Mini-review

Imaging bone structure and osteoporosis using MRI

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Summary

In addition to Bone Mineral Density (BMD), bone quality plays an important role in defining bone strength. Trabecular bone quality can potentially be defined by several factors, for example trabecular micro-architecture, matrix composition of trabeculae and trabecular bone damage repar. Considerable effort is being expended in developing techniques to assess trabecular bone micro-architecture non-invasively. Site-specific bone structural information would significantly contribute to understanding the results of different therapeutic interventions, and potentially assist in optimizing the course of treatment. Three dimensional techniques that reveal trabecular bone structure are emerging as important contenders for defining bone quality, at least partially. Techniques such as micro-computed tomography have recently been developed and provide high resolution images of the trabecular architecture. A more recent development in the assessment of trabecular bone structure is the use of magnetic resonance imaging techniques that make it possible to obtain non-invasive bone biopsies at multiple anatomic sites. Cortical and trabecular bone have a low water content and short T2 and are not detectable using routine MR imaging methods. However, the narrow surrounding the trabecular bone network, if imaged at high resolution, reveals the trabecular network. Using such images, multiple image processing and image analysis algorithms have been developed. The goal of all of these is to quantify the trabecular bone structure in 2 or 3 dimensions. The measures that have been derived so far are many, some of them synonymous with the histomorphometric measures such as trabecular bone volume fraction (BV/TV), trabecular thickness (TbTh), trabecular spacing (TbSp), trabecular number (TbN), others include connectivity or Euler number, fractal dimension, tubularrity, maximal entropy, etc. A number of calibration and validation studies (in vitro and in vivo) have been undertaken in which MR-derived measures of structure are compared with measures derived from other modalities, such as histology, micro-CT, BMD, and with biomechanics. With recent advances in phased array coils and higher strength magnets, the potential of MR imaging of bone structure is ever increasing. At the present time, the skeletal sites most commonly imaged are the radius and calcaneus. Studies currently underway are exploring the possibility of obtaining micro-architectural features of trabecular bone and the understanding whether bone turnover and micro-architecture are related, and the underlying relationship between turnover, bone mineral density and architecture, is the first step towards untraveling the therapeutic efficacy of different treatment regimens.

KEY WORDS: trabecular microarchitecture, magnetic resonance, non-invasively.

Introduction

Osteoporosis is a metabolic disorder that results in a decrease in bone mineral density and in alteration in the trabecular architectural structure. Osteoporotic bone has decreased mechanical strength making it prone to fracture, especially atraumatic vertebral fractures and fall-related hip and radius fractures. Osteoporosis is clinically diagnosed using measurement of bone mineral density. Bone mineral density is usually measured using x-ray or ultrasound imaging techniques. In x-ray imaging (such as dual energy x-ray absorptiometry, DEXA, and quantitative computer tomography, QCT) the image intensity relates to the tissue mineral density. In ultrasound, image intensity reflects the change in frequency and amplitude of the sound wave traveling through the tissue. X-ray techniques use ionizing radiation, which can have deleterious effects in sufficient doses. Ultrasound, though harmless, provides only a small field of view, which may limit the accuracy of the measurement. In addition to bone density, the quality of bone which includes bone micro-architecture is of interest. Recent advances in micro-computed tomography, a x-ray based 3D technique has made it possible to obtain images of trabecular bone micro-architecture. Another promising imaging modality for measurement of trabecular architecture is magnetic resonance imaging (MRI). MRI does not use ionizing radiation and can provide three dimensional images of the bone structure. Figure 1 illustrates different imaging modalities, such as radiographs, DXA, and MRI, used to obtain images of the calcaneus and the proximal femur.

MRI basics

Nuclei with an odd number of protons and neutrons (such as hydrogen) have a magnetic moment causing the nucleus to act like a small magnet in the presence of an external magnetic field. The magnetic field of the nucleus aligns in the direction of the external magnetic field. Magnetic resonance imaging uses radio frequency (RF) pulses in a magnetic field in order to alter the spin of protons in the tissue. Coils detect the change in net magnetization, which after mathematical reconstruction pro-
vides spatial and compositional information of the tissue being imaged. Because clinical MRI usually detects magnetic nuclei hydrogen, compositional information is limited to molecules containing hydrogen, such as water, body fat, and cholesterol. In an MRI scanner, proton spins in the body align in the direction of the external magnetic field. When an RF pulse is applied, the proton spins change, altering the magnetization. The time it takes for the protons to align with the external magnetic field is the spin-lattice relaxation time (T1). A measure of energy transfer to the surroundings (lattice) as the proton recovers its alignment with the external magnetic field. When an RF pulse is applied, the spins are excited to create the echo. The echo time (TE) is the time between the original RF pulse and the peak echo signal. The type of sequence affects the appearance of the trabecular structure. In both spin-echo and gradient-echo sequences, the dimensions of sequence affects the appearance of the trabecular structure. In both spin and gradient echo sequences, the magnetic field is re-sults in shorter T2* relaxation times due to more bone-marrow spaces, and the field strength. In general a denser network results in shorter T2* relaxation times due to more bone-marrow interfaces and increased inhomogeneities (2-6).

The sequence and timing of RF pulses determines the image contrast. Common sequences in bone imaging include the spin-echo and gradient-echo sequences. An “echo” reverses the spin, which refocuses the magnetization and in effect cancels out external magnetic field inhomogeneities, which is intrinsic in the magnet of the scanner. In a spin-echo sequence a 90° pulse is followed by a 180° RF pulse, which produces the echo. In gradient echo sequences, the magnetic field is reversed to create the echo. The echo time is the time between the original RF pulse and the peak echo signal. The type of sequence affects the appearance of the trabecular structure. In both spin and gradient echo sequences, the magnetic field is reversed to create the echo. The echo time is the time between the original RF pulse and the peak echo signal. The type of sequence affects the appearance of the trabecular structure. In both spin and gradient echo sequences, the magnetic field is reversed to create the echo. The echo time is the time between the original RF pulse and the peak echo signal. The type of sequence affects the appearance of the trabecular structure. In both spin and gradient echo sequences, the dimensions of trabeculae may be amplified due to differences in magnetic susceptibility (the amount which a material becomes magnetized in a magnetic field) between the marrow and bone. The amount of distortion artifact is dependent on TE with longer TEs resulting in more distortion. In addition, gradient-echo sequences produce more susceptibility artifacts than spin-echo sequences (3, 9). Representative images of the distal radius are shown in Figure 3. Spin-echo sequences, however, require a considerably longer scan time and require in-vitro samples or smaller fields of view (such as the finger and wrist) because of signal-to-noise and total imaging time considerations (8). Therefore, in vivo imaging of trabecular bone typically is performed using gradient-echo sequences with TEs as short as possible. Alternatively a fast large angle spin echo (FLASE) sequence can be used which uses an initial RF pulse greater than 90°. The following 180° pulse then partially restores the longitudinal magnetization and reduces the time to repeat (TR), making the spin-echo faster (10).

The typical maximum resolution of a 1.5T scanner is 78-200
μm in-plane and 400-1000 μm out-of-plane (slice thickness) (11). Trabeculae are the same dimensions as the in-plane resolution, resulting in partial volume effects, in which the depiction of a trabecula in the image is a projection or average of multiple trabeculae. As a result the trabecular measures obtained from MRI are different than those obtained from histomorphometry or microCT at higher resolutions (20 μm).

The magnetic field strength of the scanner affects the resolution and acquisition time of the scan. A 1.5T magnet is the standard scanner used clinically and can provide a maximum resolution of approximately 150x150x250 μm (12). With high-resolution MRI requiring a stronger magnetic field strength (7-9.4 T) and a small-bore (limited to in vitro scans), resolutions can be improved to 50x50x100 μm (B). Nuclear magnetic resonance imaging has even a smaller field of view (2-12 mm) but can obtain isotropic resolutions as high as 10 μm. NMR imaging can additionally determine chemical shift making it possible to establish distribution of a given chemical (13). Generally, higher magnetic field strength improves signal-to-noise ratio, scan time, and image quality, but often with limited field of view and other factors such as tissue susceptibility to consider (14).

Image processing techniques

After obtaining an MR image, pre-processing of the image is usually required in order to improve the signal-to-noise ratio and image quality and make it possible to differentiate marrow from bone trabeculae. Pre-processing may include coil correction, noise reduction, motion correction, and thresholding. Coil correction is required to correct spatial variations in the sensitivity of the detection coil as tissue close to the coil usually appears brighter than tissue further away from the coil. Coil correction algorithms depend on the structure of the specific coil. Coils that completely surround the object being scanned (e.g. bird-cage coil) provide sufficient in-plane homogeneity, making longitudinal correction sufficient. In surface coils, which may not provide in-plane homogeneity, a low-pass filter (LPF) based coil correction scheme is necessary (15, 16) (Figure 4).

Noise reduction improves the signal-to-noise ratio and may be accomplished using a median low pass filter, in which the median of the pixels in a certain kernel size (e.g. 3x3 pixels) surrounding a pixel becomes the new filtered value for the pixel (11). A low pass filter removes high signal noise, while preserving the low signal data. The kernel median allows edge detection, whereas the kernel mean would smooth the data and blur the edges. Hwang et al. proposed a histogram deconvolution method in order to obtain a noiseless histogram for trabecular bone (17). In this method a probability distribution of the noise (e.g. Gaussian) and an initial estimate of the noiseless histogram are assumed in order to predict a histogram. The predicted histogram is iteratively im-

Proven by comparing it to the measured histogram. The noiseless histogram and raw image are used to produce a noiseless image. Others have proposed wavelet-based thresholding that allows more local noise reduction while retaining relevant detail information (18-20).

Imaging trabeculae on the order of 100 μm means that a small amount of motion will affect the image. Various techniques have been devised to correct for motion artifacts. Navigator correction alters the echo sequence, adding echoes to sense small displacements (21). The data is acquired in k-space by analyzing the phase shift and adjusting for translational motions. Studies have shown that navigator correction improves reproducibility and accuracy of trabecular bone parameters (22). Retrospective motion correction can also be performed with pulse-occuring (23, 24) (Figure 5). This technique applies new phase shifts to the data and compares the resulting image with the original. An entropy focusing criterion is applied to minimize the amount of entropy in the image and obtain maximum contrast.

Perhaps the most critical pre-processing step is thresholding, which allows delineation of the trabeculae and the marrow. Because the resolution of in vivo MR images is on the same scale as the trabecular width, partial volume effects occur. In partial voluming, a single voxel may contain signals from multiple tissue types. The voxel intensity is the average signal from the various tissues. The histogram of trabecular bone, therefore, is not bi-modal with marrow and bone peaks, but rather mono-
modal with a peak intensity between the values of marrow and bone. Various thresholding methods have been established in order to segment the bone from the marrow where partial volume effects are an issue. Majumdar et al. proposed a dual thresholding method in which the threshold for bone was a mean pixel value taken in the cortical shell and the threshold for marrow was the lower signal intensity at which the histogram reached half its peak (11). Link et al. compared global and local thresholding methods (25). Global thresholding applies the same threshold throughout the entire image. The disadvantage of global thresholding is that images of with a dense trabecular structure appear completely black, while images with a sparse trabecular structure appear white. Using local thresholding the intensity of a square region surrounding a pixel is averaged. If the central pixel has an intensity lower than the average, it is considered bone; higher than average pixels are considered marrow. Local thresholding is not affected by bone density, but is dependent on noise in the image. It was found that global thresholding was more accurate in calculating trabecular thickness and local thresholding was more accurate in predicting trabecular spacing.

Wu et al. introduced a Bayesian approach to segment bone from marrow in which each voxel was divided into subvoxels (26). The local tissue environment influenced the distribution of bone and marrow within the subvoxels with a Gibbs distribution modeling the interaction between subvoxels. This approach improves segmentation but has only been performed on images from small-bore NMR microscopes and has yet to be applied to clinical scans. Hwang et al. proposed a spatial auto-correlation analysis which also used the local tissue environment to determine the probability of finding bone at specific locations (27). This method was used to analyze images at in vivo resolution (voxel size of 156x156x391 µm³). Similarly, a relaxation labeling process that takes into account the spatial context, in particular local contextual information (as in Markov fields) was used by Antoniadis et al. to segment trabecular bone (28). Each pixel was assigned a probability of being bone or marrow and then iteratively updated according to the local and surrounding segments until the probability of each pixel was either 0 or 1. This allowed using one of these techniques results in a binarized image that consists of only bone or marrow voxels.

Post-processing: architectural parameters

Bone mineral density and trabecular structure together determine the mechanical strength of trabecular bone. The main objective of imaging trabecular bone structure is to determine morphological parameters of the trabecular architecture. These morphologic parameters may help to determine the efficacy of therapeutic treatments for osteoporosis and predict individuals at risk for bone fracture. Standard histomorphometric measures of bone structure include: bone volume fraction (BV/TV), trabecular thickness (Tb.Th), mean intercept length, trabecular number (Tb.N), and trabecular spacing (Tb.Sp). These parameters have been adapted to analyze MR images of trabecular structure.

Because the resolution of in vivo MR images is on the same scale as trabecular dimensions, these histomorphometric parameters are the measures of the trabeculae projected across the slice thickness. Majumdar et al. introduced “apparent” measures, indicating that the morphometric measures obtained from in vivo MR images may not be exactly equivalent, howevcer are related to those obtained from higher resolution modalities (11). It was found that trabecular spacing and trabecular number are relatively independent of resolution (29). Trabecular thickness, however, was strongly dependent on resolution with lower resolutions resulting in thicker trabeculae. A 3 dimensional distance technique was introduced by Hildebrand and Rüegsegger to determine mean thickness by fitting spheres within the structure (30). This measure was able to distinguish between trabecular bone composed of a greater percentage of plates or rods (30). It has also been used calculate histomorphometric parameters such as app.Tb.Th and app.Tb.Sp from MR images (14, 31). The morphological parameters calculated using the distance technique correlated well with those calculated using the mean intercept length (14).

Because osteoporosis is thought to result in a thinning of trabeculae and loss of trabecular connectivity, measures of connectivity are important in determining osteoporotic bone quality. Connectivity measures have been established to measure the degree of connectivity of the trabecular network in trabecular bone (32, 33). Connectivity indicates the maximum number of branches that can be broken before the structure is separated into two parts. It is a topological invariant, which means it does not change if the structure is stretched, bent, twisted or otherwise rubber-like deformation. Connectivity can be calculated in terms of the Euler characteristic. Previous studies have used the Euler number to analyze MR images of trabecular bone and found that connectivity can vary between regions within a bone (34) and is significantly correlated with bone density and bone volume fraction (9, 35, 36).

Fractal dimensions are a measure of the self-similarity of a structure over different scales and have also been used to characterize trabecular architecture. Fractal dimension (D) can be determined using a box-counting technique in which a grid of boxes is superimposed on the trabecular structure (37-39). The number of boxes (N) that contain trabeculae is determined for various sizes (ε) of grids. Others have used analysis based on Brownian motion to estimate the Hurst exponent (H), which indicates if the structure is random or contains patterns, and derived the fractal dimension from H (40). Studies found that fractal dimension decreased with age (11, 37), was significantly lower in patients with vertebral compression fracture (37) and hip fracture, (41, 42) and was not correlated with bone mineral density (41, 43). Interestingly it was found that fractal dimension was not different between those with osteopenia and osteoporosis, but was nonetheless an independent predictor of bone failure strength (43). It has been proposed that a decrease in fractal dimension is related to a disorganization of trabecular architecture and loss of connectivity (40).

Pothuaud et al. proposed further classification of the trabecular architecture using a skeleton graph of the trabecular network (44, 45). The skeleton graph preserved topographical equivalence with the original network, meaning the connectivity did not change as the trabeculae were thinned to 1 pixel width. This method provides further insight into the influence of connectivity on overall trabecular structure. Others went on to classify the connectivity in terms of curves, surfaces, and junctions of the two (46, 47). They found that parameters from this digital topological analysis correlated well with bone volume fraction and measures of mechanical integrity, such as Young's modulus.

Trabecular bone structure is anisotropic, and architectural measures may, therefore, differ depending on the orientation. Spatial autocorrelation analysis (48, 49) is a method to quantify not only the distance between trabeculae, but also how this varies with respect to orientation (i.e. the amount of anisotropy). The autocorrelation function (ACF) is a measure of the probability of finding bone n pixels away from a certain pixel and is equal to the product of the bone volume fractions for
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the two pixels. Parameters derived from the ACF provide measures of the structure’s alignment perpendicular to the slice plane (tubularity) and distribution within the slice plane (transverse contiguity). One advantage of autocorrelation analysis is that it does not depend on thresholding or binarizing the images into bone and marrow. It was found that ACF measures of anisotropy correlate well with Young’s modulus and are different for normal and osteoporotic trabecular bone (27, 48). The scaling index method (SIM) has also been used to measure non-linear structural information from non-binarized trabecular bone images (50). The scaling index ($\alpha$) is a measure of the isotropy of the structure with larger values of $\alpha$ indicating a more random structure. The scaling index correlated better with mechanical strength and BMD than traditional histomorphometric measures.

Comparison with other imaging modalities

Several studies have explored how MR images compare with other imaging modalities in determining structural parameters (Table I). Hipp et al. and Hopper et al. used small-bore MRI with resolutions of $92x92x92 \mu m^3$ and $23x23x39 \mu m^3$ respectively (51, 52). All other studies were performed on 1.5 or 3T scanners with in-plane resolution of 100-150 mm and a slice thickness of 300 $\mu m$ on in vivo bone cubes. Weber et al. compared MR in vivo and in vitro trabecular bone images from mice with histological sections (53). They found parameters derived from in vivo images correlated better with histological parameters than did in vitro images and attributed the difference to the better MR signal from bone marrow than femoral. These studies indicate that MR derived architectural parameters correlate well with measures taken at much higher resolutions. In general, MR tended to overestimate BV/TV and Tb.Th and underestimate Tb.Sp due to partial volume effects.

Architectural parameters have also been compared to bone mineral density (BMD) and mechanical strength in the radius, lumbar vertebrae (54), femur (55), calcaneus (56) and other cross sights (30). In these studies, correlations coefficients for BV/TV, Tb.Th, and Tb.N with BMD or mechanical strength were between 0.5 and 0.8. All studies found that Tb.Sp had a correlation coefficient with BMD or mechanical strength of -0.5 to -0.6, indicating that the spacing between the trabeculae increases as BMD and mechanical strength decrease. Studies also found that combining BMD and trabecular structural parameters improved correlations with mechanical strength.

In vivo imaging in humans

DXA is the gold standard for diagnosing osteoporotic bone, however only provides an areal measure of bone mineral density. Multi-slice CT can be used for volumetric bone mineral density and structural measurements. Though MR cannot provide measures of BMD, it can provide trabecular bone structural measures and does not require radiation. Trabecular bone structure also varies considerably depending on the skeletal site, as well as within a given skeletal site (Figure 6). Studies have examined the trabecular structure in the calcaneus of normal and osteoporotic women and found that structural parameters (especially BV/TV, Tb.Sp, Tb.N, and connectivity measures) were significantly different between normals and osteoporotic trabecular bone (41, 57, 58). The same was found to be true in the calcaneus of normal and osteoporotic men (59) and in the radius of premenopausal, postmenopausal normal and postmenopausal patients with hip fractures (11). Tb.Sp demonstrated that largest change with age, increasing significantly in postmenopausal women with hip fractures. Banito et al. detected bone loss in hypogonadal men using MR (60). They found that the ratio of plates to rod surface voxels to curve voxels in their analysis and bone volume fraction decreased in hypogonadal men. Correspondingly, the erosion index, a combination of topological parameters that increases as bone architecture deteriorates, was higher in men with hypogonadism.

MR has been used to measure structural bone changes in steroid induced osteoporosis in patients after renal and cardiac transplantation (61). Structural parameters were significantly lower (except for Tb.Sp, which was higher) after cardiac transplantation

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Bone Type</th>
<th>BV/TV</th>
<th>Tb.Sp</th>
<th>Tb.N</th>
<th>Tb.Th</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray tomographic microscopy (18 $\mu m$)</td>
<td>Distal radius</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>0.87</td>
<td>77</td>
</tr>
<tr>
<td>Optical images (23 $\mu m$)</td>
<td>Bovine (various)</td>
<td>0.9</td>
<td>0.85</td>
<td>0.73</td>
<td>–</td>
<td>51</td>
</tr>
<tr>
<td>Optical images (20 $\mu m$)</td>
<td>Calcaneus, femur</td>
<td>0.69</td>
<td>0.89</td>
<td>0.78</td>
<td>n.s.</td>
<td>36</td>
</tr>
<tr>
<td>Scanning electron microscopy (20x)</td>
<td>Rat femur</td>
<td>0.72</td>
<td>0.82</td>
<td>0.91</td>
<td>0.89</td>
<td>52</td>
</tr>
<tr>
<td>Macro section radiograph (5 $\mu m$)</td>
<td>Distal radius</td>
<td>0.67</td>
<td>0.59</td>
<td>n.s.</td>
<td>0.66</td>
<td>78</td>
</tr>
<tr>
<td>Macro section radiograph (5 $\mu m$)</td>
<td>Calcaneus</td>
<td>0.63</td>
<td>0.58</td>
<td>n.s.</td>
<td>0.68</td>
<td>79</td>
</tr>
<tr>
<td>CT (247x247x1000 $\mu m^3$)</td>
<td>Distal radius</td>
<td>0.72</td>
<td>0.49</td>
<td>0.47</td>
<td>0.57</td>
<td>78</td>
</tr>
<tr>
<td>MicroCT (22 $\mu m$)</td>
<td>Femoral head</td>
<td>0.9</td>
<td>0.92</td>
<td>.90</td>
<td>.82</td>
<td>14</td>
</tr>
</tbody>
</table>

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Recent advances in micro-CT imaging in vivo (66, 67) make it possible to obtain radius and tibia images using this methodology. However, comparative studies, in-vivo case-control studies, longitudinal studies using micro-CT in vivo in humans have not been undertaken and are clearly warranted. MR imaging has been used to determine mechanical properties of trabecular bone (72-74). This allows the in vivo estimation of mechanical properties, which are usually determined by in vitro compression testing. In FE models derived from MR images it is possible to incorporate soft tissue structures in the model. This would be useful not only in mechanobiological models of tissue differentiation and bone remodeling (75), but also in models of fracture healing where cartilage formation is critical to the process (76).

Bone quality has been an emerging concept in the area of osteoporosis. Trabecular bone micro-architecture, bone geometry and associated marrow changes in osteoporosis can all be probed using MRI. Thus, MR techniques have the potential for providing a complete whole-organ assessment of skeletal status in osteoporosis, and further developments in this imaging modality and research studies are clearly warranted.

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