ADVANCED QUANTITATIVE MRI OF BONE STRUCTURE AND MECHANICS

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Magnetic Resonance Imaging (MRI) plays a pivotal role for clinical evaluation of the musculoskeletal system, including muscle, tendon and ligaments, bone marrow, and more recently bone. The study of degenerative bone disease requires quantitative imaging approaches. MRI has made major strides as a potential modality for osteoporosis fracture risk assessment and treatment monitoring. Unlike computed tomography, MRI is truly noninvasive as it does not use ionizing radiation and is therefore particularly suited for follow-up studies in patients undergoing treatment. Lastly, the modality 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 has been on quantifying trabecular architecture by high-resolution imaging at the distal extremities, similar to high-resolution peripheral QCT, albeit with general-purpose clinical MRI systems requiring only minimal customization in terms of radiofrequency coils, imaging pulse sequences, processing and analysis software (for a recent review of the subject, see, for example, (1)). Unlike X-ray based modalities that create images on the basis of the much greater density of bone relative to soft tissues, MRI detects protons in bone marrow and adjacent soft tissue. In contrast, under ordinary imaging conditions, bone appears with close to background intensity. From a set of contiguous image slices the three-dimensional trabecular network can be reconstructed and 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) can be quantified. 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 (2)). A number of patient studies demonstrating the method's potential for assessing the structural and mechanical implications in response to intervention in patients for various conditions based on high-resolution MRI have been published in recent years (3-9). Hallmarks of studies involving treatment with antiresorptives (estrogen, testosterone or synthetic osteoclast inhibitors) were improvement in trabecular network connectivity and plate architecture (3,6,8) evaluated on the basis of topological measures, paralleling increases in estimated mechanical competence (5,7).

Fairly stringent technical requirements are to 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. 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 (9) and 156x156x500μm^3 ($1.2x10^{-2}$ mm^3 voxel volume) (8)) with the largest dimension along the bone's 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, therefore 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 (10). Further, given the heterogeneity of the trabecular architecture (in both axial and transverse direction), accurate serial three-dimensional image registration is critical (11,12).

The recognition of the role of cortical bone (CB) architecture as a modulator of fracture susceptibility has spurred interest in image-based assessment of CB quality (13). MRI has shown significant potential to study CB, both in terms of macrostructure, applicable to any anatomic site (including, for example, the femoral neck (14)). One confounding factor that may complicate visualization and quantification of macrostructural parameters, such as cortical thickness and area, is that highly collagenated soft tissues (notably ligaments contiguous with bone), have very low inherent signal intensity similar to bone. Nevertheless, recent work aimed at establishing the 3D geometry of the proximal femur and its relationship to experimentally measured failure strength, are promising (15).

Even though bone contains about 20-30% water, it is almost invisible in conventionally acquired images as pointed out above, largely due to its short T2. However, detection and quantification has been shown to be possible by ultra-short echo-time (UTE) imaging that allows capturing the short-T2 proton signals from bone water. While measurement of bulk bone water has been shown to be clinically relevant (16) 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 (60-80%), with the remainder occupying the pore spaces of the Haversian system (17,18). 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 (19) as well as in vivo (20). The importance of these developments is that they will allow measurement of pore volume fraction (i.e. porosity) 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 (21)). By means of spectroscopic imaging Wehrli et al first observed in osteoporotic women that vertebral marrow fat fraction alone was a significant discriminator of fracture status (marrow fat volume fraction (0.55±0.08 versus 0.45± 0.10 in groups with and without fracture, respectively; $p<0.001$) (22). These observations have since been corroborated in a number studies using vertebral marrow MR spectroscopy (23-25), with some of the work also showing low BMD to be positively associated with lower fatty acid unsaturation (23,25).

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