Title

Sex differences in the spatial distribution of bone in relation to incident hip fracture: Findings from the AGES-Reykjavik study

Authors

Marques, Elisa A
Carballido-Gamio, Julio
Gudnason, Vilmundur
et al.

Publication Date

2018-09-01

DOI

10.1016/j.bone.2018.05.016

Peer reviewed

HHS Public Access

Author manuscript

Bone. Author manuscript; available in PMC 2019 September 01.

Published in final edited form as:

Bone. 2018 September ; 114: 72–80. doi:10.1016/j.bone.2018.05.016.

Sex differences in the spatial distribution of bone in relation to incident hip fracture: Findings from the AGES-Reykjavik study

Elisa A. Marques[a,*], **Julio Carballido-Gamio**[b], **Vilmundur Gudnason**[c,d], **Gunnar Sigurdsson**[c,d,e], **Sigurdur Sigurdsson**[c], **Thor Aspelund**[c,f], **Kristin Siggeirsdottir**[b], **Lenore Launer**[a], **Gudny Eiriksdottir**[c], **Thomas Lang**[g], and **Tamara B. Harris**[a]

[a]National Institute on Aging, Intramural Research Program, Laboratory of Epidemiology and Population Sciences, Bethesda, MD, USA [b]Department of Radiology, School of Medicine, University of Colorado Denver, Denver, CO, USA [c]Icelandic Heart Association Research Institute, Kópavogur, Iceland [d]University of Iceland, Reykjavik, Iceland [e]Landspitalinn University Hospital, Reykjavik, Iceland [f]Centre of Public Health Sciences, University of Iceland, Reykjavik, Iceland [g]Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA, USA

Abstract

In this case-cohort study, we used data-driven computational anatomy approaches to assess within and between sex spatial differences in proximal femoral bone characteristics in relation to incident hip fracture. One hundred male and 234 female incident hip fracture cases, and 1047 randomly selected noncase subcohort participants (562 female) were chosen from the population-based AGES-Reykjavik study (mean age of 77 years). The baseline –i.e. before hip fracture– hip quantitative computed tomography scans of these subjects were analyzed using voxel-based morphometry, tensor-based morphometry, and surface-based statistical parametric mapping to assess the spatial distribution of volumetric bone mineral density (vBMD), internal structure, and cortical bone properties (thickness, vBMD and trabecular vBMD adjacent to the endosteal surface) of the proximal femur, respectively, in relation to incident hip fracture. Results showed that in both men and women: 1) the superior aspect of the femoral neck and the trochanteric region (except for cortical bone thickness) were consistently identified as being associated with incident hip fracture, and 2) differences in bone properties between noncases and incident hip fracture cases followed similar trends, were located at compatible regions, and manifested heterogeneity in the spatial distribution of their magnitude with focal regions showing larger differences. With respect to sex differences, most of the regions with a significant interaction between fracture group and sex showed: 1) differences of greater magnitude in men between noncases and incident hip fracture cases with different spatial distributions for all bone properties with the exception of cortical bone thickness, and 2) that while most of these regions showed better bone quality in male cases than in

*Corresponding author at: National Institute on Aging, National Institutes of Health, 7201 Wisconsin Avenue, Gateway Building, Suite 2N300, Bethesda, MD 20892-9205, USA. emarques@ismai.pt (E.A. Marques).

Disclosures

All authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2018.05.016.

female cases, female cases showed higher vBMD in the principal compressive group and higher endotrabecular vBMD at several regions including the anterior, posterior, and lateral aspects of the proximal femur. These findings indicate the value of these image analysis techniques by providing unique information about the specific patterns of bone deterioration associated with incident hip fracture and their sex differences, highlighting the importance of looking to men and women separately in the assessment of hip fracture risk.

Keywords

Bone; Quantitative computed tomography (QCT); Bone mineral density (BMD); Cortical bone thickness; Voxel-based morphometry (VBM); Statistical parametric mapping (SPM); Tensor-based morphometry (TBM)

1. Introduction

Bone mechanical competence is determined by its size and shape and by the spatial distribution, organization and intrinsic properties of bone tissue [1,2]. Prior in vivo proximal femur computational anatomy studies have been performed with quantitative computed tomography (QCT) to understand focal differences in bone properties in relation to many factors, including the etiology of fracture risk [3–8], osteoporosis treatment [9–11], the effects of age [4,5], and exercise [12,13]. However, to further understand the structural basis of hip fracture risk and its differences between men and women, more in-depth analyses are needed.

Although focal and structural weaknesses have recently been linked to hip fracture [5,8,14–16], focal variations in bone structure have not yet been described across gender. Previous computational anatomy approaches have utilized data gathered mostly from cohorts composed only of women [4–8]. So far, only two studies investigated older men, using case-cohort samples selected from the MrOS study [3,17]. No comparisons across gender have been published.

To address this gap in knowledge, we used QCT scans of the proximal femur of older men and women from the well-described population-based AGES-Reykjavik study. The spatial distribution of bone was analyzed using three image-based computational anatomy approaches: (i) voxel-based morphometry (VBM) to assess volumetric bone mineral density (vBMD) maps, (ii) tensor-based morphometry (TBM) to assess structure, and (ii) statistical parametric mapping (SPM) to assess cortical bone feature maps.

Specifically, we aimed to compare at baseline noncases versus incident hip fracture cases within each sex, and to examine if the effect of fracture group on the spatial distribution of vBMD, internal structure, and cortical bone thickness, cortical bone vBMD, and trabecular vBMD in a layer adjacent to the endosteal surface (endotrabecular vBMD) differed by sex.

In this case-cohort study, bone properties were compared between 485 male noncases and 100 male incident hip fracture cases, and between 562 female noncases and 234 female incident hip fracture cases. Previous case-control studies within gender were limited to a

smaller number of participants and bone features. We hypothesized that fracture cases and noncases would diverge in their spatial distribution of vBMD, structure and cortical bone properties and that these patterns would be different for men and women. By using the data-driven multi-parametric bone assessments mentioned above we will be able to perform a bias-free identification and visualization of differences associated with incident hip fracture throughout the proximal femur, in contrast with the conventional averaging of tissue features over predefined regions of interest [4–8,17]. From the point of view of hip fracture treatment and prevention, gender differences in these parametric maps between noncases and cases might lead to differences in how to monitor bone or target bone strength interventions with a focus on different spatial regions.

2. Methods

2.1. Study design and participants

Individuals were participants in the Age, Gene/Environment Susceptibility (AGES) - Reykjavik Study, a single-center prospective population study of Icelandic men and women. Design and recruitment have been previously described in detail [18]. Our analytical sample included a final subcohort of 1047 noncase subjects and 334 incident hip fracture cases. A complete description of the number of participants (supplemental Fig. 1), criteria for inclusion in this case-cohort study, and assessments of covariates are reported in Supplemental Data. Written informed consent was obtained from all participants, and the study was approved by the Icelandic National Bioethics Committee (VSN: 00-063), the Institutional Review Board of the Intramural Research Program of the National Institute of Aging, and the participating Universities.

2.2. Image acquisition

Bilateral hip QCT images of all subjects were acquired at baseline before incidence of hip fracture using a four-detector CT system (Sensation, Siemens Medical Systems, Erlangen, Germany) and a solid QCT calibration phantom (Image Analysis, Inc., Columbia, KY, USA) containing cells of 0, 75, and 150 mg/cm^3 equivalent concentrations of calcium hydroxyapatite. The scans extended from 10mm superior to the superior aspect of the femoral head to 5mm inferior to the inferior aspect of the lesser trochanter of the hips. Images were reconstructed to an in-plane voxel size of 0.98 × 0.98 mm^2 and a slice thickness of 1mm.

2.3. Image processing

QCT images were de-identified, and CT Hounsfield Units were converted to equivalent concentrations of calcium hydroxyapatite using the calibration phantom. Images were then processed using the automatic pipeline described by Carballido-Gamio et al. [19]. The pipeline automatically segmented the left proximal femora and yielded voxel-based maps of vBMD, and surface-based maps of cortical bone thickness, cortical vBMD, and endotrabecular vBMD. The quality of the segmentations was visually assessed on a subject-by-subject basis and manually corrected if necessary.

Calibrated images were prepared for VBM as previously described [4]. Briefly, voxel-based maps of vBMD were spatially normalized to a common femoral template based on affine and nonlinear registrations of the segmented femora, thus bringing corresponding anatomical regions across the population into alignment. Gaussian smoothing was then applied to the spatially-normalized vBMD maps yielding them suitable for voxel-wise comparisons with VBM.

To perform TBM, images were spatially normalized to the femoral template also using affine and nonlinear registrations. However, as previously described by Carballido-Gamio et al. [5], registrations were based on both femoral segmentations and actual gray-level values within the proximal femur. The logs of the voxel-based representations of local contractions and expansions (determinants of the Jacobian matrices of the deformations) that were needed to match the structure of the template to that of each subject in the population were then smoothed with a Gaussian filter before voxel-wise comparisons.

The VBM registrations were also used to spatially normalize the surface-based maps of cortical bone properties to the triangulated surface of the femoral template. As with VBM and TBM, maps of cortical bone thickness, cortical vBMD, and endotrabecular vBMD were smoothed before vertex-wise comparisons with SPM.

2.4. Statistical analysis

2.4.1. Study population and compartmental vBMD and cortical bone thickness—

Mean ± standard deviation (SD) or percentages for categorical variables were used to summarize the characteristics of the participants, and comparisons between cases and noncases within sex were assessed by the Mann-Whitney U test for continuous variables and by the chi-squared test for categorical data. The main effect of sex and fracture status, and the combined effect of sex and fracture status (interaction term) on four integral vBMD (cortical and trabecular) measures (total hip, head, neck and trochanter) and two measures of cortical bone thickness (neck and trochanter) were evaluated using multivariate linear regression. Age, height, weight, and use of bone-altering medications were included as covariates. Estimated marginal means ± standard errors (SE) were calculated using the General Linear Model procedure. Significance testing was two-sided and based on a 5% probability level. Statistical analyses were conducted using SPSS software, version 22.0 (IBM, USA).

2.4.2. VBM, TBM, and SPM—

VBM, TBM, and SPM of cortical bone properties followed a similar plan of statistical comparisons: 1) noncases vs. cases in men, 2) noncases vs. cases in women, and 3) combined effect (interaction) of gender (men, women) and fracture status (control, case). The aim of the first two analyses was the identification of significant spatial differences in bone properties between noncases and cases within each gender, while the aim of the third analysis was to investigate significant sex differences in the spatial distribution of differences in bone properties between noncases and cases. For the within gender comparisons, voxel/vertex-wise general linear models were evaluated where at each voxel/vertex the bone feature (vBMD, structure, cortical bone thickness, cortical vBMD, or endotrabecular vBMD) was used as the dependent variable, group membership

(control or case) as the independent variable, and age, height, weight, use of bone medications (yes or no) and the first 5 principal scores of shape [17,20] as covariates. In the third analysis, voxel/vertex-wise general linear models were evaluated where at each voxel/vertex the bone feature was used as the dependent variable, and the model included terms for fracture status (control or case), age, height, weight, use of bone medications (yes or no), 5 principal scores of shape, sex (male or female), and sex * fracture status (interaction). False discovery rate (FDR) [21] correction (q=0.05) was used to correct for multiple comparisons in all analyses, and the femoral head was excluded from all surface-based analyses due to its thin cortical bone. The voxel/vertex-wise general linear models enabled the generation of Student's *t*-test statistical maps of the proximal femur indicating the location, strength and directionality of significant differences in bone properties for each statistical comparison in this study.

3. Results

3.1. Characteristics of participants

The study population consisted of 1381 older adults, aged 66–92 years (mean age ± SD; 77.0 ± 5.6 years) and 57.6% were women. Hip fractures occurred in 100 men and 234 women during an average of 4.8 ± 2.2 years of follow-up after the QCT measures were obtained. Overall, fracture cases were older than noncases (79.6 ± 5.3 years vs. 76.1 ± 5.4 years) and had lower BMI than noncases (25.5 kg/m^2 vs. 27.1 kg/m^2). Similar use of bone-altering medication was reported in both, cases and noncases, and also between male and female participants (Table 1).

3.2. Compartmental analysis of vBMD and cortical bone thickness

Male participants (both noncases and cases) had significantly higher integral vBMD and cortical thickness in all regions of interest (ROIs), except for femoral neck vBMD, compared to females (Table 2). Fracture cases (men and women) had lower vBMD at all ROIs and lower femoral neck cortical bone thickness compared to noncases. In addition to these significant main effects, significant interactions between the effect of fracture status and the effect of sex on all integral vBMD ROIs were observed; meaning that the effect of fracture status (being a control or an incident case) on these bone parameters was different for men than it was for women. For men, the difference between noncases and fracture cases was more accentuated than in women; thus, the vBMD differences between male noncases and female noncases were significantly larger than the differences between male cases and female cases.

3.3. VBM

When examining the Student's *t*-test statistical maps, which we will refer as T-maps, of the voxel-wise vBMD comparisons (Fig. 1), large regions of significantly higher vBMD (positive T-values) were evident for both male noncases and female noncases compared to fracture cases. In men (Fig. 1a), the main regions were located at the femoral head, superior and inferior aspects of the femoral neck, intertrochanteric region, and inferior regions of the lesser trochanter. In women (Fig. 1b), differences were more evident in the superolateral region of the femoral head, superior and inferior aspects of the femoral neck, and in the

intertrochanteric region (yellow-red regions). Interactions between fracture status and sex (Fig. 1c) were more evident at the femoral head, superior aspect of the femoral neck, intertrochanteric region, and at a small patch in the inferior region of the lesser trochanter. Significant regions in Fig. 1c consistently indicated larger vBMD differences between male noncases and male cases than between female noncases and female cases (negative T-values).

3.4. TBM

Four regions of mostly significant higher expansions of the template to match the cases compared to the expansions needed to match the noncases (Fig. 2a–b; positive T-values; hot colors) were evident for both men and women. These were located at the superolateral region of the femoral head, trabecular bone compartment in the femoral neck, trabecular bone compartment in the greater trochanter, and at the trabecular bone compartment in the proximal shaft. The TBM T-maps maps of Fig. 2a–b also indicate several regions of mostly significant higher contractions of the template to match the cases (negative T-values; cool colors) across the principal compressive group, the inferior and superior aspects of the femoral neck (cortical bone compartment), and at the proximal shaft (cortical bone); while the TBM T-map of Fig. 2c shows significant regions for fracture status and sex interaction at the femoral head, superiorly at the cortical bone in the femoral head-neck junction, at the cortical bone in the superior aspect of the femoral neck, and at the trabecular bone compartment in the trochanter and proximal shaft. Significant positive T-values in Fig. 2c indicate that template contraction differences between cases and noncases were larger in males than in females, while the significant negative T-values indicate that template expansion differences between cases and noncases were larger in males than in females, i.e. structural differences were larger between noncases and cases in men.

3.5. SPM – cortical vBMD

In general, Fig. 3a–b show cortical vBMD differences that were of greater magnitude for males compared to females. Focal regions of higher magnitude differences were evident at the anterior femoral head-neck junction and at the lateral aspect of the greater trochanter for both men and women (red patches). The main findings from the T-maps in Fig. 3c–d were the generalized significant differences in cortical vBMD between male noncases and fracture cases (Fig. 3c), and the focal significant differences observed at the supero-anterior and -posterior aspects of the femoral neck, lateral aspect of the greater trochanter, and at a region medial and superior to the lesser trochanter between noncases and fracture cases in women (Fig. 3d). The T-Map of the interaction term (fracture group by sex) showed generalized differences, although more pronounced at the anterior femoral neck, and along the posterior intertrochanteric crest towards the lesser trochanter (Fig. 3e). Significant regions in the T-Map of Fig. 3e consistently indicated larger cortical vBMD differences between male noncases and male cases than between female noncases and female cases (negative T-values).

3.6. SPM – cortical bone thickness

A generalized thicker cortex across most of the proximal femur can be observed in both control men (Fig. 4a) and control women (Fig. 4b) with respect to cases (positive values; hot

colors). However, when examining the T-maps of Fig. 4c and d, only small patches with significant cortical bone thickness differences between noncases and cases were evident in both men and women. A common focal region of thicker cortical bone (positive T-values; hot colors) was observed at the superoanterior aspect of the femoral neck in noncases compared to fracture cases in both males and females. In addition, only in men, significant focal differences were also evident at the inferoposterior region of the femoral neck and at a region medial to the lesser trochanter. These focal regions also denoted thicker cortical bone in noncases compared to fracture cases. There were no regions indicating a significant interaction between fracture group and sex.

3.7. SPM – endotrabecular vBMD

Both endotrabecular vBMD difference maps and T-maps of Fig. 5 show in general similar results for male (Fig. 5a and c) and female (Fig. 5b and d) comparison groups. The main findings were two patches of significant higher endotrabecular vBMD located at the superoanterior aspect of the femoral neck and towards the anterior part of the greater trochanter in noncases compared to fracture cases, particularly in women. The T-map of the interaction term (fracture status by sex; Fig. 5e) shows significant regions that were spread across the proximal femur where endotrabecular vBMD differences between noncases and cases were larger in men than in women (negative T-values).

3.8. Interaction of fracture group with sex

Although the interaction term maps of Figs 1c, 2c, 3e and 5e indicate that the differences in bone properties are larger between noncases and cases in men than between noncases and cases in women, they do not provide insight into differences in bone properties between male noncases and female noncases, and more importantly between male cases and female cases. Fig. 6 shows proximal femoral maps indicating the spatial distribution of the direction of the significant differences in bone properties between male noncases and female noncases, and between male cases and female cases for vBMD, structure, cortical vBMD, and endotrabecular vBMD. Fig. 6a clearly indicates that in most of the significant interactions yielded by VBM between fracture group and sex, male cases had significantly higher vBMD than female cases (blue region), however, the principal compressive group and sub-regions in the superior aspect of the femoral neck showed significantly higher vBMD in female cases than in male cases (yellow and red regions). Regarding TBM (Fig. 6b), female cases showed less favorable structure than male cases in the principal compressive group (larger template contractions; magenta regions), while male cases showed less favorable structure than female cases in a small cortical patch at the superior aspect of the femoral neck (larger template contractions; blue regions). Female cases also showed less favorable structure than male cases medially and laterally in the femoral head, at the trochanteric region, and in the proximal shaft (larger template expansions; red regions). With respect to cortical vBMD, in general, male cases showed higher cortical vBMD than female cases (Fig. 6c; blue regions). Endotrabecular vBMD, on the other hand, showed a more complicated pattern with large regions for both scenarios, male cases with higher endotrabecular vBMD than female cases (blue regions), and female cases with higher endotrabecular vBMD than male cases (yellow and red regions). The latter was mostly observed anteriorly and posteriorly in the femoral neck region.

4. Discussion

In this prospective case-cohort study of incident fracture, we used data-driven image analysis techniques, to quantify spatial differences in baseline vBMD and structure (using VBM and TBM, respectively), and cortical bone properties, including cortical vBMD, cortical bone thickness and endotrabecular vBMD (using surface-based SPM analyses) of the proximal femur of older men and women with and without incident hip fracture, and spatially assess the interaction between fracture group and sex. Our principal findings were: 1) in both men and women, the femoral neck and the trochanteric regions were the most associated with incident hip fracture; 2) in both men and women, the spatial differences in bone features between noncases and incident hip fracture cases followed similar trends and were generally located at similar regions, but were spatially heterogenous, i.e. of focal nature; 3) differences in bone properties between noncases and cases were larger in men than in women; and 4) differences in bone quality between male cases and female cases were spatially heterogeneous. Thus, our results suggest that the effect of incident hip fracture (having a high fracture risk compared to low risk - noncases) differed for men and women, as shown in Table 2 and by the significant regions displayed in the color-coded interaction maps for vBMD (VBM; Figs. 1c and 6a), structure (TBM; Figs. 2c and 6b), cortical vBMD (surface-based SPM; Figs. 3e and 6c) and endotrabecular vBMD (surface-based SPM; Figs. 5e and 6d).

Our VBM analyses showed that (in both men and women) hip fracture was associated with a global vBMD deficit, however, stronger significant differences between noncases and cases were observed in the cortical bone at both the superior and inferior aspects of the femoral neck, and in the trabecular bone at the intertrochanteric region (Fig. 1a–b), in line with previous observations reported in women [4,6]. While some regions did not show interaction between fracture group and sex, others showed greater vBMD differences between male noncases and male cases than between female noncases and cases, specifically at the femoral head. Similarly, our TBM analyses identified common regions of significant focal higher expansions and contractions of the template (structural patterns) associated with incident hip fracture in both male and female groups, and these regions were mostly consistent with previous data reported only in women [5]. And as with VBM, the femoral head was the main region showing larger structural differences between male cases and noncases compared to female cases and noncases. Therefore, our analyses of spatial differences in vBMD (VBM) and structure (TBM) suggest a potentially important role of sex particularly at the femoral head, and to a lesser extent, at the superior aspect of the femoral neck and at the intertrochanteric region (Figs. 1c and 2c).

Further, in agreement with VBM, there was a generalized deficit of cortical vBMD in both male and female cases compared to noncases as displayed in the cortical vBMD difference maps and corresponding T-maps of Fig. 3. Also consistent with VBM, these differences were larger in men (Fig. 3a and c) than in women (Fig. 3b and d). However, significant focal differences in cortical vBMD between noncases and incident hip fracture cases in both men and women were identified in the superoanterior aspect of the femoral neck and laterally at the greater trochanter. These results are, however, in contrast with those of the acute hip fracture study of Yu et al. [8] where cortical vBMD differences between controls (n=50) and

neck fracture cases (n=72), and between controls (n=50) and trochanteric fracture cases (n=21) were basically inexistent in Chinese women. With respect to sex differences, the interaction term map of Fig. 3e indicated that men showed higher significant differences in cortical vBMD between noncases and cases than women in most of the regions of the proximal femur except in the medial compartment. In terms of cortical bone thickness, results were in partial agreement with those of the acute hip fracture study in women of Poole et al. [7] where significant differences between controls and neck fracture cases were observed in the superoanterior aspect of the femoral neck, and between controls and trochanteric fracture cases in the lateral aspect of the greater trochanter (not observed here) and in a small patch above the lesser trochanter. Interestingly, there were no vertices with a significant interaction term of fracture group and sex after FDR correction in the whole proximal femur for cortical bone thickness.

In parallel with cortical bone, the anatomic distribution of trabecular bone and subcortical trabecular bone in the proximal femur are also key determinants of bone strength and fracture risk [8,16,22,23]. In agreement with two recent works of Poole et al. [16] and Yu et al. [8], in our study, incident hip fracture cases in both men and women had large focal trabecular bone defects located within the superior neck (anterior and posterior aspects), and within the anterior part of the intertrochanteric region compared with noncases. Also, consistent with the endocortical trabecular density SPM analysis reported by Poole et al. [16], in our study, the loaded inferior cortex was relatively protected from trabecular bone loss (small T-values, particularly in women in Fig. 5).

The superior aspect of the femoral neck and the trochanteric region were the areas of the proximal femur most consistently identified by our image-based computational anatomy approaches (VBM, TBM, and SPM of cortical bone feature maps) as being associated with incident hip fracture in both men and women. This finding suggests that the superoanterior aspect of the femoral neck is an important region for close monitoring in patients with high risk of fracture. Overall, the existent literature based on QCT images using different analytical techniques has identified weaker bone structure (i.e. diminished vBMD and cortical bone thickness) focally located at the superior region of the femoral neck to be associated with both aging and hip fracture risk [4,6,7,16,17]. Indeed, the femoral neck has a highly asymmetrical internal structure, with a thin cortical zone in the upper femoral neck and a thicker inferior cortex [14], but the involvement of these geometrically opposed locations is distinct, depending on loading conditions and direction. The sideways falls on the greater trochanter impose the greatest compressive stresses and strains in the thin, superolateral cortex of the femoral neck, while the lower tensile ones occur in the inferior region [24–26]. Our in vivo findings agree with the age-related changes at the material level (bone density and cortical thickness) that have been previously described using in vitro models [27,28]; these changes are, in part, responsible for triggering hip fracture in a sideways fall [14,24–26]. From a fracture prevention point of view, gaitrelated stimulus will only lightly load (tensile stresses) the superolateral cortex, thus the possible protection against hip fracture with walking-based exercise in old age [29] is not due to a direct strengthening of this most vulnerable region of the hip. Therefore, some types of physical activities can be effective in reducing hip fracture incidence mostly by indirect mechanisms such as improving strength, gait, balance and mood, and lessen the occurrence of falls. With

respect to the trochanteric region, the greater trochanter is the primary attachment site of the gluteus medius and gluteus minimus (hip abductor muscles). Based on our findings, that high fracture risk subjects display lower cortical and trabecular vBMD at the greater trochanter, simple exercises designed to challenge those muscles, such as squat walks with external resistance (elastic bands), or side leg raises, can be easily performed by older adults to stimulate bone formation at that site, as no complex motor skills or high physical fitness level are required. Thus, computational anatomy studies may help designing better and specifically targeted exercise interventions to fragile populations.

Thus, the pathogenesis of bone fragility seems to involve mechanisms that can target specific regions, but their extent varies by feature (thickness vs. density) or compartment (cortical vs. trabecular). Key candidate mechanisms would include those involving locally reduced mechanical loading and muscle contraction. Pharmacological approaches may reduce osteoporotic hip fracture risk [30], and recent studies applying SPM techniques have shown improvements in cortical thickness after therapy [9,10,31]. However, they are typically limited to older adults with already signs of bone fragility. In this scenario, exercise (when loading conditions are favorable) is the most appealing approach for optimizing and maintaining bone health, particularly during growth and adulthood, as extensively demonstrated by randomized control trials in diverse age groups [32–35]. Although based on limited data, maximum isokinetic hip extension, and knee flexion exercises are suggested as the most effective activities (because they induced the highest peak tensile strain) for improving the proximal neck cortex [36,37]. Another study demonstrated that 12 months of very brief (~3 min) hopping exercises performed seven days a week, may have some cortical mass and endocortical trabecular density benefits on the superolateral aspect of the femoral neck in older men [12]. Clearly, additional exercise intervention studies combining musculoskeletal modeling with 3D imaging techniques are needed to quantify which exercises induce the higher mechanoresponse at the most fracture prone regions.

Finally, while all the regions with a significant interaction of fracture group and sex showed larger differences in bone properties between noncases and cases in men compared to women, interestingly, differences in bone properties between male cases and female cases were spatially heterogeneous, with male cases showing better and worse bone properties than female cases throughout the proximal femur. Our results, therefore, show for the first time, that men with high risk of hip fracture, display a much lower bone quality compared to low-risk men, several years before the occurrence of a hip fracture. Further studies are then needed to investigate if these changes are age-related or due to a different mechanism. On the other hand, in women, these marked differences between low and high hip fracture risk subjects, although present, are less evident compared to men, highlighting the difficulty to reliably predict hip fracture in women.

This prospective case-cohort study has several important strengths. First, our study is the largest computational anatomy study of the hip in older men and women conducted to date. Second, QCT-scans were acquired at a single-center, and participants were imaged before the occurrence of hip fractures, and cases and noncases are part of the same cohort, which ensures their comparability. Finally, we applied VBM and TBM which incorporate both trabecular and cortical bone for spatial assessments of vBMD and structure, respectively,

and surface-based SPM for the spatial assessments of cortical bone properties, thus providing a comprehensive assessment of the proximal femur associated with sex and hip fracture risk. However, there are also some limitations in our study. First, hip fracture types were not differentiated due to reduced statistical power to test differences between groups, although marked phenotypic difference between the hips of patients sustaining femoral neck or trochanteric hip fracture are expected [7,8]. Of note, no differences in the distribution of type of fracture were found between men and women in the present study. Second, the femoral head was excluded from our SPM analyses due to the thin cortical bone. And third, our Caucasian with European ancestry cohort limits our ability to generalize our findings to other non-Caucasian populations, however, the highest fracture rates are observed in white women [38].

In conclusion, this study identified focal differences in bone properties associated with incident hip fracture throughout the proximal femur which had an overall common location in men and women. Thus, in both sexes, the pathogenesis of bone fragility (causing thinner, less dense and more porous bones) leading to hip fracture might be characterized by focal areas of bone defects. In addition, results also suggest that sex might play a significant role in the relationship between spatial bone properties and fracture risk. This was demonstrated by the combined effect of fracture group and sex, where men showed an accentuated difference between noncases and cases compared to women. Importantly, these differences in bone properties associated with incident hip fracture were detected in older men and women, years before (4.8 ± 2.2 years) the hip fracture participants experienced a hip fracture. Thus, computational anatomy-based studies suggest that focal spatial differences in bone properties might play a key role in determining fracture risk and might have important clinical implications for fragility fracture prevention and treatment. Although CT examinations have some relevant limitations such as the patient's exposure to ionizing radiation, cannot assess bone microarchitecture, and is more expensive than DXA, the usefulness of clinical CT imaging is increasing, and it may provide relevant surrogate measures for future fracture risk detection. CT imaging and image processing using computational anatomy approaches is a promising area of future research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding

This work was supported by the National Institutes of Health [contract number N01-AG-1-2100], the Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament). This research was also supported in part by the Intramural Research Program of the NIH, National Institute on Aging, and by NIH/NIAMS [grant number R01AR068456].

References

[1]. Bouxsein ML, Karasik D., Bone geometry and skeletal fragility, Curr. Osteoporos. Rep. 4 (2) (2006) 49–56. [PubMed: 16822403]

[2]. Seeman E, Bone quality: the material and structural basis of bone strength, J. Bone Miner. Metab. 26 (1) (2008) 1–8. [PubMed: 18095057]

[3]. Bredbenner TL, Mason RL, Havill LM, Orwoll ES, Nicolella DP, S, Osteoporotic fractures in men, fracture risk predictions based on statistical shape and density modeling of the proximal femur, J. Bone Miner. Res. 29 (9) (2014) 2090–2100. [PubMed: 24692132]

[4]. Carballido-Gamio J, Harnish R, Saeed I, Streeper T, Sigurdsson S, Amin S, Atkinson EJ, Therneau TM, Siggeirsdottir K, Cheng X, Melton LJ, 3rd, Keyak J, Gudnason V, Khosla S, Harris TB, Lang TF, Proximal femoral density distribution and structure in relation to age and hip fracture risk in women, J. Bone Miner. Res. 28 (3) (2013) 537–546. [PubMed: 23109068]

[5]. Carballido-Gamio J, Harnish R, Saeed I, Streeper T, Sigurdsson S, Amin S, Atkinson EJ, Therneau TM, Siggeirsdottir K, Cheng X, Melton LJ, 3rd, Keyak JH, Gudnason V, Khosla S, Harris TB, Lang TF, Structural patterns of the proximal femur in relation to age and hip fracture risk in women, Bone 57 (1) (2013) 290–299. [PubMed: 23981658]

[6]. Li W, Kornak J, Harris T, Keyak J, Li C, Lu Y, Cheng X, Lang T, Identify fracture-critical regions inside the proximal femur using statistical parametric mapping, Bone 44 (4) (2009) 596–602. [PubMed: 19130910]

[7]. Poole KE, Treece GM, Mayhew PM, Vaculik J, Dungl P, Horak M, Stepan JJ, Gee AH, Cortical thickness mapping to identify focal osteoporosis in patients with hip fracture, PLoS One 7 (6) (2012) e38466. [PubMed: 22701648]

[8]. Yu A, Carballido-Gamio J, Wang L, Lang TF, Su Y, Wu X, Wang M, Wei J, Yi C, Cheng X, Spatial differences in the distribution of bone between femoral neck and trochanteric fractures, J. Bone Miner. Res. 32 (8) (2017) 1672–1680. [PubMed: 28407298]

[9]. Poole KE, Treece GM, Ridgway GR, Mayhew PM, Borggrefe J, Gee AH, Targeted regeneration of bone in the osteoporotic human femur, PLoS One 6 (1) (2011) e16190. [PubMed: 21264263]

[10]. Poole KE, Treece GM, Gee AH, Brown JP, McClung MR, Wang A, Libanati C, Denosumab rapidly increases cortical bone in key locations of the femur: a 3D bone mapping study in women with osteoporosis, J. Bone Miner. Res. 30 (1) (2015) 46–54. [PubMed: 25088963]

[11]. Whitmarsh T, Treece GM, Gee AH, Poole KE, The effects on the femoral cortex of a 24 month treatment compared to an 18 month treatment with teriparatide: a multi-trial retrospective analysis, PLoS One 11 (2) (2016) e0147722. [PubMed: 26859142]

[12]. Allison SJ, Poole KE, Treece GM, Gee AH, Tonkin C, Rennie WJ, Folland JP, Summers GD, Brooke-Wavell K, The influence of high-impact exercise on cortical and trabecular bone mineral content and 3D distribution across the proximal femur in older men: a randomized controlled unilateral intervention, J. Bone Miner. Res. 30 (9) (2015) 1709–1716. [PubMed: 25753495]

[13]. Lang TF, Saeed IH, Streeper T, Carballido-Gamio J, Harnish RJ, Frassetto LA, Lee SM, Sibonga JD, Keyak JH, Spiering BA, Grodsinsky CM, Bloomberg JJ, Cavanagh PR, Spatial heterogeneity in the response of the proximal femur to two lower-body resistance exercise regimens, J. Bone Miner. Res. 29 (6) (2014) 1337–1345. [PubMed: 24293094]

[14]. Mayhew PM, Thomas CD, Clement JG, Loveridge N, Beck TJ, Bonfield W, Burgoyne CJ, Reeve J, Relation between age, femoral neck cortical stability, and hip fracture risk, Lancet 366 (9480) (2005) 129–135. [PubMed: 16005335]

[15]. Johannesdottir F, Poole KE, Reeve J, Siggeirsdottir K, Aspelund T, Mogensen B, Jonsson BY, Sigurdsson S, Harris TB, Gudnason VG, Sigurdsson G, Distribution of cortical bone in the femoral neck and hip fracture: a prospective case-control analysis of 143 incident hip fractures; the AGES-REYKJAVIK study, Bone 48 (6) (2011) 1268–1276. [PubMed: 21473947]

[16]. Poole KE, Skingle L, Gee AH, Turmezei TD, Johannesdottir F, Blesic K, Rose C Vindlacheruvu M Donell S Vaculik J Dungl P Horak M Stepan JJ Reeve J Treece GM, Focal osteoporosis defects play a key role in hip fracture, Bone 94 (2017) 124–134. [PubMed: 27777119]

[17]. Treece GM, Gee AH, Tonkin C, Ewing SK, Cawthon PM, Black DM, Poole KE, S, For the osteoporotic fractures in men, predicting hip fracture type with cortical bone mapping (CBM) in the osteoporotic fractures in men (MrOS) study, J. Bone Miner. Res. 30 (11) (2015) 2067–2077. [PubMed: 25982802]

[18]. Harris TB, Launer LJ, Eiriksdottir G, Kjartansson O, Jonsson PV, Sigurdsson G, Thorgeirsson G, Aspelund T, Garcia ME, Cotch MF, Hoffman HJ, Gudnason V, Age, gene/environment

susceptibility—Reykjavik study: multidisciplinary applied phenomics, Am. J. Epidemiol. 165 (9) (2007) 1076–1087. [PubMed: 17351290]

[19]. Carballido-Gamio J, Bonaretti S, Saeed I, Harnish R, Recker R, Burghardt AJ, Keyak JH, Harris T, Khosla S, Lang TF, Automatic multi-parametric quantification of the proximal femur with quantitative computed tomography, Quant. Imaging Med. Surg. 5 (4) (2015) 552–568. [PubMed: 26435919]

[20]. Gee AH, Treece GM, Systematic misregistration and the statistical analysis of surface data, Med. Image Anal. 18 (2) (2014) 385–393. [PubMed: 24440743]

[21]. Genovese CR, Lazar NA, Nichols T, Thresholding of statistical maps in functional neuroimaging using the false discovery rate, Neuroimage 15 (4) (2002) 870–878. [PubMed: 11906227]

[22]. Milovanovic P, Djonic D, Marshall RP, Hahn M, Nikolic S, Zivkovic V, Amling M, Djuric M, Micro-structural basis for particular vulnerability of the superolateral neck trabecular bone in the postmenopausal women with hip fractures, Bone 50 (1) (2012) 63–68. [PubMed: 21964412]

[23]. Thomas CD, Mayhew PM, Power J, Poole KE, Loveridge N, Clement JG, Burgoyne CJ, Reeve J, Femoral neck trabecular bone: loss with aging and role in preventing fracture, J. Bone Miner. Res. 24 (11) (2009) 1808–1818. [PubMed: 19419312]

[24]. de Bakker PM, Manske SL, Ebacher V, Oxland TR, Cripton PA, Guy P, During sideways falls proximal femur fractures initiate in the superolateral cortex: evidence from high-speed video of simulated fractures, J. Biomech. 42 (12) (2009) 1917–1925. [PubMed: 19524929]

[25]. Lotz JC, Cheal EJ, Hayes WC, Stress distributions within the proximal femur during gait and falls: implications for osteoporotic fracture, Osteoporos. Int. 5 (4) (1995) 252–261. [PubMed: 7492864]

[26]. Verhulp E, van Rietbergen B, Huiskes R, Load distribution in the healthy and osteoporotic human proximal femur during a fall to the side, Bone 42 (1) (2008) 30–35. [PubMed: 17977813]

[27]. Bell KL, Loveridge N, Power J, Garrahan N, Meggitt BF, Reeve J, Regional differences in cortical porosity in the fractured femoral neck, Bone 24 (1) (1999) 57–64. [PubMed: 9916785]

[28]. Bell KL, Loveridge N, Power J, Garrahan N, Stanton M, Lunt M, Meggitt BF, Reeve J, Structure of the femoral neck in hip fracture: cortical bone loss in the inferoanterior to superoposterior axis, J. Bone Miner. Res. 14 (1) (1999) 111–119. [PubMed: 9893072]

[29]. Feskanich D, Flint AJ, Willett WC, Physical activity and inactivity and risk of hip fractures in men, Am. J. Public Health 104 (4) (2014) e75–81.

[30]. Freemantle N, Cooper C, Diez-Perez A, Gitlin M, Radcliffe H, Shepherd S, Roux C, Results of indirect and mixed treatment comparison of fracture efficacy for osteoporosis treatments: a meta-analysis, Osteoporos. Int. 24 (1) (2013) 209–217. [PubMed: 22832638]

[31]. Whitmarsh T, Treece GM, Gee AH, Poole KE, Mapping bone changes at the proximal femoral cortex of postmenopausal women in response to alendronate and teriparatide alone, combined or sequentially, J. Bone Miner. Res. 30 (7) (2015) 1309–1318. [PubMed: 25639838]

[32]. Marques EA, Mota J, Carvalho J, Exercise effects on bone mineral density in older adults: a meta-analysis of randomized controlled trials, Age (Dordr.) 34 (6) (2012) 1493–1515. [PubMed: 21922251]

[33]. Behringer M, Gruetzner S, McCourt M, Mester J, Effects of weight-bearing activities on bone mineral content and density in children and adolescents: a meta-analysis, J. Bone Miner. Res. 29 (2) (2014) 467–478. [PubMed: 23857721]

[34]. Guadalupe-Grau A, Fuentes T, Guerra B, Calbet JA, Exercise and bone mass in adults, Sports Med. 39 (6) (2009) 439–468. [PubMed: 19453205]

[35]. Xu J, Lombardi G, Jiao W, Banfi G, Effects of exercise on bone status in female subjects, from young girls to postmenopausal women: an overview of systematic reviews and meta-analyses, Sports Med. 46 (8) (2016) 1165–1182. [PubMed: 26856338]

[36]. Martelli S, Femoral neck strain during maximal contraction of isolated hip-spanning muscle groups, Computational and Mathematical Methods in Medicine 2017 (2017) 10.

[37]. Martelli S, Kersh ME, Schache AG, Pandy MG, Strain energy in the femoral neck during exercise, J. Biomech. 47 (8) (2014) 1784–1791. [PubMed: 24746018]

[38]. Cummings SR, Melton LJ, Epidemiology and outcomes of osteoporotic fractures, Lancet 359 (9319) (2002) 1761–1767. [PubMed: 12049882]

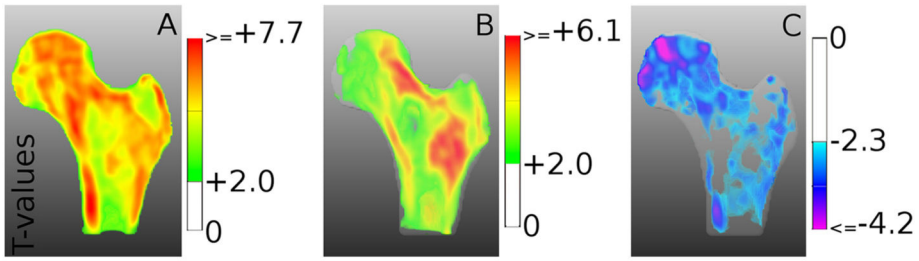

Fig. 1.

Mid-coronal cross-sections of the VBM T-maps of the voxel-wise vBMD comparisons between male noncases and hip fracture cases (A); between female noncases and hip fracture cases (B); and the fracture status by sex interaction (C). Voxels were assigned transparency according to their T-values with nonsignificant voxels being rendered fully transparent.

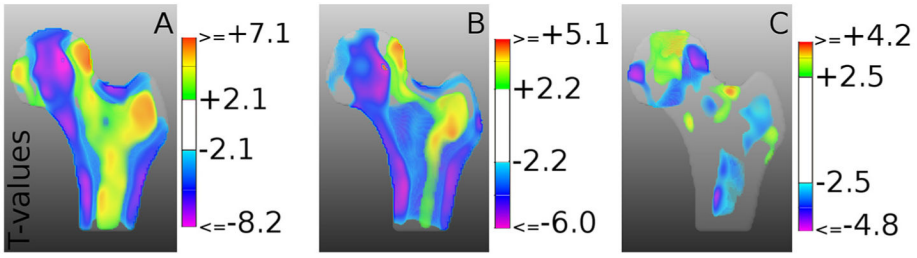

Fig. 2.

Mid-coronal cross-sections of the T-maps of TBM analyses showing local structural differences on a voxel-by-voxel basis between male noncases and cases (A); between female noncases and cases (B); and the fracture status by sex interaction (C). As in Fig. 1, voxels were also assigned transparency according to their T-values with nonsignificant voxels being rendered fully transparent.

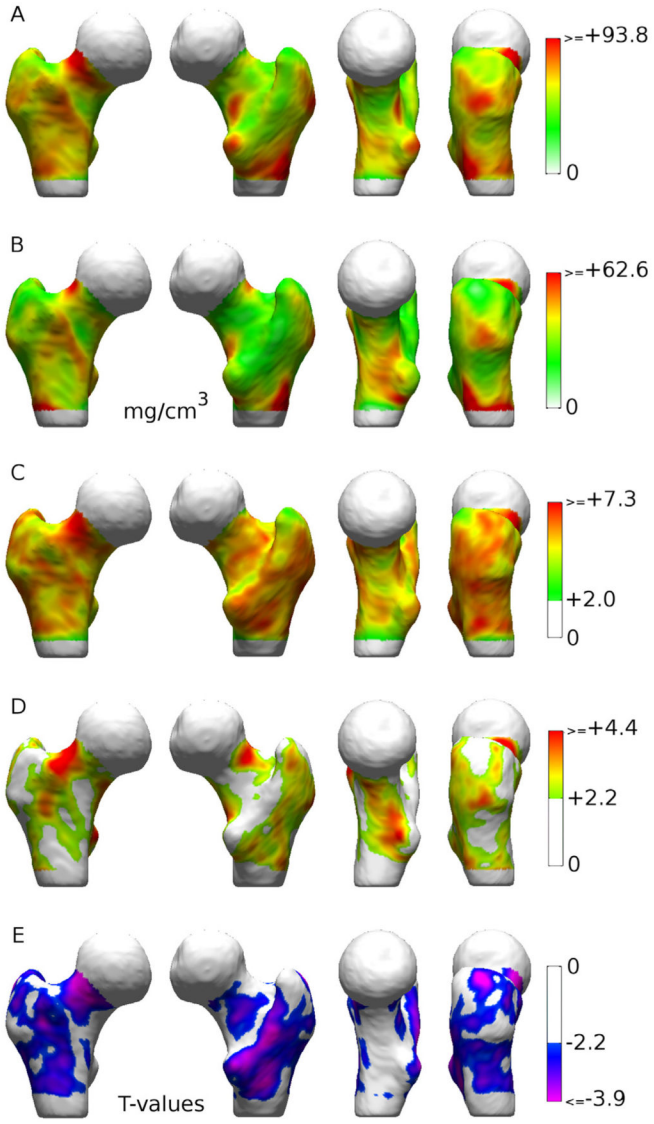

Fig. 3.

Color-coded maps of A) cortical vBMD differences between male noncases and cases, B) cortical vBMD differences between female noncases and cases, C) T-map of significant cortical vBMD differences in men, D) T-map of significant cortical vBMD differences in women, and E) T-map of significant interaction between fracture status and sex. The white color in the T-maps of panels C-E indicates nonsignificant vertices. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

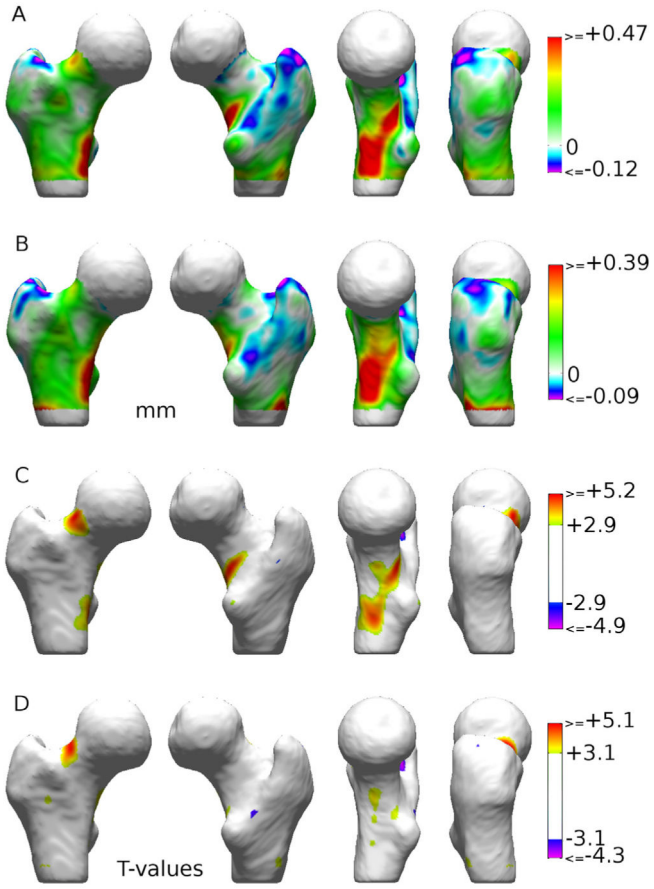

Fig. 4.

Color-coded maps of A) cortical thickness differences between male noncases and cases, B) cortical thickness differences between female noncases and cases, C) T-map of significant cortical thickness differences in men, and D) T-map of significant cortical thickness differences in women. The white color in the T-maps of panels C–D indicates nonsignificant differences. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

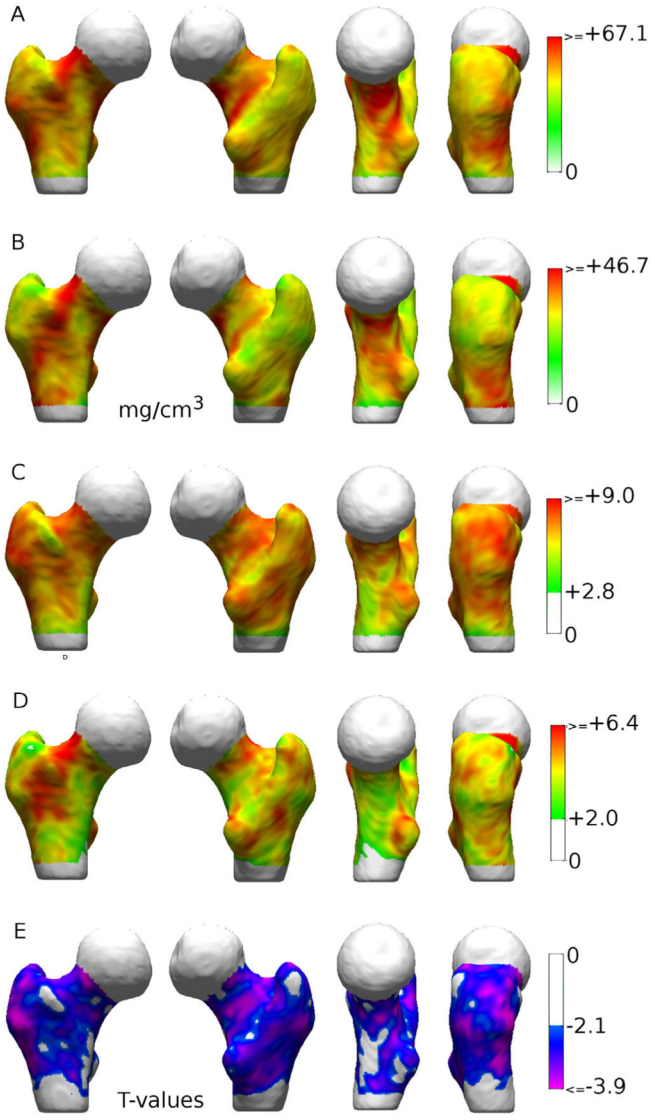

Fig. 5.

Color-coded maps of A) endotrabecular vBMD differences between male noncases and cases, B) endotrabecular vBMD differences between female noncases and cases, C) T-map of significant endotrabecular vBMD differences in men, D) T-map of significant endotrabecular vBMD differences in women, and E) T-map of significant interaction between fracture status and sex. The white color in the T-maps of panels C–E indicates nonsignificant vertices. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

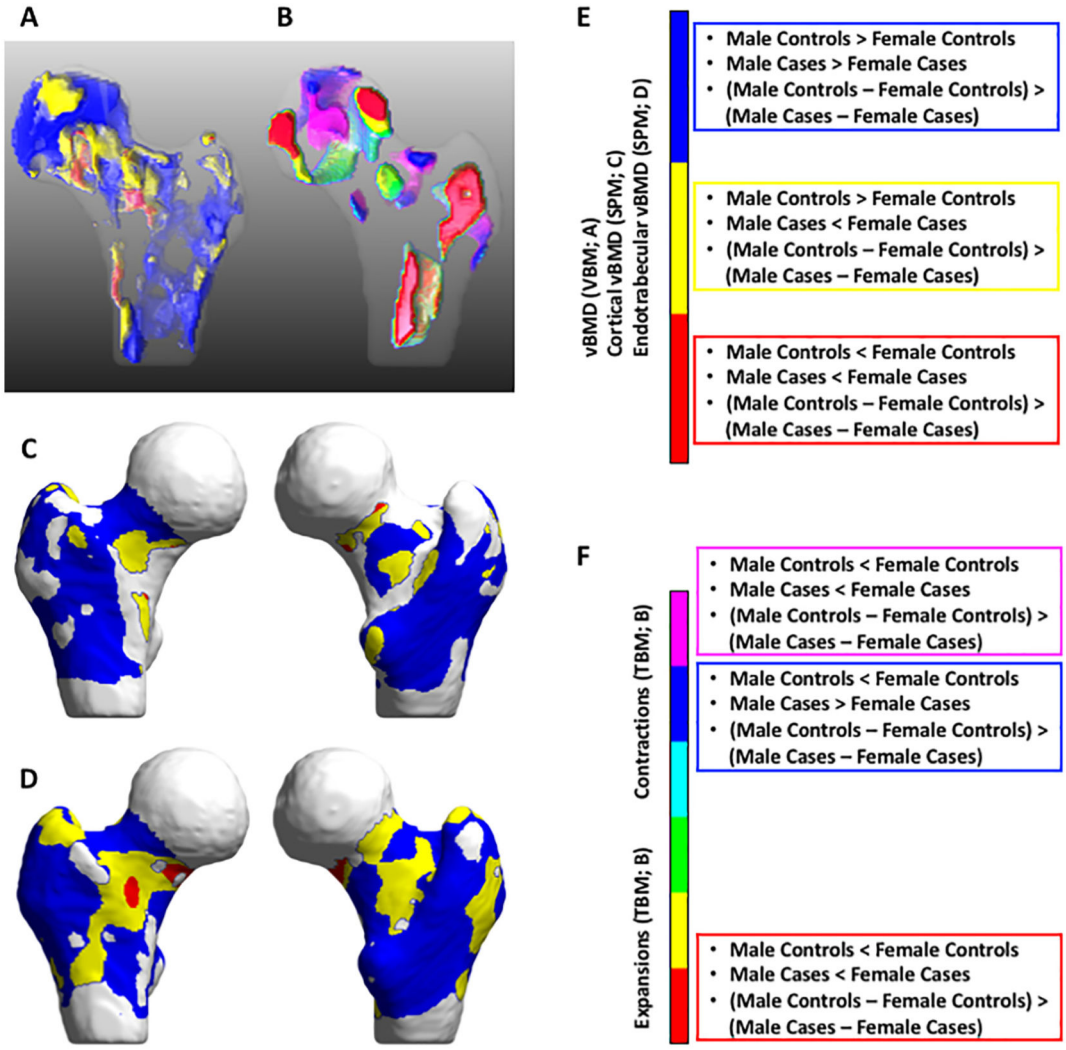

Fig. 6.

Femoral maps showing the direction of differences in bone properties between male noncases and female noncases, and between male cases and female cases for the different regions showing a significant interaction between fracture group and sex in: A) VBM of vBMD (mid-coronal cross-section; Fig. 1C), B) TBM (mid-coronal cross-section; Fig. 2C), C) SPM of cortical vBMD (Fig. 3E), and D) SPM of endotrabecular vBMD (Fig. 5E). The color-bar to interpret Figs. A, C and D is shown in E, while the color-bar to interpret B is shown in F. Patterns in the cyan, green and yellow regions in B were not explained due to their reduced size and for the sake of clarity. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1

Baseline characteristics of hip fracture cases and noncases by sex.

Variables	Males			Females			p-Value*
	Noncases (n=485)	Cases (n=100)	p-Value	Noncases (n=562)	Cases (n=234)	p-Value	
Mean ± SD							
Age, years	76.3 ± 5.4	80.3 ± 5.4	<0.001	76.0 ± 5.4	79.4 ± 5.2	<0.001	0.85
Height, cm	175.5 ± 6.0	174.4 ± 6.9	0.10	161.2 ± 5.5	159.8 ± 5.8	0.001	<0.001
Weight, kg	82.8 ± 13.6	78.9 ± 14.4	0.008	71.2 ± 12.6	64.8 ± 12.9	<0.001	<0.001
BMI, kg/m^2	26.8 ± 3.8	25.9 ± 4.2	0.041	27.4 ± 4.6	25.3 ± 4.6	<0.001	0.65
% (n)							
Bone-altering medications	28.7 (139)	23.0 (23)	0.27	51.2 (288)	47.9 (112)	0.39	<0.001

BMI=body mass index.

* p values for the differences between males and females.

Table 2

Compartmental analysis of integral vBMD and cortical thickness.

ROI	Men		Women		p-Value (sex)	p-Value (FS)	p-Value (Int)
	Noncases (n=485)	Cases (n=100)	Noncases (n=562)	Cases (n=234)			
Integral vBMD (mg/cm^3)							
TH	252.1 ± 2.6	209.4 ± 4.8^b	225.6 ± 2.2^a	204.5 ± 3.2^b	<0.001	<0.001	<0.001
FH	233.8 ± 2.6	191.0 ± 4.7^b	204.2 ± 2.2^a	186.9 ± 3.1^b	<0.001	<0.001	<0.001
FN	279.6 ± 3.3	228.2 ± 5.9^b	269.7 ± 2.8^a	241.2 ± 4.0^b	0.76	<0.001	0.002
TR	259.7 ± 2.9	218.6 ± 5.2^b	231.7 ± 2.5^a	209.2 ± 3.5^b	<0.001	<0.001	0.004
Cortical thickness (mm)							
FN	1.99 ± 0.01	1.90 ± 0.03	2.07 ± 0.01	2.01 ± 0.02	<0.001	<0.001	0.31
TR	2.25 ± 0.01	2.23 ± 0.02	2.18 ± 0.01	2.18 ± 0.01	<0.001	0.29	0.25

FH=femoral head, FN=femoral neck, FS=fracture status, Int=interaction, ROI=region of interest, TH=total hip, TR=trochanter; values are given as estimated marginal means ± SE adjusted by age, height, weight and bone-altering medications; adjustment for multiple comparisons – Bonferroni; covariates appearing in the model are evaluated at the following values: age=76.9783, height=166.9449, weight=74.7279, BMD-altering medications=0.4070.

^{a}Significant differences between male and female noncases.

^{b}Significant differences between noncases and cases.