Bone Structure & Bone Interface
Cortical and Trabecular Bone

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Magnetic Resonance Imaging (MRI) is the modality of choice for clinical evaluation of musculoskeletal soft tissues (muscle, tendon and ligaments, and bone marrow). However, so far, it has played a lesser role for the study of calcified tissues, which have largely been the domain of X-ray computed tomography (CT) and dual-energy X-ray absorptiometry (DXA). However, thanks to technical advances, MRI has, more recently, made significant inroads as a potential tool for assessment of degenerative and metabolic bone disease. Unlike CT, MRI is truly noninvasive as it does not use ionizing radiation and is therefore particularly suited for follow-up studies in patients undergoing treatment, as well as in children. Lastly, MRI is very widely distributed with an estimated population of over 25,000 MRI systems worldwide.

The focus of much of the work during the past decade or so has been on quantifying trabecular architecture by high-resolution imaging at the distal extremities, similar to high-resolution peripheral QCT, albeit by means of general-purpose clinical MRI systems requiring only minimal customization in terms of radiofrequency coils, imaging pulse sequences, processing and analysis software (for recent reviews of the subject, see, for example, (1,2)). Unlike X-ray based modalities, which create images on the basis of the much greater attenuation of bone relative to soft tissues, MRI detects protons in bone marrow and adjacent soft tissue while, under ordinary imaging conditions, bone appears with close to background intensity. From a set of contiguous image slices the three-dimensional trabecular network can then be reconstructed yielding parameters representative of scale (e.g. bone volume fraction), topology (e.g. plate versus rod character of the network) and orientation (parameters expressing the directional properties of trabeculae) (3-5). Alternatively, structure analysis is by-passed altogether and a 3D voxel model of the MRI data is generated and fed into a finite-element solver that provides as output measures representative of the bone's mechanical competence (e.g. stiffness, elastic modulus or failure strength (6,7)). A number of high-resolution MR studies demonstrating the method's potential for assessing the structural and mechanical implications in patients treated for various conditions have been published in recent years (8-15). Hallmarks of studies involving treatment with antiresorptives (estrogen, testosterone or synthetic osteoclast inhibitors) were improvement in trabecular network connectivity and plate architecture (8,11,13) evaluated on the basis of topological measures, paralleling increases in estimated mechanical competence (10,12).

Fairly stringent technical requirements must be met for trabecular bone MRI to enable detection of treatment effects, which are on the order of a few percent over the course of 12-24 months. A recurring question is whether the achievable resolution, given the typical thickness of trabecular struts and plates of 50-150 μm, is adequate. Currently, there is no *in vivo* imaging technology to fully resolve trabeculae, but the latter has been shown not to be necessary in that some partial volume blurring is tolerable (16). Since for a given receive coil design and magnetic field strength the signal-to-noise ratio (SNR) scales with voxel size and the square root of total scan time, the effective resolution, often expressed in terms of image voxel size, is limited. Recent treatment studies carried out at the distal extremities report voxel sizes of 137x137x410 μm^3 ($7.5x10^{-3}$ voxel volume (14,15) and 156x156x500μm^3 ($1.2x10^{-2}$ mm^3 voxel volume) (13)) with the largest voxel dimension along the bone's major anatomic axis. Nevertheless, voxel dimensions alone do not determine actual spatial resolution, which also depends on the imaging method itself. Depending on imaging method used scan times range from 6-15 minutes, thus image degradation from involuntary subject motion can mask the detected changes. This problem is typically addressed by tight immobilization of the limb (wrist, tibia,

foot), which however, may not be sufficient, and retrospective motion correction techniques have been devised to correct for sub-millimeter displacements during the scan (17). Further, given the heterogeneity of the trabecular architecture (in both axial and transverse direction), accurate serial three-dimensional image registration is critical (18,19).

Even though the wrist is a common fracture site (Colles fracture), fractures of the femur are by far the most traumatic. Hence, imaging of the femoral neck, for example, as a means to assess fracture risk, would be of particular interest. Unlike the distal extremities, the femoral neck is made up of both cortical and trabecular bone, hence assessment of its mechanical properties requires consideration of both types of bone. High-resolution imaging of the proximal femur poses particular challenges, chief among which is the limited SNR attainable at this location. The practically achievable resolution at this site, is therefore lower, with voxel sizes reported in recent work of 234x234x1,500 μm^3 (20) and, in another recent study, even 234x 234 x700 μm^3 (21). Another difficulty is to achieve sufficient coverage, given the proximal femur's much greater volume compared to the distal extremities. Nevertheless, impressive image quality has been achieved in the above work. In (20) the authors applied regional finite element analysis in the femoral head and neck, Ward's triangle, greater trochanter, and intertrochanteric region. The results showed that the elastic modulus (a measure of strength mechanical strength) was lower in subjects with osteoporotic fractures than in matched controls, while there was no difference in BMD T-scores.

As pointed out above, bone is almost invisible in conventionally acquired images, in spite of the tissue's water content of 20-30%, which is now well known to be due to bone water's very short T_2. However, detection of bone water has been shown to be possible by means of ultra-short echo-time (UTE) imaging (22). While measurement of bulk bone water has been shown to be clinically relevant (23,24) by serving as a possible surrogate for cortical porosity (which is a determinant of cortical bone strength), the problem is more complex in that the water resides in at least two major compartments. MRI has since conclusively shown in excised human cortical bone that the two dominant bone water fractions are made up by the hydration sphere of the collagen matrix (50-80%), with the remainder occupying the pore spaces of the Haversian system (25-27). While neither approach is clinically feasible, the different lifetimes of the water MR signal in the two micro-environments led to methods for quantifying pore water fraction in intact cortical bone (27) as well as in vivo (28,29). The importance of these developments is that they will allow assessment of pore volume fraction (i.e. porosity), or biomarkers thereof, without the need to spatially resolve pores (which is currently only possible at selected locations that allow resolution of some of the largest pores).

Lastly, MRI is likely to have a major impact on evaluating bone marrow adiposity as it is the method of choice for quantifying the composition of soft tissue in terms of the fractions of water and fat in tissues. There is growing interest in this field given the empirical connection between adipogenesis and osteogenesis based on the notion that mesenchymal stem cells can differentiate into either adipocytes or osteoblasts (for a recent review, see (30)). Early work showed in osteoporotic women that vertebral marrow fat fraction alone was a significant discriminator of fracture status (31). These observations have since been corroborated in a number studies using vertebral marrow MR spectroscopy (32-34), with some of the work also showing low BMD to be positively associated with lower fatty acid unsaturation (32,34).

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