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Factors associated with proximal femur fracture determined in a large cadaveric cohort

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Abstract

Many researchers have used cadaveric fracture tests to determine the relationship between proximal femur (hip) fracture strength and a multitude of possible explanatory variables, typically considered one or two at a time. These variables include subject-specific proximal femur variables such as femoral neck areal bone mineral density (aBMD), sex, age, and geometry, as well as physiological hip fracture event variables such as fall speed and angle of impact. However, to our knowledge, no study has included all of these variables simultaneously in the same experimental dataset. To address this gap, the present study simultaneously included all of these subject-specific and fracture event variables in multivariate models to understand their contributions to femoral strength and fracture type. The primary aim of this study was to determine not only whether each of these variables contributed to the prediction of femoral strength, but also to determine the relative importance of each variable in strength prediction. A secondary aim was to similarly characterize the importance of these variables for the prediction of fracture type. To accomplish these aims, we characterized 197 proximal femurs (covering a wide range of subject-specific variables) with DXA and CT scans, and then tested the femurs to fracture in a sideways fall on the hip configuration. Each femur was tested using one of three fall speed conditions and one of four angles of impact (bone orientations). During each test, we acquired measurements of relevant force and displacement data. We then reduced the test data to determine femoral strength, and we used post-fracture CT scans to classify the fracture type (e.g., trochanteric, cervical). Using these results, the explanatory variables were analyzed with mixed statistical models to explain variations in hip fracture strength and fracture type, respectively.

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Conflict of interest

The authors have no conflicts of interest to report.

Five explanatory variables were statistically significant in explaining the variability in femoral strength: aBMD, sex, age, fall speed, and neck-shaft angle ($P = 0.0135$). These five variables, including significant interactions, explained 80% of the variability in hip fracture strength. Additionally, when only aBMD, sex, and age ($P < 0.0001$) were considered in the model, again including significant interactions, these three variables alone explained 79% of the variability in hip fracture strength. So while fall speed ($P = 0.0135$) and neck-shaft angle ($P = 0.0041$) were statistically significant, the inclusion of these variables did not appreciably improve the prediction of hip fracture strength compared to the model that considered only aBMD, sex and age. For the variables we included in this study, in the ranges we considered, our findings indicate that the clinically-available information of patient age, sex and aBMD are sufficient for femoral strength assessment. These findings also suggest that there is little value in the extra effort required to characterize the effect of femoral geometry on strength, or to account for the probabilistic nature of fall-related factors such as fall speed and angle of impact. For fracture type, the only explanatory variable found to be significant was aBMD ($P = 0.0099$). We found that the odds of having intertrochanteric fractures increased by 47% when aBMD decreased by one standard deviation (0.2 g/cm^2).

Keywords

Proximal femur strength; Hip fracture; Fracture type; Bone biomechanics; Bone testing speed; Femoral orientation

1. Introduction

There are many simultaneous factors that potentially affect proximal femur (hip) fracture strength in a fall on the hip event, including clinical variables (such as femoral neck areal bone mineral density (aBMD), sex and age), fall-related variables (such as fall speed and bone orientation at impact), and geometric variables that characterize the patient-specific geometry of the proximal femur. The importance of aBMD as a clinical measure is evident through its use as the current standard of care in diagnostic fracture risk assessment, even though it lacks sensitivity and specificity [1,2]. The importance of both sex and age is also known to a great extent from clinical studies: the risk of hip fracture increases with age and is higher in women than it is in men [1]. However, the degree to which fracture risk may be explained by sex and/or age when these variables are considered together with aBMD is not clear. Also, it is difficult to ascertain the importance of fall-related variables, because they inevitably vary from one fall event to another, and they may be difficult to determine and take into account in clinical studies. Similarly, although researchers have assumed that bone geometry (shape and size) is an important factor [3,4], the effects of geometric variables have not been isolated from other possibly-related variables, such as sex.

Biomechanical studies have proven effective in determining relationships between proximal femur strength and all the aforementioned factors affecting the structural capacity of the proximal femur [5–14]. For the last few decades, experimental studies have focused on several aspects of hip fracture by testing the significance of variables affecting femoral strength, using data from benchtop testing or clinical cohorts [15,16]. However, such studies

have only considered the simultaneous influence of one or two variables on hip fracture [17–19]. Therefore, there is a paucity of data on how multiple variables, considered together, may contribute to hip fracture and the relative importance of each variable when they are considered simultaneously.

In the current study, we characterized the geometry and bone density of 197 cadaveric proximal femurs with both computed tomography (CT) and dual-energy X-ray absorptiometry (DXA) scans, and then mechanically tested the femurs to fracture while controlling testing speed and bone position in a sideways fall on the hip configuration. The primary aim of the study was to simultaneously consider the simulated fall-related variables (testing speed and proximal femur position during fracture testing) and clinically-available subject-specific variables (aBMD, sex, age, and geometry), and to determine which of these variables were influential in the resulting femoral strength and fracture type. Due to the large size of this cohort, it was possible to consider all of these variables together. This was accomplished by performing for each outcome of interest a robust multivariate statistical study that explained the influence of all variables on the variability in that outcome, and then eliminating the insignificant variables one at a time until only significant variables remained.

2. Materials and methods

2.1. Specimen preparation and imaging

After securing Institutional Review Board (IRB) approval from our institution, 197 cadaveric femoral specimens of both women and men were procured based on availability from several organ banks (Musculoskeletal Transplant Foundation, Edison, NJ; Anatomy Gifts Registry, Hanover MD; Mayo Clinic, Rochester, MN), and shipped frozen to our lab. Table 1 shows the pertinent attributes of the proximal femur cohort.

The bone preparation process is explained in detail in a prior publication [20], so it is only summarized here. Once received, the femurs were thawed and DXA scanned for femoral neck areal BMD (aBMD). Rice bags were used to mimic soft tissue surrounding the proximal femurs. The bones were then cut with an in-house fixture to leave the proximal length at 250 mm. The distal shaft of the femur was then mounted with poly-methyl-methacrylate (PMMA) cement in a polycarbonate box, using alignment fixtures designed in-house that maintained the desired orientation of the bone [20]. Using an in-house embedding fixture, the orientation of each mounted proximal femur conformed to one of four sideways fall on the hip configurations in our experimental design, where the four configurations encompassed all combinations of two adduction angles ($\alpha = 10^\circ$ or 20°) and two internal rotation angles ($\beta = 15^\circ$ or 30°). These angles are defined in Fig. 1. X-ray images of the proximal femurs were then taken in two planes to identify and remove from the study any bones with evidence of prior fractures or metastatic diseases affecting bone strength. CT scans were obtained with a clinical Siemens Definition CT scanner (Siemens, Malvern, PA). The CT scanner was operated at 120 kVp, 216 mAs, 1 s rotation time, and pitch of 1 using ultra high resolution mode (zUHR). The resulting pixel size in each slice varied between 0.30 and 0.45 mm, depending on the size of the bone, and the slice thickness was 0.4 mm with no overlap between consecutive slices.

We obtained the bone geometry from CT image reconstruction using Mimics (Materialise, Leuven, Belgium), and then measured three geometric features (femoral neck-shaft angle, femoral neck axis length, and femoral neck diameter) using 3-matic software (Materialise, Leuven, Belgium).

2.2. Pre-test, fixture and measurement description

The mechanical testing process is described in more detail in a previous publication [21], and is explained briefly here. The proximal femurs were fracture tested using an in-house designed fixture mounted to a standard servo hydraulic mechanical testing system (MTS, Minneapolis, MN). Force was measured at the greater trochanter using a single-axis 13 kN load cell (Transducer Techniques, Temecula, CA), and the relative displacement of the load frame to the test fixture was measured using an LVDT displacement sensor. The femoral strength was defined as the maximum (peak) force at the greater trochanter observed on the experimental force-displacement curve. The measuring frequency was 6250 Hz.

Just before testing, the greater trochanter was placed in an aluminum cup, which was then filled with PMMA to increase the contact area and prevent crushing. Once the PMMA had cured, the femur was mounted into the test fixture and then gently lowered by a vertical adjustment mechanism on the fixture until the trochanter aluminum cup came in contact with the trochanter load cell. The actuator was then gently lowered until it came in contact with the femoral head. In order to avoid crushing the femoral head, an aluminum cup with a spherical contact surface was attached to the load cell to more evenly apply the compressive load on a considerable area of the femoral head (see Fig. 1). The test was displacement controlled at the speed designated for each proximal femur per the experimental design until 25 mm of displacement was reached, at which point the femur was fractured. Femurs were tested at three simulated fall speeds (5 mm/s, 100 mm/s, and 700 mm/s). It should be noted that the average effective speed in proximal femur fracture resulting from a simulated fall was found to be around 114 mm/s [22]. Therefore, the three speeds (from 5 mm/s to 700 mm/s) considered in the current study span a sufficiently wide range of effective loading speeds. After mechanical testing of each femur was complete, post-fracture CT scanning was performed to facilitate fracture type classification.

2.3. Data and statistical analysis

Testing occurred in several cohorts over the course of 7 years. The cohort contains test groups (where a group is defined as a set of specimens that were tested with the same set of fall-related variables) that consist of 72 pairs (144 bones) and 53 singles. Of 72 pairs, 48 pairs were tested for 100 mm/s vs 5 mm/s; one bone from each pair was randomly assigned to one speed group and all were tested at an adduction angle of 10° and an internal rotation angle of 15°. Also, 24 pairs were tested for 100 mm/s vs 700 mm/s. One bone in each pair was tested at one of the two speeds. For each load speed of 100 or 700 mm/s, 6 femurs were assigned to each of the four combinations of adduction angle (10° or 20°) and internal rotation angle (15° or 30°). All single femurs were tested at 100 mm/s and 10° adduction and 15° internal rotation angles, because these are the commonly reported set of conditions for a simulated fall on the hip. The multivariate statistical mixed model employed in this

study was well-suited to test the significance and rank the variables contributing to femoral strength and fracture type.

The proximal femur fracture types were classified into categories by a radiologist (JS) experienced in classification of clinical fractures, using post-fracture CT images. This analysis resulted in five fracture categories. The four categories representing simple fractures were intertrochanteric, basicervical, transcervical, and subcapital (Fig. 3A). The fifth category (complex) was used when multiple simple fracture types occurred simultaneously. However, during data analysis, it was determined that a fracture re-classification was necessary, because there were not enough samples in all fracture categories to perform meaningful statistical analyses. Thus, the intertrochanteric fractures were assigned to one group (intertrochanteric fractures), and the basicervical, transcervical and subcapital fractures were assigned to a second group (“neck” fractures). The nine complex fractures were removed from the analysis because they could not reasonably be placed into either of the two new categories, and statistically there were not enough of them to form their own category. In other words, the intertrochanteric fracture category counted all simple fractures in the trochanteric region, while the “neck” fracture category included all simple cervical and head fractures.

The data was analyzed using JMP version 10.0.0 and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). SAS was only used for the assessment of fracture type, which was a nominal response variable. The level of significance was set to 0.05 for all statistical analyses. First, generalized linear regression analyses were performed to determine the relationships between explanatory variables and outcomes. The explanatory variables included fall-related variables (test speed and bone orientation angles) and subject-specific variables (aBMD, sex, age, and three bone geometry parameters: neck-shaft angle, neck diameter and neck axis length). The biomechanical response variables (outputs) were femoral strength and fracture type. First, the statistical analyses were performed using all the explanatory variables (without interactions). Next, the insignificant variables were removed one at a time from the models using backward elimination, each time removing the most insignificant variable. For femoral strength, once all the insignificant explanatory variables had been eliminated, interaction terms between the remaining significant explanatory variables were then included and statistically tested. Finally, insignificant interactions were removed from the model and the analysis was repeated with only significant variables and interactions. For fracture type, interaction terms between independent variables were not included due to the complexity of the model with categorical response variables. Random effects were taken into account for all mixed models, as there were partially paired and partially unpaired femurs in our cadaveric cohort. Adjusted coefficients of determination (R^2) were also calculated for femoral strength using a marginal method proposed by Nakagawa and Schielzeth [23].

3. Results

The multivariate analysis results of explanatory variable contributions to explain femoral strength and fracture type are shown in Table 2.

3.1. Femoral strength analysis

As expected, the common clinically-measured variables aBMD, sex, and age were all found to be significant ($P < 0.0001$). Among the geometry parameters, only neck-shaft angle was found to be significant ($P = 0.0152$). Neck diameter and neck axis length did not contribute significantly to femoral strength ($P = 0.74$). Among fall-related variables, only testing speed was significant ($P = 0.0126$), while bone orientation (defined as adduction and internal rotation angles) was insignificant ($P = 0.11$) in the range of angles that we considered. All nine explanatory variables considered together explained 78% ($R^2 = 0.783$) of the variability in femoral strength. Note that this initial model did not consider interactions between explanatory variables.

Next, using backward elimination, the most insignificant explanatory variable was removed and the analysis was performed again. This elimination process was repeated, removing one insignificant variable per analysis, until all the insignificant variables were removed and only significant explanatory variables remained (see Table 2). In this model, aBMD, sex, age, neck-shaft angle, and testing speed remained significant ($P = 0.0198$), and R^2 (again with no interactions included in the model) remained unchanged from the value determined when including all nine variables (i.e., $R^2 = 0.783$). When interactions were then included in this model, there were only two significant interactions: (1) aBMD and age ($P = 0.0069$), and (2) neck-shaft angle and testing speed ($P = 0.0260$). After adding the two interactions to the model, R^2 increased by about 2% ($R^2 = 0.805$). The mathematical expression of this optimal model for strength, including the five significant variables and significant interactions, is as follows:

$$\text{Femoral strength} = \begin{cases} 9400(\text{aBMD}) + 14.9(\text{Age}) - 19.2(\text{angle}) + 15.1(\text{speed}) \\ \quad - 55.36(\text{aBMD} \times \text{Age}) - 0.1127(\text{angle} \times \text{speed}) \\ \quad + 404.7; [\text{Women}] \\ 9400(\text{aBMD}) + 14.9(\text{Age}) - 19.2(\text{angle}) + 15.1(\text{speed}) \\ \quad - 55.36(\text{aBMD} \times \text{Age}) - 0.1127(\text{angle} \times \text{speed}) \\ \quad + 1428.7; [\text{Men}] \end{cases} \quad (1)$$

Finally, in order to understand the importance of the three clinical variables that are readily available (aBMD, sex, and age), we also performed a generalized linear regression analysis using only these three variables to explain femoral strength (without interactions). The R^2 value resulting from this simpler analysis did not decrease considerably ($R^2 = 0.775$) compared to the model with all five significant variables, excluding interactions ($R^2 = 0.783$). When interactions were included in this three-variable model, there was only one significant interaction, between aBMD and age ($P = 0.0097$). The three clinical variables along with the significant interaction of aBMD and age explained 79% of the variability in femoral strength ($R^2 = 0.790$). The resulting mathematical expression for this model, with aBMD, sex, and age as explanatory variables for strength and including the significant interaction between aBMD and age, is as follows:

$$\text{Femoral strength} = \begin{cases} 9283(\text{aBMD}) + 16.68(\text{Age}) - 54.44(\text{aBMD} \times \text{Age}) \\ \quad - 2072; [\text{Women}] \\ 9283(\text{aBMD}) + 16.68(\text{Age}) - 54.44(\text{aBMD} \times \text{Age}) \\ \quad - 1002; [\text{Men}] \end{cases} \quad (2)$$

Fig. 2A shows the variation of femoral strength with aBMD in both sexes with their corresponding regression lines. As expected, the men cohort has stronger proximal femurs than the women cohort. Fig. 2B also shows the variation of femoral strength with age. Similar trends of decline with age are found in both men and women cohorts.

3.2. Fracture type analysis

The CT images after fracture led to a categorization of fracture types (Fig. 3A), which consisted of 101 intertrochanteric, 64 basicervical, 16 transcervical, 7 subcapital, and 9 complex fractures. To create statistically meaningful categories, these fractures were re-categorized into 101 “intertrochanteric” fractures and 87 “neck” fractures. The 9 complex fractures were excluded from the analyses.

A multivariate statistical analysis was performed to examine the significance of all nine explanatory variables, considered simultaneously, to explain fracture type (see Table 2). The only two variables found to be significant were aBMD ($P = 0.0022$) and neck-shaft angle ($P = 0.0174$), while sex, age, neck diameter, neck axis length, testing speed and bone orientation were found to be insignificant contributors ($P = 0.11$). Following the same procedure used for fracture strength, backward elimination was then performed for fracture type to find optimal explanatory variables by removing insignificant variables one at a time. After the elimination process was completed, only aBMD ($P = 0.0099$) remained significant.

It should be noted that both neck-shaft angle and internal rotation angle were marginally insignificant when they were successively eliminated as explanatory variables. In the elimination step when only aBMD, neck-shaft angle, and internal rotation angle remained as explanatory variables, aBMD was significant ($P = 0.01$), internal rotation angle was marginally significant ($P = 0.04$), and neck-shaft angle was marginally insignificant ($P = 0.06$), and so neck-shaft angle was eliminated from the model. In the next elimination step (with only aBMD and internal rotation angle), aBMD was significant ($P = 0.01$) and internal rotation angle became marginally insignificant ($P = 0.06$), and so internal rotation angle was eliminated from the model.

Finally, the changes in odds ratio (OR) for “trochanteric” and “neck” fracture types were calculated for individual changes in the lone significant variable, aBMD. The odds of having intertrochanteric fractures increased by 47% (OR: 1.47, 95% CI: 1.1–1.97) when aBMD decreased by 0.2 g/cm^2 (representing one standard deviation for the aBMD distribution of the entire cohort). For the sake of discussion, changes in odds ratios were also calculated for the two marginally insignificant variables, neck-shaft angle and internal rotation angle. The odds ratios for these variables were calculated using the model that included only aBMD, neck-shaft angle and internal rotation angle. The odds of having an intertrochanteric fracture

increased by 42% (OR: 1.42, 95% CI: 1.01–1.99) when the internal rotation angle increased by 5°. Also, the odds of having an intertrochanteric fracture increased by 35% (OR: 1.35, 95% CI: 0.99–1.85) when the neck-shaft angle decreased by 5° (representing one standard deviation for the neck-shaft angle distribution of the entire cohort).

Fig. 3B summarizes the fracture types for the three different bone density categories. Normal femurs ($N = 57$) had fewer “intertrochanteric” fractures ($N = 23/57$, 40%) than “neck” fractures ($N = 34/57$, 60%). Osteopenic femurs ($N = 78$) had a comparable number of “intertrochanteric” fractures ($N = 43/78$, 55%) and “neck” fractures ($N = 35/78$, 45%). Osteoporotic femurs ($N = 53$), however, had a larger share of “intertrochanteric” fractures ($N = 35/53$, 66%) than “neck” fractures ($N = 18/53$, 34%).

4. Discussion

The statistical analyses of proximal femur fracture strength performed for this study showed that the three clinically available variables (aBMD, sex, and age), along with neck-shaft angle and testing speed, were significant. Taken together, these five variables predicted the maximum explainable variability for fracture strength ($R^2 = 0.805$ with interactions included). In an additional analysis, we found that considering only aBMD, sex, and age explained a slightly smaller amount of the variability in femoral strength ($R^2 = 0.790$ with interactions included) then when all five significant variables (aBMD, sex, age, neck-shaft angle, and testing speed) were included. So while neck-shaft angle and testing speed were statistically significant, their impact on the explainable variability in the femoral strength was small (1.5%) when considered along with aBMD, sex and age. This finding is clinically important because while aBMD, sex, and age are commonly obtained during clinical visits, neck-shaft angle (which can be determined from medical imaging) is not, and fall speed is a fall-related variable that cannot be predicted by the clinician. The results of this study indicate that the current practice of using aBMD, sex, and age to estimate fracture strength for identification of appropriate preventive therapies is reasonable, and that including the fall-related or bone-geometry-related variables does not significantly improve femoral strength estimates.

The statistical significance of neck-shaft angle and testing speed discussed above has been an area of interest for other researchers. Pulkkinen et al. [4] found that neck-shaft angle was significant for fracture strength. Courtney et al. [8] showed the significance of testing speed (varied from 2 mm/s to 100 mm/s) for fracture strength, for a similar fall on the hip configuration. However, the present study expands on the outcomes of these previous studies by demonstrating that while neck-shaft angle and testing speed are statistically significant, the inclusion of these two variables does not substantially improve strength estimates over those given by only aBMD, sex and age.

While aBMD has been the predominant predictor of fracture strength by clinicians, this study showed that fracture strength depends also on sex and age. When using either Eq. (1) or Eq. (2) as the femoral strength model, the variable sex accounted for a significant difference of > 1000 N in femoral strength between women and men. The importance of age

for proximal femur strength, even when including aBMD and sex, was also shown in previous studies [13,17].

The experiments in the present study used internal rotation angle settings of 15° and 30°, which did not result in statistical significance in explaining variability in femoral strength. This finding is consistent with the results of a previous experimental study that used a smaller cohort of 33 cadaveric femurs [11]; that study investigated only the effect of femoral orientation on fracture strength, and did not find statistical significance of the internal rotation angle when changed from 15° to 30°.

In the assessment of fracture type, the only variable in this study that was found to be significant was aBMD (see Table 2). We found that normal bones had a smaller percentage of “intertrochanteric” fractures (40%) than “neck” fractures, and osteoporotic bones had more “intertrochanteric” (66%) than “neck” fractures. The analysis indicated that osteoporotic femurs were more susceptible to “intertrochanteric” fractures. This is in agreement with a previous study that showed the BMD measurements of the trochanter were significantly lower in patients with trochanteric hip fractures [24].

Finally, consider the two marginally insignificant variables for fracture type (neck-shaft angle and internal rotation angle). Our current study suggests that an increase in neck-shaft angle may reduce the chance of intertrochanteric fracture. In a previous biomechanical study, neck-shaft angle was found to be a significant predictor for fracture type, and this angle was found to be substantially larger in femoral neck fractures [25]. Our current study supplements this finding by further suggesting that an increase in the internal rotation angle during fracture may increase the risk of intertrochanteric fracture.

Similar to the results of the current study, several prior studies have also shown that femoral strength and aBMD are highly correlated. However, Stone et al. [26] argued that aBMD is a poor predictor of fracture risk, after their study found that only 28% of hip fractures occurred in women with established osteoporosis at baseline. This implies that femoral strength may be a poor predictor of fracture risk. Further studies are necessary to investigate how well femoral strength can predict femoral fracture risk.

The primary limitation of the current study is related to the unbalanced experimental design resulting from the combination of paired and unpaired femurs that were available to test a large number of variables. The logistics of procuring, storing and testing the femurs, and the desire to test more specimens at combinations of variables commonly reported in the literature, did not allow for balanced subpopulations to be tested at every combination of test variables. However, as discussed in the Methods section, the statistical methods selected for this study were chosen with our unbalanced dataset in mind, and are very capable of handling such unbalanced designs. Another limitation is that the application of loads at a constant rate in a laboratory setting may not be representative of a real life fall. In reality, the initial impact speed due to a fall may be as high as 3500 mm/s [27], before eventually reducing to 0 mm/s. Soft tissue, not considered in the present study, also significantly affects the load rate. In a recent study by Gilchrist et al. [22], however, an impact speed of about 3000 mm/s resulted in an average loading speed of 114 mm/s in proximal femurs. However,

the results of our current study (where the testing speed was varied from 5 mm/s to 100 mm/s to 700 mm/s) suggest that loading speed may not play a significant role in explaining femoral strength. Finally, the results of the current study are based on cadaveric data and might be different in patient cohorts.

In conclusion, this study presented fracture data and statistical analyses of femoral strength and fracture type measured experimentally from 197 cadaveric proximal femurs. Explanatory variables included aBMD, sex, age, neck-shaft angle, neck diameter, and neck axis length as subject-specific variables, as well as testing speed and bone orientation as control variables. aBMD, sex, and age together (including significant interactions) explained about 79% of the variability in measured proximal femur strength in our cadaveric cohort. While test speed and femoral neck-shaft angle were found to be statistically significant for femoral strength, the inclusion of these variables did not substantially improve the model coefficient of determination for femoral strength (R^2 increased from 0.790 to 0.805). This is an important finding for clinicians, since the inclusion of probabilistic fall-related variables or bone-geometry-related variables (which are difficult to determine) did not significantly improve fracture strength estimates.

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References

- [1]. Kanis JA, Diagnosis of osteoporosis and assessment of fracture risk, *Lancet* 359 (9321) (2002) 1929–1936. [PubMed: 12057569]
- [2]. Trémollières FA, Pouillès JM, Drewniak N, Laparra J, Ribot CA, Dargent-Molina P, Fracture risk prediction using BMD and clinical risk factors in early post-menopausal women: sensitivity of the WHO FRAX tool, *J. Bone Miner. Res* 25 (5) (2010) 1002–1009. [PubMed: 20200927]
- [3]. Rivadeneira F, Zillikens MC, De Laet CE, Hofman A, Uitterlinden AG, Beck TJ, Pols HA, Femoral neck BMD is a strong predictor of hip fracture susceptibility in elderly men and women because it detects cortical bone instability: the Rotterdam Study, *J. Bone Miner. Res* 22 (11) (2007) 1781–1790. [PubMed: 17638578]
- [4]. Pulkkinen P, Partanen J, Jalovaara P, Jämsä T, Combination of bone mineral density and upper femur geometry improves the prediction of hip fracture, *Osteoporos. Int* 15 (4) (2004) 274–280. [PubMed: 14760516]
- [5]. Abraham AC, Agarwalla A, Yadavalli A, McAndrew C, Liu JY, Tang SY, Multiscale predictors of femoral neck in situ strength in aging women: contributions of BMD, cortical porosity, reference point indentation, and nonenzymatic glycation, *J. Bone Miner. Res* 30 (12) (2015) 2207–2214. [PubMed: 26060094]
- [6]. Bouxsein ML, Szulc P, Munoz F, Thrall E, Sornay-Rendu E, Delmas PD, Contribution of trochanteric soft tissues to fall force estimates, the factor of risk, and prediction of hip fracture risk*, *J. Bone Miner. Res* 22 (6) (2007) 825–831. [PubMed: 17352651]
- [7]. Cheng X, Lowet G, Boonen S, Nicholson P, Brys P, Nijs J, Dequeker J, Assessment of the strength of proximal femur in vitro: relationship to femoral bone mineral density and femoral geometry, *Bone* 20 (3) (1997) 213–218. [PubMed: 9071471]
- [8]. Courtney A, Wachtel E, Myers E, Hayes W, Effects of loading rate on strength of the proximal femur, *Calcif. Tissue Int* 55 (1) (1994) 53–58. [PubMed: 7922790]

- [9]. Johannesdottir F, Thrall E, Muller J, Keaveny TM, Kopperdahl DL, Bouxsein ML, Comparison of non-invasive assessments of strength of the proximal femur, *Bone* 105 (2017) 93–102. [PubMed: 28739416]
- [10]. Nawathe S, Akhlaghpour H, Bouxsein ML, Keaveny TM, Microstructural failure mechanisms in the human proximal femur for sideways fall loading, *J. Bone Miner. Res* 29 (2) (2014) 507–515. [PubMed: 23832419]
- [11]. Pinilla TP, Boardman KC, Bouxsein ML, Myers ER, Hayes WC, Impact direction from a fall influences the failure load of the proximal femur as much as age-related bone loss, *Calcif. Tissue Int* 58 (4) (1996) 231–235. [PubMed: 8661953]
- [12]. Rezaei A, Dragomir-Daescu D, Femoral strength changes faster with age than BMD in both women and men: a biomechanical study, *J. Bone Miner. Res* 30 (12) (2015) 2200–2206. [PubMed: 26096829]
- [13]. Rezaei A, Giambini H, Rossman T, Carlson KD, Yaszemski MJ, Lu L, Dragomir-Daescu D, Are DXA/aBMD and QCT/FEA stiffness and strength estimates sensitive to sex and age? *Ann. Biomed. Eng* (2017) 1–10.
- [14]. Roberts BJ, Thrall E, Muller JA, Bouxsein ML, Comparison of hip fracture risk prediction by femoral aBMD to experimentally measured factor of risk, *Bone* 46 (3) (2010) 742–746. [PubMed: 19854307]
- [15]. Hambli R, Allaoui S, A robust 3D finite element simulation of human proximal femur progressive fracture under stance load with experimental validation, *Ann. Biomed. Eng* 41 (12) (2013) 2515–2527. [PubMed: 23864338]
- [16]. Keyak J, Rossi S, Jones K, Les C, Skinner H, Prediction of fracture location in the proximal femur using finite element models, *Med. Eng. Phys* 23 (9) (2001) 657–664. [PubMed: 11755810]
- [17]. Courtney AC, Wachtel EF, Myers ER, Hayes WC, Age-related reductions in the strength of the femur tested in a fall-loading configuration, *J. Bone Joint Surg* 77 (3) (1995) 387–395. [PubMed: 7890787]
- [18]. Gebauer M, Stark O, Vettorazzi E, Grifka J, Püschel K, Amling M, Beckmann J, DXA and pQCT predict pertrochanteric and not femoral neck fracture load in a human side-impact fracture model, *J. Orthop. Res* 32 (1) (2014) 31–38. [PubMed: 24019186]
- [19]. Dall'Ara E, Luisier B, Schmidt R, Pretterklieber M, Kainberger F, Zysset P, Pahr D, DXA predictions of human femoral mechanical properties depend on the load configuration, *Med. Eng. Phys* 35 (11) (2013) 1564–1572. [PubMed: 23684578]
- [20]. Dragomir-Daescu D, Rezaei A, Uthamaraj S, Rossman T, Bronk JT, Bolander M, Lambert V, McEligot S, Entwistle R, Giambini H, Proximal cadaveric femur preparation for fracture strength testing and quantitative CT-based finite element analysis, *J. Vis. Exp* 121 (2017) (e54925–e54925).
- [21]. 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, *J. Vis. Exp* 126 (2017) (e54928–e54928).
- [22]. 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, *J. Biomech* 47 (15) (2014) 3744–3749. [PubMed: 25443780]
- [23]. Nakagawa S, Schielzeth H, A general and simple method for obtaining R² from generalized linear mixed-effects models, *Methods Ecol. Evol* 4 (2) (2013) 133–142.
- [24]. Karlsson M, Johnell O, Nilsson B, Sernbo I, Obrant K, Bone mineral mass in hip fracture patients, *Bone* 14 (2) (1993) 161–165. [PubMed: 8334034]
- [25]. Pulkkinen P, Eckstein F, Lochmüller EM, Kuhn V, Jämsä T, Association of geometric factors and failure load level with the distribution of cervical vs. trochanteric hip fractures, *J. Bone Miner. Res* 21 (6) (2006) 895–901. [PubMed: 16753020]
- [26]. Stone KL, Seeley DG, Lui LY, Cauley JA, Ensrud K, Browner WS, Nevitt MC, Cummings SR, BMD at multiple sites and risk of fracture of multiple types: long-term results from the study of osteoporotic fractures, *J. Bone Miner. Res* 18 (11) (2003) 1947–1954. [PubMed: 14606506]

- [27]. Feldman F, Robinovitch SN, Reducing hip fracture risk during sideways falls: evidence in young adults of the protective effects of impact to the hands and stepping, J. Biomech 40 (12) (2007) 2612–2618. [PubMed: 17395188]

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Fig. 1.
Experimental setup for mechanical testing of proximal femurs.

Fig. 2. Change in femoral strength with (A) neck aBMD, and (B) age (in years) in both men and women cohorts.

Fig. 3. (A) Fracture Type Categorization: 1) Intertrochanteric; 2) Basicervical; 3) Transcervical; 4) Subcapital; and 5) Complex; (B) Distribution of fracture type and bone conditions after re-categorization into two types: 'intertrochanteric' and 'neck'.

Table 1

Characteristics of 197 proximal femurs.

	Women	Men	Combined cohort
Number	128	69	197
Age (years)	69.9 ± 13.2	67.3 ± 15.4	68.9 ± 14.0
Side, right/left	60/68	35/34	95/102
Normal (%)	27 (14%)	30 (15%)	57 (29%)
Osteopenic (%)	52 (26%)	30 (15%)	82 (42%)
Osteoporotic (%)	49 (25%)	9 (5%)	58 (29%)
Femoral neck aBMD (g cm ⁻²)	0.763 ± 0.192	0.889 ± 0.192	0.808 ± 0.201
Neck-shaft angle (°)	128.75 (± 5.31)	128.21 (± 5.76)	128.56 (± 5.09)
Neck axis length (mm)	94.13 (± 5.94)	105.77 (± 5.76)	98.21 (± 8.09)
Neck diameter (mm)	31.06 (± 2.44)	35.99 (± 2.21)	32.78 (± 3.33)

Table 2

P-values for each explanatory variable in multivariate statistical models including all variables simultaneously, as well as models including only significant variables, for femoral strength and fracture type outcomes.

Variables	Strength		Fracture type	
	All variables included	Only significant variables included, with interactions ^a	All variables included	Only significant variables included
aBMD	< 0.0001	< 0.0001	0.0022	0.0099
Sex	< 0.0001	< 0.0001	0.35	Not included
Age	< 0.0001	< 0.0001	0.11	Not included
Neck-shaft angle	0.0152	0.0041	0.0174	Not included
Neck diameter	0.74	Not included	0.30	Not included
Neck axis length	0.86	Not included	0.28	Not included
Testing speed	0.0126	0.0135	0.40	Not included
Angle α	0.73	Not included	0.70	Not included
Angle β	0.11	Not included	0.23	Not included

^a Interaction terms aBMD $\times$ age ($P = 0.0069$) as well as neck-shaft angle $\times$ testing speed ($P = 0.0260$) were significant.