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RESEARCH ARTICLE

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3D Finite Element Models Reconstructed From 2D Dual-Energy X-Ray Absorptiometry (DXA) Images Improve Hip Fracture Prediction Compared to Areal BMD in Osteoporotic Fractures in Men (MrOS) Sweden Cohort

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ABSTRACT

Bone strength is an important contributor to fracture risk. Areal bone mineral density (aBMD) derived from dual-energy X-ray absorptiometry (DXA) is used as a surrogate for bone strength in fracture risk prediction tools. 3D finite element (FE) models predict bone strength better than aBMD, but their clinical use is limited by the need for 3D computed tomography and lack of automation. We have earlier developed a method to reconstruct the 3D hip anatomy from a 2D DXA image, followed by subject-specific FE-based prediction of proximal femoral strength. In the current study, we aim to evaluate the method's ability to predict incident hip fractures in a population-based cohort (Osteoporotic Fractures in Men [MrOS] Sweden). We defined two subcohorts: (i) hip fracture cases and controls cohort: 120 men with a hip fracture (<10 years from baseline) and two controls to each hip fracture case, matched by age, height, and body mass index; and (ii) fallers cohort: 86 men who had fallen the year before their hip DXA scan was acquired, 15 of which sustained a hip fracture during the following 10 years. For each participant, we reconstructed the 3D hip anatomy and predicted proximal femoral strength in 10 sideways fall configurations using FE analysis. The FE-predicted proximal femoral strength was a better predictor of incident hip fractures than aBMD for both hip fracture cases and controls (difference in area under the receiver operating characteristics curve, ΔAUROC = 0.06) and fallers (ΔAUROC = 0.22) cohorts. This is the first time that FE models outperformed aBMD in predicting incident hip fractures in a population-based prospectively followed cohort based on 3D FE models obtained from a 2D DXA scan. Our approach has potential to notably improve the accuracy of fracture risk predictions in a clinically feasible manner (only one single DXA image is needed) and without additional costs compared to the current clinical approach. © 2023 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: FRACTURE RISK ASSESSMENT; OSTEOPOROSIS; BIOMECHANICS; DXA; SCREENING

Introduction

Fragility fractures annually affect millions of people worldwide, with a new fragility fracture occurring every third second.[1] The health and socioeconomic impact of fragility fractures is further projected to grow as a consequence of the aging society.[2,3] The most devastating fragility fracture, the hip fracture, usually follows an accidental fall to the side with impact on the posterolateral side of the greater trochanter.[4] Despite continuous updates in operation methods and management of this type of

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fracture, mortality rates reach 20%–24% in the first year after a hip fracture,[5-7] most patients do not regain prefracture functional level,[8] and hip fractures contribute to more than 40% of the disability-adjusted life years caused by osteoporosis.[1] It is therefore of greatest importance to prevent osteoporotic fractures by, eg, prescribing pharmacological treatment and physical activity. It is then essential to be able to identify patients at the highest risk of sustaining fractures. Such identification needs a multifactorial analysis that accounts for a series of risk factors, including surrogate measures of bone mechanical properties, neuromuscular control, as well as other epidemiological parameters.[9] Most multifactorial predictive tools in use, such as the fracture risk assessment tools (FRAX) and the Garvan,[10,11] use areal bone mineral density (aBMD) as a surrogate measurement for bone strength. However, aBMD is at best a moderate predictor of proximal femoral strength and future fractures.[12,13] Finding better measures of bone strength is therefore a crucial step in improving fracture risk prediction tools. This is also required to improve the low sensitivity of fracture risk assessment tools that can jeopardize the cost-effectiveness and overall efficacy of hip fracture prevention strategies.[14-16]

Subject-specific finite element (FE) models have been proposed as a tool to improve hip fracture risk assessment by providing an accurate estimate of the individual bone strength.[17,18] There is ample evidence that subject-specific FE models can predict proximal femoral strength better than aBMD in ex vivo experimental conditions.[19-21] Despite that, subject-specific FE models struggle to be implemented into the daily clinical practice to predict incident hip fractures. This is partly because this superior ability to predict proximal femoral strength has not been conclusively translated into a significant improvement in the sensitivity and specificity of hip fracture risk assessment in clinical cohorts when compared to aBMD.[18,22] Additionally, subject-specific FE models often come with additional hinders in terms of increased cost, time, and lack of automation, which may make their clinical adoption less cost-effective despite an increased prediction accuracy compared to aBMD.[22,23] Many studies using FE-derived strength to predict risk for fracture did not report a statistically significant improvement in hip fracture cases prediction when compared to aBMD.[24] One possible contributing factor to this is that the low number of total and fracture cases that can be included in a time consuming FE analysis study results in a low statistical power, which increased the odds of a type II error.[25] Other studies reported higher areas under the receiver operating characteristic curves (AUROCs) when using FE-predicted proximal femoral strength compared to aBMD, but performed their analyses in case–control settings where clinical images on the fractured cases were acquired postfracture, thus leaving some questions unanswered about the true ability of FE models to predict future fractures.[26] Recently, some studies reported relevant improvements in fracture risk assessment when using subject-specific FE models.[18,24] In particular, two studies conducted on a randomly selected subcohort from the AGES Reykjavik Study and using advanced biofidelic FE models of a fall to the side, reported some promising outcome. Enns-Bray and colleagues[27] did not improve the identification of incident hip fractures compared to aBMD on 254 female patients, but reported that FE models performed better than aBMD when patients who did not fall were excluded from the analysis, which can be seen as a way to exclude the covariate of risk of falling. Fleps and colleagues[28] further developed the FE modeling pipeline by Enns-Bray and colleagues[27] and extended the analysis to 601 patients, reporting significant improvements compared to aBMD when multiple loading conditions were investigated using nonlinear FE models. Despite these promising results, all the abovementioned techniques are limited by the need of three-dimensional (3D) computed tomography (CT) images to build the 3D FE models, whereas two-dimensional (2D) dual-energy X-ray absorptiometry (DXA) images are instead used to assess fracture risk in the daily clinical practice. The higher costs and radiation doses associated with CT make CT-based FE approaches only suitable for opportunistic screening in a clinical setting.[24,29,30] Any methodology to predict fracture risk that aims to improve upon state-of-the-art aBMD should aim at using DXA images as input to be clinically applicable and maintain cost-effectiveness.[22,23]

One approach to obtain DXA-based subject-specific FE models is to create 2D FE models. DXA-based 2D FE models predict proximal femoral strength ex vivo with a similar accuracy to CT-based 3D FE models.[31] However, much like the 3D FE models, they have not consistently been able to improve fracture risk prediction in clinical cohorts.[32-34] Naylor and colleagues[35] used load-to-strength ratio from 2D DXA-based FE models to predict incident hip fractures on 728 female patients. They found a small improvement in the AUROC compared to aBMD (ΔAUROC = 0.02). One of the inherent limitations of 2D DXA-based FE approaches is the inability to replicate some key features of a fall to the side of the hip, such as the full dynamic balance of energy dissipation in 3D[36] or the variability in loading configurations in a fall to the side.[26] Reconstructing 3D FE models from 2D DXA images using 2D-to-3D reconstruction techniques could overcome some of these limitations, while keeping the notable advantage of only requiring a 2D DXA image. The first implementations of this approach, consisting of warping an average 3D shape template to a 2D radiological image, already showed the superiority of such a method in predicting proximal femoral strength ex vivo compared to aBMD.[37] More recent implementations of 2D-to-3D reconstruction algorithms for human femurs adopt statistical shape and appearance models (SSAMs) to obtain more accurate reconstructions of the 3D anatomy by being able to describe the anatomical variability in a population.[38-40] A 2D-to-3D SSAM-based reconstruction algorithm was proposed and validated for accurate anatomical reconstruction by our group,[40] and FE models built from these 3D reconstructions recently reported high accuracy in predicting proximal femoral strength ex vivo both in quasi-static[41] and dynamic conditions.[42] However, it remains to be shown if these frameworks based on SSAMs can improve the accuracy of fracture risk prediction in clinical cohorts.[38]

The aim of this study was to examine whether FE-predicted proximal femoral strength obtained from 2D DXA images could predict the risk of incident hip fracture better than aBMD. We used our SSAM-based 2D-to-3D reconstruction algorithm[40] in combination with our subject-specific FE modeling pipeline[41,42] in a clinical cohort of men (Osteoporotic Fractures in Men [MrOS] Sweden).[43,44]

Subjects and Methods

Cohort

The MrOS Sweden study is a prospective population-based multicenter observational study that was designed with the primary aim to identify risk factors for osteoporosis and fracture in men.[43,44] To be included, the men had to be able to communicate in Swedish, have a contact address, be able to walk without assistance, and be without bilateral hip replacements. The MrOS Sweden data collection from Malmö and Uppsala, which included 2004 male participants aged 69–81 years at baseline, was available for this study. DXA images were collected at

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baseline (GE Lunar Prodigy; GE Healthcare., Madison, WI, USA, images collected between October 2001 and December 2004) and during follow-ups after 3 and 5 years. DXA images that were analyzed with a software version seven or below of the GE encore software were excluded from the analysis since the 2D-to-3D reconstruction algorithm[40] was developed and validated for later software versions. Participants also answered questionnaires at baseline and at each follow-up that included a question on falls during the previous 12 months. Incident fracture history following the baseline exam was collected until 2020 by reviewing the archives of digital radiologic images in Malmö and Uppsala. Each fracture was verified by an orthopedic surgeon looking at the radiographic reports and classifying all fractures. Any questionable case was assessed by looking at the radiographs themselves.

Two subcohorts were defined from the data collection for this study:

- Hip fracture cases and controls cohort ($n = 360$): This subcohort included all (120) men who suffered an incident hip fracture within 10 years from their DXA scan and 2 controls for each hip fracture case, matched by age, height, and body mass index (BMI). Whenever multiple DXA scans were available for the subject within 10 years from the time of the hip fracture, the earliest DXA image was selected. Controls were selected from all available hip DXA images, thus including baseline and follow-up images, provided fracture history had been recorded for at least 10 years after imaging time. The age at imaging of the controls did not differ from that of the hip fracture case by more than 1 year ($|\Delta age| < 1\,year$). Among those, the two participants with the smallest combined difference of height and BMI, according to: $\min\left(\sqrt{\left(\frac{\Delta height}{SD(height)}\right)^2 + \left(\frac{\Delta BMI}{SD(BMI)}\right)^2}\right)$ were selected as the controls. Only one hip DXA image per subject was allowed to be included in the subcohort.
- Fallers cohort ($n = 86$): This subcohort included all men who reported to have fallen at least once in the 12 months before their baseline exam and whose history of fracture was recorded for at least 10 years after the time of the hip DXA image. For the cases in which the baseline hip DXA image was not available, a later hip DXA image was considered, provided the subject reported to have fallen also in the questionnaire taken in conjunction with the later hip DXA image. Only one hip DXA image per subject was allowed to be included in the subcohort. The subcohort included 86 participants, 15 sustained an incident hip fracture during the 10 years following their hip DXA scan. The reported number of falls occurred during the 12 months before the time of the hip DXA scan is reported in Table S2 for both hip fracture cases and controls and fallers sub-cohorts.

Patient-specific 3D-reconstructed FE models

The methodology adopted in this study is summarized in Fig. 1 and consists in combining a 2D-to-3D reconstruction of the proximal femur anatomy from 2D hip DXA scans with a subject-specific FE modeling pipeline to predict femoral strength. The FE-predicted proximal femoral strength is then used as a predictor for incident hip fractures and its predictive ability compared to that of aBMD. This approach has been developed over several years and validated extensively. We guide the readers to the following studies for full details regarding the development and validation of the 2D-to-3D reconstruction[40] and the subject-specific FE modeling pipeline to predict proximal femoral strength.[45,46] The combination of 2D-to-3D reconstruction with 3D FE modeling was presented and validated against ex vivo mechanical tests for both quasi-static[41] and dynamic load cases.[42] The methods are briefly described below for both 2D-to-3D reconstruction and FE-prediction of proximal femoral strength in sideways fall.

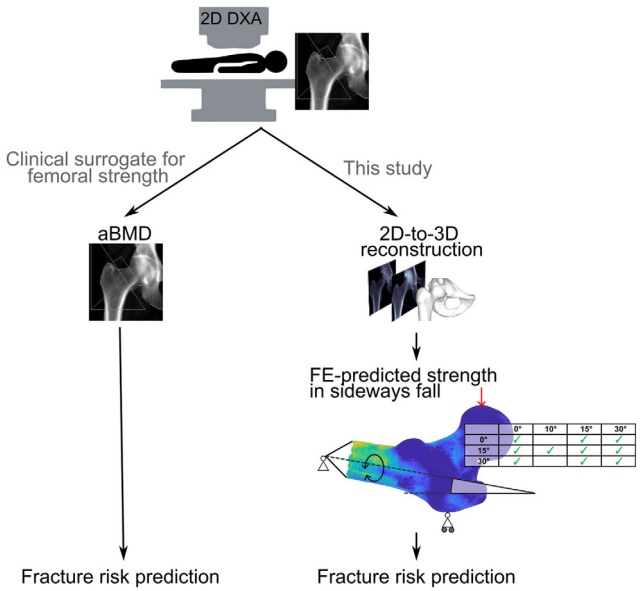

Fig. 1. Schematic of the concept of this study. Left column, a two-dimensional (2D) dual energy x-ray absorptiometry image (DXA) is typically acquired to measure areal bone mineral density (aBMD) in the hip or femoral neck region. The latter is included in fracture risk prediction tools as a surrogate measurement for proximal femoral strength. Right column, our proposal used the same 2D DXA image to reconstruct the 3D anatomy of the individual femur, over which the proximal femoral strength is estimated using finite element (FE) simulations in 10 different configurations resembling a fall to the side. The FE-predicted proximal femoral strength is a better biomarker than aBMD of the true femoral strength[19] and can replace aBMD in fracture risk prediction tools due to the clinical feasibility of the proposed FE modeling pipeline.

2D-to-3D reconstruction

The individual patient shape and element-specific distribution of volumetric bone mineral density (vBMD) was obtained from a single 2D DXA image. The DXA image of the left hip was used for the 2D-to-3D reconstruction when DXA images from both sides were available. The 2D-to-3D reconstructions worked by retrieving the instance of a SSAM whose projection simulating 2D DXA image fitted best with the target DXA image. The procedure was described in detail in Väänänen and colleagues[40] and Grassi and colleagues[42] and is briefly reported here for clarity. SSAMs of the proximal femur and hemipelvis were first built. The SSAM of the proximal femur was trained on 59 unpaired proximal femurs (40 men, 19 women, median age 58 years, range 18–88 years) for which CT images were available, whereas the SSAM of the hemipelvis was trained on 14 anatomies (all females, median

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age 74 years, age range 69–78 years). Template meshes (19,532 nodes, 103,761 linear tetrahedral elements for the femur, 84,893 nodes and 451,229 linear tetrahedral elements for the pelvis) were morphed to the shape of each femur and hemipelvis in the training sets. Bone periosteal and endocortical surfaces were captured for each bone with a deconvolution technique that corrects errors arising from point spread function and partial volume artifact.[47,48] Element-specific vBMD values were captured based on the underlying CT intensities using a densitometric calibration phantom (Model 3 QCT; Mindways Software, Inc., Austin, TX, USA) and a dedicated numerical integration scheme for material mapping (Bonemat V2,[49]). Rigid transformation and scaling between the bones were removed using generalized Procrustes analysis.[50] The normalized shape and vBMD information of all morphed meshes were collected and the principal modes of variation were calculated, thus obtaining one SSAM for the femur and one for the hemipelvis. The SSAMs were then used to perform 2D-to-3D reconstruction from a 2D DXA image. First, the SSAMs were roughly registered in space to the target 2D DXA image using eight anatomical landmarks that were manually selected on the 2D DXA image. A digitally reconstructed radiograph (DRR) was then created by projecting the two SSAM instances onto the coronal plane. A genetic optimization algorithm was run in MATLAB (R2021a; The Mathworks, Inc., Natick, MA, USA) to find the instance of the SSAMs that minimized the sum of the absolute differences between the pixel-wise aBMD of the DRR and that of the target DXA image. The 2D-to-3D reconstruction method was previously validated in terms of reconstruction accuracy against in vivo hip DXA scans, reporting an average absolute error of 1.4 mm for the periosteal femur geometry and of 0.18 g/cm^3 for the volumetric BMD.[40]

FE-predicted strength in sideways fall

The 3D-reconstructed proximal femur anatomy was in the format of a 3D FE model with linear tetrahedral elements with element-specific vBMD values. An in-house written MATLAB code automatically converted the 3D reconstructions into FE simulations that can be solved in Abaqus (Dassault Systèmes SE, Vélizy-Villacoublay, France). First, linear tetrahedral elements were converted into quadratic elements[51] and element-specific vBMD values were converted to moduli of elasticity using a previously validated combination of empirical relations proposed by Schileo and colleagues.[52] The modulus of elasticity for elements on the periosteal surface was set to a minimum of 5 GPa[41,42] to correct possible artifacts in the 2D-to-3D reconstruction. An anatomical reference system consistent with Bergmann and colleagues[53] was calculated for all proximal femurs by first scaling and warping a template full femoral anatomy over its shape, and then by running an automated tool for automatic identification of the needed femoral landmarks.[54] Boundary conditions mimicking a fall to the side were applied to each femur, simulating 10 different sideways fall configurations, which covered the 0-degree−30-degree range for adduction and internal rotation in a full factorial scheme,[26] as well as the widely adopted configuration of 10-degree adduction and 15-degree internal rotation[55] (Fig. 1). Quasi-static linear elastic simulations were solved in Abaqus/Standard and proximal femoral strength was calculated based on a previously validated criterion based on principal strain limit values.[46] The prediction accuracy of 3D FE models obtained from 2D-to-3D reconstruction has been previously determined against ex vivo mechanical tests for both quasi-static[41] and dynamic[42] load cases, reporting in both cases an accuracy comparable to state-of-the-art CT-based 3D FE models.

Statistical analysis

Logistic regression analyses were performed to compare the fracture predictive ability of the FE-predicted proximal femoral strength to that of aBMD, using AUROC. The FE-predicted proximal femoral strength, ie, the load at which the FE simulations predicted the proximal femur to fracture, was expressed in units of body weight (BW, calculated as FE-strength [BW] = FE-strength [N]/(Weight [kg] × 9.81 [m/s^2])), so that the obtained proximal femoral strength values were normalized between subjects of different weight. For the logistic regression analysis of the FE-predicted proximal femoral strength, all the 10 values of FE-predicted proximal femoral strength obtained from the 10 different simulated sideways fall configurations were used as covariates. For the logistic regression analysis with aBMD, BMI was included as covariate, as FE-predicted proximal femoral strength was normalized to the subjects' body weight. Statistically significant differences in the obtained AUROCs were examined using the DeLong method in R ([56] pROC package, threshold for significance set to $p < 0.05$). All logistic regression analyses were performed using 10-fold cross validation.[57,58] That consists in splitting the dataset into 10 sets of equal size, and one by one using one set as the test set and the other nine sets as training set for the logistic regression. An analysis of covariance was performed in R with age as the covariate to determine whether FE-predicted proximal femoral strength was different between hip fracture cases and healthy controls for any given age.

Results

The right proximal femur (in the case that only left proximal femur were available, they were mirrored to obtain right femur anatomies) of 411 participants was reconstructed in 3D from 427 unique 2D DXA images and analyzed under 10 loading alignments, resulting in 4270 FE simulations that successfully calculated proximal femoral strength. The FE simulations predicted fractures to occur on the superolateral side of the femoral neck, with a proximal femoral strength ranging between 2.5 and 7.7 times the subjects' body weight.

Both aBMD and average FE-predicted proximal femoral strength over the 10 load cases were lower in the hip fracture cases compared to the controls, in both sub-cohorts (hip fracture cases and controls: −14% aBMD, −25% FE-predicted strength; fallers: −20% aBMD, −27% FE-predicted strength), whereas differences in age, height, weight, and BMI were all below 5% between hip fracture cases and controls (Table 1). The notches in the boxplots in Fig. 2*A,B* did not overlap between hip fracture cases and healthy controls, which is a visual indication that the medians differ with 95% confidence.[59] The AUROC of the FE-predicted proximal femoral strengths (all FE-predicted proximal femoral strengths from the 10 load cases were normalized by the subjects' body weight and used together as covariates in the logistic regression) was larger than the AUROC of aBMD+BMI for the hip fracture cases and controls cohort (Fig. 3*A*). The difference between the two AUROCs (0.78 versus 0.72) was statistically significant using DeLong method[56] ($p = 0.017$). An even larger difference in the AUROCs (0.90 versus 0.68, $p = 0.035$)

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Table 1. Comparison of Mean ± Standard Deviation Characteristics for the Two Subcohorts Analyzed in this Study

Characteristic	Hip fracture cases and controls ($n = 360$)		Fallers ($n = 86$)	
	Hip fractures ($n = 120$)	Controls ($n = 240$)	Hip fractures ($n = 15$)	Controls ($n = 71$)
Age (years)	78.6 ± 3.2	78.5 ± 3.2	77.4 ± 2.9	75.8 ± 3.2
Height (cm)	173.9 ± 6.4	174.0 ± 6.0	174.4 ± 7.4	174.5 ± 6.2
Weight (kg)	78.2 ± 11.8	78.6 ± 10.3	74.1 ± 11.8	80.6 ± 10.6
BMI (kg/m^2)	25.8 ± 3.4	25.9 ± 3.0	24.3 ± 3.7	26.4 ± 2.8
Total hip aBMD (g/cm^2)	0.81 ± 0.12	0.92 ± 0.13	0.78 ± 0.12	0.94 ± 0.15
Mean FE-predicted strength (%BW)	6.1 ± 0.4	7.6 ± 0.5	6.0 ± 0.6	7.6 ± 0.4

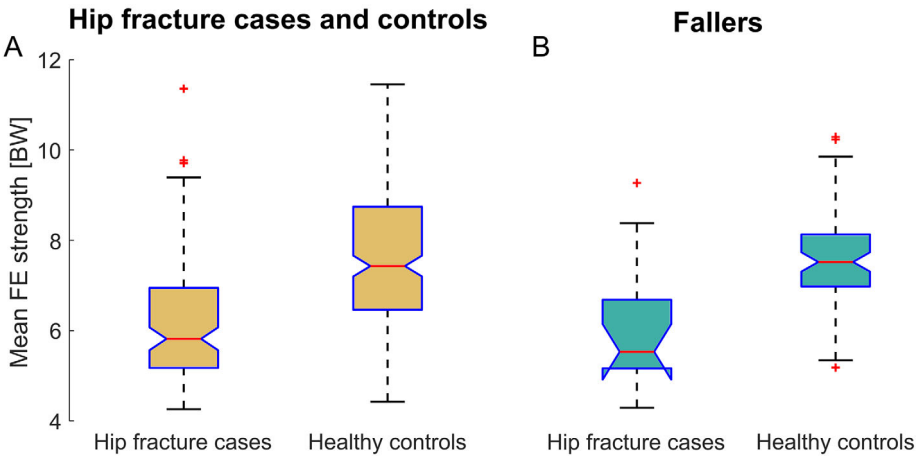

Fig. 2. Boxplots of the average finite element (FE)-predicted proximal femoral strength for the 10 simulated configurations resembling a fall to the side. (*A*) The hip fracture cases and controls subcohort, including the hip fracture cases and the healthy controls, and (*B*) the fallers subcohort. The nonoverlapping of the notches of the boxplot means that the medians of the FE-predicted proximal femoral strength differ with a 95% confidence.

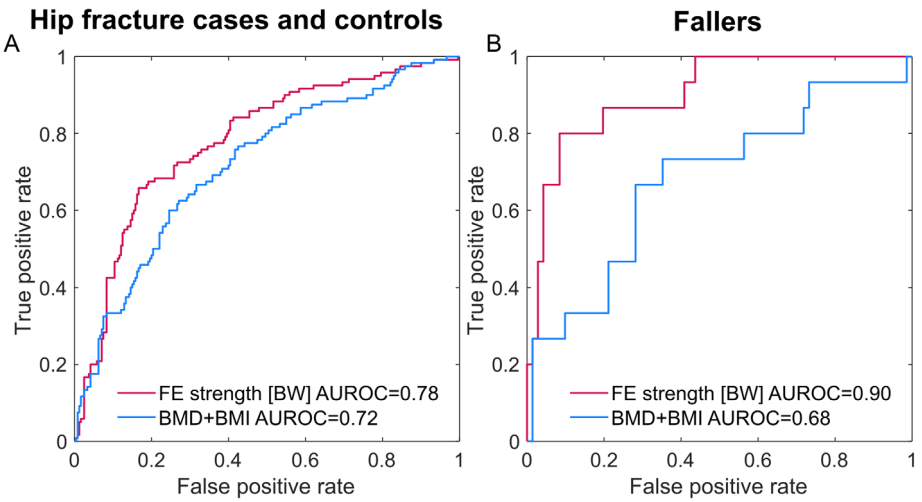

Fig. 3. Receiver operating characteristics curves for the hip fracture cases and controls (*A*) and fallers (*B*) cohorts for the finite element (FE)-predicted proximal femoral strength (debian red) and areal bone mineral density combined with body mass index (clear blue).

was obtained for the fallers cohort (Fig. 3*B*). The superior ability of FE-predicted proximal femoral strength to predict hip fractures was also reflected in the reduced overlap between the probability histograms of controls and hip fractures for both hip fracture cases and controls (Fig. 4*A*,*B*) and fallers cohorts (Fig. 4*C*,*D*). Hip fracture cases occurred predominantly in subjects whose aBMD and

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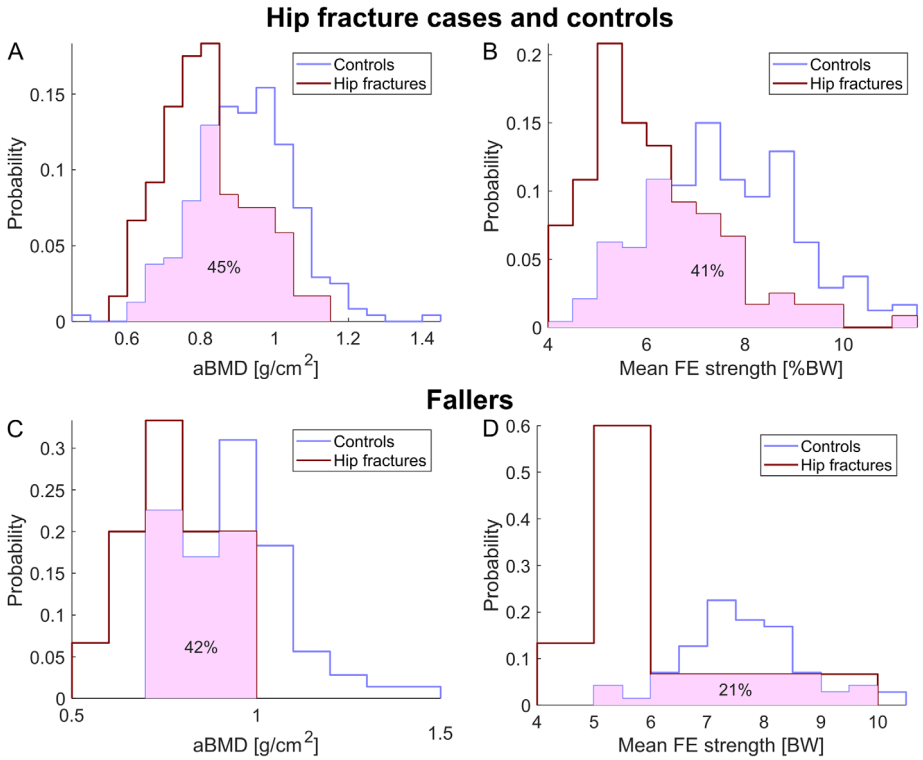

Fig. 4. Probability histograms for hip fracture cases and controls (*A*,*B*) and fallers (*C*,*D*) cohorts for areal bone mineral density (aBMD, left) and the average FE-predicted proximal femoral strength for the 10 simulated configurations resembling a fall to the side (right). The area shaded in purple is the overlapping area between the histograms of hip fracture cases and controls.

FE-predicted proximal femoral strength was low (Fig. 5*A*,*C*). The analysis of covariance of FE-predicted proximal femoral strength with the subjects' age as the covariate showed that FE-predicted femoral strength was lower for the hip fracture cases at a given age for both hip fracture cases and controls (1.1 BW difference, $p = 3e\text{-}13$, Fig. 5*B*) and fallers (1.2 BW difference, $p = 5e\text{-}05$, Fig. 5*D*).

Discussion

The aim of this study was to investigate if subject-specific predictions of proximal femoral strength were able to predict incident hip fractures better than aBMD in a large clinical cohort for which 2D DXA images were available. We used our established and previously validated SSAM-based 2D-to-3D reconstruction algorithm[40] to create 3D subject-specific FE models.[41,42] We found that FE-predicted proximal femoral strength was a better predictor of incident hip fracture at 10 years than aBMD, with the AUROC being larger for both the defined subcohorts (hip fracture and controls and fallers). The differences between AUROCs were statistically significant for both subcohorts. We used the FE-predicted proximal femoral strength normalized to the subject's body weight and considered all the 10 load cases combined as co-predictors in the logistic regression analysis, because that was previously reported to improve upon the hip fracture prediction ability of FE models.[26] Our results confirmed that FE-predicted proximal femoral strength from multiple load cases provided improved AUROC compared to other measures such as average or minimum strength from the FE-calculated strengths (Fig. S1). Importantly, we adopted a 10-fold cross validation design to reduce the risk for possible overfitting or selection bias. This is important as using cross validation means our predictions were all generated for cases that were not included in the training set, giving a clear indication of how the model will generalize to an independent dataset. To our best knowledge, only Taylor and colleagues[60] used a cross validation design to predict fracture risk using FE-based proximal femoral strength.

Despite that subject-specific FE models have been shown to predict individual proximal femoral strength better than aBMD for decades,[19] their ability to improve fracture risk assessment in a clinical setting is not given.[18,24] There are primarily two other studies that are important to discuss in this context. First of all, Falcinelli and colleagues[26] reported an improvement in the AUROC compared to aBMD (0.88 versus 0.79), but on a lower number of subjects (22 hip fracture cases, 33 controls unmatched for age) and, crucially, the CT images of the fracture cases were taken after fracture by scanning the contralateral femur, whereas our study adopted a prospective approach by using 2D DXA images collected at baseline and then looking at incident fractures in the 10 years following baseline imaging. Falcinelli and colleagues[26] reported higher AUROCs when using FE-predicted proximal femoral strength from multiple loading conditions as compared to a single load case. Our study adopted an identical set of load cases for the sideways fall and confirmed those findings (a table with the AUROCs when using each individual load case is available as supplementary material, Table S1). The adopted proximal femoral strength criterion was also the same,[46]

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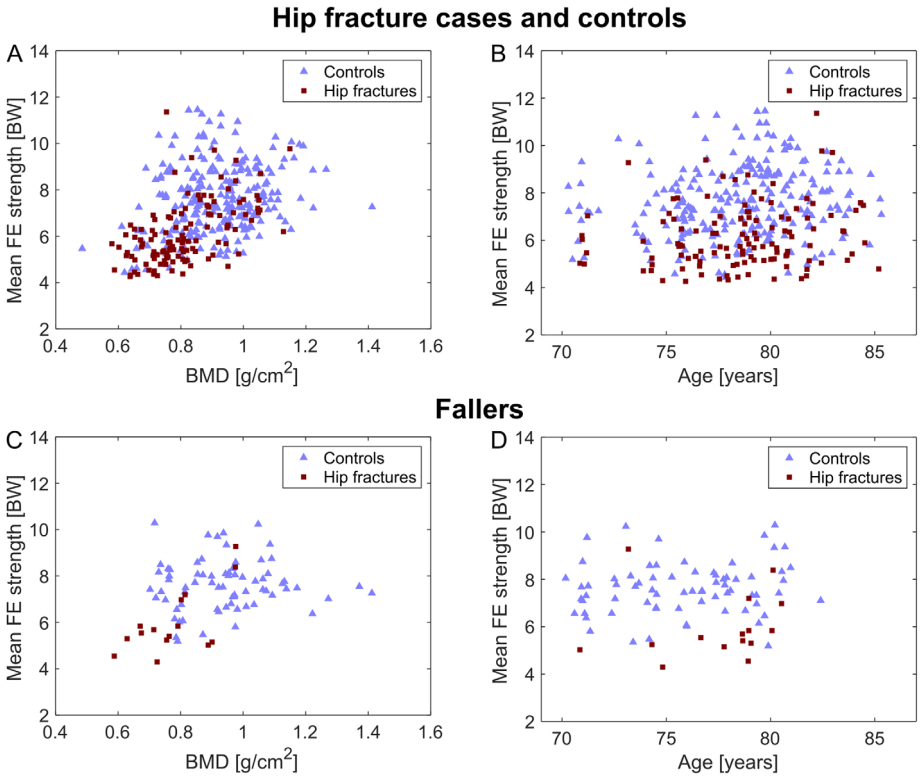

Fig. 5. Scatter plots for the average FE-predicted proximal femoral strength for the 10 simulated configurations resembling a fall to the side as a function of areal bone mineral density (aBMD, left) and of the patients' age (right). The top row (*A*,*B*) shows the scatter plots relative to the hip fracture cases and controls cohort, and the bottom row (*C*,*D*) shows the equivalent plots for the fallers cohort.

but in our study the predicted proximal femoral strength was normalized to the subjects' body weight. That was because we hypothesized that the normalized proximal femoral strength would better account for the intersubject differences in body weight and morphometrics, thus increasing the ability to identify incident hip fractures. Our analyses indeed confirmed our hypothesis that normalized femoral strength was a slightly better predictor of incident hip fracture than absolute femoral strength (ΔAUROC = 0.02 for hip fracture and controls, Fig. S1). Secondly, Fleps and colleagues[28] also reported improvements in fracture risk prediction using CT-based FE models compared to aBMD, (AUROC 0.78 versus 0.72 for the male subjects in their cohort) using a prospective approach and on a high number of patients (59 hip fracture cases and 180 controls for the male subjects alone). Our study reported an identical improvement in the AUROC (0.78 versus 0.72) for the hip fracture cases and controls cohort on 120 hip fracture cases and 240 controls matched by age, height, and BMI, but with three important differences in terms of potential for future clinical applicability. The most important one is that our study is based on 2D DXA images instead of 3D CT images. Moreover, we use linear elastic material properties instead of nonlinear material properties, thus speeding up the FE simulation noticeably (from 2 hours per simulation in Fleps and colleagues[28] to 5 min per simulation) while maintaining a high prediction accuracy (R^2 = 0.89 between CT-based FE-predicted proximal femoral strength and experimental data in Schileo and colleagues[46]). Also, Fleps and colleagues[28] looked at the fracture risk at 5 years after baseline, whereas we looked at the fracture risk at 10 years after imaging, which is comparable to the prediction provided by current clinical standards such as, eg, FRAX.[10]

Other studies have tried to predict hip fracture risk from 2D DXAs using FE models, with the goal to increase compliance with current clinical settings. DXA-based 2D FE models of the hip have reached excellent results in ex vivo validation studies,[31] but have not consistently been able to improve upon aBMD in clinical cohorts,[18] most likely because of the inherent limitation of modeling a complex fall to the side of the hip in 2D. Naylor and colleagues[35] reported statistically significant improvements in AUROC using DXA-based 2D FE models on a large cohort of women (ΔAUROC = 0.02). The present study obtained an even larger improvement (ΔAUROC = 0.06). 2D-to-3D reconstructions like the one proposed in this study offer the possibility to overcome the major limitations of 2D FE approaches while keeping the clinical applicability that comes with basing the information on a single 2D DXA images. Ruiz Wills and colleagues[61] used a commercially available 2D-to-3D reconstruction tool[39] to build 3D FE models from 2D DXA scans, reporting improved classification of prevalent hip fractures compared to volumetric BMD. However, the fact that DXA images for the hip fracture cases were collected post fracture limits the assessment of the true ability to predict incident hip fractures. To our knowledge, our present study is the first one to report a statistically significant improvement in the ability to predict incident hip fractures using 2D-to-3D subject-specific FE models.

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Interestingly, the AUROC for the fallers cohort was substantially larger for FE-predicted strength compared to aBMD (0.90 versus 0.68). Our result is in agreement with Enns-Bray and colleagues,[27] who first reported that exclusion of nonfallers from the analysis improved the differences in AUROC between FE-predicted strength and aBMD. We speculate that the risk for fracture can be seen as a combination of the risk of falling (most hip fractures occur as a result of a fall to the side)[4] and the strength of the bone (only a minority of falls result in major injuries).[62] The fallers cohort included subjects who reported a fall in the year before their hip DXA scan, so we can assume that all subjects in this cohort have an equally high risk for falling. Consequently, their risk for fracture within this cohort is mainly determined by the proximal femoral strength, where our results show that FE-predicted proximal femoral strength is a better biomarker of the true proximal femoral strength compared to aBMD. In this context and given the potential for clinical applicability of the proposed approach, it seems logical that DXA-derived proximal femoral strength could replace aBMD and work alongside other epidemiological risk factors for hip fractures in complex, multifactorial predictors of future hip fractures.

The FE models used in this study were obtained by following a procedure that has been extensively validated ex vivo in terms of 2D-to-3D reconstruction accuracy[40] and ability to predict proximal femoral strength both in quasi-static[41] and dynamic conditions.[42] The FE-predicted proximal femoral strengths ranged between 2.5 and 7.7 times the subjects' body weight, which is well in line with what reported in literature for ex vivo mechanical tests in similar loading configurations.[63,64] The fracture onset was predicted to occur on the superolateral side of the femoral neck, which is consistent both with ex vivo experimental findings[64,65] and with the adopted criterion to calculate femoral strength.[46]

A potential limitation of this study is that the MrOS Sweden cohort by design included only elderly men living in Sweden, which makes it difficult to speculate how the current results could translate to other populations or to cohorts including women. On the other hand, the strength of the selected cohort is indeed that it was specifically designed to assess the risk of osteoporotic fractures. The SSAM used in this study was trained on both male and female anatomies (approximately 2/3 men and 1/3 women,[42]), which points to the generality of the proposed approach. Also, other cohorts including women have been identified and their analysis is planned as future work.

Another limitation is connected to the execution time of the 2D to 3D reconstruction, which currently takes about 6 h per DXA image using 20 cores for the computation. However, the only credible alternative to the adopted algorithm for 2D-to-3D reconstruction, despite being much faster and also commercially available,[39] has not been as extensively validated ex vivo in terms of accuracy in predicting proximal femoral strength and fall outcome from the obtained reconstructions.[41,42] Also, our 2D-to-3D reconstruction algorithm requires a human operator to manually select eight anatomical landmarks on the patient's DXA image. This operation takes less than 30 s per DXA image. All the rest of the pipeline, including the full process of 3D reconstruction, FE models generation, solving, and postprocessing of the FE simulations, is automatic. We are currently working on completely automating the process by using neural networks for landmarks selection as well as on reducing the overall computation time, and we believe that the promising results obtained in the current study will motivate more efforts into optimizing the reconstruction algorithm for speed. Eliminating the need for user interaction and reducing the computational cost of the 2D-to-3D reconstruction would improve the cost-effectiveness and increase the potential for clinical applicability of the approach, and also unlock the possibility of running analyses on full (and multiple) clinical cohorts to perform, eg, survival analyses.

In conclusion, we presented a pipeline based on a previously proposed 2D-to-3D reconstruction that unlocks the full potential of 3D subject-specific FE models to predict proximal femoral strength and incident fracture risk while still using the widely available 2D DXA scans as the input image for the analysis. The potential for clinical applicability of the pipeline was corroborated by the presented results on MrOS Sweden cohort, which showed that the proposed pipeline performed substantially better than aBMD in predicting incident hip fractures at 10 years, both when looking at the sub-cohort with hip fracture and controls and when looking at the subcohort of only fallers.

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Author Contributions

Lorenzo Grassi: Writing – original draft; conceptualization; methodology; investigation; data curation; formal analysis. **Sami P. Väänänen:** Writing – review and editing; conceptualization; methodology. **Lars Jehpsson:** Writing – review and editing; data curation; formal analysis. **Östen Ljunggren:** Writing – review and editing; resources. **Björn E. Rosengren:** Writing – review and editing; conceptualization. **Magnus K. Karlsson:** Writing – review and editing; conceptualization; resources. **Hanna Isaksson:** Writing – review and editing; funding acquisition; conceptualization; supervision; resources.

Disclosures

The authors declare no conflicts of interest.

Peer Review

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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