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Are DXA/aBMD and QCT/FEA stiffness and strength estimates sensitive to sex and age?

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Abstract

Dual X-ray absorptiometry (DXA) measures areal bone mineral density (aBMD) by simplifying a complex 3D bone structure to a 2D projection and is not equally effective for explaining fracture strength in women and men. Unlike DXA, subject-specific quantitative computed tomography-based finite element analysis (QCT/FEA) estimates fracture strength using 3D bone mineral distribution and geometry. By using experimentally-measured femoral stiffness and strength from a one hundred sample cadaveric cohort that included variations in sex and age, we wanted to determine if QCT/FEA estimates were able to better predict the experimental variations than DXA/aBMD. For each femur, DXA/aBMD was assessed and a QCT/FEA model was developed to estimate femoral stiffness and strength. Then, the femur was mechanically tested to fracture in a sideways fall on the hip position to measure stiffness and strength. DXA/aBMD and QCT/FEA estimates were compared for their sensitivity to sex and age with multivariate statistical analyses. When comparing the measured data with DXA/aBMD predictions, both age and sex were significant (P 0.0398) for both femoral stiffness and strength. However, QCT/FEA predictions of stiffness and strength showed sex was insignificant (P 0.23). Age was still significant (P 0.0072). These results indicate that QCT/FEA, unlike DXA/aBMD, accounted for bone differences due to sex.

Keywords

hip fracture; bone biomechanics; sex differences; aging; finite element analysis

INTRODUCTION

Currently, the clinical gold standard for diagnosing osteoporosis and assessing femoral fracture risk is femoral neck areal bone mineral density (aBMD), measured by dual x-ray absorptiometry (DXA).¹⁴ However, DXA simplifies the complex three-dimensional (3D)

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CONFLICT OF INTEREST

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bone structure to a two-dimensional (2D) projection of DXA/aBMD that is quantified by a single figure of merit. Additionally, fracture risk assessment relying only on DXA/aBMD does not fully take into account two significant explanatory variables: sex and age. This is recognized, for example, in the Fracture Risk Assessment Tool (FRAX), which separately considers DXA/aBMD, sex, and age, among other factors.³² A potential weakness of using DXA/aBMD without accounting for sex in fracture risk assessment was evident in a recent study involving mechanical testing of 100 cadaveric femurs, which found that for a given DXA/aBMD value, women's proximal femurs had lower fracture strengths than men's proximal femurs.²⁷ Other studies concluded that DXA/aBMD is a better predictor of hip fracture in men than in women,^{7, 26} indicating that sex may be an important factor. With respect to the ability of DXA/aBMD to account for changes related to age, a recent study found that femoral strength decreased with age faster than did DXA/aBMD.²⁷ This corroborated another study that concluded age-related reductions in femoral strength were significantly greater than what was indicated by DXA/aBMD.¹⁶

It is hypothesized that accounting for the 3D bone geometry and distribution of bone mineral density may better account for inherent influences of the biological variables of sex and age in the prediction of stiffness and fracture strength. Subject-specific quantitative computed tomography-based finite element analysis (QCT/FEA) accounts for 3D bone geometry and volumetric bone mineral density distribution, enabling this method to more accurately predict fracture stiffness and strength compared to DXA/aBMD.^{5, 6, 8, 17, 20} QCT/FEA can also assess femoral stiffness and strength under various physiological and/or traumatic loading conditions.^{9, 13, 24} The purpose of this study was to determine if DXA/aBMD or QCT/FEA, used independently to estimate femoral stiffness and fracture strength, accounted for experimentally observed differences due to sex and age.

MATERIALS AND METHODS

Specimen preparation, mechanical testing and QCT/FEA model development are described in detail in prior publications,^{9–11} and are summarized here for convenience.

Experimental Process

One hundred unpaired, fresh-frozen human cadaveric femora were obtained from two organ banks (Musculoskeletal Transplant Foundation, Edison, NJ, and Anatomy Gifts Registry, Hanover, MD) after IRB approval from our institution. A description of the specimens is shown in Table 1. The difference in age between the two sexes was not statistically significant ($p=0.13$; t-test). While mean DXA/aBMD values are different between women and men, this study considers DXA/aBMD as an explanatory variable along with sex. Our study considers the differences in experimental outcomes found between the two sexes at the same DXA/aBMD value.

The femurs were screened to rule out metastatic disease or fractures. Soft tissue on thawed specimens was carefully removed using a scalpel to avoid bone damage. Neck areal DXA/aBMD of each specimen was measured using a GE Lunar iDXA system (GE Healthcare Inc., Madison, WI), with rice bags placed below and on top of the specimen to simulate surrounding soft tissues. The femurs were then frozen at -20°C until the day before testing.

Femurs were thawed at room temperature for 24 hours, and then tested to fracture. All bones were fractured in a fall on the hip configuration at 100 mm/s, a value found to reasonably approximate the speed of bone deformation due to a fall,¹² in order to measure the force at the greater trochanter and the displacement of the femoral head. The peak force from the experimental force vs. displacement curve was considered to be the femoral strength. The experimental stiffness value of each femur was obtained in the linear region of the force-displacement curve, where the linear region was defined as the region between 20% and 80% of the measured yield force.

QCT/FEA Modeling

The QCT/FEA process included CT scanning of the femurs prior to mechanical testing, segmentation, rendering a watertight 3D model, generation of the finite element mesh, the application of boundary conditions and material properties, and simulation of a sideways fall on the hip.⁹ CT imaging was performed using a Siemens Somatom Definition Dual Source CT scanner (120 kVp, 216 mAs, 1s rotation time, pitch = 1, slice thickness = 0.4mm, and in-plane resolution = 0.3–0.45mm). DICOM images of the femurs from the CT scans were imported into Mimics editing software (Materialise, Ann Arbor, MI, USA) for further processing. For each scan, the bone geometry was segmented and a surface mesh consisting of triangular elements was obtained from the 3D segmented model. Surface meshes were imported to ICEM (ANSYS, Canonsburg, PA) and a volume mesh was developed using an advancing front meshing method.⁹ Each finite element in the volume mesh was assigned an average Hounsfield unit (HU) number calculated from the CT voxels contained within the element.

The range of HU values within a femur is expected to fall between about 0 and 3000 HU, so we created 300 bins with width 10 HU's. All values of $HU < 0$ were put into one bin, representing less dense materials like fat and marrow. The range of Hounsfield units covering the tissue domain was thus divided into 301 bins, approximating a continuous distribution of grey scale values. Finite elements were then grouped into their respective bins depending on their calculated average HU value. Ash density (ρ_{ash}) was calculated based on the HU value from each element and the manufacturer's phantom calibration specifications (Mindways Inc., Austin, TX, USA). Isotropic elastic modulus [E] and yield strain [ϵ_y] for each material bin were calculated from ρ_{ash} based on power law density-dependent relations ($E = 14664 \rho_{ash}^{1.49}$ and $\epsilon_y = 0.0081 \rho_{ash}^{-1.42}$).^{25, 9} Poisson's ratio was set to 0.3 for all materials.

The femur models were imported and simulations were conducted using ANSYS Mechanical APDL (ANSYS, Canonsburg, PA, USA). A quasi-static analysis was performed using multi-point constraint (MPC) boundary conditions (BCs) to best match those from experimental testing.²⁸ The analysis was driven with displacement applied in small increments of 0.1 mm to a pilot node connected through MPCs to contact nodes on the femoral head surface.²⁸ Bone damage was evaluated on an element-by-element basis using a von Mises strain (ϵ_{VM}) criterion. After each load step, elements whose equivalent von Mises strain (ϵ_{VM}) exceeded the yield strain ϵ_y were assigned a Young's modulus of 0.01 MPa.⁹ Force-displacement data were obtained for each QCT/FEA simulation. Stiffness was

calculated from the initial, linear region of the curve, and femoral strength was calculated as the maximum force at the greater trochanter.

Statistical Analysis

JMP version 10.0.0 (SAS Institute Inc., NC, USA) was used for statistical analysis. In all analyses, the outcomes were the experimentally measured femoral stiffness or strength. Univariate regression analyses were performed using either DXA/aBMD or QCT/FEA-estimated stiffness to explain experimentally measured femoral stiffness, and using either DXA/aBMD or QCT/FEA-estimated strength to explain experimentally measured femoral strength. Multivariate analyses of covariance (ANCOVA) were then performed by adding sex and age, first separately and then together, to each main explanatory variable (DXA/aBMD or QCT/FEA-estimated stiffness or QCT/FEA-estimated strength) to test the significance of all the explanatory variables. The level of significance was set to 0.05. The analyses were performed first with consideration of all possible two-way interactions between significant explanatory variables. All insignificant interactions were then excluded from the models and the analyses were re-run. The results of the analyses without insignificant interactions were then reported. In all analyses, adjusted coefficients of determination (R^2) were calculated.

RESULTS

Stiffness Analysis

The average experimentally measured femoral stiffness values for women and men were 1515 (± 596) N/mm and 2156 (± 669) N/mm, respectively. The average QCT/FEA-estimated stiffness values for women and men were 1649 (± 890) N/mm and 2582 (± 685) N/mm, respectively. The experimentally measured femoral stiffness is plotted against DXA/aBMD in Figs. 1A and 1B, and against QCT/FEA-estimated stiffness in Figs. 1C and 1D. The lines represent linear regression least-squares fits to each set of data. Figure 1A shows how DXA/aBMD correlated with measured stiffness for the entire cohort (women and men together), while Fig. 1B shows the same data with sex-specific regression lines. Similarly, Fig. 1C shows how QCT/FEA-estimated stiffness correlated with measured stiffness for the entire cohort, and Fig. 1D shows the corresponding sex-specific analysis. We observed a difference between femoral stiffness in women and men when DXA/aBMD was used as the explanatory variable, evidenced by the vertical distance between the two regression lines in Fig. 1B. However, a clear difference was not observed when QCT/FEA-estimated stiffness was used as the explanatory variable (Fig. 1D). Next, quantitative ANCOVA analyses were performed to test the significance of these observations and the significance of sex as a variable for predicting stiffness.

Table 2 shows the outcomes of ANCOVA and regression analyses performed with four separate sets of explanatory variable combinations, in order to determine which combination best accounted for the variability in the experimentally measured stiffness. The four cases were: 1. DXA/aBMD alone, 2. DXA/aBMD and sex, 3. DXA/aBMD and age, and 4. DXA/aBMD, sex, and age. Corresponding outcomes are also shown with QCT/FEA-estimated stiffness replacing DXA/aBMD as the primary explanatory variable.

DXA/aBMD alone was significant ($P<0.0001$), explaining 62% of the variability in experimentally measured stiffness ($R^2=0.62$). This model resulted in the following equation:

$$Stiffness = 2572(DXA/aBMD) - 277.2 \quad [\text{for both sexes}] \quad (1a)$$

In Eq. (1a), *Stiffness* has units of N/mm, and *DXA/aBMD* has units of g/cm². When sex, as a second explanatory variable, was combined with DXA/aBMD to predict experimental stiffness, both DXA/aBMD ($P<0.0001$) and sex ($P=0.0168$) were significant. This combination accounted for an additional 2% of the variability in measured stiffness, for a total of 64%. The equations (separated by sex) for this model including aBMD and sex are:

$$Stiffness = \begin{cases} 2372(DXA/aBMD) - 197.6 & [\text{women}] \\ 2372(DXA/aBMD) + 34.84 & [\text{men}] \end{cases} \quad (1b)$$

The inability of DXA/aBMD to fully account for sex is apparent in Eq. 1b: for a given DXA/aBMD value, men had significantly stiffer femurs ($P=0.0168$) than women (the stiffness is larger by about 232 N/mm, or 15% of the average experimental stiffness value for women in our cohort). Next, when added as a second explanatory variable to DXA/aBMD to predict experimental stiffness, age was insignificant ($P=0.08$), and yet it explained an additional 1% of the variability in femoral stiffness compared to DXA/aBMD alone (total 63%). Finally, when DXA/aBMD, sex, and age were combined together as explanatory variables, all three variables were significant ($P=0.0398$), explaining 65% of the variability in measured stiffness. None of the two-way interactions was significant ($P=0.54$). The equations (separated by sex) for the final DXA/aBMD stiffness model, including all three significant variables, are:

$$Stiffness = \begin{cases} 2051(DXA/aBMD) - 7.237(age) + 551.7 & [\text{women}] \\ 2051(DXA/aBMD) - 7.237(age) + 804.5 & [\text{men}] \end{cases} \quad (1c)$$

In Eq. (1c), *age* has units of years.

Table 2 also shows the outcomes when QCT/FEA-estimated stiffness is used as the main explanatory variable, rather than DXA/aBMD. It is important to note that QCT/FEA alone explains 7% more of the variability in the measured stiffness (72%) than DXA/aBMD, sex, and age combined (65%). This model resulted in the following equation:

$$Stiffness = 0.6244(QCT/FEA_{stiffness}) + 504.6 \quad [\text{for both sexes}] \quad (1d)$$

In Eq. (1d), *QCT/FEA_{stiffness}* is the QCT/FEA-estimated stiffness value in N/mm. Contrary to DXA/aBMD, sex was found to be insignificant ($P=0.40$) when combined with QCT/FEA-estimated stiffness, and adding sex did not explain any additional variability in the measured stiffness. Provided only for the purpose of comparison, the equations (separated by sex)

resulting from this model, including QCT/FEA stiffness and the insignificant variable sex, are:

$$Stiffness = \begin{cases} 0.6066(QCT/FEA_{stiffness}) + 514.8 & \text{[women]} \\ 0.6066(QCT/FEA_{stiffness}) + 589.3 & \text{[men]} \end{cases} \quad (1e)$$

This indicates that if a woman and a man had the same measured stiffness, the QCT/FEA model would predict similar values of stiffness for both sexes. Age, when combined with QCT/FEA-estimated stiffness, was significant ($P=0.0103$), but explained only about 1% more of the variability in the measured stiffness (total 73%). Finally, when both sex and age were considered with QCT/FEA stiffness, sex remained insignificant ($P=0.23$), age remained significant ($P=0.0072$), and all three variables considered together did not explain any additional variability compared with just QCT/FEA and age together. The equations for the final QCT/FEA stiffness model, including only significant variables (QCT/FEA stiffness and age), are:

$$Stiffness = 0.5634(QCT/FEA_{stiffness}) - 7.392(age) + 1141 \quad \text{[for both sexes]} \quad (1f)$$

Strength Analysis

The average experimentally measured femoral strength in women and men were 3254 (± 1710) N and 5421 (± 1850) N respectively. The estimated average strength values from QCT/FEA for women and men were 3139 (± 1158) N and 4760 (± 1116) N, respectively. Figure 2 shows experimentally measured femoral strength vs. DXA/aBMD and QCT/FEA-estimated strength. As in Fig. 1, the lines in Fig. 2 represent linear regression least-squares fits to each set of data. Figure 2A shows the correlation between DXA/aBMD and measured strength for the entire cohort, and Fig. 2B shows the sex-specific correlations for DXA/aBMD. Similarly, the correlation between QCT/FEA-estimated strength and measured strength is shown for the entire cohort in Fig. 2C, and grouped by sex in Fig. 2D. As with stiffness, the vertical distance between the lines for women and men in Fig. 2B visually indicates a difference between femoral strength in women and men when DXA/aBMD is used as the explanatory variable. However, a clear difference is not observed when QCT/FEA-estimated failure loads are used to predict experimentally measured femoral fracture loads (Fig. 2D). Similar to stiffness, ANCOVA analyses were performed to test quantitatively whether the observed differences due to sex in Fig. 2 are statically significant.

Table 3 shows ANCOVA and regression analyses analogous to Table 2, but replacing the experimentally measured femoral stiffness with the measured femoral strength, and replacing the QCT/FEA-estimated stiffness with QCT/FEA-estimated strength. Considered alone, DXA/aBMD was significant ($P<0.0001$), explaining 79% of the variability in femoral fracture loads. This model resulted in the following equation:

$$Strength = 8565(DXA/aBMD) - 2703 \quad \text{[for both sexes]} \quad (2a)$$

In Eq. (2a), *Strength* has units of N, and *DXA/aBMD* has units of g/cm². Next, sex and age were added to DXA/aBMD, separately, to predict measured strength. Both sex ($P<0.0001$) and age ($P=0.0066$), added individually to DXA/aBMD, were significant predictors of experimental strength. The equations (separated by sex) for the model including aBMD and sex are:

$$Strength = \begin{cases} 7862(DXA/aBMD) - 2424 & \text{[women]} \\ 7862(DXA/aBMD) - 1610 & \text{[men]} \end{cases} \quad (2b)$$

The significance of sex as an explanatory variable along with DXA/aBMD is evident in Eq. 2b: for a given DXA/aBMD value, men have significantly stronger femurs ($P<0.0001$) than women (larger by 814 N, or 25% of the average experimental strength value for women in our cohort).²⁷ Next, DXA/aBMD, sex, and age were included together in a statistical model. In this model, all three explanatory variables were significant ($P=0.0015$), and they explained 85% of the variability in measured femoral strength. The equations (separated by sex) for the final DXA/aBMD strength model, including all three significant variables, are:

$$Strength = \begin{cases} 10207(DXA/aBMD) + 18.40(age) - 52.09(age)(DXA/aBMD) - 2828 & \text{[women]} \\ 10207(DXA/aBMD) + 18.40(age) - 52.09(age)(DXA/aBMD) - 1914 & \text{[men]} \end{cases} \quad (2c)$$

In Eq. (2c), *age* has units of years. Note that in this model, the interaction between DXA/aBMD and age ($P=0.0176$) was found to be significant. We also modeled this combination of variables without this interaction, and that model explained 84% of the variability in strength; thus, this interaction accounted for less than 1% of the explained variability in strength. It is worth noting that the interaction between DXA/aBMD and age was not significant ($P=0.07$) when DXA/aBMD and age were the only explanatory variables in the model to explain femoral strength.

Table 3 also shows that QCT/FEA-estimated strength, alone, explained 82% of the variability in the measured strength. This model resulted in the following equation:

$$Strength = 1.336(QCT/FEA_{strength}) - 937.2 \quad \text{[for both sexes]} \quad (2d)$$

In Eq. (2d), $QCT/FEA_{strength}$ is the QCT/FEA-estimated strength value in N. When added to the statistical model for predicting the measured failure loads, sex was found to be insignificant ($P=0.99$). Again provided only for the purpose of comparison, the equations (separated by sex) resulting from this model, including QCT/FEA strength and the insignificant variable sex, are:

$$Strength = \begin{cases} 1.335(QCT/FEA_{strength}) - 935.9 & \text{[women]} \\ 1.335(QCT/FEA_{strength}) - 932.3 & \text{[men]} \end{cases} \quad (2e)$$

This implies that if a woman and a man had the same value of measured femoral strength, the QCT/FEA model would predict about the same strength value for both sexes. When age was added as a new explanatory variable along with QCT/FEA-estimated strength, it was significant ($P < 0.0001$), explaining about 4% more of the variability in measured femoral strength (total 86%). Combining sex with QCT/FEA-estimated strength and age did not further improve the predictive power of the model for measured femoral strength. Note that in this model, the interaction between QCT/FEA-estimated strength and age was insignificant ($P = 0.11$), unlike the corresponding model with DXA/aBMD as the main explanatory variable where DXA/aBMD and age interacted. The equation for the final QCT/FEA strength model, including only significant variables (QCT/FEA strength and age), is:

$$Strength = 1.160(QCT/FEA_{strength}) - 32.58(age) + 1987 \quad \text{[for both sexes]} \quad (2f)$$

Statistical Interpretation

Finally, considering Eqs. 1 and 2 together with the ANCOVA results in Tables 2 and 3, we noted that the two equations for women and men in each of Eqs. 1b (stiffness) and 2b (strength) are significantly different from each other because sex is a significant predictor when added as an explanatory variable to DXA/aBMD for both measured stiffness ($P = 0.0168$) and strength ($P < 0.0001$). However, the equations for women and men in Eqs. 1e and 2e are similar within each equation because sex is not significant ($P = 0.40$) when added as an explanatory variable to QCT/FEA-predicted values to explain experimental variability. Note that the final statistical models with QCT/FEA-predicted values as the primary explanatory variable (Eqs. 1f and 2f) are simpler than the corresponding models with aBMD as the primary explanatory variable (Eqs. 1c and 2c). Also, note that Eqs. 1e and 2e are similar to Eqs. 1d and 2d, respectively, because sex is insignificant.

It should be noted that a test of variable collinearity using the variance inflation factor (VIF)²¹ was performed, and this test showed no noteworthy variable confounding in our statistical models.

DISCUSSION

This study illustrates the unique ability of the QCT/FEA technique to implicitly account for the attribute of sex in its predictions of femoral stiffness and strength. In other words, the use of QCT/FEA to predict femoral strength and stiffness was found to be equally effective for both women and men. This ability was not seen with DXA/aBMD, which showed improvement in explaining variability when sex was added as a second explanatory variable.

However, similar to DXA/aBMD, the effects of age could not be completely explained and accounted for by QCT/FEA.

Significant differences in biomechanical parameters due to sex have been found previously, at multiple scale levels.^{2, 4, 23} Dissimilarities in porosity of the femoral shaft cortex,³¹ osteon size,³ and microstructural parameters⁴ between women and men have been reported. The results of this study indicate that DXA/aBMD is unable to fully account for significant sex-related differences in measured femoral stiffness and strength for similar mineral density values in women and men. This implies that this clinical tool is not equally effective in predicting femoral strength in women and men, which may be a source of the debate that the diagnosis of osteoporosis should be established at different DXA/aBMD levels in women and men.¹⁵ QCT/FEA outcomes however, better accounted for femoral sex-dimorphism, because femurs of women and men with similar QCT/FEA-estimated stiffness and strength values were found to have similar measured stiffness and fracture strength values. These results indicate that estimation of fracture strength and assessment of fracture risk with QCT/FEA may not be sex-specific. Therefore, the differences found between female and male femurs at smaller scales (which are not considered in QCT/FEA models) may not be significant contributors in predicting stiffness and strength. This implies that current imaging modalities and FEA modeling approaches are fully capable of accounting for sex differences. This implication is supported by the analysis of our QCT/FEA modeling results: if one accounts for differences in geometry and bone heterogeneity, sex does not remain a contributing factor in the estimation of fracture properties. This finding suggests that clinicians using QCT/FEA estimates of bone strength in place of DXA/aBMD could improve predictions of bone fracture risk in patients undergoing routine screening, irrespective of sex.

Our previous study using the same cadaveric cohort measured three geometric parameters considered to be representative of femoral geometry: neck diameter, neck-axis length, and neck-shaft angle.²⁷ Although the women cohort had, in general, smaller femurs compared to the men cohort, these size differences (as represented by the aforementioned geometry parameters) did not statistically account for any significant explained variability in measured femoral strength. These results suggest that the 3D distribution of minerals obtained using CT imaging may provide additional information to help explain the differences in femoral strength between women and men, compared to DXA and femoral geometry measurements.

When DXA/aBMD, sex, and age were used together to explain femoral strength, the interaction between DXA/aBMD and age became significant. However, for QCT/FEA-estimated strength, the interaction between QCT/FEA-estimated strength and age was still insignificant. Thus the model using QCT/FEA estimated strength and age is linear in both variables and therefore simpler for strength predictions compared with the model based on DXA/aBMD, sex, and age. QCT/FEA, similar to DXA/aBMD, did not completely explain the influence of age in predicting femoral strength, suggesting that the effects of age cannot be fully captured by either method. Although CT imaging may detect age-related variations of bone minerals and differences in bone geometry, aging also increases micro-cracks significantly at load-bearing sites,^{1, 30} and transitions fracture properties from ductile to brittle.^{22, 29} Detecting such variations is beyond the capacity of the available imaging tools

used routinely for patient screening. Age should be taken into consideration in the constitutive equations for elastic and fracture properties in the FEA modeling approach to improve predictions of femoral stiffness and fracture strength. A multi-scale analysis approach may provide a better understanding of how aging impacts bone to enhance QCT/FEA estimations.

While the correlation between QCT/FEA-estimated and experimentally measured stiffness and strength was higher than the corresponding correlations using DXA/aBMD, the improvements in femoral strength estimations were not substantial. Estimated QCT/FEA values could be improved by obtaining more optimal material and failure criterion equations; the equations utilized in the current study were obtained from the literature and resulted from experimental datasets, which might not be an ideal representation of various populations.

This study has several limitations. First, limitations of the computed tomography imaging technique might have prevented us from evaluating the true effect of age in the model predictions. We used the maximum clinical CT scanner resolution, resulting in voxel sizes of 0.30 to 0.45 mm. However, even this resolution is much larger than a single trabecula, which means that information on this scale is not captured by the CT scans on which the FE meshes are based. In addition, the protein elements of the bone matrix, which are a source of tensile strength in the bone tissue, cannot be detected using current CT scanners. It should be noted that we previously performed a sensitivity analysis on the mesh density, and we determined the mesh density required for our QCT/FEA outcomes to be independent of the mesh.⁹ This information was used to ensure mesh independence in the present study. Improvements in the imaging resolution used for patient screening may enable the acquisition of smaller scale effects, to further improve the predictive power of the QCT/FEA models and to allow for the simultaneous evaluation of the effect of age. Another potential limitation in our QCT/FEA technique is that we assumed the same material properties in tension and compression.^{17, 24} A previous study¹⁸ evaluated differences between outcomes generated by models that accounted for differences in tensile and compressive material strength, and those that did not. This study found no significant differences in the outcomes of models whether or not they separately modeled tension and compression. A final limitation of this work is that, compared with DXA/aBMD, the cost and radiation doses required for CT scanning are higher in QCT/FEA. However, the high resolution clinical CT scans result in clinically acceptable radiation exposure.⁹ Also, while cost may prevent QCT/FEA from becoming the current clinical standard, the improved predictive ability of QCT/FEA over DXA/aBMD may warrant its use for certain applications with target populations. This likelihood will increase as improvements are made to the QCT/FEA technology platform to further enhance its ability to predict femoral stiffness and strength.

In conclusion, unlike DXA/aBMD, QCT/FEA-estimated stiffness and strength outcomes were found to account for the inherent differences between sexes. On the other hand, neither QCT/FEA nor DXA/aBMD could fully account for the effects of age. These findings show that taking into account the 3D geometry and bone mineral distribution in a finite element model can improve upon the inherent limitations in current fracture risk assessments.

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References

1. Augat P, Schorlemmer S. The role of cortical bone and its microstructure in bone strength. Age and ageing. 2006; 35:ii27–ii31. [PubMed: 16926200]
2. Bousson V, Meunier A, Bergot C, Vicaud É, Rocha MA, Morais MH, Laval-Jeantet AM, Laredo JD. Distribution of intracortical porosity in human midfemoral cortex by age and gender. Journal of bone and mineral research. 2001; 16:1308–1317. [PubMed: 11450707]
3. Britz HM, Thomas CDL, Clement JG, Cooper DM. The relation of femoral osteon geometry to age, sex, height and weight. Bone. 2009; 45:77–83. [PubMed: 19303955]
4. Chen H, Shoumura S, Emura S, Bunai Y. Regional variations of vertebral trabecular bone microstructure with age and gender. Osteoporosis International. 2008; 19:1473–1483. [PubMed: 18330606]
5. Cody DD, Gross GJ, Hou FJ, Spencer HJ, Goldstein SA, Fyhrie DP. Femoral strength is better predicted by finite element models than QCT and DXA. Journal of biomechanics. 1999; 32:1013–1020. [PubMed: 10476839]
6. Cristofolini L, Juszczak M, Martelli S, Taddei F, Viceconti M. In vitro replication of spontaneous fractures of the proximal human femur. Journal of biomechanics. 2007; 40:2837–2845. [PubMed: 17475269]
7. Cummings SR, Cawthon PM, Ensrud KE, Cauley JA, Fink HA, Orwoll ES. BMD and risk of hip and nonvertebral fractures in older men: a prospective study and comparison with older women. Journal of bone and mineral research. 2006; 21:7.
8. Dall'Ara E, Eastell R, Viceconti M, Pahr D, Yang L. Experimental Validation of DXA-based Finite Element models for prediction of femoral strength. Journal of the Mechanical Behavior of Biomedical Materials. 2016
9. Dragomir-Daescu D, Op Den Buijs J, McEligot S, Dai Y, Entwistle RC, Salas C, Melton LJ 3rd, Bennet KE, Khosla S, Amin S. Robust QCT/FEA models of proximal femur stiffness and fracture load during a sideways fall on the hip. Annals of biomedical engineering. 2011; 39:742–755. [PubMed: 21052839]
10. Dragomir-Daescu D, Rezaei A, Rossman T, Uthamaraj S, Entwistle R, McEligot S, Lambert V, Giambini H, Jasiuk I, Yaszemski M, Lichun L. Method and Instrumented Fixture for Femoral Fracture Testing in a Sideways Fall-on-the-Hip Position. JoVE (Journal of Visualized Experiments). 2017:e54928–e54928.
11. Dragomir-Daescu D, Rezaei A, Uthamaraj S, Rossman T, Bronk JT, Bolander M, Lambert V, McEligot S, Entwistle R, Giambini H, Jasiuk I, Yaszemski M, Lichun L. Proximal Cadaveric Femur Preparation for Fracture Strength Testing and Quantitative CT-based Finite Element Analysis. JoVE (Journal of Visualized Experiments). 2017:e54925–e54925.
12. Gilchrist S, Nishiyama K, De Bakker P, Guy P, Boyd S, Oxland T, Crompton P. Proximal femur elastic behaviour is the same in impact and constant displacement rate fall simulation. Journal of biomechanics. 2014; 47:3744–3749. [PubMed: 25443780]
13. Hambli R, Allaoui S. A robust 3D finite element simulation of human proximal femur progressive fracture under stance load with experimental validation. Annals of biomedical engineering. 2013; 41:2515–2527. [PubMed: 23864338]
14. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. The Lancet. 2002; 359:1929–1936.
15. Kanis JA, Melton LJ, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. Journal of bone and mineral research. 1994; 9:1137–1141. [PubMed: 7976495]

16. Keaveny TM, Kopperdahl DL, Melton LJ, Hoffmann PF, Amin S, Riggs BL, Khosla S. Age-dependence of femoral strength in white women and men. *Journal of bone and mineral research*. 2010; 25:994–1001. [PubMed: 19874201]
17. Keyak J, Rossi S, Jones K, Les C, Skinner H. Prediction of fracture location in the proximal femur using finite element models. *Medical engineering & physics*. 2001; 23:657–664. [PubMed: 11755810]
18. Keyak JH, Kaneko TS, Tehranzadeh J, Skinner HB. Predicting proximal femoral strength using structural engineering models. *Clinical orthopaedics and related research*. 2005; 437:219–228.
19. Keyak JH, Rossi SA. Prediction of femoral fracture load using finite element models: an examination of stress-and strain-based failure theories. *Journal of biomechanics*. 2000; 33:209–214. [PubMed: 10653034]
20. Koivumäki JE, Thevenot J, Pulkkinen P, Kuhn V, Link TM, Eckstein F, Jämsä T. Ct-based finite element models can be used to estimate experimentally measured failure loads in the proximal femur. *Bone*. 2012; 50:824–829. [PubMed: 22306697]
21. Kutner, MH., Nachtsheim, C., Neter, J. *Applied linear regression models*. McGraw-Hill/Irwin; 2004.
22. Launey ME, Buehler MJ, Ritchie RO. On the mechanistic origins of toughness in bone. *Annual review of materials research*. 2010; 40:25–53.
23. Mirzaali MJ, Schwiedrzik JJ, Thaiwichai S, Best JP, Michler J, Zysset PK, Wolfram U. Mechanical properties of cortical bone and their relationships with age, gender, composition and microindentation properties in the elderly. *Bone*. 2016; 93:196–211. [PubMed: 26656135]
24. Mirzaei M, Keshavarzian M, Naeini V. Analysis of strength and failure pattern of human proximal femur using quantitative computed tomography (QCT)-based finite element method. *Bone*. 2014; 64:108–114. [PubMed: 24735974]
25. Morgan EF, Bayraktar HH, Keaveny TM. Trabecular bone modulus–density relationships depend on anatomic site. *Journal of biomechanics*. 2003; 36:897–904. [PubMed: 12757797]
26. Nasiri M, Luo Y. Study of sex differences in the association between hip fracture risk and body parameters by DXA-based biomechanical modeling. *Bone*. 2016; 90:90–98. [PubMed: 27292653]
27. Rezaei A, Dragomir-Daescu D. Femoral Strength Changes Faster With Age Than BMD in Both Women and Men: A Biomechanical Study. *Journal of bone and mineral research*. 2015; 30:2200–2206. [PubMed: 26096829]
28. Rossman T, Kushvaha V, Dragomir-Daescu D. QCT/FEA predictions of femoral stiffness are strongly affected by boundary condition modeling. *Computer methods in biomechanics and biomedical engineering*. 2016; 19:208–216. [PubMed: 25804260]
29. Sabet FA, Najafi AR, Hamed E, Jasiuk I. Modelling of bone fracture and strength at different length scales: a review. *Interface focus*. 2016; 6:20150055. [PubMed: 26855749]
30. Seref-Ferlengez Z, Kennedy OD, Schaffler MB. Bone microdamage, remodeling and bone fragility: how much damage is too much damage [quest]. *BoneKEy reports*. 2015; 4
31. Thomas CDL, Feik SA, Clement JG. Regional variation of intracortical porosity in the midshaft of the human femur: age and sex differences. *Journal of anatomy*. 2005; 206:115–125. [PubMed: 15730477]
32. Unnanuntana A, Gladnick BP, Donnelly E, Lane JM. The Assessment of Fracture Risk. *Journal of Bone and Joint Surgery*. 2010; 92:743–753.

Figure 1.

Experimentally measured stiffness vs. DXA/aBMD (A) for the entire cohort, and (B) for women and men separately. Experimentally measured stiffness vs. QCT/FEA-estimated stiffness (C) for the entire cohort, and (D) for women and men, separately.

Figure 2.

Experimentally measured strength vs. DXA/aBMD (A) for the entire cohort, and (B) for women and men, separately. Experimentally measured strength vs. QCT/FEA-estimated strength (C) for the entire cohort, and (D) for women and men, separately.

TABLE 1

Number of samples, mean $\pm$ SD and range of age values, and mean $\pm$ SD of DXA/aBMD of the cadaveric cohort

	Women	Men	Total/Average
No. of samples	67	33	100
Age [range]	72 $\pm$ 14 [37–99]	67 $\pm$ 16 [34–91]	70 $\pm$ 15 [34–99]
Neck aBMD (g/cm²)	0.722 $\pm$ 0.193	0.894 $\pm$ 0.201	0.779 $\pm$ 0.211

TABLE 2

P values and adjusted R^2 values for the four sets of explanatory variable combinations used to account for the variability in experimental femoral stiffness. The top portion of the table uses DXA/aBMD as the primary explanatory variable, while the bottom portion uses QCT/FEA-estimated stiffness.

<i>Predictors</i>	<i>P</i> (DXA/aBMD)	<i>P</i> (Sex)	<i>P</i> (Age)	R^2
DXA/aBMD	<0.0001	-	-	0.62
DXA/aBMD + Sex	<0.0001	0.0168	-	0.64
DXA/aBMD + Age	<0.0001	-	0.08	0.63
DXA/aBMD + Sex + Age	<0.0001	0.0087	0.0398	0.65

<i>Predictors</i>	<i>P</i> (QCT/FEA Stiffness)	<i>P</i> (Sex)	<i>P</i> (Age)	R^2
QCT/FEA	<0.0001	-	-	0.72
QCT/FEA + Sex	<0.0001	0.40	-	0.72
QCT/FEA + Age	<0.0001	-	0.0103	0.73
QCT/FEA + Sex + Age	<0.0001	0.23	0.0072	0.73

TABLE 3

P values and adjusted R^2 values for the four sets of explanatory variable combinations (without interactions) used to account for the variability in experimental femoral strength. The top portion of the table uses DXA/aBMD as the primary explanatory variable, while the bottom portion uses QCT/FEA-estimated strength.

<i>Predictors</i>	<i>P</i> (DXA/aBMD)	<i>P</i> (Sex)	<i>P</i> (Age)	R^2
DXA/aBMD	<0.0001	-	-	0.79
DXA/aBMD + Sex	<0.0001	<0.0001	-	0.82
DXA/aBMD + Age	<0.0001	-	0.0066	0.81
DXA/aBMD + Sex + Age *	<0.0001	<0.0001	0.0006	0.84

<i>Predictors</i>	<i>P</i> (QCT/FEA Strength)	<i>P</i> (Sex)	<i>P</i> (Age)	R^2
QCT/FEA	<0.0001	-	-	0.82
QCT/FEA + Sex	<0.0001	0.99	-	0.82
QCT/FEA + Age	<0.0001	-	<0.0001	0.86
QCT/FEA + Sex + Age	<0.0001	0.33	<0.0001	0.86

* In this model, the interaction between DXA/BMD and age was found to be significant ($P=0.0176$). However, when including this interaction to the model, R^2 increased by less than 1%.