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Bone Microarchitecture Predicts Fractures in Older Women

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Disclosures: none

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Abstract

HR-pQCT gives more detailed information than DXA, and has given insights into the role of bone microstructure in fragility. The new study by Burt shows that radius and tibia HR-pQCT measures are associated with incident fracture in postmenopausal women. However, it is not yet clear whether HR-pQCT improves fracture risk prediction enough to justify use in clinical practice.

The standard diagnostic test for osteoporosis is dual-energy x-ray absorptiometry (DXA) measurement of bone mineral density (BMD) of the lumbar spine and total hip (Eastell 2016 (1)). This test has been available now in clinical practice for more than 30 years. It involves only a very small radiation dose and so is widely used in research as well as clinical practice. Osteoporosis is defined as a DXA BMD T-score of -2.5 or lower. The T-score can be combined with clinical risk factors to make obtain a 10-year risk of fracture and to inform treatment decisions. However, its predictive power is limited; many patients who fracture have a T-score above -2.5. Also, it doesn't provide separate information about cortical and trabecular bone, or bone structure.

Quantitative computed tomography (QCT) images bone in three dimensions and can provide separate information about cortical and trabecular bone. QCT measurement of the spine and proximal femur have proven to be at least as good, if not better at fracture prediction compared to DXA. However, at these central sites the radiation dose is high and the images are relatively low resolution. QCT can be applied to the peripheral skeleton where the effective radiation dose is much lower and higher resolution images can be obtained; high-resolution quantitative computed tomography (HR-pQCT). The voxel size is 82 microns (close to the diameter of trabeculae and larger cortical pores), so in addition to BMD, the images can be used to quantify geometric and microstructural properties including trabecular bone volume, number, thickness, spacing and heterogeneity, and cortical thickness and porosity. The images can also be used to generate virtual models for micro Finite Element Analysis (FEA) to estimate bone stiffness and failure load.

The early clinical studies with HR-pQCT described the expected age-related decreases in bone mineral density, but offered some new insights into microstructural ageing. For example, in women trabecular number decreases, but in men trabecular thickness decreases and trabecular number is relatively preserved (Khosla J Bone Miner Res 2006;21:124–131). It was also shown that microarchitectural properties differed between women with and without fragility fractures, partially independently of DXA BMD (Sornay-Rendu JBMR 2007; 22: 425–433), and that bone density,

microarchitecture and microFEA were all associated with prevalent fractures (Vilayphiou Bone 2010; 46: 1030–1037).

A recent paper from a Canadian epidemiology study, the CaMos Study (Burt 2018 (2)) evaluated the association between HR-pQCT measures of the radius and tibia and 5-year incident fracture in 149 women over age 60 years. Women who fractured had lower baseline BMD, with different geometric and microstructural properties at the radius (trabecular number and spacing), and tibia (trabecular area, cortical area, cortical thickness and failure load) compared to women who did not fracture. For a one standard deviation decrease in total BMD or trabecular BMD at the radius and tibia, the risk of non-vertebral fracture increased 1.7 to 2.1-fold. This was similar to the effect size of baseline DXA femoral neck BMD. Surprisingly, there was no association between fracture risk and baseline DXA BMD of the lumbar spine and total hip, or bone loss assessed by DXA or HR-pQCT.

The study is interesting as it adds to the evidence base on the value of HRpQCT for fracture prediction. It is the third paper to evaluate this issue prospectively (Table). The common results among the studies are strong associations of total BMD and trabecular BMD at the radius with vertebral and non-vertebral fractures. The only microstructural variable consistently associated with fracture is trabecular number. The fracture prediction in some of the studies (Biver 2017 (3), Sornay-Rendu 2017 (4)) was independent of DXA BMD of the hip, 10-year fracture risk, falls, use of drugs for osteoporosis, current smoking, prior fracture, and age. The results were not independent of ultradistal radius BMD in one study (Biver 2017 (3)).

The most important finding in these three studies is that HRpQCT measurements strongly predict non-vertebral fractures. The association with major fractures (distal radius, proximal humerus, proximal femur, vertebrae) was even stronger than for non-vertebral fractures. Equally interesting was the finding that trabecular bone rather than cortical bone was most strongly associated with fracture risk (although it should be recognised that the separation of cortical from trabecular bone with HR-pQCT is imperfect). Osteoporotic fractures tend to occur at the metaphyses of bones (distal radius, proximal humerus and femur) where the proportion of trabecular bone is high. We need to be cautious in the interpretation of

microarchitectural features such as trabecular thickness, because these studies used the first-generation HR-pQCT, and the voxel size of 82 micron is insufficient to directly measure trabecular thickness. We should also be cautious about the interpretation of strength using finite elements models of the radius and tibia as most fractures occurred at other sites.

Is it likely that HR-pQCT will become a commonly used test in clinical practice? The challenges here relate to the limited use of the technique. We do not have enough data to test whether the measurements can usefully be incorporated into 10-year fracture predictions, or set a treatment threshold. The technique wasn't included in the clinical trials for most drugs licensed for osteoporosis, so we don't know what level of HR-pQCT is associated with successful fracture risk reduction with any drug. Until these studies are done, we won't be able to use the technique in clinical practice.

One suprising finding from the CaMos study (Burt 2018 (2)) was that rate of bone loss was not associated with fracture risk. There have been at least three cohort studies (Berger 2009 (5), Nguyen 2005 (6), Sornay-Rendu 2005 (7)) that have shown that rates of bone loss from the proximal femur or distal radius predict non-vertebral fractures independent of baseline BMD (or other key risk factors such as prior fracture). Indeed, one of these reports is from the CaMos Study (the same as for Burt et al 2018) but is a much larger group and includes men and women, many more fractures and most importantly, separated out people who were taking osteoporosis medications. The study of Burt 2018 (2) included only women, and half of them were taking osteoporosis medications, a factor known to have a big influence on rate of bone loss. Thus, we shouldn't put too much weight on the finding of no association of fracture with change in HR-pQCT measurements; that remains an open question.

Table 1. Cohort studies examining the relationship between HR-pQCT measurements and non-traumatic non-vertebral fractures.

Study	Burt et al (2018)	Sornay-Rendu (2017)	Biver (2017)
Country	Canada	France	Switzerland
Number of women	149	589	740
Number with non-traumatic fracture	22	135	68
Duration, years	5	9	5
Statistics	Odds ratio/SD	Hazard ratio/quartile, age adjusted	Hazard ratio/SD
Radius, Tt.BMD	2.1*	1.33**	1.68***
Radius, CtBMD	1.3	1.14	na
Radius, TbBMD	2.0*	1.49***	1.67***
Radius, Tb.N	1.7*	1.44***	na
Radius, Ct.Th	1.6	1.17	na
Tibia, Tt.BMD	2.1*	1.38***	na
Tibia, CtBMD	1.2	1.19	na
Tibia, TbBMD	1.7*	1.33***	na
Tibia, Tb.N	1.3	1.25**	na
Tibia, Ct.Th	2.2*	0.96	na

*, significant (p-value not given)

**, $p < 0.01$

***, $p < 0.001$

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