the course of a study, which is something that is difficult to achieve. 'There are some unique challenges because CT is a general purpose machine in the clinic and DXA is only used for bone imaging, so one has less control over whether or not the same machine will be around in 3–5 years when you want to revisit the patient,' Professor Keaveny said. However, ensuring that the systems do not change mid-study is not even enough. 'Cross calibration between [skeletal] sites is very important, because even if the device is the same, there might be differences not only in density but in the structure and geometry of the bone microarchitecture,' said panelist Stephanie Boutroy (INSERM and Université de Lyon, France). Professor Boutroy noted she is working on a study with several of the panelists that hopes to address this issue.

Such improvements may go a long way toward making the machines better able to predict fractures (and of course this will make them better research tools to study fracture mechanisms as well). Interestingly, though, Professor Khosla concluded with the thought that to focus mainly on improving fracture risk prediction is, perhaps, to succumb to a bit of a red herring. Fracture, after all, depends on a host of factors, some of which have very little to do with bone *per se*, such as the risk of falling. Thus, any study that evaluates a bone drug on the basis of how often patients fracture while taking it carries this inherent limitation. Bone strength, however, is a 'purer' outcome upon which to measure the effects of medications as, unlike fracture, it is strictly bone-related. If the newer imaging modalities can be honed to generate an accurate and reproducible measure of bone strength, then the bone field will have made an important advance. The techniques may still not replace DXA for fracture risk prediction, but they would have a much more profound impact by actually changing the design of clinical trials. These new strength-based studies would now reveal more about the efficacy of new osteoporosis medications than trials based on fracture outcomes ever could.

Conflict of Interest

The author declares no conflict of interest.

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