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Original Article

Hylonome

Postmenopausal changes in the distribution of the volumetric BMD of cortical bone. A pQCT study of the human leg

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Abstract

Three different regions of interest (ROIs) were defined in pQCT scans (XCT-3000 machine, Stratec, Germany) taken at the tibial mid-diaphyses of 12 pre-menopausal (pre-MP) and 12 post-menopausal (post-MP) women who were otherwise normal, according to the volumetric bone mineral density (vBMD) value of their corresponding pixels (voxels) as assessed by their respective attenuation values. They were classified as "low-vBMD" (*LD-ROI*, with a vBMD of 200-400 mg/cm^3), corresponding chiefly to trabecular-subcortical bone; "medium-vBMD" (*MD-ROI*, vBMD = 400-800 mg/cm^3), corresponding mainly to porous cortical bone or cortical-subcortical bone, and "high-vBMD" (*HD-ROI*, vBMD higher than 800 mg/cm^3), corresponding to dense cortical bone. The fraction of the total cross-sectional bone area covered by the HD-ROI was 16% higher, and that covered by the MD-ROI 20% lower, in pre-MP than post-MP women. No differences concerning the LD-ROIs were found. A close, linearly negative relationship was found between the MD- and HD-ROI fractions in all the women together, with no inter-group differences in slope. The Stress-Strain Index (an indicator of the torsional stiffness and strength of the whole bones that involved both the vBMD and the spatial disposition of the HD bone in the cross-section – torsional moment of inertia –) correlated linearly and positively with the cross-sectional area of the HD-ROI, with a higher slope for pre-MP than post-MP women. Qualitatively, a. post-MP women showed a significantly more prevalent discontinuity of the voxels in the HD-ROI than pre-MP women, and b. the tendency of LD-ROIs to accumulate along the mechanically less-effective (antero-posterior) axis of the image – a characteristic of pre-MP bones – was visually less evident in post-MP bones. These features describe non-invasively some changes induced by menopause in the human tibia that may be critical for defining the skeletal condition and to monitor the effects of treatments addressed either to protect or to improve mechanically the bone structure, beyond the possibilities of standard densitometry.

Keywords: Bone Structure, Bone Biomechanics, Bone Strength, Cortical Bone, Human Tibia, Non-Invasive Determination, Volumetric Densitometry, Peripheral Quantitative Computed Tomography (pQCT), Bone Geometric Properties, Menopausia

Introduction

Bone mass loss affects every woman after menopause, of which 1/3 have an increased risk to suffer a fracture. It is not known whether this fragility status (osteoporosis) depends on the magnitude of such bone mass loss (as widely reported) or on critical structural changes, or both. Estrogen replacement therapy may halt or minimize the postmenopausal bone loss but fractures may not consequently be fully avoided. Hence, the role of estrogens on the biological determinants of bone strength, rather of bone mass, deserve further study.

Indeed, the strength of bones as organs results from a combination of two complementary properties expressed at lower-hierarchy levels of structural organization[1]. These are the bone "material" and "geometric" properties. Bone material properties concern the intrinsic stiffness and strength of the "solid" bone substance, regardless of bone mass, size, shape and macrostructure. Bone geometric properties concern the whole-bone macroarchitecture or design, comprising all bone mass, size, shape and macrostructure[2,3]. Bone "mass" (the amount of mineralized bone tissue) is the physical substratum for the manifestation of those properties, but it does not influence the whole-bone strength directly[4-8].

Both material and geometric properties of bone depend largely on two different levels of structural anisotropy rather

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than on the mere bone "mass". A differential distribution of some elements confers on the bone or bone tissue structure or microstructure a higher degree of stiffness and strength in the spatial directions in which the skeleton is predominantly stressed by customary mechanical usage[9]. Bone material properties are not only related to the degree of tissue mineralization, but also to the spatial disposition of crystals around collagen fibrils, fibrils within lamellae, lamellae within osteons, and osteons within the hard substance (bone "microstructure"), as well as to the density and distribution of microporosity and microdamage[1,3,10-12]. Analogously, bone geometric properties are determined, in cancellous bone, by the spatial disposition, thickness, connectivity and microfractures of the trabecular network. In cortical bone, they are given by the cortical cross-sectional diameters, perimeters, thickness, area, and moments of inertia (CSMIs) concerning bending or torsion[2,8,13].

In composite bones working in compression like the vertebral bodies, it is difficult to assess the different proportions of the whole-bone strength that are separately afforded by cortical and trabecular bone[14,15]. In tubular bones usually working in bending or torsion, however, the strength of the whole-bone is practically given by that of the cortical shell. The cortical strength is on time determined by the more or less peripheral distribution of the cortical bone with respect to the regionally specific, bending or torsional axes that are relevant to analyze the strains produced by customary mechanical usage (CSMIs)[13].

It has been proposed that both those structural levels of bone anisotropy are controlled by a feedback mechanism called the bone "mechanostat"[16]. This system is thought to keep bone deformability (and hence bone strength, not bone "mass") within physiological limits[17,18] through a directional modulation of bone modeling (that may affect bone geometry[19]) and remodeling (that may affect the microstructure and porosity of the mineralized tissue, and hence the bone material properties[20]). Therefore, the non-invasive assessment of the whole-bone strength requires more than the mere determination of bone "mass"[4-7]. A proper determination of the strength of a bone should take into account both its material and geometric properties[2,3,21].

The chief influence on the directional orientation of bone modeling and remodeling by the mechanostat seems to come from the skeletal strains produced by the contractions of the regional muscles[17,18,22-25]. Besides that influence, the mechanostat is also systemically (i.e., nondirectionally) influenced by nonmechanical factors like hormones, metabolites, nutrients, and drugs that may alter the biomechanical control of bone structure[16,26].

Quantitative computed tomography (QCT, pQCT) can provide accurate determinations of:

1. at least one of the physical determinants of the bone material properties, namely, the degree of mineralization or of intracortical porosity of the "solid" bone tissue – as assessed by the volumetric mineral density (vBMD) of the cortical bone[10], and

2. the cross-sectional properties of many kinds of bones[24,25,27-32]. This information can be combined in order to calculate some suitable "bone strength indices" (BSIs) that allow predicting bone strength non-invasively in different, specific instances[27,34]. The development of the BSIs has enhanced the importance of determining suitable indicators of the material and geometric properties of cortical bone for assessing bone strength non-invasively[2,27,28,30,33].

In addition to bone strength and its biological components, QCT and pQCT can also measure the cross-sections of the regional muscles[35]. Therefore, these techniques could provide useful information concerning:

1. the biological components of bone strength,

2. the muscle-bone interactions that are essential for determining the bone mechanostat condition, and

3. the systemic modulation of the directional control of bone modeling and remodeling by the bone mechanostat that is caused either naturally, pathologically or pharmacologically by hormones, nutrients or drugs[24-26,35].

We had developed a method, based on the selection of different attenuation threshold "windows" in pQCT machines[36], that allows defining regions of interest (ROIs) with specific ranges of volumetric bone mineral density (vBMD) in different kinds of bones. In the present study, this method was applied to show the differential distribution of the vBMD and of different indicators of bone geometry and strength in scans of the tibial diaphysis in pre- and post-MP women. This information is interpreted according to the current concepts in bone biomechanics.

Materials and methods

Twelve Caucasian pre-MP women (mean age 41.1 years) and 12 post-MP ones (mean age 72.4 years, time since menopause over 15 years in all cases) who were free from bone diseases or treatments that may affect the skeleton were studied. No significant inter-group differences in body weight (58.9 ± 6.4 vs. 60.1 ± 9.6 kg) and height (160.6 ± 9.0 vs. 157.0 ± 6.8 cm) were found.

Transversal, 2.5-mm thick scans of the right tibial and fibular diaphyses positioned at the midpoint between the end of the internal malleolus and the articular surface of the knee were taken with an XCT-3000 pQCT machine (Stratec, Pforzheim, Germany). All the determinations were performed by a trained radiologist and the images were analyzed by a different person. These operators were blinded to the nature of the study and the menstrual status of the subjects.

The images were obtained with a voxel size of 0.5 mm. A contour-finding algorithm automatically defined the edges of the tibial cross-sections, using a median filter of the image[37] to provide a continuous-line boundary. The attenuation threshold fixed for selecting the pixels of the image (voxels) that defined the outer margin of the cortical bone working centripetally was 0.7 cm^{-1} with a proportional weighting factor for voxel elements below 0.9 cm^{-1}. This minimized partial volume effects better than a fixed threshold.

The volumetric bone mineral content (vBMC) of the different voxels within the bone cross-section was calculated expressing the mean linear attenuation coefficients as hydroxyapatite-equivalent mineral content. Standards using epoxy resin as a bone marrow equivalent were used to calibrate the values. Volumetric BMDs were then obtained by dividing the BMC by the cross-sectional area of selected bone regions of interest (ROIs).

Three special ROIs were defined by selecting specific limits for the range of attenuation values (or vBMD) obtained for each voxel within the bone image, namely,

1. "*low-vBMD*" (LD) ROI (vBMD = 200-400 mg/cm^3), corresponding chiefly to trabecular-subcortical bone voxels;
2. "*medium-vBMD*" (MD) ROI (vBMD = 400-800 mg/cm^3), corresponding mainly to porous cortical bone or cortical-subcortical bone, and
3. "*high-vBMD*" (HD) ROI (vBMD higher than 800 mg/cm^3), corresponding to dense cortical bone.

The extension of these ROIs was measured as their cross-sectional area (CSA). The torsional or "polar" CSMI (pCSMI) of each HD-ROI CSA was also determined as the integral sum of the products of the areas of the HD pixels and the square of their distances to the center of mass of the bone cross-section[27]. The pCSMI is regarded as an ubiquitous indicator of the torsional bone strength of long bones that has been shown to discriminate well between individuals with and without a recent wrist fracture when calculated for the distal radius[28,23].

An adaptation of the formula for calculating a previously described BSI for long bones, namely, the Stress-Strain Index (SSI)[38] was then applied to calculate the SSI of the HD-ROIs as:

$$SSI = \frac{\text{HD-vBMD x pCSMI}}{\text{vBMD}_{Max} \text{ x } d_{Max}}$$

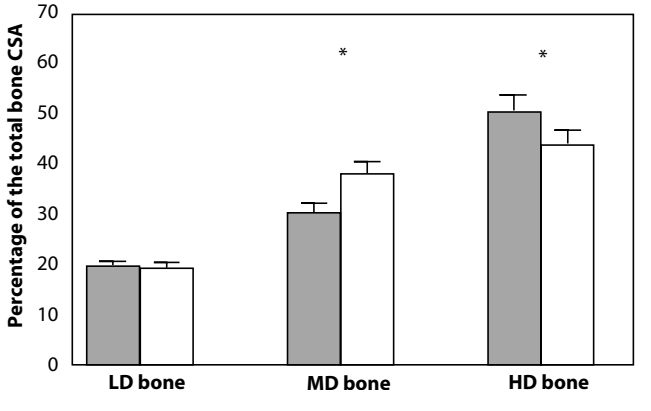

Figure 1. Percentual distribution (means and SE of the normalized samples) of the CSAs of the different types of bone in the pre-MP (left bars) and post-MP (right bars) women studied. Asterisks indicate a $p<0.05$ level of significance of the differences.

where $vBMD_{Max}$ is the maximal value that vBMD can theoretically assume (i.e., 1.80 g/cm^3) and d_{Max} is the maximal distance from a point of the periosteal bone perimeter to the center of mass of the bone cross-section studied.

The determinations had in general an accuracy of 1%[52] and a precision better than 2.5% in our hands.

Some qualitative aspects, such as the geometrical integrity (visual continuity of the set of voxels within a given ROI at the degree of definition obtained) or the particular distribution of the LD bone ROIs in the tibial and fibular cross-sections were also described as related to the reproductive status of the women.

Statistical analyses (Statistica software, StatSoft, USA). After normalization of the samples as needed, the inter-group differences were tested by one-way ANOVA. The slope differences in regression analyses were tested by ANCOVA. The qualitative data were compared by standard *chi-square* tests.

Results

As expected, the HD, MD and LD bone ROIs were located predominantly at the outer, medial and inner regions of the bone cross-sections, respectively, in all the analyzed scans.

The pre-MP women showed 16% more HD bone and 20% less MD bone than the post-MP ones, with no differences in the LD bone (Fig.1).

A close, negative linear relationship was found between the percentual proportions of MD and HD CSAs with respect to the total-bone CSA (Fig. 2), whilst no association was shown between those of the LD and MD bone.

The obviously positive association between the tomographic SSI and the amount of HD bone CSA (Fig. 3) showed a significantly higher slope for the pre-MP than for the post-MP women.

The scans from the post-MP women were also characterized for showing the following qualitative features.

1. A visible geometric discontinuity of the set of voxels in at least one point within the HD-ROI at the obtained definition in both the tibial and fibular images (Fig. 4). The prevalence

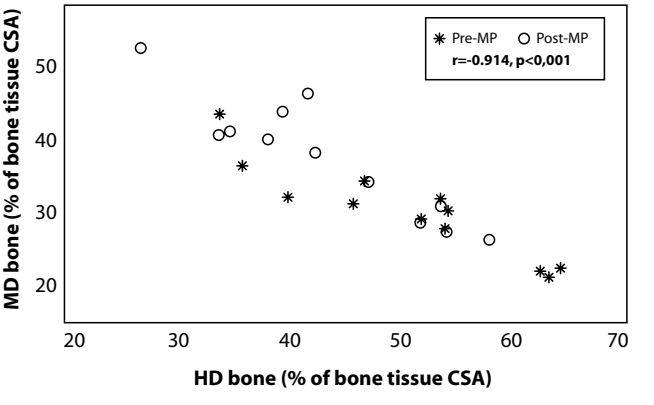

Figure 2. Association between the percentages of the MD and HD bone CSAs in the pre-MP and post-MP women studied.

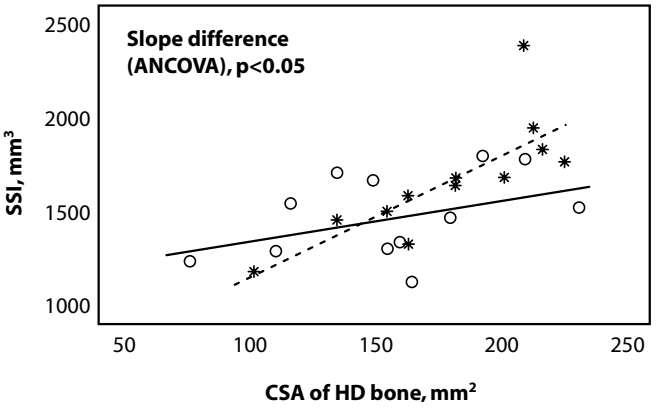

Figure 3. Correlation between the SSI and the HD bone CSA in the pre-MP (asterisks, dashed line) and post-MP (circles, solid line) women studied.

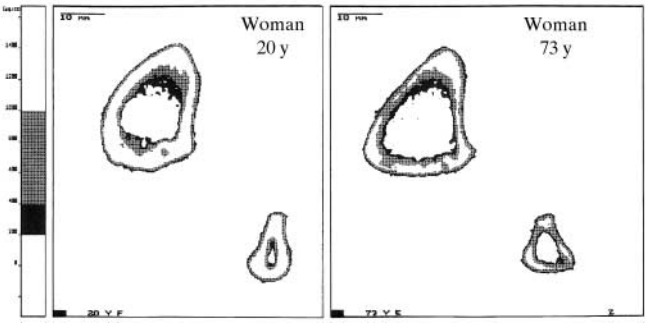

Figure 4. pQCT scans of the tibial and fibular midshafts of two representative cases among the pre-MP (left) and post-MP (right) women studied. From the outside to the inside of the image, the HD-ROI is represented in white, the MD-ROI in grey, and the LD-ROI in black, as indicated by the scale on the left. The anterior-posterior axis of the tibia (AP) is also indicated. The geometrical discontinuity of the HD-ROI is evident in the image on the right.

of that discontinuity in pre- and post-MP women was 2/10 vs. 9/3 in the tibial images (*chi-square* = 10.9, $p<0.001$), and 4/8 vs. 12/0 when both the tibial and fibular images were counted (*chi-square* = 12.0, $p<0.001$).

2. A lack of the preferential distribution of the LD bone voxels along the mechanically less relevant cross-sectional axis of the tibia (i.e., the anterior-posterior diameter; Fig. 4).

This last characteristic (2) was impossible to quantitate other than by visual appreciation because of the inability of the software to analyze specific sectors of the images.

Discussion

These results suggest a role of sex hormones or related factors in the maintenance of at least two biomechanically relevant bone features, as follows.

1. The higher percentage of HD-bone CSA in pre-MP than in post-MP women would indicate a greater proportion of cortical bone with the lowest levels of intracortical porosity in the former. The HD-ROIs corresponded always to the outermost regions of the cortical cross-section. Therefore, this finding would reflect a tendency to maintain the compact bone tissue with the highest available stiffness in the mechanically most relevant sites, i.e., those more peripheral concerning the relevant, torsional or lateral-bending axes determined by the customary mechanical usage. The significant relationship shown in Figure 2 could provide a reference to monitor the tendency to shift to a lower proportion of HD-bone voxels and a higher proportion of MD-bone voxels within the bone image after menopause.

2. The pre-MP women showed:
   a. a significantly higher pCSMI of the HD-ROI's, supporting the biomechanical assumption in (1) above,
   b. a significantly higher tendency of those ROIs to show a geometrical continuity, and
   c. a significantly higher slope in the SSI / HD-CSA relationship (Fig. 3) than the post-MP women.

These findings would also indicate that in the pre-MP women the available compact tissue in the cortical shell (represented by the CSA of the HD-bone ROIs) would be more efficiently distributed on the cross-sections from the biomechanical point of view (i.e., concerning torsional strength) than in the post-MP ones.

Those biomechanical advantages of the pre-MP women should be related to the well-known, positive effects of estrogens on the ability of bone cells to respond to mechanical stimuli[39-42] and hence on the interaction between muscles and bones in the human calf. A preliminary study of our group has shown that the slope of the correlations between the pQCT-assessed, tibial cortical bone CSA or SSI (y) and calf-muscles CSA (x) were significantly higher for pre-MP than post-MP women of the same ethnical origin as those studied here[43], suggesting a different response of bone mass and structure to muscle strength after the menopause. Similar, sex hormone-related differences in muscle-bone relationships were shown in the lumbar spine employing QCT[44] and analyzing bone and muscle (lean) mass relationships in a large sample of male and female normal individuals aged 2 to 87 years employing DEXA[45].

The preferential distribution of certain "surplus" endosteal LD bone mass of pre-MP women in regions in which it should have little effect on bone strength, such as along the anterior-posterior axis of the cross section of the tibiae (bones that work predominantly in lateral bending; Fig. 4), would reflect a direct effect of estrogen (inhibition of negative-balance bone remodeling) on the bone tissue close to marrow[46-48]. It can be speculated that the estrogen-induced accumulation of endosteal bone, which has already been shown by others and by ourselves[24,25,49], would represent a positively-selected bone condition that provides a convenient storage of mineral (that could be eventually passed to offspring) in the mechanically least relevant sites. Bone tissue located at that region would have a relatively low probability to be eliminated by the bone mechanostat as "mechanically excessive" material.

All these effects seem to cease after menopause, in

coincidence with the observed impairment in the mechanical stimulation of bones by muscles and in the efficiency with which the available cortical bone is distributed in the diaphyseal cross-sections (CSMI)[43].

These results could be regarded as evidencing the nonmechanical (i.e., nondirectional) influence of sex hormones on the control of bone structural strength by the bone mechanostat (that is thought to be the cause of most of the so-called "true" osteopenias and osteoporoses after menopause)[50]. Accordingly, at least part of the postmenopausal bone loss (affecting the endosteal LD bone) does not seem to be associated with bone fragility, suggesting that the variable "mass" needs to be discriminated considering its spatial localization.

Similar but milder differences from those shown here have been detected between pQCT scans of the same region taken in men aged 20-30 or 60-70 years[51]. Perhaps the methodology employed in this study could be extended to the investigation of the cortical bone condition or distribution in men concerning the same disturbing factors.

The pQCT-assisted, threshold-analysis of vBMD[36] as applied in this study may help to define the effects of the lack of estrogen and related conditions or treatments on compact bone from a biomechanical point of view. Perhaps the analysis of the proportions shown in Figure 1 or of curves like those shown in Figures 2 & 3 compared to suitable reference charts, could allow the detection of significant failures in the biomechanical control of bone structural strength that are outside the scope of standard densitometric techniques[4-7].

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