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Structural adaptations to bone loss in aging men and women

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Abstract

Introduction: Bone apposition on the subperiosteal surface and bone loss from the endocortical surface during aging establish the external diameter, total cross-sectional area (tCSA), cortical thickness (Ct.Th) and the distance the cortex is placed from the neutral axis of a long bone, all determinants of bone strength. We tested the hypothesis that sex-related differences in these processes produces a sexual dimorphism in tibial fragility.

Methods: The above traits were assessed in 688 women and 561 men (20–102 years old) using peripheral QCT.

Results: Total and medullary areas were greater in young adult men than young adult women. As age advanced, in men, tCSA area increased by 0.79 SD, and medullary area increased by 0.54 SD so that cortical area, cortical thickness and minimum and maximum moments of inertia (I_{min} and I_{max}) were similar at all ages. In women, tCSA increased by 0.2 SD, while medullary area increased by 2.6 SD so that cortical area and thickness and the moments of inertia diminished. Cortical apparent volumetric bone mineral density (vBMD) declined more in women (by 3.1 SD) than men (by 0.5 SD). In both sexes, the lower the cortical apparent vBMD, the higher the tCSA (women $R^2 = 0.13$, men $R^2 = 0.16$, both $P < 0.0001$), whereas the lower the Ct.Th, the lower the tCSA (women $R^2 = 0.30$, men $R^2 = 0.32$, both $P < 0.0001$).

Conclusions: Bone loss reduces cortical thickness and increases intracortical porosity. These changes tend to be compensated for by periosteal apposition in both sexes but more greatly in men than in women, perhaps because this mechanism may be ineffective when cortical thinning is severe.

Keywords: Aging; Computed tomography; Bone biomechanics; Cross-sectional area

Introduction

Age-related bone loss is the result of an imbalance in the volumes of bone resorbed and formed in each focal basic multicellular unit (BMU) that remodels the bone tissue. Imbalance in the remodeling on the endocortical surface causes cortical thinning, while the imbalance in remodeling on the intracortical surface of the haversian canals increases intracortical porosity and reduces cortical apparent vBMD [1]. The age-associated decline in cortical thickness and increase in cortical porosity reduce the effective amount of mineralized cortical tissue area upon which loads are distributed. Consequently, the load per unit area (stress) rises, producing strains (deformations), that increase the risk of microdamage, progression of microcracks and, if the cortex becomes excessively thin, structural failure [2].

Several studies suggest that compensatory strategies exist that partially offset the progression to complete structural failure. As the cortical bone area declines, relatively greater loading is localized to the bone periphery furthest from the neutral or long axis and stimulates subperiosteal bone formation producing slight enlargement of the bone CSA. This mechanism

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may reduce the stresses on bone as the same loads are now dispersed on a larger CSA [3–6].

This process of periosteal apposition is believed to be a compensatory response to avert structural failure [2–6]. Indeed, the higher incidence of fractures in women than men is partly attributed to the observation in most, but not all, studies that periosteal apposition is less in women than in men. In other words, the greater net loss of bone and bone strength in women compared to men is due to lower periosteal apposition, as well as greater net endocortical bone resorption [4,6–9].

We tested the hypothesis that the age-related increment in tibial tCSA produced by periosteal apposition is a compensatory response to the decrease in cortical apparent vBMD, and that the lesser increase in tibial CSA in women compared to men results from an impairment of adaptation by periosteal apposition in the face of extreme cortical thinning.

Materials and methods

InCHIANTI is an epidemiological study conducted in two towns in the Chianti countryside: *Greve in Chianti* (11,709 inhabitants; rural area) and *Bagno a Ripoli* (village of Antella, 4704 inhabitants; just outside Florence). The design and data collection method have been reported [10]. Potential participants were 1530 subjects aged 65 years and older and 30 men and 30 women in each decade between 20 and 70 years randomly selected from the general population. Of these, 1453 (94%) agreed to participate.

The analyses were based on measurements of the tibia using peripheral quantitative computerized tomography (pQCT, XCT 2000, Stratec Medizintechnik, Pforzheim, Germany) in 1249 participants (688 women and 561 men). The most common reason for failed pQCT evaluation was poor mobility or transportation problems. The length of the tibia was measured as the distance between the medial knee joint cleft and the medial malleolus. Transverse scans (2.1 mm thick) were obtained at 38% of the tibial length from the tibio-talar joint cleft using a 0.5 mm voxel size. The cross-sectional images were analyzed using the *Geanie2.1* software that identifies cortical and trabecular bone (BonAlyse Oy, Jyvaskyla–Finland, http://www.bonalyse.com). Areas above 710 mg/cm^3 were considered cortical, areas between 180 and 710 mg/cm^3 were considered trabecular. Beam hardening (attenuation of the low-energy photons) by soft tissues surrounding bone is corrected using the Stratec QCT [11].

Cortical apparent vBMD (mg/cm^3) is a function of intracortical porosity and tissue mineral density. About 70% of age-related reduction in cortical apparent vBMD is attributable to increased porosity [12]. The threshold for cortical bone above 710 mg/cm^3 excludes low-density trabecularized inner cortex so a decrease in cortical apparent vBMD likely reflects increased intracortical porosity. Partial volume effect, the measurement as "cortical bone" of those voxels comprised of both cortical bone and surrounding tissues, makes the measurement of cortical bone density by QCT unreliable if the Ch.Th is lower than 3 times the voxel [13] or, according to other reports, if Ch.Th is lower than 3–4 mm [14]. Voxel size of 0.5 mm was used, and a value of Ch.Th lower than 3.3 mm was present in less than 10% of participants. Thus, we assumed that partial volume error was limited in this study; however, we also controlled statistically for a possible residual partial volume error (see Statistical analysis).

Tibial tCSA (mm^2) is the subperiosteal area defined as the total area within the periosteum, including cortical and medullary areas. tCSA was obtained using a threshold of 180 mg/cm^3 to separate bone from surrounding soft tissues. Cortical CSA is the bone CSA within the internal and external margin of the cortical ring, using an inner threshold of 710 mg/cm^3 to separate cortical from medullary area. Medullary area (mm^2) is the difference between total and cortical bone areas. It includes the marrow space and areas of the inner cortex trabecularized by endocortical resorption that have a cortical apparent vBMD <710 mg/cm^3. Therefore, an age-related expansion in medullary area is sensitive to endocortical resorption.

Ct.Th (mm) is the average thickness of cortical bone in the slice. The calculation, averaged over 360 directions (increments of one degree), makes no geometrical model assumptions as it is performed on the true shape of the bone. I_{min} and I_{max} are density-weighted area moments of inertia calculated along the direction of the smallest and greatest rigidity, respectively, according to the following formula: $I = \int ar^2\rho$ where "I" is the moment of inertia, "a" is the voxel area; "r" is the distance between each voxel and the neutral axis of the section; "ρ" is the density of the voxel [15]. I_{min} and I_{max} are accurate estimates of the minimum and maximum bending strength because they take both cortical apparent vBMD and geometric distribution of bone material into account.

Weight was measured to the nearest 0.1 kg using a high-precision mechanical scale with the participant wearing light clothes and without shoes. Height without shoes was measured to the nearest 0.1 cm. Body mass index (BMI) was calculated as kg/m^2. Some of the results of age-associated changes in cortical apparent vBMD, cortical and total bone area and I_{min} are published [5]. The study protocol was approved by the INRCA ethical committee. All subjects gave informed consent.

Statistical analysis

Data were reported as mean ± standard errors (SE). Comparison among groups was performed by analysis of variance (ANOVA) and analysis of covariance (ANCOVA). To account for sex differences and secular increases in height in later born generations, tibial areas, cortical thickness and moments of inertia were adjusted by tibial length [16]. Tibial areas were divided by tibial length squared in each subject and multiplied by the sample mean tibial length squared. Cortical thickness and moments of inertia were divided by tibia length in each subject and multiplied by the sample mean tibia length. Standardized values for bone CSAs, cortical thickness and moments of inertia were used in all the analyses and presentations. The interaction term age*sex was used in a general linear model to compare the age-associated increments in tibial tCSA and medullary area between genders. The Dunnett's "post hoc" test was used to compare CSA and cortical apparent vBMD in specific age groups with values of participants <50 year olds as the reference group. Age-related trends for different variables were tested using general linear models.

The effect of age, sex, cortical apparent vBMD and Ct.Th on tibial tCSA was evaluated in a multivariate linear model and graphically depicted by scatter plots. As a significant "sex*Ct.Th" interaction was observed, sex-specific models were also fitted. We adjusted the regression model for Ch.Th to examine the effect of low Ct.Th on the association between tCSA and cortical apparent vBMD. Moreover, to further control for possible effects of residual partial volume errors on the results, the regression analysis was repeated after excluding 167 women and 56 men with a Ct.Th <3.3 mm (10th percentile) [13,14]. In this subset of the study population, cortical apparent vBMD was independent of Ct.Th and remained an independent predictor of the tibial tCSA in men and women (data not shown). The relationships between age and Ct.Th and moments of inertia were examined by scatter plots and summarized by locally weighted regression smoothers. Analyses were performed using SAS 8.2 statistical software.

Results

In men, tibial tCSA and medullary areas increased across age, with the maximum increment after 85 years of age so that men older than 85 years had higher tCSA (by 19.6% or 0.79