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Age-related loss of proximal femoral strength in elderly men and women: The Age Gene/Environment Susceptibility Study — Reykjavik

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ABSTRACT

The risk of hip fracture rises rapidly with age, and is particularly high in women. This increase in fracture risk reflects both the age-related change in the risk of falling and decrements in the strength of the proximal femur. To better understand the extent to which proximal femoral density, structure and strength change with age as a function of gender, we have carried out a longitudinal analysis of proximal femoral volumetric quantitative computed tomographic (vQCT) images in men and women, analyzing changes in trabecular and cortical bone properties, and using subject-specific finite element modeling (FEM) to estimate changes in bone strength. In the AGES-Reykjavik Study vQCT scans of the hip were performed at a baseline visit in 2002–2006 and at a second visit 5.05 ± 0.25 years later. From these, 223 subjects (111 men, 112 women, aged 68–87 years) were randomly selected. The subjects were evaluated for longitudinal changes in three bone variables assessed in a region similar to the total femur region quantified by DXA: areal bone mineral density (aBMD), trabecular volumetric bone mineral density (tBMD) and the ratio of cortical to total tissue volume (cvol/ivol). They were also evaluated for changes in bone strength using FEM models of the left proximal femur. Models were analyzed under single-limb stance loading (F_{Stance}), which approximates normal physiologic loading of the hip, as well as a load approximating a fall onto the posterolateral aspect of the greater trochanter (F_{Fall}). We computed five-year absolute and percentage changes in aBMD, tBMD, cvol/ivol, F_{Fall} and F_{Stance}. The Mann–Whitney Test was employed to compare changes in bone variables between genders and the Wilcoxon Signed Rank Test was used to compare changes in bone strength between loading conditions. Multiple (linear) regression was employed to determine the association of changes in F_{Fall} and F_{Stance} with baseline age and five-year weight loss. Both men and women showed declines in indices of proximal femoral density and structure (aBMD: men −3.9 ± 6.0%, women −6.1 ± 6.2%; tBMD: men −14.8 ± 20.3%, women −23.9 ± 26.8%; cvol/ivol: men −2.6 ± 4.6%, women −4.7 ± 4.8%, gender difference: $p<0.001$). Both men and women lost bone strength in each loading condition (F_{Stance}: men −4.2 ± 9.9%, women −8.3 ± 8.5%; F_{Fall}: men −7.0 ± 15.7%, women −12.8 ± 13.2%; all changes from baseline $p<0.0001$). The gender difference in bone strength loss was statistically significant in both loading conditions ($p<0.001$ for F_{Stance} and $P<0.01$ for F_{Fall}) and F_{Fall} was lost at a higher rate than F_{Stance} in men ($p<0.01$) and women ($p<0.0001$). The gender difference in strength loss was statistically significant after adjustment for baseline age and weight loss in both loading conditions ($p<0.01$). In these multi-linear models, men showed increasing rates of bone loss with increasing age (F_{Fall}: $p=0.002$; F_{Stance}: $p=0.03$), and women showed increasing bone strength loss with higher degrees of weight loss (F_{Stance}: $p=0.003$). The higher loss of F_{Fall} compared to F_{Stance} supports previous findings in animal and human studies that the sub-volumes of bone stressed under normal physiologic loading are relatively better protected in aging. The gender difference in hip bone strength loss is consistent with the higher incidence of hip fracture among elderly women.

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Introduction

Age-related bone loss leads to osteoporosis and its associated skeletal fractures. At the proximal femur, the site of the most clinically serious osteoporotic fractures, age-related bone loss occurs through a set of underlying structural changes that collectively result in diminished proximal femoral whole bone strength, increasing the likelihood of structural failure in the case of a fall [1–5]. Clinical evaluation of age-related changes in proximal femoral strength has become possible with the advent of subject-specific finite element modeling (FEM) based on volumetric quantitative computed tomography (vQCT) [6, 7]. The FEM technique employs the vQCT image to specify the three-dimensional bone geometry and distribution of material properties of the proximal femur, allowing estimation of structural strength with respect to clinically relevant loading conditions, such as a fall to the side with an impact on the greater trochanter. This approach has been validated as an important predictor of strength in vitro as well as a predictor of hip fracture in prospective studies [8, 9]. In a recent cross-sectional study, Keaveny et al. examined bone strength loss in a cohort of men and women ranging in age from 20 to 80 years, finding that proximal femoral whole bone strength, evaluated with respect to a lateral fall onto the lateral aspect of the greater trochanter, declined 55% and 39% over the lifetime in women and men respectively [10]. Although this study was the first to document cross-sectional estimates of lifetime losses of bone strength in both men and women, it was subject to limitations associated with cohort effects and included relatively small number of elderly subjects.

To determine longitudinal patterns of proximal femoral strength loss in elderly subjects, we have carried out a 5-year study, based on vQCT and FEM, of aging men and women enrolled in a population-based epidemiologic cohort, the Age/Gene Environment Susceptibility Study-Reykjavik (AGES-Reykjavik). Our goals were to examine gender differences in rate of bone strength loss, to determine whether the rate of bone strength loss differs between loading conditions simulating normal function and those simulating a fall, and to determine the extent to which the rate of bone strength loss varies with factors such as age and weight loss. By obtaining more accurate and more detailed measures of proximal femoral strength loss, we expect to better understand the pathophysiology of hip fracture, including the three-fold higher rate of hip fracture in elderly women compared to men, and the rapid rise of hip fracture risk at later ages in elderly males.

Materials and methods

Subjects

We studied a group of subjects selected from the Age Gene/Environment Susceptibility (AGES) Reykjavik cohort. The AGES-Reykjavik Study is an ongoing population-based study of men and women continuing the Reykjavik Study, which has been described in detail [11]. Baseline CT scans of 5500 subjects from this cohort were obtained between 2002 and 2006. Subjects were rescanned 5.05 ± 0.25 years after the baseline measurements. Informed consent was obtained from all participants in the study, which was approved (VSN 00–063) by the National Bioethics Committee in Iceland as well as the Institutional Review Board of the Intramural Research Program of the National Institute on Aging. Scans of a subset of 223 (111 men, 112 women) subjects were randomly chosen from the cohort, with the only constraint being equal sample sizes per decade of age for each sex and lack of metallic hardware within the field of view of the hip scan. For each subject, in addition to age, height and weight, the history of medications that may induce changes in BMD (e.g. hormone replacement therapy, bisphosphonates, thiazides or glucocorticoids), was recorded. Additionally, the subjects reported their state of health on a scale of 1–5 with a score of 1 indicating poor health and a score of 5 indicating excellent health.

Imaging

CT measurements in the hip were performed using a 4-detector CT system (Sensation 4, Siemens Medical Systems, Erlangen, Germany). To calibrate CT Hounsfield units to equivalent bone mineral concentration, all subjects were positioned supine on top of a calibration phantom (Image Analysis, Columbia, KY, USA), which extended from superior to the L1 vertebral body to the mid-femoral shaft. The phantom contained calibration cells of 0, 75 and 150 mg/cm^3 equivalent concentrations of calcium hydroxyapatite. A helical study of the hip (120 kVp, 140 mA s, 1-mm slice thickness, pitch = 1, coarsened to 3-mm slice thickness) encompassed the proximal femur from a point 1 cm superior to the acetabulum to a point 3–5 mm inferior to the lesser trochanter.

Finite element modeling

From the baseline (pre-fracture) QCT data for the left hip of each subject at each time point, we computed hip bone strength using our FE modeling method. The FE models incorporated patient-specific geometry and heterogeneous material properties that were computed from the QCT density data. The specific methodology has been described in detail previously and will be briefly outlined here [6, 12, 13]. Two loading conditions were studied (Fig. 1). One approximately represented single-limb stance loading, with displacement applied to the femoral head in the coronal plane at 20° to the shaft axis. The second simulated loading from a fall onto the posterolateral aspect of the greater trochanter, with force applied to the femoral head at 60° to the shaft axis and 25° to the coronal plane while the opposing surface of the greater trochanter was constrained in the direction of the force.

For single-limb stance loading, heterogeneous nonlinear properties were used to describe the nonlinear stress–strain relationship for the 3-mm cube of bone that was represented by each finite element. Use of nonlinear properties allowed modeling of the failure process as displacement was incrementally applied to the femoral head and the equivalent reaction force on the femoral head was calculated by the model. The FE-computed bone strength under stance loading (F_{Stance}) was defined as the maximum total reaction force on the femoral head. This nonlinear modeling method was necessary for the stance loading condition because linear models did not provide adequate precision for predicting fracture loads under this type of loading. In contrast, for fall loading, linear models employing heterogeneous linear elastic material properties were used. The fracture load for the fall loading condition (F_{Fall}) was defined as the force on the femoral head at the onset of fracture, i.e. the point at which local failure begins within the proximal femur. The fracture loads computed using this FE modeling method and these particular stance and posterolateral fall loading conditions have been validated previously via mechanical testing of cadaveric specimens, with high correlations of finite element prediction fracture load to measured fracture load in both loading conditions (stance, $r^2 = 0.93$ [12]; fall, $r^2 = 0.90$ [13]).

vQCT measures of proximal femoral structure

CT images were transferred from the CT scanner to a network of computer workstations equipped with the Linux operating system (Red Hat Version 7.2) and the AVS5 visualization program (AVS, Waltham MA, USA). Proximal femoral vQCT images were processed to extract measures of BMD and cortical structure [14] in the total femur region (Fig. 2). This involved calibration of the images and segmentation procedures to determine trabecular, cortical and integral regions of interest in a region of interest similar to the total femur region used in DXA. In this region, we computed several parameters which have been shown to predict hip fracture in cross-sectional and prospective studies [15, 16]. These included trabecular BMD (tBMD,