Osteoporos Int (2003) 14: 531–538
DOI 10.1007/s00198-002-1322-y

ORIGINAL ARTICLE

Aging bone in men and women: beyond changes in bone mineral density

**C.R. Russo · F. Lauretani · S. Bandinelli · B. Bartali
A. Di Iorio · S. Volpato · J.M. Guralnik · T. Harris
L. Ferrucci**

Received: 16 May 2002 / Accepted: 6 September 2002

Abstract Using peripheral quantitative computed tomography (pQCT) we assessed trabecular and cortical bone density, mass and geometric distribution at the tibia level in 512 men and 693 women, age range 20–102 years, randomly selected from the population living in the Chianti area, Tuscany, Italy. Total, trabecular and cortical bone density decreased linearly with age ($p < 0.0001$ in both sexes), and the slope of age-associated decline was steeper in women than in men. In men, the cortical bone area was similar in different age groups, while in women older than 60 years it was significantly smaller by approximately 1% per year. The total cross-sectional area of the bone became progressively wider with age, but the magnitude of the age-associated increment was significantly higher in men than in women ($p < 0.001$). The minimum moment of inertia, an index of mechanical resistance to bending, remained stable with age in men, while it was significantly lower in older compared with younger women (0.5% per year). The increase in bone cross-sectional area in aging men may contribute to the maintenance of adequate bone mechanical competence in the face of declining bone density. In women this compensatory mechanism appears to be less efficient and, accordingly, the bone mechanical competence declines with age. The geometric adaptation of increasing cross-sectional bone size is an important component in the assessment of bone mechanical resistance which is completely overlooked, and potentially misinterpreted, by traditional planar densitometry.

Keywords Bone mechanical properties · Elderly · Osteoporosis · pQCT

C.R. Russo · S. Bandinelli · B. Bartali · L. Ferrucci (✉)
Laboratory of Clinical Epidemiology,
INRCA Geriatric Department,
Viale Michelangiolo 41, 50127 Florence, Italy
Tel.: +1-410-3503936
Fax: +1-410-3503979

F. Lauretani
Department of Critical Care Medicine and Surgery,
Section of Gerontology and Geriatric Medicine,
University of Florence, Florence, Italy

A. Di Iorio
Department of Medicine and Aging,
University of Chieti, Chieti, Italy

S. Volpato · J.M. Guralnik · T. Harris
Laboratory of Epidemiology,
Demography and Biometry,
NIA, Bethesda, Maryland, USA

L. Ferrucci
Clinical Research Branch,
National Institute on Aging (NIH),
Baltimore, Maryland, USA

Introduction

The skeletal bone mass increases during infancy and adolescence, reaches a peak in the third or fourth decade and then declines over the following years [1, 2]. In women, bone mass declines slowly and progressively in the years prior to menopause and then declines more rapidly with the postmenopausal drop in estrogen levels [3]. It is widely acknowledged that the age-associated decline in bone mass accounts for the high rates of bone fractures experienced by older persons, and especially by older women. Accordingly, current guidelines suggest that in clinical practice, the risk of fractures should be estimated by measuring bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA). This recommendation is based on the assumption that BMD is a good measure of bone strength. However, a number of recent reports have challenged this view, arguing that DXA provides a measure that does not account for changes in the quantitative and geometric distribution of trabecular and cortical bone tissues, which are important factors affecting bone strength in both the appendicular and axial skeleton [4, 5, 6, 7, 8, 9]. Several lines of research suggest that, over the aging process, bone tissue goes through a remodeling process mostly involving an enlargement of the cortical bone "ring". Although this remodeling process increases the bone mechanical resistance to fractures [8], it is detected by DXA simply as a reduction in BMD. Indeed, since most epidemiologic studies on aging bone have been based on DXA measures, very little is known about the dynamics of cortical bone mass in growth and aging.

In order to circumvent this problem, a peripheral quantitative computed tomography (pQCT) device has recently been developed which allows for separate assessments of cortical and trabecular bone and provides direct information on bone geometry. From the analysis of cross-sectional images provided by pQCT, information on mass and distribution of bone material can be integrated into indexes of bone stability in response to bending and torsional loads, which are the two most important biomechanical measures of susceptibly to appendicular fractures [10] and may improve our accuracy in the prediction of fractures [11, 12].

The aim of this study was to describe the age-related differences in purely trabecular and cortical bone density and mass and in the indexes of bone strength. The data presented in this report were obtained using pQCT in the participants of the InCHIANTI study, a large population-based sample of persons over the age range 20–102 years [13].

Materials and methods

The population sample

InCHIANTI is an epidemiologic study in two Italian towns in the Chianti countryside: Greve in Chianti (11,709 inhabitants; rural area) and Bagno a Ripoli (village of Antella, 4704 inhabitants; just outside the urban area of Florence). The study population consisted of a random sample of the population aged 65 years and older living in the two catchment areas, and 30 men and 30 women randomly selected in each decade between 20 and 70 years. A detailed description of the design and data collection methods of InCHIANTI have been published previously [13]. Of the 1,530 subjects originally sampled, 1,453 (94%) agreed to participate in the study. Of these, 612 men and 693 women underwent a pQCT examination (78% of men and 76% of women were older than 65 years). The study protocol was approved by the INRCA ethics committee. All subjects received an extensive description of the purposes and known risks of the study procedures, and all gave their informed consent.

Lower leg pQCT

Lower leg pQCT was performed in all the study participants by means of a recent-generation device (XCT 2000, Stratec Medizintechnik, Pforzheim, Germany). The subjects were seated in front of the apparatus with the right leg extended, positioned inside the gantry of the device. The distal end of the tibia (the tibio-talar joint cleft), identified using a pQCT longitudinal scout view, was used as an anatomic marker for the identification of the measurement sites. The length of the tibia had been previously assessed as the distance between the medial knee joint cleft and the medial malleolus (both identified by manual palpation) while the participant was lying supine. Standard 2.5 mm thick transverse scans were obtained at 4% of the tibial length, where trabecular bone is most abundant, and at 38% of the tibial length, where the cortical shell is usually thicker than 2.5 mm, thus allowing an accurate detection of the bone boundaries [14]. The cross-sectional images obtained from the pQCT were analyzed using BonAlyse (BonAlyse Oy, Jyvaskyla, Finland; http://www.bonalyse.com), software for processing pQCT scans that automatically identifies bone tissue (cortical and trabecular) and assesses its density and geometry. Different tissues in the analysis were separated according to different density thresholds. In particular, areas with density values above 710 mg/cm^3 were considered as "cortical bone" [15], while areas with density values between 180 and 710 mg/cm^3 were considered as "trabecular bone". The following bone parameters were derived from the pQCT images:

- *Total bone density* (mg/cm^3): assessed as the average density of the whole bone cross-section measured at the 4% site, including both the spongiosa and the thin surrounding cortical shell. Since bone marrow is also included in the measurement, and spongiosa is not measured separately from the cortex, it cannot be considered a measure of bone material property; rather, it provides a complex value, similar to the BMD obtained by DXA.
- *Trabecular bone density* (mg/cm^3):assessed as the average density of the trabecular bone area detected at the 4% site. Cortical bone was excluded from the measurement.
- *Cortical bone density* (mg/cm^3): a selective measure of the apparent volumetric density of cortical bone measured at the 38% site, which is a good marker of bone material property.
- *Total bone area* (mm^2): assessed as the cross-sectional area of the voxels with a density higher than 180 mg/cm^3 measured at the 4% site which is a measure of bone size.
- *Cortical bone area* (mm^2): assessed as the cross-sectional area of the voxels with a density higher than 710 mg/cm^3, measured at the 38% site. The cortical bone area is a good measure of total cortical bone mass and a valid marker of bone resistance against compression and tensile loads [15]. To obtain information on the mechanical bone competence against bending and torsional loads, we calculated two composite parameters, which take into account the characteristics and the spatial distribution of bone material:
- *Minimum moment of inertia* (g/cm): calculated as a density weighted moment of inertia at the 38% site, according to the following formula: $I = \int ar^2\rho$, where I is the minimum moment of inertia, a is the voxel area, r is the distance between each voxel and the neutral axis of the section, and ρ is the density of the voxel that is considered [16]. The minimum moment of inertia provides an estimate of the minimal resistance to bending of the examined section [10].
- *Eccentricity index* (I_y/I_x): calculated at the 38% site, as the ratio of the moment of inertia calculated along the y-axis (which coincides with the direction of the widest bone width that passes through the center of mass of the cross-section) and the moment of inertia calculated along the x-axis (defined as perpendicular to the y-axis). The eccentricity index provides a measure of the bone material cross-sectional distribution. For circular cross-sections, this ratio equals 1. However, as the bone cross-section becomes more elliptical, i.e., the bone assumes an eccentric shape, the I_y/I_x ratio increases [17].

The precision error of the XCT2000 is below 1% for volumetric trabecular and cortical density and for cortical bone area [15, 18], and between 1% and 3% for composite geometric parameters [15].

Standing height and weight were objectively measured in each participant, and body mass index (BMI) was calculated as the weight (kilograms) divided by the square of height (meters).

Statistical analysis

All analyses were performed using SAS 8.2 statistical software. Data are reported as mean values ± standard deviations (SD). To minimize the interference of secularization on measures of bone geometry, bone areas and the moment of inertia were normalized by tibial length according to Ruff [19].

The relationships between age and bone parameters were examined by scatter plots and visually summarized by locally weighted regression smoothers. To test whether the cross-sectional relationship between age and each bone parameter was linear, we fitted both linear models and generalized additive models where age as a linear predictor was substituted by a smoothing function of age. Relationships that were found to be non-linear were further examined using a series of piecewise regression models. In all cases of non-linearity, a two-segment model allowing different slopes before and after 60 years of age yielded the best fit. The slopes estimated for men and women were compared by testing an "agexsex" interaction terms [20] under the "null" hypothesis that the magnitude of age-associated difference in the specific parameter "per year" was similar in men and women.

Results

Data on anthropometric variables are reported in Table 1. Within each sex, height, weight and BMI were statistically different across age groups. In particular, height declined with increasing age in both sexes and men were taller than women in each age group. The age-related differences in body size could not be fully explained by the postural changes and reduction in intervertebral spaces which typically occur over the aging process. In fact, similar age-related trends were observed when the tibial length, a marker of body size that remains stable with aging, was considered.

In both men and in women, older age was associated with lower total, trabecular and cortical bone density (Table 2). Total and trabecular bone density were always lower in women than in men in each age group. Interestingly, average cortical bone density, the only parameter that directly assesses the bone material properties, was higher in women in the two age groups 20–39 years and 40–49 years, and became higher in men than in women thereafter. In men, cortical bone area, a marker of cortical bone mass, was similar in different age groups while total bone increased with aging. It is noteworthy that in women the cortical bone area was substantially lower at older ages, while the total bone area increased, although the magnitude of the age-associated increment was smaller than in men. In men, the *minimum moment of inertia*, a derived parameter that summarizes how parallel changes in bone material and in bone geometry translate into changes in bone mechanical properties, was not statistically different across age groups. On the contrary, in women we observed average values that were progressively smaller with age. The cross-sectional shape of bone and spatial homogeneity in the distribution of the cortical material in the bone ring appeared to be unaffected by age, as indicated by the lack of age-related differences in the eccentricity index in both sexes.

Further analyses were performed to test the hypothesis that bone structural and geometric parameters do not change linearly with age and that the form of such a relationship is different in the two sexes.

The relationship between age and trabecular and cortical bone density is depicted in the scatterplots of Fig. 1. For both parameters, and in both men and women, no significant departure from linearity was detected. Similar results were found when total bone density was analyzed. The sex-specific equations describing the relationships between age and total, trabecular and cortical bone density show that the slope of decline with age for all three parameters was statistically steeper in women (Table 3). The most striking difference concerned the cortical bone density, whose decline per year was 3 times higher in women than men.

Consistent with the data shown in Table 2, the size of the cortical bone area was not correlated with age in men, even when a non-linear form of the relationship was allowed. On the contrary, we found that in women the reduction of cortical bone area was much steeper at later ages (Fig. 2). Table 3 reports the slope of change in cortical bone area before and after the age of 60 years. This age threshold was selected because it maximized the

Table 1 Anthropometric data according to sex and age groups (InCHIANTI study population). Values are mean ± SD

	n	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	Tibial length (mm)
Men						
20–39 years	56	31.2 ± 5.2	175.2 ± 6.2	78.9 ± 13.2	25.6 ± 3.0	390.4 ± 25.0
40–49 years	48	45.1 ± 3.4	171.1 ± 7.0	83.1 ± 13.1	28.4 ± 4.5	396.0 ± 21.2
50–64 years	46	58.2 ± 5.1	171.7 ± 7.3	80.1 ± 11.7	27.4 ± 3.3	382.5 ± 23.1
65–74 years	254	70.1 ± 3.0	167.0 ± 7.1	76.5 ± 11.3	27.4 ± 3.2	373.0 ± 23.4
75–85 years	128	78.8 ± 3.8	163.9 ± 7.1	72.4 ± 12.2	26.9 ± 4.2	367.8 ± 24.6
85+ years	80	88.8 ± 3.3	158.8 ± 7.3	64.3 ± 7.6	25.4 ± 3.0	359.8 ± 20.5
ANOVA[a]		$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0005$	$p < 0.0001$
Women						
20–39 years	55	30.8 ± 5.2	162.3 ± 6.2	61.5 ± 10.1	23.4 ± 4.2	357.0 ± 22.2
40–49 years	47	44.4 ± 3.3	159.7 ± 6.2	65.6 ± 11.4	25.8 ± 5.4	348.8 ± 18.4
50–64 years	60	57.8 ± 5.1	158.0 ± 6.7	67.1 ± 11.2	26.8 ± 4.2	351.6 ± 23.5
65–74 years	283	70.8 ± 3.0	154.7 ± 6.1	67.4 ± 11.6	28.2 ± 4.2	346.1 ± 22.1
75–85 years	180	79.3 ± 3.7	151.3 ± 7.6	63.0 ± 11.4	27.5 ± 4.6	341.4 ± 21.0
85+ years	68	88.5 ± 3.6	148.3 ± 7.5	58.0 ± 10.1	26.3 ± 4.2	339.9 ± 20.5
ANOVA[a]		$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$

[a] Comparing mean values across age groups within sexes

Table 2 Parameters of bone density, mass and geometry according to sex and age groups (InCHIANTI study population). Values are mean ± SD

	Age group[a] (years)						ANOVA[b]
	20–39	40–49	50–64	65–74	75–84	85+	
Total bone density 4% (mg/cm^3)							
Men	342.3 ± 44.9	315.2 ± 38.2	302.1 ± 31.8	288.6 ± 35.5	290.0 ± 45.4	284.8 ± 45.1	$p < 0.0001$
Women	307.1 ± 34.8	286.9 ± 27.9	274.6 ± 40.3	253.9 ± 32.2	241.6 ± 36.8	229.2 ± 33.1	$p < 0.0001$
Trabecular bone density 4% (mg/cm^3)							
Men	332.5 ± 36.3	312.5 ± 35.7	294.4 ± 26.4	284.0 ± 33.3	284.8 ± 40.0	279.4 ± 40.4	$p < 0.0001$
Women	299.1 ± 33.1	283.3 ± 24.6	270.4 ± 39.4	251.5 ± 35.0	239.7 ± 41.4	228.9 ± 33.9	$p < 0.0001$
Cortical bone density 38% (mg/cm^3)							
Men	1057.6 ± 36.4	1039.0 ± 67.4	1025.7 ± 72.3	1025.4 ± 50.8	1020.6 ± 64.8	1001.6 ± 66.3	$p < 0.0001$
Women	1068.7 ± 44.0	1073.4 ± 33.3	1013.7 ± 72.2	994.9 ± 88.1	977.5 ± 78.0	941.6 ± 83.9	$p < 0.0001$
Cortical bone area 38% (mm^2)							
Men	318.9 ± 47.9	329.1 ± 54.9	319.7 ± 56.8	324.9 ± 42.2	326.8 ± 46.0	332.7 ± 51.2	$p = 0.28$
Women	288.8 ± 41.2	289.2 ± 34.3	287.9 ± 53.5	281.1 ± 52.7	265.0 ± 60.0	230.2 ± 72.4	$p < 0.0001$
Total bone area 4% (mm^2)							
Men	372.2 ± 54.4	391.1 ± 57.2	388.0 ± 56.8	399.04 ± 45.1	404.5 ± 48.9	423.2 ± 60.3	$p < 0.0001$
Women	341.6 ± 47.8	349.4 ± 38.2	358.8 ± 53.6	363.6 ± 56.9	367.5 ± 53.2	353.2 ± 61.0	$p < 0.05$
Minimum moment of inertia 38% (g/mm)							
Men	1250.8 ± 238.9	1231.6 ± 169.2	1209.0 ± 206.3	1211.8 ± 200.5	1215.1 ± 207.2	1200.3 ± 178.3	$p = 0.33$
Women	878.2 ± 250.3	830.1 ± 183.7	870.4 ± 194.0	858.5 ± 197.1	836.6 ± 193.1	759.1 ± 187.2	$p < 0.005$
Eccentricity index 38%							
Men	0.50 ± 0.09	0.51 ± 0.07	0.51 ± 0.08	0.51 ± 0.08	0.52 ± 0.08	0.56 ± 0.09	$p = 0.52$
Women	0.54 ± 0.09	0.51 ± 0.09	0.56 ± 0.08	0.54 ± 0.08	0.54 ± 0.09	0.54 ± 0.09	$p = 0.54$

[a] Linear regression models relating each parameter with age as a continuous variable

[b] Sample sizes for each age group identical to those reported in Table 1

improvement in fit obtained with the piecewise model, compared with the linear model. Before the age of 60 years, no significant age-related difference in cortical bone area was detected in men and in women. However, in women after age 60 years the cortical bone area declined by approximately 1% per year (average 2 mm^2) while it remained stable in men. The total bone cross-sectional area was progressively higher at older ages and no substantial departure from linearity could be detected in either men or women (Fig. 2, Table 3). The average magnitude of the age-related increment was 2-fold higher in men than in women and the two slopes were statistically different.

The age-related trends detected in the minimum moment of inertia paralleled those observed for the cortical bone area (Figs. 2, 3; Table 3). In fact, the analysis performed in men did not show any significant linear or nonlinear relationship. On the contrary, in women the minimum moment of inertia was substantially stable up to the age of 60 years, and then declined significantly thereafter by 0.5% per year. Finally, the eccentricity index remained stable over all the age groups, and was not different between men and women.

Discussion

Using an approach based on the analysis of pQCT images we assessed mass, density and geometric distribution of the trabecular and cortical bone at the lower leg in a large, population-based sample of persons living in the Chianti area of Italy. These data were used to estimate age-related differences in bone mechanical competence over a wide age range. Bone trabecular density declined linearly with age in both men and women, while changes in cortical density and geometry were substantially different in the two sexes. In men, along with an age-dependent decline in cortical bone density, but not in the total amount of cortical bone, we observed a significant increase in bone size. As a consequence, in aging men the minimum moment of inertia, a parameter which estimates bone mechanical resistance to bending, remained almost stable with age. In women, the decline in cortical bone mass and density was steeper than in men and was accompanied by a less pronounced increase in size, resulting in a progressive decrease in the minimum moment of inertia.

A linear pattern of decline in trabecular bone density, starting in early adulthood in both men and women, has been reported in studies using QCT at the spine or appendicular sites [21], and lateral DXA [22], suggesting that the age-associated reduction in trabecular bone density is not due solely to changes in circulating hormones. Our findings, based on a population-based sample of persons distributed over a large age range, support this interpretation. In men, cortical bone density declined slightly over the entire lifespan while the amount of cortical bone was similar at all ages. In women, we found that the amount of cortical bone remained substantially stable before the age of 60 years

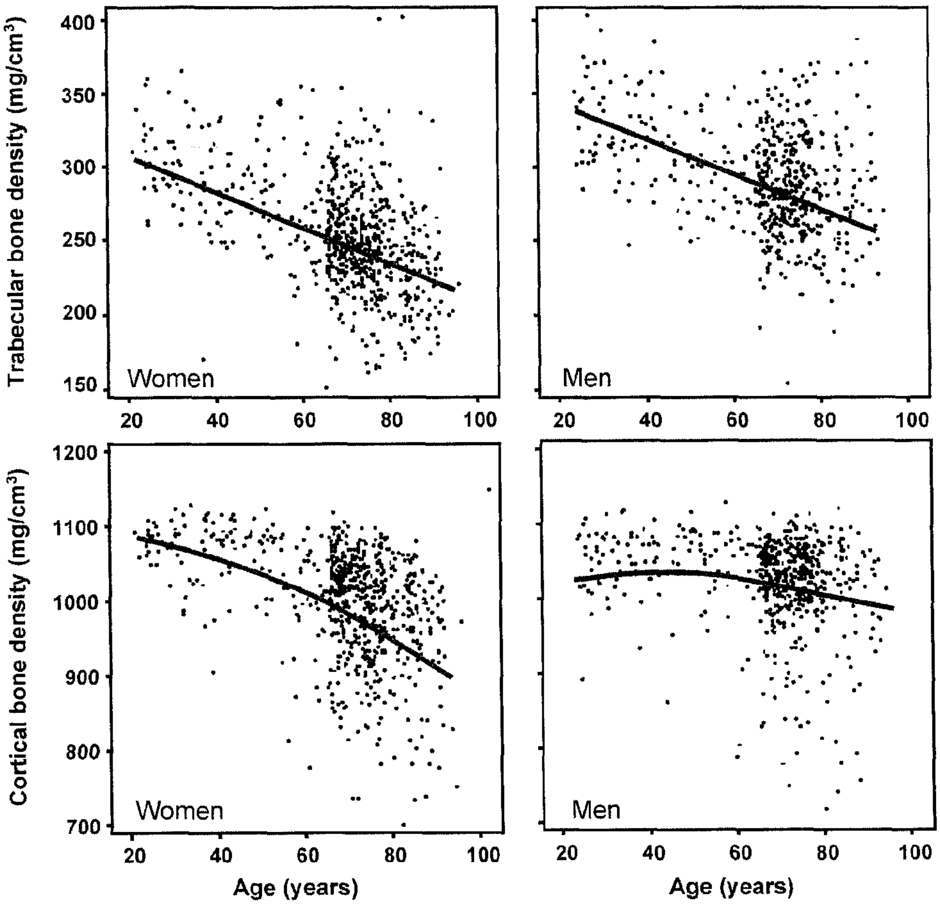

Fig. 1 Scatterplots of trabecular and cortical bone density according to age in men and women who participated in the InCHIANTI study. In each panel, the form of the relationship is summarized by a locally weighted regression smoother

and became progressively lower thereafter. These findings further support the idea that changes in the bone structure, due to the postmenopausal reduction in sex hormones, affect cortical bone as well as trabecular bone. A possible alternative explanation for our findings is that the cortical bone mass is reduced in older women more than in older men because of sex-related differences in lifestyle, such as physical activity and nutrition. Since the volumetric cortical bone density is a good marker of the property of the bone material in terms of resistance to stress and since the amount of cortical bone largely determines the resistance against compressive loads [8], the changes in bone geometry and mass described in this study may explain, at least in part, the higher rates of fractures observed in women compared with age-matched men. In keeping with this hypothesis, in a recent QCT-based study, the coexistence of reduced mass at both the trabecular core and cortical shell of vertebral body was observed in fractured as opposed to nonfractured vertebrae, in which only trabecular bone was reduced [23].

We believe that our observations have important clinical implications. Currently, the standard diagnosis of osteoporosis is based on the assessment of BMD performed with DXA. Although this method is widely used in both clinical and research settings, it has some important limitations: (1) The estimate of BMD can be strongly altered by the size of the bone because it is averaged on a two-dimensional projection of the bone, while variations in the third dimension are ignored. This potential source of systematic error may be especially important when individuals of different body size are compared. (2) No information is provided on the geometric distribution of trabecular and cortical bone and, therefore, the geometric component of bone competence is completely ignored. (3) The measures provided by DXA are inherently inaccurate since they are strongly influenced by the composition of the soft tissue surrounding the bone. This last limitation is particularly important in frail older women in whom, independently of other common sources of error, such as the positioning of the patient or the presence of extraskeletal calcifications, the magnitude of the measurement error can be as high as 20% [24, 25, 26].

The findings of this study improve our understanding of the different modifications that occur in the mechanical structure of the bone in men and in women over the aging process. Men appear to develop a very efficacious active geometric adaptation by apposition at the periosteal surface of new bone material (therefore increasing bone size); on the other hand, women appear to show mainly a passive geometric adaptation that

Table 3 Simple and piecewise linear regression model summarizing the cross-sectional relationship between age and pQCT parameters in men and women of the InCHIANTI study population

Parameter	Intercept	Slope 1[a]		Slope 2[b]	
		Beta + SE	*p*	Beta + SE	*p*
Total bone density (mg/cm^3)					
Men	364	–1.01 + 0.12	< 0.0001		
Women	348	–1.34 + 0.09	< 0.0001		
Men vs women (*p* value)	0.13^c	< 0.05^d			
Trabecular bone density (mg/cm^3)					
Men	354	–0.94 + 0.11	< 0.0001		
Women	338	–1.23 + 0.09	< 0.0001		
Men vs women (*p* value)	0.11^c	< 0.05			
Cortical bone density (mg/cm^3)					
Men	1077	–0.75 + 0.18	< 0.0001		
Women	1145	–2.16 + 0.20	< 0.0001		
Men vs women (*p* value)	< 0.001^c	< .0001			
Cortical bone area (mm^2)					
Men	321	0.00 + 0.29		0.33 + 0.32	0.32
Women	274	0.43 + 0.30	0.99	–2.05 + 0.29	
Men vs women (*p* value)	< 0.05^c	0.32	0.15	< .001^e	< 0.0001
Total bone area (mm^2)					
Men	353	0.68			
Women	338	0.34	< 0.0001		
Men vs women (*p* value)	< 0.0001^c	< 0.05	< 0.05		
Minimum moment of inertia (g/mm)					
Men	1290	–1.34 + 1.29	0.30	0.20 + 1.42	0.89
Women	830	1.15 + 1.06	0.28	–4.08 + 1.04	< 0.0001
Men vs women (*p* value)	< 0.0001^c	0.14		< 0.05^e	

[a] Average age-related difference "per year" in the parameter, within the age range 20–60 years

[b] Average age-related difference "per year" in the parameter after the age of 60 years. *Note*: Slope 2 is reported in the table only when statistically different from slope 1 in at least one sex. When slope 2 is not reported, the average change of the parameter "per year" is assumed to be constant over the entire age range

[c] p for the H_0 hypothesis of same intercept (predicted value for the age = 0) in men and women

[d] p for the H_0 hypothesis of same slope 1 (difference "per year" between age 20 and age 60 years) in men and in women

[e] p for the H_0 hypothesis of same slope 2 (difference "per year" after age 60 years) in men and in women

consists of selective sparing of the more peripheral bone material. This hypothesis is in keeping with the findings reported by Ruff and Hayes [10] and Mosekilde [27] on cadavers and by Duan et al. in vivo studies [28] and may explain why in the oldest women the reduction in mechanical competence of bone was less pronounced than expected given the magnitude of reduction in cortical bone density and cross-sectional area [29]. Furthermore, our findings suggest that, at least in part, the age-associated decline in total bone density described in other studies using DXA does not reflect a parallel decline in cortical bone mass and mechanical competence, but rather, especially in men, a geometric redistribution of cortical bone material which improves bone mechanical properties [30].

We could not find any age- or sex-related differences in the eccentricity index, suggesting that neither age- nor sex-related differences in bone mechanical competence can be explained by a more or less pronounced ovalization of the cross-sectional shape of the appendicular bones.

The most important limitation of this study is certainly its cross-sectional nature. We inferred the natural history of the aging bone by comparing individuals of different ages, but other uncontrolled differences between individuals may account for our findings. As already mentioned, some anthropometric measures suggest that the size of individuals of different ages was likely to be influenced by an important secular trend. Using a method widely employed by other investigators we tried to minimize this potential source of bias by normalizing the bone structural parameters according to the tibial length [17, 19]. However, we are aware that this approach may remove only in part the effect of the secular trend and, therefore, our findings need to be validated in a longitudinal prospective study. The measurement of bone density and structural parameters at the level of the tibia, a bone seldom involved in osteoporotic fractures, constitutes a further limitation of this study. However, data recently published from the NORA study, indisputably demonstrated the clinical usefulness of peripheral bone densitometry using different techniques and measurement sites [31].

In spite of these limitations, this is the first large, population-based study in which, using appropriate, direct methods, bone structural parameters relevant to prediction of fracture risk have been measured over the

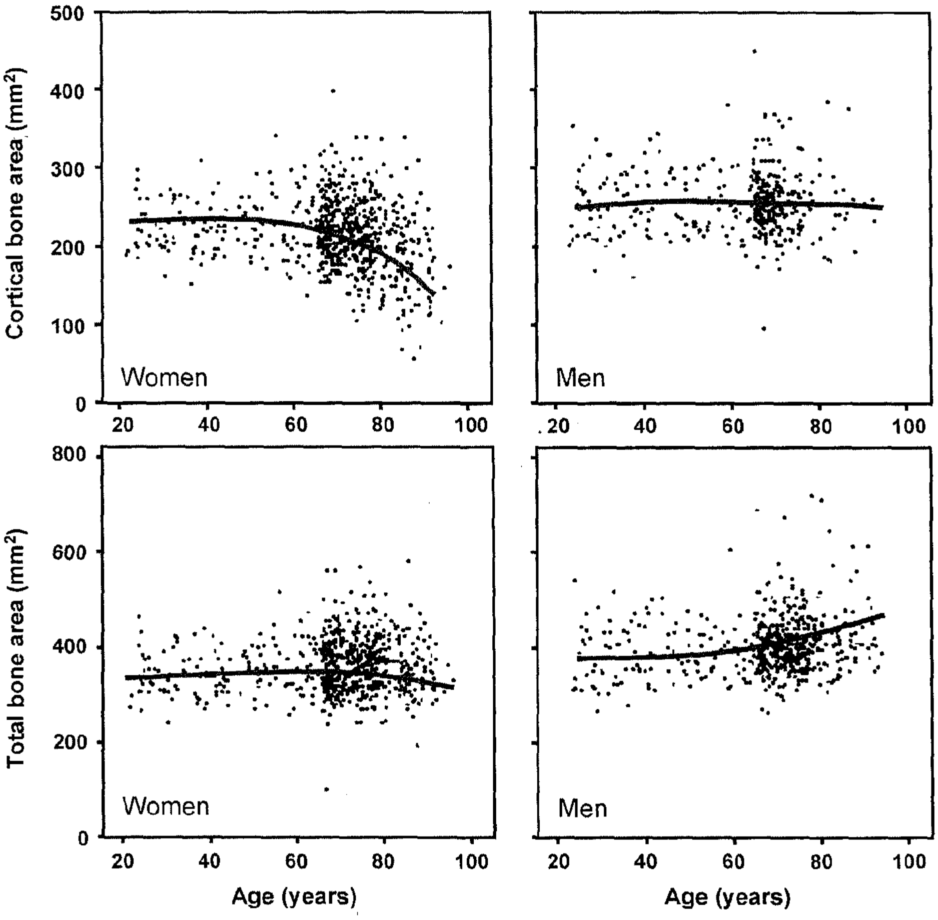

Fig. 2 Scatterplots of cortical and total bone cross-sectional area according to age in men and women who participated in the InCHIANTI study. In each panel, the form of the relationship is summarized by a locally weighted regression smoother

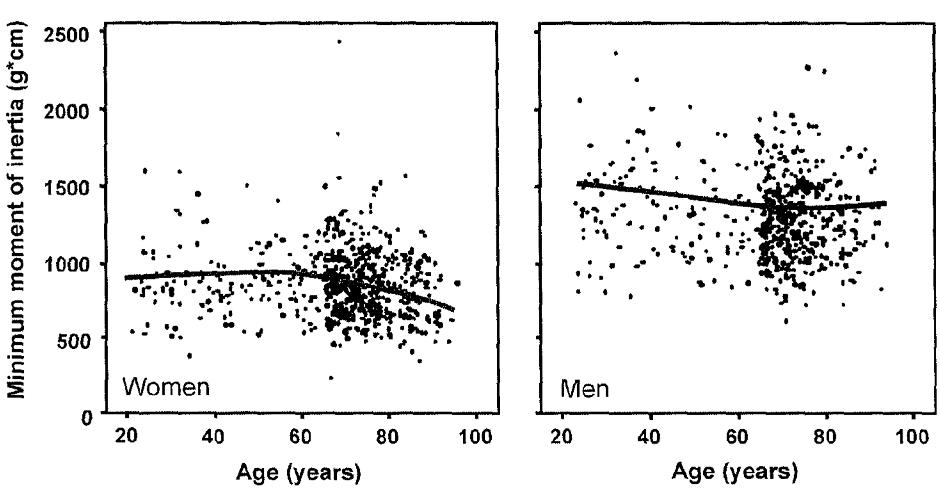

Fig. 3 Scatterplots of the minimum moment of inertia according to age in men and women who participated in the InCHIANTI study. In each panel, the form of the relationship is summarized by a locally weighted regression smoother

entire adult lifespan. The follow-up of this population, currently in the field, will provide the data to verify whether the additional information provided by pQCT, in comparison with DXA, may allow a better prediction of the risk of fractures and a better way to understand the effect of different treatments of osteoporosis on trabecular and cortical bone as well as on other geometric components of bone mechanical competence in men and in women.

Acknowledgements Supported as a "targeted project" (ICS 110.1\RS97.71) by the Italian Ministry of Health and in part by the

US National Institute on Aging (Contracts 263-MD-9164-13 and 263-MD-821336). We are grateful to Stratec Medizintechnik (Pforzheim, Germany) and Unitrem (Rome, Italy) for their continuous encouragement and support.

References

1. Wasnich RD (1998) Perspective on fracture risk and phalangeal bone mineral density. J Clin Densitom 1:259–268
2. Kanis JA, Delmas P, Burckhardt P, Cooper C, Torgerson D (1997) Guidelines for diagnosis and management of osteoporosis. Osteoporos Int 7:390–406
3. Parfitt AM (1998) A structural approach to renal bone disease. J Bone Miner Res 13:1213–1220
4. Guglielmi G, Schneider P, Lang TF, Giannatempo GM, Cammisa M, Genant HK (1997) Quantitative computed tomography at the axial and peripheral skeleton. Eur Radiol 7:32–42
5. Augat P, Gordon CL, Lang TF, Iida H, Genant HK (1998) Accuracy of cortical and trabecular bone measurements with peripheral quantitative computed tomography (pQCT). Phys Med Biol 43:2873–2883
6. Russo CR, Ricca M, Ferrucci L (2000) True osteoporosis and frailty-related osteopenia: two different clinical entities. J Am Geriatr Soc 48:1738–1739
7. Ferretti JL, Frost HM, Gasser JA, High WB, Jee WS, Jerome C, et al (1995) Perspectives on osteoporosis research: its focus and some insights from a new paradigm. Calcif Tissue Int 57:399–404
8. Augat P, Reeb H, Claes LE (1996) Prediction of fracture load at different skeletal sites by geometric properties of the cortical shell. J Bone Miner Res 11:1356–1363
9. Schneider P, Butz S, Allolio B, Borner W, Klein K, Lehmann R, et al (1995) Multicenter German reference data base for peripheral quantitative computer tomography. Technol Health Care 3:69–73
10. Ruff CB, Hayes WC (1982) Subperiosteal expansion and cortical remodeling of the human femur and tibia with aging. Science 217:945–948
11. McCreadie BR, Goldstein SA (2000) Biomechanics of fracture: is bone mineral density sufficient to assess risk? J Bone Miner Res 15:2305–2308
12. Forwood MR (2001) Mechanical effects on the skeleton: are there clinical implications? Osteoporos Int 12:77–83
13. Ferrucci L, Bandinelli S, Benvenuti E, Di Iorio A, Macchi C, Harris TB, et al (2000) Subsystems contributing to the decline in ability to walk: bridging the gap between epidemiology and geriatric practice in the InCHIANTI study. J Am Geriatr Soc 48:1618–1625
14. Louis O, Boulpaep F, Willnecker J, Van den Winkel P, Osteaux M (1995) Cortical mineral content of the radius assessed by peripheral QCT predicts compressive strength on biomechanical testing. Bone 16:375–379
15. Rittweger J, Beller G, Ehrig J, Jung C, Koch U, Ramolla J, et al (2000) Bone-muscle strength indices for the human lower leg. Bone 27:319–326
16. Cheng S, Toivanen JA, Suominen H, Toivanen JT, Timonen J (1995) Estimation of structural and geometrical properties of cortical bone by computerized tomography in 78-year-old women. J Bone Miner Res 10:139–148
17. Bouxsein ML, Myburgh KM, van der Meulen MCH, Lindenberger E, Marcus R (1994) Age-related differences in cross-sectional geometry of the forearm bones in healthy women. Calcif Tissue Int 54:113–118
18. Sievanen H, Koskue V, Rauhio A, Kannus P, Heinonen A, Vuori I (1998) Peripheral quantitative computed tomography in human long bones: evaluation of in vitro and in vivo precision. J Bone Miner Res 13:871–882
19. Ruff C (1984) Allometry between length and cross-sectional dimensions of the femur and tibia in *Homo sapiens*. Am J Phys Anthropol 65:347–358
20. Armitage P, Berry G (1994) In: Statistical methods in medical research, 3rd edn. Oxford: Blackwell Scientific:312–341
21. Russo CR (1998) Correlation of radial SPA and pQCT with the femoral DEXA measurement in elderly women. J Intern Med 244:358–359
22. Guglielmi G, Grimston SK, Fischer KC, Pacifici R (1994) Osteoporosis: diagnosis with lateral and postero-anterior dual x-ray absorptiometry compared with quantitative CT. Radiology 192:845–850
23. Andresen R, Haidekker MA, Radmer S, Banzer D (1999) CT determination of bone mineral density and structural investigations on the axial skeleton for estimating the osteoporosis-related fracture risk by means of a risk score. Br J Radiol 72:569–578
24. Bolotin HH (1998) A new perspective on the causal influence of soft tissue composition on DXA-measured in vivo bone mineral density. J Bone Miner Res 13:1739–1746
25. Bolotin HH, Sievanen H, Grashuis JL, Kuiper JW, Jarvinen TL (2001) Inaccuracies inherent in patient-specific dual-energy X-ray absorptiometry bone mineral density measurements: comprehensive phantom-based evaluation. J Bone Miner Res 16:417–426
26. Bolotin HH, Sievanen H (2001) Inaccuracies inherent in dual-energy X-ray absorptiometry in vivo bone mineral density can seriously mislead diagnostic/prognostic interpretations of patient-specific bone fragility. J Bone Miner Res 16:799–805
27. Mosekilde L (2000) Age-related changes in bone mass, structure, and strength: effects of loading. Z Rheumatol 59(Suppl 1):1–9
28. Duan Y, Turner CH, Kim BT, Seeman E (2001) Sexual dimorphism in vertebral fragility is more the result of gender differences in age-related bone gain than bone loss. J Bone Miner Res 16:2267–2275
29. Hangartner TN, Gilsanz V (1996) Evaluation of cortical bone by computed tomography. J Bone Miner Res 11:1518–1525
30. Ferrucci L, Russo CR, Lauretani F, Bandinelli S, Guralnik JM (2002) A role for sarcopenia in late life osteoporosis. Aging Clin Exp Res 14:1–4
31. Siris ES, Miller PD, Barrett-Connor E, Faulkner KG, Wehner KG, Abbott TA, et al (2001) Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: results from the National Osteoporosis Risk Assessment. JAMA 28:2815–2822