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Assessment of trabecular bone yield and post-yield behavior from high-resolution MRI-based nonlinear finite-element analysis at the distal radius of pre- and postmenopausal women susceptible to osteoporosis

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Abstract

Rationale and Objectives—To assess the performance of a nonlinear micro-finite element model on predicting trabecular bone (TB) yield and post-yield behavior based on high-resolution in-vivo MR images via the serial reproducibility.

Materials and Methods—The nonlinear model captures material nonlinearity by iteratively adjusting tissue-level modulus based on tissue-level effective strain. It enables simulations of TB yield and post-yield behavior from micro-MR images at in-vivo resolution by solving a series of

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nonlinear systems via an iterative algorithm on a desktop computer. Measures of mechanical competence (yield strain/strength, ultimate strain/strength, modulus of resilience and toughness) were estimated at the distal radius of pre- and postmenopausal women (N=20; age 50–75) in whom osteoporotic fractures typically occur. Each subject underwent three scans (20.2 ± 14.5 days). Serial reproducibility was evaluated via coefficients of variation (CV) and intra-class correlation coefficient (ICC).

Results—Nonlinear simulations were completed in an average of 14 minutes per 3D image data set involving analysis of 61 strain levels. The predicted yield strain/strength, ultimate strain/strength, modulus of resilience and toughness had a mean value of 0.78%, 3.09 MPa, 1.35%, 3.48 MPa, 14.30 kPa and 32.66 kPa, respectively, covering a substantial range by a factor of up to four. ICC ranged from 0.986 to 0.994 (average 0.991); CV ranged from 1.01% to 5.62% (average 3.6%), with yield strain and toughness having the lowest and highest CV values, respectively.

Conclusion—The data suggest that the yield and post-yield parameters have adequate reproducibility to evaluate treatment effects in interventional studies within short follow-up periods.

Keywords

Finite element analysis; Trabecular bone mechanics; MRI; reproducibility and reliability

Introduction

Osteoporosis is a degenerative disorder of the skeleton, leading to increased risk of fracture. The most common sites of osteoporotic fractures are the hip, spine and wrist; all sites with a significant fraction of trabecular bone (TB). Fractures of the distal radius (e.g., Colles fracture) account for approximately 15% of all fractures in adults (1). They are more prevalent at earlier age than hip fractures (2, 3) and have been shown to be a risk factor of future spine and hip fractures (4, 5). The incidence of Colles fracture is greater in women than in men, especially after menopause (6). For these reasons, the distal radius is an anatomic site of great interest for early detection of osteoporosis.

The ability of bone to resist stresses without failure (often referred to as “bone mechanical competence”) is impaired in subjects with osteoporosis. Improvements in mechanical competence, for example via medication or exercise, can help prevent osteoporosis or alleviate its symptoms. In many earlier studies, bone structural and topological parameters have been used as surrogates for fracture susceptibility based on the associations found between micro-architecture and presence or extent of osteoporotic fractures (7–9). However, structural parameters are only surrogates for the bone’s mechanical failure behavior. The most direct approach to evaluate bone mechanical competence is via image-based micro-finite element (μ FE) analysis (10–12). Constructed from high-resolution images of bone micro-structure comprising both trabecular and cortical compartments, μ FE models are capable of directly estimating bone elastic moduli, predicting bone strength and assessing osteoporotic fracture risk (12–14).

In order to accurately estimate mechanical or structural parameters, images of adequate signal-to-noise ratio (SNR) and spatial resolution are essential. Advanced imaging modalities, such as HR-pQCT and micro-MRI (μ MR), enable in-vivo acquisition of images partially resolving individual trabeculae. During the past decade, μ MRI has proven its potential as a non-invasive method for in-vivo 3D high-resolution imaging of trabecular and cortical bone micro-architecture in the absence of ionizing radiation (15, 16). Specifically, μ MR image-based structural and mechanical analysis has demonstrated its ability to detect alterations due to disease progression or in response to treatment (17–19).

Recently, nonlinear μ FE analysis has been suggested as a means to directly predict bone strength and simulate failure behavior (14, 20, 21). Targeted modeling of complex geometries such as trabecular bone, μ FE models typically involve solving large-scale systems requiring extensive computing resources. To alleviate computational demands, most μ FE models used in computational bone mechanics have been confined to the linear-elastic regime, which limits their applications to small deformations and limits their estimates to elastic moduli. In contrast, nonlinear μ FE models have been shown to provide information more relevant to bone mechanical competence, for instance, tensile and compressive yield and post-yield properties (20–23). Furthermore, in addition to providing simple illustrations of strain distributions as in the linear model, nonlinear analysis can also simulate local changes in strain and predict the site of failure as stress increases.

In this work, the performance of a recently developed nonlinear μ FE model (24) is examined in terms of serial reproducibility and reliability of TB yield and post-yield estimates at the distal radius of twenty women using high-resolution in-vivo MR images. The nonlinear algorithm and program takes advantage of a computationally optimized algorithm for linear μ FE analysis (25) complemented by a strain-based criteria allowing dynamic adjustment of tissue-level modulus. Here, it has been applied in conjunction with a pipeline for image acquisition, registration and preprocessing. Previous studies mostly focused on evaluating the reproducibility of μ MR or HR-pQCT image-derived structural parameters of trabecular bone; those targeting TB biomechanics have been solely confined to the linear loading regime (26–29). The present study is the first to assess variability and reproducibility of nonlinear μ FE analyzed data in a substantial group of subjects in whom osteoporotic fractures typically occur.

Materials and Methods

Image acquisition

In-vivo μ MR images of the right distal radius from twenty female subjects (age ranges 50–75; 17 postmenopausal, 3 premenopausal) were drawn from a prior study described in (29). All subjects signed an informed consent in accordance with study guidelines of the Institutional Review Board. None of the subjects had a history of fracture, treatment of osteoporosis or bone cancer. Each subject had been scanned three times (baseline, follow-ups 1 and 2) over the course of eight weeks, with the mean interval between being 20.2 days. All imaging was performed on a Siemens 1.5T MAGNETOM Sonata MR scanner (Siemens Medical Solution, Erlangen, Germany) using a transmit-receive elliptical birdcage wrist radiofrequency coil (InsightMRI, Worcester, MA) with a modified 3D fast large-angle spin echo (FLASE) pulse sequence (30) (ROI = $70 \times 42 \times 13 \text{ mm}^3$, matrix = $512 \times 460 \times 32$, voxel size = $137 \times 137 \times 410 \text{ }\mu\text{m}^3$, TR/TE = 80/10 ms, flip angle = 140° and acquisition time = 10.4 min).

Image processing

The raw μ MR data were corrected for subject motion during the scan using either the navigator data collected during the FLASE acquisition (31) or an auto-focusing correction algorithm (32). The normalized gradient squared (NGS) value was used as the image sharpness metric for selecting the best motion-corrected images. To ensure that the VOI was consistent across the three time-points, follow-up images were retrospectively registered to the baseline images (33). Subsequently, image intensity variations caused by inhomogeneous sensitivity of the receiver coil were corrected using a local thresholding algorithm (34). The resultant images were then masked to isolate the TB region and processed to generate 3D grayscale bone volume fraction (BVF) maps (3D arrays) (25) as

input to the μ FE model. Each voxel value in the BVF maps represents the fractional occupancy of bone in that voxel, ranging from 0% for pure marrow to 100% for pure bone.

Simulation of yield and post-yield behavior

TB yield and post-yield parameters were estimated via a two-step procedure. First, a series of strains were applied incrementally to vertices on the proximal surface of the input BVF map to simulate compressive loading along the axial direction. At very small strains, trabecular tissue was assumed to be linearly elastic with an empirically determined Young's modulus (E) of 15GPa and a Poisson's ratio (ν) of 0.3 (35). A linear system, $\mathbf{A}\mathbf{u}=\mathbf{b}$, was solved (25) for the resultant stress, where $\mathbf{A}$ is a sparse matrix referred to as the global stiffness matrix, $\mathbf{u}$ represents the displacements at all free vertices in each principal direction, and $\mathbf{b}$ is defined according to the applied boundary conditions. The boundary conditions were set to represent axial compression with no friction along the transverse directions. Tissue-level modulus (TM) was assumed on each element to be linearly proportional to voxel intensity (BVF) as $TM = E \times BVF$. This approach accounts for partial volume effects in the limited spatial resolution regime of in-vivo μ MR images.

At large deformations, trabecular tissue exhibits nonlinear stress-strain behavior. Material nonlinearity was thus included by assuming a nonlinear relationship $\sigma = C(\epsilon)$ between the local stress (σ) and strain (ϵ). $C(\epsilon)$ is the stiffness matrix, which in the linear regime for isotropic material is given as:

$$\mathbf{C} = \frac{E}{(1+\nu)(1-2\nu)} \begin{bmatrix} 1-\nu & \nu & \nu & 0 & 0 & 0 \\ \nu & 1-\nu & \nu & 0 & 0 & 0 \\ \nu & \nu & 1-\nu & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{1-2\nu}{2} & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{1-2\nu}{2} & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{1-2\nu}{2} \end{bmatrix} \cdot [1]$$

In the nonlinear case, $\mathbf{C}$ further depends on ϵ . Trabecular bone post-yield behavior was assumed to follow that of an elastic-plastic material. Thus, the dependence of $\mathbf{C}$ on ϵ was expressed in our model via a nonlinear relationship between E and ϵ derived on an element-by-element basis from the stress-strain relation for an elastic-plastic body (36) via the following function (24):

$$E(\epsilon_{tissue}) = ((\text{sech}((50 \times \epsilon_{tissue} + 0.53)^{1.4}))^{0.6} + 0.05) \times 15 \text{ GPa}. [2]$$

Here sech stands for hyperbolic secant and the quantity ϵ_{tissue} is the tissue-level effective strain calculated for each element using $\epsilon_{tissue} = \sqrt{2 \times U/E}$ (37) with $E=15$ GPa and U being the strain-energy density of that element. All other parameters in (2) were empirically calibrated so that the resultant stress-strain curves were consistent with those observed by mechanical testing in work performed by others (14, 20, 21, 38). Equation [2] used to relate the local strain to the modulus of elasticity is illustrated in Figure 1 of (24). A nonlinear system, $\mathbf{A}(\mathbf{u})\mathbf{u} = \mathbf{b}$, was thereby established in a way analogous to that in the linear case (25). This nonlinear system was solved for the resultant stress via an iterative algorithm (24). The maximum number of iterations was empirically set to 30. A total of 61 strain levels were applied in all experiments with the smallest strain and the step size both being 0.05%.

Stress-strain curves were computed as the best-fit cubic polynomial to the points of applied strains and resultant stresses. The various mechanical parameters derived are defined in the

cartoon of Figure 1. TB yield and post-yield behavior was assessed in terms of the following mechanical properties: strain (yield and ultimate strain), strength (yield and ultimate strength), energy (modulus of resilience and toughness). The yield point is the location on the stress-strain curve at which plastic deformation begins to occur, i.e. where the stress-strain relationship changes from linear to nonlinear, which was obtained here using the 0.2% offset rule (20). The strain (stress) value at this point was taken as the yield strain (strength). Further, the peak location of the load deformation curve was defined as the ultimate point and its corresponding strain (stress) value as the ultimate strain (strength). The mechanical energy per unit volume, i.e., the area under the stress-strain curve, was also computed providing modulus of resilience and toughness. The modulus of resilience corresponds to the energy the bone can absorb without sustaining damage while toughness represents the energy bone can absorb before it fails. The former was calculated here as the integral of the fitted polynomial to the stress-strain curve up to the yield point; the latter as the integral up to the ultimate point. In mechanical testing toughness is usually determined as the area up to failure strain. However, there is currently no unique quantitative criterion to identify the fracture point from simulated stress-strain curves.

All simulations were performed on a laboratory desktop computer (dual-quad core Xeon 3.16 GHz CPUs equipped with 40 GB of RAM).

Statistical Analysis

Coefficients of variation (CV) and intra-class correlation coefficient (ICC) were calculated as metrics of reproducibility and reliability, respectively. All statistical analyses were performed using JMP Discovery Software (JMP 9.0; SAS Institute Inc., Cary, NC, USA), with $p < 0.05$ indicating statistical significance.

Results

Micro-FE models derived from in-vivo μ MR images of the distal radius contained an average of 65.2 thousand elements requiring approximately 13.7 minutes per 3D image dataset. On average, 62% of the originally acquired volume was retained as the common volume for μ FE analysis after retrospective registration. Good visual reproducibility and anatomical alignment are illustrated by the cross-sectional images as well as their BVF maps and 3D volume-rendered images from a subject at three scan time-points (Figure 2), indicating the effectiveness of registration. Examples of simulated stress-strain curves (Figure 3) as well as resultant maximum strain intensity projection maps at 0.8% applied strain (Figure 4) demonstrate within-group similarities and between-subject variations in the simulated results. Also note that subject 1 exhibits consistently greater proportion of failed trabeculae and overall less-strained trabeculae across all three time-points than subject 2, suggesting TB of subject 2 to sustain more even loading than that of subject 1, thus having greater ultimate strain value, which is consistent with that shown in the simulated stress-strain curves (Figure 3).

The means ($\pm$ S.D.), ranges, CVs (averaged over subjects) and ICCs for all predicted parameters are listed in Table 1.

Notable is the substantial range of the various mechanical measures in the twenty subjects studied, in particular in terms of ultimate strain (covering a range of about a factor of two), yield strength, ultimate strength (these two spanning a factor of about three), modulus of resilience and toughness (the latter both by a factor of four). In comparison, the variation in yield strain was much smaller, which is in the range reported in (38). For instance, two data sets from two subjects at one single time-point show distinctly different structural features in

their MR images and simulated stress-strain curves (Figure 5) as well as calculated yield and post-yield parameters (Table 2).

ICCs ranged from 0.986 to 0.994 with an average value of 0.991, CVs from 1.01% to 5.62% (average 3.6%), with yield strain and toughness having the lowest and highest values, respectively. Overall, the results indicate that between-subject variances dominated over within-subject variances for all parameters, also evident in the examples of simulated stress-strain curves (Figure 3) and strain maps (Figure 4).

Figure 6 displays the test-retest plots for all the nonlinear μ FEA-predicted parameters, depicting strong correlations ($R^2 = 0.92$, all $p < 0.0001$) between estimates at baseline and follow-ups, which is consistent with the ICC values (Table 1). Also notable are the resultant regression lines being close to the line of identity (slope range: 0.97~1.09; and small intercepts), illustrating the consistency of estimates on the same subject at different time-points as well as the degree of reliability of our nonlinear modeling.

Discussion

Reproducibility of MR or HR-pQCT image-derived structural and elastic parameters has been reported previously (26–29, 39, 40). However, no prior studies have evaluated the reproducibility of μ MR image-based nonlinear μ FEA-derived mechanical parameters. The present work demonstrates a high level of longitudinal reproducibility and reliability for both TB yield and post-yield parameters in subjects who, based on their age, are more prone to osteoporosis-associated fracture.

Reproducibility is fundamental to detection of subtle short-term changes in the progression of degenerative bone disease or in response to treatment. The coefficient of variation (CV) has typically been used to assess reproducibility in terms of consistency of repeated measurements. However, this single metric is not sufficient to measure the parameter's ability to differentiate subjects. By contrast, the intra-class correlation coefficient (ICC) includes both sources of intra- and inter-subject variations, thus serving as a more informative metric of precision. For example, in the present work, average CV of yield strain is much smaller than that of toughness which, however, does not necessarily suggest that yield strain has greater sensitivity to detect changes than toughness does, because ICCs of these two parameters are very close due to the larger inter-subject variation in toughness. The estimated CVs and ICCs in Table 1 suggest all parameters to have comparable sensitivity of detection, with yield strength and ultimate strength being slightly more sensitive and ultimate strain and toughness slightly less so.

The assessment of the reproducibility can be affected by many sources, for instance, the stability of the imaging equipment, the technician carrying out the study, subject cooperation (e.g. involuntary subject movement during the scan), the image preprocessing algorithms and the technique used for quantitative analysis. In serial studies, consistent subject repositioning of follow-up relative to baseline scans is important for the achievement of adequate reproducibility. However, the latter is not ensured even when the exam is performed by a highly skilled technician. Image registration is thus essential for the achievement of good reproducibility, particularly in the study of trabecular bone due to its complicated and highly location-dependent 3D micro-structure. Prospective registration (particularly during the scan) helps to improve the accuracy of manual repositioning (41) and retrospective registration further ensures that exactly the same ROIs are analyzed across the time series (33). The registration techniques used in the present study yielded a common volume corresponding to a slab of 8.1 mm thickness, which is approximately 62% of the total acquired volume. In μ FE simulations of compressive loading along the longitudinal

direction, a thicker imaging slab as input to the model is always preferable since it better represents the global trabecular structure and thus guarantees more realistic and accurate simulation results. When simulating failure behavior in the nonlinear regime, an imaging volume representing the intact trabecular structure as input is even more critical.

Another major source of error is subject motion, which can cause image artifacts such as blurring and ghosting. Degraded image quality by even subtle displacements has been shown to significantly affect estimates of structural and mechanical parameters as well as their reproducibility (28, 39). Tight subject immobilization (29) and retrospective motion correction techniques (31, 32) have been utilized in the present study to minimize and correct for subject movement during the scan, contributing to the achieved reproducibility.

The level of reproducibility of TB yield and post-yield parameters demonstrated here is superior to those reported previously for structural and elastic parameters. Newitt et al. (40) indicated CVs for 2D structural parameters in eight healthy distal radii to range from 2.5% to 8.3% whereas for Young's moduli estimated from 3D μ FE analysis the range was much larger (10~22%). Gomberg et al. (39) reported RMS-CV of 4.6~10% for 3D structural parameters in the distal radius and 6.1~9.5% in the distal tibia of six healthy subjects, as well as ICCs from 0.95 to 0.97 in the radius and 0.68~0.92 in the tibia. Images in both of these studies were acquired at 1.5T field strength as in the present work. However, our results show an improved reproducibility of the nonlinear μ FE-derived parameters in the distal radius. In a few more recent investigations from the authors' laboratory, conducted at higher field strength, reproducibility found for structural and elastic parameters in the distal tibia was comparable to our results. For example, Wald et al (27) reported CVs of range 1~5.2% and ICCs 0.75~0.99 in the distal tibia of seven healthy volunteers scanned at 3T. Bhagat et al (28) reported a mean CV of 3.6% (range 1.5~4.9%) and ICCs ranging from 0.95 to 0.99 in five healthy tibiae scanned at 7T. However, errors from inaccurate matching of the analysis volume of repeat scans can be more significant in the radius than in the tibia (39), rendering achievement of comparable reproducibility more challenging. Also notable in the present work is the much larger study population involving patients rather than highly compliant test subjects. A recent study (29) involving the same subjects and using the same raw images evaluated here, reported an average RMS-CVs of 4.4% (range 1.8~7.7%) for structural parameters and 4% for axial stiffness. The average ICC they found was 0.976 (range 0.947~0.986) for structural parameters and 0.992 for axial stiffness. By comparison, lower CVs (1~5.6%) and higher ICCs (0.986~0.994) were found for our estimated post-yield parameters. The present work suggests some of the structural parameters such as surface-to-curve ratio (S/C) and erosion index (EI) to be less sensitive to detect subtle differences than mechanical parameters, as also demonstrated in (27, 29) where average CV of axial stiffness was lower than that of structural parameters.

A limitation of the present study is that only axial compression was considered. Tension or shear-type fractures as well as bending are also very common in the distal radius (42). However, compression typically occurs in addition to bending in Colles' fracture, which is most common in people with osteoporosis. Further, our model can be easily extended to tension-type loadings.

In conclusion, the program for nonlinear micro-FE simulation presented in the present work in conjunction with the image acquisition and preprocessing protocol previously developed produced excellent reproducibility of TB yield and post-yield parameters. The results therefore provide the basis for sample size estimates in future longitudinal studies using image-based nonlinear micro-FEA for the assessment of changes in bone strength and failure behavior in response to intervention.

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References

1. Davis DI, Baratz M. Soft tissue complications of distal radius fractures. *Hand Clinics*. 2010; 26(2): 229–35. [PubMed: 20494749]
2. Kanis J, Johnell O, Oden A, et al. Long-term risk of osteoporotic fracture in Malmö. *Osteoporosis Int*. 2000; 11(8):669–74.
3. Maravic M, Le Bihan C, Landais P, Fardellone P. Incidence and cost of osteoporotic fractures in France during 2001. A methodological approach by the national hospital database. *Osteoporosis Int*. 2005; 16(12):1475–80.
4. Lauritzen J, Schwarz P, McNair P, Lund B, Transbøl I. Radial and humeral fractures as predictors of subsequent hip, radial or humeral fractures in women, and their seasonal variation. *Osteoporosis Int*. 1993; 3(3):133–7.
5. Mallmin H, Ljunghall S, Persson I, Naessén T, Krusemo UB, Bergström R. Fracture of the distal forearm as a forecaster of subsequent hip fracture: a population-based cohort study with 24 years of follow-up. *Calcified tissue international*. 1993; 52(4):269–72. [PubMed: 8467406]
6. Spiegel, P. *Osteoporosis, Etiology, Diagnosis, and Management*. LWW; 1996.
7. Majumdar S, Genant HK, Grampp S, et al. Correlation of trabecular bone structure with age, bone, mineral density, and osteoporotic status: in vivo studies in the distal radius using high-resolution magnetic resonance imaging. *Journal of Bone and Mineral Research*. 1997; 12:111–8. [PubMed: 9240733]
8. Ulrich D, van Rietbergen B, Laib A, Ruegsegger P. The ability of three-dimensional structural indices to reflect mechanical aspects of trabecular bone. *Bone*. 1999; 25(1):55–60. [PubMed: 10423022]
9. Wehrli FW, Gomberg BR, Saha PK, Song HK, Hwang SN, Snyder PJ. Digital topological analysis of in vivo magnetic resonance microimages of trabecular bone reveals structural implications of osteoporosis. *J Bone Miner Res*. 2001; 16(8):1520–31. [PubMed: 11499875]
10. Van Rietbergen B, Weinans H, Huiskes R, Odgaard A. A new method to determine trabecular bone elastic properties and loading using micromechanical finite-element models. *Journal of biomechanics*. 1995; 28(1):69–81. [PubMed: 7852443]
11. Boutroy S, Van Rietbergen B, Sornay-Rendu E, Munoz F, Bouxsein ML, Delmas PD. Finite element analysis based on in vivo HR-pQCT images of the distal radius is associated with wrist fracture in postmenopausal women. *J Bone Miner Res*. 2008; 23(3):392–9. [PubMed: 17997712]
12. Mueller TL, Christen D, Sandercott S, et al. Computational finite element bone mechanics accurately predicts mechanical competence in the human radius of an elderly population. *Bone*. 2011; 48(6):1232–8. [PubMed: 21376150]
13. Van Rietbergen B, Odgaard A, Kabel J, Huiskes R. Direct mechanics assessment of elastic symmetries and properties of trabecular bone architecture. *Journal of Biomech*. 1996; 29:1653–7.
14. Bevill G, Keaveny TM. Trabecular bone strength predictions using finite element analysis of micro-scale images at limited spatial resolution. *Bone*. 2009; 44(4):579–84. [PubMed: 19135184]
15. Majumdar S. Magnetic resonance imaging of trabecular bone structure. *Top Magn Reson Imaging*. 2002; 13(5):323–34. [PubMed: 12464745]
16. Wehrli FW. Structural and functional assessment of trabecular and cortical bone by micro magnetic resonance imaging. *J Magn Reson Imaging*. 2007; 25(2):390–409. [PubMed: 17260403]
17. Wehrli FW, Rajapakse CS, Magland JF, Snyder PJ. Mechanical implications of estrogen supplementation in early postmenopausal women. *J Bone Miner Res*. 2010; 25(6):1406–14. [PubMed: 20200948]
18. Zhang XH, Liu XS, Vasilic B, 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. *J Bone Miner Res*. 2008; 23(9):1426–34. [PubMed: 18410234]

19. Rajapakse CS, Leonard MB, Bhagat YA, Sun W, Magland JF, Wehrli FW. Micro-MR Imaging-based Computational Biomechanics Demonstrates Reduction in Cortical and Trabecular Bone Strength after Renal Transplantation. *Radiology*. 2012; 262(3):912–20. [PubMed: 22357891]
20. Niebur GL, Feldstein MJ, Yuen JC, Chen TJ, Keaveny TM. High-resolution finite element models with tissue strength asymmetry accurately predict failure of trabecular bone. *Journal of biomechanics*. 2000; 33(12):1575–83. [PubMed: 11006381]
21. Verhulp E, Van Rietbergen B, Muller R, Huiskes R. Indirect determination of trabecular bone effective tissue failure properties using micro-finite element simulations. *Journal of biomechanics*. 2008; 41(7):1479–85. [PubMed: 18423473]
22. Macneil JA, Boyd SK. Bone strength at the distal radius can be estimated from high-resolution peripheral quantitative computed tomography and the finite element method. *Bone*. 2008; 42(6):1203–13. [PubMed: 18358799]
23. Charlebois M, Jirásek M, Zysset PK. A nonlocal constitutive model for trabecular bone softening in compression. *Biomechanics and modeling in mechanobiology*. 2010; 9(5):597–611. [PubMed: 20238139]
24. Zhang N, Magland JF, Rajapakse CS, Bhagat YA, Wehrli FW. Potential of in-vivo MRI-based nonlinear finite-element analysis for the assessment of trabecular bone post-yield properties. *Med Phys*. 2013; 40(5)
25. Magland JF, Zhang N, Rajapakse CS, Wehrli FW. Computationally-Optimized Bone Mechanical Modeling from High-Resolution Structural Images. *PLoS ONE*. 2012; 7(4):e35525. [PubMed: 22558164]
26. Müller R, Hildebrand T, Häuselmann H, Rüegsegger P. In vivo reproducibility of three-dimensional structural properties of noninvasive bone biopsies using 3D-pQCT. *Journal of Bone and Mineral Research*. 1996; 11(11):1745–50. [PubMed: 8915782]
27. Wald MJ, Magland JF, Rajapakse CS, Wehrli FW. Structural and mechanical parameters of trabecular bone estimated from in vivo high-resolution magnetic resonance images at 3 tesla field strength. *J Magn Reson Imaging*. 2010; 31(5):1157–68. [PubMed: 20432352]
28. Bhagat YA, Rajapakse CS, Magland JF, et al. Performance of muMRI-Based virtual bone biopsy for structural and mechanical analysis at the distal tibia at 7T field strength. *J Magn Reson Imaging*. 2011; 33(2):372–81. [PubMed: 21274979]
29. Lam SCB, Wald MJ, Rajapakse CS, Liu Y, Saha PK, Wehrli FW. Performance of the MRI-based virtual bone biopsy in the distal radius: Serial reproducibility and reliability of structural and mechanical parameters in women representative of osteoporosis study populations. *Bone*. 2011; 49(4):895–903. [PubMed: 21784189]
30. Magland JF, Wald MJ, Wehrli FW. Spin-echo micro-MRI of trabecular bone using improved 3D fast large-angle spin-echo (FLASE). *Magn Reson Med*. 2009; 61(5):1114–21. [PubMed: 19215044]
31. Song HK, Wehrli FW. In vivo micro-imaging using alternating navigator echoes with applications to cancellous bone structural analysis. *Magnetic Resonance in Medicine*. 1999; 41:947–53. [PubMed: 10332878]
32. Lin W, Ladinsky GA, Wehrli F, Song HK. Image metric-based correction (autofocusing) of motion artifacts in high-resolution trabecular bone imaging. *J Magn Reson Imaging*. 2007; 26:191–7. [PubMed: 17659555]
33. Magland JF, Jones CE, Leonard MB, Wehrli FW. Retrospective 3D registration of trabecular bone MR images for longitudinal studies. *J Magn Reson Imaging*. 2009; 29(1):118–26. [PubMed: 19097098]
34. Vasilic B, Wehrli FW. A novel local thresholding algorithm for trabecular bone volume fraction mapping in the limited spatial resolution regime of in-vivo MRI. *IEEE Trans Med Imaging*. 2005; 24:1574–85. [PubMed: 16353372]
35. Zysset PK, Guo XE, Hoffer CE, Moore KE, Goldstein SA. Elastic modulus and hardness of cortical and trabecular bone lamellae measured by nanoindentation in the human femur. *Journal of biomechanics*. 1999; 32(10):1005–12. [PubMed: 10476838]
36. Betten J. Generalization of nonlinear material laws found in experiments to multiaxial states of stress. *Eur J Mech-A/Solids*. 1989; 8:325–39.

37. Pistoia W, van Rietbergen B, Lochmuller EM, Lill CA, Eckstein F, Ruegsegger P. Estimation of distal radius failure load with micro-finite element analysis models based on three-dimensional peripheral quantitative computed tomography images. *Bone*. 2002; 30(6):842–8. [PubMed: 12052451]
38. Kopperdahl DL, Keaveny TM. Yield strain behavior of trabecular bone. *Journal of biomechanics*. 1998; 31(7):601–8. [PubMed: 9796682]
39. Gombert BR, Wehrli FW, Vasilic B, et al. Reproducibility and error sources of micro-MRI-based trabecular bone structural parameters of the distal radius and tibia. *Bone*. 2004; 35(1):266–76. [PubMed: 15207767]
40. Newitt DC, van Rietbergen B, Majumdar S. Processing and analysis of in vivo high-resolution MR images of trabecular bone for longitudinal studies: reproducibility of structural measures and micro-finite element analysis derived mechanical properties. *Osteoporos Int*. 2002; 13(4):278–87. [PubMed: 12030542]
41. Rajapakse CS, Magland JF, Wehrli FW. Fast prospective registration of in vivo MR images of trabecular bone microstructure in longitudinal studies. *Magn Reson Med*. 2008; 59(5):1120–6. [PubMed: 18421688]
42. Fernandez, DL.; Jupiter, JB. Fractures of the distal radius: a practical approach to management. Springer; 2002.

Figure 1.

Hypothetical load deformation curve with definition of the μ FE-derived mechanical parameters: yield point is the point on the stress-strain curve at which plastic deformation begins to occur, which is calculated here using the 0.2% offset rule; yield strain/strength is the corresponding strain/stress value at the yield point; ultimate strength is set as the peak stress value on the stress-strain curve and the corresponding strain value is referred to as the ultimate strain; modulus of resilience is calculated as the integral of the stress-strain curve from zero to the yield strain point and toughness as the integral from zero to the ultimate strain point.

Figure 2. MR images of the distal radius in a study subject at three time-points (top to bottom: baseline, follow-ups 1 and 2, visually illustrating similarities across.): (a) Cross-sectional view of acquired unprocessed images; (b) Bone volume fraction maps; (c) magnified 3D volume renderings of a small subregion ($2.6 \times 2.6 \times 10.3 \text{ mm}^3$).

Figure 3. Simulated stress-strain curves from two subjects (a, b) scanned at three time-points highlighting within-group similarities and between-subject differences.

Figure 4.

Longitudinal maximum intensity projections of the simulated strain maps for a thin slab of 1.1 mm thickness at 0.8% applied strain for two subjects (a, b in Figure 3) evaluated at three time-points: baseline, follow-ups 1 and 2, highlighting within-group similarities and between-subject differences. Also note that subject 2 has relatively fewer failed trabeculae (shown in white) and overall higher strain values than subject 1, suggesting TB of subject 2 to exhibit greater ultimate strain, which is consistent with that shown in the simulated stress-strain curves (Figure 3).

Figure 5.

Example MR images and simulated stress-strain curves from two subjects showing distinctly different mechanical features reflected by the different stress-strain behaviors. TB in subject 1 has considerably lower toughness and ultimate strength than that of subject 2 (also see Table 2). Distinctly different structural features are apparent with thicker but sparser trabeculation in the bone of subject 2.

Figure 6.

Test-retest plots for nonlinear μ FEA-estimated mechanical parameters from all twenty subjects; blue: follow-up 1 versus baseline; red: follow-up 2 versus baseline; light grey: line of identity ($p < 0.0001$ for all correlations).

Table 1

Parameter means $\pm$ S.D. and ranges for all 20 subjects; average CV and ICC of estimated mechanical parameters from nonlinear simulations for three repeat studies.

	Mean $\pm$ S.D.	Range	Average CV (%)	ICC
Yield strain (%)	0.78 $\pm$ 0.05	[0.70, 0.87]	1.01	0.988
Yield strength (MPa)	3.09 $\pm$ 1.01	[1.62, 5.11]	3.65	0.995
Ultimate strain (%)	1.35 $\pm$ 0.28	[0.90, 1.95]	3.68	0.987
Ultimate strength (MPa)	3.48 $\pm$ 1.05	[1.75, 5.51]	3.42	0.994
Modulus of resilience (kPa)	14.30 $\pm$ 5.39	[6.83, 25.85]	4.19	0.996
Toughness (kPa)	32.77 $\pm$ 12.22	[16.09, 60.22]	5.62	0.986

Table 2

Yield and post-yield parameters for the two subjects in Figure 5.

	Subject 1	Subject 2
Yield strain (%)	0.74	0.87
Yield strength (MPa)	1.97	5.11
Ultimate strain (%)	0.90	1.50
Ultimate strength (MPa)	2.03	5.50
Modulus of resilience (kPa)	8.60	25.85
Toughness (kPa)	16.09	60.22