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Noninvasive imaging of bone microarchitecture

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Abstract

The noninvasive quantification of peripheral compartment-specific bone microarchitecture is feasible with high-resolution peripheral quantitative computed tomography (HR-pQCT) and high-resolution magnetic resonance imaging (HR-MRI). In addition to classic morphometric indices, both techniques provide a suitable basis for virtual biomechanical testing using finite element (FE) analyses. Methodical limitations, morphometric parameter definition, and motion artifacts have to be considered to achieve optimal data interpretation from imaging studies. With increasing availability of *in vivo* high-resolution bone imaging techniques, special emphasis should be put on quality control including multicenter, cross-site validations. Importantly, conclusions from interventional studies investigating the effects of antiosteoporotic drugs on bone microarchitecture should be drawn with care, ideally involving imaging scientists, translational researchers, and clinicians.

Keywords

high-resolution peripheral quantitative computed tomography (HR-pQCT); high-resolution magnetic resonance imaging (HR-MRI); bone microarchitecture; bone quality

Introduction

The term *bone strength* describes the ability of the skeleton to resist fractures. For the last several decades, bone mineral density (BMD) has been used as the main surrogate for bone strength. The definitions of osteoporosis and clinical decision making have been strongly influenced by this density-based approach, and dual X-ray absorptiometry (DXA) is clearly the current clinical gold standard technique for bone density assessment. DXA is widely available, provides good precision and reproducibility, but does not offer insight into compartment-specific bone densities. Being a projectional technique, DXA underestimates the density of smaller bones that play a role when assessing BMD in children and with regards to gender-specific studies.¹ In addition, bone strength is independently modulated by

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Conflicts of interest

The authors declare no conflict of interest.

a wide spectrum of tissue-based measures, including bone microarchitecture, bone turnover, bone matrix status (e.g., collagen properties and mineralization), as well as accumulated microdamage.² All these factors have been often comprehensively termed *bone quality*. In the past, most of these features were determined using histology and bone biopsies, and while that is still the case for some of the parameters, during the past 20 years, novel high-resolution imaging techniques that are capable of noninvasive assessment of bone microarchitecture have emerged. These techniques include high-resolution peripheral quantitative computed tomography (HR-pQCT) and high-resolution magnetic resonance imaging of bone (HR-MRI). In the following sections a few of the methods for the non-invasive assessment of bone microarchitecture will be reviewed.

High-resolution peripheral quantitative computed tomography

High-resolution peripheral quantitative computed tomography (HR-pQCT) imaging requires a dedicated extremity scanner. Using HR-pQCT, measures of three-dimensional (3D) bone geometry, overall and compartment-specific bone density and bone microarchitecture can be acquired within a scan time of 3 minutes. To obtain a 3D stack of images with an isotropic voxel size of 82 μm (110 slices, 9 mm scan length), the patient radiation exposure is $\sim 4 \mu\text{Sv}$, which is about 500–1000 fold smaller compared to a clinical abdominal CT scan.³ The standard imaging region is located proximal to the radiocarpal joint at the ultradistal radius and proximal to the ankle joint at the ultradistal tibia. While limits of the scanner geometry constrain the range that is possible to scan, acquisition protocols can be modified to specifically capture more proximal zones dominated by cortical bone or more distal zones to capture joints/metacarpals/metatarsals. Nevertheless, imaging mid-diaphyseal regions of the adult distal radius and tibia or more proximal long bones sites are not possible at present.

HR-pQCT image analysis

For the evaluation of quantitative measures, the periosteal contours are drawn in a semiautomatic manner. Prior to the application to a fixed segmentation threshold, a smoothing and edge enhancement procedure is performed on grayscale images.⁴ HR-pQCT does not only provide a global, three-dimensional, volumetric BMD but also separately yields compartment-specific bone densities for the trabecular core and the cortical shell. Global, volumetric BMD is convertible into areal BMD values.⁵ BV/TV is derived from trabecular volumetric BMD assuming a fixed mineralization of 1200 mg HA/cm^3 for compact bone. Standard morphometric parameters are analogous to those used in classical static histomorphometry.⁶ Trabecular number (Tb.N) and network heterogeneity are directly measured by 3D distance transformations.⁷ Trabecular thickness (Tb.Th in micrometers) and trabecular separation (Tb.Sp in micrometers) are derived from Tb.N and/or trabecular density using stereological standard relations assuming a plate-model geometry.⁸ Measurement reproducibility has been shown to be higher for density parameters ($<1\%$ root mean square coefficient of variance–RMSCV) than for microarchitectural metrics ($<4.5\%$ RMSCV).⁹

Validation experiments comparing *ex vivo* HR-pQCT with DXA and micro-computed tomography (μ CT) at resolutions ranging from 10 to 25 μ m (the gold standard) yielded strong correlations between the methods, but also stressed resolution dependence.^{9–12}

HR-pQCT also provides measures of cortical bone properties.¹³ The noninvasive assessment of cortical bone density and quality is highly clinically relevant as cortical integrity has been shown to be a crucial determinant of overall bone strength.^{14,15} Especially cortical porosity is increasingly recognized as a pathomorphologic surrogate of poor bone quality.^{14,16} However, it remains to be stressed that due to the *in vivo* voxel size of HR-pQCT data, noninvasive imaging captures only relatively large pores ($>82 \mu$ m).¹⁴

In addition to cortical bone analyses, region-specific evaluation can enhance the sensitivity of HR-pQCT with regard to age- and gender-related changes.¹⁷ Regional analysis of cortical and trabecular bone subdivided in standardized quadrants was also shown to improve the detectability of longitudinal changes in bone microarchitecture caused by alendronate treatment when compared with global evaluations.¹⁸

Various other postprocessing techniques including finite element (FE) modeling are applicable to HR-pQCT data. FE modeling is a biomechanical computation method that yields loading scenario-specific, image-based estimates of bone strength (e.g., ultimate force required to fracture upon a certain type of fall). Prior to the introduction of HR-pQCT, FE analyses have been performed with central QCT (hip and lumbar spine) and μ CT data.^{19–21} QCT-derived FE models have been used to monitor antiosteoporotic drug effects in clinical trials.^{22–26} HR-pQCT-based FE analyses can be carried out on the entire scan volume as well as a defined sub-volume.^{27–29} Both have been shown to discriminate men and postmenopausal women with and without fragility fractures independent of BMD.^{30,31}

Another specific image evaluation algorithm, termed *individual trabecula segmentation* (ITS), provides insight into trabecular topological characteristics by separately quantifying plate- and rodlike structures.³² This technique also describes the axial bone volume fraction, that is, the number of trabecular structures that are aligned with the longitudinal bone/scan axis. ITS-based metrics were shown to display high correlations with FE-derived biomechanical indices.³³

Motion artifacts play a significant role in impairing image quality and parameter calculations. They are more frequent and more severe in radius than tibia scans. Motion affects morphometric indices to a larger extent than density measures. Currently, motion artifacts are subjectively evaluated on the basis of a semiquantitative, visual grading scale (Fig. 1).³⁴ While there has been some effort to develop fully quantitative estimates of patient motion, more optimization and validation is warranted to translate these tools to routine use in clinical research studies.^{35,36} Of practical relevance, an optimized patient set-up with detailed explanations highlighting the importance of avoiding motion during the scan, proper arm and leg fixation and a quiet room atmosphere, will help to reduce subject motion.

Besides resolution and motion, beam-hardening and X-ray scatter effects can also impair HR-pQCT-derived measures. Accordingly, variations in trabecular bone density and cortical thickness can introduce a relevant bias in cross-sectional studies.³⁷

Comparison with iliac crest biopsies, DXA, and QCT

For decades, histology and histomorphometry of iliac crest biopsies have represented the gold-standard techniques for the assessment of bone microarchitecture. Compared with bone biopsies, noninvasiveness and the possibility of multiple local follow-ups are major advantages of HR-pQCT. However, HR-pQCT can only quantify mineralized bone properties but not osteoid or bone cell characteristics. Conclusions regarding global or focal mineralization defects such as osteomalacia or secondary causes of osteoporosis including malignant bone marrow infiltration (e.g., by mast cells or lymphoma cells) cannot be drawn without invasive sampling. Thus clinical biopsy indications remain unchanged for certain applications or for investigating the aspects of bone health not captured by imaging. Comparing iliac crest bone biopsies with *in vivo* HR-pQCT of the radius, Cohen *et al.* found significant but modest associations between measures of microarchitecture and stiffness obtained from both methods.³⁸

Neither iliac crest biopsies nor HR-pQCT imaging provide direct information on bone quality of the central skeleton. Since the ability to draw reliable conclusions from peripheral bone microarchitecture to central bone quality is of major clinical interest, several studies have investigated these relations. For the radius, Sornay-Rendu reported good agreement between local aBMD by DXA and densities and microstructure obtained by HR-pQCT. Correlations were also significant but slightly weaker for HR-pQCT of the distal tibia and DXA of the hip.³⁹ Vico *et al.* also found significant associations of HR-pQCT of the radius and tibia with spine and hip BMD by DXA. Stressing the fact that the spine mainly represents a trabecular bone site, they reported correlations with cortical parameters to be weak at the radius and even absent at the tibia.⁴⁰ More recently, Liu *et al.* demonstrated that HR-pQCT-based measurements of bone density, bone microstructure and FE analyses at both sites are significantly related to QCT/FE-derived biomechanical properties of the lumbar spine and hip.⁴¹

Cross-sectional studies

Highlighting that noninvasive assessment of bone microarchitecture could add to the refinement of clinical fracture risk prediction, HR-pQCT has been shown to differentiate patients with and without prevalent fragility fractures irrespective of their BMD. Boutroy *et al.* found significantly lower trabecular density (−12.3%), lower trabecular number (−8.5%) and higher standard deviations in trabecular separation (+25.6%) in osteopenic women with fractures when compared to nonfracture subjects with identical BMD. Fracture history did, but DXA alone did not adequately depict impaired bone health.⁴² Poor peripheral bone microarchitecture was also a characteristic feature in male and female patients with spine, hip and peripheral fractures.^{40,43,44} One study showed that with increasing grade of spine fracture severity, HR-pQCT parameters also deteriorated stepwise.³⁹

Cross-sectional HR-pQCT studies have also provided insight into age- and gender-specific aspects of bone quality.^{16,45,46} Compartment-specific analyses of bone density and microarchitecture seem of particular interest in clarifying osteologic paradoxes with discrepancies between fracture prevalence and mere densitometric risk prediction (e.g.,

lower fracture rates in Asians or elevated fracture risk in diabetic bone disease): Asian men and women have smaller bones; thus areal BMD as measured by DXA tends to underestimate their real bone density. Nevertheless, Asians sustain fewer fractures. Using HR-pQCT, Wang *et al.* found that in spite of relatively low total bone area, premenopausal Asian women displayed significantly thicker cortices and a richer trabecular microarchitecture than Caucasians.⁴⁷ Accordingly, FE analyses yielded higher estimates of bone stiffness/strength.⁴⁸ Menopause diminishes some of these microstructural advantages but significant racial differences remain detectable.⁴⁹ However, differences in bone length are currently an unaccounted bias in HR-pQCT studies that investigate gender- or race-specific bone characteristics. Since the standard region of interest is currently positioned with a fixed offset with regard to anatomical landmarks of the wrist and ankle joint irrespective of total bone length, radii, and tibiae of taller subjects (e.g., men versus women) are scanned relatively more distal than shorter bones. This could confound differences found for densities and morphometric parameters.

Patients with type 2 diabetes mellitus present with an opposite clinical situation. DXA-based risk assessment typically attributes normal to high BMD to diabetics, nevertheless they were shown to fracture more often than age- and gender-matched non-diabetics.⁵⁰ Burghardt *et al.* have suggested that this increased fracture risk in individuals with type 2 diabetes mellitus may be attributable to ultrastructural deficits in cortical bone.⁵¹ However, in accordance with older studies using DXA, they also reported normal to slightly elevated trabecular BMD in diabetic subjects. Somehow contrasting these data, another recent HR-pQCT study found almost similar bone microarchitecture in postmenopausal women with and without diabetes but Shu *et al.* did not include fracture patients and cortical bone has not been specifically analyzed for porosity.⁵²

Moreover, HR-pQCT has been used to address gender-specific research questions.⁴⁶ Although it had been repeatedly postulated that osteoporotic women displayed different alterations in bone microarchitecture than men, the actual evidence for a specific male microstructural disease pattern remained limited for a long time.^{53,54} Using an HR-pQCT prototype, Khosla *et al.* were the first to noninvasively address gender differences in bone microstructure.⁴⁵ In accordance with previous biopsy studies they found that BV/TV and Tb.Th. were significantly higher in young men than in young women. They further stated that the rate of age-related decline in trabecular bone volume seemed independent of gender, but also reaffirmed that in aging but otherwise healthy men trabecular thinning seemed to predominate over actual loss of trabeculae. Larger bones, greater periosteal apposition upon aging, conservation of trabecular structures and the lack of a real menopause equivalent contribute to lower fracture risk in men.⁵⁵ Bone properties of patients with renal osteodystrophy and primary hyperparathyroidism have also been characterized by HR-pQCT.^{56–59} The use of HR-pQCT is specifically promising in patients with chronic kidney disease (CKD; Fig. 2). These patients are particularly prone to fractures but DXA often remains false negative due to vascular calcifications that are erroneously integrated in projectional bone density. In addition, a compartment-specific approach appears favorable in CKD patients because secondary or tertiary hyperparathyroidism is predominantly leading to cortical bone loss.

Longitudinal and multicenter HR-pQCT studies

As with DXA before it, the utility of HR-pQCT to address important questions related to the epidemiology of osteoporosis, therapeutic antifracture efficacy, and the development of normative databases for clinical assessment of skeletal health requires scalability to standardized multicenter data pools. To fully realize the potential of HR-pQCT to investigate the role of bone quality in these contexts, appropriate tools are needed to characterize long-term and interscanner sources of variability, evaluate new acquisition and postprocessing techniques designed to improve comparability longitudinally and amongst scanners, and develop appropriate cross-calibration procedures to standardize the quantitative outcomes. Burghardt *et al.* proposed the use of structure- and composition-realistic anthropomorphic phantoms constructed from static cadaveric bone tissue to monitor longitudinal stability of HR-pQCT measures and characterize interscanner variability.⁶⁰ Based on phantom measurements at six imaging centers, they reported interscanner variability (RMSCV%) comparable in magnitude to short term *in vivo* reproducibility reported elsewhere.^{9,61} Densitometric measures had the highest interscanner reproducibility (approximately 1%) while geometric and microstructural measures were moderately less precise (4–6%). The sources of error were found to be variable and specific to each individual scanner, including differences in noise or resolution performance, the geometric and density calibration, or related to postprocessing factors.

Among other caveats in longitudinal studies, the assumption of a fixed matrix mineralization for HR-pQCT-based bone assessment has to be considered. Many drugs with proven antifracture efficacy significantly affect tissue mineralization.^{62,63} Irrespective of drug effects on bone volume, such changes in mineralization would be expected to cause an additional increase in volumetric BMD (vBMD). Due to derivation of BV/TV, Tb.Th and Tb.Sp from trabecular vBMD, this could confound interpretation of temporal trends.

Somewhat surprisingly, longitudinal HR-pQCT data interpretation has proven to be challenging.^{18,64–67} Burghardt *et al.* followed alendronate versus placebo-treated osteopenic postmenopausal women for two years and found treatment-related increases in tibial cortical area and thickness without changes in cortical density. At the same time, global trabecular bone loss was prevented. As opposed to the tibia as a weight-bearing bone, no positive treatment-related changes were detectable in the radius.¹⁸ Few studies have used data acquired at multiple imaging centers: Seeman *et al.* reported the results of a multicenter, 12-month placebo-controlled trial of denosumab and alendronate in postmenopausal women.⁶⁷ In this study, the failure to detect significant longitudinal changes in microstructural measures, despite pronounced densitometric treatment effects, may have been partially due to unaccounted intersite variability.

High-resolution magnetic resonance imaging

As opposed to computed tomography, magnetic resonance imaging (MRI) lacks ionizing radiation. Besides providing significantly better insight to soft tissue properties than CT, the mechanisms of image generation differ significantly between these two modalities. While mineralized tissues attenuate X-rays and thereby finally generate direct image contrast in

CT, MRI of bone microstructure is based on a negative image effect (i.e., the missing signal from bone versus the intense signal arising from the marrow). Differing electromagnetic properties—that is, different magnetic susceptibility—are the physical background of tissue-specific signal generation. The mix of trabecular bone and bone marrow causes magnetic field inhomogeneities that are detectable by MRI. These inhomogeneities depend on the number of bone-bone marrow interfaces, the size of individual trabeculae but also on the strength of the static magnetic field.^{68–70} As a consequence nuclear spins are dephased and the MR signal is decayed (which is referred to as T2*).⁷¹ T2* decay characteristics of spine but also hip bone marrow were shown to differentiate postmenopausal women with manifest osteoporosis from nonfracture controls.^{71,72} From these first clinically relevant steps, bone MRI has developed into an accurate and reproducible high-resolution method with reasonable acquisition time providing detailed insight to bone microstructure. Like HR-pQCT that is technically limited to the distal extremities, HR-MRI has mostly been performed in the peripheral skeleton. However, using SNR efficient sequences, high magnetic field strength (3 Tesla), and phased array coils, high-resolution magnetic resonance imaging has been shown to be feasible at the proximal femur.^{73,74} In general, higher field strengths contribute significantly to increased performance of HR-MRI. In an *ex vivo* validation study, Phan *et al.* demonstrated higher correlations for trabecular parameters at 3T than at 1.5T when compared with μ -CT as the gold standard.⁷⁴

HR-MRI of trabecular bone

Based on signal differences of trabecular bone (low signal, i.e., dark striations) and bone marrow (high intertrabecular signal, i.e., bright zones), structural indices, such as app. Tb.N, app. Tb.Th, and app. Tb.Sp, and distance transformation techniques, can be applied to three-dimensional MR images.⁷⁵ Further, the ratio of surface voxels (representing trabecular plates) to curve voxels (representing trabecular rods) and the erosion index can be computed. Indicating the predominance of more plate-like trabeculae, a higher surface to curve-ratio is found with more intact bone microstructure. Figure 3 shows an example of a high-resolution MR image obtained at 3 Tesla. Several *ex vivo* validation studies relating MR-derived measures of trabecular structure with bone strength have been conducted.^{76–79} The relationship between whole bone strength and bone structure measures has been demonstrated in radii and in the proximal femur.^{80,81}

A number of cross-sectional and longitudinal HR-MRI studies have been conducted. In line with lower spinal and trabecular radial BMD, MR-derived trabecular bone volume fraction, trabecular spacing and trabecular number showed significant differences in postmenopausal osteoporotic women with and without fractures when compared with premenopausal healthy controls.⁸² Other studies specifically enrolled women with hip fractures and found significantly disturbed trabecular microstructure including low trabecular number at the radius⁸³ but also the calcaneus.⁸⁴ Hypogonadal men with secondary osteoporosis were also studied by HR-MRI and displayed a significantly higher erosion index (+36%) and a significantly lower surface-to-curve ratio (–36%) than eugonadal controls.⁸⁵

Examples for the longitudinal use of HR-MRI include research studies published by Benito *et al.*⁸⁶ and Chestnut *et al.*⁸⁷ Ninety-one postmenopausal osteoporotic women (n = 46 for

nasal spray calcitonin, $n = 45$ for placebo) were followed for two years. Repeated MRI assessment of trabecular microarchitecture at individual regions of the distal radius revealed preservation (i.e., no significant loss) of structures in the treated group compared with significant deterioration in the placebo control group.⁸⁷ Benito *et al.* reported positive effects of testosterone replacement on bone microstructure in ten men with severe hypogonadism after 24 months of treatment.⁸⁶

MRI of cortical bone

MR can also be used to image cortical bone, specifically the proximal femur. The ability of MRI to align the image plane perpendicular to the femoral neck is a great advantage as it enables image acquisition with accurate cortical boundary definitions.⁸⁸ Besides cortical morphometry (e.g., quantification of cortical thickness), MRI allows the visualization of soft tissues. Complementing HR-pQCT-based morphometric and biomechanical approaches to cortical porosity, HR-MRI has been used to characterize the tissue properties of pore contents (e.g., marrow fat versus vasculature).⁸⁹ Using advanced MRI methods with ultra short echo times (UTE), cortical bone water content in the microscopic pores of the Haversian canals and the lacunocanalicular systems can be quantified in addition.^{90,91} This is of relevance because a significant number of cortical pores is too small a number to be directly detected even by high-resolution imaging techniques. Thus quantification of cortical bone water could provide a potential indirect surrogate measure of bone porosity without resolving these individual small pores. The *in vivo* quantification of cortical bone water revealed a 65% increase in postmenopausal versus premenopausal women.⁹² Patients with renal osteodystrophy had even more pronounced increases (+135% compared with controls). In this study, cortical bone water was shown to be a highly sensitive parameter with group differences exceeding those of DXA.

Additional applications of MRI in bone research

Besides high-resolution imaging, MRI can complement bone research by its capability to quantify bone and bone marrow properties on a biochemical level. Using bone marrow spectroscopy, the content of fat, water, and other metabolites can be assessed quantitatively within a defined volume of interest.⁹³ In the light of the emerging importance of the interactions between marrow fat and bone, the possibility of noninvasive characterization of bone marrow composition is being increasingly recognized as an independent surrogate for bone quality.^{94–96} Besides evidence for the negative effects of increases in marrow fat content, fat composition appears to be linked with bone density.⁹⁷

Summary

In conclusion, HR-pQCT and HR-MRI provide novel, noninvasive and accurate options for the quantification of bone microarchitecture. Although current research focusing on potential clinical applications seems promising, both techniques are still limited to research use. Conclusions from high-resolution bone imaging studies should only be drawn with recognition of technical caveats. Moreover, quality control should be standardized.

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References

1. Lewiecki EM, Baim S, Binkley N. Report of the International Society for Clinical Densitometry 2007 Adult Position Development Conference and Official Positions. *South Med J*. 2008; 101:735–739. [PubMed: 18580720]
2. NIH Consensus Development Panel on Osteoporosis Prevention and Therapy. *JAMA*. 2001; 285:785–795. [PubMed: 11176917]
3. Damilakis J, Adams JE, Guglielmi G, et al. Radiation exposure in X-ray-based imaging techniques used in osteoporosis. *Eur Radiol*. 2010; 20:2707–2714. [PubMed: 20559834]
4. Laib A, Ruegsegger P. Comparison of structure extraction methods for *in vivo* trabecular bone measurements. *Comput Med Imaging Graph*. 1999; 23:69–74. [PubMed: 10227372]
5. Burghardt AJ, Kazakia TM, Link GJ, et al. Automated simulation of areal bone mineral density assessment in the distal radius from high-resolution peripheral quantitative computed tomography. *Osteoporos Int*. 2009; 20:2017–2024. [PubMed: 19330422]
6. Parfitt AM, Drezner MK, Glorieux FH, et al. Bone histomorphometry: standardization of nomenclature, symbols, and units. Report of the ASBMR Histomorphometry Nomenclature Committee. *J Bone Miner Res*. 1987; 2:595–610. [PubMed: 3455637]
7. Hildebrand T, Ruegsegger P. A new method for the model-independent assessment of thickness in three-dimensional images. *J Microsc*. 1997; 185:67–75.
8. Laib A, Hauselmann HJ, Ruegsegger HP. *In vivo* high resolution 3D-QCT of the human forearm. *Technol Health Care*. 1998; 6:329–337. [PubMed: 10100936]
9. MacNeil JA, Boyd SK. Accuracy of high-resolution peripheral quantitative computed tomography for measurement of bone quality. *Med Eng Phys*. 2007; 29:1096–1105. [PubMed: 17229586]
10. Macneil JA, Boyd SK. Bone strength at the distal radius can be estimated from high-resolution peripheral quantitative computed tomography and the finite element method. *Bone*. 2008; 42:1203–1213. [PubMed: 18358799]
11. Sode M, Burghardt AJ, Nissenson RA, et al. Resolution dependence of the non-metric trabecular structure indices. *Bone*. 2008; 42:728–736. [PubMed: 18276202]
12. Liu XS, Zhang XH, Sekhon KK, et al. High-resolution peripheral quantitative computed tomography can assess microstructural and mechanical properties of human distal tibial bone. *J Bone Miner Res*. 2010; 25:746–756. [PubMed: 19775199]
13. Burghardt AJ, Buie HR, Laib A, et al. Reproducibility of direct quantitative measures of cortical bone microarchitecture of the distal radius and tibia by HR-pQCT. *Bone*. 2010; 47:519–528. [PubMed: 20561906]
14. Nishiyama KK, Macdonald HM, Buie HR, et al. Postmenopausal women with osteopenia have higher cortical porosity and thinner cortices at the distal radius and tibia than women with normal aBMD: an *in vivo* HR-pQCT study. *J Bone Miner Res*. 2010; 25:882–890. [PubMed: 19839766]
15. Holzer G, von Skrbensky G, Holzer LA, et al. Hip fractures and the contribution of cortical versus trabecular bone to femoral neck strength. *J Bone Miner Res*. 2009; 24:468–474. [PubMed: 19016592]
16. Burghardt AJ, Kazakia GJ, Ramachandran S, et al. Age- and gender-related differences in the geometric properties and biomechanical significance of intracortical porosity in the distal radius and tibia. *JBoneMinerRes*. 2010; 25:983–993.
17. Sode M, Burghardt AJ, Kazakia G, et al. Regional variations of gender-specific and age-related differences in trabecular bone structure of the distal radius and tibia. *Bone*. 2010; 46:1652–1660. [PubMed: 20188877]
18. Burghardt AJ, Kazakia G, Sode M, et al. A longitudinal HR-pQCT study of alendronate treatment in post-menopausal women with low bone density: relations among density, cortical and trabecular microarchitecture, biomechanics, and bone turnover. *J Bone Miner Res*. 2010; 25:2558–2571. [PubMed: 20564242]

19. Keaveny TM. Biomechanical computed tomography-noninvasive bone strength analysis using clinical computed tomography scans. *Ann N Y Acad Sci.* 2010; 1192:57–65. [PubMed: 20392218]
20. van Rietbergen B, Weinans H, Huiskes R, et al. A new method to determine trabecular bone elastic properties and loading using micromechanical finite-element models. *J Biomech.* 1995; 28:69–81. [PubMed: 7852443]
21. van Rietbergen B. Micro-FE analyses of bone: state of the art. *Adv Exp Med Biol.* 2001; 496:21–30. [PubMed: 11783621]
22. Black DM, Greenspan SL, Ensrud KE, et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *N Engl J Med.* 2003; 349:1207–1215. [PubMed: 14500804]
23. Black DM, Bilezikian JP, Ensrud KE, et al. One year of alendronate after one year of parathyroid hormone (1–84) for osteoporosis. *N Engl J Med.* 2005; 353:555–565. [PubMed: 16093464]
24. Graeff C, Chevalier Y, Charlebois M, et al. Improvements in vertebral body strength under teriparatide treatment assessed *in vivo* by finite element analysis: results from the EUROFORs study. *J Bone Miner Res.* 2009; 24:1672–1680. [PubMed: 19419306]
25. Eastell R, Lang T, Boonen S, et al. Effect of once-yearly zoledronic acid on the spine and hip as measured by quantitative computed tomography: results of the HORIZON Pivotal Fracture Trial. *Osteoporos Int.* 2010; 21:1277–1285. [PubMed: 19802508]
26. Genant HK, Engelke K, Hanley DA, et al. Denosumab improves density and strength parameters as measured by QCT of the radius in postmenopausal women with low bone mineral density. *Bone.* 2010; 47:131–139. [PubMed: 20399288]
27. Liu XS, Zhang XH, Sekhon KK, et al. CAVE: 2x. High-resolution peripheral quantitative computed tomography can assess microstructural and mechanical properties of human distal tibial bone. *J Bone Miner Res.* 2010; 25:746–756. [PubMed: 19775199]
28. Macneil JA, Boyd SK. Bone strength at the distal radius can be estimated from high-resolution peripheral quantitative computed tomography and the finite element method. *Bone.* 2008; 42:1203–1213. [PubMed: 18358799]
29. Mueller TL, Christen D, Sandercott S, et al. Computational finite element bone mechanics accurately predicts mechanical competence in the human radius of an elderly population. *Bone.* 2011; 4:1232–1238. [PubMed: 21376150]
30. Boutroy S, Van Rietbergen B, Sornay-Rendu E, et al. Finite element analysis based on *in vivo* HR-pQCT images of the distal radius is associated with wrist fracture in post-menopausal women. *J Bone Miner Res.* 2008; 23:392–399. [PubMed: 17997712]
31. Vilayphiou N, Boutroy S, Szulc P, et al. Finite element analysis performed on radius and tibia HR-pQCT images and fragility fractures at all sites in men. *J Bone Miner Res.* 2011; 26:965–973. [PubMed: 21541999]
32. Liu XS, Cohen A, Shane E, et al. Individual trabeculae segmentation (ITS)-based morphological analyses of high resolution peripheral quantitative computed tomography images detect abnormal trabecular plate and rod microarchitecture in premenopausal women with idiopathic osteoporosis. *J Bone Miner Res.* 2010; 25:1486–1505.
33. Liu XS, Shane E, McMahon DJ, et al. Individual trabeculae segmentation (ITS)-based morphological analysis of micro-scale images of human tibial trabecular bone at limited spatial resolution. *J Bone Miner Res.* 2011; 26:2184–2193. [PubMed: 21557311]
34. Pialat JB, Burghardt AJ, Sode M, et al. Motion artifacts in high-resolution peripheral quantitative computed tomography of wrist and ankle: usefulness of visual grading to assess image quality. *J Bone Miner Res.* 2010; 25:S373.
35. Sode M, Burghardt AJ, Pialat JB, et al. Quantitative characterization of subject motion in HR-pQCT images of the distal radius and tibia. *Bone.* 2011; 48:1291–1297. [PubMed: 21421091]
36. Pauchard Y, Ayres FJ, Boyd SK. Automated quantification of three-dimensional subject motion to monitor image quality in high-resolution peripheral quantitative computed tomography. *Phys Med Biol.* 2011; 56:6523–6543. Epub ahead of print. [PubMed: 21937776]
37. Sekhon K, Kazakia G, Burghardt AJ, et al. Accuracy of volumetric bone mineral density measurement in high-resolution peripheral quantitative computed tomography. *Bone.* 2009; 45:473–479. [PubMed: 19501201]

38. Cohen A, Dempster DW, Müller R, et al. Assessment of trabecular and cortical architecture and mechanical competence of bone by high-resolution peripheral computed tomography: comparison with transiliac bone biopsy. *Osteoporos Int.* 2010; 21:263–273. [PubMed: 19455271]
39. Sornay-Rendu E, Boutroy S, Munoz F, et al. Alterations of cortical and trabecular architecture are associated with fractures in postmenopausal women, partially independent of decreased BMD measured by DXA: the OFELY study. *J Bone Miner Res.* 2007; 22:425–433. [PubMed: 17181395]
40. Vico L, Zouch M, Amirouche A, et al. High-resolution pQCT analysis at the distal radius and tibia discriminates patients with recent wrist and femoral neck fractures. *J Bone Miner Res.* 2008; 23:1741–1750. [PubMed: 18665795]
41. Liu XS, Cohen A, Shane E, et al. Bone density, geometry, microstructure and stiffness: relationships between peripheral and central skeletal sites assessed by DXA, HR-pQCT, and cQCT in premenopausal women. *J Bone Miner Res.* 2010; 25:2229–2238. [PubMed: 20499344]
42. Boutroy S, Bouxsein ML, Munoz F, et al. *In vivo* assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. *J Clin Endocrinol Metab.* 2005; 90:6508–6515. [PubMed: 16189253]
43. Vilayphiou N, Boutroy S, Szulc P, et al. Finite element analysis performed on radius and tibia HR-pQCT images and fragility fractures at all sites in men. *J Bone Miner Res.* 2011; 26:965–973. [PubMed: 21541999]
44. Stein EM, Liu XS, Nickolas TL, et al. Abnormal microarchitecture and stiffness in postmenopausal women with ankle fractures. *J Clin Endocrinol Metab.* 2011; 96:2041–2048. [PubMed: 21508142]
45. Khosla S, Riggs BL, Atkinson EJ, et al. Effects of sex and age on bone microstructure at the ultradistal radius: a population-based noninvasive *in vivo* assessment. *J Bone Miner Res.* 2006; 21:124–131. [PubMed: 16355281]
46. Macdonald HM, Nishiyama KK, Kang J, et al. Age-related patterns of trabecular and cortical bone loss differ between sexes and skeletal sites: a population-based HR-pQCT study. *J Bone Miner Res.* 2011; 26:50–62. [PubMed: 20593413]
47. Wang XF, Wang Q, Ghasem-Zadeh A, et al. Differences in macro- and microarchitecture of the appendicular skeleton in young Chinese and white women. *J Bone Miner Res.* 2009; 24:1946–1952. [PubMed: 19459783]
48. Liu XS, Walker MD, McMahon DJ, et al. Better skeletal microstructure confers greater mechanical advantages in Chinese–American women versus white women. *J Bone Miner Res.* 2011; 26:1783–1792. [PubMed: 21351150]
49. Walker MD, Liu XS, Stein E, et al. Differences in bone microarchitecture between postmenopausal Chinese-American and white women. *J Bone Miner Res.* 2011; 26:1392–1398. [PubMed: 21305606]
50. Schwartz AV, Sellmeyer DE. Women, type 2 diabetes, and fracture risk. *Curr Diab Rep.* 2004; 4:364–369. [PubMed: 15461902]
51. Burghardt AJ, Issever AS, Schwartz AV, et al. High-resolution peripheral quantitative computed tomographic imaging of cortical and trabecular bone microarchitecture in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab.* 2010; 95:5045–5055. [PubMed: 20719835]
52. Shu A, Yin MT, Stein E, et al. Bone structure and turnover in type 2 diabetes mellitus. *Osteoporos Int.* 2011 Mar 19. Epub ahead of print.
53. Aaron JE, Makins NB, Sagreiy K. The microanatomy of trabecular bone loss in normal ageing men and women. *Clin Orthop.* 1987; 215:260–271. [PubMed: 3802645]
54. Seeman E. Unresolved issues in osteoporosis in men. *Rev Endocrinol Metab Disord.* 2001; 2:45–64.
55. Patsch JM, Deutschmann J, Pietschmann P. Gender aspects of osteoporosis and bone strength. *Wien Med Wochenschr.* 2011; 161:117–123. [PubMed: 21461801]
56. Bacchetta J, Boutroy S, Vilayphiou N, et al. Early impairment of trabecular microarchitecture assessed with HR-pQCT in patients with stage II–IV chronic kidney disease. *J Bone Miner Res.* 2010; 25:849–857. [PubMed: 19775204]
57. Nickolas TL, Stein E, Cohen A, et al. Bone mass and microarchitecture in CKD patients with fracture. *J Am Soc Nephrol.* 2010; 21:1371–1380. [PubMed: 20395370]

58. Cejka D, Jäger-Lansky A, Kieweg H, et al. Sclerostin serum levels correlate positively with bone mineral density and microarchitecture in haemodialysis patients. *Nephrol Dial Transplant*. 2011 May 25. Epub ahead of print.
59. Hansen S, Beck Jensen JE, Rasmussen L, et al. Effects on bone geometry, density, and microarchitecture in the distal radius but not the tibia in women with primary hyperparathyroidism: A case-control study using HR-pQCT. *J Bone Miner Res*. 2010; 25:1941–1947. [PubMed: 20499376]
60. Burghardt AJ, Hermannsson B, Pialat JB, et al. Cross-site reproducibility of cortical and trabecular bone density and micro-architecture measurements by HR-pQCT. *Osteoporos Int*. 2010; 21:S45–S46.
61. Kazakia GJ, Hyun B, Burghardt AJ, et al. In vivo determination of bone structure in postmenopausal women: a comparison of HR-pQCT and high-field MR imaging. *J Bone Miner Res*. 2008; 23:463–474. [PubMed: 18052756]
62. Boivin GY, Chavassieux PM, Santora AC, et al. Alendronate increases bone strength by increasing the mean degree of mineralization of bone tissue in osteoporotic women. *Bone*. 2000; 27:687–694. [PubMed: 11062357]
63. Roschger P, Manjubala I, Zoeger N, et al. Bone material quality in transiliac bone biopsies of postmenopausal osteoporotic women after 3 years of strontium ranelate treatment. *J Bone Miner Res*. 2010; 25:891–900. [PubMed: 20437609]
64. Macdonald HM, Nishiyama KK, Hanley DA, et al. Changes in trabecular and cortical bone microarchitecture at peripheral sites associated with 18 months of teriparatide therapy in postmenopausal women with osteoporosis. *Osteoporos Int*. 2011; 22:357–362.
65. Rizzoli R, Laroche M, Krieg MA, et al. Strontium ranelate and alendronate have differing effects on distal tibia bone microstructure in women with osteoporosis. *Rheumatol Int*. 2010; 30:1341–1348. [PubMed: 20512336]
66. Li EK, Zhu TY, Hung VY, et al. Ibandronate increases cortical bone density in patients with systemic lupus erythematosus on long-term glucocorticoid. *Arthritis Res Ther*. 2010; 12:R198. [PubMed: 20964867]
67. Seeman E, Delmas PD, Hanley DA, et al. Microarchitectural deterioration of cortical and trabecular bone: differing effects of denosumab and alendronate. *J Bone Miner Res*. 2010; 25:1886–1894. [PubMed: 20222106]
68. Majumdar S, Thomasson D, Shimakawa A, et al. Quantitation of the susceptibility difference between trabecular bone and bone marrow: experimental studies. *Magn Reson Med*. 1991; 22:111–127. [PubMed: 1798386]
69. Weisskoff RM, Zuo CS, Boxerman JL, et al. Microscopic susceptibility variation and transverse relaxation: theory and experiment. *Magn Reson Med*. 1994; 31:601–610. [PubMed: 8057812]
70. Ford JC, Wehrli FW, Chung HW. Magnetic field distribution in models of trabecular bone. *Magn Reson Med*. 1993; 30:373–379. [PubMed: 8412611]
71. Link TM, Majumdar S, Augat P, et al. Proximal femur: assessment for osteoporosis with T2* decay characteristics at MR imaging. *Radiology*. 1998; 209:531–536. [PubMed: 9807585]
72. Wehrli FW, Ford JC, Haddad JG. Osteoporosis: clinical assessment with quantitative MR imaging in diagnosis. *Radiology*. 1995; 196:631–641. [PubMed: 7644622]
73. Krug R, Banerjee S, Han ET, et al. Feasibility of in vivo structural analysis of high-resolution magnetic resonance images of the proximal femur. *Osteoporos Int*. 2005; 16:1307–1314. [PubMed: 15999292]
74. Phan CM, Matsuura M, Bauer JS, et al. Trabecular bone structure of the calcaneus: comparison of mr imaging at 3.0 and 1.5 t with micro-ct as the standard of reference. *Radiology*. 2006; 239:488–496. [PubMed: 16569786]
75. Laib A, Newitt DC, Lu Y, et al. New model-independent measures of trabecular bone structure applied to in vivo high-resolution mr images. *Osteoporos Int*. 2002; 13:130–136. [PubMed: 11905523]
76. Majumdar S, Newitt D, Mathur A, et al. Magnetic resonance imaging of trabecular bone structure in the distal radius: relationship with x-ray tomographic microscopy and biomechanics. *Osteoporos Int*. 1996; 6:376–385. [PubMed: 8931032]

77. Hwang SN, Wehrli FW, Williams JL. Probability-based structural parameters from three-dimensional nuclear magnetic resonance images as predictors of trabecular bone strength. *Med Phys.* 1997; 24:1255–1261. [PubMed: 9284249]
78. Pothuau L, Laib A, Levitz P, et al. Three-dimensional-line skeleton graph analysis of high-resolution magnetic resonance images: a validation study from 34-microm-resolution microcomputed tomography. *J Bone Miner Res.* 2002; 17:1883–1895. [PubMed: 12369792]
79. Majumdar S, Kothari M, Augat P, et al. High-resolution magnetic resonance imaging: Three-dimensional trabecular bone architecture and biomechanical properties. *Bone.* 1998; 22:445–454. [PubMed: 9600777]
80. Ammann P, Rizzoli R. Bone strength and its determinants. *Osteoporos Int.* 2003; 14(Suppl 3):S13–S18. [PubMed: 12730800]
81. Link TM, Bauer J, Kollstedt A, et al. Trabecular bone structure of the distal radius, the calcaneus, and the spine: which site predicts fracture status of the spine best? *Invest Radiol.* 2004; 39:487–497. [PubMed: 15257210]
82. Majumdar S, Genant H, Grampp S, et al. Correlation of trabecular bone structure with age, bone mineral density and osteoporotic status: in vivo studies in the distal radius using high resolution magnetic resonance imaging. *J Bone Miner Res.* 1997; 12:111–118. [PubMed: 9240733]
83. Majumdar S, Link T, Augat P, et al. Trabecular bone architecture in the distal radius using mr imaging in subjects with fractures of the proximal femur. *Osteoporos Int.* 1999; 10:231–239. [PubMed: 10525716]
84. Link TM, Majumdar S, Augat P, et al. In vivo high resolution mri of the calcaneus: differences in trabecular structure in osteoporosis patients. *J Bone Miner Res.* 1998; 13:1175–1182. [PubMed: 9661082]
85. Benito M, Gomberg B, Wehrli FW, et al. Deterioration of trabecular architecture in hypogonadal men. *J Clin Endocrinol Metab.* 2003; 88:1497–1502. [PubMed: 12679429]
86. Benito M, Vasilic B, Wehrli FW, et al. Effect of testosterone replacement on trabecular architecture in hypogonadal men. *J Bone Miner Res.* 2005; 20:1785–1791. [PubMed: 16160736]
87. Chesnut CH 3rd, Majumdar S, Newitt DC, et al. Effects of salmon calcitonin on trabecular microarchitecture as determined by magnetic resonance imaging: results from the quest study. *J Bone Miner Res.* 2005; 20:1548–1561. [PubMed: 16059627]
88. Gomberg BR, Saha PK, Wehrli FW. Method for cortical bone structural analysis from magnetic resonance images. *Acad Radiol.* 2005; 12:1320–1332. [PubMed: 16179209]
89. Goldenstein J, Kazakia G, Majumdar S. In vivo evaluation of the presence of bone marrow in cortical porosity in postmenopausal osteopenic women. *Ann Biomed Eng.* 2010; 38:235–246. [PubMed: 19953321]
90. Wehrli FW, Fernández-Seara MA. Nuclear magnetic resonance studies of bone water. *Ann Biomed Eng.* 2005; 33:79–86. [PubMed: 15709708]
91. Krug R, Larson PEZ, Wang C, et al. Ultrashort echo time MRI of cortical bone at 7 tesla field strength: a feasibility study. *J Magn Reson Imaging.* 2011 Epub ahead of print. 10.1002/jmri.22648
92. Techawiboonwong A, Song HK, Leonard MB, et al. Cortical bone water: in vivo quantification with ultrashort echo-time MR imaging. *Radiology.* 2008; 248:824–833. [PubMed: 18632530]
93. Li X, Kuo D, Schaefer AL, et al. Quantification of vertebral bone marrow fat content using 3 Tesla MR spectroscopy: reproducibility, vertebral variation, and applications in osteoporosis. *J Magn Reson Imaging.* 2011; 33:974–979. [PubMed: 21448966]
94. Meunier P, Aaron J, Edouard C, et al. Osteoporosis and the replacement of cell populations of the marrow by adipose tissue. A quantitative study of 84 iliac bone biopsies. *Clin Orthop Relat Res.* 1971; 80:147–154. [PubMed: 5133320]
95. Justesen J, Stenderup K, Ebbesen EN, et al. Adipocyte tissue volume in bone marrow is increased with aging and in patients with osteoporosis. *Biogerontology.* 2001; 2:165–171. [PubMed: 11708718]
96. Bredella MA, Fazeli PK, Miller KK, et al. Increased bone marrow fat in anorexia nervosa. *J Clin Endocrinol Metab.* 2009; 94:2129–2136. [PubMed: 19318450]

97. Yeung DK, Griffith JF, Antonio GE, et al. Osteoporosis is associated with increased marrow fat content and decreased marrow fat unsaturation: a proton MR spectroscopy study. *J Magn Reson Imaging*. 2005; 22:279–285. [PubMed: 16028245]

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Figure 1. Influence of subject motion of scan-quality HR-pQCT scans of the distal radius of a single individual (left: grade 5—not usable for analysis; middle: grade 3—still usable; right: grade 2—almost motionless, good image quality). Arrows point at artifact streaks induced by rotational motion.

Figure 2.

Three examples of HR-pQCT scans of the distal tibia. (A) Normal premenopausal control. (B) Postmenopausal women with chronic kidney disease. Morphologic features include cortical thinning, loss of trabeculae, and severe arterial calcifications. (C) Postmenopausal and age-related cortical porosity with relative preservation of the trabecular compartment.

Figure 3.
Comparison of HR-pQCT and HR-MRI in an osteopenic, early postmenopausal woman.
Upper row: HR-pQCT of the distal radius and tibia. HR-MRI at identical skeletal sites
(below) depicts trabecular structures by inverse contrast.