Mechanical Implications of Estrogen Supplementation in Early Postmenopausal Women

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ABSTRACT

Whereas the structural implications of drug intervention are well established, there are few data on the possible mechanical consequences of treatment. In this work we examined the changes in elastic and shear moduli (EM and SM) in a region of trabecular bone in the distal radius and distal tibia of early postmenopausal women on the basis of MRI-based micro-finite-element (μFE) analysis. Whole-section axial stiffness (AS) encompassing both trabecular and cortical compartments was evaluated as well. The study was conducted on previously acquired high-resolution images at the two anatomic sites. Images were processed to yield a 3D voxel array of bone-volume fraction (BVF), which was converted to a μFE model of hexahedral elements in which tissue modulus was set proportional to voxel BVF. The study comprised 65 early postmenopausal women (age range 45 to 55 years), of whom 32 had chosen estrogen supplementation (estradiol group); the remainder had not (control group). Subjects had been scanned at baseline and 12 and 24 months thereafter. At the distal tibia, EM and SM were reduced by 2.9% to 5.5% in the control group (p < .05 to < .005), but there was no change in the estradiol subjects. AS decreased 3.9% (4.0%) in controls (p < .005) and increased by 5.8% (6.2%) in estradiol group subjects (p < .05) at 12 (24) months. At the distal radius, EM and SM changes from baseline were not significant, but at both time points AS was increased in estradiol group subjects and decreased in controls (p < .005 to < .05), albeit by a smaller margin than at the tibia. EM and SM were strongly correlated with BV/TV (r² = 0.44 to 0.92) as well as with topologic parameters expressing the ratio of plates to rods (r² = 0.45 to 0.82), jointly explaining up to 96% of the variation in the mechanical parameters. Finally, baseline AS was strongly correlated between the two anatomic sites (r² = 0.58), suggesting that intersubject variations in the bone’s mechanical competence follows similar mechanisms. In conclusion, the results demonstrate that micro-MRI-based μFE models are suited for the study of the mechanical implications of antiresorptive treatment. The data further highlight the anabolic effect of short-term estrogen supplementation. © 2010 American Society for Bone and Mineral Research.

KEY WORDS: MRI; TRABECULAR BONE; CORTICAL BONE; STRUCTURE; FINITE ELEMENT; MENOPAUSE; ESTROGEN

Introduction

The notion that besides bone mineral density, parameters related to architecture at the macro- and microstructural levels,1 as well as mineral and matrix chemistry,2 collectively summarized under the term bone quality,3 determine overall bone strength is now generally accepted. There is also consensus that changes in many of the parameters occurring during aging and disease progression (or regression in response to treatment) can affect the bone’s mechanical behavior in a manner independent of the measured changes in material density.4

While initially confined to measurements in small specimens, advances in imaging technology, both computed tomography (CT) and magnetic resonance imaging (MRI), now allow detailed models to be reconstructed from high-resolution 3D images of both trabecular and cortical microarchitecture acquired in vivo in patients. These and related imaging technologies and their merits and current limitations have been reviewed extensively (see, for example, refs. (5–7)). On the basis of such imaging data, it has become possible to derive a host of structural measures expressing properties of the trabecular network in terms of scale, topology, and orientation, known from specimen studies to be relevant to the bone’s mechanical properties.5 Similarly, macro- and microstructural properties can be assessed for cortical bone, such as cortical thickness and cross-sectional area, via direct quantification of these structural measures on the basis of MRI6 or CT.10 Microstructural parameters such as porosity...
have been shown to be obtainable indirectly, for example, via MRI-based quantification of bone water.\(^\text{[11]}\)

There are a number of reports showing associations between structural measures at peripheral sites such as the radius or calcaneus and vertebral or femur fracture status.\(^\text{[12–15]}\) It also has been demonstrated recently that modern imaging technologies, notably micro-magnetic resonance imaging (\(\mu\)MRI), whole-body multislice CT, and high-resolution peripheral quantitative computed tomography (HR-pQCT), are able to detect age-related loss of trabecular network integrity,\(^\text{[16]}\) as well as structural changes in response to drug intervention.\(^\text{[17–20]}\)

Whereas there is evidence that certain structural features make trabecular bone more prone to failure (e.g., rodlike versus platelike\(^\text{[21]}\) or increased degree of structural anisotropy\(^\text{[22]}\)), only recently, capabilities have become available to identify such structural properties on the basis of in vivo images and quantify changes serially over time in human subjects.\(^\text{[17,18,20]}\) However, even though empirically established associations are known between biomechanical and structural parameters, the latter largely represent surrogates for strength. Since mechanical testing in vivo is not possible, alternate approaches have been pursued to estimate strength on the basis of image-derived finite-element meshes (see, for example, ref. \(^\text{[23]}\)). Micro-finite element (\(\mu\)FE) models established from high-resolution \(\mu\)CT images yielded mechanical constants in excellent agreement with those obtained by mechanical testing.\(^\text{[24]}\) Further, strong correlations with actual measures of elastic moduli and image-derived values have been shown recently to be obtainable even after downsampling the \(\mu\)CT images to lower resolution and superposition of noise to simulate in vivo imaging conditions.\(^\text{[25]}\)

These and other data instill significant confidence that meaningful biomechanical data are obtainable from in vivo image-based FE models.

Early work by Muller and Rueeggger, based on simulated atrophy of images acquired at in vivo resolution by peripheral CT in a cadaver specimen, subjected to \(\mu\)FE computation of elastic moduli, showed that a relatively small amount of bone loss can have disproportionately large mechanical consequences.\(^\text{[26]}\) The work suggested the feasibility of evaluating disease and aging-related effects on the bone's mechanical behavior. Van Rietbergen and colleagues examined the potential of \(\mu\)MRI to quantify the effects of drug intervention in patients treated with a selective estrogen receptor modulator.\(^\text{[27]}\) A recent article showed in 10 hypogonadal subjects that 2-year treatment with testosterone resulted in significant increases in some elastic and shear moduli,\(^\text{[28]}\) computed from a region of trabecular bone in the distal tibial metaphysis, commensurate with changes in topology of the trabecular network reported earlier.\(^\text{[18]}\)

The preceding study is of limited scope in terms of both the number of subjects studied and the size of the imaging volume used for construction of the \(\mu\)FE model. In the present work, we have performed \(\mu\)FE analysis on MR data in the distal tibia and radius from a recent structural imaging study in early postmenopausal women who elected estrogen supplementation compared with those who did not during a 2-year period. The image data were reprocessed yielding grayscale FE models of both central trabecular subregions used for multidirectional estimation of Young's and shear moduli, as well as whole-section simulated compressive testing, including both trabecular and cortical bone compartments, at three time points.

### Materials and Methods

#### Subjects and image acquisition

This work is based on imaging data from a recently completed study in the authors' laboratory,\(^\text{[20]}\) involving 65 early postmenopausal women, 45 to 55 years of age, who had been recruited for the study. Thirty-two of the women had chosen estrogen supplementation (estradiol group); the remainder had not (control group). \(\mu\)MRI in the metaphysis of the distal radius and distal tibia had been performed at 137 × 137 × 410 \(\mu\)m\(^3\) voxel size at baseline and 12 and 24 months to determine the temporal changes in the trabecular architecture. The imaging volume was 70 × 40 × 13 mm\(^3\) (scan time 12 minutes) and 70 × 50 × 13 mm\(^3\) (scan time 16 minutes) for the distal radius and distal tibia, respectively, with the third dimension representing the axial direction. Full details of the subject characteristics and image acquisition protocol are given in ref. 20.

#### Image processing

Images from the prior study were reprocessed using more advanced algorithms. The raw images were corrected for translational displacements during the scan owing to involuntary subject motion with the aid of navigator echo data acquired simultaneously with the image data.\(^\text{[29]}\) Motion-corrected k-space data then were Fourier-transformed to yield 32 image slices. Some examinations did not provide images of sufficient quality for analysis because of artifacts caused by subject motion during scanning that could not be removed via navigator correction (e.g., rotational motion) or wrap-around artifacts resulting from field-of-view restrictions for some subjects with particularly large wrists and ankles. These images were excluded from analysis by following a procedure described previously.\(^\text{[20,30]}\) Further, if the common image volume between the three time points was less than 2.5 mm in the axial direction (owing to registration errors), those images also were excluded from the analysis. In summary, the number of subjects who provided distal tibia data with adequate image quality for the baseline to 12-month (24) interval was 28 (23) for the control group and 23 (19) for the estradiol group. Similarly, the corresponding numbers for the distal radius were 23 (14) and 13 (12), respectively.

The preprocessed images were subjected to a cascade of processing steps before being used as input to the mechanical and topologic analysis (Fig. 1). First, image intensity variations across the volume produced by inhomogeneous sensitivity of the MR receive coil were corrected using a local thresholding algorithm.\(^\text{[31]}\) The grayscale voxel values of the intensity-corrected images then were scaled linearly to cover the range from 0% to 100%, with pure marrow and pure bone having minimum and maximum values, respectively. We refer to the resulting 3D array as the bone-volume fraction (BVF) map, with individual voxel values representing the fraction of the voxel occupied by bone (i.e., BV/TV). Subsequently, the BVF maps were subjected to two different processing paths in preparation for
the full cross-sectional and subregional analysis. To enable full cross-sectional analysis, the soft tissue was first segmented out from bone by delineating the periosteal boundary using an operator-guided region-selection program developed in-house. Finally, common 5-mm sections along the bone’s axial direction were extracted from the images at the three time points for each subject. To prepare the images for subregional analysis, BVF maps were first sinc-interpolated by a factor of 3 in all three image coordinate axes to improve apparent resolution, yielding 45.7 μm³ voxels. The 12- and 24-month repeat images of each subject then were registered in 3D to match the corresponding baseline volume using trilinear interpolation. Finally, 10-μm³ cuboid subvolumes were extracted from the center of the trabecular bone (TB) region for analysis.

Grayscale-based μFE modeling

To create a finite-element mesh, each voxel in the BVF map was converted directly to a hexahedral (brick) finite element with dimensions corresponding to the voxel size. The bone tissue material properties were chosen as isotropic and linearly elastic, with each element’s Young’s modulus (YM) set to be linearly proportional to the voxel’s BV/TV value such that YM = 15 GPa × BVF, while Poisson’s ratio was kept constant at 0.3 for all elements. A partial threshold was applied by setting finite elements with BVF < 20% to zero to remove the contributions from image noise.

Subregional μFE analysis

To estimate the mechanical properties of the cuboid subregion from the generated μFE model, Young’s and shear moduli, scalar quantities that express the relationship between stress and strain, were determined by simulating compression and shear tests on the μFE model by imposing different boundary conditions on the eight surfaces of the modeled bone region. The Young’s moduli, representing the stiffness along each of the three principal axes (E₁₁, E₂₂, and E₃₃) of the coordinate system (x, y, and z), were found by performing three simulated “compressive” tests along each of the three orthogonal axes. Since the patients had been imaged in the supine position with the tibia’s long axis parallel to the magnet bore, the scanner coordinate system was essentially collinear with the anatomic coordinate frame. Thus the subscripts 1, 2, and 3 correspond to anteroposterior, mediolateral, and inferosuperior directions, respectively. The value of E₁₁, for example, was obtained by applying a small simulated displacement (compressive strain of approximately 1%) along the x direction to all nodes on one of the boundary surfaces perpendicular to the x axis in such a manner that the nodes on the opposite surface were restrained along the x direction while lateral displacements remained unrestrained. The unknown displacements at each node then were found by minimizing the total strain energy of the system. Subsequently, the resulting stress along the x direction was calculated by summing the x components for the reaction force and dividing by the surface area. Finally, E₁₁ was estimated as the ratio of calculated stress to the applied strain. E₂₂ and E₃₃ also were obtained analogously. Using a similar approach, shear moduli (G₂₃, G₃₁, and G₁₂), expressing the ratio of shear stress to shear strain of the modeled region, were estimated by simulating shear displacements applied to nodes on opposite surfaces along antiparallel directions.

Full cross-sectional μFE analysis

Axial stiffness of the distal radius and distal tibia was estimated via μFE analysis of the full FE mesh comprising both trabecular and cortical bone compartments generated as described earlier. First, simulated compression was applied along the bone’s
Parameter Baseline to Both Follow-Up Time Points
Tibia Derived from Young’s Moduli ($E/C_6$) The binary volumes then were subjected to a background voxels were assigned values of 1 and 0, respectively, using an empirically optimized threshold level of 20% of pure bone intensity. The binary volumes then were subjected to a topology-preserving thinning algorithm yielding the 3D skeleton of the trabecular bone network. Subsequently, topologic classification was performed by identifying each voxel as belonging to a surface, curve, or mutual junctions between these entities. Finally, the composite topologic parameters surface-to-curve ratio (S/C) and erosion index (EI) were computed from the DTA maps of the skeleton. BV/TV was computed as described in ref. 31.

Statistical analysis
The statistical analysis was analogous to the one outlined in the parent article based on multivariate analysis of variance (MANOVA). Following determination that the data were normally distributed, MANOVA was performed with time (repeated) and treatment (nonrepeated) factors along with inclusion of the treatment x time cross-product to assess second-order interaction. When a response variable was associated with significant treatment x time interaction, simple effects over time were assessed within each treatment group using two-sided paired t tests. Between-group differences in the changes from baseline were evaluated by unpaired t tests. Intersite correlation of full cross-sectional stiffness, as well as correlations between mechanical and topologic parameters of trabecular bone, were evaluated by least-squares regression in terms of the Pearson correlation coefficient. All statistical analyses were performed using JMP Discovery Software, Version 7.02, (SAS Institute, Inc., Cary, NC), with $p < .05$ indicating statistical significance.

Results
Subregional μFE analysis
The mean values of Young’s and shear moduli, as well as BV/TV, all computed from matching trabecular bone subvolumes in the distal tibia at all three time points, as well as the relative changes from baseline, are summarized in Tables 1 and 2. The relative temporal changes in parameters are charted in Fig. 2. The subregional mechanical parameters did not show any significant change from baseline to the two follow-up time points in the estradiol group, suggesting that estrogen supplementation preserves the integrity of the trabecular network, as shown in some of our prior work. On the other hand, in the control subjects, three of the mechanical parameters suggest significant reduction already after 12 months (3.0% to 5.5%, $p = .01$ to .002), whereas the change in BV/TV was not significant. At 24 months, all six mechanical parameters were reduced significantly in the control group relative to baseline values (2.9% to 5.1%, $p = .03$ to .002), at which point the reduction in BV/TV also became significant (1.8%, $p < .05$). None of the subregional between-group differences of changes from baseline were significant.

For the distal radius (Tables 3 and 4), the temporal changes in mean values of subregional mechanical parameters did not reach statistical significance except for $E_{22}$ (at 12 months) and $G_{22}$ (at 24 months) for the estradiol group, for which 6.1% ± 2.2% ($p = .02$) and 3.8% ± 1.5% ($p = .04$) increases were observed, respectively. Further, the detected change in BV/TV was nonsignificant for both groups at both time points. Again, at this site, there was no significant difference in the temporal changes between groups.

Full cross-sectional μFE analysis
Tables 1 through 4 also provide mean values and relative temporal changes in full cross-sectional axial stiffness at the two anatomic sites from baseline to the follow-up time points. Figure 3 displays the fractional changes from baseline to 12 and 24 months. Estrogen supplementation increased whole-section stiffness of the proximal face. The full cross-sectional modulus of the proximal face was obtained as the strain. Finally, the axial full cross-sectional modulus was obtained as the ratio of the resulting stress on the proximal face to the applied strain.
Table 2. Subregional Young’s Moduli ($E_{11}, E_{22}, E_{33}$), Shear Moduli ($G_{12}, G_{13}, G_{23}$), Cross-Sectional Stiffness (All in MPa), and BV/TV (%) at the Distal Tibia, Derived from μMR Images in Estradiol Subjects at Baseline and 12 and 24 Months, Including Relative Changes of Mean Values from Baseline to Both Follow-Up Time Points

| Parameter | Mean value | Baseline to 12 mos. | Baseline to 24 mos. |
|-----------|------------|---------------------|---------------------|
|           | Baseline | 12 mos. | 24 mos. | Relative change (%) | $p$ | Relative change (%) | $p$ |
| $E_{11}$  | 230 ± 68 | 231 ± 60 | 241 ± 59 | 2.89 | .49 | 3.79 | .44 |
| $E_{22}$  | 193 ± 38 | 194 ± 36 | 194 ± 30 | 0.96 | .66 | −1.63 | .60 |
| $E_{33}$  | 840 ± 149 | 838 ± 140 | 859 ± 128 | 0.27 | .90 | 0.10 | .97 |
| $G_{12}$  | 153 ± 26 | 153 ± 24 | 156 ± 19 | 0.45 | .79 | −0.58 | .80 |
| $G_{13}$  | 179 ± 45 | 179 ± 39 | 184 ± 40 | 1.75 | .55 | 1.64 | .61 |
| $G_{23}$  | 97 ± 20 | 98 ± 18 | 99 ± 16 | 2.38 | .32 | 0.37 | .91 |
| Stiffness | 1158 ± 139 | 1218 ± 116 | 1177 ± 80 | 5.76 | .03 | 6.22 | .03 |
| BV/TV     | 11.2 ± 1.1 | 11.1 ± 1.0 | 11.3 ± 1.0 | −0.35 | .68 | −0.26 | .81 |

Fig. 2. Within-group mean temporal changes (%) in subregional mechanical parameters and BV/TV of distal tibia from baseline to 12 and 24 months. The $p$ values indicate the significance of the computed changes. Between-group changes from baseline were not significant.

axial stiffness after 12 and 24 months of treatment at both anatomic sites. At the tibia, the increases were 5.8% and 6.3% (both $p = .03$) at 12 and 24 months, respectively. At the radius, axial stiffness increased 2.5% ($p = .02$) at 12 months and 3.2% at 24 months, but the latter effect did not quite reach significance ($p = .065$). In control subjects, the data further revealed substantial and highly significant reductions in axial stiffness (3.9% and 4.0%, $p = .0004$ and .001 at 12 and 24 months, respectively) at the tibia and 3.6% and 3.7% ($p = .002$ and .03) at the radius at the two time points.

The intergroup differences in the observed temporal changes in axial stiffness were highly significant at both follow-up time points and for both anatomic sites. However, the values were greater for the distal tibia than for the distal radius at 12 months (9.7% ± 2.5%, $p = .0001$, versus 6.1% ± 1.5%, $p = .0003$). At 24 months, the corresponding intergroup changes were 10.2% ± 2.3% ($p = .0002$) at the tibia versus 6.8% ± 2.1% ($p = .004$) at the radius. Further, the full cross-sectional axial stiffness values at tibial and radial sites were highly correlated with each other, indicating the systemic nature of these parameters (Fig. 4).

Relationship between mechanical and topologic parameters

Strong correlations were observed between the mechanical and composite topologic parameters (S/C and EI) computed from the same trabecular bone subvolumes at the distal tibia (Table 5). The strength of the correlations differed for the three directions of Young’s moduli, being largest for the axial direction ($E_{33}$). Further, the predictive ability of two-parameter linear regression

Table 3. Subregional Young’s Moduli ($E_{11}, E_{22}, E_{33}$) and Shear Moduli ($G_{12}, G_{13}, G_{23}$), Cross-Sectional Stiffness (All in MPa) and BV/TV (%) at the Distal Radius Derived from μMR Images in Control Subjects at Baseline and 12 and 24 Months, Including Relative Changes of Mean Values from Baseline to Both Follow-Up Time Points

| Parameter | Mean value | Baseline to 12 mos. | Baseline to 24 mos. |
|-----------|------------|---------------------|---------------------|
|           | Baseline | 12 mos. | 24 mos. | Relative change (%) | $p$ | Relative change (%) | $p$ |
| $E_{11}$  | 302 ± 84 | 290 ± 67 | 286 ± 62 | 2.89 | .49 | 3.79 | .44 |
| $E_{22}$  | 404 ± 99 | 391 ± 82 | 373 ± 73 | 0.96 | .66 | −1.63 | .60 |
| $E_{33}$  | 838 ± 117 | 813 ± 102 | 824 ± 127 | 0.27 | .90 | 0.10 | .97 |
| $G_{12}$  | 249 ± 47 | 242 ± 38 | 235 ± 37 | 0.45 | .79 | −0.58 | .80 |
| $G_{13}$  | 211 ± 40 | 203 ± 33 | 201 ± 31 | 1.75 | .55 | 1.64 | .65 |
| $G_{23}$  | 170 ± 49 | 161 ± 40 | 152 ± 35 | 2.38 | .32 | 0.37 | .91 |
| Stiffness | 1547 ± 206 | 1542 ± 207 | 1487 ± 188 | −3.57 | .002 | −3.65 | .03 |
| BV/TV     | 9.8 ± 1.2 | 9.8 ± 1.0 | 10.2 ± 1.7 | −0.35 | .68 | −0.26 | .81 |
models involving BV/TV and either S/C or EI improved relative to a single predictor. Similar trends were observed for the correlations between mechanical and composite topologic parameters computed from the distal radius. However, the correlations ($r^2$ ranging from 0.24 to 0.89) generally were somewhat weaker than those observed at distal tibia.

**Discussion**

The results from this work show that μMRI-based structural images from trabecular and cortical bone at the distal extremities acquired in patients are suited to derive finite-element models for estimating the mechanical consequences of estrogen loss following menopause and estrogen supplementation. This study is only one of a small number of in-vivo image-based studies.

| Parameter | Mean value Baseline to 12 mos. | Baseline to 24 mos. | Relative change (%) | $p$ | Relative change (%) | $p$ |
|-----------|--------------------------------|---------------------|---------------------|-----|---------------------|-----|
| $E_{11}$  | 281 ± 82                       | 310 ± 111           | 327 ± 132           | 2.89| .490                | .790|
| $E_{22}$  | 376 ± 94                       | 407 ± 114           | 409 ± 120           | 0.96| .655                | 1.63|
| $E_{33}$  | 813 ± 88                       | 799 ± 108           | 823 ± 133           | 0.27| .901                | .10 |
| $G_{12}$  | 230 ± 42                       | 239 ± 53            | 245 ± 60            | 0.45| .792                | 0.59|
| $G_{13}$  | 197 ± 39                       | 207 ± 53            | 212 ± 62            | 1.75| .554                | 1.64|
| $G_{23}$  | 157 ± 50                       | 172 ± 65            | 177 ± 74            | 2.38| .322                | 0.37|
| Stiffness | 1382 ± 384                     | 1477 ± 163          | 1486 ± 145          | 2.52| .024                | 3.16|
| BV/TV     | 9.4 ± 0.9                      | 10.7 ± 3.6          | 12.7 ± 5.6          | -0.35| .677                | -0.26|

**Table 4.** Subregional Young’s Moduli ($E_{11}$, $E_{22}$, $E_{33}$) and Shear Moduli ($G_{12}$, $G_{13}$, $G_{23}$), Cross-Sectional Stiffness (All in MPa), and BV/TV (%) at the Distal Radius Derived from μMR Images in Estradiol Subjects at Baseline and 12 and 24 months, Including Relative Changes of Mean Values from Baseline to Both Follow-Up Time Points

**Table 5.** $R^2$ Values for the Correlation Between Mechanical and Structural Parameters Computed from the Same 10 × 10 × 5 mm$^3$ Trabecular-Bone Subregion of the Distal Tibia at Baseline for All Subjects

| $E_{11}$ | $E_{22}$ | $E_{33}$ | $G_{23}$ | $G_{31}$ | $G_{12}$ |
|----------|----------|----------|----------|----------|----------|
| BV/TV    | 0.71     | 0.44     | 0.92     | 0.69     | 0.81     | 0.66     |
| S/C      | 0.76     | 0.45     | 0.85     | 0.68     | 0.82     | 0.62     |
| EI       | 0.64     | 0.35     | 0.74     | 0.54     | 0.72     | 0.50     |
| BV/TV and S/C | 0.80 | 0.47 | 0.96 | 0.74 | 0.88 | 0.69 |
| BV/TV and EI | 0.77 | 0.44 | 0.95 | 0.71 | 0.87 | 0.66 |

All correlations were significant ($p < .0001$).
compellingly showing not only the structural but also mechanical manifestations of intervention. A prior study involving a smaller number of subjects had provided evidence of the architectural changes had been previously observed in paired biopsies (mean approximately 1 year from last menstrual period), in contrast to testosterone-deficient men who had been hypogonadal for very long times and therefore eliciting a very strong treatment response. Further, this work goes considerably beyond the prior pilot study in that we performed subregional μFE analysis of a small cuboid trabecular subregion (which, however, was larger than in ref 28)—10 × 10 × 5 mm³ versus 5 × 5 × 5 mm³—but also examined the role of the cortex by performing full cross-sectional stiffness analysis similar to that described by MacNeil and Boyd. Further, we studied the hypothesized mechanical treatment effects at both the distal tibia and the radius, that is, a load-bearing and a non-load-bearing anatomic site. We further brought advanced registration methods to bear for mutual alignment of the images at the three time points and with the scanner coordinate frame.

In the tibia, the subregion analysis revealed significant reductions in all six moduli in the control group (ie, women who elected not to take estrogen) ranging from 3% to 5% from baseline after 24 months (p < .05 to < .005), whereas only three of the moduli were significantly lower after 12 months. In contrast, in the estradiol group, all six mechanical constants remained unaltered at both follow-up time points. Between-group changes in the elastic moduli, in contrast to whole-section axial stiffness in the estradiol group suggest that estrogen supplementation not only preserves but actually improves bone mechanical competence, in contrast to prior structural studies indicating mere preservation of architecture. Nevertheless, the anabolic effects of estrogen replacement are well documented. Khastgir and colleagues found that estrogen supplementation increased mineral/matrix ratio, mineral crystallinity/maturity, and the relative ratio of collagen cross-links, clearly showing that antiresorptive treatment affects material properties. The same group recently showed that antiresorptive treatment affects material properties. The group recently showed that antiresorptive treatment affects material properties. The group recently showed that antiresorptive treatment affects material properties. However, the work did not provide data on structural group differences, and
BMD was matched at the proximal femur rather than at the vertebrae.

As with all CT-based μFE work using in vivo structural images to create the FE model, our model analyzes the structural implications only of longitudinal changes on mechanical parameters. While CT can, in principle, make use of variations in mineralization density, such differences are not distinguishable from the tissue modulus assigned to bone. We found in preliminary work grayscale-based μFE analyses to be more accurate than those relying on binarized images, which is what prompted us to avoid binarization, since it is well known to be fraught with error at the resolution achievable by in vivo structural imaging of trabecular bone. Finally, the study is limited to the linear regime in that ultimate strength was not evaluated, which could be obtained from the present data by invoking the Pistoia criterion, which suggests that failure will occur once 2% of the bone tissue is strained beyond 0.7% (52). Nevertheless, there is substantial evidence that trabecular thickness, nor would CT be able to resolve the elastic modulus of human trabecular bone. As with all CT-based μFE work using in vivo structural images, which is what prompted us to avoid binarization, since it is well known to be fraught with error at the resolution achievable by in vivo structural imaging of trabecular bone.

In conclusion, MRI-based μFE analysis is able to predict the short-term mechanical implications of drug intervention of both trabecular and cortical bone. The data provide evidence of an anabolic effect of estrogen supplementation in terms of whole-section axial stiffness at both the distal and radius, but the effects, in terms of both reduction in mechanical competence in the absence of estradiol administration and the observed increases in subjects receiving hormone supplementation, were greater at the tibia than at the radius.

Disclosures

All authors state that they have no conflicts of interest.

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