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Prediction of Incident Hip Fracture with the estimated Femoral Strength by Finite Element Analysis of DXA Scans in the Study of Osteoporotic Fractures

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Abstract

A bone fractures only when loaded beyond its strength. The purpose of this study was to determine the association of femoral strength, as estimated by finite element (FE) analysis of DXA scans, with incident hip fracture in comparison to hip BMD, FRAX[®] and hip structure analysis (HSA) variables. This prospective case-cohort study included a random sample of 1941 women and 668 incident hip fracture cases (295 in the random sample) during a mean±SD follow-up of 12.8±5.7 yrs from the Study of Osteoporotic Fractures (n=7860 community-dwelling women ≥67 yr of age). We analyzed the baseline DXA scans (Holgoic 1000) of the hip using a validated plane-stress, linear-elastic finite element (FE) model of the proximal femur and estimated the femoral strength during a simulated sideways fall. Cox regression accounting for the case-cohort design assessed the association of estimated femoral strength with hip fracture. The age-BMI-adjusted hazard ratio (HR) per SD decrease for estimated strength (2.21, 95% CI 1.95–2.50) was greater than that for TH BMD (1.86, 95% CI 1.67–2.08; p<0.05), FN BMD (2.04, 95% CI 1.79–2.32; p>0.05), FRAX[®] scores (range 1.32–1.68; p<0.0005) and many HSA variables (range 1.13–2.43; p<0.005), and the association was still significant (p<0.05) after further adjustment for hip BMD or FRAX[®] scores. The association of estimated strength with incident hip fracture was strong (Harrell's C index 0.770), significantly better than TH BMD (0.759, p<0.05) and FRAX[®] scores (0.711–0.743, p<0.0001) but not FN BMD (0.762, p>0.05) Similar findings were obtained for intra- and extra-capsular fractures.

In conclusion, the estimated femoral strength from FE analysis of DXA scans is an independent predictor and performs at least as well as FN BMD in predicting incident hip fracture in postmenopausal women.

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DISCLOSURES

All authors state that they have no conflict of interest.

Keywords

Hip fracture; Osteoporosis; finite element analysis; DXA

INTRODUCTION

Osteoporotic hip fracture in older persons causes excess morbidity, disability and mortality^(1;2), and it is a major health problem which is likely to be exacerbated by the aging of population⁽³⁾. Bone mineral density (BMD) as measured by dual-energy x-ray absorptiometry is highly associated with clinical risk of hip fracture⁽⁴⁾ and forms the basis of current clinical practice guidelines for diagnosing osteoporosis. However, its accuracy in assessing individual fracture risk is limited since most of hip fracture occurs in patients who do not have low BMD (BMD T-score ≤ -2.5)^(5;6). The FRAX[®] fracture risk assessment tool has recently been developed and recommended by the WHO to evaluate an individual's 10-year probability of hip fracture based on a number of clinical risk factors and hip BMD^(7;8).

Many factors in combination cause hip fracture, but a major contributor is reduced mechanical strength of the proximal femur. Development of non-invasive and reliable measures of femoral strength could provide insight into hip fracture etiology and might improve clinical assessment of hip fracture risk. Considerable effort has been directed towards a variety of patient-specific structural engineering and finite element (FE) models of the proximal femur to estimate femoral strength and assess hip fracture risk. Such models make use of geometry and bone density distribution information embedded in medical images of the hip acquired by DXA and quantitative computer tomography (QCT). Great advances have been achieved in FE models of the proximal femur based on QCT. The estimated femoral strength derived from such models have recently been used in clinical studies to investigate age- and gender-related differences^(9;10), to examine effects of drug therapy for osteoporosis⁽¹¹⁻¹³⁾ and of micro-gravity⁽¹⁴⁾, to predict incident hip fracture in older men⁽¹⁵⁾ and prevalent fracture discrimination⁽¹⁶⁾. On the other hand, DXA-based FE models have not been evaluated in clinical studies as extensively as QCT models. Due to its relatively high radiation dose, high cost and limited availability, QCT is not routinely performed in clinical management of patients and likely remain a powerful tool only in research settings in the near future, whereas DXA is likely to continue its dominance as the primary imaging modality in osteoporosis clinics.

We developed a DXA-based FE model of the proximal femur and showed its potential usefulness in discriminating hip fracture cases from controls in a case-control study⁽¹⁷⁾. Recently we validated an updated version of the model and showed that it could discriminate incident hip fracture cases from controls independently from femoral neck (FN) BMD, prior fracture, VFA and FRAX[®] score in a longitudinal, nested case-control study of elderly (>73 yrs) community dwelling women. In that study fracture cases and controls were individually matched by age, height and weight, which prevented us from considering the time to fracture. The mean age of the elderly women (82 yr) was older than the mean age of hip fracture for UK population (77 years, The National Institute for Health and Clinical

Excellence 2009) and the size of study population was only moderately large (182 cases and 728 controls).

The purpose of this study was to determine whether the estimated bone strength from our DXA-based FE model of the proximal femur is able to predict hip fracture risk independently of BMD and other risk factors in a large case-cohort sample of the Study of Osteoporotic Fractures, a large observational study of post-menopausal women.

MATERIALS AND METHODS

Study population

A total of 9704 Caucasian women aged ≥ 5 years were enrolled in the SOF study from community and population-based listings in 4 areas of the USA between September 1986 and October 1988⁽¹⁸⁾ and they received a scan of the left hip using Hologic QDR 1000 (Hologic, Waltham, MA, USA) DXA scanner between January 1989 and December 1990 (visit 2, the baseline for this analysis). Age, weight and height at DXA scan were recorded at visit 2. The women were contacted every 4 months by postcard or telephone and asked whether they sustained any fracture or fall. All hip fractures were centrally confirmed by reviewing pre-operative radiographs or radiology reports.

This prospective case-cohort study included a random sample of 1941 women and 668 incident hip fracture cases (295 in the random sample) during a mean \pm SD follow-up of 12.8 \pm 5.7 yrs.

FE analysis of DXA scans

Our methodology of performing a linear-elastic, plane stress FE analysis of DXA scans has been described in detail previously⁽¹⁹⁾. Pixel-by-pixel BMD maps, extracted from the original DXA scans for the purpose of perform hip structure analysis^(20;21), were provided by Quantum Medical Metrics LLC, Baltimore, MD, USA. Based on the BMD map, we identified the proximal femur using an image processing algorithm that combined edge detection and thresholding followed by manual addition and/or removal. We assumed that each femur is a plate with a patient-specific constant thickness t and derived the thickness as $t=3.5\pi W/16$ (where W is the mean width of the middle third cross sections of the femoral neck on the BMD map) by imposing a condition that the cross section areas and moments of inertia are as close as possible between the plate's rectangular and the assumed anatomical circular cross sections. We converted areal BMD to volumetric BMD $vBMD=BMD/t$, then to apparent density $\rho_{app}=vBMD/(1.14\times 0.598)^{(22)}$, and derived material properties from ρ_{app} by using the empirical equations of Morgan *et al*^(23;24):

$$\begin{aligned}
 \text{Modulus of Elasticity}(MPa) &= \begin{cases} 15010\rho_{app}^{2.18} & \text{if } \rho_{app} \leq 0.280g/cm^3 \\ 6850\rho_{app}^{1.49} & \text{if } \rho_{app} > 0.280g/cm^3 \end{cases} \\
 \text{Compressive yield stress}(MPa) &= \begin{cases} 85.5\rho_{app}^{2.26} & \text{if } \rho_{app} \leq 0.355g/cm^3 \\ 38.5\rho_{app}^{1.48} & \text{if } \rho_{app} > 0.355g/cm^3 \end{cases} \\
 \text{Tensile yield stress}(MPa) &= \begin{cases} 50.1\rho_{app}^{2.04} & \text{if } \rho_{app} \leq 0.355g/cm^3 \\ 22.6\rho_{app}^{1.26} & \text{if } \rho_{app} > 0.355g/cm^3 \end{cases}
 \end{aligned}$$

The above material properties were increased by a factor of 1.28 to account for the side-artifact errors in biomechanical testing of cadaveric trabecular specimen to determine the relationship between bone density and material properties^(25;26). We simulated a fall on the greater trochanter: a peak impact force, a function of body height and weight⁽²⁷⁾, was applied to the greater trochanter, with prevention of medial displacement of the femoral head and prevention of displacement of the distal femoral shaft (Figure 1). We performed linear-elastic analysis without considering the post-yield behaviour since the proximal femur behaves linearly elastic until failure⁽²⁸⁾. We defined the estimated femoral strength as the onset impact force that caused the von Mises stress in a contiguous area of 25 mm² (comprising about 100 elements), within an anatomical region bounded proximally by the subcapital line and distally by a transverse line passing through the distal end of the lesser trochanter, to exceed an apparent yield stress (an average of compressive and tensile yield stress). We generated a stress ratio map (von Mises stress divided by the apparent yield stress), identified a contiguous area of at least 25 mm² that contained the highest stress ratio and noted the minimum stress ratio β in that area. Since the FE analysis was linear-elastic and the stress level was proportional to the applied force, the estimated femoral strength was derived by scaling the peak impact force by $1/\beta$. This approach to define failure has been successfully applied by Keyak *et al*^(29;29).

Statistical analysis

All statistical analyses were performed at UCSF using SAS (version 9) after FE analyses were completed on DXA scans in Sheffield. Correlations between DXA derived variables were calculated using Spearman rank correlations. For the case-cohort design, time to first incident fracture was analyzed using Cox proportional hazards models with the Prentice weighting method and robust variance estimate⁽³⁰⁾. Hazard ratios (HR) we expressed per one SD increase or decrease of the continuous covariates. Covariates were sequentially included in the same model and a Wald test was used to assess their effect on the HR. A Wald test was also used to test the difference between HRs for pairs of covariates of interest (estimated FE strength v. total hip BMD or femoral neck BMD or FRAX[®] 10-year hip fracture probabilities or selected hip structure analysis variables) in separate models. This was accomplished by running 2 models simultaneously using repeated-measures on data configured with 2 records per subject, each record with one of the covariates of interest. Predictive abilities of different models were compared using the Harrell's C index, a concordance measure for survival data analogous to the area under a receiver operating characteristic curve (AUC).

RESULTS

All baseline characteristics and estimated strength were correlated to each other (Table 1, $P < 0.05$ for all). Estimated strength and BMDs were positively correlated to each other and negatively correlated to FRAX[®] fracture probabilities.

Compared with women without incident hip fracture, women with incident hip fracture were older, had lower BMI, hip BMDs and estimated femoral strength and higher FRAX[®] fracture probabilities (Table 2, $P < 0.05$ for all).

Total hip (TH) and femoral neck (FN) BMDs and estimated strength were associated with incident hip fracture risk, the age- and BMI-adjusted HRs were 2.09, 2.27 and 2.57 for each standard deviation (SD) decrease in TH and FN BMDs and estimated strength (Table 3), respectively. Hip BMDs and estimated strength were also independent of each FRAX[®] scores in association with hip fracture. The association with hip fracture for estimated strength was stronger than those for TH BMD ($P < 0.05$ for Wald test) but not for FN BMD. When estimated strength and hip BMD were in the same model, estimated strength had higher HR than the hip BMD. The FRAX[®] fracture probabilities were associated with hip fracture, but the associations were weaker than that of estimated strength (Table 3, $p < 0.05$ from Wald test).

TH and FN BMDs, estimated strength and FRAX[®] probabilities were associated with both intra-capsular and extra-capsular fractures (Table 3). The HR for estimated strength was greater than TH BMD and FRAX[®] probabilities ($P < 0.05$) but not FN BMD. The associations with extra-capsular fracture for hip BMD and estimated strength were generally but not always stronger than the associations with intra-capsular fracture.

Table 4 shows the Harrell's C indices (AUC for survival data) demonstrating the ability of various Cox regression models to predict incident hip, intra-capsular and extra-capsular fractures. Based on paired Cox models, the estimated strength performed significantly ($P < 0.05$) better than TH BMD and FRAX[®] scores in predicting hip or intra- and extra-capsular fractures, and better but just short of significance ($P = 0.0539$) than FN BMD in predicting extra-capsular fractures. Combination of hip BMDs and estimated strength did not improve the prediction of hip, intra- or extra-capsular fractures over estimated strength.

DISCUSSION

This is the first report on using DXA-based, patient-specific finite element models of the proximal femur to examine its association with the time to first hip fracture in a population-based large cohort of postmenopausal women. The finite element analysis technique, which incorporates density distribution and geometry information embedded in DXA images and loading conditions of sideways fall known to cause hip fracture, has been validated in vitro and shown to independently predict hip fracture in older postmenopausal women in a previous case-control study⁽¹⁹⁾. In this case-cohort study we are able to take the time to first hip fracture into consideration and confirmed that estimated femoral strength from the finite element model are significant predictors of new hip fractures, independent of age, BMI and hip BMDs or the FRAX[®] scores. In particular, the age- and BMI-adjusted hazard ratios and

fracture prediction ability as judged by Harrell's C index for estimated strength were significantly greater than that for TH BMD and FRAX[®] 10-year hip fracture probabilities. However, there were no differences in FN BMD and estimated strength. Similar findings were observed when intra- and extra-capsular fractures were analyzed separately.

Several DXA-based structural engineering models of the proximal femur have been developed to assess the stress or strength and their association with hip fracture risk and our FE model compares well with them. Mourada et al developed a curved-beam model⁽³¹⁾ and validated it against cadaver experiment data⁽³²⁾, but its clinical evaluation has not been reported. Based on the beam bending theory, Yoshikawa et al⁽³³⁾ calculated a femur strength index, the ratio of estimated compressive yield strength of the femoral neck to the expected compressive stress of a fall on the greater trochanter adjusted for the patient's age, height and weight. This index has been found to be an independent predictor of hip fracture with an odd ratio per SD of 1.5⁽³⁴⁾. Crabtree et al showed that the estimated compressive stress, age and body mass index was significantly better at predicting hip fracture than FN BMD alone. Testi et al developed a DXA-based FE model of the proximal femur⁽³⁵⁾ and showed that including BMD, height, neck-shaft angle, and maximum tensile strain from this model into the regression analysis enhanced the prediction accuracy from 64.5% for BMD alone to 81.7%. We developed and compared three different structural engineering models (beam, curved beam and FE models) in a cross-sectional case-control study of 204 postmenopausal women and found that the FE model performed best in discriminating fracture cases from controls⁽¹⁷⁾. However none of the above models estimates the proximal femoral strength during sideways fall. We further developed and validated our FE model in a longitudinal case-control study of 728 older postmenopausal women (mean 85 yrs, range 75 to 95 yrs) and found that the estimated femoral strength derived from the FE model predicted hip fracture (OR 1.7) independently of hip BMD⁽¹⁹⁾. The most important strength of this analysis is its case-cohort design in a cohort of community dwelling women recruited without specific recruitment restrictions of a randomized trials and treatment. The case-cohort design incorporates the best features of both cohort and case-control designs⁽³⁰⁾. Previous studies with DXA-based finite element analysis techniques were all of cross-sectional or longitudinal case-control design^(17;19;36), where the time to fracture information was not considered. Other strengths of this analysis include the largest number of cases (n=668) and longest follow-up period (mean 12.8 yrs) among similar studies. All these allowed us to compare with greater power the ability of FE estimated strength and BMD to predict new hip fracture or intra-capsular and extra-capsular fractures. This analysis establishes that estimated femoral strength from finite element analysis of DXA scans can be used to identify postmenopausal women at high risk of new hip fracture. The whole process of FE analysis takes less than 8 minutes to complete on a modern personal computer and is completely automated once the proximal femur is segmented. It is therefore suitable for clinical use and could be widely available if implemented by DXA manufacturers.

The HSA technique^(20;37) measures femur geometry variables and is widely used to study the structural basis of hip fracture. Variable findings were reported. Hip axis length was found to discriminate/predict hip fracture independent of hip BMD in some studies^(34;38-41) but others found no association⁽⁴²⁻⁴⁵⁾. Some reported significant independent association of the femoral neck width with hip fracture^(40;42;46) but others did not^(45;47;48). Kaptoge et

al⁽²¹⁾ reported the HSA results on the hip DXA from SOF. Age-adjusted univariate HRs for incident hip fracture associated with 1 SD changes in the HSA variables are all but one (femoral neck length) significant ($P < 0.05$), with average cortical thickness at the femoral neck having the largest HR of 2.10 followed by the femoral neck BMD of 2.08. These HR values are similar to our age-adjusted HR of 2.25 for estimated strength. We, for the first time, directly compared age- and BMI-adjusted HRs for the femoral neck axis length (FNAL), neck-shaft angle (NSA) and 6 other HSA variables with that for estimated strength (Table 5 as Supplemental Material) and found that estimated strength had significantly ($P < 0.0005$) higher HR for hip, IC and EC fractures than any HSA variables at the narrow neck (except for cortical thickness and BMD), intertrochanter (except for cortical thickness and BMD for EC fracture) and femoral shaft. This demonstrates advantages of FE modelling that incorporate density distribution, geometry and loading condition of sideways fall. However, estimated strength did not outperform BMD and HSA geometrical measures as judged by the Harrell's C-indices (Table 6 as Supplemental Material). FE model integrates BMD distribution, geometry and fracture-causing loading conditions to estimate femoral strength - a single overall measure of bone quality, which is an advantage as a potential diagnostic measure for clinical implementation.

We found that patients with EC fracture had lower estimated strength than patients with IC fracture and that estimated strength had higher HR and Harrell's C for EC than for IC fractures. This is in line with the findings in this and other studies⁽⁴⁹⁻⁵¹⁾ that patients with EC fracture are generally older and have lower hip BMD than patients with IC fracture, which lead to lower elastic modulus and yield stress of bone in our FE model. It has been shown that the current BMD-based clinical assessment procedure is adequate to predict EC fracture⁽⁵²⁾ but may under-diagnose IC fracture⁽⁵³⁾, since women with IC fracture tend to have a much more complex risk profile such as longer femoral neck length, wider neck-shaft angle and narrower neck width than in the control or patient with EC fracture^(40-42;45;49;54). The estimated strength in this study is independently associated with both IC and EC fractures, its association is stronger than TH BMD and many HSA variables, and it predicts IC and EC fractures significantly better than TH BMD).

Our FE model, like other DXA-based models, is restricted by the inherent limitations of DXA scans to a 2 dimensional approach, thus ignoring variations of geometry, bone density and impact force in the anterior-posterior direction. Methods have been developed to generate 3 dimensional femur models from 2 dimensional scans^(55;56), which can then be used to generate 3D FE models. Although the relationship between bone density and material properties of the human femoral neck and trochanter were used, we did not model cortical bone separately since it was not possible to identify cortical bone correctly in DXA scans. We chose to perform linear-elastic analysis without considering post-yield behaviour since the human proximal femur has been found to behave linearly elastic up to failure⁽²⁴⁾. We did not consider the different yield stresses of bone in tension and in compression. We only analyzed left hip, the only side scanned, but incident fractures occurred in both sides. In the literature, there are conflicting reports on the side-differences of hip BMD^(57;58) and one report of significant yet small intra-subject asymmetry in femoral geometry (mainly in the infero-medial cortex)⁽⁵⁹⁾. We do not know any study on side-differences in FE strength and can only speculate that side-asymmetry in FE strength exist if side-asymmetry in femoral

BMD or/and geometry present, which may affect its performance in fracture risk assessment. Hologic QDR 1000 scanners used in the SOF were pencil-beam scanners, which does not have the magnification problem of the modern fan-beam scanner but suffers lower resolution. Thus, another limitation is that we do not know how the comparison of estimated strength to BMD measures may differ when more modern fan beam scanners would be used.

In conclusion, this large case-cohort study of postmenopausal women establishes that the estimated femoral strength from the FE analysis of DXA scans associated with the first incident hip fracture, generally independent of BMD. Its association with and ability to predict all types of hip fracture is significantly stronger than TH BMD, HSA and FRAX[®] hip fracture probabilities (but not FN BMD).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Authors' role: Study conception and design (LY, DB, RE), FE modelling (LY), statistical analysis (LP), interpretation data (LY, LP, DB, RE), drafting manuscript (LY, LP), and manuscript revision and approval (LY, LP, DB, RE). LY takes responsibility for the integrity of the data analysis.

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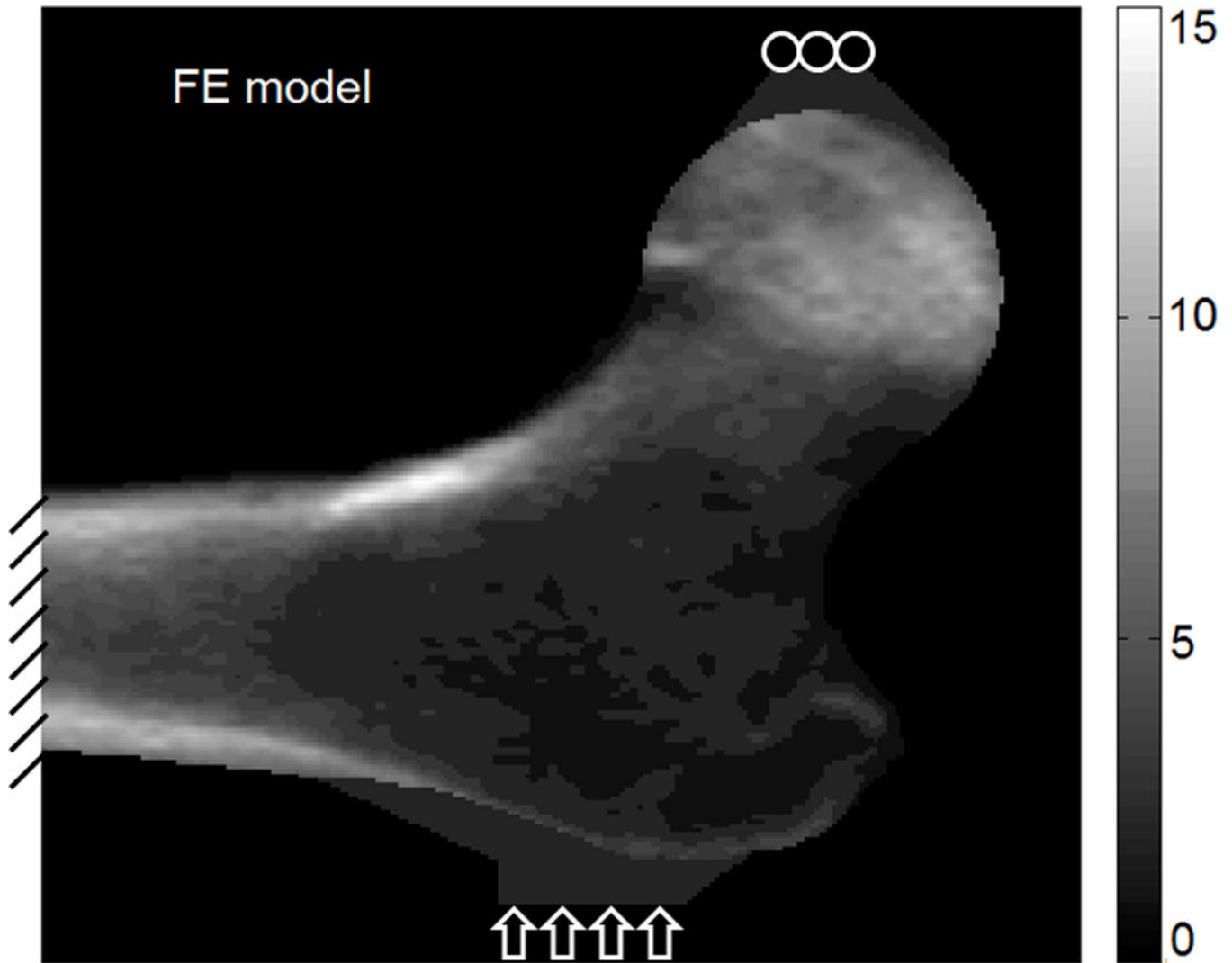


Figure 1. The DXA-based FE model of the proximal femur showing the loading conditions that simulates sideways fall: impact forces applied to the greater trochanter, the distal end fixed and femoral head restrained in the vertical direction. The image intensity demonstrates the distribution of elastic modulus in GPa.

Table 1

Spearman Correlation Coefficients in the cohort

	FE	DXA		FRAX®	
	strength	TH BMD	FN BMD	HIPW	HIPWO
<i>FE strength</i>	1.00	0.83	0.81	-0.72	-0.40
<i>TH BMD</i>		1.00	0.84	-0.76	-0.44
<i>FN BMD</i>			1.00	-0.86	-0.42
<i>HIPW</i>				1.00	0.76
<i>HIPWO</i>					1.00

HIPW: 10-yr hip fracture probability with BMD; HIPWO: 10-yr hip fracture probability without BMD.

Table 2

Comparison of patient characteristics between patients with and without incident hip fracture

		No fracture (n=1646)	IC fracture (n=351)	EC fracture (n=309)	All hip fractures (n=668)
<i>Age (yrs)</i>		73.3±5.1	74.6±5.4 ^b	76.1±5.8 ^b	75.3 ± 5.6 ^b
<i>BMI (kg/m²)</i>		26.3 ± 4.6	24.7±3.9 ^b	25.4±4.3 ^a	25.0 ± 4.1 ^b
<i>TH BMD (g/cm²)</i>		0.77 ± 0.13	0.70±0.11 ^b	0.67±0.12 ^b	0.69 ± 0.11 ^b
<i>FN BMD (g/cm²)</i>	n	1634 0.66 ± 0.11	349 0.59±0.09 ^b	307 0.59±0.10 ^b	664 0.59 ± 0.10 ^b
<i>FE strength (N)</i>		3027 ± 1203	2292±925 ^b	2159±963 ^b	2236 ± 945 ^b
<i>Follow-up duration (yrs)</i>		12.7 ± 5.9	13.3±4.9	12.8±4.8	13.1 ± 4.9
<i>10-yr hip fx probability with BMD (%)</i>	n	1307 4.8 ± 6.9	276 8.7±9.8 ^b	230 9.4±10.6 ^b	511 9.0 ± 10.2 ^b
<i>10-yr hip fx probability without BMD (%)</i>	n	1316 6.4 ± 6.8	278 9.6±9.5 ^b	232 9.9±9.8 ^b	515 9.8 ± 9.6 ^b

1. Variables are presented as mean ± 1 standard deviation

2. IC and EC: Intra-capsular and extra-capsular, respectively

3. Subscripts a and b indicate that the variable's means in incident fracture group were significantly different from that in no fracture group at P<0.01 and 0.001, respectively

Table 3

Hazard ratio (95% CI) of incident hip, intra- and extra-capsular fractures associated with 1 SD increment in hip BMD, estimated strength or FRAX fracture probabilities

	Adjusted for			
	age BMI	Age BMI BMD	age BMI HIPW	age BMI HIPWO
Hip fracture (n=668)				
<i>TH BMD</i>	1.86 (1.67, 2.08)	1.14 (0.96, 1.35) ^a	1.60 (1.40, 1.83)	1.76 (1.56, 1.98)
<i>FN BMD</i>	2.04 (1.79, 2.32)	1.40 (1.17, 1.66) ^b	1.73 (1.49, 2.01)	1.86 (1.63, 2.13)
<i>FE strength</i>	2.21 (1.95, 2.50) ^h	1.98 (1.64, 2.39) ^a 1.71 (1.43, 2.04) ^b	1.98 (1.71, 2.30)	1.24 (1.11, 1.37)
<i>HIPW</i>	1.36 (1.25, 1.48)			
<i>HIPWO</i>	1.32 (1.20, 1.45)			
Intra-capsular (IC) fracture (n=351)				
<i>TH BMD</i>	1.65 (1.45, 1.88)	0.89 (0.72, 1.09) ^a	1.37 (1.16, 1.62)	1.56 (1.36, 1.80)
<i>FN BMD</i>	2.03 (1.74, 2.36)	1.46 (1.18, 1.81) ^b	1.74 (1.42, 2.12)	1.86 (1.58, 2.19)
<i>FE strength</i>	2.13 (1.82, 2.49) ^h	2.36 (1.85, 3.00) ^a 1.59 (1.27, 1.99) ^b	1.89 (1.56, 2.28)	2.04 (1.71, 2.43)
<i>HIPW</i>	1.38 (1.26, 1.51)			
<i>HIPWO</i>	1.36 (1.22, 1.53)			
Extra-capsular (EC) fracture (n=317)				
<i>TH BMD</i>	2.24 (1.92, 2.61)	1.43 (1.12, 1.83) ^a	1.13 (0.96, 1.32)	1.26 (1.06, 1.49)
<i>FN BMD</i>	2.23 (1.87, 2.66)	1.37 (1.08, 1.73) ^b	1.76 (1.43, 2.18)	2.00 (1.67, 2.38)
<i>FE strength</i>	2.59 (2.15, 3.11) ^h	1.87 (1.42, 2.48) ^a 2.03 (1.58, 2.60) ^b	2.29 (1.84, 2.83)	2.51 (2.05, 3.08)
<i>HIPW</i>	1.44 (1.29, 1.61)			
<i>HIPWO</i>	1.36 (1.18, 1.56)			

- Superscripts a and b indicate that the models have age, BMI, FE strength and TH or FN BMD as covariates, respectively.
- Superscript h indicate that the HR for FE strength is significantly (P<0.05) higher than the HR for TH BMD from the Wald test between models
- The HRs for FRAX fracture probabilities were significantly (P<0.0001) lower than the HR for FE strength.
- HIPW: 10-yr hip fracture probability with BMD; HIPWO: 10-yr hip fracture probability without BMD

Table 4

Harrell's C indices showing ability of Cox regression models to predict incident hip, intra- and extra-capsular fractures

Covariate+age+BMI	Hip fracture (n=668)	IC fracture (n=351)	EC fracture (n=317)
<i>TH BMD</i>	0.759 ^b	0.733 ^b	0.802 ^a
<i>FN BMD</i>	0.762	0.753	0.788
<i>FE strength</i>	0.770	0.755	0.803
<i>HIPW</i>	0.728 ^b	0.721 ^b	0.750 ^b
<i>HIPWO</i>	0.711 ^b	0.704 ^b	0.732 ^b
<i>TH BMD+FE strength</i>	0.771	0.754	0.809
<i>FN BMD+FE strength</i>	0.774	0.761	0.805

HIPW: 10-yr hip fracture probability with BMD; HIPWO: 10-yr hip fracture probability without BMD.

Superscripts a and b indicate that the Harrell's C index is significantly different from that for FE strength at $p < 0.05$ and $p < 0.0001$ respectively.