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MRI-Based Assessment of Proximal Femur Strength Compared to Mechanical Testing

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Abstract

Half of the women who sustain a hip fracture would not qualify for osteoporosis treatment based on current DXA-estimated bone mineral density criteria. Therefore, a better approach is needed to determine if an individual is at risk of hip fracture from a fall. The objective of this study was to determine the association between radiation-free MRI-derived bone strength and strain simulations compared to results from direct mechanical testing of cadaveric femora.

Imaging was conducted on a 3-Tesla MRI scanner using two sequences: one balanced steady-state free precession sequence with 300 μ m isotropic voxel size and one spoiled gradient echo with anisotropic voxel size of 234 $\times$ 234 $\times$ 1500 μ m. Femora were dissected free of soft-tissue and 4 350-ohm strain-gauges were securely applied to surfaces at the femoral shaft, inferior neck, greater trochanter, and superior neck. Cadavers were mechanically tested with a hydraulic universal test frame to simulate loading in a sideways fall orientation.

Sideways fall forces were simulated on MRI-based finite element meshes and bone stiffness, failure force, and force for plastic deformation were computed. Simulated bone strength metrics from the 300 μ m isotropic sequence showed strong agreement with experimentally obtained values of bone strength, with stiffness ($r = 0.88$, $p = 0.0002$), plastic deformation point ($r = 0.89$, $p < 0.0001$), and failure force ($r = 0.92$, $p < 0.0001$). The anisotropic sequence showed similar trends for stiffness, plastic deformation point, and failure force ($r = 0.68, 0.70, 0.84$; $p = 0.02, 0.01, 0.0006$, respectively). Surface strain-gauge measurements showed moderate to strong agreement with simulated magnitude strain values at the greater trochanter, superior neck, and inferior neck ($r = -0.97, -0.86, 0.80$; $p = <0.0001, 0.003, 0.03$, respectively). The findings from this study support the use of MRI-based FE analysis of the hip to reliably predict the mechanical competence of the human femur in clinical settings.

Introduction

Hip fracture is a prevalent and dangerous occurrence. Following a fracture event, 50% of patients are unable to walk, while up to 30% will die within a year, making it the deadliest of all osteoporotic fractures [1, 2]. Furthermore, it especially is costly, accounting for up to 70% of costs in fracture care—or about \$70 million per year [3–5]. Osteoporosis medications have been shown to be effective in reducing fracture risk, but it is unclear which people would benefit the most from treatment [6–8].

Clinical assessment of bone health and fracture risk in the hip is based on bone mineral density (BMD) measurements, which are typically obtained with Dual Energy X-ray Absorptiometry (DXA). DXA scanners are fairly ubiquitous and provide precise measurements of bone density in short scan times [9]. However, DXA's accuracy is inherently limited because it takes 2D projections of complicated 3D anatomy and cannot differentiate between intra- and extra-osseous soft tissue [10]. As a result, DXA BMD values are relatively insensitive to short term physical changes in bone strength and have been shown to have systemic inaccuracies above 20% [11, 12]. Unsurprisingly, some clinical studies have shown that DXA is incapable of accurately predicting which people will sustain an incident fracture [13, 14].

The major determinants of bone strength include the amount and quality of the material components, the macroscopic 3D morphology, and the microstructure of bone [15, 16]. Some of the limitations of DXA can be overcome by using quantitative computed tomography (QCT), which allows for evaluation of both the 3D morphology of bone as well as the spatial distribution of bone density [17–19]. QCT also has inherent utility with respect to computational modeling, since CT voxel attenuation values in bone are linearly proportional to bone density, which means voxels can be linearly scaled to hexahedral meshes for direct use in image-based finite element analysis (FEA) [20–22]. Image-based FEA simulates patient-specific bone strength noninvasively which is often thought of as a surrogate for fracture risk. Indeed, several studies have found this method to be effective at predicting incident hip fracture [23, 24]. FEA is especially useful for evaluating fracture risk in the hip by simulating the forces experienced during a sideways fall, which is the orientation in which 90% of hip fractures occur [24–26]. Predictions of bone competence and failure loads from CT FEA have been compared to *ex vivo* mechanical testing in cadaveric specimens with excellent agreement [27–29].

Though promising, CT FEA does have some limitations. First, CT scans produce ionizing radiation which have known health risks. Moreover, the accuracy of finite element models may depend upon imaging resolution [16, 30–33], and the resolution of CT scans is proportional to the amount of radiation it produces. Since the pelvic region is especially radiosensitive, due to bowels and pelvic organs, clinical CT scans of the hip are typically limited to 1mm voxels, which prohibits accurate characterization of bone microstructure. As a result, only continuum level FE models of the proximal femur are possible *in vivo*. To the best of the authors' knowledge, there has never been a high resolution, *in vivo* CT FEA study performed on the hip.

Magnetic resonance imaging (MRI) is particularly advantageous for imaging of the hip because it is capable of imaging proximal femur microstructure *in vivo* and it does not produce ionizing radiation [25, 34–40]. Finite element analysis of microstructural MR images have been performed *in vivo* for several bones, including the radius, the tibia, and most recently at the proximal femur [41–43], which is the most clinically important bone for fracture risk evaluation. In an *in vivo* proximal femur study, MRI FEA was able to effectively discriminate between postmenopausal women with and without fractures, even though they had similar DXA BMD scores [44]. Moreover, this technique has been shown to be highly reproducible for the hip *in vivo* [45, 46]. The first *ex vivo* validation study for MRI FEA was recently performed for simulated axial compression at the tibia [47]; however, MRI FEA bone strength evaluation has never been validated for the clinically significant proximal femur.

Therefore, the goals of this study were twofold: first, to compare the accuracy of microstructural MRI-derived FEA to gold-standard values of bone strength obtained from *ex vivo* mechanical testing of human cadaveric proximal femora; second, to evaluate the effect of resolution on accuracy of the FEA models. Finally, we performed a preliminary evaluation of the simulated strains from our complete custom, image-based finite element solver by comparing the outputs with strains measured during mechanical testing.

Materials and Methods

Specimen Collection

A total of 12 cadaveric femurs—six male and six female—were used, with an average $\pm$ standard deviation (SD) age of 76.2 ± 20.0 years and an age range of 36–99 years. The average $\pm$ SD body mass index of the donors was 26.6 ± 5.41 kg/m². Specimens were obtained from the National Disease Research Interchange at an average of 11.7 hours post mortem and were frozen at -30°C for an average of 17 months before being used. Exclusion criteria included donors with a history of bone or metabolic diseases.

MR Imaging

Whole frozen cadaveric femora specimens were obtained with a thin layer of soft tissue surrounding the periosteum. Specimens were wrapped with gauze to prevent dehydration and were thawed at room temperature for a minimum of 12 hours prior to imaging, which, based on previous work, provides image quality and a signal to noise ratio that best resembles *in vivo* results [47]. The specimens were loaded onto the scanner bed in a manner that mimicked a feet-first supine position, as is standard for MRI clinical hip scans. All MRI scans of the cadavers were performed at the Hospital of the University of Pennsylvania. All cadaveric femora were imaged twice with two different product pulse sequences (Siemens, Erlangen, Germany), using established, clinically feasible protocols and hardware setup. The first scan was a balanced steady-state free precession (bSSFP) sequence, which produced isotropic voxel sizes of $300 \times 300 \times 300 \mu\text{m}$ and is hereafter referenced as “isotropic” or “bSSFP.” Other scan parameters were TR/TE 7.55/3.35 ms, flip angle 37° , BW 310 Hz/Pixel, and a scan time of 16 minutes. The second scan was a spoiled gradient echo (SPGR) sequence that produced greater resolution in-plane, but at the cost of a much larger slice

thickness, resulting in anisotropic voxel sizes of $234 \times 234 \times 1500 \mu\text{m}$, and is hereafter referenced as “anisotropic” or “SPGR.” Other scan parameters were TR/TE 25.0/4.28 ms, flip angle 25° , BW 200 Hz/pixel, acceleration factor 2, and a scan time of 10 minutes. All images were obtained on a whole-body 3 Tesla MRI Scanner (Siemens Prisma, Erlangen, Germany) with an 18-element body coil (Siemens Body 18, Erlangen, Germany).

Preprocessing of Images

The periosteal boundary of each cadaver was segmented by trained laboratory members to exclude any remaining tissue outside of the cortical surface and reduce the field of view and corresponding data size for the 3D meshes, similar to previously established methods that provided a high degree of reproducibility [46]. From there, two 6×6 regions of interest (ROI) were manually defined, with one taken from the thickest part of cortical bone in the femoral shaft which was assumed to be pure bone, and one taken from the medullary canal which was assumed to be pure marrow without trabecular bone. The signal intensities within the bone were then inverted so the bone became the brightest intensity and the marrow became the darkest, and the values within each voxel were scaled between 0 and 100. We refer to the resultant mesh between 0 and 100 as the bone volume fraction (BVF) map. Finally, the distal portions of the bone were cropped to the inferior margin of the lesser trochanter to ensure consistency between the meshes. An example of the BVF is shown in the “Finite Element Analysis” section of Figure 1, along with a superimposed diagram depicting boundary conditions for sideways fall loading configuration. The BVF map can also be seen with proper boundary conditions in the middle column of Figure 6.

Finite Element Analysis Model Generation

The BVF maps were used for 3D reconstruction and creation of the mesh input to the finite element solver, based on an assumption of a linear, isotropic relationship between BVF values and elastic modulus of pure bone, where $0\% \text{ BVF} = 0 \text{ GPa}$ and $100\% \text{ BVF} = 15 \text{ GPa}$ [48, 49]. The application of the BVF allows for inclusion of partial volume effects resulting from incomplete coverage of bone or marrow within the voxel, thus allowing us to simultaneously scale both cortical and trabecular regions[50]. The Poisson’s ratio was defined as 0.3 [48]. The 3D bone mesh was then oriented sideways to simulate the compressive forces experienced during a sideways fall, which is the most common environment for hip fractures [46]. The boundary conditions were defined in the form of homogenous force pads which surrounded the greater trochanter and the femoral head. The trochanter force pad was assumed to be a simple rectangular shape and the femoral head force pad a hemispherical cup. It is important to note that our *in vivo* simulations use the same trochanter force pad shape and have a similar hemispherical cup shape around the femur, with the only difference being that the *in vivo* force pad is defined by directly by segmenting the subject’s acetabulum and the *ex vivo* conditions are merely an approximated shape. The femoral shaft was free to move in our model.

Nonlinear Finite Element Analysis

Femoral bone strength was calculated via nonlinear FEA simulations with a complete custom, computationally optimized solver that is designed for image-based simulations on bone voxels, as described previously [51]. The model simulated compression on the medial

portion of the femoral head and the lateral portion of the greater trochanter. Bone was assumed to behave in an elastic-plastic manner with linear behavior for strains of 0.05% and nonlinear behavior for larger strains [50, 52]. Nonlinear behavior of tissue elastic modulus was simulated via a hyperbolic secant function, where the resultant strain was proportional to the strain energy density function divided by the elastic modulus, as described previously [50, 52]. Each model was run until a predetermined stopping criteria of 3 % percent strain [52]. The plastic deformation point, which is the point on the load-displacement curve where the bone changes from elastic to plastic deformation and that corresponds to the yield point on stress-strain curve, was defined by the 0.2% offset rule [46]. The failure force was similarly computed as the maximum point on the force-displacement curve [50, 52]. In addition to the aggregate bone strength values, our finite element model also produces 3D strain maps of the total magnitude strain within each voxel, which have been previously described [50, 52]. For each of the 3D strain maps, small 4×4 voxel ROIs were manually drawn near the periosteum corresponding to the location where the strain gauges were affixed, as described below. The reported strain gauge values are merely the average within those ROIs.

Mechanical Testing

Following imaging, the gauze and soft tissue was removed from the femora to help ensure consistency between finite element boundary conditions and conditions used in mechanical testing and all 12 specimens were mechanically tested in a sideways fall orientation. A rigid base of polymethylmethacrylate (PMMA, Trim Plus PMMA, Patterson Companies, Mendota Heights, Minnesota) was formed around the greater trochanter and was placed in contact with a metal base but was free to slide along its bottom surface. The femoral head was affixed in a similar PMMA cup to mimic the acetabulum. The femoral shaft was rigidly held in a 3-degree of freedom vise, such that the femoral head was pointed upwards and the shaft of the bone was oriented approximately 10 degrees relative to the horizontal, similar to Keyak et. al [27, 53] (see Figure 1). The actuator of the test frame (10 kN load cell; Model 8874, Instron, Norwood, MA) was brought in contact with the top of the acetabular cup until a nominal amount of compression (<10N) was observed. The cadavers were then compressed at a rate of 1.67 mm/s until a pronounced drop in the applied load (loss of 50% or more) occurred. Mechanical testing was performed at room temperature. Load-displacement curves were obtained from the beginning of mechanical testing until the time of the maximum force. Time (sec), displacement (mm), and force (N) data were collected at 100 Hz throughout the test.

Strain Measurement

Prior to mechanical testing, strain gauges were affixed to the femora in order to assess agreement between experimentally measured surface strain in the cadavers and linear 3D magnitude strain maps output by our finite element models. Four thin-film linear 350-ohm wired strain gauges (1033–1009-ND, Vishay Precision Group, Raleigh, NC) were used, similar to previous studies [53–55]. Strain gauges were affixed at four locations: the greater trochanter, the superior neck, the inferior neck, and the femoral shaft (Figure 1). Prior to adhesion, a scalpel was used to strip residual soft tissue and periosteum from the regions of interest, and acetone was used to clean the area. Once the area was appropriately prepared,

the gauges were securely attached to the femoral bone with an adhesive (454, Loctite, Westlake, OH). Gauges were aligned along the axis of expected maximal tension/compression. Strain gauge leads were connected to a quarter-bridge Wheatstone setup with the three remaining arms made of 350-ohm resistors (ALSR3J-350-ND, Vishay/Dale, Raleigh, NC). The bridge was excited with 5V and the change in resistance was measured with a 12-bit digital acquisition card connected to LabView (Labview 2013, National Instruments, Austin, TX). The manufacture-provided and calibrated gauge factor was used to convert observed change in resistance to microstrain. All data was collected at 1000 Hz and smoothed with a Butterworth filter. In order to consistently map the computational strain values to experimental values, strain values for each cadaver were chosen when the applied load was at 60% of the failure force. At this time point, strains from the 4 gauges were compared to ROIs from computational strain maps (Figure 1). Of the 12 specimens that were mechanically tested, three were excluded from analysis due to failures in experimental setup, either as a result of the DAQ acquiring data too late or from strain gauges being improperly fixed to the surface of the bone. Furthermore, the inferior neck strain gauges short-circuited during two experiments and were excluded, leaving nine data points for the trochanter, superior neck, and femoral shaft region and seven data points for the inferior neck.

Statistical Analyses

Stiffness, force at onset of plastic deformation, and failure force for each femur following mechanical testing was calculated. Pearson correlation coefficients were calculated to assess agreement between mechanical testing parameters and simulated bone strength metrics, as well as to compare simulated to experimentally determined strain values. p -values were calculated for all correlations, with values less than 0.05 indicating statistical significance. All statistical analysis was performed in Matlab version 9.3 R2017b (Mathworks, Natick, MA, USA).

Results

Linear Domain

Simulated stiffness from the 300 μ m isotropic scans showed strong correlations with mechanical testing data ($r = 0.88$, $p = 0.0002$, Figure 2A). Mechanical and computational-defined plastic force also showed strong agreement between ($r = 0.89$, $p < 0.0001$, Figure 2B). Mean $\pm$ SD of all parameters calculated from mechanical testing and computational modeling are shown in Table 1.

Simulated axial stiffness values from the anisotropic scans demonstrated strong correlations with mechanically derived stiffness data ($r = 0.68$, $p = 0.02$, Figure 3A). The simulated plastic point values from the anisotropic scan also showed good agreement with the mechanical data ($r = 0.70$, $p = 0.01$, Figure 3B).

Nonlinear Domain

Failure force showed the highest level of agreement between experimental and the 300 μm isotropic computational values ($r = 0.92$, $p = 0.0001$). Additionally, the anisotropic model showed good agreement with experimental results ($r = 0.84$, $p = 0.0006$).

Comparison Between Models

There were significant correlations found between the isotropic and anisotropic models for stiffness, plastic point, and failure force ($r = 0.69$, 0.75 , and 0.83 ; $p = 0.02$, 0.005 , and 0.0009 , respectively, Figure 4).

Strain Data

The simulated magnitude strain values from the 300 μm isotropic bSSFP image showed strong to moderate correlations with experimentally obtained surface microstrain for the greater trochanter, superior neck, and inferior neck ($r = 0.97$, 0.86 , and -0.80 ; $p = <0.0001$, 0.003 , and 0.03 , respectively). There were no correlations found between the experimentally obtained surface microstrain and the simulated magnitude strain values for the femoral shaft ($p = 0.07$, Figure 5A–D). A representative graph of the time-dependent strain values for all four gauges and the time point chosen for analysis can be seen in Supplemental Figure 1. Furthermore, Figure 6 demonstrates the differences in scans, finite element meshes, and resultant strain maps between specimens from an old and a young donor of very different mechanical strengths.

Computation Time and Overall Measurements

The finite element meshes from the 300 μm isotropic sequence had an average $\pm$ SD of $6.1 \pm 2.0 \times 10^6$ elements (range of 3.0 – 9.6×10^6 elements). These required an average $\pm$ SD of 7.6 ± 1.5 hours (range of 5.4 – 9.9 hours) to compute on a powerful desktop computer with two 14-core hyperthreading enabled Xeon Gold 5120 processors (Intel, Santa Clara, California) and 128 GB of random-access memory. The computation time required showed linear complexity with the number of finite elements, as seen in Supplemental Figure 2.

Discussion

Research in image-based finite element analysis as a method to non-invasively assess bone strength *in vivo* has become increasingly common in the past two decades due to its potential to improve clinical outcomes in osteoporosis. Although these methods have shown considerable promise in clinical studies, these methods must be thoroughly tested and validated with *ex vivo* gold standards before they can be implemented clinically. To our knowledge, this is the first study to compare the accuracy of MRI-based FEA to mechanical testing of cadaveric proximal femora.

The most important result from this study was that our finite element simulations from the higher resolution isotropic scan showed strong agreement with all mechanically obtained metrics of bone strength, both linear and nonlinear. Simulated axial stiffness, plastic deformation point, and failure force all showed excellent agreement with mechanical testing ($r = 0.88$, 0.89 , and 0.92 , respectively). Furthermore, the slope of the best fit lines for the

axial stiffness, plastic point, and failure force curves were close to unity (slopes = 1.02, 0.93, and 1.09, respectively). We can conclude from the data that our finite element models are accurate for predicting both linear and nonlinear response to loads. Similarly, the simulations created from the anisotropic scan, which has similar in-plane resolution but a larger slice thickness than the isotropic sequence, showed moderate correlations with linear values of axial stiffness and plastic point and strong correlations with failure force ($r = 0.68$, 0.70 , and 0.84). The slope of best fit lines for the anisotropic images also had slopes close to unity, albeit worse than the higher resolution scan, for all values (slopes = 1.14 , 0.96 , and 1.25 , respectively). This further supports the notion that higher resolution images and isotropic voxel sizes will produce better results for modeling bone strength, especially for nonlinear simulations [56]. It is also important to reiterate that all simulated bone strength metrics from the two different scans were strongly correlated within the same specimen ($r = 0.69$, 0.75 , and 0.83). These findings indicate that our finite element model's method of simulating bone yield and post-yield properties is consistent and is dependent on resolution.

MRI FEA has been used in numerous research studies. We have previously validated MR finite element models compared to mechanical testing in the tibia under simple axial compression [47]. Mechanical tests of cadaveric tibiae showed strong to moderate correlations with simulated values of stiffness, yield strength, and ultimate strength ($r = 0.77$, 0.61 , and 0.63 , respectively) [47]. The data presented here demonstrates similar trends to the previous study with substantially more complicated loading conditions. Moreover, the proximal femur is more clinically relevant because hip fractures are vastly more common and more life threatening [4]. MRI FEA has also shown strong correlations to μ CT derived FEA in cadavers at distal sites [30, 40, 56]. Furthermore, a linear version of the current FEA differentiated between fracture and non-fracture groups from postmenopausal women with similar BMD [44]. Lastly, the nonlinear model employed in the current study has shown great reproducibility *in vivo*, both when scanned on the same day or different days and when segmented by the same or different users [46].

The last goal of this study was to conduct a preliminary investigation into the accuracy of the simulated 3D strain maps from our finite element solver. Although we have included strain maps in our previous finite element studies, we have yet to evaluate their accuracy compared to the ground truth. In previous studies, strain maps were reported with arbitrary scaling bars because the calibration to physical values was unknown [45, 46]. Here, we present the first attempt at evaluating and calibrating our automatic strain graphs. Of the strain gauges used, three of the four showed significant correlations. Only the association between the femoral shaft strain gauge and corresponding simulated data did not reach statistical significance, although there is a general trend in the data. This is not surprising since the simulated strain values within the femoral shaft were substantially less than those in the other three regions and had the narrowest dynamic range.

Our results mirror that of several other previously reported studies which investigated the accuracy of DXA and QCT-derived FEA in predicting failure load in a side fall. Johannesdottir et. al [29] mechanically tested 76 proximal femora in a sideways fall configuration and found strong correlations between failure load and DXA or QCT-derived FEA ($r = 0.84$, $r = 0.89$). Similarly, strong correlations between failure load and DXA or

QCT-derived FEA were found in Dall'Ara et. al's study [57] of 36 proximal femora ($r = 0.89$, $r = 0.92$), in Pottecher et. al's study [58] of 40 proximal femora ($r = 0.89$, $r = 0.91$), and in Dragomir-Deascu et. al's study [59] of 9 proximal femora ($r = 0.81$, $r = 0.93$). Although these studies vary slightly in their scope and in their computational and mechanical testing methods, they all independently produced correlations of similar magnitude to each other and to the present study, which found the correlation between failure load and MRI-derived FEA to be $r = 0.92$. Additionally, the failure loads in the aforementioned studies all ranged between 1000–7000 N for specimens with an average of around 75 years old. Courtney et. al investigated age-related fracture loads for the proximal femur in side fall by comparing the failure loads between two different age groups and found that younger cadavers with an average age of 33 had failure loads of 7200 N while older cadavers with an average age of 74 years old failed with an average of 3400 N [60]. The present study had comparable results to those studies, with an average age of 76 and an average failure load of 3300 N, thus suggesting that MRI-derived FEA of the proximal femur would be sensitive enough to evaluate age-related changes in bone quality. It is important to note that, although the referenced DXA correlation values seem relatively close to those from QCT FEA, DXA scans of cadaveric specimens are performed in well-regulated settings which control for the soft tissue thickness and the scanning location [61–63]. This effectively reduces errors in DXA's quantifications and produces correlations which are vastly superior to what they would be *in vivo*, whereas the MRI- and QCT-derived methods would be more robust [63].

We acknowledge some challenges with our experimental procedure for recording the strain. First, we experienced some failures in testing, resulting from improper adhesion to the surface of the cadaver or from the gauges short circuiting. Second, the strain gauges used measured only uniaxial strain and could not resolve the principal strain component. In order to accurately measure this, strain gauge rosettes should be employed in future studies. Finally, due to the inherent design of our voxel-based finite element solver, the strain values are computed as absolute value and are not assigned a direction. Nonetheless, the data presented herein from the strain gauges is promising and warrants further investigation to support its validity.

There were other limitations in this study outside of the localized strain analysis. First, the cadaveric specimens do not move during the scan. Patient motion *in vivo* would cause artifacts in scans at high resolutions, although minor motion can be corrected for. Second, the soft tissue layer was removed from the cadavers after we scanned them. Although we felt this necessary to reduce susceptibility artifacts in the scans and to accurately emulate boundary conditions *in silico*, manual segmentation of the periosteal boundary and the manual removal of soft tissue from the cadavers could result in slight discrepancies between simulated and mechanically tested cadavers, which would have a noticeable effect near the boundary conditions. A third limitation is that the proposed method, like CT and DXA, assumes a constant amount of mineralization per unit volume of bone. This assumption works well for most people but will cause systemic overestimation of bone strength for those with diseases that impact the quality of bone mineralization but not the amount of bone, such as osteomalacia [64]. The only way to non-invasively assess the degree of mineralization of bone *in vivo* is through the use of solid-state MR imaging of bone ^{31}P with ultrashort or zero

echo time pulse sequences [65]. An additional limitation is that the load rate for our mechanical tests, 1.67 mm/s, is less than those typically seen during an *in vivo* sideways fall. Since bone is a known viscoelastic material, some prior studies have elected to load bone in a side fall orientation at 100 mm/s to elicit the most accurate results [29, 59, 66]. However, this study and others have tested bone around 1 mm/s [57, 58] and found similar load ranges to those with 100 m/s. This is supported by the findings from Courtney et. al [66] which showed that increasing the load rate from 2 mm/s to 100 m/s maintained age-related differences in bone strength and only increased the failure load by 20%, indicating that, although bone is viscoelastic, it is relatively constant within these loading regimes.

Another limitation is that our simulations do not model soft tissues, viscoelasticity, moduli anisotropy, and other more complicated mechanics. The cadavers were also frozen for months prior to scanning and testing, which some groups have reported can affect the elastic moduli of bone [67]. Moreover, our powerful desktop computer required around ten hours to compute nonlinear simulations on the higher resolution images. Future studies will investigate methods to reduce computation time and improve the clinical translatability of this method. Lastly, from an imaging standpoint, we have not compared our *ex vivo* images to the gold standard of μ CT.

Conclusion

This study validates MRI-derived finite element analysis as an accurate method for predicting bone strength. MRI-derived finite element analysis holds great clinical promise, as it produces no ionizing radiation. This method would also be particularly useful in research studies evaluating the efficacy of new pharmaceutical and interventions aimed at improving bone strength. These studies often require repeated scans over short periods of time in which CT could be potentially hazardous because of its ionizing radiation. MRI would provide a safer alternative, especially in applications involving the hip.

Although the method proposed herein has been demonstrated to be robust, there is still substantial work required before it can be implemented clinically. The first and most obvious drawback to clinical implementation is the cost of MRI relative to DXA. However, it is conceivable that this method could become a second-line diagnostic test for borderline at-risk patients, in the same manner that more expensive nuclear imaging, exercise treadmill, or CT tests are used in the field of cardiology to risk-stratify patients' risk for ischemic heart disease. The second drawback is the sheer amount of time and expertise required to segment the images, define the thresholds, and create the finite element meshes. In the future, automated image analysis programs will improve the attractiveness of these methods and make clinical translation more viable.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Brauer CA, et al., Incidence and mortality of hip fractures in the United States. *Jama*, 2009 302(14): p. 1573–9. [PubMed: 19826027]
2. Magaziner J, et al., Changes in functional status attributable to hip fracture: a comparison of hip fracture patients to community-dwelling aged. *Am J Epidemiol*, 2003 157(11): p. 1023–31. [PubMed: 12777366]
3. Oden A, et al., Assessing the impact of osteoporosis on the burden of hip fractures. *Calcif Tissue Int*, 2013 92(1): p. 42–9. [PubMed: 23135744]
4. Burge R, et al., Incidence and economic burden of osteoporosis-related fractures in the United States, 2005–2025. *J Bone Miner Res*, 2007 22(3): p. 465–75. [PubMed: 17144789]
5. Quigley PA, et al., Incidence and cost of serious fall-related injuries in nursing homes. *Clin Nurs Res*, 2012 21(1): p. 10–23. [PubMed: 21788448]
6. Cadarette SM, et al., Relative effectiveness of osteoporosis drugs for preventing nonvertebral fracture. *Ann Intern Med*, 2008 148(9): p. 637–46. [PubMed: 18458276]
7. Tabatabaei-Malazy O, et al., New horizons in treatment of osteoporosis. *Daru*, 2017 25(1): p. 2. [PubMed: 28173850]
8. Lin TC, et al., Comparative effectiveness of osteoporosis drugs in preventing secondary nonvertebral fractures in Taiwanese women. *J Clin Endocrinol Metab*, 2013 98(12): p. 4717–26. [PubMed: 24081731]
9. Blake GM and Fogelman I, The role of DXA bone density scans in the diagnosis and treatment of osteoporosis. *Postgraduate medical journal*, 2007 83(982): p. 509–517. [PubMed: 17675543]
10. Kanis JA, et al., Interpretation and use of FRAX in clinical practice. *Osteoporos Int*, 2011 22(9): p. 2395–411. [PubMed: 21779818]
11. Bolotin HH, The significant effects of bone structure on inherent patient-specific DXA in vivo bone mineral density measurement inaccuracies. *Med Phys*, 2004 31(4): p. 774–88. [PubMed: 15124995]
12. Bolotin HH, DXA in vivo BMD methodology: an erroneous and misleading research and clinical gauge of bone mineral status, bone fragility, and bone remodelling. *Bone*, 2007 41(1): p. 138–54. [PubMed: 17481978]
13. Siris ES, et al., Bone mineral density thresholds for pharmacological intervention to prevent fractures. *Arch Intern Med*, 2004 164(10): p. 1108–12. [PubMed: 15159268]
14. Marshall D, Johnell O, and Wedel H, Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *Bmj*, 1996 312(7041): p. 1254–9. [PubMed: 8634613]
15. Boskey AL, Bone composition: relationship to bone fragility and antiosteoporotic drug effects. *Bonekey Rep*, 2013 2: p. 447. [PubMed: 24501681]
16. Ruppel ME, Miller LM, and Burr DB, The effect of the microscopic and nanoscale structure on bone fragility. *Osteoporos Int*, 2008 19(9): p. 1251–65. [PubMed: 18317862]
17. Lang TF, et al., Volumetric quantitative computed tomography of the proximal femur: precision and relation to bone strength. *Bone*, 1997 21(1): p. 101–8. [PubMed: 9213015]
18. Ramamurthi K, et al., An in vivo comparison of hip structure analysis (HSA) with measurements obtained by QCT. *Osteoporos Int*, 2012 23(2): p. 543–51. [PubMed: 21394495]
19. Black DM, et al., Proximal femoral structure and the prediction of hip fracture in men: a large prospective study using QCT. *J Bone Miner Res*, 2008 23(8): p. 1326–33. [PubMed: 18348697]
20. Keaveny TM, et al., Femoral and vertebral strength improvements in postmenopausal women with osteoporosis treated with denosumab. *J Bone Miner Res*, 2014 29(1): p. 158–65. [PubMed: 23794225]

21. Keyak JH, et al., Effect of finite element model loading condition on fracture risk assessment in men and women: the AGES-Reykjavik study. *Bone*, 2013 57(1): p. 18–29. [PubMed: 23907032]
22. Nishiyama KK, et al., Women with previous fragility fractures can be classified based on bone microarchitecture and finite element analysis measured with HR-pQCT. *Osteoporos Int*, 2013 24(5): p. 1733–40. [PubMed: 23179565]
23. Kopperdahl DL, et al., Assessment of incident spine and hip fractures in women and men using finite element analysis of CT scans. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*, 2014 29(3): p. 570–580.
24. Keyak JH, et al., Male-female differences in the association between incident hip fracture and proximal femoral strength: a finite element analysis study. *Bone*, 2011 48(6): p. 1239–45. [PubMed: 21419886]
25. Carballido-Gamio J, et al., Proximal femoral density distribution and structure in relation to age and hip fracture risk in women. *J Bone Miner Res*, 2013 28(3): p. 537–46. [PubMed: 23109068]
26. Alffram PA, AN EPIDEMIOLOGIC STUDY OF CERVICAL AND TROCHANTERIC FRACTURES OF THE FEMUR IN AN URBAN POPULATION. ANALYSIS OF 1,664 CASES WITH SPECIAL REFERENCE TO ETIOLOGIC FACTORS. *Acta Orthop Scand Suppl*, 1964 65: p. Suppl 65:1–109.
27. Keyak JH, et al., Prediction of fracture location in the proximal femur using finite element models. *Med Eng Phys*, 2001 23(9): p. 657–64. [PubMed: 11755810]
28. Langton CM, Pisharody S, and Keyak JH, Comparison of 3D finite element analysis derived stiffness and BMD to determine the failure load of the excised proximal femur. *Med Eng Phys*, 2009 31(6): p. 668–72. [PubMed: 19230742]
29. Johannesdottir F, et al., Comparison of non-invasive assessments of strength of the proximal femur. *Bone*, 2017 105: p. 93–102. [PubMed: 28739416]
30. Rajapakse CS, et al., Computational biomechanics of the distal tibia from high-resolution MR and micro-CT images. *Bone*, 2010 47(3): p. 556–63. [PubMed: 20685323]
31. Knowles NK, Ip K, and Ferreira LM, The Effect of Material Heterogeneity, Element Type, and Down-Sampling on Trabecular Stiffness in Micro Finite Element Models. *Ann Biomed Eng*, 2019 47(2): p. 615–623. [PubMed: 30362084]
32. Yeni YN, et al., Effect of microcomputed tomography voxel size on the finite element model accuracy for human cancellous bone. *J Biomech Eng*, 2005 127(1): p. 1–8. [PubMed: 15868782]
33. Lu Y, et al., The effect of in situ/in vitro three-dimensional quantitative computed tomography image voxel size on the finite element model of human vertebral cancellous bone. *Proc Inst Mech Eng H*, 2014 228(11): p. 1208–13. [PubMed: 25500865]
34. Engelke K, et al., The effect of the cathepsin K inhibitor ONO-5334 on trabecular and cortical bone in postmenopausal osteoporosis: the OCEAN study. *J Bone Miner Res*, 2014 29(3): p. 629–38. [PubMed: 24038152]
35. Yang L, et al., Site-specific differential effects of once-yearly zoledronic acid on the hip assessed with quantitative computed tomography: results from the HORIZON Pivotal Fracture Trial. *Osteoporos Int*, 2013 24(1): p. 329–38. [PubMed: 23128664]
36. Han M, et al., Variable flip angle three-dimensional fast spin-echo sequence combined with outer volume suppression for imaging trabecular bone structure of the proximal femur. *J Magn Reson Imaging*, 2015 41(5): p. 1300–10. [PubMed: 24956149]
37. Krug R, et al., Feasibility of in vivo structural analysis of high-resolution magnetic resonance images of the proximal femur. *Osteoporos Int*, 2005 16(11): p. 1307–14. [PubMed: 15999292]
38. Chang G, et al., Feasibility of three-dimensional MRI of proximal femur microarchitecture at 3 tesla using 26 receive elements without and with parallel imaging. *J Magn Reson Imaging*, 2014 40(1): p. 229–38. [PubMed: 24711013]
39. Chang G, et al., MRI assessment of bone structure and microarchitecture. *J Magn Reson Imaging*, 2017 46(2): p. 323–337. [PubMed: 28165650]
40. Liu XS, et al., Accuracy of high-resolution in vivo micro magnetic resonance imaging for measurements of microstructural and mechanical properties of human distal tibial bone. *J Bone Miner Res*, 2010 25(9): p. 2039–50. [PubMed: 20499379]

41. Newitt DC, et al., In vivo assessment of architecture and micro-finite element analysis derived indices of mechanical properties of trabecular bone in the radius. *Osteoporos Int*, 2002 13(1): p. 6–17. [PubMed: 11878456]
42. Zhang XH, et al., In vivo microMRI-based finite element and morphological analyses of tibial trabecular bone in eugonadal and hypogonadal men before and after testosterone treatment. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*, 2008 23(9): p. 1426–1434.
43. Wehrli FW, et al., Digital topological analysis of in vivo magnetic resonance microimages of trabecular bone reveals structural implications of osteoporosis. *J Bone Miner Res*, 2001 16(8): p. 1520–31. [PubMed: 11499875]
44. Chang G, et al., Finite element analysis applied to 3-T MR imaging of proximal femur microarchitecture: lower bone strength in patients with fragility fractures compared with control subjects. *Radiology*, 2014 272(2): p. 464–74. [PubMed: 24689884]
45. Chang G, et al., Measurement reproducibility of magnetic resonance imaging-based finite element analysis of proximal femur microarchitecture for in vivo assessment of bone strength. *Magma*, 2015 28(4): p. 407–12. [PubMed: 25487834]
46. Rajapakse CS, et al., Patient-specific Hip Fracture Strength Assessment with Microstructural MR Imaging-based Finite Element Modeling. *Radiology*, 2017 283(3): p. 854–861. [PubMed: 27918708]
47. Rajapakse CS, et al., Accuracy of MRI-based finite element assessment of distal tibia compared to mechanical testing. *Bone*, 2018 108: p. 71–78. [PubMed: 29278746]
48. Zysset PK, et al., Elastic modulus and hardness of cortical and trabecular bone lamellae measured by nanoindentation in the human femur. *Journal of Biomechanics*, 1999 32(10): p. 1005–1012. [PubMed: 10476838]
49. Rajapakse CS, et al., Micro-MR imaging-based computational biomechanics demonstrates reduction in cortical and trabecular bone strength after renal transplantation. *Radiology*, 2012 262(3): p. 912–20. [PubMed: 22357891]
50. Zhang N, et al., Assessment of trabecular bone yield and post-yield behavior from high-resolution MRI-based nonlinear finite element analysis at the distal radius of premenopausal and postmenopausal women susceptible to osteoporosis. *Academic radiology*, 2013 20(12): p. 1584–1591. [PubMed: 24200486]
51. Magland JF, et al., Computationally-Optimized Bone Mechanical Modeling from High-Resolution Structural Images. *PLOS ONE*, 2012 7(4): p. e35525. [PubMed: 22558164]
52. Zhang N, et al., Potential of in vivo MRI-based nonlinear finite-element analysis for the assessment of trabecular bone post-yield properties. *Med Phys*, 2013 40(5): p. 052303. [PubMed: 23635290]
53. Grassi L, et al., Accuracy of finite element predictions in sideways load configurations for the proximal human femur. *J Biomech*, 2012 45(2): p. 394–9. [PubMed: 22079387]
54. Liebl H, et al., In-vivo assessment of femoral bone strength using Finite Element Analysis (FEA) based on routine MDCT imaging: a preliminary study on patients with vertebral fractures. *PloS one*, 2015 10(2): p. e0116907–e0116907. [PubMed: 25723187]
55. Keyak JH, et al., Validation of an automated method of three-dimensional finite element modelling of bone. *Journal of Biomedical Engineering*, 1993 15(6): p. 505–509. [PubMed: 8277756]
56. Rajapakse CS, et al., Implications of noise and resolution on mechanical properties of trabecular bone estimated by image-based finite-element analysis. *J Orthop Res*, 2009 27(10): p. 1263–71. [PubMed: 19338030]
57. Dall'Ara E, et al., Experimental validation of DXA-based finite element models for prediction of femoral strength. *J Mech Behav Biomed Mater*, 2016 63: p. 17–25. [PubMed: 27341287]
58. Pottecher P, et al., Prediction of Hip Failure Load: In Vitro Study of 80 Femurs Using Three Imaging Methods and Finite Element Models-The European Fracture Study (EFFECT). *Radiology*, 2016 280(3): p. 837–47. [PubMed: 27077380]
59. Dragomir-Daescu D, et al., Robust QCT/FEA models of proximal femur stiffness and fracture load during a sideways fall on the hip. *Ann Biomed Eng*, 2011 39(2): p. 742–55. [PubMed: 21052839]
60. Courtney AC, et al., Age-related reductions in the strength of the femur tested in a fall-loading configuration. *J Bone Joint Surg Am*, 1995 77(3): p. 387–95. [PubMed: 7890787]

61. Lekamwasam S, Sumith R, and Lenora J, Effect of Leg Rotation on Hip Bone Mineral Density Measurements. *Journal of Clinical Densitometry*, 2003 6(4): p. 331–336. [PubMed: 14716045]
62. Watts NB, Fundamentals and pitfalls of bone densitometry using dual-energy X-ray absorptiometry (DXA). *Osteoporos Int*, 2004 15(11): p. 847–54. [PubMed: 15322740]
63. Yu EW, et al., Simulated increases in body fat and errors in bone mineral density measurements by DXA and QCT. *Journal of Bone and Mineral Research*, 2012 27(1): p. 119–124. [PubMed: 21915902]
64. Grynblas M, Age and disease-related changes in the mineral of bone. *Calcified tissue international*, 1993 53 Suppl 1: p. S57–S64. [PubMed: 8275381]
65. Zhao X, et al., Feasibility of assessing bone matrix and mineral properties in vivo by combined solid-state ¹H and ³¹P MRI. *PloS one*, 2017 12(3): p. e0173995–e0173995. [PubMed: 28296979]
66. Courtney AC, et al., Effects of loading rate on strength of the proximal femur. *Calcif Tissue Int*, 1994 55(1): p. 53–8. [PubMed: 7922790]
67. Lee W and Jasiuk I, Effects of freeze-thaw and micro-computed tomography irradiation on structure-property relations of porcine trabecular bone. *J Biomech*, 2014 47(6): p. 1495–8. [PubMed: 24612985]

Highlights

- MRI can be used to assess proximal femur strength.
- MRI-derived finite element analysis correlates with mechanical testing in cadaveric proximal femora specimens.
- The accuracy of MRI-derived finite element measures of bone strength may depend on imaging resolution.

Figure 1:

Diagram demonstrating both the computational and experimental workflow for this study. For the computational half of this study, MR images were acquired in cadaveric femora specimens with a thin layer of soft tissue surrounding the periosteum. Following MR scans, we performed 3D reconstruction, segmentation, and linearly scaled signal intensities to create the bone volume fraction (BVF) map. A representative slice of the MR scan and the corresponding BVF map slice are shown at the bottom in the “MR Image” and “Finite Element Analysis” section. Boundary condition diagrams simulating sideways fall loading conditions are superimposed over the BVF map in the FEA section at the bottom. On the experimental side, four strain gauges were attached to the periosteal surface in the regions illustrated by the cartoon on the “Attach Strain Gauges” section. Cadavers were then destructively tested in a sidefall configuration as shown in the “Mechanical Testing” section. Comparisons were drawn between experimental and computational results.

Figure 2:
 Correlation plots between mechanical and computational measures of bone strength from higher resolution isotropic bSSFP sequence.

Figure 3:
 Correlations between mechanical parameters and computational measures of bone strength from the anisotropic SPGR sequence.

Figure 4:

Correlations between computational measures of bone strength from our two models, the isotropic bSSFP model and the anisotropic SPGR model.

Figure 5:

Correlations between local microstrain values obtained from strain gauges compared to magnitude strains from finite element models from the 300 μm isotropic bSSFP sequence.

Figure 6:

Comparison of results from a young, 44-year-old donor and an old, 83-year-old donor. From left to right, the columns show the higher resolution isotropic scan, the finite element mesh with boundary conditions, and the resultant strain maps. The finite element mesh is equivalent to the scaled Bone Volume Fraction (BVF) map of the bone with the added boundary conditions.

Table 1:

Mean $\pm$ SD determined by mechanical testing and computational modeling.

	Stiffness (N/mm)	Onset of Plastic Deformation (Newtons)	Failure Force (Newtons)
Mechanical Testing	871.3 $\pm$ 327.4	2461.8 $\pm$ 896.7	3298.6 $\pm$ 1355.9
bSSFP Isotropic Model	894.4 $\pm$ 347.0	2295.4 $\pm$ 889.3	2697.7 $\pm$ 1317.2
SPGR Anisotropic Model	1041.0 $\pm$ 547.1	2576.6 $\pm$ 936.9	4511.4 $\pm$ 1531.3