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Hip fractures risk in older men and women associated with DXA-derived measures of thigh subcutaneous fat thickness, cross-sectional muscle area, and muscle density

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Abstract

Mid-thigh cross-sectional muscle area (CSA), muscle attenuation, and greater trochanter soft tissue thickness have been shown to be independent risk factors of hip fracture. Our aim was to determine whether muscle and adipose tissue measures derived from DXA scans would have a similar risk association as those measured using other imaging methods. Using a case-cohort study design, we identified 169 incident hip fracture cases over an average of 13.5 years among participants from the Health ABC Study, a prospective study of 3,075 individuals initially aged 70–79. We modeled the thigh 3D geometry and compared DXA and CT measures. DXA-derived thigh CSA, muscle attenuation, and subcutaneous fat thickness were found to be highly correlated to their CT counterparts (Pearson's r = 0.82, 0.45, and 0.91, respectively; $p < 0.05$). The fracture risk of men and women were calculated separately. We found that decreased subcutaneous fat, CT thigh muscle attenuation, and appendicular lean mass by height squared (ALM/Ht^2) were associated with fracture risk in men, hazard ratios (HR) equal 1.44 (1.02, 2.02), 1.40 (1.05, 1.85), and 0.58 (0.36, 0.91) respectively after adjusting for age, race, clinical site, BMI, chronic disease, hip BMD, self-reported health, alcohol use, smoking status, education, physical activity, cognitive function. In a similar model for women, only decreases in subcutaneous fat and DXA CSA were associated with hip fracture risk, HR equal 1.39 (1.07, 1.82) and 0.78 (0.62, 0.97) respectively. Men with a high ALM/Ht^2 and low subcutaneous fat thickness had over 8 times higher risk for hip

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AVAILABILITY/DISCLOSURE OF MATERIALS AND METHODS AND AUTHOR ACCESS TO DATA. Requests for data should be addressed to: Peggy Cawthon

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fracture compared to those with low ALM/Ht^2 and high subcutaneous fat. In women, ALM/Ht^2 did not improve the model when subcutaneous fat included. We conclude that the DXA-derived subcutaneous fat thickness is a strong marker for hip fracture risk in both men and women, and especially men with high ALM/Ht^2.

Keywords

hip fracture; dual-energy X-ray absorption; body composition; osteoporosis; skeletal muscle attenuation; aging

INTRODUCTION

Progression of osteoporosis, especially in the early stages of disease, is elusive to detect. Models for hip fracture risk currently only utilize clinical risk factors including weight, height, and age, personal and family history of fracture, ethnicity, smoking, and steroid use. The most sophisticated risk factor included in clinical models, such as FRAX (http://www.sheffield.ac.uk/FRAX), is hip bone density measured using an x-ray imaging method such as dual-energy X-ray absorptiometry (DXA) or quantitative computed tomography (QCT). Although fracture rates increase with decreasing BMD, the bulk of fractures occur in subjects with low BMD, not osteoporosis (1). Additional clinical risk factors may provide better selection of high-risk individuals for fracture prevention strategies.

There is evidence that several soft tissue measures are independent predictors of hip fracture risk. Recent studies (2,3) have shown an increased risk of hip fracture of 40–60% per each standard deviation decrease in either mid-thigh cross-sectional muscle area (CSA) or muscle X-ray attenuation even after adjusting for hip BMD. Muscle X-ray attenuation is thought to be a surrogate measure for the amount of adiposities interlaced with muscle and of triglyceride storage within the muscle cells themselves (4,5). In addition, the thickness of soft tissue near the greater trochanter has been found to be protective of hip fractures in some but not all reports (6,7). In women, each standard deviation decrease in trochanteric soft tissue thickness increased fracture risk by 80% (7). However, in older men, no association was found between hip fracture and trochanteric soft tissue thickness (6). Neither trochanteric soft tissue thickness nor muscle attenuation is readily available to clinicians. For example, adding CT scans to a clinical osteoporosis workup is problematic because of the increase in cost, increased radiation exposure, and limited availability.

DXA systems can be used to quantify soft tissue composition and tissue geometry for many regions of the body including the arms, legs (lower extremity), trunk, and whole body. However, muscle attenuation and subcutaneous fat thicknesses are superimposed on 2-dimensional views, and have mainly been quantified using cross-sectional 3-dimensional images generated by CT. In this study, our objective was to derive cross-sectional view measures of soft tissue from DXA using geometrical modeling. We focus our attention on three risk factors that have previously been shown to be independent hip fracture risk factors measured using either CT (cross-sectional thigh muscle area and muscle attenuation) or projection x-ray images (trochanteric soft tissue thickness). In addition, we investigated additional DXA measures of lean soft tissue mass, appendicular and leg lean masses. Our

hypothesis is that DXA estimates of mid-thigh muscle attenuation and cross sectional area, subcutaneous fat thickness will have a similar association to hip fractures as those derived directly from CT scans. We also compare these newly derived measures to the soft tissue measures already available from clinical DXA systems including appendicular lean and leg lean masses. Lastly, since previous reports have found that the range of lean tissue volumes and sizes in men and women often don't overlap, we have chosen to study these risk factors independently for men and women. With DXA already the preferred method for assessing BMD, adding these measures could improve fracture risk assessment without adding significant cost or X-ray exposure.

METHODS

We analyzed data from the Health, Aging and Body Composition study (Health ABC). Health ABC is an ongoing prospective cohort study of 3075 white and black men and women aged 70 to 79. Begun in 1997 and sponsored by the National Institute on Aging, Health ABC is designed to find the impact of changes in body composition and health conditions on age-related physiologic and functional status. The measures available from the study include a health assessment questionnaire, hip DXA scans, whole body DXA scans, and CT single slice scans of the mid-thigh. For comparability to previous CT results, our study design followed that of case-cohort study of Lang, et al (8). A complete description of the overall protocol and Health ABC study design can be found in (9–11). At baseline, each participant received numerous clinical evaluations including DXA whole body and proximal femur scans, and a CT scan of the mid-thigh. Strength testing was performed and an extensive health questionnaire was also filled out. The details of these procedures have been previously described (11–13).

Fracture assessment

Hip fractures were adjudicated (N = 169 over 13.5 years, 5.5% of population). Participants were asked about fractures every 6 months either during an in-person visit yearly or over the phone. Radiographic reports confirmed all reported hip fractures.

CT Imaging

The CT CSA and x-ray attenuation were estimated by the method described in (8) and references in it. In short, a single 10-mm thick axial image (120 kVp, 200 to 250 mA) of both thighs was obtained at the mid-femur. Intermuscular adipose tissue was segmented from subcutaneous fat by drawing contours along the visible edges between intermuscular adipose tissue and muscle tissue to remove intermuscular adipose pockets. Muscle attenuation was represented as the average Hounsfield units (HU) within the slice (11). Lower thigh muscle attenuation means greater fat infiltration (9). Previously reported inter scan precision was 0.51% at the midthigh and 0.85% for the midcalf (4).

DXA Imaging

Areal BMD (aBMD, g/cm^2) of the total hip was assessed by dedicated proximal femur DXA scans using Hologic QDR 4500A systems (Hologic, Inc., Bedford, MA) and software version 9.03. Soft tissue measures of the whole body and thighs were derived from the DXA

whole body scans. Total body and regional (arms, legs, and trunk) lean masses defined as soft tissue lean mass without bone mineral content were captured directly from the DXA system's standard analysis and report. The regional values of the arms and legs were delineated from the trunk with cut lines through the humeri and femur necks respectively using the recommendations of the International Society for Clinical Densitometry (14). Test-retest precisions for these standard lean mass measures were evaluated by the authors in a large sample of adults with duplicate scans, and was found to range between 1.7% (total appendicular) and 2.1% (arms) (15). Studies of the validity of fan-beam dual-energy X-ray absorptiometry for measuring fat-free mass and leg muscle mass have been previously performed (16). In our analysis we used three parameters provided by DXA system's release software: appendicular lean soft tissue mass (ALM), ALM normalized by dividing by squared height (ALM/Ht^2), and leg lean mass. All three are commonly used as an indicator of muscle mass. To derive muscle attenuation, CSA and subcutaneous fat thickness measures, the DXA whole body scans of participants were analyzed using the in-house UCSF DXA algorithm.

DXA mid-thigh analysis

The UCSF DXA algorithm was intended to estimate mid-thigh muscle attenuation, subcutaneous fat thickness and muscle CSA values after subtracting off the contributions from the overlaying subcutaneous fat. To accomplish this, a combination of composition based segmentation and creation of geometric model of the mid-thigh subcutaneous fat and muscle cross-sectional areas was used. The UCSF DXA algorithm is publically available for download by other researchers at http://radiology.ucsf.edu/research/labs/breast-bone-density/resources.

First,, thigh region of interest extended from the outside lateral edges of the left and right thighs in x direction and the superior point of the femur head as a top and the inferior points of the condyles as bottom in y direction were manually placed. Fig. 1a. demonstrate the image of this region of interest around the thighs. Then, the mid-thigh rectilinear region of interest was automatically placed centered on the midpoint between above mentioned points (shown by white arrow in the Fig. 1a). The region extended from the outside lateral edges of the left and right thighs (shown by horizontal line in the Fig. 1a). Within the total thigh region of interest, the ratios of the low and high-energy X-ray attenuations, commonly referred to as ratio values, were automatically calculated. The ratio value is related to the tissue composition (17). The ratio values of the total tissue were used to segment the pixels within the region of interest into four distinct tissue types (18) as follows: 1) muscle, subcutaneous fat, and bone; 2) muscle and subcutaneous fat; 3) subcutaneous fat alone; and 4) no tissue (air pixels). Threshold values were then estimated representing the skin edges, muscle/subcutaneous fat edges, and muscle/bone edges. The mid-thigh subcutaneous fat thicknesses were calculated as distances between skin edges and muscle/subcutaneous fat edges (Fig. 1b). We then created a cylindrical model of the subcutaneous fat with a lateral wall thickness equal to half the difference between the total thigh diameter and the segmented muscle diameter. The muscle CSA was defined as $\mathrm{CSA}=\frac{\pi}{4}(\mathrm{d}_{\mathrm{ID}}^2-\mathrm{d}_{\mathrm{bone}}^2)$ where d_{ID} = the inner diameter of the subcutaneous fat cylinder, and d_{bone} = the diameter of the

bone. DXA muscle attenuation was defined as the percent lean mass of the muscle mass after subtracting off the attenuation due to the overlaying subcutaneous adipose tissue. A correction factor was empirically created by comparing the DXA subcutaneous fat thickness (i.e. the subcutaneous fat cylinder thickness) to direct measures of the mid-thigh sagittal and coronal fat thicknesses from CT images on a subset of 270 randomly selected participants. The muscle attenuation ratio values were then calibrated to a two compartment model derived from phantoms made from plastic water (CIRS, Inc., Norfolk, VA) and machinable wax (McMaster Carr, Santa Fe Springs, CA). The calibration equations were derived by scanning the phantom multiple times with a variety of thicknesses and compositions as detailed elsewhere (19). To reduce measurement noise, our DXA-derived muscle attenuation was defined using the average of 4 lines perpendicular to the femur axis centered on the middle thigh. Thus, the mid-thigh ROI height covered 4 lines was approximately 5.2 cm and equal to heights of 4 pixels. One line height is equal to the height of one pixel (1.4 cm). It does not vary based on subject height/femur length. Thus, the region is explicitly reproducible. The placement of all the total and mid-thigh regions of interested were validated for all the patients by manually inspecting all the images. The final output of the UCSF DXA algorithm has four mid-thigh variables: muscle CSA, muscle attenuation, subcutaneous fat thickness, and total thigh (muscle plus subcutaneous fat) attenuation. **Error! Reference source not found.** shows a pair of DXA and CT scans from one participant with intermediate steps of the UCSF DXA algorithm. The line in the middle matches CT mid-thigh cross section.

Other covariates

We used the following covariates for adjustment in our models: age, race, clinical site, cognitive function, alcohol (never, former, current), smoking (never, former, current), education (<high school, high school, >high school), chronic disease, self-reported physical activity in the prior week, measured BMI, hip BMD, and self-reported health (poor, fair, good, very good, excellent). The chronic disease index consisted of 11 conditions: cancer, myocardial infarction, congestive heart failure, depression, diabetes, hypertension, knee osteoarthritis, osteoporosis, peripheral arterial disease, pulmonary disease, and gastrointestinal disease. The cognitive function was estimated with the Teng modified Mini-Mental Status Examination (20). The clinical site covariate is related to adjustment for the Memphis clinical site. The characteristics of men enrolled in Memphis and Pittsburgh differ and therefore, it's important to adjust for clinical site. The description of how the covariates were measured is detailed in (8).

Statistical Considerations

Statistical analyses were carried out using the SAS statistical analysis program (SAS Institute, Cary, NC, USA). Characteristics of participants were compared across quartiles of CT CSA and by hip fracture status: chi-square tests were used for categorical variables; t-scores and ANOVA were used for normally distributed continuous variables; and Mann-Whitney and Kruskall-Wallis tests were used for non-normally distributed continuous variables. Proportional hazards regression analyses was employed to determine the individual associations of derived DXA and CT measures with incident hip fracture. Our models included the following: unadjusted (Model 0), adjusted for age, race, and DXA

clinical site (Model 1), Model 1 with further adjustments for BMI, chronic disease, physical activity, self-reported health, and total hip BMD (Model 2), and Model 2 with further adjustments for alcohol use, smoking status, education, physical activity and cognitive function (Model 3). To estimate the joint effects of subcutaneous fat and ALM/Ht^2, we classified participants into eight groups: high ALM/Ht^2 and each of the four quartiles of subcutaneous fat; and low ALM/Ht^2 and each of the four quartiles of subcutaneous fat. High ALM/Ht^2 was defined as being in quartiles 3 or 4 of ALM/Ht^2; low ALM/Ht^2 was defined as being in quartiles 1 or 2 of ALM/Ht^2. We then estimated the risk of hip fracture across these eight mutually exclusive groups, with the low ALM/Ht^2/high subcutaneous fat group serving as the referent group.

RESULTS

Descriptive statistics of the total population by sex are shown in Table 1 by quartiles of CT CSA. There was little overlap between men and women for CT CSA with men having approximately 40% higher values on average. Only, the highest quartile for women and lowest quartile of CT CSA for men had values that overlapped. A similar lack of overlap in range of values by sex was true for all the DXA lean mass measures and Total Hip BMD. Participants in the higher sex-specific CT CSA quartiles tend to be younger, taller and have higher BMI and BMD than those in lower quartiles of CT CSA. Both CT and DXA mid-thigh muscle attenuations modestly varied by CT thigh muscle CSA quartiles. However, muscle attenuation became lower for larger muscle CSA when measured using CT, and higher for DXA for both men and women. Men had much lower subcutaneous fat thickness than women with no overlap in the range.

The modeling of the DXA subcutaneous fat thickness and shape was modeled with men and women combined. The CT sagittal subcutaneous fat thickness was correlated with coronal subcutaneous fat thickness with correlation coefficient $r = 0.91$ ($p < 0.001$). DXA and CT CSA measures demonstrated a high correlation as well with $r = 0.82$ ($p < 0.001$). The DXA subcutaneous fat thickness was highly correlated to the CT coronal subcutaneous fat thickness with $r = 0.94$ ($p < 0.001$). CT and DXA thigh muscle attenuations showed weak and moderate correlations to the coronal subcutaneous fat thickness, $r = 0.23$ and 0.41 respectively. The low correlation of DXA muscle attenuation and subcutaneous fat thickness suggests that the deformed cylindrical model had sufficiently corrected the overlaying effects of subcutaneous fat, given that the DXA thigh total attenuation measure was highly correlated ($r = 0.84$) to subcutaneous fat thickness. However, the correlation between CT and DXA thigh muscle attenuations was only $r = 0.5$. DXA CSA was highly correlated to ALM and leg lean mass, $r = 0.78$ and 0.75 respectively.

Details of the DXA and CT thigh measures by fracture status are shown in Table 2. Those with fractures were older and more likely to be women so consequently also more likely to be shorter, to weigh less, and have lower BMI, lower total hip BMD, and lower fat mass although percent body fat did not differ by fracture status. However, once separated by sex, only being older, white, low subcutaneous fat thickness, and low total hip BMD were statistically associated with fracture status for both men and women. Women with hip fractures, but not men, also had lower weight, BMI, total body fat mass and %fat, and lean

mass no matter if expressed as ALM, ALM/Ht^2, or leg lean. There were no risk factors found in men that were not present in women. Note that Table 1 was restricted to those with CT data (3011 patients) while Table 2 is in all participants (3075 patients).

Table 3 demonstrates the results of proportional hazard regression analyses of men and women estimating adjusted hazard ratios for hip fracture per SD decrease (95% Confidence Interval) of DXA and CT measures for different model adjustments. Of the variables studied, only DXA subcutaneous fat thickness was significant in all models for men and women. For either men or women, there is approximately a 4% increase in fracture risk for every 1-mm decrease in mid-thigh subcutaneous fat. Furthermore, the HR of subcutaneous fat thickness was only slightly attenuated in the fully adjusted models compared to the unadjusted model. CT thigh muscle attenuation was significant in all models for men but in no model for women. However, DXA thigh muscle attenuation was not significant in any of the adjusted models. All DXA lean mass measures had similar associations to fracture risk that differed by sex. In men, decreased DXA lean measures were protective of hip fractures in the more fully-adjusted models 2 and 3. In women, decrease in lean mass measures increased fracture risk but only in models 0 and 1. After more adjustments (model 2 and 3), lean mass was no long significant. The variable adjustment that most changed the risk association of the lean mass measures in models 2 and 3 was hip BMD (analysis not shown). In summary, we found that our estimates of CT measures using DXA were not equivalent in their relationships to fracture risk in men and women.

When both ALM/Ht^2 and subcutaneous fat were included with all other risk factors (model 3) both remained significant for men (higher DXA ALM/Ht^2 = greater fracture risk and lower DXA subcutaneous fat thickness = greater fracture risk). However, this was not true for women. Model 3 with subcutaneous fat thickness did not improve when ALM/Ht^2 was also included. See Figure 2. Men with a high ALM/Ht^2 and low subcutaneous fat thickness had over 8 times higher risk for hip fracture compared to those with low ALM/Ht^2 and high subcutaneous fat in fully adjusted models.

DISCUSSION

In this study that included 169 hip fractures over an average of 13.5 years among participants from the Health ABC Study, we found that muscle attenuation, measured using CT slices of the mid-thigh, was a strong risk factor for hip fracture in men but not in women. However, muscle attenuation measure derived from 2D DXA images was not associated to fracture risk for either men or women. To our knowledge, this study was the first to derive mid-thigh muscle attenuation from DXA. Overall, in fully adjusted models, low CT thigh muscle attenuation, low DXA subcutaneous fat thickness, and high appendicular lean mass were associated with increased fracture risk in men. In women, only increased DXA CSA and decreased subcutaneous fat thickness were associated with increased fracture risk in fully-adjusted models.

Our goal was to derive mid-thigh muscle attenuation and CSA values from DXA scans that would be analogous their CT counterparts. We were able to successfully subtract off the effects of subcutaneous fat on muscle attenuation as evidenced by their lack of correlation.

However, we were unable to remove the effects of intermuscular fat from the DXA muscle attenuation. The CT measure explicitly removed the marbled characteristics of intermuscular fat from between the muscle bundles using simple thresholding techniques only possible with 3D imaging. Of interest, CT muscle attenuation was not a significant risk factor for women. The average values of muscle attenuation in women were lower than in men but the ranges did overlap. An earlier analysis in the same cohort (2008 versus 2014) with fewer hip fractures (63 versus 169) and where men and women were included in the same model found a HR of 1.35 (0.99 – 1.83) per SD decrease of CT muscle attenuation. We now see that with more fractures, we can isolate the men and women and find that the HR to be 1.40 (1.05 – 1.85) for men and no significant association for women. It may be that the range of muscle density is too narrow in older women to be predictive of hip fracture. Frank et al. (21) found that Community-dwelling female fallers have lower muscle density in their lower legs than non-fallers. However, in their study, there was no difference in CSA while in our study the women with fractures had a significantly smaller (approximately 10%) CSA. The Franke et al. study was too small (n=147 total) to look at hip fractures as an outcome and didn't adjust for hip BMD. Thus, there may be something unique between fracture risk and fall risk regarding muscle density, bone density, and muscle size.

Lower DXA subcutaneous fat thickness was associated with increased hip fracture risk in adjusted models, consistent with trends seen in other studies. Bouxsein et al. (7) found a 1.8 fold increase of hip fracture for every 17-mm decrease of trochanteric soft tissue thickness, or in other words, a 5% increase in fracture risk for every mm decrease of trochanteric soft tissue. Our result was very similar with a 4% increase in fracture risk for every 1-mm decrease in mid-thigh subcutaneous fat. Trochanteric soft tissue and mid-thigh subcutaneous fat thickness should be highly correlated since they are near each other, but we did not perform that analysis. Robinovitch et al. (22) found that the peak force applied to the hip was reduced at a rate of approximately 70 N per 1-mm increase in trochanteric soft tissue thickness. Interestingly, the odds ratios decreased (1.82 to 1.44) and were no longer statistically significant in the Bouxsein study after adjustment for hip BMD. In our study, the odds ratio was attenuated after similar adjustment but remained highly significant. This could be due to the increased statistical power of our study due to the higher number of fractures (169 fractures) versus 21 fractures in the Bouxsein study.

An unexpected result was how high appendicular lean mass was associated with high fracture risk in men in the models that included hip BMD but not in women. This is counterintuitive since appendicular lean mass was on average lower, not higher, in women that fractured, and there was no difference on average in men by fracture status. The adjustment of hip BMD reversed the anticipated trends for lean mass by sex seen in Table 2. More massive thigh muscles deliver larger loads on the hip than smaller muscles. This seems to be counteracting the decreased resistance to falling offered by the larger muscles. Reversals of fracture risk association (risk to protective) have been seen in BMI as well (23). When BMD was held constant in men, high BMI was associated with an increased risk of fracture while when BMD is not held constant, high BMI is protective. We also investigated if our analysis of appendicular lean mass violated the positivity assumption (24). The positivity assumption, or experimental treatment assignment assumption, requires that there be both exposed and unexposed participants at every combination of the values of the

observed confounders in the population under study. Because of the wide range of appendicular lean mass, the lowest quartiles of appendicular lean mass were only women, a clear violation. To address this, we performed separate analysis for men and women with their own appendicular lean mass ranges. However, our results were the same in both cases; decreased appendicular lean mass was protective in the fully adjusted models whether we performed mixed or single sex analysis. Other methods (such as use of propensity score matching (25) to control for confounding variables) could be employed to evaluate the potential impact of violations of this assumption. As we wanted to consider the individual effects of the covariates we did not apply this method.

Other studies have compared CT muscle CSA to DXA lean mass (16,26,27). Hansen et al. (26) compared the lean soft tissue mass at the mid-thigh to CT CSA. They found the two highly correlated with r = 0.85. Visser et al. (16) and Levine et al. (27) also found that CT CSA was highly correlated to DXA lean mass in either a small subregion at the mid-thigh (16) or the total thigh (27). In our hands, DXA appendicular lean mass was more strongly associated with fracture status in fully adjusted models than CT CSA.

There were limitations to our study. We modeled the muscle as a simple deformed cylinder. By observation of CT images, we know that the true shape of muscle cross sections can be very complex. It may be that a more sophisticated shape model may better estimate the muscle and fat parameters. Secondly, we could not isolate intermuscular fat for DXA muscle attenuation. Future research may identify a way to model the intermuscular fat that may improve our DXA muscle attenuation measure. Furthermore, we used single slices from CT that are prone to reconstruction artifacts and noise. Averaging sequential CT slices may further improve the CT results and provide a better standard for comparison. Lastly, our results were observed in a population with too few fractures to explore ethnic differences and were non-disabled and thus our ability to extend these findings to other populations may be limited.

We found that both DXA subcutaneous fat thickness in both men and women, and ALM/Ht^2 in men are significant contributors to fracture risk in a fully adjusted model. Adjusted hazard ratios for hip fracture per SD decrease (95% Confidence Intervals) in subcutaneous fat were 1.4 for both men and women, and 0.58 (0.36, 0.91) for ALM/Ht^2 for men.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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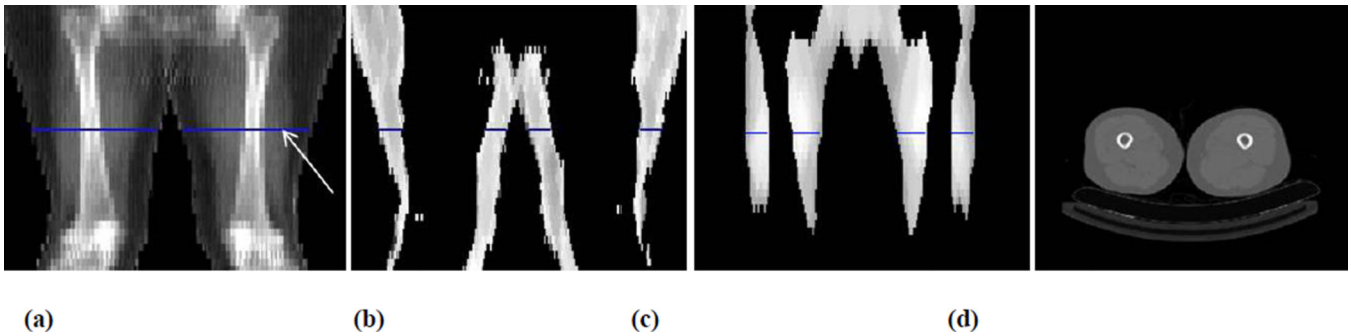
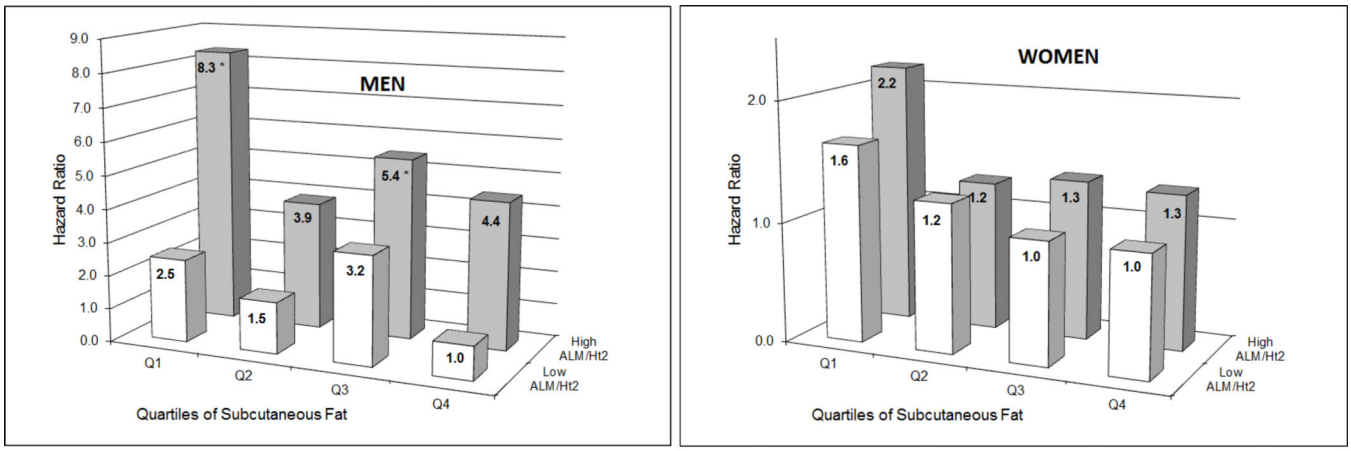


Figure 1.

Image example of thigh DXA analysis compared to CT. (a) Thigh section of total body image showing the grey scale proportional to a custom tissue density map where 0% lean is defined using a wax reference and 100% lean as water; (b) Segmented thigh subcutaneous fat region and its grey scale variation; (c) Segmented thigh muscle values after exclusion of overlaying subcutaneous fat. Blue line shows the center line of the DXA ROI matching CT slice (pointed by arrow); in our analysis the DXA ROI (height=5.2 cm) consists of 4 pixel/lines (d) CT tomography of same participant at the mid-thigh with grey scale shown in HU.



(a) **(b)**

Figure 2.

Combine effect of appendicular lean mass divided by height squared and subcutaneous fat thickness on fracture risk for men (a) and women (b). The model is equivalent to Model 3 (adjustments for age, race, clinical site, chronic disease, physical activity, self-reported health, BMI, hip BMD, cognitive function, alcohol, smoking and education) in Table 3 with both ALM/Ht2 and subcutaneous fat included. * = $p < 0.05$ compared to referent group (low ALM/Ht2 and Q4 subcutaneous fat group). Low ALM/Ht2 is ALM/Ht2 quartiles 1 and 2; high ALM/Ht2 is ALM/Ht2 quartiles 3 and 4;

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Table 1

Characteristics of the Health, Aging, and Body Composition Study Population by sex and quartiles of CT thigh muscle cross-sectional area.

	Quartiles of CT thigh muscle cross-sectional area (cm^2), mean (standard deviation)							
	Men				**Women**			
Quartile (number)	QT1 (364)	QT2 (365)	QT3 (365)	QT4 (365)	QT1 (388)	QT2 (388)	QT3 (388)	QT4 (388)
Age	74.5 (2.8)	73.9 (2.9)	73.6 (2.9)	72.9 (2.7)**	74 (2.9)	73.9 (3)	73.5 (2.8)	72.6 (2.6)**
White race, number (%)	268 (73.6)	259 (71)	232 (63.6)	159 (43.6)**	308 (79.4)	269 (69.3)	195 (50.3)	72 (18.6)**
Height (cm)	171 (6.3)	173 (6.5)	173 (6.6)	175 (6.6)**	159 (6.2)	159 (6.2)	159.6 (5.8)	161 (6.1)**
Weight (kg)	70.3 (9.3)	78.2 (8.53)	84 (10.5)	92.7 (12.4)**	58.2 (9.5)	66.7 (9.6)	72.9 (10.5)	83.4 (14)**
BMI (kg/m^2)	24 (3.01)	26.1 (2.7)	27.9 (3.2)	30.3 (3.6)**	23.2 (3.7)	26.4 (3.8)	28.7 (4.3)	32.2 (5.1)**
Total percent fat	28.3 (5.5)	29.2 (4.8)	29.4 (4.9)	29.9 (4.7)**	38.3 (6.1)	40.4 (5.6)	41 (5.4)	42 (5.3)**
Alcohol consumption								**
No consumption in past year	141 (39.2)	149 (41.2)	159 (43.8)	168 (46.2)	202 (52.2)	204 (52.6)	230 (59.4)	254 (65.5)
Less than once per week	67 (18.6)	75 (20.7)	73 (20.11)	70 (19.2)	86 (22.2)	89 (22.9)	86 (22.2)	79 (20.4)
1 – 7 times per week	99 (27.5)	97 (26.8)	102 (28.1)	84 (23.1)	79 (20.4)	79 (20.4)	66 (17.1)	40 (10.3)
More than 1 per day	53 (14.7)	41 (11.3)	29 (8)	42 (11.5)	20 (5.2)	16 (4.1)	5 (1.3)	15 (3.9)
Smoking status				*				**
Never	98 (27.1)	100 (27.5)	117 (32.1)	118 (32.3)	224 (57.7)	231 (59.7)	216 (55.7)	222 (57.4)
Current	56 (15.5)	34 (9.3)	41 (11.2)	27 (7.4)	56 (14.4)	42 (10.9)	23 (5.9)	30 (7.8)
Former	208 (57.5)	230 (63.2)	207 (56.7)	220 (60.3)	108 (27.8)	114 (29.5)	149 (38.4)	135 (34.9)
Completed years of education								**

	Quartiles of CT thigh muscle cross-sectional area (cm^2), mean (standard deviation)							
	Men				Women			
Less than High School	88 (24.2)	88 (24.1)	110 (30.2)	111 (30.5)	59 (15.2)	72 (18.7)	105 (27.3)	120 (31)
High School graduate	93 (25.6)	98 (26.9)	94 (25.8)	88 (24.2)	151 (38.9)	150 (38.9)	155 (40.3)	155 (40.1)
Postsecondary	183 (50.3)	179 (49)	160 (44)	165 (45.3)	178 (45.9)	164 (42.5)	125 (32.5)	112 (28.9)
Total hip BMD (g/cm^2)	0.88 (0.15)	0.95 (0.13)	0.99 (0.14)	1.1 (0.14) **	0.71 (0.13)	0.78 (0.12)	0.83 (0.12)	0.9 (0.14) **
Fair or Poor Self Rated Health	76 (20.9)	44 (12.1)	55 (15.1)	61 (16.7) *	38 (9.8)	54 (14)	58 (15)	88 (22.8) **
Has a Chronic Disease *	259 (71.2)	244 (66.9)	256 (70.1)	248 (68)	258 (66.5)	271 (69.9)	265 (68.3)	302 (77.8) *
CT CSA (cm^2)	105 (9.8)	123 (4)	137 (4.3)	160 (14) **	71.7 (6.5)	85.7 (3.3)	97.2 (3.5)	115 (9.7) **
CT thigh Muscle Attenuation (HU)	38.4 (7)	37.6 (6.5)	37.1 (6.1)	35.9 (5.8) **	35.6 (6.9)	34.1 (6.3)	33.3 (7.2)	31.6 (6.9) **
DXA CSA (cm^2)	153 (36.3)	175 (33.2)	189 (34.5)	214 (38.2) **	71.8 (19.8)	83 (18.4)	96.7 (19.2)	115 (22.2) **
DXA thigh total attenuation (%lean)	77.1 (4.4)	77.2 (3.7)	78 (3.6)	78.5 (3.3) **	70 (3.9)	70.4 (3.3)	70.7 (3.4)	71.7 (3.7) **
DXA Subcutaneous fat thickness (cm)	1.3 (1.1)	1.5 (1.1)	1.5 (1.1)	1.8 (1.1) **	4.6 (2)	5.1 (1.8)	5.2 (1.9)	5.4 (1.8) **
DXA thigh muscle attenuation (%lean)	82.1 (3.8)	82.8 (3.2)	83.7 (3)	84.8 (2.9) **	81.9 (3.4)	83.2 (3.2)	83.5 (3.3)	84.8 (3.4) **
DXA ALM (kg)	20.3 (2.2)	22.8 (2)	24.7 (2.1)	27.8 (2.9) **	13.6 (1.7)	15.4 (1.6)	17.2 (1.8)	20 (2.7) **
DXA leg lean (kg)	14.7 (1.6)	16.4 (1.4)	17.7 (1.5)	20 (2.1) **	10.3 (1.4)	11.7 (1.3)	13 (1.5)	15.1 (2.1) **
ALM/Ht^2 (kg/m^2)	6.9 (0.6)	7.6 (0.5)	8.2 (0.5)	9.1 (0.8) **	5.4 (0.7)	6.1 (0.5)	6.8 (0.7)	7.7 (0.9) **

Note: Chronic diseases included 11 chronic health conditions using self-report with confirmation by treatment and medications (cancer, myocardial infarction, congestive heart failure, depression, diabetes, hypertension, knee osteoarthritis, osteoporosis, peripheral arterial disease, pulmonary disease, and gastrointestinal disease) (11).

Statistical significance levels:

* *p-value* < 0.05;

** *p-value* < 0.001.

Abbreviations: BMD=bone mineral density, DXA=dual-energy X-ray absorptiometry, ALM= appendicular lean mass, CT= computed tomography, CSA= cross sectional area, ALM/Ht^2= ALM divided by height squared.

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Table 2

Characteristics of the study population with key measures. The mean (+/− standard deviation) is shown for the Fracture versus No Fracture groups for men and women separately*.

	Men			Women		
VARIABLE	**No Fracture**	**Hip Fracture**	**P value**	**No Fracture**	**Hip Fracture**	**P value**
Number	1427	64		1479	105	
Age at Year 1 Clinic Visit (years)	73.7+/−2.9	74.8+/−2.8	0.004	73.4 +/− 2.8	74.9 +/− 2.9	<.001
White race, number (%)	889 (62.3)	50 (78.1)	0.010	778 (52.6)	77 (73.3)	<.001
Height, cm	173.3+/−6.6	172.8+/−6	0.49	159.6	159.6	0.970
Weight (kg)	81.5+/−13.3	79.8+/−11.7	0.26	71.0 +/− 14.7	63.8 +/− 12.8	<.001
BMI, kg/m^2	27.1+/−4	26.7+/−3.4	0.36	27.9 +/− 5.5	25.0 +/− 4.9	<.001
Total Body Fat Mass (kg)	24.2+/−7.2	23.2+/−5.8	0.17	29.5 +/− 9.4	25.0 +/− 8.1	<.001
Total Body %Fat	29.2+/−5	28.6+/−4.2	0.27	40.6 +/− 5.7	38.3 +/− 6.2	<.001
DXA CSA (cm^2)	182.8+/−41.8	180.9+/−46.8	0.73	92.2 +/− 25.6	87.2 +/− 29	0.053
DXA thigh total attenuation (%lean)	77.7+/−3.8	77.8+/−4.1	0.76	70.6 +/− 3.6	71.2 +/− 3.8	0.137
DXA subcutaneous fat thickness (cm)	1.54+/−1.08	1.27+/−0.87	0.017	5.16 +/− 1.93	4.332 +/− 1.85	<.001
DXA thigh muscle attenuation (%lean)	83.3+/−3.4	82.9+/−3.8	0.34	83.4 +/− 3.5	82.5 +/− 3.8	0.019
CT CSA (cm^2)	131.6+/−22	128.8+/−22.3	0.33	93.1 +/− 17.1	83.2 +/− 15.6	<.001
CT thigh muscle attenuation (HU)	37.3+/−6.4	35.8+/−6.7	0.07	33.6 +/− 6.9	34.1 +/− 7.7	0.455
Total hip BMD (g/cm^2)	0.98+/−0.15	0.83+/−0.12	<.001	0.817 +/−0.144	0.68 +/− 0.13	<.001
DXA ALM (kg)	23.9+/−3.6	23.7+/−3.6	0.66	16.7 +/− 3.2	15.3 +/− 2.8	<.001
DXA leg lean (kg)	17.2+/−2.6	17.2+/−2.7	0.94	12.7 +/− 2.5	11.5 +/− 2.17	<.001
DXA ALM/Ht^2 (kg/m^2)	8+/−1	7.9+/−1	0.82	6.56 +/− 1.13	6.00+/− 1.03	<.001

Abbreviations: BMD=bone mineral density, DXA=dual-energy X-ray absorptiometry, ALM= appendicular lean mass, CT= computed tomography, CSA= cross sectional area, ALM/Ht^2= ALM divided by height squared.

Table 3

Proportional hazard regression analyses estimating hazard ratios (HR) and 95% confidence intervals for hip fracture per SD decrease in various DXA and CT parameters. Significant associations ($p<0.05$) are bolded.

Variable (men)	SD	MODEL 0	MODEL 1	MODEL 2	MODEL 3
CT thigh muscle attenuation (HU) *	6.42	**1.34 (1.04, 1.71)**	**1.28 (1.01, 1.64)**	**1.42 (1.07, 1.89)**	**1.40 (1.05, 1.85)**
CT CSA (cm^2) *	22.1	1.24 (0.95, 1.61)	1.05 (0.79, 1.41)	0.72 (0.50, 1.04)	0.75 (0.52, 1.10)
DXA thigh muscle attenuation (%lean)	6.46	1.20 (0.93, 1.55)	1.07 (0.81, 1.40)	0.96 (0.72, 1.28)	0.98 (0.74, 1.30)
DXA CSA (cm^2)	631.2	1.05 (0.82, 1.35)	0.95 (0.73, 1.23)	0.82 (0.63, 1.06)	0.86 (0.66, 1.11)
DXA thigh total attenuation (%lean)	3.82	0.98 (0.75, 1.26)	0.90 (0.69, 1.17)	0.80 (0.60, 1.06)	0.85 (0.65, 1.12)
DXA subcutaneous fat thickness (cm)	3.79	**1.39 (1.04, 1.86)**	**1.36 (1.01, 1.83)**	**1.50 (1.07, 2.09)**	**1.44 (1.02, 2.02)**
DXA ALM (kg) *	3.60	1.09 (0.85, 1.40)	0.95 (0.72, 1.25)	**0.64 (0.45, 0.89)**	**0.65 (0.46, 0.92)**
DXA leg lean mass (kg) *	2.60	1.04 (0.81, 1.34)	0.92 (0.70, 1.20)	**0.65 (0.47, 0.89)**	**0.67 (0.49, 0.93)**
DXA ALM/Ht^2 (kg/m^2) *	1.02	1.07 (0.83, 1.37)	0.90 (0.68, 1.20)	**0.57 (0.36, 0.89)**	**0.58 (0.36, 0.91)**
Variable (women)	**SD**	**MODEL 0**	**MODEL 1**	**MODEL 2**	**MODEL 3**
CT thigh muscle attenuation (HU) *	6.98	0.96 (0.79, 1.17)	0.95 (0.77, 1.16)	1.12 (0.88, 1.43)	1.08 (0.85, 1.38)
CT CSA (cm^2) *	17.15	**1.92 (1.54, 2.40)**	**1.66 (1.29, 2.14)**	0.96 (0.69, 1.33)	0.94 (0.68, 1.32)
DXA thigh muscle attenuation (%lean)	11.63	**1.28 (1.07, 1.54)**	1.16 (0.96, 1.41)	1.02 (0.84, 1.25)	1.03 (0.84, 1.26)
DXA CSA (cm^2)	387.5	1.22 (0.99, 1.51)	0.95 (0.75, 1.19)	**0.77 (0.62, 0.96)**	**0.78 (0.62, 0.97)**
DXA thigh total attenuation (%lean)	3.63	0.87 (0.72, 1.06)	0.80 (0.65, 0.97)	0.82 (0.65, 1.02)	0.83 (0.66, 1.05)
DXA subcutaneous fat thickness (cm)	3.50	**1.60 (1.31, 1.95)**	**1.54 (1.26, 1.89)**	**1.42 (1.09, 1.84)**	**1.39 (1.07, 1.82)**
DXA ALM (kg) *	3.16	**1.69 (1.34, 2.12)**	**1.40 (1.08, 1.81)**	0.76 (0.53, 1.08)	0.76 (0.53, 1.08)
DXA Leg Lean Mass (kg) *	2.45	**1.71 (1.36, 2.16)**	**1.43 (1.11, 1.84)**	0.81 (0.57, 1.15)	0.80 (0.56, 1.14)
DXA ALM/Ht^2 (kg/m^2) *	1.14	**1.80 (1.42, 2.27)**	**1.56 (1.19, 2.03)**	1.00 (0.64, 1.55)	1.04 (0.66, 1.63)

Each predictor was included in a separate model.

Model 0: unadjusted, Model 1 adjustments: age, race, clinical site, Model 2 adjustments: model 1 plus BMI, chronic disease, hip BMD, self-reported health, Model 3 adjustments: model 2 + alcohol use, smoking status, education, physical activity and cognitive function.

* p for interaction with gender <0.05 – specific p value for interaction: CT thigh muscle attenuation, p=0.040; CT CSA p=0.001, DXA ALM p = 0.006; DXA leg lean mass p = 0.003; ALM/Ht^2 p=0.006.

Abbreviations: BMD=bone mineral density, DXA=dual-energy X-ray absorptiometry, ALM= appendicular lean mass, CT= computed tomography, CSA= cross sectional area, ALM/Ht^2= ALM divided by height squared.