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Comparison of hip fracture risk prediction by femoral aBMD to experimentally measured factor of risk

Benjamin J. Roberts *, Erica Thrall, John A. Muller, Mary L. Bouxsein

Orthopedic Biomechanics Laboratory, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

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ABSTRACT

Areal BMD (aBMD) derived from DXA is currently the gold standard for diagnosis of osteoporosis. A biomechanical approach to fracture risk assessment comparing the ratio of applied load to bone strength, termed the factor of risk (Φ), may be useful to better identify patients at risk for fracture. We obtained 73 human cadaveric femurs (48 women and 25 men, aged 74.2 ± 8.7 years, range 55–98 years), measured femoral neck (FN) aBMD by DXA, and mechanically tested the femurs to failure in a sideways fall configuration. The force applied to the hip during a sideways fall was estimated from height and weight, and accounted for trochanteric soft tissue thickness. Compared to men, women had significantly lower FN aBMD and femoral strength, and tended to have higher factor of risk for hip fracture Φ. Fifty-three of 54 (98%) specimens that had a FN aBMD T-score below −2.5 also had a $\Phi > 1$. However, 10/19 (53%) specimens with FN aBMD T-score above −2.5 also had $\Phi > 1$. These data indicate that whereas an aBMD-based diagnosis of osteoporosis is highly associated with fracture risk as assessed by the factor of risk, about 50% of individuals not designated as osteoporotic by aBMD testing would be at high risk for hip fracture should they experience a sideways fall. These findings strongly support the investigation of new biomechanically-based methods of fracture risk prediction.

Introduction

Hip fractures are among the most serious consequences of osteoporosis. Approximately 20% of hip fractures result in death in the following year, and those who survive often experience marked disability and loss of independence. Furthermore, the lifetime cost of a single hip fracture is estimated to exceed $80,000 [1]. The current standard for assessment of fracture risk is areal bone mineral density (aBMD, g/cm^2) by dual-energy X-ray absorptiometry (DXA). However, recent clinical studies have demonstrated the limitations of aBMD measurements in assessing fracture risk, as less than half of those who suffer a hip or non-vertebral fracture have aBMD values in the osteoporotic range [2–4]. A biomechanical approach to assessing fracture risk may improve the identification of this at-risk segment of the population.

Fracture is a dichotomous event that occurs when applied loads exceed the capacity of the structure to handle them. A biomechanical approach to fracture risk prediction takes into account these two inputs, such that when the ratio of applied load to bone strength Φ, termed the factor of risk, is greater than one, fracture is expected [5]. Several recent clinical studies have compared load-to-strength ratios at various anatomical sites [6–12]. However, few have addressed fracture in the hip, instead focusing mainly on vertebral fractures. Additionally, since all were clinical studies, bone strength was estimated from non-invasive imaging modalities, rather than measured directly.

Our overall goal was to determine the agreement between two different methods of fracture prediction: a biomechanical approach employing direct measurements of femoral strength in human cadaveric specimens, and a imaging based approach based on aBMD from DXA. We compared aBMD diagnosis of osteoporosis to predicted fracture risk, as assessed by the factor of risk. Additionally, we determined the age- and sex-related differences in the factor of risk and its determinants.

Materials and methods

Specimens

We obtained 78 fresh frozen human cadaveric proximal femora from human tissue banks. Specimens were excluded if below age 55 years, and/or if the cause of death was from cancer known to metastasize to bone (lung, breast, prostate and colon). All femora were radiographed (HP Faxitron series cabinet X-ray system) to ensure that they were free of pre-existing fractures and/or metastatic

* Corresponding author.
E-mail addresses: bjrobert@bidmc.harvard.edu (B.J. Roberts), erica.j.thrall.98@alum.dartmouth.org (E. Thrall), jamuller@alum.rpi.edu (J.A. Muller), mbouxsei@bidmc.harvard.edu (M.L. Bouxsein).

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lesions. Two femora were excluded, one due to pre-existing fracture and the other due to myeloma. Three specimens were excluded for non-pathologic reasons: two were missing height and weight data, and one was missing femoral neck aBMD data from DXA. Thus, data presented here includes 73 specimens (48 women, 25 men, mean age = 74.38 ± 8.91 years, range 55–98 years).

Areal bone mineral density

Areal bone mineral density was assessed using dual-energy X-ray absorptiometry (QDR4500 Discovery, Hologic, Inc., Bedford, MA). Femora were scanned in a 15-cm-deep water bath to simulate the presence of soft tissue. A custom-made holder was used to ensure uniform positioning equivalent to the positioning of a patient during a hip DXA scan. Outcomes included areal bone mineral density (aBMD, g/cm^2), bone mineral content (BMC, g), and sex-specific T-scores [13] for the femoral neck and total femur regions.

Femoral strength testing

Following imaging, femurs were mechanically tested in a sideways fall configuration at impact loading rates (Fig. 1). The femora were cut distal to the lesser trochanter, and this distal end was embedded in poly(methyl methacrylate) (PMMA) using custom molds. Adduction and internal rotation were set to 10° and 15°, respectively, to mimic a sideways fall configuration [14]. The greater trochanter was also embedded in PMMA to distribute the load, and eliminate point-loading on this surface. As visible in the figure, translation in the *x*–*y* plane (but not in *z*) was freely allowed at the shaft and greater trochanteric interfaces. Rotation about the *x*-axis was allowed at the shaft and head interfaces. Compressive force was applied to the greater trochanter at a constant rate of 100 mm/s using a servohydraulic materials testing system (Model 1331, Interlaken Technology Corporation, Chaska, MN). Load and displacement data were acquired at 1000 Hz. A high-speed video acquisition system (MotionScope PCI 8000S, Redlake Imaging Corporation) was used to image the failure process at 500 frames/s. Subsequent to testing, videos were reviewed to characterize fracture type. Load-displacement data were used to calculate stiffness and failure (maximum) load (Fig. 2).

The factor of risk for hip fracture

The factor of risk for hip fracture (Φ) was defined as the ratio of the force applied to the hip during a sideways fall to the femoral strength in a sideways fall configuration. We estimated the peak force that would be applied to the hip during a sideways fall from the individual's reported height and weight, according to the following equations [11]:

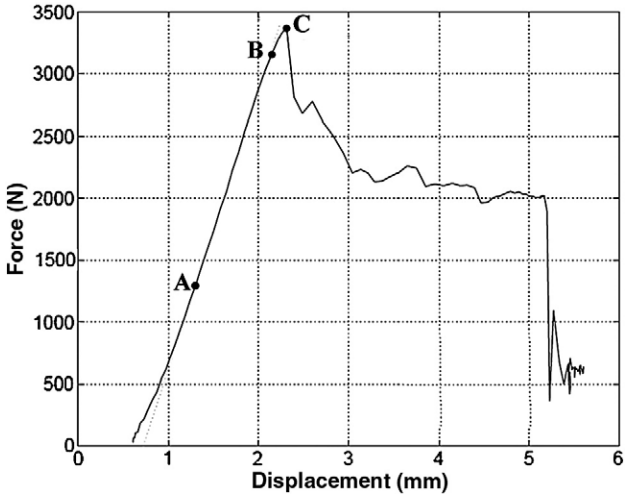

Fig. 2. Representative force-displacement graph. The *y*-axis is force (in Newton, N) and the *x*-axis is displacement (in mm). Femoral strength (i.e., failure load) was taken as the maximum force sustained (point C), and stiffness was defined as the slope of the linear region (segment AB).

$$v = \sqrt{2*g*h_{cog}} \quad 1.1$$

$$F_{peak} = v*\sqrt{k_{stiff}*\frac{m}{2}} \quad 1.2$$

where h_{cog} is the height of the subject's center of gravity, k_{stiff} is a sex-specific stiffness of the femur, and m is the subject's mass. Since the soft tissues overlying the hip attenuate the force applied to the greater trochanter during a fall, we also computed an "attenuated force," F_{atten}, which accounts for the force-mitigating effects of trochanteric soft tissue padding. This was calculated using the observation that the peak force applied to the hip is reduced by trochanteric soft tissue [15]:

$$F_{atten} = F_{peak} + k_{fat}*STT \quad 2.1$$

where k_{fat} is −71 N/mm of soft tissue. Trochanteric soft tissue thickness was estimated using previously established sex-specific relationships between body mass index and direct measurements of trochanteric soft tissue thickness [11,12]. For the denominator of the factor of risk, we used direct measurements of femoral strength. We thus computed the factor of risk for hip fracture (Φ) as the ratio of the

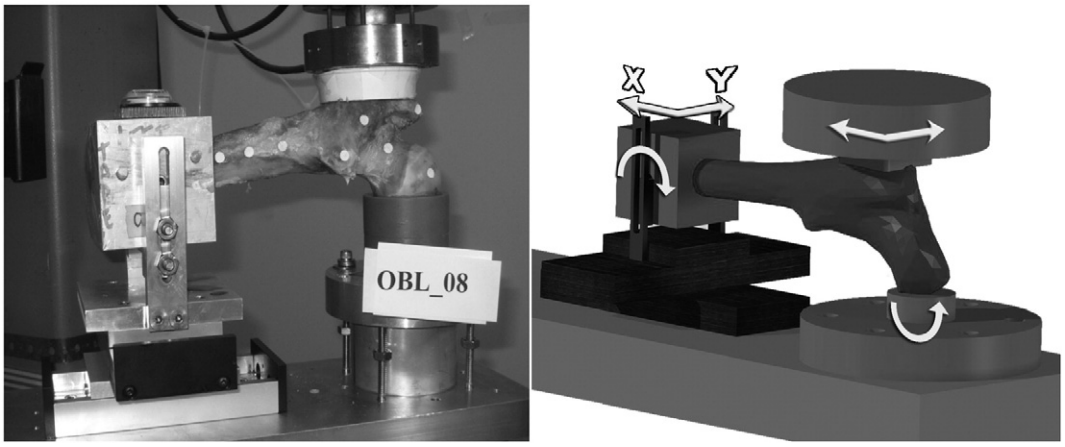

Fig. 1. Mechanical testing setup. Actual (left) and diagrammatic (right) representations of the mechanical testing setup.

Table 1
Sex-specific differences in outcomes and correlation with age.

Parameter	All	Men ($n=25$)	Women ($n=48$)	Correlation with age (r)
Estimated soft tissue thickness (mm)	41.86 ± 30.84	22.23 ± 15.95	51.46 ± 31.9	−0.23 ($p=0.05$)
FN aBMD (g/cm^2)	0.506 ± 0.187	0.599 ± 0.212	0.457 ± 0.153[b]	−0.26 ($p=0.03$)
TH aBMD (g/cm^2)	0.65 ± 0.21	0.76 (0.21)	0.59 (0.18)[a]	−0.25 ($p=0.03$)
Failure load (n)	3573 ± 1821	4882 ± 2209	2893 ± 1099[a]	−0.14 ($p=0.08$)
F_{peak} (n)	6553 ± 1391	7528 ± 1411	6075 ± 1113[a]	−0.15 ($p=0.07$)
F_{atten} (n)	3748 ± 1778	5949 ± 733	2624 ± 852[a]	0.13 ($p=0.08$)
Φ_{peak}	2.23 ± 1.10	1.94 ± 1.00	2.37 ± 1.12[c]	0.05 ($p=0.63$)
Φ_{atten}	1.68 ± 0.79	1.54 ± 0.86	1.76 ± 0.74	0.15 ($p=0.21$)

Means ± SD, and correlation presented as Spearman correlation coefficient.
Abbreviations: FN, femoral neck; TH, total hip.
[a] $p<0.001$ for men vs. women.
[b] $p<0.01$ for men vs. women.
[c] $p<0.05$ for men vs. women.

estimated applied force to the actual failure load from mechanical testing. The factor of risk was calculated using both F_{peak} and F_{atten}; we refer to these respectively as Φ_{peak} and Φ_{atten}.

Statistical analysis

All variables were checked for normality by creation of quartile–quartile plots and use of Kolmogorov–Smirnov tests. We generated bivariate regressions for Φ vs. age, Φ vs. femoral neck T-score, and T-score vs. femoral strength. Unpaired t-tests were used to test for differences between those predicted to fracture ($\Phi>1$) and those not ($\Phi<1$), and between men and women; in the case of non-normally distributed variables, nonparametric tests were used.

Results

Women had lower femoral neck aBMD, total hip aBMD and femoral failure load than men ($p<0.01$ for all, Table 1). As expected due to their lower height and weight, women also had significantly lower F_{peak} and F_{atten} than men. Conversely, the factor of risk for hip fracture was higher in women regardless of whether it was estimated using peak or attenuated applied forces, though the latter did not reach statistical significance ($p=0.10$). The mean factor of risk values, even after accounting for the force-attenuating properties of trochanteric soft tissue, exceeded the "fracture threshold" of 1.0 in both men and women, indicating many of these elderly individuals would be predicted to fracture should they experience a sideways fall with impact to the greater trochanter. We note that if the force-attenuating effects of trochanteric soft tissue were not taken into account, the mean Φ value rises to 1.94 in men and 2.37 in women (Table 1). This increase changes the fracture prediction results: all of the women are predicted to fracture, and all but three men are predicted to fracture should they suffer a sideway fall with impact to the greater trochanter. This result highlights the potentially important role of trochanteric soft tissues and/or artificial trochanteric padding on hip fracture risk.

Femoral neck aBMD and femoral failure load were moderately negatively correlated with age ($r=-0.26$ and -0.14, respectively). FN aBMD correlated with femoral failure load with $r^2=0.70$. The factor of risk for hip fracture was not associated with age (Fig. 3).

The factor of risk for hip fracture was negatively associated with femoral neck aBMD T-score in a nonlinear fashion, with $r^2=0.67$ for the exponential regression (Fig. 4). This regression intercepts the $\Phi=1$ line at a T-score of −1.48, indicating that if a sideways fall occurs, a fracture would be predicted to occur at femoral neck aBMD T-scores much higher than the WHO osteoporosis diagnosis threshold of −2.5. The regression intercepts the T-score = −2.5 at a Φ value of 1.8 (Fig. 4a). Furthermore, high Φ is associated with low Failure Load (Fig. 5). However, at a given Φ, failure load can vary as much as 75%, due to differences in height, weight, and soft tissue thickness. Note that the 1/x relationship shown is due to failure load being used in the denominator of the factor of risk calculation..

Based on femoral neck aBMD T-score, 74% of specimens had osteoporosis. In comparison, when specimens were classified based on the biomechanical risk of fracture (i.e., when $\Phi_{atten}\geq 1$), 86% were predicted to fracture if they experienced a sideways fall (Table 2). Among those diagnosed with osteoporosis by femoral neck aBMD, 98% (i.e., 53/54 specimens) also had $\Phi_{atten}\geq 1$, and would be predicted to fracture if they fell to the side, indicating that osteoporosis diagnosis by aBMD has a very high positive predictive value (Table 2). However,

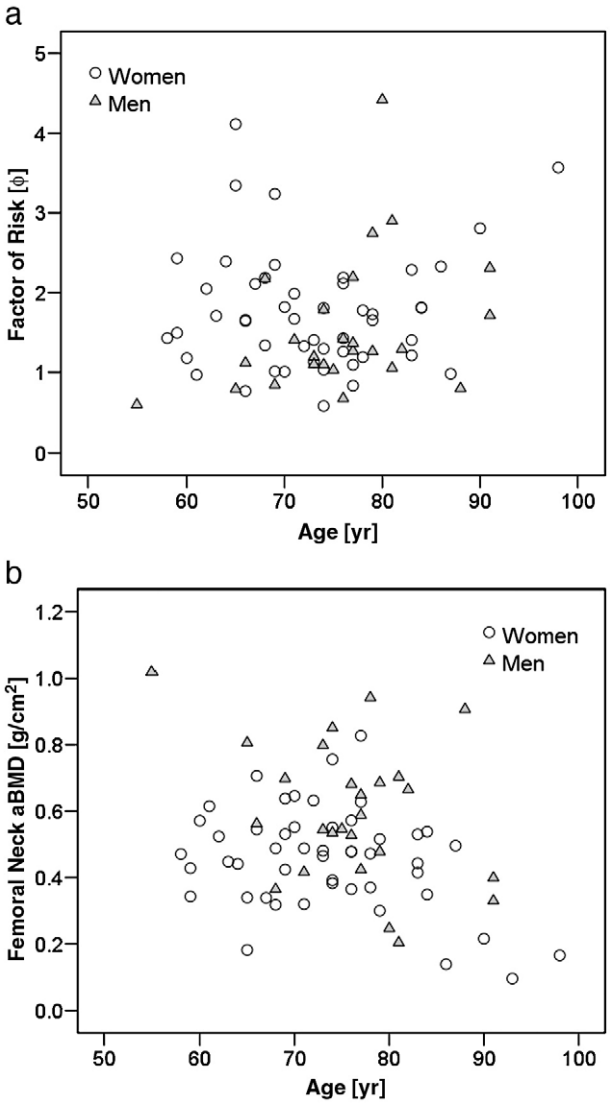

Fig. 3. (a) Age vs. factor of risk (Φ_{atten}). (b) Age vs. femoral neck T-score.

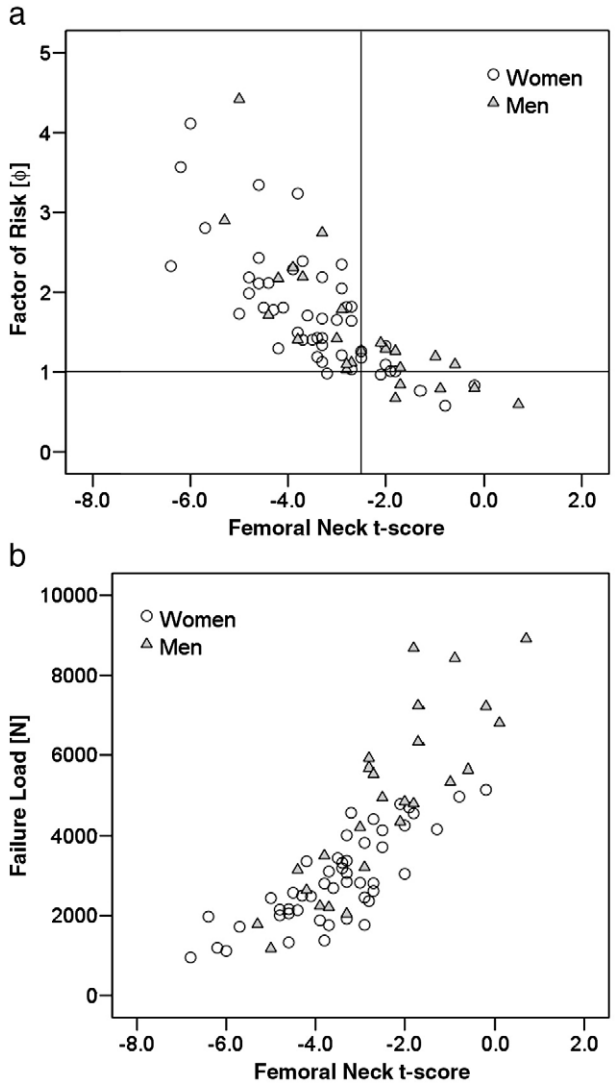

Fig. 4. Factor of risk for hip fracture (Φ_{atten}) vs. femoral neck BMD T-score and failure load vs. femoral neck BMD T-score. Lines are drawn on the graph at femoral neck T-score = −2.5, and at $\Phi_{atten} = 1$. The regression equation for FN aBMD vs. Φ is $y = 0.687e^{-0.253x}$.

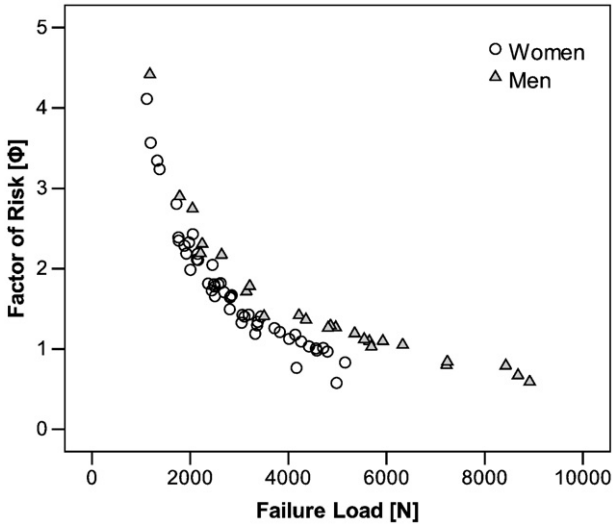

Fig. 5. Failure load vs. factor of risk.

Table 2
Comparison of fracture risk assessment by femoral neck aBMD T-score and factor of risk for hip fracture.

	Predicted to fracture $\Phi_{atten} > 1$	Not predicted to fracture $\Phi_{atten} \leq 1$	Total
OP FN T-score < −2.5	53	1	54 (74%)
No-OP FN T-score ≥ −2.5	10	9	19 (26%)
Total	63 (86%)	10 (14%)	73

among those who were not diagnosed with osteoporois, 52% (10/19 specimens) would be predicted to fracture if they fell to the side, indicating that osteoporosis diagnosis by femoral neck aBMD has a relatively poor negative predictive value. Of these non-osteoporotic specimens, those predicted to fracture had significantly lower aBMD T-scores at the neck ($p = 0.03$) and intertrochanteric regions ($p = 0.02$), but had similar height, weight, age, and trochanteric soft tissue thickness compared to non-osteoporotic specimens not predicted to fracture. In comparison, total hip aBMD had a similarly high positive predictive value, as 38/39 individuals with osteoporosis by total hip aBMD T-score were predicted to fracture if falling to the side. However, among those not diagnosed with osteoporosis by total hip aBMD, 74% (25/34) would be predicted to fracture if they fell to the side (Table 3).

Discussion

The goal of this study was to investigate a biomechanical approach, namely, the ratio of applied load to femoral strength, to assessing hip fracture risk using human cadaveric specimens. A diagnosis of osteoporosis by aBMD (i.e., femoral neck T-score < −2.5) was very successful in identifying those who would be at risk for fracture should they suffer a sideways fall. However, slightly over half of the specimens with femoral neck aBMD T-scores above −2.5 and two-thirds of specimens with total hip aBMD T-scores above −2.5 were also predicted to fracture if they suffered a sideways fall. Thus, in our sample of low aBMD specimens 55 years of age and older, a diagnosis of osteoporosis by aBMD indicates very high risk for fracture, but those whose aBMD is higher than the osteoporosis diagnostic threshold are not necessarily at low risk of fracture. We note that it is misleading to calculate the precise sensitivity and specificity (or correspondingly, a ROC curve) of this sample, since this sample is not representative of the total clinical population, but rather intentionally biased towards the low aBMD spectrum.

This study had several strengths. The use of cadaveric specimens provides an accurate measurement of femoral strength in a sideways fall configuration, as opposed to estimates from non-invasive imaging, which were able to describe only 70% of the variation in failure load in the current study. Moreover, the use of specimens over age 55 and with low aBMD ensures that findings are relevant to the demographic most at risk for hip fracture. Furthermore, aBMD was determined in excised specimens using precisely controlled positioning and a consistent soft tissue environment, thereby eliminating some of the factors that lead to variability in clinical assessment of aBMD.

Table 3
Comparison fracture risk assessment by total hip aBMD T-score and factor of risk for hip fracture.

	Predicted to fracture $\Phi_{atten} > 1$	Not predicted to fracture $\Phi_{atten} \leq 1$	Total
OP TH T-score < −2.5	38	1	39 (53%)
Non-OP TH T-score > −2.5	25	9	34 (47%)
Total	63 (86%)	10 (14%)	73

Use of cadaveric specimens also presents some limitations. For example, the aBMD values may be lower than usual, due to the presence of gas inside the femur as a result of marrow decomposition. This may have been the case in our specimens as they presented with low aBMD, even when adjusted for age. An examination of z-score reveals that the average z-score was -1.05 ± 1.33, and was not significantly correlated with age. Thus, while our specimens were on average one standard deviation lower in aBMD than what is seen clinically, there was no age-related bias—that is to say, the older cadaveric specimens were no more susceptible to gas evolution than the younger specimens. However, in the case that aBMD values are artifactually low, the regression curve between Φ and aBMD for equivalent *in vivo* scans would be shifted to the right, implying that while the same number of cases would fracture, even fewer would be diagnosed as osteoporotic. In addition, we estimated soft tissue thickness from body mass index. Whereas trochanteric soft tissue was fairly well correlated with BMI in previous studies ($r^2 = 0.56$ for both men and women), we acknowledge that direct measurements of trochanteric soft tissue thickness would be preferable. Nonetheless, our range of soft tissue thicknesses was consistent with previous reports [11,12,16]. Furthermore, the error induced by using a regression-based approach to estimate soft tissue thickness is theoretically unbiased and will overestimate as frequently as it underestimates; hence, the regressions and trends observed in this study are still likely valid. A final limitation of this study is that it only addresses one loading configuration—the sideways fall with direct impact to the greater trochanter. In reality, falls do not always occur at precisely the same angle, nor do the subjects brace themselves equally with their upper bodies. However, it is outside the scope of this study to address variable loading configurations. Furthermore, although it would have been interesting to compare femoral specimens who suffered a fracture in life to those that did not, unfortunately it is impractical, as the medical history is not available to us, and furthermore, obtaining sufficient sample of specimens with prior history of a contralateral hip fracture is likely to be challenging.

In clinical practice, the biomechanical approach to fracture risk assessment would be different from the one presented in this study. Chief among the differences would be the ability to directly measure trochanteric tissue thickness and the inability to directly measure failure load in a clinical environment. It should be noted, however, that trochanteric soft thickness is currently not a standard outcome from DXA, and it may be useful to develop a robust DXA-based measure for soft tissue thickness [16]. Since direct measurements of femoral strength are impossible, a surrogate for femoral failure load determination would be used, such as an estimation using a aBMD regression or one from finite element analysis. In the current study, the correlation for aBMD vs. femoral failure load was $r^2 = 0.70$; for finite element analysis, correlations with experimental failure load range from $r^2 = 0.8$ to 0.9 [17–19]. Thus, the clinical implementation of this biomechanical approach to fracture risk assessment would benefit from use of imaging modalities with higher correlations with failure load, and also from more accurate measurements of soft tissue thickness. Future studies should include retrospective application of the factor of risk analysis to cohorts with hip fractures to examine the clinical efficacy of the method.

In summary, our data in human cadaveric femora have shown differences between aBMD-based and biomechanically-based approach to assessment of hip fracture risk. Importantly, the factor-of-risk values begin to exceed the "fracture threshold" well before the osteoporotic threshold by aBMD is reached. Whereas a change in the aBMD-based diagnostic threshold is one way to address the elevated fracture risk in the osteopenic population, ultimately methods are needed to provide more accurate estimates of femoral failure load and to identify who is at risk for falling. Our results require validation in a clinical study with hip fracture as outcome; nonetheless, these findings in human cadaveric specimens provide strong motivation for further exploration of a biomechanically-based approach for assessing hip fracture risk.

Conflicts of interest

All authors have no conflicts of interest.

Acknowledgments

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