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Micro Finite-Element Analysis of the Proximal Femur on the Basis of High-Resolution Magnetic Resonance Images

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Abstract

Purpose of review: Hip fractures have catastrophic consequences. The purpose of this article is to review recent developments in high resolution magnetic resonance imaging (MRI) guided finite element analysis (FEA) of the hip as a means to determine subject-specific bone strength.

Recent findings: Despite the ability of DXA to predict hip fracture, the majority of fractures occur in patients who do not have BMD T-scores < -2.5 . Therefore, without other detection methods, these individuals go undetected and untreated. Of methods available to image the hip, MRI is currently the only one capable of depicting bone microstructure *in vivo*. Availability of microstructural MRI allows generation of patient-specific micro finite element models that can be used to simulate real-life loading conditions and determine bone strength.

Summary: MRI-based FEA enables radiation-free approach to assess hip fracture strength. With further validation, this technique could become a potential clinical tool in managing hip fracture risk.

Keywords

MRI; proximal femur; hip; finite element analysis; bone strength

Introduction

Osteoporosis is defined as a disease of bone fragility predisposing an individual to fracture (1). In the United States alone, approximately two million fragility fractures occur annually, resulting in over \$17 billion in direct costs for fracture care (2). Of the different types of fragility fractures, hip fractures have the most devastating consequences. Though they represent only one-sixth of the fragility fractures that occur, they account for greater than 70% (\$12 billion) of the direct annual costs for fracture care (2). Aside from impairing an

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Conflict of Interest

Chamith Rajapakse and Gregory Chang have a patent pending (62/593,626).

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

individual's quality of life and ability to perform daily activities, hip fractures increase an individual's risk of dying with mortality rates rising as high as 20-24% in the first year after a fracture (3, 4).

Dual-energy X-ray absorptiometry (DXA) of areal bone mineral density (BMD) is the standard-of-care for assessment of bone quality, diagnosis of osteoporosis, and estimation of fracture risk (1). Osteoporosis in postmenopausal women is defined as having a BMD value that is greater than 2.5 standard deviations below the mean BMD value for a population of gender and race matched young women (T-score < -2.5) (5). Site-specific measurements are key for accurate prediction of fracture risk (5, 6). For example, measurement of areal BMD in the hip predicts hip fracture with a gradient risk of 2.6 (6). That is, for every standard deviation reduction in BMD, an individual's risk of hip fracture increases 2.6-fold (i.e. an individual with a T-score of -2.5 would therefore have a 10.9-fold higher hip fracture risk ($2.6^{2.5}$). However, the same T-score in the lumbar spine has a gradient of risk for hip fracture of 1.6, which would yield a marked underestimation of risk of 3.2 ($1.6^{2.5}$) (6).

Despite the ability of DXA to predict an individual's risk of fracture, the majority of fractures occur in patients who do not have BMD T-scores < -2.5 (7-9). Therefore, without other detection methods, these individuals go undetected and untreated. Over the past 25 years, the medical community has developed a vast interest in advancing methods to better identify individuals who are at risk for fragility fracture and in need of therapy. One approach has been the development of FRAX, a fracture risk calculator, which evaluates 11 clinical features (age, body mass index, parental history) to better assess risk of hip fracture and major osteoporotic fracture (10, 11).

Other approaches have focused on the development of novel image analysis and imaging methods for *in vivo* assessment of bone tissue properties that standard DXA cannot assess. More specifically, since standard DXA is a 2-dimensional (2-D), low resolution projection imaging method, it cannot assess bone tissue properties such as: bone geometry, 3-D measures of bone (such as the 3-D spatial distribution of cortical bone and BMD), trabecular microarchitecture, and cortical microarchitecture, including cortical porosity. Hip structural analysis (HSA) of DXA images (12) was developed to permit extraction of limited geometric information from 2-D DXA hip scans; however, this is not felt to be a replacement for 3-D information (13). Trabecular bone score (TBS) assessment of lumbar spine DXA images permits indirect assessment of lumbar spine trabecular microarchitecture based on the pixel gray-scale variation in the 2-D DXA images (14); however, it cannot currently be performed in the hip. Quantitative computed tomography (CT) assessment of volumetric BMD in the lumbar spine and hip provides more accurate quantification of BMD compared to DXA and also permits the assessment of the 3-D spatial distribution of BMD (15, 16). And CT-based cortical thickness assessment (17, 18) and CT-based finite element analysis (FEA) estimation of lumbar vertebral body and hip mechanical properties (19, 20) have been shown to provide some useful additional information about bone quality and fracture risk beyond DXA; however, all CT-based methods require the administration of ionizing radiation. High-resolution peripheral quantitative computed tomography (HR-pQCT) imaging permits assessment of cortical and trabecular microarchitecture at low radiation dose (21, 22); however, it can only be performed in the distal extremities at the

present time. Finally, magnetic resonance imaging (MRI) methods for assessment of bone structure and microarchitecture in the distal extremities and most recently in the hip (23, 24) have been developed. Though MRI does not provide BMD information, this is captured by standard DXA; furthermore, MRI does not require the administration of ionizing radiation.

Of those methods available to image the hip, MRI is currently the only one capable of depicting bone microarchitecture *in vivo*. This review focuses on MRI-based FEA of the hip and discusses its potential for osteoporosis diagnosis and fracture risk assessment.

MRI Data Acquisition

MRI is able to depict bone microarchitecture based on its ability to detect the signal from protons associated with water and fat within the bone marrow. In brief, the MRI scanner causes tissue “excitation”, resulting in a changing magnetic field within the tissue. This change is detected as a fluctuating electrical current within the looped copper wire detector. The fluctuating electrical signal is decomposed via Fourier transform into spatial information, which can then be converted into an image.

Imaging of bone microarchitecture via MRI requires sufficient signal-to-noise ratio (SNR), which is directly proportional to voxel size. Therefore, reducing the dimension of a voxel in half, in one plane, reduces SNR by 50%, and reducing the voxel dimensions in half, in two planes, results in a four-fold reduction in SNR. From a hardware perspective, in order to boost SNR and achieve smaller voxel sizes, there are several strategies that can be pursued: 1. MRI scanning can be performed on a higher field strength magnet (with field strength being approximately linearly proportional to SNR), 2. the detector can be placed as close to the patient as possible, 3. a multichannel detector composed of multiple smaller copper elements can be used (to reduce noise).

MRI of bone microarchitecture was initially described in the late 1990s in the distal radius and the ankle (25-27), and can now be performed in the proximal femur *in vivo* on clinical MRI scanners (28, 29). The initial papers describing MRI of proximal femur microarchitecture use 3-D steady state free precession (28) or 3-D gradient echo sequences (29) to acquire data, resulting in voxel sizes of $0.234 \text{ mm} \times 0.234 \text{ mm} \times 1.5 \text{ mm}$. A more recent paper from Han et al. describes the use of a 3-D fast spin-echo sequence, which permits a voxel size of $0.234 \text{ mm} \times 0.234 \text{ mm} \times 0.700 \text{ mm}$ (30). While the voxel size achieved by MRI is not as small as that of high-resolution peripheral quantitative computed tomography (HR-pQCT), it is sufficient to visualize larger trabeculae within the proximal femur, and advantageously does not require the administration of ionizing radiation. However, even with the use of parallel imaging acceleration methods, the imaging time is 15 minutes and it is important that the patient be comfortable in the scanner to avoid motion artifacts. With further improvements in scanner software and hardware, we expect even higher resolution imaging in the hip to become achievable.

Application of Finite Element Analysis (FEA) to Microstructural MRI Data

The ability to image bone microarchitecture by MRI allows for a patient-specific generation of three-dimensional micro-level computer models that can be used to estimate bone

strength through the simulation of real-life loading conditions. Finite element analysis (FEA), an engineering concept, has been used for decades for modeling physical structures to determine their failure loads. FEA has been adapted to determine the mechanical competence of bone on the basis of high-resolution MRI (31, 32). Numerous translational studies have shown the usefulness of MRI-based FEA for detecting often subtle treatment effects (33-36), and deterioration of bone due to diseases such as osteoporosis (35, 37) and renal failure (38). It has been also shown that patient-specific micro finite element models can be generated though MRI data obtained at various field strengths, including 1.5 Tesla (39), 3 Tesla (40, 41), and 7 Tesla (42-44). Typically, tetrahedral finite elements have been utilized to reflect imaging voxel dimensions, both at isotropic and anisotropic MRI resolutions ranging from 0.060 mm (45) to 1.0 mm (43). While most MRI-derived finite element simulations have been limited to the linear elastic regime due to computational simplicity, recent studies have shown that it is now feasible to derive post-yield mechanical parameters through nonlinear simulations (46, 47). MRI-based microstructural FEA models have typically been generated to simulate compressive loading conditions predominantly at extremity anatomical sites such as the distal tibia (31), distal fibula (34), proximal tibia (43), distal femur (43, 44), and distal radius (37, 39).

Microstructural MRI-Based FEA of the Hip

Quantitative computed tomography (QCT) images of the hip have been shown to be useful in developing finite element models for estimating hip strength by simulating a sideways fall onto the hip (48-50). However, due to ionizing radiation dose imposed restrictions on spatial resolution (0.6-1 mm), development of only “continuum-level” finite element models have been feasible, in which a continuum of X-ray attenuation coefficients between pure bone tissue and marrow is assumed (51-53). The ability to obtain high-resolution images of the hip through MRI now allows us to resolve bone microstructure and develop “micro-level” finite-element models to determine hip strength by making use of the three-dimensional microstructural arrangement of the trabeculae and cortex.

Generation of FE Models from MRI Data

A number of image processing and computational steps are involved in the FE-based estimation of bone's mechanical competence on the basis of MR images (54). First, acquired MR images are converted to a bone-volume-fraction (BVF) map representing the percentage of each voxel occupied by bone by linearly scaling the grayscale MRI pixel values to cover the range from 0 to 100 with pure marrow and pure bone having minimum and maximum values, respectively (Figure 1). Voxels in the BVF map are then converted to hexahedral (brick) finite elements with dimensions corresponding to image voxel size. Material properties of bone are typically assumed as isotropic and linearly elastic with each finite element's elastic modulus (E) set to be linearly proportional to the BVF value such that $E = (15 \text{ GPa}) \times (\text{BVF})$ while the Poisson's ratio is kept constant at 0.3. Using this FE models, either sub-regional (55) or whole bone (56) mechanical simulations can be performed to mimic real life loading conditions such as stance and fall to the side.

Sub-Regional FEA of the Hip

FEA modeling has been performed only recently using microstructural MRI of more proximal sites. In 2014, FEA was applied to 3T MR-derived images of the proximal femurs of postmenopausal women with osteoporosis (55). The primary goal of that study was to investigate if MRI-based FEA could provide information not captured by DXA. In that study, mechanical competence of proximal femur in those with ($n = 22$) and without ($n = 22$) fragility fractures, as quantified using the elastic moduli of five sub-regions: femoral head and neck, greater trochanter, lesser trochanter, and Ward triangle was compared. There were no significant differences in age, height, weight, or body mass index between the two groups. Loading conditions were simulated along three axes (Figure 1). DXA scores were also obtained. Because both FEA-derived elastic moduli and DXA scores were extracted from the same site, more direct comparisons between the two were possible.

In all five sub-regions, fracture patients demonstrated lower elastic moduli than did controls matched for age and body mass index (0.65 – 8.73 GPa vs. 1.96 – 9.67 GPa, respectively; $p = .006 - .04$). Patients' elastic moduli ranged from 8.7% to 66.8% lower than the elastic moduli of controls. The two groups' DXA T scores, however, were not different. Furthermore, DXA T scores and elastic moduli were only weakly correlated among patients, within just the intertrochanteric region, greater trochanter, and femoral neck ($p = 0.02 - 0.04$). DXA T scores and elastic moduli were not correlated among controls in any region.

Reproducibility of MRI-based FEA Measures

In order to validate the precision of MRI-based FEA analysis of the proximal femur, Chang et al. tested the reproducibility of FEA-computed metrics of bone strength (57). Twelve participants without any bone fracture were scanned three times over the course of a week. As with DXA, bone stiffness was assessed in the proximal femur and elastic modulus was determined within a 10 mm³ VOI in the femoral neck (Figure 4). In order to mimic a sideways fall, the sole fall type associated with hip fracture (58), loading conditions were simulated along the medial-lateral axis of the femoral head, while the greater trochanter was kept constrained.

Within both the whole proximal femur and the femoral neck VOI, intraclass correlations of the metrics computed from each participant's three scans ranged from 0.96 – 0.98, and coefficients of variation ranged from 3.5% – 6.6%. These results suggest FEA-derived measures of bone strength are highly precise, and therefore clinically useful. Furthermore, these findings provide information necessary to calculate power and determine sample sizes required for future studies that employ FEA.

Effects of Glucocorticoids on the Hip

MRI-based FEA has enabled clinically-relevant studies previously not feasible. One such study investigated the effects of long-term glucocorticoid use on bone quality. Compared to control subjects ($n = 6$; 2 males, 4 females, median age = 65.5 years (interquartile range (IQR) = 10.5 years), median BMI = 23.1 kg/m² (IQR = 6.8 kg/m²)), long-term (> 1 year) glucocorticoid users ($n = 6$ subjects; 2 males, 4 females, median age = 52.5 years (IQR =

19.5 years), median body mass index = 22.8 kg/m² (IQR = 6.6 kg/m²), demonstrated detrimental changes in MRI-computed bone mechanical and microarchitecture properties, despite DXA-derived bone mineral density measurements showing no differences (59). Loading conditions were simulated along three axes (Figure 1B).

Long-term glucocorticoid users had lower FEA-derived trabecular numbers, trabecular plate-to-rod ratios, and elastic moduli than did the subjects who did not use glucocorticoids (−74.8% – −20.1%; $P = .02 - .04$). Users had greater femoral neck trabecular separation (192%; $P = .02$), and no difference in femoral neck trabecular thickness. There were no differences in DXA-derived femoral neck BMD T scores, and paradoxically, users had higher DXA-derived total hip BMD T scores than did non-users (46.8%; $P = 0.002$). Furthermore, neither femoral neck nor total hip BMD T scores correlated with any MRI parameter among glucocorticoid users or non-users.

Overall, long-term glucocorticoid users had more trabecular deterioration than did non-users (Figure 4), which was reliably reflected in FEA-generated metrics, but not in DXA-derived T scores. FEA elucidated the relationship between trabecular deterioration and skeletal fragility in glucocorticoid users, which was not possible using DXA. A major limitation of this study is the small number of subjects and the results should be confirmed in larger cohorts; however, it is still notable that MRI could detect differences between groups. In addition to being more sensitive than DXA, in the future MRI-based FEA could potentially be used to pinpoint specific manifestations of various diseases and therapies that affect the mechanical integrity of bone.

Microstructural MRI-based Nonlinear FEA of the Whole Hip

While linear FEA provides information on mechanical behavior in the elastic regime only, nonlinear FEA can be implemented for a more thorough approach to determining bone's mechanical integrity beyond the yield point. Although linear FEA may be sufficient at distal sites, such as the distal tibia (31, 54), nonlinear FEA could be more useful at highly microstructurally anisotropic sites such as the proximal femur (60). Leveraging the ability of MRI to capture microstructural variation across the whole proximal femur, Rajapakse et al. implemented a nonlinear finite element model that can be tailored to each participant's microanatomy, then validated the reliability of this analysis (56). The nonlinear FEM can provide multiple metrics relating to fracture risk, i.e., bone stiffness, yield point, ultimate point, resilience, and toughness (Figure 4). Using a whole proximal femur FEA model, the investigators examined two typical loading conditions—one along the medial-lateral axis while constraining the greater trochanter, to simulate a sideways fall, and another approach to mimic stance loading. Reproducibility was assessed by scanning 13 subjects three times each over the course of a week. Four operators were then asked to analyze the same ten scans on two separate occasions two weeks apart. Interoperator reliability was assessed by comparing the four operators results; intraoperator reliability was assessed by comparing each operator's initial results with the results from the second analysis. Additionally, two subjects were scanned as case studies—one with DXA-diagnosed osteoporosis, but no fracture, and one with fracture, who had been determined via DXA not to have osteoporosis.

For all FEA-derived metrics, both in standing and falling loading configurations, test-retest reproducibility, interoperator reliability, and intraoperator reliability had extremely low coefficients of variation (0.47% – 7.96%; 0.33% – 8.36%; and 0.20% – 4.96%, respectively) and intraclass correlation coefficients above 0.99. These results indicate a high degree of precision. Furthermore, of the two case studies, the participant without fracture was determined via FEA to have much stronger bones than the participant with fracture (25% more ultimate strength in falling conditions and 9% more ultimate strength in standing conditions), despite DXA results predicting the opposite to be the case. This further supports the notion that MRI-based FEA could provide additional information on mechanical integrity of the hip not captured by DXA.

Conclusions

MRI-based FEA has the ability, without exposing patients to ionizing radiation, to detect discrepancies that DXA does not. The method's sensitivity to subtle changes could improve the accuracy of monitoring disease progression and treatment effectiveness over time, and improve accuracy rates of diagnosing osteoporosis, the very definition of which includes bone microarchitecture (5, 61). Additionally, the ability of FEA to directly measure the mechanical competence of bone renders it an ideal tool for predicting fracture risk, the most clinically relevant aspect of osteoporosis detection. The capacity of MRI-based FEA to predict localized and whole-bone mechanical behavior of the hip could allow for a more comprehensive assessment of hip fracture susceptibility, which is essential to pinpointing specific areas of bone weakness that would not otherwise be detected and incorporating them into a risk assessment to ensure proper treatment before the occurrence of preventable fractures.

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Figure 1.

FEA was applied to (A) five volumes of interest within the proximal femur, (B) with compressive loading conditions simulated along three axes. Reprinted with permission from Chang et al. *Radiology* 2014;272(2):464-474.

Figure 2.

A bone volume fraction map was generated from the proximal femur MRI. Mirroring the DXA protocol, the whole proximal femur was used to compute bone stiffness, while a 10 mm³ section of the femoral neck was used to compute elastic modulus. Reprinted with permission from Chang et al. *MAGMA* 2015;28(4):407-412.

Figure 3.

An example of differences in trabecular integrity between a glucocorticoid user and a healthy control subject (non-user). (A) A segment from each femoral neck was used to generate (B) a bone volume fraction map and a strain map. Reprinted with permission from Chang et al. *J Magn Reson Imaging* 2015;42(6):1489-1496.

Figure 4.

The point at which the amount of simulated stress would elicit plastic deformation of a bone was considered the bone's yield point, while the point at which the amount of stress would cause fracture was the bone's ultimate point. The tangent to the curve represents bone stiffness. Adapted with permission from Rajapakse et al. *Radiology* 2017;283(3):854-861.