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High-resolution Imaging Techniques for the Assessment of Osteoporosis

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Synopsis

The importance of assessing the bone's microarchitectural make-up in addition to its mineral density in the context of osteoporosis has been emphasized in a number of publications. The high spatial resolution required to resolve the bone's microstructure in a clinically feasible scan time is challenging. Currently, the best suited modalities meeting these requirements *in vivo* are high-resolution peripheral quantitative imaging (HR-pQCT) and magnetic resonance imaging (MRI). Whereas HR-pQCT is limited to peripheral skeleton regions like the wrist and ankle, MRI can also image other sites like the proximal femur but usually with lower spatial resolution. In addition Multidetector-CT has been used for high-resolution imaging of trabecular bone structure, however, the radiation dose is a limiting factor. This article provides an overview of the different modalities, technical requirements and recent developments in this emerging field. Details regarding imaging protocols as well as image post-processing methods for bone structure quantification are discussed.

Keywords

Magnetic Resonance Imaging; High-Resolution peripheral quantitative computed tomography (HR-pQCT); Micro computed tomography (MicroCT); Trabecular Bone Imaging; Cortical Bone Imaging

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I. Introduction

Osteoporosis is a metabolic disease characterized by low bone mass and structural deterioration with an increased fracture risk. Atraumatic fragility fractures mainly affect the proximal femur, the spine, and distal radius. Osteoporosis is a major public health problem, with a high impact on quality of life and high rates of morbidity. Currently the established modality to diagnose and monitor osteoporosis in a clinical setting is dual-energy X-ray absorptiometry (DXA), which provides areal bone mineral density (BMD). It is a projectional imaging technique and hence measures integral BMD of both cortical and trabecular bone. In addition to DXA, volumetric quantitative computed tomography (vQCT) has been used to assess BMD. This three dimensional technique measures volumetric BMD (vBMD) and thus permits separate characterization of bone geometry and bone density as elements of fracture risk. Furthermore, vQCT can examine cortical and trabecular bone separately. The aforementioned modalities only measure BMD and macroscopic geometry. However, there is a disparity between bone density and bone microarchitecture in the assessment of bone strength and fracture risk. It has been found that BMD only explains about 70–75% of the variance in strength, while the remaining variance is due to the cumulative and synergistic effect of other factors such as bone architecture, tissue composition and micro damage. Also in the context of therapeutic changes, it has been shown that density alone has limitations in predicting the outcome. Furthermore, in a multi-center fracture intervention trial, it was found that the anti-fracture effects of all drugs tested in trials only partially explained by their effects on BMD. In fact, BMD explained less than half the effect (1). In a meta-analysis of 38 studies investigating measures of bone strength it was concluded that BMD is a limited predictor of fracture risk and it was concluded that bone's architectural make-up significantly contributes to bone strength (2). Besides trabecular thinning, changes in topology, notably a conversion from trabecular plates to rods, and eventually disconnection of trabeculae all contribute to architectural deterioration and loss of bone strength (3). Furthermore, cortical thinning and cortical porosity also contribute to increased bone fragility (4). Accordingly, there is a demand for high-resolution imaging techniques to evaluate bone microstructure.

II. General Considerations for Bone Imaging

For the assessment of bone structure, both trabecular and cortical bone play important roles. Sites containing predominantly trabecular bone such as the hip, spine and wrist are also sites of increased fracture risk. Furthermore, trabecular bone remodels up to an order of magnitude faster than cortical bone and is thus the main target of therapeutic approaches. Cancellous bone is prevalent near the joints of long bone (wrist, ankle) and in the axial skeleton (hip, spine) and is surrounded by a cortical bone shell. Cortical bone is usually very compact (cortical thickness varies between 1–5 mm) and is primarily found in the shafts of long bones such as the femur, tibia and radius. It constitutes about 80% of the skeleton. In previous studies, it has been emphasized that cortical thinning (5,6) as well as increased cortical porosity (4,7) are important factors in the assessment of osteoporosis and bone strength. Especially in the context of the proximal femur, a site with high fracture rates and morbidity, the importance of cortical bone structure has been established in previous publications (8,9). The cortical bone ratio is more than a magnitude higher in the femur than for instance in the shaft or diaphysis of the radius. Considering the ratio of trabecular versus cortical bone, the vertebral body is primarily trabecular (up to 90%), the intertrochanteric region of the proximal femur is approximately 50% trabecular and the femoral neck is only 25% trabecular. The structure of cortical bone is related to its mechanical strength and thus plays an important role in bone strength (10). Furthermore, age, gender, and osteoporotic status all affect the cortical bone structure. Recently, there has been an increased focus on porosity of the cortical bone that can be attributed to resorption spaces, merging of haversian canals, and clustering of osteons. Since cortical porosity has a significant impact on mechanical properties of cortical bone (11),

characterizing cortical porosity is also important in the context of bone strength and prediction of fracture risk.

Traditionally, the trabecular network has been assessed from bone biopsies by two dimensional (2D) histomorphometry. More recently, these techniques were replaced by 3D imaging techniques, which depict the bone architecture more accurately. Using micro-computed tomography, bone biopsies from the iliac crest can be analyzed with an isotropic voxel size below 8 μm . The disadvantage of this method is its invasiveness and the restriction to small local regions for bone assessment, which are not critical fracture sites. Multi-detector CT has been used to image bone structure in the axial skeleton *in vivo* but is associated with high radiation exposure and limited spatial resolution. Another CT based method to assess bone structure at peripheral sites, albeit with much lower radiation dose, is high-resolution peripheral quantitative CT (HR-pQCT) with isotropic voxel size as small as 41 μm in a clinical setting. An additional modality, which is increasingly being used for high-resolution assessment of bone is magnetic resonance imaging (MRI). The absence of ionizing radiation and its excellent soft tissue contrast render MRI a prime modality for *in vivo* assessment of bone structure. This article will mainly focus on the two last aforementioned techniques (HR-pQCT and MRI), which are presently the most promising for the assessment of bone structure *in vivo*. Multi-detector CT will be briefly discussed in this review as well.

III. Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is an emerging technology for acquiring high-resolution images of cortical and trabecular bone *in vivo*. It is a non-invasive modality and does not require ionizing radiation. Therefore, it is well suited for assessing bone structure in a clinical setting. In conventional MRI, bone yields low signal and appears dark due to the relatively low abundance of protons and an extremely short T2 relaxation time ($<1\text{ms}$) similar to most solid-state tissues. The MR signal stems largely from bone marrow and depends on the pulse sequence used and the fat content of the marrow (fatty versus hematopoietic bone marrow). As a result, in MRI bone is usually depicted with a negative contrast relative to the high background signal from bone marrow. Information regarding structure, topology, and orientation of the trabecular bone network as well as cortical thickness and area can be extracted from the images by applying digital post-processing techniques. A large number of analysis parameters have been investigated in the past and related to osteoporotic fracture risk and response to treatment as outlined below. Because there are different requirements for the measurement and analysis of trabecular versus cortical bone the following text will treat both in separate chapters.

1. Trabecular Bone Assessment using MRI

MR image acquisition

Signal to noise and spatial resolution: In MRI, spatial resolution and SNR are trade-off parameters and it is not yet clear whether enhancing resolution at the expense of SNR increases or decreases detection sensitivity and what errors are incurred by imaging at anisotropic resolution. Li et al. (12) investigated the impact of limited spatial resolution and noise on structural parameters. The authors noted systematic changes in the derived structural parameters with decreasing SNR below a certain threshold. They also showed that these errors at smaller SNR levels are correctable using simple linear transformations, thereby allowing the data to be normalized. Rajapakse et al. (13) investigated the implications of noise and resolution on mechanical properties of trabecular bone as estimated by image-based finite-element analysis. They found that the elastic moduli computed from simulated MR images were highly correlated with those obtained from μCT ($R^2=0.99$). The elastic moduli became increasingly underestimated with decreasing SNR. However, the high correlation between

elastic parameters derived from μ CT and simulated MR data suggested that there is potential for estimating mechanical moduli on the basis of *in vivo* MR images.

Although there has been a lot of effort to develop trabecular bone imaging of peripheral sites such as the radius, tibia and calcaneus, very little work has been done on the proximal femur, a site of high fracture incidence. This is primarily due to SNR limitations for deep body locations and is related to the fact that the RF signal is attenuated by surrounding tissues such as fat and muscle. Only recently, through pulse sequence and coil optimization, the femur was made accessible for trabecular bone analysis (14). Further optimization in the authors' laboratory led to enhanced SNR efficiency and improved MR images of the proximal femur (Figure 1). The depicted *in vivo* images are acquired in 12 minutes with a high spatial resolution of $234 \times 234 \times 500 \mu\text{m}^3$.

Pulse Sequences: A pulse sequence is a preselected set of defined radiofrequency and gradient pulses, usually repeated many times during a scan. The signal reception and thus the contrast of the image depend on the exact sequence executed. Pulse sequences are computer programs that control all hardware aspects of the MR measurement process. In principle, two main types of pulse sequences can be defined and are both used for bone imaging. Namely, spin-echo (SE) based pulse sequences and gradient-echo (GE) based pulse sequences. A gradient-echo is usually always required in order to readout the necessary wave numbers of the Fourier Transformation. A second RF pulse can additionally create a spin-echo. This method ensures, that all spins are in-phase at the time of the gradient-echo no matter what field inhomogeneities they experience. Deviations from the main magnetic field are in particular strong near trabecular bone and bone marrow transitions. As bone is more diamagnetic than bone marrow, off-resonance frequencies of 100 Hz and more are expected (15) at 3 Tesla and more than 200 Hz at ultra high field strength of 7 Tesla (16). The result is an intra voxel spin dephasing, which can lead to significant signal attenuation even complete signal cancellation. In order to choose a suitable pulse sequence for bone MRI, a few guidelines have to be considered. Firstly, a 3-dimensional (3D) excitation usually provides higher SNR than a 2D sequence. However, 2D acquisition techniques have also been used previously to image the trabecular structure of the calcaneus (17–19) albeit with lower spatial resolution. Secondly, the gradient-echo has to be acquired immediately after the excitation pulse in order to avoid signal loss due to T2 relaxation. Finally, the imaging time has to be in a clinically feasible range.

The simplest sequence that fulfills the aforementioned requirements is a basic gradient-echo sequence. By adjusting the flip angle the steady state of GE pulse sequences can be maximized in terms of signal efficiency (signal per unit time) if the scan time (and TR) is short (20). Further improvements of SNR efficiency can be made by fully balancing all magnetic gradients during one repetition. The so-called balanced steady state gradient-echo pulse sequence (bSSFP) maximizes SNR efficiency but is also very prone to magnetic field inhomogeneities. Krug et al. (21) pointed out some advantages of this signal attenuation. Smaller trabeculae that would normally disappear due to partial volume effects were enhanced and thus visible due to increased signal cancellation using bSSFP (22) compared to a spin-echo approach. Bauer et al. (23) found a similar advantage when imaging 43 calcaneous specimens at 3 Tesla and 1.5 Tesla. Since these susceptibility effects scale with field strength, the trabecular structure is usually enhanced at higher field strength. Bauer et al. showed that previously demonstrated advances at the higher field strength for visualization and quantification of trabecular structure are only partially dependent on SNR and that the susceptibility induced accentuation of small structures was most beneficial at higher noise levels which yielded a superior image quality at 3 Tesla regarding the trabecular bone network. Therefore, due to its very high SNR efficiency, SSFP has become the sequence of choice among gradient-echo based pulse sequences for trabecular bone imaging (14–16, 24–27).

Spin-echo based pulse sequences avoid these susceptibility induced off-resonance effects entirely at the time of the gradient echo (21,28). However, SE pulse sequences usually demand a relatively long scan times due to larger TRs ($TR > 60\text{ms}$). One advantage of the longer TR is the possibility to implement motion correction for the relatively long scans (29). Song et al. (30) presented a retrospective 2D correction of translational motion for spin-echo imaging using navigator echoes albeit without correcting for rotational patient movements. In the authors' laboratory, careful patient positioning has proven to largely prevent motion artifacts. Furthermore, imaging time was considerably reduced by employing accelerated image acquisition techniques (parallel imaging). For trabecular bone imaging this was first introduced by Banerjee *et al.* (31) for gradient-echo imaging followed by Krug et al. (21) for spin-echo based pulse sequences. Both implementations were done using generalized autocalibrating partially parallel acquisitions (GRAPPA) (32).

Image analysis and post processing—Image analysis of trabecular bone images in MRI involves several post processing steps; mainly the outlining of the trabecular bone region of interest (ROI), the correction of the coil sensitivity, bone/marrow segmentation, structural calculations and if needed serial image registration (33). Before analysis, the ROI containing the trabecular bone structure has to be defined. This can be done manually by an operator or in a semi-automatic fashion as published by Newitt et al. (33). The next steps in the processing chain are described in the following.

Coil Correction: In order to accurately analyze the MR images, the spatial variations due to the coil's sensitivity profile have to be corrected. For quadrature or birdcage coils with satisfactory in-plane homogeneity, a simple phantom-based correction can be applied as demonstrated by Newitt et al. (33). However, this method strongly depends on the accurate placement of the scanner landmark at the center of the coil. Another approach previously used for images acquired with surface coils (33) is based on a low-pass filter (LPF) correction scheme described by Wald et al. (34) where the image is LP filtered by convolution with a Gaussian kernel. Vasilic et al. (35) estimated the local bias field by finding the intensity for which the discrete Laplacian is zero as a part of a local thresholding algorithm. More recently, Folkesson et al. (36) compared the performance of LPF with a fully automatic coil correction scheme based on a nonparametric non-uniform intensity normalization N3 approach (37) for coil-induced intensity inhomogeneities in trabecular bone MR imaging. The authors concluded that N3 coil correction preserves image information while accurately correcting for coil-induced intensity inhomogeneities, which makes it very suitable for quantitative analysis of trabecular bone.

Image Post Processing: There are many different approaches for extracting structural information from 3D images of the trabecular bone. The most fundamental parameter in MRI is related to bone volume fraction (BVf) and is also denoted BV/TV (bone volume to total volume fraction). This number can be easily extracted from high-resolution images where the intensity histogram is bimodal by setting a single threshold and counting the number of bone pixels and total pixels within an ROI. In the presence of partial volume effects, this becomes much more difficult and the two peaks of the intensity histogram blur into a single peak. Different approaches have been used to solve this problem. One approach is to binarize the image into bone and bone marrow phases. This technique requires a threshold, which can be found empirically (38). The drawback of this method is a significant loss of image information through binarization due to partial volume effects. Other methods seek to circumvent the binarization step and instead investigate the original grayscale image. Hwang et al. (39) introduced a method for noise removal by deconvolution. From the resulting noiseless image, a bone volume fraction map can be generated and from the voxel intensities the marrow volume

fraction can be determined. Vasilic *et al.* (35) presented an alternative method based on local thresholding which estimates the local marrow intensities within a nearest neighbor framework.

Trabecular Bone Analysis: Structural parameters are commonly divided into three classes including scale, topology, and orientation (40,41). Scale is primarily described by the volume of bone in a ROI and the thickness of the trabeculae or the spacing between the trabeculae. Topology can be assessed by investigating the plate- or rod-like structure of the network. And finally orientation methods characterize the degree of anisotropy of the structure. Early assessment of trabecular bone applying the principles of stereology are based on scale. In MRI, trabecular thickness can be obtained from the mean intercept length (MIL) of parallel test lines across the ROI averaged over multiple angles. From MIL and BV/TV measurements, trabecular thickness (Tb.Th), trabecular spacing (Tb.Sp) and trabecular number (Tb.N) are obtained as described by Majumdar *et al.* (38). Also 3D approaches have been proposed. Krug *et al.* (42) used 3D wavelets to compute a trabecular bone thickness map without the need for image binarization. The authors calculated BV/TV from these maps by counting the number of pixels with thickness values different from zero and by dividing this number by the total number of pixels in the corresponding ROI.

Saha *et al.* (43) introduced a fuzzy distance transform for trabecular bone analysis where the Tb.Th is obtained by computing the fuzzy distance along the medial axis of the trabeculae. The method obviated the need of image binarization and is very robust to noise. Carballido-Gamio *et al.* (44) used fuzzy clustering for trabecular bone segmentation and to evaluate BV/TV measurements. More recently, Folkesson *et al.* (45) extended this approach incorporating a local bone enhancement feature at multiple scales (BE-FMC). This method allows noise suppression while enhancing local relative intensity anisotropy and thus accounting for partial volume effects, noise, and signal intensity inhomogeneities. The new method proved to perform better than both the fuzzy clustering and the dual thresholding approach. BE-FMC could also significantly differentiate between control and fracture groups of 30 calcaneus specimens (from 17 subjects with and 13 without vertebral fracture).

In the literature, it has been emphasized that osteoporotic bone loss is strongly associated with changes in bone topology which results in a fenestration of trabecular plates and ultimately loss of connectivity. Saha *et al.* (46) introduced *digital topological analysis* (DTA) and applied it to trabecular bone topology (47). With this method, each voxel is classified into three categories it belongs to: curve, surface or junction. The disadvantage of this approach is the requirement for binarized images since the trabecular network has to be skeletonized prior to DTA analysis. As previously discussed, the determination of an appropriate threshold is challenging and alters the result. Gomberg *et al.* (47) used a fixed threshold at BVF=0.25. Pothaud *et al.* (48) presented a 3D skeletonization technique based on topological invariant, and implemented with a sequential thinning algorithm. A 3D skeleton graph analysis was then implemented to count and to isolate all the vertices and branches of the skeleton graph. Carballido-Gamio *et al.* (49) introduced a new technique to provide a complete assessment of scale, topology, and anisotropy using geodesic topological analysis (GTA). GTA quantifies the trabecular bone network in terms of its junctions, which play a central role in connectivity, and geodesic distances, defined as the shortest path between two points as demonstrated in Figure 2. The authors found that fracture discrimination was improved by combining GTA parameters as shown by logistic regression analysis. It was further demonstrated that GTA combined with BMD allowed for better discrimination than BMD alone (AUC = 0.95; $p < 0.001$).

It is intuitively clear, that in order to maximize bone strength, the trabecular orientation has to follow major stress lines. Very early, this concept has been applied to trabecular bone structure using MIL (50) and used to investigate its relation to bone strength and bone loss. More recent

approaches include topology based orientation analysis of trabecular bone networks (47) and 3D spatial autocorrelation function (ACF) (51,52). Wald et al. (52) compared the structural anisotropy and principal direction of the computed fabric tensor for ACF with MIL in ten healthy postmenopausal women and found that ACF is faster and considerably more robust to noise. They found good agreement between the two methods, but ACF analysis yielded greater anisotropy than MIL for both TB thickness and spacing.

Image Registration: For treatment monitoring it is important to analyze the same trabecular sections at baseline and follow-up in order to detect small changes in the fine trabecular structure. Two basic registration approaches can have been proposed. The images can be aligned after acquisition (retrospective registration) or the acquisition process of the follow-up scan is adapted in respect to field of view to exactly match the baseline scan. The later technique is termed *prospective registration* and has only recently been applied to trabecular bone imaging (53–55). Newitt et al. (33) used the coronal scout image on which the HR scan was prescribed to provide a longitudinal anatomic reference point for comparing results in similar regions between subjects. For follow-up scans on the same subject, retrospective registration was done using only rigid body translations and rotations, and the aligned image was generated using nearest-neighbor interpolation. Magland et al. (56) developed an algorithm that uses local pattern of the trabecular structure near 100 randomly selected points to enable true 3D registration. Prospective registration for trabecular bone MRI was first implemented by Blumenfeld et al. (53). This method does not require image interpolation since the images are aligned at the acquisition stage. This is a significant advantage for high-resolution MRI where the slice thickness is usually larger than the in-plane resolution and partial volume effects may be substantial. Thus, some image information and structure is lost during the interpolation process. Furthermore, the technique ensures that the ROI is placed on the same slice for both the baseline and follow-up and thus simplifies the subsequent post processing. The method presented by Blumenfeld et al. works as follows. First, the baseline images of the subject are acquired including a 3D low-resolution scan and a high-resolution bSSFP scan. For the follow-up scan, one low spatial resolution scan is obtained for registration purposes (about four minutes scan time). The low-resolution axial baseline and follow-up scans are then registered using mutual information (57) based rigid registration scheme and the new field of view is adapted to the previous baseline scan. This registration is performed while the patient remains in the scanner and usually takes less than one minute, including the time to upload the baseline and follow-up volumes. Figure 3 visualizes the difference between prospective registered follow-up images of the proximal femur and non-registered follow-up images. As seen in Figure 4, there is a substantial difference between the slices in the calculated bone volume fraction (BV/TV) comparing baseline and follow-up scans of non-registered images which could lead to substantial errors when monitoring treatment over a longer time interval. The method was validated in five healthy subjects. The registration error found was $\sim 0.2^\circ$ for rotations and ~ 1.1 mm for translations. The coefficient of variance was within a 2–4.5 % range.

2. Cortical Bone Assessment using MRI

MR image acquisition—The advantage of using MRI for cortical bone measures is the ability to align the field of view perpendicular to the femoral neck and thus to depict its three dimensional cortical architecture more accurately (58). In contrast, HR-pQCT can image the cortical shell in much shorter scan time and isotropic voxel size (27) but is restricted to peripheral sites like the distal radius and the distal tibia as depicted in Figure 5. As previously mentioned, in conventional MRI bone appears with background signal intensity. Thus, the cortex is usually nicely distinguished from the bone marrow, which provides high signal intensity. However, the outer cortical shell yields less contrast with the surrounding dark muscle (long T1) and dark connective tissues like tendons and ligaments (short T2). Another issue for segmentation is partial volume averaging which demands high spatial resolution.

Furthermore, the chemical shift of fatty bone marrow requires relatively high readout bandwidths. Investigating the cortical thickness of 41 post-menopausal osteopenic women (age 58.6 ± 6.4 yrs) and 22 post-menopausal osteoporotic women with spine fractures (65.7 ± 9.95 yrs) Hyun et al. (59) found similar age trends but also significant changes in the cortical thickness between the two groups (Figure 5) underlying the importance of geometric measurements of the cortical bone.

More recently, Goldenstein et al. (60) looked at intracortical porosity using MRI. They compared HR-pQCT with MRI (Figure 6), which allows the visualization of soft tissues such as bone marrow and thus a quantification of the amount of cortical porosity that contains bone marrow. In this work, images of the distal radius and distal tibia of 49 post-menopausal osteopenic women (age 56 ± 3.7) were acquired at an image resolution of $156 \times 156 \times 500 \mu\text{m}^3$. After aligning the images from both modalities using a normalized mutual information registration algorithm, the authors determined the percentage, the number, and the size of each cortical pore containing marrow as seen in the MR images. While the amount of cortical porosity did not vary greatly between subjects, they found that the type of cortical pore, containing marrow versus not containing marrow, varied highly between subjects. Additionally, the number of cortical pores containing marrow did not depend on the amount of porosity and there was no relationship between cortical pore size and the presence of bone marrow. The data suggested that cortical pore spaces contain different components and that there may be more than one mechanism for the development of cortical porosity and more than one type of bone fluid present in cortical pores. It has to be noted though, that this approach only captures relatively large cortical pores, which can be visualized within the resolution limits of the modality.

Hence, another method of more recent interest is the quantification of bone water in the microscopic pores of the haversian and the lacunocanalicular systems of cortical bone containing approximately 20% water by volume. A smaller water fraction is also bound to collagen and the matrix substrate and imbedded in the crystal structure of the mineral. These micro pores are in general too small (a few micrometers) to be captured within one voxel but the quantification of bone water using MRI could potentially provide a surrogate measure of bone porosity without resolving the individual pores. Since the pore water protons possess a very short T2 ($T_2 < 500 \mu\text{sec}$), ultra short echo times (UTE) have to be employed in order to capture the decaying signal immediately after RF excitation. The hydrated state of bone is essential in conferring bone material its unique viscoelastic properties. Techawiboonwong et al. (61) implemented a UTE pulse sequence and validated bone water quantification measurements in sheep and human cadaveric specimens. They also performed a pilot study to evaluate the method's sensitivity to distinguish subjects of different age and disease state. The data were compared with areal and volumetric bone mineral density (BMD) from dual x-ray absorptiometry (DXA) and peripheral quantitative CT respectively. The bone water content was calibrated with the aid of an external reference (10% H_2O in D_2O doped with 27 mmol/L MnCl_2) which was attached anteriorly to the subject's tibial midshaft. Excellent agreement ($R^2=0.99$) was found in the specimen between the water displaced by using D_2O exchange and water measured with respect to the reference sample. *In-vivo*, the bone water content was increased 65% in the postmenopausal group compared to the premenopausal group. Issever et al. (62) further improved the spatial resolution of 3D-UTE MRI to an isotropic voxel size of $0.4 \times 0.4 \times 0.4 \text{ mm}^3$ allowing instant image reformation. Their imaging was performed on a human cadaver proximal femur (Figure 7). Bone marrow was largely removed prior to imaging. For reference purposes, two 27 mmol/L MnCl_2 doped phantoms consisting of 10% H_2O and 20% D_2O concentrations were used as shown in the figure similar to Techawiboonwong et al. (61).

Pulse Sequences: Hyun et al. (59) acquired MR images of the distal radius (Figure 8a) at 1.5 Tesla using a 3D fast gradient recalled echo (FGRE) pulse sequence featuring an in-plane resolution of $0.16 \times 0.16 \text{ mm}^2$ and 2 mm slice thickness. The same protocol was employed by Kazakia et al. (27) who measured the distal radius and the distal tibia at 3 Tesla field strength. Gomberg et al. (58) imaged the tibial cortex using a 2D fast spin-echo (FSE) sequence with a voxel size of $0.47 \times 0.47 \times 2 \text{ mm}^3$. The authors also acquire images of the proximal femur with an in-plane resolution of $0.625 \mu\text{m}$ and 2 mm slice thickness. The hip joint is a very important site for cortical bone measurements which might be responsible for intracapsular hip fractures (9). Cortical analysis of the hip is complicated by its deep location within the pelvis and the double-oblique angle between the neck and the body's orthogonal axes. Thus, the measurements by Gomberg et al. were performed on oblique slices perpendicular to the femoral axes using a 2D spoiled gradient recalled echo (2D-SPGR) pulse sequence (TR=150 ms, TE=4.8 ms). More recently, one of the authors (R. Krug) further maximized the contrast between the dark cortical bone and the relatively dark muscle signal (Figure 8b), using a 2D-FGRE sequence with long TR (TR=300 ms) and shorter TE (TE=2.29 ms). Since muscle has a relatively long T1 relaxation time of more than 1 ms (63), a very long TR is preferred to increase SNR. Although 3D pulse sequences deliver higher SNR, the advantage of a 2D pulse sequence is the possibility of multiple interleaved acquisitions allowing for much longer TR without compromising the clinically feasible scan time. For measurements of cortical porosity, Goldenstein et al. (60) chose a bSSFP sequence with parameters similar to Banerjee et al. (15) in order to maximize spatial image resolution in order to resolve the small cortical pores. For UTE MRI, both two- and three-dimensional pulse sequences with radial readout have been used in the past. Issever et al. (62) applied a 3D UTE imaging with an echo time as short as TE = 64 μs . Similar values can also be achieved with 2D UTE pulse sequences for cortical bone measurements (61,64) on clinical MR scanners.

Image analysis and post processing—Hyun et al. (59) designed a semi-automatic segmentation algorithm to segment both the endosteal and periosteal cortical boundary from their surroundings. The algorithm featured a deformable contour to conform to the strongest gradient edges in the neighborhood of the user placed model. The accuracy of the method was tested by comparing MR images $0.16 \times 0.16 \times 2 \text{ mm}^3$ at 1.5 Tesla to CT images (voxel size $0.07 \times 0.07 \times 0.8 \text{ mm}^3$) of ex vivo porcine femora specimens as depicted in Figure 9. The *in vivo* feasibility was also tested in the distal radius of a cohort of human subjects. The cortical area was calculated as the area enclosed by the concentric contours. The mean thickness was calculated as area divided by mean contour length. Using this method, Hyun et al. found very good *in vivo* reproducibility for cortical volume (CV=2.19%) and for cortical thickness (CV=1.96%). Kazakia et al. (27) used the distance transform method (65) to further improve the measurements of cortical thickness by fitting a sphere into the segmented cortical shell. They also compared thickness measurements from MR data with HR-pQCT and found significant correlations. Gomberg et al. (58) presented a semi-automatic segmentation approach where, after a rough manual outline of the cortical contour, radial profiles perpendicular to the cortex were normalized to the marrow signal and further processed by morphological operators before computing the cross-sectional area and thickness. They found a similar CV of around 2% for the reproducibility of their technique.

3. Clinical Applications

Over the past few years, the technological developments have made quantitative MRI of bone structure more clinically practical. The substantial improvement in fracture discrimination by including structural information in addition to BMD has been well established. Wehrli et al. (66) showed that topological bone parameters investigated in 79 women (29 with vertebral fracture) could much better discriminate the fracture group from the non-fracture group than BMD. Benito et al. (67) investigated the effect of testosterone replacement on trabecular

architecture in hypogonadal men in the distal tibial metaphysis of 10 severely testosterone-deficient hypogonadal men. They found dramatic topological changes in the bone suggesting that antiresorptive treatment results in improved structural integrity. Chestnut et al. (68) looked at the effect of salmon calcitonin on bone structure at the distal radius and calcaneus of 91 postmenopausal women during a period of 2 years. The treatment group showed improved trabecular structure compared to the placebo group but no significant change in BMD was detected. More recently, Wehrli et al. (69) reported on topological changes of the trabecular bone network after menopause and the protective effect of estradiol. The authors observed short-term temporal changes in trabecular architecture after menopause, and found a protective effect of estradiol maintaining the plate-like trabecular architecture. They concluded that MRI-based *in vivo* assessment of trabecular bone has great promise as a tool for monitoring osteoporosis treatment. Zhang et al. (70) tested the hypothesis that testosterone replacement in hypogonadal men would improve the mechanical properties of their bone. The results of the study suggested that 24 month of testosterone treatment of hypogonadal men improves estimated elastic moduli of tibial trabecular bone by increased trabecular plate thickness.

Most of the previous studies were done at 1.5 Tesla field strength. However, as high field (3 Tesla) and ultra high field (7 Tesla and higher) modalities become more widely available at clinical sites, there is an increasing trend to use these scanners for bone imaging. Sell et al. (71) found high correlations between trabecular bone structure measured *in vitro* at 3 Tesla using 15 femoral head specimens, compared to microcomputed tomography (μ CT), as the standard of reference. Phan et al. compared 1.5 Tesla with 3 Tesla MRI in differentiating donors with spinal fractures from those without spinal fractures. The authors concluded that MR imaging at 3 Tesla provided a better depiction of the trabecular bone structure than did MR imaging at 1.5 Tesla. Banerjee et al. (15) compared and optimized different gradient-echo pulse sequences for trabecular bone imaging *in vivo* at 1.5 Tesla and 3 Tesla field strength. They scanned eight healthy subjects at the proximal femur, calcaneus, and the distal tibia and found a significant increase in SNR at the higher field strength but also increased susceptibility induced effects between the more diamagnetic bone and the bone marrow. Krug et al. (16,25, 26) investigated the impact on bone imaging using field strengths as high as 7 Tesla. The authors imaged six healthy subjects at 3 Tesla and 7 Tesla and additionally with HR-pQCT. They found a substantial increase in SNR at 7 T and also an alteration in structural bone parameters as expected from susceptibility induced off-resonances (25).

IV. Computed Tomography Imaging

Computed tomography (CT) is a 3D x-ray imaging technique. Unlike most MRI musculoskeletal applications, CT provides positive contrast of mineralized tissues. The image formation process begins with the acquisition of serial radiographic projections over a range of angular positions around the object of interest. The cross-sectional field of view is then reconstructed using established computational techniques based on Radon projection theory. Similar to simple radiography, the reconstructed image intensity values represent the local x-ray attenuation – a material property related to the electron density. Contrast between soft and mineralized tissues in CT is high due to the relative electron-dense inorganic component (calcium hydroxyapatite) of the bone matrix (72). Quantitative calibration of x-ray attenuation to bone mineral density is accomplished by imaging reference phantoms containing objects of known hydroxyapatite concentrations.

Several classes of CT devices are presently used for high-resolution imaging of trabecular and cortical bone micro-architecture. Application of standard whole-body multi-detector CT to imaging trabecular bone in the axial and peripheral skeleton has been investigated at several research institutes (73–77). Recently a standard MDCT gantry has been combined with 2D flat panel detector technology to provide rapid continuous acquisitions at high isotropic spatial

resolution (78,79). In the last five years a high-resolution, limited field of view CT device has become commercially available for dedicated imaging of bone structure in the peripheral skeleton (high resolution peripheral QCT, HR-pQCT) (27,80–82).

1. Multi-detector computed tomography (MDCT)

MDCT is a clinical CT technique, which is available in most diagnostic imaging departments and thus a dedicated scanner is not required. The spatial resolution of this technique is limited and minimum slice thickness in clinical studies is in the order of 0.6 mm while minimum pixel sizes range around 0.25–0.3 mm. These spatial resolutions are above trabecular dimensions and imaging of individual trabeculae is subjected to significant partial volume effects; however, it has been shown that trabecular bone parameters obtained with this technique correlate with those determined in contact radiographs from histological bone sections and μ CT (83,84). In one of these studies corresponding sections of contact radiographs and MDCT images of the distal radius were analyzed and structure parameters analogous to bone histomorphometry were determined. Significant correlations between MDCT-derived structure parameters and those derived from the contact radiographs were found ($p < 0.01$) with r values of up to 0.70 (84).

The advantage of the MDCT technique is that more central regions of the skeleton such as the spine and proximal femur can be visualized; these are sites where osteoporotic fractures are found and which would be important to monitor therapy. However, in order to achieve adequate spatial resolution and image quality the required radiation exposure is substantial, which offsets the technique's applicability in clinical routine and scientific studies. High-resolution CT scanning is associated with considerably higher radiation dose compared with standard techniques for measuring bone mineral density. Compared with the 0.01 to 0.05 mSv effective dose associated with DXA in adult patients and 0.06 to 0.3 mSv delivered through 2D QCT of the lumbar spine, studies show that protocols used to examine vertebral microstructure using high-resolution MDCT provide an effective dose of about 3 mSv (1.5 years of natural background radiation) (73,75).

MDCT has been used *in vivo* to study the trabecular bone at the lumbar spine and results have been promising in differentiating subjects with and without osteoporotic spine fractures and in monitoring therapy induced changes of trabecular microarchitecture (73,75). Ito et al. demonstrated that MDCT derived trabecular bone structure parameters of the L3 vertebral body better separated patients with, and without, vertebral fractures than did BMD of the spine, obtained by DXA (73). Graeff et al. showed that teriparatide treatment effects were better monitored by architectural parameters of the spine obtained through MDCT than by BMD (75).

Using clinical imaging in more central regions of the skeleton such as spine and femur, however, it is still noted that the trabecular bone architecture visualized with MDCT is more a texture of the trabecular bone than a true visualization of the individual trabecular structure (Fig. 10).

2. High-resolution peripheral quantitative computed tomography (HR-pQCT)

A dedicated extremity imaging system designed for trabecular-scale imaging is currently available from a single manufacturer (XtremeCT, Scanco Medical AG, Brüttisellen, Switzerland). The development of HR-pQCT represents the convergence of clinical CT with many of the technological features of desktop micro-computed tomography (μ CT) used widely for basic research in specimen and small animal models of skeletal disorders (85,86). This device has the advantage of significantly higher SNR and spatial resolution compared to MDCT and MRI (nominal isotropic voxel dimension of 82 μ m). Furthermore, the radiation dose is several orders of magnitude lower compared to whole body CT, and primarily does not involve

critical, radiosensitive organs. There are also several disadvantages to this technology. Most notably it is limited to peripheral skeletal sites and therefore can provide no direct insight into bone quality in the lumbar spine or proximal femur – common sites for osteoporotic fragility fractures, which are associated with the most significant financial and quality of life burden for patients. Additionally, there are presently a limited number of devices installed across the world and they are primarily located at major research institutions.

Image acquisition

Hardware: The HR-pQCT imaging system consists of a microfocus x-ray source with a 70 μm focal spot size. The scanner operates at a fixed voltage of 60 kVp and current of 900 μA . Filters of 0.3 mm Cu and 1 mm Al are positioned at the aperture to filter soft x-rays in order to reduce patient dose and limit beam hardening effects. The cone beam x-ray field is incident upon a structured CsI (40 mg/cm²) scintillator coupled by a fiber optic taper to a 2D 3072 $\times$ 256 element CCD detector with a 41 μm pitch. The x-ray source and detector ensemble interface a high-resolution motorized gantry that allows translation along the z-axis of the scanner and axial rotation across 180-degrees for tomographic acquisitions. The readout electronics of the detector interface a computer workstation and associated data storage resources through a SCSI connection.

Scan setup: A standard, manufacturer recommended scan protocol has been used in the majority of the published literature to date. The techniques involved were primarily adapted from a previous generation pQCT device (87). The subject's forearm or ankle is immobilized in a carbon fiber cast that is fixed within the gantry of the scanner. A single dorsal-palmar projection image of the distal radius or tibia is acquired to define the tomographic scan region. This region spans 9.02 mm in length (110 slices) and is localized to a fixed offset proximal from the mid-jointline and extending proximally. In the radius the offset is 9.5 mm while in the tibia it is 22.5 mm (Figure 11). It is important to note that this method does not account for differences in bone length and therefore may be a confounding source of variability in cross-sectional studies (88). In the radius, the default axial scan location has been found to partially overlap with the most common site for fracture and region of the most significant biomechanical consequence (89).

There are several different protocol modifications that have been employed for developmental studies in children and adolescents to account for patient size and designed to avoid radiation exposure to the epiphyseal growth plate. In a cross-sectional study of age and gender related differences in the micro-structure of the distal forearm of adolescent boys and girls Kirmani *et al.* used a fixed offset (1 mm) with respect to the proximal extent of the distal epiphyseal growth plate of the radius (90). This ensured no direct irradiation of the growth plate and is consistent with the most common site of forearm fractures during adolescence (91). In a similar population participating in a longitudinal study of bone development, Burrows *et al.* selected a region offset 8% of the total tibial length proximal to the tibial plafond. In their cohort this approach resulted in no overlap with the growth plate, allowed comparable localization for longitudinal measurements during growth, and did not require operator identification of the proximal extent of the growth plate – which can be highly variable and is therefore a potential source of operator-related error (92). While there are a number of studies underway investigating other scan locations in adults – including more proximal sites dominated by cortical bone – hardware constraints for this device preclude imaging true diaphyseal sites in the radius or tibia.

Tomography: Prior to each tomographic acquisition, a pre-calibration procedure is performed to measure the dark bias signal in the detector (x-ray shutter closed) and the reference intensity of the x-ray source with an empty field of view (x-ray shutter open). For the actual tomographic

acquisition, 750 projections are acquired over 180 degrees with a 100 ms integration time at each angular position. The 12.6 cm field of view (FOV) is reconstructed across a 1536×1536 matrix using a modified Feldkamp algorithm, yielding $82 \mu\text{m}$ isotropic voxels (Figure 12) (93). The total scan time is 2.8 minutes and results in an effective dose to the subject of approximately $4.2 \mu\text{Sv}$ – several orders of magnitude smaller than clinical CT and comparable to DXA and other planar radiographic modalities. In total, the raw projection data, reconstructed image data, and other derivative data require approximately 1GB (1,024 MB) of digital storage space per scan.

Image analysis and post processing—The reconstructed images are analyzed using a standard protocol provided by the manufacturer. The operator initiates the segmentation process by drawing an approximate contour around the periosteal perimeter of the radius or tibia in the first slice of the dataset. This contour is then automatically adjusted using an edge detection process to precisely identify the periosteal boundary. The software iteratively proceeds through the remaining slices in the dataset while the operator visually verifies the accurate contouring of the periosteal surface, adjusting where necessary. The cortical bone compartment is segmented using a 3D Gaussian smoothing filter followed by a simple fixed threshold. The trabecular compartment is identified by digital subtraction of the cortical bone from the region enclosed by the periosteal contours. The trabecular bone structure is extracted using a laplace-hamming edge enhancement process followed by a second fixed threshold (94). Based on this semi-automated contouring and segmentation process, the trabecular and cortical compartments are segmented automatically for subsequent densitometric, morphometric, and biomechanical analyses. For some scenarios, this segmentation procedure may be unsatisfactory (27,95), and more sophisticated techniques are an active area of research (96,97). In general reproducibility of densitometric measures is very high ($\text{CV} < 1\%$), while biomechanical and morphometric measures typically have a coefficient of variation of 4–5% (27,80,81,98,99).

Densitometric Analysis: The linear attenuation values of the tomographic images are converted to hydroxyapatite (HA) mineral densities using a beam-hardening correction and phantom calibration procedure previously described for an *ex vivo* micro-tomography system (100). The calibration phantom (Scanco Medical AG, Brüttisellen, Switzerland) is composed of 5 cylinders of HA-resin mixtures with a range of mineral concentrations (0, 100, 200, 400, 800 mg HA/cm^3) where 0 mg HA/cm^3 represents a soft tissue equivalent background devoid of mineral. Based on this calibration volumetric BMD can be determined independently for cortical and trabecular bone compartments based on the segmentation process described above. HR-pQCT images have also been used to derive surrogate measures of areal BMD in the ultra-distal radius (101). This technique has shown a high level of agreement with multiple clinical DXA devices ($R^2 > 0.8$).

Morphometric Analysis: Morphometric indices analogous to classical histomorphometry are calculated from the binary image of the trabecular bone. Unlike MRI and MDCT, which have a large slice thickness relative to the in-plane resolution, the high isotropic resolution of HR-pQCT ($82 \mu\text{m}$) permits direct, 3D assessment of inter-trabecular distances. These measures have been well validated against μCT gold standards in a number of studies (82,97,102). From the binary image of the extracted trabecular structure, 3D distance transformation techniques are used to calculate trabecular number (Figure 13) (103). While the inter-trabecular distances are large compared to the voxel dimension, the average trabecular thickness ($100\text{--}150 \mu\text{m}$) is on average only 1–2 voxels wide. Accordingly, direct measures of thickness and bone volume are complicated by significant partial volume effects. In the standard analysis protocol bone volume fraction (BV/TV) is derived from the trabecular volumetric BMD assuming a fixed mineralization of 1200 mg HA/cm^3 for compact bone ($\text{BV/TV} = \text{Tb.vBMD}/1200$). From the

direct measure of Tb.N and the densitometrically-derived BV/TV, trabecular thickness and separation (Tb.Th, Tb.Sp) are derived using standard stereological relations assuming a plate-model geometry (87,104).

There are several potential concerns with this approach. First, phantom studies by Sekhon *et al.* have documented significant errors in the measurement of trabecular vBMD related to biologically relevant variations in cortical thickness, as well as the magnitude of trabecular vBMD itself (105). This is most likely related to x-ray scatter effects – the HR-pQCT does not have a collimated detector to block Compton scattered x-rays – and residual beam-hardening artifacts. These errors are primarily a concern for cross-sectional studies when cortical thickness and trabecular vBMD may span a broad range. It is less of a concern, and indeed may not be significant, in longitudinal studies where %-change is the primary endpoint as age, pathology, and therapy-related changes in cortical thickness and trabecular vBMD are comparatively small. Second, the assumption of a fixed matrix mineralization is not consistent with the established action of many common anti-fracture therapeutic agents (106). Changes in bone tissue mineral density would be expected to cause an increase in vBMD irrespective of bone volume changes and therefore result in an overestimation of BV/TV and propagate error to the derivative measures of trabecular thickness and separation, confounding any actual therapy-related effect on trabecular bone volume and structure.

Several studies have investigated other measures of bone micro-architecture and topology from HR-pQCT images including connectivity, structure model index (a measure of the rod or plate-like appearance of the structure), and anisotropy. However there is mixed evidence of their reliability at in vivo resolutions (82,97,102,107). Recently, more sophisticated approaches to cortical bone segmentation have been proposed (96), which allow direct 3D assessment of cortical thickness (Ct.Th) as well as quantification of cortical micro-architecture, including intra-cortical porosity (Figure 14) (108,109).

Biomechanical Analysis: While volumetric density and micro-architectural information provide improved fracture risk prediction and some explanation for treatment efficacy, more direct estimates of bone mechanical strength inherently accounting for geometry, micro-architecture, and even composition are the ultimate goal for improving fracture risk prediction and management of osteoporosis. To that end computational modeling approaches have been introduced to take advantage of the detailed information in high-resolution images of bone. Finite element analysis (FEA) is a common computational tool in classical engineering fields critical to design and failure analysis. The basic concept is that the behavior of a complicated system under a simulated loading condition – in this case the biomechanical properties of bone – can be determined through subdivision into smaller constitutive elements for which the behavior is trivial to determine. Applied to high-resolution images of bone, the apparent biomechanical properties (e.g. stiffness, elastic modulus) of a biologically complex microstructure are computed by decomposing the structure into small cubic elements (i.e. the voxels) with assumed mechanical properties (Figure 15) (110,111). For HR-pQCT this technique has been validated against both higher resolution models (μ CT) as well as empirical measures of strength (102,112). In addition to whole bone mechanics, μ FEA can be used to determine the relative load distribution between cortical and trabecular compartments (113), and estimate mechanical implications of specific structural features such as intra-cortical porosity (108).

Longitudinal Analysis: For clinical investigations into longitudinal changes in HR-pQCT derived measures of bone quality several important considerations must be addressed. First, because bone structure and geometry can change substantially along the axial direction (88) it is critical that baseline and followup scans be matched. To this end the scout scan and reference line position for all baseline measurements are recorded automatically. When a followup

measurement is performed, the operator is automatically presented with an image of the baseline scout denoted with the original reference position as a visual aid for positioning the reference line for the followup acquisition. Nevertheless this is a subjective process subject to operator error. At our imaging center, repeat measurements are typically associated with a margin of error in the axial positioning of approximately 1mm. Accordingly automated methods are needed to ensure comparable regions of interest are used for the image analysis. To that end the manufacturer provides software that automatically matches slices based on periosteal cross-sectional area and limits the analyzed region to the slices common to both baseline and followup (87). Alternatively, MacNeil *et al.* have demonstrated that 3D image registration techniques can provide improved short and medium-term reproducibility compared to the default slice-matching approach (98). This approach may also be more appropriate in longitudinal studies where changes in cortical thickness would compromise registration based strictly on cross-sectional area. As discussed earlier, meaningful longitudinal comparisons in children or adolescents experiencing rapid growth is not trivial, and requires more careful consideration of standardization of scan positioning and analysis protocols (92).

3. Clinical Applications

There is a growing body of clinical research literature featuring HR-pQCT assessment of bone quality. The first cross-sectional studies by Boutroy *et al.* and Khosla *et al.* demonstrated significant, gender specific age-related differences in bone micro-architecture (80,81) while Dalzell *et al.* and Burghardt *et al.* have reported analogous findings for μ FEA biomechanical measures (108,114). A micro-structural basis for ethnicity-related differences in bone strength between East Asian and Caucasian women has been reported in two recent studies (115,116) Sornay-Rendu *et al.* demonstrated cortical and trabecular morphology provided some additional fracture discrimination independent of aBMD in osteopenic women (117). In the same OFELY cohort, Boutroy *et al.* later showed that μ FEA mechanical measures provided additional discriminatory power between osteopenic women with and without distal radius fractures (118). While the initial focus has predominantly been investigations of post-menopausal osteopenia and osteoporosis, a number of more recent studies have utilized HR-pQCT to investigate developmental changes in bone quality and fracture risk (90,119,120) as well as secondary causes of bone loss (121,122). While there are a number of single and multicenter longitudinal studies currently underway or recently completed, few results have yet to be published at the time of the preparation of this manuscript (123).

V. Conclusion

The field of high-resolution bone imaging has made tremendous progress in the recent past. Both imaging modalities, computed tomography as well as MR imaging, have improved image quality. New developments such as HR-pQCT now make it possible to acquire *in vivo* images at peripheral sites with isotropic voxel size in a very short time. Further enhancements in the MR field have made it possible to image more central body sites such as the proximal femur with very high spatial resolution. New analysis methods can obtain direct estimates of biomechanical properties and important information related to bone's topology, as well as parameters of scale and orientation. These accomplishments will be essential in the non-invasive assessment of osteoporosis and fracture risk. They also provide insight into the mechanisms behind bone loss and will increasingly play a role as a tool for assessing treatment efficacy.

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Figure 1.

In vivo MR image of the proximal femur acquired in 12 minutes using a bSSFP pulse sequence along with an eight-channel phased array RF coil. The images have a spatial resolution of $234 \times 234 \times 500 \mu\text{m}^3$.

Figure 2.

Shown is a high-resolution MR image of the calcaneus acquired at 3 Tesla and a selected region of interest. The left side of the zoomed region is the original ROI and the right part is the color-coded map that illustrates the different assignments of bone voxel to their closest junction based on minimum geodesic distances. (Image courtesy: Dr. Julio Carballido-Gamio).

Figure 3. Comparison of follow-up MR scans with image registration versus follow-up scans without image registration. The difference image is a subtraction of baseline and follow-up and the surface difference image is a 3D rendering of registered and non-registered proximal femur surfaces (green= baseline, red= follow-up) (Image courtesy: Dr. Janet Goldenstein).

Figure 4.

Change in Bone Volume Fraction (BVF), slice by slice moving from anterior to posterior. The difference between the red line, the BVF without image registration and the green line, the BVF with image registration represents the error removed due to an aligned VOI (Image courtesy: Dr. Janet Goldenstein)

Figure 5.

Mean cortical thickness is depicted for each subject in two populations. The regression lines for the osteoporotic and osteopenic populations show a similar age trend. The osteoporotic subjects have significantly decreased cortical thickness.

Figure 6.

Left: MR image of the distal tibia acquired at 3 Tesla. The thin cortical bone shell with some marrow infiltration can be appreciated from this image.

Right: The same subject scanned by HR-pQCT. Due to the smaller voxel size, the porosity within the cortical bone is more pronounced. (Image courtesy: Dr. Galateia Kazakia)

Figure 7. 3D UTE images of a human femoral shaft are depicted in axial (a), sagittal (b), and coronal (c) plane with isotropic voxel size ($0.4 \times 0.4 \times 0.4 \text{ mm}^3$). The green cross locates the reconstructed slice position in each of the three planes. The white arrow indicates the cortical bone, residual bone marrow is marked with a black star. (Issever et al. (62)).

Figure 8.

- a) MR *in vivo* images of the distal radius acquired by Hyun et al. with a 3D FGRE pulse sequence at 1.5 Tesla (left).
- b) Double-oblique MR image (right) of the femoral neck acquired by R. Krug at 3 Tesla using a 2D FGRE pulse sequence.

Figure 9.

a) CT images: Cortical bone was segmented using a threshold set at the midpoint between the peaks representing the high intensity bone and low intensity soft tissue.

b) MR images: Inner and outer cortical boundary contours were generated with a semi-automatic segmentation program using a deformable contour and then adjusted by a trained operator.

c) Scatter plot of cortical volume for each specimen for a 16 mm long section centered on the minimum cross sectional area. A good agreement between CT and MR derived measures was found ($R^2 = 0.96$).

Figure 10.

MDCT of the proximal femur obtained using 120 kVp, automatic current modulation between 70 and 500 mA, noise index of 50, 0.625 mm slice thickness and reconstructed at 1.25 mm. A standard bone kernel algorithm was used to reconstruct the axial images. Note osteoporotic right intertrochanteric fracture. The left proximal femur was used for trabecular bone structure analysis, however, note that given significant noise in this section the resulting image shows more of a texture instead of individual bone trabeculae.

Figure 11. Scout acquisition used to define the HR-pQCT scan region for the distal radius (A) and distal tibia (B). The solid green region corresponds to the imaging location and consists of 110 slices spanning 9.02mm longitudinally. In the radius the scan region is fixed 9.5mm proximal from the mid-jointline, while in the tibia the scan region is 22.5mm proximal from the tibial plafond.

Figure 12.

Typical HR-pQCT images from the distal radius (A–C) and distal tibia (D–F). Images A and D correspond to the distal most slices of the scan, while images B and E correspond to the proximal most slices. Images C and F are 3D reconstructions of the extracted mineralized structure with the segmented cortical compartment highlighted in dark gray.

Figure 13. Three dimensional visualization in the distal radius (A) and distal tibia (B) with the color range indicating the magnitude of local inter-trabecular distances calculated using a 3D distance transform. The mean value of this distance map is equivalent to the inverse of trabecular number (Tb.N)

Figure 14.

Three-dimensional visualization from quantitative analyses of cortical bone geometry and micro-architecture in the distal radius (A) and distal tibia (B) showing direct 3D measures of cortical thickness (top) and the segmentation of intra-cortical pore volume (bottom)

Figure 15.

Three-dimensional visualization from μ FEA simulation of 1% axial compression in the distal tibia with (A) and without intra-cortical porosity. The pseudo-color renderings show the distribution of strain energy density (SED) in each model.