Potential of *in vivo* MRI-based nonlinear finite-element analysis for the assessment of trabecular bone post-yield properties

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Purpose: Bone strength is the key factor impacting fracture risk. Assessment of bone strength from high-resolution (HR) images have largely relied on linear micro-finite element analysis (μ FEA) even though failure always occurs beyond the yield point, which is outside the linear regime. Nonlinear μ FEA may therefore be more informative in predicting failure behavior. However, existing nonlinear models applied to trabecular bone (TB) have largely been confined to micro-computed tomography (μ CT) and, more recently, HR peripheral quantitative computed tomography (HR-pQCT) images, and typically have ignored evaluation of the post-yield behavior. The primary purpose of this work was threefold: (1) to provide an improved algorithm and program to assess TB yield as well as post-yield properties; (2) to explore the potential benefits of nonlinear μ FEA beyond its linear counterpart; and (3) to assess the feasibility and practicality of performing nonlinear analysis on desktop computers on the basis of micro-magnetic resonance (μ MR) images obtained *in vivo* in patients.

Methods: A method for nonlinear μ FE modeling of TB yield as well as post-yield behavior has been designed where material nonlinearity is captured by adjusting the tissue modulus iteratively according to the tissue-level effective strain obtained from linear analysis using a computationally optimized algorithm. The software allows for images at *in vivo* μ MRI resolution as input with retention of grayscale information. Associations between axial stiffness estimated from linear analysis and yield as well as post-yield parameters from nonlinear analysis were investigated from *in vivo* μ MR images of the distal tibia ($N = 20$; ages: 58–84) and radius ($N = 20$; ages: 50–75).

Results: All simulations were completed in 1 h or less for 61 strain levels using a desktop computer (dual quad-core Xeon 3.16 GHz CPUs equipped with 40 GB of RAM). Although yield stress and ultimate stress correlated strongly ($R^2 > 0.95$, $p < 0.001$) with axial stiffness, toughness correlated moderately at the distal tibia ($R^2 = 0.81$, $p < 0.001$) and only weakly at the distal radius ($R^2 = 0.34$, $p = 0.007$). Further, toughness was found to vary by up to 16% for bone of very similar axial stiffness ($< 2\%$).

Conclusions: The work demonstrates the practicality of nonlinear μ FE simulations at *in vivo* μ MRI resolution, as well as its potential for providing additional information beyond that obtainable from linear analysis. The data suggest that a direct assessment of toughness may provide information not captured by stiffness. © 2013 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4802085>]

Key words: micro-finite element analysis, trabecular bone mechanics, micro-MRI

I. INTRODUCTION

Osteoporosis is a common skeletal disease caused by an imbalance in bone remodeling. The disorder is characterized by decreased bone strength that leads to increased risk of fracture. Osteoporosis-related fractures are most common in older adults, with one in three women and one in five men over the age of 50 years predicted to suffer a fracture in their remaining lifetime.¹ Osteoporosis and associated fractures are therefore major public health concerns.

Osteoporosis and fracture risk have been typically assessed with dual-energy x-ray absorptiometry (DXA) and quantitative computed tomography (QCT) yielding areal and volumetric bone mineral density (BMD), respectively.^{2,3} However, it has been shown that fracture incidence cannot be predicted

by BMD alone.^{4–6} Other factors such as bone microstructural and mechanical properties contribute significantly to fracture risk.^{7–9}

With advances in imaging techniques and computational methods, image-based micro-finite element analysis (μ FEA) has become a valuable noninvasive tool for evaluating bone mechanical properties in response to external loads.^{10–12} Linear-elastic μ FE models are most often utilized to keep computational demands at a manageable level. High-resolution image-based linear μ FE estimates, notably elastic moduli, have been shown to agree very well with measurements from mechanical compression tests.^{13–15} Further, predictions at *in vivo* μ MRI resolution have been shown to correlate strongly with high-resolution μ FE estimates.¹⁶ However, linear models provide only bone's elastic properties.

Several investigators therefore attempted to predict bone failure using data obtained under linear-elastic conditions. Pistoia *et al.*¹⁷ proposed that failure can be predicted by assuming it to occur when 2% of the bone volume is strained above 0.7%. They reported that failure predicted in this way correlated well with failure observed experimentally ($R^2 = 0.75$). Using their criteria, linear models have also been used in other studies to predict failure loads at peripheral sites such as the distal tibia¹⁸ and radius.¹⁹ However, the authors in Ref. 17 concluded that failure prediction could be improved and obtained more directly by describing bone's post-yield nonlinear behavior.

Other studies investigated whether linear models can indirectly assess fracture risk based on observations indicating good correlation between bone strength and elastic modulus.^{20–22} However, some unexplained variability typically remained in these associations. In contrast, nonlinear μ FE models should be able to more realistically simulate bone's failure behavior and provide measures more directly relevant to bone strength.^{23,24} We therefore posit that nonlinear μ FEA might be a more powerful tool to predict fracture risk.^{21,25–28}

A few studies showed the ability of nonlinear μ FEA to predict tensile and compressive yield properties of bone.^{23,28,29} However, there is little work aimed at predicting trabecular bone *post-yield* behavior through nonlinear analysis.^{24,30} Trabecular bone *post-yield* behavior is considerably more complicated as suggested by observations from mechanical testing of bovine specimens indicating that damaged bone after monotonic overloading can be reloaded but with biomechanically significant reductions in their mechanical properties, which may provide the basis to investigate the associated weakening of the whole bone.³¹ Furthermore, nonlinear μ FE models so far have largely been derived from μ CT specimen images,^{22,23} while only in a few recent studies, simulations based on *in vivo* high-resolution peripheral QCT images have been reported.^{28,29} Finally, although some studies have reported good correlation between TB yield stress and axial stiffness using either μ CT-based μ FE simulation of bovine tibial specimens²³ or mechanical testing in cadaver specimens,²² it is still unclear whether axial stiffness can serve as an accurate predictor of TB *post-yield* properties and failure behavior.

High-resolution magnetic resonance (μ MR) imaging is an emerging noninvasive technology able to generate *in vivo* images adequate to resolve TB microstructure at the distal extremities.^{32,33} Micro-MRI based bone structure analysis is of particular interest given the modality's wide availability in clinical medicine. Linear-elastic μ FE models generated from μ MR images have recently demonstrated their potential to monitor alterations in bone mechanical properties resulting from disease progression or drug intervention.^{11,12,18} However, to the best of the authors' knowledge, there have been no reports on image-derived nonlinear μ FEA based on *in vivo* μ MR data.

In this work, a custom-designed algorithm and program is presented for nonlinear μ FE modeling of TB yield and *post-yield* behavior, suited for μ CT as well as *in vivo* μ MR im-

ages as input into the model. Associations between parameters in the failure regime and axial stiffness estimated from linear μ FEA were explored based on *in vivo* μ MR images of the distal tibia and radius. Our goals were threefold: First, to present an efficient nonlinear μ FE program for modeling trabecular bone yield as well as *post-yield* behavior; second, to demonstrate the feasibility and practicality of *in vivo* μ MR image-based nonlinear μ FE modeling of trabecular bone on desktop computers; third, to explore if nonlinear μ FEA can provide additional information in terms of trabecular bone's estimated mechanical properties beyond those achievable by linear analysis.

II. MATERIALS AND METHODS

II.A. Imaging

In vivo μ MR images of the left distal tibia of postmenopausal women with osteoporosis ($N = 20$; ages: 58–84) were taken from an ongoing interventional study.³⁴ The patients had randomly been assigned to two treatment arms: Reclast® (Zoledronic acid, Novartis, Basel, Switzerland) or Forteo® (Teriparatide, Eli Lilly and Company, Indianapolis, IN), and scanned at the start of intervention (baseline) and re-examined 12 and 24 months thereafter to evaluate the effect of treatment with the two drugs. Imaging was performed on a 3T Siemens TIM Trio scanner (Erlangen, Germany) using a four-channel receive-only phased-array radiofrequency (RF) coil (Insight MRI, Worcester, MA). The setup of the RF coils along with the positioning device was described in Ref. 35. Images were acquired using a 3D FLASE pulse sequence³⁶ with: FOV = $70 \times 64 \times 13 \text{ mm}^3$, Matrix = $512 \times 460 \times 32$, TR/TE = 80/11 ms, flip angle = 140° , bandwidth = 16.67 KHz, and an acquisition time of 15 min yielding anisotropic voxels of $137 \times 137 \times 410 \mu\text{m}^3$. The present study only used datasets acquired at the baseline.

In vivo μ MR images of the right distal radius of female subjects ($N = 20$; ages: 50–75; 17 postmenopausal, 3 premenopausal) had been acquired as part of a previous study.³⁷ No subject had a history of fractures, treatment for osteoporosis, or the presence of bone cancer. 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). Subjects were scanned using an improved 3D fast large-angle spin echo (FLASE) sequence³⁸ with: ROI = $70 \times 42 \times 13 \text{ mm}^3$, Matrix = $512 \times 312 \times 32$, TR/TE = 80/10 ms, flip angle = 140° , and an acquisition time of 10 min yielding anisotropic voxels of $137 \times 137 \times 410 \mu\text{m}^3$.

All subjects participating in the *in vivo* studies signed an informed consent in accordance with study guidelines of the Institutional Review Board.

II.B. Image processing

The reconstructed data from *in vivo* μ MR images were first corrected for subject motion during scans using an

autofocusing algorithm³⁹ or navigator data collected during the scan,⁴⁰ with normalized gradient square (NGS) value as the image sharpness metric. The resultant images were then corrected for intensity variations caused by inhomogeneous sensitivity of the receive coil via a local thresholding algorithm.⁴¹ Subsequently, TB regions were isolated and processed to generate 3D grayscale bone volume fraction (BVF) maps⁴² where voxel intensity represents the percentage occupied by bone (0% for pure marrow and 100% for pure bone). These 3D arrays were then used as input to the μ FE model.

II.C. Computation of axial stiffness

Axial stiffness was calculated by linear μ FEA using a custom-designed program⁴² where bone tissue was assumed linear-elastic under small strains. Each voxel in the input BVF map was modeled as an equally sized hexahedral element with a Poisson's ratio (ν) of 0.3 and tissue-level modulus (E_{tissue}) proportional to its BVF value via $E_{\text{tissue}} = \text{BVF} \times 15 \text{ GPa}$. A linear FE system was established by setting the total force at equilibrium to zero, and solved for the equilibrium displacements using a parallel preconditioned conjugate gradient method. Boundary conditions were set to represent axial compression with no friction along the transverse directions. Specifically, a small displacement (corresponding to 0.05% strain) in the axial direction was applied to nodes at the proximal surface while nodes at the distal surface were fixed. Nodes at both the proximal and distal surfaces were free to move in the transverse plane. Axial stiffness was then obtained as the primary stress divided by the applied strain.

II.D. Nonlinear μ FE model

In the linear-elastic regime, the local stress (σ) and strain (ϵ) are linearly related by $\sigma = C\epsilon$, where C is the stiffness matrix. For an isotropic material, it can be expressed as

$$C = \frac{E}{(1 + \nu)(1 - 2\nu)} \times \begin{bmatrix} 1 - \nu & \nu & \nu & 0 & 0 & 0 \\ \nu & 1 - \nu & \nu & 0 & 0 & 0 \\ \nu & \nu & 1 - \nu & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{1-2\nu}{2} & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{1-2\nu}{2} & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{1-2\nu}{2} \end{bmatrix},$$

where E is Young's modulus and ν is Poisson's ratio (15 GPa and 0.3, respectively, in our linear model⁴²). When a small displacement is applied to simulate the axial compression, each element is displaced inducing forces to its neighbor elements. At equilibrium, the total force at each vertex in each direction is equal to zero. Thus, organizing forces at all vertices establishes a linear system⁴²

$$Au = b, \quad (1)$$

where A is a sparse matrix referred to as the global stiffness matrix, u contains the displacements at all free vertices in each principal direction, and b is defined according to the applied boundary conditions. In practical TB simulations, due to the huge size of the system (1) and the correspondingly significant memory requirements, the element-by-element (EBE) approach⁴³ has been applied in many implementations instead of actually assembling the coefficient matrix A .

However, at large deformations bone tissue exhibits nonlinear stress-strain behavior. Thus, stress and strain are no longer linearly proportional. Instead, C depends on ϵ when material nonlinearity is assumed. In our implementation, trabecular tissue was modeled as an elasto-plastic material. Since it has been shown that the stress-strain relationship can be described by a power function of the hyperbolic tangent,⁴⁴ the derivative with respect to the strain ϵ , yields the Young's modulus in an element-dependent manner

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

where sech stands for hyperbolic secant and ϵ_{tissue} is the tissue-level effective strain (referred to as "element strain" in the following) which was calculated for each element using¹⁷

$$\epsilon_{\text{tissue}} = \sqrt{2 \times U/E}$$

with $E = 15 \text{ GPa}$ and U , being the strain-energy density of that element. A constant was further added after the hyperbolic secant term. In this manner, the Young's modulus decreases continuously until down to about 95% analogous to the nonlinear model used in Ref. 23. Figure 1 illustrates (a) the nonlinear dependence of $E(\epsilon_{\text{tissue}})$ on element strain for an element of pure bone and (b) its associated maximum principal stress versus element strain. The shape of this simulated stress-strain curve is in agreement with that previously reported from mechanical testing.⁴⁵⁻⁴⁷ The tissue-level modulus $E_{\text{tissue}}(\epsilon_{\text{tissue}})$ was then chosen, as in the linear case, proportional to the BVF value of each element by $E_{\text{tissue}}(\epsilon_{\text{tissue}}) = \text{BVF} \times E(\epsilon_{\text{tissue}})$, and the Poisson's ratio set to 0.3.

Correspondingly, the linear system (1) becomes a nonlinear system,

$$A(u)u = b, \quad (3)$$

which can be derived in a way analogous to that in the linear case. The most time-consuming part in nonlinear μ FE modeling is to solve this nonlinear system (3). Traditionally, the Newton-Raphson method is applied to solve (3) as has been done in previous work.^{23,48} In our implementation, the following iterative algorithm was utilized, which executed a

FIG. 1. (a) Dependence of Young's modulus $E_{\text{tissue}}(\varepsilon_{\text{tissue}})$ on element strain $\varepsilon_{\text{tissue}}$ according to formula (2); (b) the corresponding maximum principal stress versus element strain.

computationally efficient algorithm⁴² at each iteration, thus substantially saving simulation time.

Nonlinear Iterative Algorithm

For $i = 1$ to the total number of applied strain values, repeat **Steps 1–7**.

Step 1: For the applied strain ε_i which results in b_i , solve $A(u_i)u_i - b_i = 0$ for u_i in **Steps 2–5**;

Step 2: If $i = 1$, select an initial displacement u_i^0 ; otherwise, adjust the resultant equilibrium displacements from the previous applied strain ε_{i-1} linearly so that the boundary displacements match the present applied strain ε_i , and then set it to be u_i^0 ;

Step 3: Solve the linear system $Au_i^1 - b_i = 0$ for u_i^1 with the initial displacement u_i^0 .⁴² For $n = 1$ to the maximum iteration number N , repeat **Steps 4–5**.

Step 4: Update $A(u_i^n)$ via adjusting the tissue-level modulus $E_{\text{tissue}}^n(\varepsilon_{\text{tissue}}^n)$ with formula (2);

Step 5: Solve the linear system $A(u_i^n)u_i^{n+1} - b_i = 0$ for u_i^{n+1} .⁴²

Step 6: Set u_i^{N+1} as an approximated solution to $A(u_i)u_i - b_i = 0$.

Step 7: Increase the amount of applied strain by $\Delta\varepsilon = 0.05\%$ to obtain $\varepsilon_{i+1} = \varepsilon_i + \Delta\varepsilon$.

Here, the maximum iteration number N was empirically set to 30 and a total of 61 strain levels were applied in each experiment. The smallest and largest compressive strains were 0.05% and 3.05%, respectively. All simulations were performed on a laboratory desktop computer (dual-quad core Xeon 3.16 GHz CPUs equipped with 40 GB of RAM).

II.E. Estimation of TB yield and post-yield parameters

TB yield and post-yield parameters were estimated via a two-step procedure starting with computation of a series of points of gradually applied incremental strains and corresponding stresses. At very small strains, the linear μ FE model was used to obtain the resulting stresses. At larger strains, however, the above-described nonlinear model was applied with the same boundary conditions as in the linear case. The second step consisted of fitting the stress–strain curve to the points of applied strains and corresponding stresses by means

of cubic polynomials. Finally, the apparent yield stress and strain were obtained based on the 0.2% offset rule.²³ The peak value of the stress–strain curve was set as the apparent ultimate stress. The strain value at this peak point was correspondingly referred to as the ultimate strain. In addition, modulus of resilience was calculated as the integral of the fitted polynomial to the stress–strain curve from zero to the yield point. Similarly, toughness was calculated as the integral of the polynomial from zero to the ultimate strain point, since there is currently no unique criterion for the point of failure on the stress–strain curve, short of mechanical testing.

II.F. Experiments

Two sets of experiments were performed in the present study: one each based on the *in vivo* μ MR images of the distal tibia and distal radius, with the aim to show that at both anatomic sites, nonlinear μ FEA provides additional information, particularly regarding TB failure behavior which is poorly predictable from linear analysis. Results illustrating that additional information via simulated stress–strain curves are given in Subsection III.A; and Subsection III.B provides evidence via a study on the associations between parameters predicted from linear and nonlinear analyses.

II.G. Statistical analysis

Associations between estimates from linear and nonlinear μ FEA were evaluated in terms of the Pearson correlation coefficient. All statistical analyses were performed using JMP Discovery Software (JMP 8.0; SAS Institute, Inc., Cary, NC), with $p < 0.05$ indicating statistical significance.

III. RESULTS

In vivo μ MR images of the distal tibia and radius resulted in μ FE models with an average of 382 and 68 thousand elements, respectively. Nonlinear simulations required an average of 60 and 15 min, respectively, for analyzing 61 strain levels on the desktop computer described in Sec. II. The means

TABLE I. Mean $\pm$ SD of the estimated mechanical parameters from nonlinear analysis in the distal tibia and radius.

Mean $\pm$ SD	Axial stiffness (GPa)	Yield strain (%)	Yield stress (MPa)	Ultimate strain (%)	Ultimate stress (MPa)	Modulus of resilience (kPa)	Toughness (kPa)
Tibia	0.79 $\pm$ 0.10	0.84 $\pm$ 0.02	5.08 $\pm$ 0.69	1.20 $\pm$ 0.04	5.76 $\pm$ 0.77	23.64 $\pm$ 3.63	44.37 $\pm$ 6.91
Radius	0.56 $\pm$ 0.12	0.78 $\pm$ 0.03	3.31 $\pm$ 0.90	1.34 $\pm$ 0.23	3.86 $\pm$ 0.95	14.65 $\pm$ 4.51	33.69 $\pm$ 6.58

($\pm$ SD) of the predicted mechanical parameters in the distal tibia and radius are provided in Table I.

In addition, comparisons in computation time with previous reports from the literature are summarized in Table II.

III.A. Stress–strain curve simulations

Figure 2 displays simulated stress–strain curves obtained from *in vivo* μ MR images of the distal tibia in six patients. Of note is that bone with similar axial stiffness can show quite different stress–strain behavior as exemplified by comparing load–deformation curves I versus II, III versus IV, and V versus VI. In each pair, the two stress–strain curves were found to be nearly identical up to the yield point. Thereafter, bone from subjects II, IV, and VI required less stress for the same amount of strain compared to those from I, III, and V, respectively. Furthermore, II, IV, and VI exhibited comparatively smaller ultimate strain and toughness suggesting greater brittleness than I, III, and V, respectively. The cross-sectional μ MR images (slices were chosen at a similar distance from the distal end of the tibia), along with the grayscale BVF maps and the 3D sub-volume renderings ($2.5 \times 2.5 \times 11.5 \text{ mm}^3$) of the corresponding TB structures for datasets I–IV are provided in Fig. 3. Bone from subjects II and IV has denser trabeculation compared to that from I and III as shown by their trabecular numbers (Table III). Estimated structural and mechanical parameters for datasets I–VI are listed in Table III. In addition, longitudinal projections of the simulated strain maps for a thin

slab in the anterior region (Fig. 4) show that a greater proportion of trabeculae in dataset II are failed than in I whereas overall the trabeculae in I are strained more than in II, suggesting I to have greater ultimate strain than II.

III.B. Associations between linear and nonlinear mechanical parameters

Associations between linear and nonlinear μ FE derived mechanical parameters are shown in Fig. 5. Yield stress, ultimate stress, modulus of resilience, and toughness in the distal tibia correlated significantly and strongly with axial stiffness ($R^2 \geq 0.813$, all $p < 0.001$). However, in the distal radius, toughness was only weakly associated with axial stiffness ($R^2 = 0.34$, $p < 0.01$). Furthermore, associations of yield strain and ultimate strain with axial stiffness varied substantially between anatomic sites. For example, yield strain had a higher correlation with axial stiffness in the distal radius than in the tibia ($R^2 = 0.793$ versus 0.356 ; both $p < 0.005$). However, there was no significant correlation between ultimate strain and axial stiffness in the distal tibia ($p > 0.05$).

IV. DISCUSSION

A mathematical model for image-based nonlinear finite-element simulation of bone yield as well as *post-yield* behavior has been designed and implemented. The primary purpose of the present work was to explore if nonlinear analysis can

TABLE II. Comparisons in computation time with literature-reported data.

Ref.	Year	Anatomic location	Number of elements (thousand)	Number of processors	Nonlinear μ FE solver	Computer type	Comp. time
23	2000	Bovine tibia	108–157	16	N/A	Cray T3E	12.2 h
56	2004	Femoral neck	108–187	N/A	N/A	Cray T3E or IBM SP2	236 CPU hours
57	2004	Femoral neck	107.5–187.4	N/A	N/A	IBM SP2	128 CPU hours
58	2006	Femoral neck, greater trochanter, proximal tibia, vertebral body	Up to 2700	56	Olympus	Cray-Dell PowerEdge Xeon cluster supercomputer	11.3 h
59	2008	Bovine tibia	156	1	N/A	N/A	14 h
29	2008	Distal Radius	1245 on average	16	N/A	Supercomputer	25 h
60	2011	Proximal femur	600	8	N/A	SUN X4400	10 h
61	2012	Proximal femur	195–324	4	ABAQUS	Personal computer	1 h
Ours		Distal tibia and radius	68–382	8		Desktop computer	0.25–1 h

Note: The performance figures cited are accurate to the best of the authors' knowledge even though comparisons are made based on computations with models of varying size and on computer systems differing in the number of processors.

FIG. 2. Simulated stress-strain curves from *in vivo* μ MR images of distal tibiae. Of note are the TB load-deformation curves with similar axial stiffness but distinctly different post-yield behavior (I vs II, III vs IV, and V vs VI) showing that ultimate strain and toughness can be quite different even when axial stiffness is comparable (black star marks the ultimate strain point on each curve).

provide additional information beyond that from its linear counterpart. Toward this goal, nonlinear μ FEA was performed to simulate compression tests using a custom-

designed program on *in vivo* μ MR images of the distal tibia and radius. The work suggests that mechanical parameters such as toughness, predicted from nonlinear analysis, may provide insights beyond those estimated from linear analysis (e.g., elastic modulus).

So far, no standard algorithms exist for nonlinear μ FE modeling for fracture risk assessment. The precise failure mechanisms are still not well understood.⁴⁹ The most frequently used nonlinear model proposed by Niebur *et al.*²³ showed that the simulated strength in the human radius correlated highly with *in vitro* mechanical tests ($R^2 = 0.95$).²⁹ Although this model accurately predicted yield behavior, it was not able to predict post-yield behavior.²⁴ The nonlinear μ FE model in the present study assumed TB tissue to behave as an elasto-plastic material. According to the theory of perfect plasticity, a hyperbolic tangent function had been used previously^{44,50} to characterize the nonlinear stress-strain behavior of vertebral TB. Since this formula did not well capture the post-yield behavior, a modified expression was utilized in the present study producing a more plausible post-yield stress-strain behavior (Fig. 2). All parameters used in our formula were empirically calibrated so as to yield stress-strain curves consistent with those observed by mechanical testing

FIG. 3. Two pairs of image datasets (I vs II and III vs IV in Fig. 2) from four subjects with each pair having similar axial stiffness but different post-yield behavior: (a) cross-sectional μ MR images, (b) grayscale BVF maps of TB region, and (c) 3D renderings of virtual TB cores ($2.5 \times 2.5 \times 11.5 \text{ mm}^3$) extracted from the center (circles in center row). II and IV are more densely trabeculated than I and III. However, ultimate strain, ultimate stress, and toughness of II and IV are smaller than those of I and III (Table III) suggesting II and IV to be weaker than I and III.

TABLE III. Estimated structural and mechanical parameters for datasets I–VI in Fig. 2.

		Difference			Difference			Difference		
	Datasets	I	II	(I–II)/II (%)	III	IV	(III–IV)/IV (%)	V	VI	(V–VI)/VI (%)
Structural parameters	BV/TV (%)	11.08	10.84	2.16	10.01	9.99	0.28	7.97	7.47	6.58
	Tb.N (μm^{-1})	0.93	1.06	– 12.26	10.11	10.69	– 5.43	0.86	0.89	– 3.37
	Tb.Th (μm)	118.95	102.82	15.69	98.97	93.44	5.92	92.25	84.42	9.27
Mechanical parameters from linear FEA	E_z (GPa)	0.92	0.94	– 1.71	0.87	0.89	– 1.95	0.65	0.66	– 0.76
Mechanical parameters from nonlinear FEA	ε_y (%)	0.87	0.85	2.35	0.85	0.83	2.33	0.84	0.82	2.44
	σ_y (MPa)	6.19	6.05	2.42	5.65	5.60	1.06	4.17	4.03	3.58
	ε_u (%)	1.30	1.20	8.33	1.25	1.15	8.70	1.25	1.15	8.70
	σ_u (MPa)	7.02	6.81	3.01	6.45	6.24	3.50	4.83	4.55	6.22
	U_r (kPa)	29.99	28.44	5.45	26.62	25.82	3.11	19.37	18.11	6.92
	K_c (kPa)	58.93	51.70	13.99	51.57	45.18	14.12	38.37	32.95	16.42

Note: BV/TV = bone volume fraction; Tb.N = trabecular number; Tb.Th = trabecular thickness; E_z = axial stiffness; ε_y = yield strain; σ_y = yield stress; ε_u = ultimate strain; σ_u = ultimate stress; U_r = modulus of resilience; and K_c = toughness.

in previous work.^{24,29,51} Further, our nonlinear model reproduces the effect of TB tissue softening (the portion of the stress–strain curve with an initially negative modulus after the ultimate point) previously reported in Ref. 24, which incorporated both geometric nonlinearity and TB softening to calibrate material parameters, and which resulted in good agreement with experiments.

In accordance with previous reports^{20–22} based on high-resolution μCT specimen images or from mechanical testing, we found that yield stress and ultimate stress correlated highly with axial stiffness. However, we also found that axial stiffness explained only between 40% and 80% of the variation in toughness in the distal radius and tibia as shown by Fig. 5. Furthermore, substantial variations in toughness were predicted for bone with very similar axial stiffness (see examples in Fig. 2 and Table III), which is of interest since toughness is a better predictor of mechanical failure according to Griffith's theory for loaded brittle bodies. Such additional information and potential benefits of nonlinear μFEA have also been acknowledged in previous studies. The authors in Ref. 29 noted that even though strength predicted from linear models correlated well with experimental measurements, errors were appreciably reduced when nonlinear models were used (from 15% to 5%). Similar trends were also noted by Bevill and Keaveny²⁶ when using element sizes of 80 μm or less, especially for specimens with lower volume fraction.

Further, it was inferred experimentally²¹ that bone disease and aging may weaken the strength–stiffness relationship, thus affecting the predictability of bone strength from stiffness measurements. These and related findings indicate that nonlinear μFE modeling may provide particular benefits when applied to structurally impaired bone.

In this study, we have examined the performance of our nonlinear μFE model on the basis of *in vivo* μMR images. *In vivo* μMR images of TB have considerably lower resolution than is achievable on small samples *ex vivo* by μCT . However, we have previously examined the validity and accuracy of μFE modeling in the linear-elastic regime based on simulated μMR images from downsampled μCT images with a precursor of the present software showing that the mechanical parameters derived in the two different resolution regimes are highly correlated with each other.¹⁶ The difference therefore lies primarily in the image preprocessing. For example, bone regions in the high-resolution μCT images are typically segmented by binarizing with a segmentation threshold set at the midpoint between bone and marrow peaks in the voxel signal intensity histogram. For μMR images, we retain grayscale information after applying a local thresholding algorithm⁴¹ due to the voxel size being comparable to trabecular thickness.

The present study has limitations. The nonlinear μFE model used in this study considers only material nonlinearity. Under very large deformations, geometric nonlinearity

FIG. 4. Simulated strain projection images for two strain levels [(I-a) and (II-a) 0.8%; (I-b) and (II-b) 1.3%], shown for a thin slab of image datasets I and II in Fig. 2. Note that I has fewer failed trabeculae (30 975 vs 34 160 elements around their yield points; shown in white) but overall higher strain values than II, suggesting TB in I to exhibit greater ultimate strain, which is consistent with quantitative results from simulations (Table I).

FIG. 5. Associations between linear and nonlinear μ FE derived mechanical parameters obtained from *in vivo* μ MR images of the distal tibia and radius ($N = 20$, each). Toughness was moderately correlated with axial stiffness ($R^2 = 0.813$, $p < 0.001$) in the distal tibia, but only weakly in the distal radius ($R^2 = 0.34$, $p < 0.01$).

has also been shown to play a role.^{48,52} However, models incorporating geometric nonlinearity are often computationally more expensive because the element stiffness matrix varies within each element, thus significantly increasing memory usage. Second, we did not perform mechanical tests on specimens to validate the accuracy of our nonlinear model. However, results from our simulations are consistent in terms of the shape of stress-strain curves with those reported in previous work.^{24,29,51} Further, validation experiments performed outside the scope of the present work on seven human trabecular bone μ CT datasets from a previous study⁵³ yielded excellent agreement of compressive and shear moduli obtained with the parent software and those computed with the FE solver described by Boyd *et al.*⁵⁴ (data not shown). We have also shown in prior work, based on the linear precursor, that our *in vivo* resolution images gave results in good agreement with those obtained from high-resolution μ CT images, which in turn are known to correlate strongly with mechanical testing.^{13–15} Third, only compression was simulated. However, the strength of long bones under axial compression has been shown to be predictive of failure stresses most typically occurring during a fall.⁵⁵ Finally, although it has been reported³¹ that microdamage accounts for TB post-yield behavior as well, its effects were not explicitly considered in the proposed model since there is currently no imaging modality that can provide resolutions adequate to detect microdamage

such as microcracks. Nevertheless, the yield and post-yield behavior predicted and which had previously been observed experimentally, are likely a manifestation of such microdamage.

Some of the authors of the present work have previously shown that *in vivo* MRI-based μ FE simulations in the linear regime predict the expected changes in the bone's mechanical behavior in response to drug intervention^{11,12} or following renal transplantation.¹⁸ The present work is the first on *in vivo* μ MR image-based nonlinear μ FE modeling. Our findings indicate high-resolution image-derived nonlinear μ FE modeling to be a potentially useful tool for directly estimating bone strength and failure behavior. Toughness predicted and variations in strain distribution simulated herein may provide potentially more accurate information than axial stiffness when assessing fracture risk. Future work is required to compare the predictions of our model with mechanical testing and further investigations are warranted to determine whether the additional information from nonlinear μ FEA improves the evaluation of treatment effectiveness.

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