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Structural patterns of the proximal femur in relation to age and hip fracture risk in women

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ABSTRACT

Fractures of the proximal femur are the most devastating outcome of osteoporosis. It is generally understood that age-related changes in hip structure confer increased risk, but there have been few explicit comparisons of such changes in healthy subjects to those with hip fracture. In this study, we used quantitative computed tomography and tensor-based morphometry (TBM) to identify three-dimensional internal structural patterns of the proximal femur associated with age and with incident hip fracture. A population-based cohort of 349 women representing a broad age range (21–97 years) was included in this study, along with a cohort of 222 older women (mean age 79 ± 7 years) with (n = 74) and without (n = 148) incident hip fracture. Images were spatially normalized to a standardized space, and age- and fracture-specific morphometric features were identified based on statistical maps of shape features described as local changes of bone volume. Morphometric features were visualized as maps of local contractions and expansions, and significance was displayed as Student's *t*-test statistical maps. Significant age-related changes included local expansions of regions low in volumetric bone mineral density (vBMD) and local contractions of regions high in vBMD. Some significant fracture-related features resembled an accentuated aging process, including local expansion of the superior aspect of the trabecular bone compartment in the femoral neck, with contraction of the adjoining cortical bone. However, other features were observed only in the comparison of hip fracture subjects with age-matched controls including focal contractions of the cortical bone at the superior aspect of the femoral neck, the lateral cortical bone just inferior to the greater trochanter, and the anterior intertrochanteric region. Results of this study support the idea that the spatial distribution of morphometric features is relevant to age-related changes in bone and independent to fracture risk. In women, the identification by TBM of fracture-specific morphometric alterations of the proximal femur, in conjunction with vBMD and clinical risk factors, may improve hip fracture prediction.

Introduction

Bone is a dynamic organ that exhibits structural adaptation to changes in its biochemical and biomechanical environment. Recent studies of the proximal femur using volumetric quantitative computed tomography (vQCT) and finite element modeling (FEM) have compared aspects of structure and strength in older and younger female subjects, showing that older women are characterized by larger bone size, lower trabecular volumetric bone mineral density (vBMD), thinner superior but not inferior femoral neck cortices, and lower whole bone strength [1–5]. Studies of proximal femur structure in women with hip fracture compared to age-matched controls have shown similar trends, with fracture women having larger cross-sectional areas, lower trabecular vBMD, thinner cortices in all subregions of the hip, and lower whole bone

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strength [6–8]. However, although age-related changes impart increased fragility to the proximal femur, the extent to which fracture-related variations in structure differ from age-related changes is still unclear.

In vQCT studies of the proximal femur, the ability to compare geometric features between individuals requires that analyses of geometric parameters, such as femoral neck cross sectional area, assume a general uniformity of outer bone shape, while cortical bone thickness measures assume similar cortical bone anatomy. However, the internal cancellous structure of the hip [9,10] is often neglected or indirectly studied based on vBMD values of predefined volumes of interest. In this work, we quantify the three-dimensional (3D) internal structural patterns of the proximal femur in relation to age and incident hip fracture using vQCT images and a shape analysis technique known as tensor-based morphometry (TBM) [11]. For this purpose we studied two population-based cohorts: The first cohort included primarily Caucasian women across a broad range of age [1], while the second cohort included Caucasian women with and without incident hip fracture [12]. We will refer to these as the Aging Study and the Fracture Study, respectively. We used the same population-based cohorts in a recent study using voxel-based morphometry (VBM) and vQCT to study the spatial distribution of vBMD values in relation to age and incident hip fracture in women [13]. That study was based on the assumption of similar outer shapes of proximal femora between different subjects. The study presented here used TBM, which quantifies local differences in shape. Our goal was to examine, side-by-side, the internal structural patterns in the proximal femur that are associated with aging and with hip fracture to better understand normal aging and the pathophysiology of incident hip fracture.

Materials and methods

Human subjects

Aging study

Using the medical record linkage system of the Rochester Epidemiology Project, 373 women were enrolled from an age-stratified random sample of Rochester, MN, residents, and included in this study [1]. Mayo Clinic's Institutional Review Board and the Committee on Human Research at the University of California, San Francisco, approved the study. Informed consent was obtained from all participants in the study, and the analyses were based on de-identified data. For analysis, women were divided into three subgroups based on their age: young (age $<$ 45 years), middle-age (45 $\leq$ age $<$ 60 years), and older (age $\geq$ 60 years).

Fracture study

Using the AGES-Reykjavik Fracture Registry [14], a total of 222 women of the AGES Reykjavik cohort [12,15] were included in this study. The AGES Reykjavik study is an ongoing population-based study of Icelandic women and men, where baseline CT scans of 5500 subjects were obtained between 2002 and 2006, and subjects were followed for 4–7 years (mean 5 years). For this study, based on their fracture status, women were divided into two subgroups: controls (no hip fracture) and fracture (incident hip fracture but without documented hip fracture prior to CT imaging at baseline). The study was approved (VSN 00-063) by the National Bioethics Committee in Iceland and the Data Protection Authority, the Institutional Review Board of the Intramural Research Program of the National Institute on Aging, and the Committee on Human Research at the University of California, San Francisco. Informed consent was obtained from all participants in the study.

Imaging

Aging study

Single-energy CT scans of both hip joints were obtained for each subject using a multi-detector CT scanner (Light Speed QX-I; GE Medical Systems, Wakesha, WI, USA) and a QCT calibration phantom (Mindways Inc., Austin, TX, USA) to convert Hounsfield units (HU) to equivalent concentrations of K_2HPO_4. Images were reconstructed to in-plane voxel sizes of 0.74 $\times$ 0.74 mm^2, with slice thickness of 2.5 mm.

Fracture study

CT scans of both hips were obtained for each subject at baseline using a 4-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 concentration of calcium hydroxyapatite. Images were reconstructed to in-plane voxel sizes of 0.98 $\times$ 0.98 mm^2, with slice thickness of 1 mm.

Geometric and vBMD measures

Aging study

Measures of vBMD and bone cross-sectional geometry were extracted from the femoral neck region as previously described in [1,16]. From a single reformatted oblique section orthogonal to the femoral neck axis four parameters were evaluated in this study: Integral vBMD, Total Area, Cortical Area, Medullary Area and the ratio of the Cortical Area to the Total Area. These measures have been shown to be age- and sex-specific over life [1].

Fracture study

Measures of vBMD and cortical structure that have been shown to predict hip fracture in cross-sectional [17] and prospective studies [18] were extracted from a volumetric region of the femoral neck as previously described in [19]. These included Integral vBMD, Total Volume, Cortical Volume, Medullary Volume and the ratio of the Cortical Volume to the Total Volume.

Image preprocessing

The left proximal femur was semi-automatically segmented from each CT scan on a slice-by-slice basis [7,20], and images and their corresponding segmentations were upsampled to isotropic voxel sizes to match the in-plane voxel dimensions generating 3D representations of the proximal femur.

TBM

TBM is one of the most popular deformation-based approaches for analyzing macroscopic anatomy [11]. Briefly, in TBM, all images of the structure of interest in a given study are spatially normalized to a standardized space using image registration. First, an affine transformation is applied to translate, rotate, and scale (one scale for each dimension) the images. Then a nonlinear transformation is computed. The nonlinear step of the spatial normalization assigns a displacement vector to each voxel to accommodate anatomic variability. TBM processes these dense maps of displacement vectors, which are known as deformation fields, to generate feature maps representing shape in the form of local changes of volume. TBM then compares shape maps between two groups of subjects, or the same group of subjects at different time points, and detects subregions where shape is significantly associated with the effect of interest, making it possible to visualize group differences or longitudinal changes as statistical maps. Fig. 1 shows a flow diagram summarizing the major steps of TBM.

In this study, spatial normalization was performed by concatenating multi-resolution affine (9-parameter) and multi-resolution nonlinear transformations [21]. Affine transformations were computed based on level-set representations of femoral surfaces using distance maps [22,23], and nonlinear registrations were computed based on combined representations of distance maps for the background and gray-level values for the proximal femur (Fig. 1) [24]. The standardized