Published in final edited form as:

Bone. 2013 July ; 55(1): 179–188. doi:10.1016/j.bone.2013.02.009.

Three-dimensional Structural Analysis of the Proximal Femur in an Age-Stratified Sample of Women

Kristy M. Nicks¹, Shreyasee Amin^{2,3}, L. Joseph Melton III³, Elizabeth J. Atkinson³, Louise K. McCready¹, B. Lawrence Riggs¹, Klaus Engelke⁴, and Sundeep Khosla¹

Kristy M. Nicks: nicks.kristy@mayo.edu; Shreyasee Amin: amin.shreyasee@mayo.edu; L. Joseph Melton: melton.j@mayo.edu; Elizabeth J. Atkinson: Atkinson@mayo.edu; Louise K. McCready: mccready.louise@mayo.edu; B. Lawrence Riggs: riggs.lawrence@mayo.edu; Klaus Engelke: klaus.engelke@imp.uni-erlangen.de; Sundeep Khosla: khosla.sundeep@mayo.edu

¹Endocrine Research Unit, College of Medicine, Mayo Clinic, Rochester, Minnesota, USA

²Division of Rheumatology, College of Medicine, Mayo Clinic, Rochester, Minnesota, USA

³Department of Health Sciences Research, College of Medicine, Mayo Clinic, Rochester, Minnesota, USA

⁴Institute of Medical Physics, University of Erlangen, Erlangen, Germany

Abstract

Introduction—Aging is associated with worsening bone structure and increasing risk of hip fracture. However, the commonly used clinical tool, dual-energy x-ray absorptiometry, does not provide information on changes with age or disease separately in trabecular versus cortical bone or in bone geometry. Here we used 3D quantitative computed tomography (QCT) to analyze age-related changes in femoral volumetric bone mineral density (vBMD) and structure in a well characterized, population-based cohort of Rochester, Minnesota women.

Methods—MIAF-Femur (MIAF: medical image analysis framework) was used for the analysis of CT datasets from 358 women age 20 to 97 years. Integral, “apparent” cortical (rather than true cortical vBMD, due to volume averaging effects) and trabecular vBMD, volume, and bone mineral content (BMC) as well as cortical thickness of the femur head, neck, trochanter, inter-trochanteric, and proximal shaft VOIs were measured. In addition, changes in vBMD in the superior, inferior, posterior and anterior quadrants of the femur neck were assessed.

Results—Cross-sectional percent decreases in vBMD across life were 2- to 5-fold higher in trabecular versus cortical bone at all sites in the femur, although absolute changes in trabecular and cortical bone were fairly similar. In addition, the slopes of the relationships of trabecular vBMD with age were generally similar in pre- and post-menopausal women, whereas apparent cortical vBMD in the femur neck, trochanter, inter-trochanteric region, and proximal shaft remained relatively stable in premenopausal women but decreased significantly with age following the menopause. Bone volume increased at all sites, more so in pre- compared to postmenopausal women. Age-related BMC changes were not significant in premenopausal

© 2012 Elsevier Inc. All rights reserved.

Corresponding author: Sundeep Khosla, M.D., Endocrine Research Unit, Mayo Clinic, Guggenheim 7, 200 First Street SW, Rochester, MN 55905, USA. Telephone: 507-255-6663; Fax: 507-293-3853; khosla.sundeep@mayo.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of interest: None of the authors has a relevant conflict to disclose

women, but BMC losses were highly significant in postmenopausal women. Detailed analyses of femur neck cortical bone showed that percent apparent vBMD decreases in the superior quadrants were 2- to 3-fold greater than in the inferior quadrants; changes in absolute values were most different (~2-fold) between the superior-posterior and inferior-posterior quadrants.

Conclusions—These data demonstrate that patterns of changes with age within the femur differ in trabecular versus cortical bone. In the cortical compartment which, due to limitations in spatial resolution, contains some subcortical bone and should be regarded as an “apparent” cortical VOI, the superior quadrants in the femur neck undergo the greatest decreases. These findings may have important implications for understanding the structural basis for increased hip fracture risk with aging.

Keywords

osteoporosis; femur; aging

Introduction

Aging is associated with significant deterioration in bone structure [1] and increase in fracture risk [2]. However, although dual-energy x-ray absorptiometry (DXA) is an excellent clinical tool, it does not provide information on changes with age or disease separately in trabecular versus cortical bone or in bone geometry. In addition, DXA measures areal bone mineral density (aBMD), which is obtained by dividing bone mineral content by the projected area. Since wider bones also have greater depth in the anteroposterior direction, DXA overestimates the BMD of larger bones, confounding the interpretation of age- and sex-related changes [1]. To circumvent these problems, we [3] and others [4] have utilized quantitative computed tomography (QCT) to describe age-related changes in volumetric bone mineral density (vBMD) of trabecular versus cortical bone, as well as in bone size and geometry. While these studies have provided new insights into the structural basis for age-related bone fragility, a potential limitation of most previous approaches has been the restriction to the femoral neck and shaft and the use of 2-dimensional cross-sections of the 3-dimensional QCT images, which may perhaps lead to loss of important information relevant to the structural changes associated with aging.

In the present study, we analyzed age-related changes in femoral vBMD and structure in a well characterized, population-based cohort of Rochester, Minnesota women using MIAF-Femur (MIAF: medical image analysis framework), a recently described 3-dimensional analysis [5, 6]. In contrast to our previous 2-dimensional analysis of this cohort, where we were only able to assess cross-sections of the femur neck [3], the MIAF-Femur analysis allowed us to evaluate integral, volumetric measures not only at the femur neck, but also the femoral head, trochanter, inter-trochanteric region, and proximal shaft. In addition, a significant advantage of the MIAF-Femur approach is its ability to perform 3-dimensional segmentation of periosteal and endosteal surfaces [5, 6], which allows for the determination of cortical variables (vBMD, volume, and thickness). Furthermore, the femoral neck can be divided into four quadrants to address differential vBMD and geometry responses of its superior, inferior, posterior and anterior parts. Thus, in the present analysis, we sought to better understand age-related alterations in regional cortical versus trabecular vBMD and in bone geometry using MIAF-Femur.

Methods

Study subjects

We recruited subjects from an age-stratified, random sample of Rochester, MN residents [3]. This community is highly characteristic of the United States White population but underrepresented with respect to Blacks, Hispanics and Asians [7]. Reflecting the ethnic composition of the community, 99% of the women were White. The sample spanned ages from 20 to 97 years and included 375 women; for technical reasons, the femur scans could not be analyzed in 17 women; results are thus reported in 358 women (124 premenopausal and 234 postmenopausal). In addition, 59 scans did not include enough of the proximal femur shaft for the shaft analyses so this was done in 299 of the subjects. Forty-three of the premenopausal women were on estrogen-containing oral contraceptives; 79 of the postmenopausal women were receiving estrogen therapy; 7 were on a selective estrogen receptor modulator (SERM); 3 women were receiving bisphosphonate therapy; and one woman was reported to be on estrogen, SERM, and bisphosphonate therapy.

Study protocol

Subjects were evaluated at the outpatient Clinical Research Unit following an overnight fast. They consumed their habitual diet the day prior to study without any dietary restrictions. Height was obtained with a customized height gauge (Mayo Section of Engineering) and weight with an electronic scale (Model 5002, Tronic, Inc., White Plains, NY). Body mass index (BMI) was calculated as weight/height² (kg/m²). Following a blood draw, the subjects underwent the imaging procedures described below.

QCT of the proximal femur

As previously described for this cohort [3], single energy scans at the proximal femur were obtained on a LightSpeed QX/i 4 detector row CT scanner using 120 kV, 100 mAs and a pitch of 0.75 resulting in an effective 133 mAs tube current exposure time product. The reconstructed slice thickness and reconstruction element were 2.5 mm, and the Standard reconstruction kernel was used. Most datasets were reconstructed with a field of view (FOV) of 380 mm, but FOVs up to 500 mm were used. Thus, both femora and the calibration phantom (model 2 CT calibration phantom, Mindways Software Inc., Austin TX) were covered by the FOV.

We have previously reported on the 2-dimensional analysis of cross-sections of the femur neck in this cohort [3]. For the present analysis, we used the 3-dimensional MIAF-Femur (version 5.8.3M), which was developed at the Institute of Medical Physics (University of Erlangen, Erlangen, Germany). As described in detail previously [5, 6], an important advantage of this software is the 3-dimensional segmentation, i.e., the CT image stack is not analyzed slice by slice. Also the segmentation is not based on a global threshold but rather on local noise and vBMD adaptive thresholding techniques combined with volume growing and morphologic operations. Specifically, the periosteal and endosteal surfaces are segmented automatically by the analysis of local grey value profiles obtained after a 3-dimensional triangulation of the outer bone surface [5, 6]. As described in more detail in the earlier publications, 50% density thresholds were determined in the grey value profile to define the local extension of the cortex. The trabecular compartment is not segmented independently but based on the endosteal surface. In order not to include any subcortical bone in the trabecular compartment, its surface is obtained by a homogeneous peeling of the endosteal surface by 1.5 mm.

In order to improve segmentation accuracy and to better exploit the intrinsic spatial resolution of the CT scanner, as in other QCT studies using MIAF-Femur [5, 6, 8, 9] the

large FOV containing both femurs and the calibration phantom is only used for the analysis of the phantom. Then a second smaller FOV of 150 to 200 mm from the same scan is reconstructed for the actual analysis of the femur. The small FOV only covers one femur; typically, the left one is used. For the current analysis, small FOV reconstructions were not available. Therefore, for the MIAF analysis, the FOV of all datasets was resampled by a factor of two isotropically using windowed sinc interpolation with Lanczos window of width 3 [10]. For all subjects, the left hip was analyzed (Figure 1). Thus, the in plane pixel size of the analyzed images varied between $(0.35 \text{ mm})^2$ and $(0.49 \text{ mm})^2$, and the slice thickness was 1.25 mm.

The analyzed volumes of interest (VOIs) are calculated relative to an anatomic coordinate system (ACS) with its origin centered at the smallest cross section of the neck and included the femur head, neck, trochanter, inter-trochanter, and the proximal shaft (Figure 2). The borders between head and neck and between neck and trochanter are determined automatically based on anatomical landmarks and the ACS. The width of the neck is subject-specific and depends on the size of the femur and the shape of the neck. In each VOI, integral (total), trabecular, and cortical vBMD, BMC, and volume and cortical thickness were analyzed.

Due to the limited spatial resolution of the QCT scans, there is significant volume-averaging for cortical parameters. Thus, the “cortical” VOI includes both cortical and some endosteal trabecular bone. As such, the cortical VOI is better described as an “apparent cortical VOI” (and the term “apparent” cortical vBMD is used throughout), which is enriched for cortical bone but also inevitably includes some component of the endosteal surface. Therefore, we also analyzed the product of apparent cortical vBMD and cortical thickness, which can be determined with better accuracy than either of the two individual components alone.

Biochemical and hormonal assays

Serum parathyroid hormone (PTH) was measured using a two-site immunoassay for intact PTH (Diagnostic Products Corporation, Los Angeles, CA; interassay CV < 13%). Bone formation was assessed with serum amino-terminal propeptide of type I collagen (PINP) as measured by radioimmunoassay (DiaSorin, Stillwater, MN; interassay CV < 9%), and serum cross-linked C-telopeptide of type I collagen (CTX) was measured using an ELISA (Nordic Biosciences, Herlev, Denmark; interassay CV < 10) to evaluate bone resorption. Serum estradiol (E_2) and testosterone (T) were measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS; API 5000, Applied Biosystems-MDS Sciex, Foster City, CA) as previously described [11]. Values as low as 1.25 pg/mL for E_2 and 1 ng/dL for T were detectable by this method, with interassay CVs of 8% and 6% for E_2 and T, respectively. Sex hormone binding globulin (SHBG) was assessed using a chemiluminescent immunoassay (Diagnostic Products Corporation, Los Angeles, CA; interassay CV < 8%), and the non-SHBG bound (bioavailable) fraction of total E_2 and T was measured as previously described [12]; interassay CVs for bioavailable E_2 (bio E_2) and T (bio T) were each < 12%.

Statistical analysis

All results were analyzed with and without the inclusion of women who were on estrogen-containing oral contraceptives or receiving estrogen, SERM, or bisphosphonate therapy. Because there was no significant difference in any of the results with their exclusion, we retained them in the final analysis. The relationships between the femur variables and age were studied using generalized additive models, where age was modeled using a smoothing spline. Each model was compared with a linear relationship, and the simplest model was used for estimating the change in the femur variables between ages 20 and 90 years. The age

slopes of pre- and postmenopausal women were estimated and compared using a linear model testing for an age-menopause interaction. Spearman correlations were used to compare the femur variables with anthropometric, bone turnover, and sex steroid variables. Smoothing splines were also used to explore the data. Analyses were run using R 2.14 (<http://www.R-project.org/> and SAS software).

Results

Table 1 shows the age-related changes in vBMD, and Table 2 in BMC, at the various sites in the femur. As is evident, total vBMD declined significantly (all $P < 0.001$) with age at the head, neck, trochanter, inter-trochanteric region, and proximal shaft (by 35–46%). The slopes of the relationships with age were generally steeper in post- as compared to premenopausal women, although the slopes did not differ statistically between the two groups except for the trochanter. As also shown in Table 1, the magnitude of the percent decrease with age was 2- to 5-fold higher in trabecular versus cortical bone, although the absolute changes were fairly similar. Of note, the slope of the relationship with age was virtually identical in pre- versus postmenopausal women for trabecular bone in the femur neck, trochanter, and inter-trochanteric region. By contrast, these slopes were not significantly different from zero for cortical bone at these sites plus the femur shaft in the premenopausal women, but similar to the slopes for trabecular bone (and clearly different from zero) in the postmenopausal women. Thus, within the proximal femur, there was little cortical bone loss in premenopausal women; by contrast, trabecular vBMD decreased at all sites in both pre- and postmenopausal women, along with significant losses of apparent cortical vBMD in the postmenopausal women. These findings are illustrated in Figure 3 (A–D) which shows the vBMD changes in trabecular versus cortical bone in the femur neck and trochanter.

In the femoral head only integral vBMD was analyzed. In the EFFECT study this parameter discriminated new hip fractures [13]. As can be seen from Table 1, age-related vBMD changes in the head were similar to those in the other VOIs. Integral vBMD in the head in the 20–29 year group was the same as for trochanter vBMD and lower than neck and inter-trochanter vBMD, which have higher contributions of apparent cortical vBMD.

Age-related changes in femoral bone volume and cortical thickness are delineated in Table 3. Total bone volume increased significantly with age at all sites, consistent with ongoing periosteal apposition. Interestingly, the bulk of the increase in bone volume at all sites occurred in premenopausal women, as illustrated in Figure 4; the only site where there may have been some postmenopausal periosteal growth appears to have been in the inter-trochanteric region. This was accompanied, however, by increases in trabecular volume, again principally in premenopausal women (Table 2). While cortical volume increased significantly over life at the trochanter (but not the neck, inter-trochanteric region, and shaft), cortical thickness decreased significantly at all sites (neck, trochanter, inter-trochanteric region, and shaft). With the exception of the neck, the decrease in thickness was only observed in postmenopausal women.

The age related changes in BMC delineated in Table 2 are consistent with the vBMD and volume changes. On a percentage basis, age-related BMC changes were smaller than vBMD changes, reflecting the increase in volume shown in Table 2. In the neck and inter-trochanteric region, cortical volume changes were small, and BMC therefore paralleled the vBMD changes. The BMC results more clearly show the difference between pre- and postmenopausal bone loss. Differences for all parameters were highly significant. In addition, changes in apparent cortical vBMD*thickness (Table 2) were generally greater than changes in apparent cortical vBMD or BMC.

Table 4 documents age-related changes in apparent cortical vBMD, volume, and thickness in the four quadrants (superior-posterior, superior-anterior, inferior-posterior, and inferior-anterior) of the femur neck, and Table 5 shows the analogous data for BMC. As is evident, percent decreases in vBMD and in BMC in the superior quadrants were 2- to 3-fold greater than in the inferior quadrants (Figure 5 A–D show the vBMD data); changes in absolute values were most different (2-fold) between the superior-posterior and inferior-posterior quadrants. In addition, while losses of vBMD in the superior quadrants were generally similar in pre- versus postmenopausal women, premenopausal women had little or no change in vBMD in the inferior quadrants. Also for BMC, the differences between pre- and postmenopausal women were significant between the inferior but not the superior quadrants. Total bone volume increased similarly in the four quadrants, and principally in premenopausal women. However, cortical volume did not change in the superior quadrants but tended to increase in the inferior quadrants. By contrast, cortical thickness decreased similarly across life in all four quadrants, driven largely by increases in trabecular volume.

Since percent changes with age differed most for apparent cortical vBMD in the superior versus inferior quadrants, we further investigated the potential determinants of these changes. For this analysis, we only included premenopausal women who were not on oral contraceptives or estrogen/SERM/bisphosphonate therapy. As shown in Table 4, none of the anthropometric, bone turnover, or sex steroid measures was correlated with regional apparent cortical vBMD in the femur neck in premenopausal women. Among the postmenopausal women, however, BMI was positively correlated with apparent cortical vBMD in the inferior, but not the superior, quadrants. Interestingly, the bone turnover markers were negatively correlated with apparent cortical vBMD in the inferior, but not the superior, quadrants in the postmenopausal women.

Discussion

In this detailed, 3-dimensional analysis of the femur using the MIAF-Femur software, we describe changes in different parts of the femur that are associated with aging in women and may have significant implications for our understanding of the age-related increase in fracture risk. In contrast to earlier studies, in the present analysis integral, trabecular and cortical compartments of the neck, trochanter and inter-trochanter were evaluated separately; the femoral head and shaft VOI were included; and, in the neck, a separate analysis by quadrants was performed. Results are further based on a full 3-dimensional segmentation and analysis of the QCT data.

Consistent with our previous 2-dimensional analysis of trabecular versus cortical bone changes in the neck across life [3], we found that percent decreases in trabecular vBMD within the femur with age were 2- to 5-fold greater than decreases in apparent cortical vBMD, although the absolute changes were fairly similar. In addition, the slopes of the relationships of trabecular vBMD with age were generally similar in pre- and postmenopausal women, providing further support for our previous cross-sectional [3] and longitudinal [14] data showing significant losses of trabecular vBMD even in young adult life. By contrast, apparent cortical vBMD in the femur neck, trochanter, inter-trochanteric region, and proximal shaft remained relatively stable in premenopausal women but decreased significantly with age following the menopause. We have previously suggested [15] that age-related decreases in apparent cortical vBMD seem to be closely associated with the onset of estrogen deficiency. By contrast, trabecular bone loss, while accentuated by estrogen deficiency, occurs independent of decreases in estrogen levels and is seen even in young adults.

Bone volume at all femur sites also increased with age, consistent with ongoing periosteal apposition with aging [16]. Interestingly, the slopes comparing the relationships of bone volume to age were different from zero in the pre- but not the postmenopausal women. This would suggest that at least at the femur, much of the age-associated increase in bone size may occur in young adult life, prior to the menopause. This interpretation is supported by the BMC results, which reflect volume and vBMD changes. In premenopausal women, there was no significant change in BMC, i.e. trabecular vBMD decreases were compensated by an increase in volume. By contrast, in postmenopausal women the age-related BMC losses were highly significant as were those for vBMD. Thus, from a biomechanical perspective, the BMC losses may be more relevant than the BMD losses. It is also worthwhile noting that the differences between pre- and postmenopausal BMC losses were highly significant, whereas vBMD differences were less significant.

As can be seen from Table 3, in premenopausal women, the increase in total volume was paralleled by an increase in trabecular volume. Thus, there is ongoing trabecularization at the endocortical surface, but due to the periosteal apposition cortical volume and thickness remain constant. This balance changes after menopause. Our results indicate that periosteal apposition significantly slows down or even stops but that endocortical resorption continues, resulting in decreased cortical thickness and partly in cortical volume, predominantly in the inter-trochanteric and shaft VOIs. Our interpretation may be biased by accuracy errors in cortical vBMD and thickness measurements. However, percent decreases of cortical vBMD*thickness differed from decreases in apparent cortical vBMD and BMC. This can only be explained by a change of cortical volume. As total volume increases in all VOIs, cortical thickness must decrease. Accuracy errors in the shaft with a cortical thickness of 4.4 mm will be less than 5% but those in the in the other VOIs will be larger. Nevertheless, if anything, the decrease in cortical thickness, volume and vBMD will be underestimated, and our general interpretation of the data remains valid. The change in cortical vBMD can be caused by a change in osteonal mineralization or cortical porosity. Interestingly, Bousson and colleagues [17] showed using microradiography that in the mid-shaft of the femur, cortical porosity was constant until approximately the age of 40 years and then increased thereafter, consistent with our results of stable apparent cortical vBMD in premenopausal women. These data were confirmed in a recent study of cortical bone from the mid shaft in 168 Australian women, which also showed that cortical porosity was fairly stable until the age of 45 and then increased mainly due to an increase of pore area [18].

Significant decreases in cortical thickness at the neck, trochanter and shaft VOIs in postmenopausal women were also reported in the AGES-Reykjavik study [19]. However, due perhaps to a different cortical segmentation technique, absolute values of cortical thickness at age 65 in the AGES population were about 50% larger than those shown in Table 3 for ages 20–29 and therefore the percent changes are not comparable with our data.

It is interesting that areal BMD decreases with age as measured by DXA are considerably smaller compared to integral vBMD changes as measured by QCT. In the hip, one may expect at least rather similar changes as, in contrast to the spine, there are no overlying bones contributing to the projectional BMD measurement. However, in the age range 20–85 years (Table 1 lists values between 20–90), vBMD decreased by 42%, 38%, and 43% in the neck, trochanter and inter-trochanter, respectively, whereas in the NHANES III study, corresponding decreases for areal BMD were 33%, 28% and 28% [20]. The differences between QCT and areal BMD were even larger in terms of the young normal standard deviation SD: between 20 and 85 years vBMD decreased by 5.2– 5.8 SD compared to a decrease between 2.2 and 2.8 SD for areal BMD. One potential reason could be the change in bone volume that may affect QCT and DXA measurements differently. An increase in volume perpendicular to the projected area is not captured by DXA, and therefore vBMD

decreases over time may be higher. This may have important implications for the interpretation of the T-score, defined relative to the young normal population. The age-related decrease in T-score would not fully capture the decrease in vBMD but would partly be compensated by an increase in bone volume. Finally, it is possible that changes in marrow fat over life may have a greater impact on vBMD by QCT as compared to areal BMD by DXA.

Age-related decreases in femoral strength between 30 and 85 years determined earlier by finite element analysis (FEA) in the same population were ~ 55% [21]. Thus, integral vBMD or BMC changes apparently do not fully reflect strength changes. In particular, femoral strength was rather constant until the age of 45 years, whereas integral vBMD significantly decreased. Apparently, until the age of menopause, the vBMD decrease is compensated largely by constant apparent cortical vBMD and thickness in combination with a cortical volume increase. Strength is only marginally affected. This is reflected in the BMC results, where in the premenopausal women also no change was detected. During and after menopause, this picture changes: according to the results obtained in this study, apparent cortical vBMD and thickness now decrease but cortical volume stays constant, leading to a rapid decrease of strength, although there is no change in the ongoing decrease of trabecular vBMD.

As noted earlier, an important advantage of the MIAF-Femur approach is the ability to evaluate changes in the four quadrants of the femoral neck. This revealed that, on a percentage basis, age-related decreases in apparent cortical vBMD and BMC in the superior quadrants were 2- to 3-fold greater than in the inferior quadrants; changes in absolute values were most different (2-fold) between the superior-posterior and inferior-posterior quadrants. Interestingly, cortical thickness decreased with age similarly in all four quadrants. While cortical porosity could not be assessed given the resolution of central QCT, a study of neck biopsies of 19 postmortem males and females aged 79.4 ± 1.7 years without apparent diseases affecting bone metabolism found that cortical porosity was more than twice as high in the superior compared to the inferior sections [22]. Using a 2-dimensional analysis of a single slice perpendicular to the neck axis in a smaller cohort of women ($n = 100$), Poole and colleagues [23] also found that apparent cortical vBMD in the inferior-anterior quadrant was relatively preserved with age as compared to the superior quadrants, and they attributed this to the fact that the inferior quadrants of the femur neck are subjected to greater loads with standing and walking than the superior quadrants. Consistent with this, we found that body weight and body mass index were positively associated with vBMD of the inferior, but not superior, quadrants of the femur neck.

Interestingly, a case-control analysis of incident hip fracture cases from the AGES-REYKJAVIK study also found that cortical thickness in the superior region of the femoral neck was a stronger predictor of hip fracture risk than cortical thickness in the inferior region [24]. These findings were further confirmed by a number of DXA studies splitting the neckbox ROI into an upper and a lower part. All three studies found either better correlation of the upper part with bone strength [25] or improved hip fracture prediction [26, 27] compared to the complete ROI. Collectively, these findings suggest that age-related decreases in cortical bone in the superior regions of the femur neck may be particularly detrimental and predispose to hip fracture risk. It was also of interest that bone turnover markers were negatively correlated with vBMD in the inferior, but not superior, femur neck quadrants. This would suggest that age-related decreases in vBMD in the superior quadrants are relatively independent of systemic levels of bone turnover (as reflected by the bone turnover markers), driven perhaps by the relative lack of loading of these segments.

Although our study represents the largest, population-based evaluation to date of age-related regional changes in apparent cortical versus trabecular vBMD and bone geometry using a 3-dimensional analysis tool, we do recognize several limitations of our work. First, we drew inferences on changes in bone structural parameters over life using cross-sectional data. Clearly, longitudinal studies are needed to further validate our findings. Second, while we obtained information on current medication use, we do not have reliable data on previous medication use, and that could have influenced some of our findings. Third, compared to current state-of-the-art QCT imaging protocols, the CT scans used in this study had been acquired several years earlier and had larger in plane pixel sizes and larger slice thickness. Despite isotropic subsampling by a factor of 2, the spatial resolution remains limited and provides only estimates of cortical parameters due to volume-averaging artifacts. Thus, as noted in the Methods section, we acknowledge that our cortical VOI in fact includes cortical and some endosteal bone and should be best regarded as an “apparent cortical VOI/vBMD”. As a consequence the trabecular compartment may be slightly smaller than in higher resolution scans because its definition depends of the endosteal surface. Partial volume artifacts cause larger accuracy errors in cortical BMD of the neck and trochanter, where the cortex is thinner than of the inter-trochanteric and shaft VOIs, where the cortex is thicker. This is obvious from Table 1 as at least for the subjects in the group 20–29 yrs one would expect only a small variation of cortical porosity and therefore of apparent cortical vBMD among the different femur VOIs.

Nevertheless, differences in changes of apparent cortical BMD, BMC and thickness among neck, trochanter, intertrochanter and shaft changes should be interpreted cautiously. Accuracy errors depend on the ratio of the true cortical thickness (d) relative to the full width half maximum (FWHM) of the scanner, which was approximately 1 to 1.5 mm in this study.

Simulations using the segmentation technique employed in this study showed that a simulated change in cortical vBMD did not affect cortical thickness. However, a simulated change in cortical thickness also resulted in a change in cortical vBMD. In summary, accuracy errors in the determination of a change of cortical thickness were lower than 5% for $d > 2$ FWHM and for a change of apparent cortical vBMD or BMC were lower than 5% for $d > 0.5$ to 1 FWHM. In other words, the measurement of a change of cortical thickness is less accurate than of a change of apparent cortical vBMD or BMC if the cortical thickness lies approximately between 0.5 – 3. Thus, the differences in cortical thickness change among neck, trochanter and intertrochanter shown in Table 3 have to be interpreted with respect to larger accuracy errors compared to those for changes in apparent cortical vBMD, BMC or also apparent cortical vBMD * thickness, which are more homogeneous among neck, trochanter and intertrochanter.

The accuracy of cortical parameters is a problem, however, with virtually all previous studies utilizing clinical resolution CT imaging and attempting to assess cortical bone parameters at the femur (e.g., references [3, 4, 6, 8, 9, 14, 19, 23, 24, 27]). Somewhat mitigating this concern in studies like ours is the focus not on the absolute values at any given age (although that would clearly be ideal), but rather the relative changes with aging, which was our goal. As has been shown earlier, accuracy errors in the determination of cortical thickness do not preclude the detection of changes of cortical thickness, although these changes will be underestimated [28]. To the extent that this volume averaging problem is present across all ages due to the inherent limitation of the technique, we believe that these relative changes across life can still be cautiously interpreted, as we have done.

These limitations notwithstanding, our work extends previous findings regarding age-associated patterns of trabecular versus cortical bone loss in different sub-regions of the

femur. In addition, our data indicate that age-related increases in bone volume, at least at the femur, may occur principally in young adult life. Our findings also further highlight the importance of evaluating changes in cortical bone in different quadrants of the femur neck not only with aging, but likely also in patients at risk for hip fractures and in response to various treatments for osteoporosis.

Acknowledgments

We would like to thank Sara Achenbach for help with the statistical analyses and Jim Peterson for help with data management.

Funding: Supported by NIH Grants R01 AR027065 and UL1 TR000135 (Mayo CTSA).

References

1. Seeman E. From density to structure: growing up and growing old on the surfaces of bone. *J Bone Miner Res.* 1997; 12:509–521. [PubMed: 9101362]
2. Hui SL, Slemenda W, Johnston CC Jr. Age and bone mass as predictors of fracture in a prospective study. *J Clin Invest.* 1988; 81:1804–1809. [PubMed: 3384952]
3. Riggs BL, Melton LJ III, Robb RA, Camp JJ, Atkinson EJ, Peterson JM, Rouleau PA, McCollough CH, Bouxsein ML, Khosla S. Population-based study of age and sex differences in bone volumetric density, size, geometry, and structure at different skeletal sites. *J Bone Miner Res.* 2004; 19:1945–1954. [PubMed: 15537436]
4. Marshall LM, Lang TF, Lambert LC, Zmuda JM, Ensrud KE, Orwoll ES. Group OFiMMR. Dimensions and volumetric BMD of the proximal femur and their relation to age among older U.S. men. *J Bone Miner Res.* 2006; 21:1197–1206. [PubMed: 16869717]
5. Kang Y, Engelke K, Kalender WA. A new accurate and precise 3-D segmentation method for skeletal structures in volumetric CT data. *IEEE Trans Med Imaging.* 2003; 22:586–598. [PubMed: 12846428]
6. Bousson V, Le Bras A, Roqueplan F, Kang Y, Mitton D, Kolta S, Bergot C, Skalli W, Vicaud E, Kalender W, Engelke K, Laredo J-D. Volumetric quantitative computed tomography of the proximal femur: relationships linking geometric and densitometric variables to bone strength. Role for compact bone. *Osteoporos Int.* 2006; 17:855–864. [PubMed: 16547689]
7. Melton LJ III. History of the Rochester Epidemiology Project. *Mayo Clin Proc.* 1996; 71:266–274. [PubMed: 8594285]
8. Engelke K, Fuerst T, Dasic G, Davies RY, Genant HK. Regional distribution of spine and hip QCT BMD responses after one year of once-monthly ibandronate in postmenopausal osteoporosis. *Bone.* 2010; 46:1626–1632. [PubMed: 20226286]
9. Fitzpatrick LA, Dabrowski CE, Cicconetti G, Gordon DN, Fuerst T, Engelke K, Genant HK. Ronacaleret, a calcium-sensing receptor antagonist, increases trabecular but not cortical bone in postmenopausal women. *J Bone Miner Res.* 2012; 27:255–262. [PubMed: 22052452]
10. Duchon CE, Lanczos A. Filtering in one and two dimensions. *J of Applied Meteorology.* 1979; 18:1016–1022.
11. Khosla S, Amin S, Singh RJ, Atkinson EJ, Melton LJ, Riggs BL. Comparison of sex steroid measurements in men by immunoassay versus mass spectroscopy and relationships with cortical and trabecular volumetric bone mineral density. *Osteoporos Int.* 2008; 19:1465–1471. [PubMed: 18338096]
12. Khosla S, Melton LJ III, Atkinson EJ, O'Fallon WM, Klee GG, Riggs BL. Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: A key role for bioavailable estrogen. *J Clin Endocrinol Metab.* 1998; 83:2266–2274. [PubMed: 9661593]
13. Bousson V, Adams J, Engelke K, Aout M, Bergot C, Cohen-Solal M, Goldberg D, Champion K, Haguenaer D, Aksouh R, Vicaud E, Laredo JD. In vivo discrimination of hip fracture with quantitative computed tomography: Results from the prospective European femur fracture study (EFFECT). *J Bone Miner Res.* 2011; 26:881–893. [PubMed: 20939025]

14. Riggs BL, Melton LJ, Robb RA, Camp JJ, Atkinson EJ, McDaniel L, Amin S, Rouleau PA, Khosla S. A population-based assessment of rates of bone loss at multiple skeletal sites: evidence for substantial trabecular bone loss in young adult women and men. *J Bone Miner Res.* 2008; 23:205–214. [PubMed: 17937534]
15. Khosla S, Melton LJ, Riggs BL. The unitary model for estrogen deficiency and the pathogenesis of osteoporosis: is a revision needed? *J Bone Miner Res.* 2011; 26:441–451. [PubMed: 20928874]
16. Seeman E. The periosteum: a surface for all seasons. *Osteoporosis Int.* 2007; 18:123–128.
17. Bousson V, Meunier A, Bergot C, Vicaud E, Rocha MA, Morais MH, Laval-Jeantet AM, Laredo JD. Distribution of intracortical porosity in human midfemoral cortex by age and gender. *J Bone Miner Res.* 2001; 16:1308–1317. [PubMed: 11450707]
18. Thomas CD, Feik SA, Clement JG. Increase in pore area, and not pore density, is the main determinant in the development of porosity in human cortical bone. *J Anat.* 2006; 209:219–230. [PubMed: 16879600]
19. Sigurdsson G, Aspelund T, Chang MS, Jonsdottir B, Sigurdsson S, Eiriksdottir G, Gudmundsson A, Harris TB, Gudnason V, Lang TF. Increasing sex difference in bone strength in old age: the Age, Gene/Environment Susceptibility-Reykjavik study (AGES-REYKJAVIK). *Bone.* 2006; 39:644–651. [PubMed: 16790372]
20. Looker AC, Wahner HW, Dunn WL, Calvo MS, Harris TB, Heyse SP, Johnston CC Jr, Lindsay R. Updated data on proximal femur bone mineral levels of US adults. *Osteoporosis Int.* 1998; 8:468–489. [PubMed: 9850356]
21. Keaveny TM, Kopperdahl DL, Melton LJ III, Hoffmann PF, Amin S, Riggs BL, Khosla S. Age-dependence of femoral strength in white women and men. *J Bone Miner Res.* 2010; 25:994–1001. [PubMed: 19874201]
22. Bell KL, Loveridge N, Power J, Garrahan N, Meggitt BF, Reeve J. Regional differences in cortical porosity in the fractured femoral neck. *Bone.* 1999; 24:57–64. [PubMed: 9916785]
23. Poole KES, Mayhew PM, Rose CM, Brown CM, Brown JK, Bearcroft PJ, Loveridge N, Reeve J. Changing structure of the femoral neck across the adult female lifespan. *J Bone Miner Res.* 2010; 25:482–491. [PubMed: 19594320]
24. Johannesdottir F, Poole KES, 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.* 2011; 48:1268–1276. [PubMed: 21473947]
25. Boehm HF, Eckstein F, Wunderer C, Kuhn V, Lochmueller EM, Schreiber K, Mueller D, Rummeny EJ, Link TM. Improved performance of hip DXA using a novel region of interest in the upper part of the femoral neck: in vitro study using bone strength as a standard of reference. *J Clin Densitom.* 2005; 8:488–494. [PubMed: 16311437]
26. Duboeuf F, Bauer DC, Chapurlat RD, Dintin JM, Delmas P. Assessment of vertebral fracture using densitometric morphometry. *J Clin Densitom.* 2005; 8:362–368. [PubMed: 16055969]
27. Crabtree N, Lunt M, Holt G, Kroger H, Burger H, Grazio S, Khaw KT, Lorenc RS, Nijs J, Stepan J, Falch JA, Miazgowski T, Raptou P, Pols HAP, Dequeker J, Havelka S, Hozowski K, Jajic I, Czekalski S, Lyritis G, Silman AJ, Reeve J. Hip geometry, bone mineral distribution, and bone strength in European men and women: the EPOS study. *Bone.* 2000; 27:151–159. [PubMed: 10865223]
28. Prevrhal S, Engelke K, Kalender WA. Accuracy limits for the determination of cortical width and density: The influence of object size and CT imaging parameters. *Phys Med Bio.* 1999; 44:751–764. [PubMed: 10211808]

Highlights

- We analyzed age-related changes in the femur using a 3-dimensional skeletal analysis tool.
- Patterns of changes with age for volumetric bone mineral density differed in trabecular versus cortical bone.
- Apparent cortical volumetric bone mineral density in the superior quadrants in the femur neck underwent the greatest decreases with age.

Figure 1.
Volumes of interest (VOIs) analyzed in the femur: head (green), neck (red), trochanter (blue), intertrochanter (cyan) and shaft (yellow)

Figure 2.
 (A) CT scan, large field of view reconstruction used to segment the calibration phantom; (B)
 Multi-planar reformations (MPRs) of the interpolated small field of view reconstruction
 used to analyze the left femur – axial (upper left), coronal (lower left) and sagittal (upper
 right) reformations with segmented VOIs shown as contours. Lower right: slice
 perpendicular to the neck indicating the quadrants of the neck analyzed separately for
 vBMD, volume, and thickness.

Figure 3.

Relationship of (A) femoral neck trabecular vBMD (expressed as a percentage of the mean value in young women aged 20–29 years), (B) femoral neck apparent cortical vBMD, (C) trochanter trabecular vBMD, and (D) trochanter cortical vBMD to age among Rochester, Minnesota women. Dashed lines with diamonds indicate premenopausal women; solid lines with circles indicate postmenopausal women. Shown are the mean values and 95% confidence intervals.

Figure 4.

Relationship of (A) femoral head volume (expressed as a percentage of the mean value in young women aged 20–29 years), (B) femoral neck volume, (C) trochanter total volume, and (D) inter-trochanteric total volume to age among Rochester, Minnesota women. Dashed lines with diamonds indicate premenopausal women; solid lines with circles indicate postmenopausal women. Shown are the mean values and 95% confidence intervals.

Figure 5.

Relationship of apparent cortical vBMD in the femur neck by quadrants (expressed as a percentage of the mean value in young women aged 20–29 years) to age among Rochester, Minnesota women. Dashed lines with diamonds indicate premenopausal women; solid lines with circles indicate postmenopausal women. Shown are the mean values and 95% confidence intervals.

Table 1

Changes across life in femoral vBMD (mg/cm³) among Rochester, Minnesota women.

	Mean ± SD (20–29 yrs)	% change between 20 and 90 yrs	Absolute change between 20 and 90 yrs	Age Slope, Premenopausal	Age Slope, Postmenopausal	P-value, pre- vs post-menopausal slope
Total						
Head	300 ± 36	–43 ^{***}	–138 ^{***}	–1.4 ^{**}	–2.0 ^{***}	0.231
Neck	438 ± 49	–45 ^{***}	–203 ^{***}	–2.6 ^{***}	–2.6 ^{***}	0.971
Trochanter	292 ± 31	–41 ^{***}	–129 ^{***}	–1.0 [*]	–2.1 ^{***}	0.034
Inter-trochanter	421 ± 46	–46 ^{***}	–206 ^{***}	–2.0 ^{**}	–3.0 ^{***}	0.154
Proximal shaft	682 ± 80	–35 ^{***}	–247 ^{***}	–1.8 ^{***}	–3.9 ^{***}	0.076
Trabecular						
Neck	268 ± 40	–74 ^{***}	–204 ^{***}	–3.2 ^{***}	–2.7 ^{***}	0.354
Trochanter	151 ± 28	–62 ^{***}	–98 ^{***}	–1.5 ^{***}	–1.4 ^{***}	0.688
Inter-trochanter	213 ± 38	–70 ^{***}	–158 ^{***}	–2.0 ^{***}	–2.3 ^{***}	0.589
Apparent Cortical						
Neck	635 ± 51	–26 ^{***}	–168 ^{***}	–1.1 ^{***}	–2.2 ^{***}	0.106
Trochanter	521 ± 48	–28 ^{***†}	–144 ^{***}	0.0	–3.2 ^{***}	<0.001
Inter-trochanter	804 ± 49	–23 ^{***}	–192 ^{***}	–1.0 ^{***}	–2.8 ^{***}	0.023
Proximal shaft	1072 ± 52	–16 ^{***}	–170 ^{***}	–1.1 ^{***}	–2.4 ^{***}	0.177

* P < 0.05;

** P < 0.01;

*** P < 0.001 versus 0;

† non-linear.

Units for the slope are mg/cm³/year.

Table 2

Changes across life in femoral BMC (mg) and apparent cortical vBMD*thickness (mg/cm²) among Rochester, Minnesota women.

	Mean ± SD (20–29 yrs)	% change between 20 and 90 yrs	Absolute change between 20 and 90 yrs	Age Slope, Premenopausal	Age Slope, Postmenopausal	P-value, pre- vs post-menopausal slope
Total BMC						
Head	10177 ± 1687	–32***†	–3182***	–6.5	–61.1***	0.006
Neck	7343 ± 1291	–35***	–2774***	5.7	–46.7***	0.002
Trochanter	7483 ± 1584	–31***†	–2341***	4.5	–50.3***	0.003
Inter-trochanter	9401 ± 2165	–34***	–3427***	–6.8	–57.2***	0.030
Proximal shaft	3429 ± 417	–23***†	–804***	3.3	–17.2***	<0.001
Trabecular BMC						
Neck	2006 ± 454	–63***	–1399***	–9.3	–23.1***	0.012
Trochanter	2056 ± 606	–50***	–1116***	–12.5*	–19.0***	0.369
Inter-trochanter	2665 ± 735	–56***	–1647***	–12.2	–26.6***	0.055
Apparent Cortical BMC						
Neck	4454 ± 796	–22***	–1033***	15.0	–17.8***	0.003
Trochanter	4453 ± 857	–18***†	–810***	16.0	–25.3***	<0.001
Inter-trochanter	5607 ± 1322	–23***	–1402***	6.6	–24.6***	0.039
Proximal shaft	3019 ± 373	–24***	–773***	1.9	–14.7***	0.003
Apparent Cortical vBMD*Thickness						
Neck	200 ± 23	–32***	–67***	–0.55*	–0.83***	0.326
Trochanter	150 ± 16	–29***†	–44***	0.04	–0.97***	<0.001
Inter-trochanter	249 ± 27	–32***	–86***	–0.32	–1.35***	0.009
Proximal shaft	469 ± 71	–33***	–165***	–0.32	–2.83***	0.016

* P < 0.05;

** P < 0.01;

P < 0.001 versus 0;

[†] non-linear.

Units for the slope are mg/year.

Table 3
Changes across life in femoral bone volume and thickness among Rochester, Minnesota women.

	Mean $\pm$ SD (20–29 yrs)	% change between 20 and 90 yrs	Absolute change between 20 and 90 yrs	Age Slope, Premenopausal	Age Slope, Postmenopausal	P-value, pre- vs post-menopausal slope
Total volume (cm³)						
Head	34.0 $\pm$ 4.7	+15 ***	5.32 ***	0.15 **	0.06	0.130
Neck	16.9 $\pm$ 2.9	+15 **	2.68 **	0.13 **	0.00	0.006
Trochanter	25.6 $\pm$ 4.4	+20 ***	5.17 ***	0.12 *	0.05	0.169
Inter-trochanter	22.2 $\pm$ 3.9	+23 ***	5.25 ***	0.10 *	0.07 **	0.510
Shaft	5.1 $\pm$ 0.7	+16 ***	0.84 ***	0.02 *	0.01 *	0.322
Trabecular volume (cm³)						
Neck	7.5 $\pm$ 1.7	+26 ***	2.12 ***	0.08 **	0.01	0.010
Trochanter	13.6 $\pm$ 2.8	+25 ***	3.46 ***	0.08 *	0.03	0.168
Inter-trochanter	12.5 $\pm$ 2.3	+39 ***	4.87 ***	0.07 *	0.07 ***	0.783
Cortical volume (cm³)						
Neck	7.0 $\pm$ 1.1	+4	0.27	0.04 **	0.00	0.008
Trochanter	8.5 $\pm$ 1.3	+13 ***	1.17 ***	0.03 *	0.01	0.185
Inter-trochanter	6.9 $\pm$ 1.4	-1	-0.07	0.02	-0.01	0.146
Shaft	2.8 $\pm$ 0.3	-11 ***	-0.30 ***	0.005	-0.008 ***	0.003
Cortical Thickness (mm)						
Neck	3.1 $\pm$ 0.2	-9 ***	-0.29 ***	-0.003	-0.004 ***	0.910
Trochanter	2.9 $\pm$ 0.1	-3 *	-0.08 *	0.000	-0.002	0.261
Inter-trochanter	3.1 $\pm$ 0.2	-12 ***	-0.40 ***	0.000	-0.007 ***	0.008
Shaft	4.4 $\pm$ 0.5	-21 ***	-0.98 ***	0.001	-0.019 ***	0.004

* P < 0.05;

** P < 0.01;

P < 0.001 versus 0;

[†] non-linear.

Units for the slope are the units for each variable/year (mm³/year or mm/year).

Changes across life in apparent cortical vBMD, volume, and thickness by quadrant in the femur neck among Rochester, Minnesota women.

Table 4

	Mean $\pm$ SD (20–29 yrs)	% change between 20– 90 yrs	Absolute change between 20 and 90 yrs	Age Slope, Premenopausal	Age Slope, Postmenopausal	P-value, pre- vs post-menopausal slope
Apparent Cortical vBMD (mg/cm³)						
Superior-Posterior	537 $\pm$ 79	–42 ***	–235 ***	–2.5 ***	–2.7 ***	0.822
Superior-Anterior	478 $\pm$ 46	–39 ***	–193 ***	–2.10 ***	–2.17 ***	0.910
Inferior-Posterior	753 $\pm$ 60	–13 ***	–105 ***	0.32	–2.00 ***	0.011
Inferior-Anterior	767 $\pm$ 56	–22 ***	–174 ***	–1.17	–2.02 ***	0.364
Total volume (cm³)						
Superior-Posterior	4.27 $\pm$ 0.90	+12 *	0.56 *	0.034 **	0.002	0.010
Superior-Anterior	4.06 $\pm$ 0.65	+16 *, †	0.62 *, †	0.028 **	–0.004	0.005
Inferior-Posterior	4.34 $\pm$ 0.79	+16 **	0.73 **	0.030 **	0.002	0.024
Inferior-Anterior	4.18 $\pm$ 0.70	+22 ***	0.95 ***	0.035 ***	0.006	0.010
Cortical volume (cm³)						
Superior-Posterior	1.70 $\pm$ 0.33	–1	–0.01	0.008 *	–0.001	0.045
Superior-Anterior	1.76 $\pm$ 0.24	–1	–0.02	0.004	–0.002	0.152
Inferior-Posterior	1.81 $\pm$ 0.31	+9 *	0.18 *	0.011 **	–0.000	0.020
Inferior-Anterior	1.74 $\pm$ 0.27	+11 †	0.19 †	0.015 ***	–0.001	<0.001
Trabecular volume (cm³)						
Superior-Posterior	1.97 $\pm$ 0.52	+24 ***	0.51 ***	0.022 ***	0.002	0.008
Superior-Anterior	1.73 $\pm$ 0.38	+34 *** †	0.55 ***	0.021 ***	–0.002	0.001
Inferior-Posterior	1.98 $\pm$ 0.45	+23 ***	0.48 ***	0.016 *	0.002	0.050
Inferior-Anterior	1.87 $\pm$ 0.42	+37 ***	0.71 ***	0.017 **	0.006	0.112
Cortical thickness (mm)						
Superior-Posterior	3.08 $\pm$ 0.22	–10 ***	–0.31 ***	–0.005	–0.003 *	0.506

	Mean $\pm$ SD (20–29 yrs)	% change between 20– 90 yrs	Absolute change between 20 and 90 yrs	Age Slope, Premenopausal	Age Slope, Postmenopausal	P-value, pre- vs post-menopausal slope
Superior-Anterior	3.02 $\pm$ 0.19	–10 ^{***†}	–0.31 ^{***}	–0.008 ^{***}	–0.001	0.004
Inferior-Posterior	3.32 $\pm$ 0.21	–8 ^{***}	–0.26 ^{***}	–0.001	–0.004 ^{**}	0.302
Inferior-Anterior	3.16 $\pm$ 0.22	–12 ^{***}	–0.38 ^{***}	0.002	–0.007 ^{***}	0.014

* P < 0.05;

** P < 0.01;

*** P < 0.001 versus 0;

[†] non-linear.

Units for the slope are the units for each variable/year (mg/cm³/year, mm³/year, or mm/year).

Table 5
Changes across life in apparent cortical BMC by quadrant in the femur neck among Rochester, Minnesota women.

	Mean $\pm$ SD (20–29 yrs)	% change between 20–90 yrs	Absolute change between 20 and 90 yrs	Age Slope, Premenopausal	Age Slope, Postmenopausal	P-value, pre- vs post-menopausal slope
Apparent Cortical BMC (mg)						
Superior-Posterior	915 $\pm$ 219	–41 ^{***}	–395 ^{***}	–0.58	–4.71 ^{***}	0.062
Superior-Anterior	842 $\pm$ 134	–38 ^{***}	–346 ^{***}	–2.28	–4.60 ^{***}	0.204
Inferior-Posterior	1364 $\pm$ 287	–6 [†]	–73	9.03 [*]	–3.81	0.005
Inferior-Anterior	1333 $\pm$ 229	–16 ^{**}	–234 ^{**}	8.82 ^{**}	–4.64 [*]	<0.001

* P < 0.05;

** P < 0.01;

*** P < 0.001 versus 0.

Units for the slope are mg/year.

Table 6

Age-adjusted correlation coefficients between apparent cortical vBMD by quadrant in the pre- and postmenopausal women and anthropometric, bone turnover, and sex steroid variables in the pre- and postmenopausal women not using oral contraceptives, estrogen, SERMs, or bisphosphonates. S-P, superior-posterior; S-A, superior-anterior; I-P, inferior-posterior; I-A, inferior-anterior.

Variable	Premenopausal				Postmenopausal			
	S-P	S-A	I-P	I-A	S-P	S-A	I-P	I-A
Anthropometric								
Weight	-0.08	-0.07	0.03	-0.01	0.19 *	0.10	0.22 **	0.21 *
Height	0.15	0.10	-0.05	-0.11	0.21 *	0.09	0.17 *	0.13
BMI	-0.12	-0.10	0.07	0.04	0.13	0.08	0.20 *	0.18 *
Bone Turnover								
PINP	-0.00	0.05	0.11	-0.01	-0.10	-0.04	-0.24 **	-0.17 *
CTX	-0.07	-0.01	0.14	0.02	-0.08	0.01	-0.18 *	-0.11
PTH	-0.20	-0.19	-0.14	-0.16	-0.01	-0.09	-0.10	-0.20 *
Sex Steroid								
E2	0.07	-0.03	-0.01	0.02	0.16	0.10	0.11	0.08
Bio E2	0.15	0.03	0.07	0.08	0.15	0.16	0.14	0.12
T	-0.01	-0.04	-0.02	0.02	0.13	0.08	0.02	0.05
Bio T	0.06	-0.03	0.08	0.08	0.13	0.20 *	0.08	0.15

* P < 0.05;

** P < 0.01