J Musculoskelet Neuronal Interact 2014; 14(1):29-40

Original Article

Hylonome

# The pQCT "Bone Strength Indices" (BSIs, SSI). Relative mechanical impact and diagnostic value of the indicators of bone tissue and design quality employed in their calculation in healthy men and pre- and post-menopausal women

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**Abstract**

The pQCT-assessed Bone Strength Indices (BSI's, SSI) depend on the product of a "quality" indicator, the cortical vBMD (vCtD), and a "design" indicator, one of the cross-sectional moments of inertia or related variables (MIs) in long bones. As the MIs vary naturally much more than the vCtD and represent different properties, it could be that the *variation of the indices might not reflect the relative mechanical impact of the variation of their determinant factors* in different individuals or circumstances. To understand this problem, we determined the vCtD and MI's in tibia scans of 232 healthy men and pre- and post-MP women, expressed in SD of the means calculated for each group, and analyzed the independent influence of 1 SD unit of variation of each factor on that of the indices by multiple correlations. Results showed: 1. that the independent influence of the MIs on the indices was generally larger than that of the vCtD, and 2. that in post-MP women the influence of the vCtD was larger than it was in the other groups. This confirms the view that inter-individual variation of vCtD is comparatively small, and that mechanical competence of human bone is mostly determined by 'design' factors.

**Keywords:** Bone Structure, Bone Biomechanics, Moment of Inertia, Bone Density, Bone Quality, pQCT, Bone Strenght Index, Bone Strength Evaluation

## Introduction

The ultimate strength of a bone under a given load depends: a. upon the structure's resistance against deformation, and thus its prevention of crack generation by avoiding excessive stretching (structural stiffness), and b. upon its ability to prevent crack propagation (structural toughness). A bone's structural stiffness and toughness are thus determined by its material's stiffness and toughness (material properties) and by the spatial distribution of that tissue (geometric properties, or bone design), obviously in relation to the origin and direction of applied forces[1-6].

In general terms, bone material properties are chiefly determined by genetic factors[7] and tend to vary relatively little, either between bones of the same individual or between groups of individuals of comparable ages, and to show variable age-related associations with bone strength[5,8]. By contrast, the architectural distribution of the mineralized tissue of bones depicts high variability between different individuals, and even in the same individual[5,6,9-12], is highly dependent on the mechanical stimulation of the bone by the habitual usage of the skeleton throughout life, with high directional and site specificity[13-19], and is strongly correlated to bone strength at any age.

The authors have no conflict of interest.

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*Edited by: F. Rauch*
*Accepted 29 November 2013*

Thus, it is fair to state that the structural properties of bones, but not their material properties, can be thought of as being subject to a servo-control mechanism. A great variety of homeostatic servo-control mechanisms have been proposed for bone, of which Frost's *mechanostat*[20] has received most of the attention. The *mechanostat* system is proposed to directionally modulate bone formation and destruction as a function of the usage-derived strains sensed by osteocytes. The resulting alterations in bone design tend to keep bone strains constantly below some critical threshold value. In the long bones' diaphysis this mechanism tends to optimize the resistance to bending and torsion stresses through the achievement of adequate values of the corresponding cross-sectional moments of inertia (MIs) of the cortical bone area[21,22]. In fact, the MIs have been shown to predict bone fracture strength significantly better than other "non-directional" geometric indicators of diaphyseal design as the cortical thickness[2]. Taking these strands of reason together, it follows that a given bone's geometrical shape can reveal the habitual loads that have been placed on it, as long as it does not suffer from deficiencies in either its material properties or in its ability to mechano-adapt. There are many phylogenetic and ontogenetic evidences of such geometric adaptation of bones to their mechanical environment[23-25].

Experience demonstrates that combining the different pQCT indicators of cortical bone tissue "quality" and distribution can improve the stiffness/strength estimation of hollow bones over that provided by each indicator[2-4,9-11,15,16,26-36]. Cortical vBMD (vCtD), an obvious correlate of bone matrix mineralization and micro-porosity, can be taken as a correlate of the elastic modulus of the "solid" bone tissue[8,37]. On the other hand, bending or torsion MI's can be regarded as representatives of the architectural quality of the diaphyseal design to resist bending and torsion, provided that the cross-section geometry do not vary too much throughout the bone[3].

To note, the flexural stiffness of regular tubular structures is given by the product of the elastic modulus E of the constitutive material and the MI calculated for the mode of deformation[34,38]. In the case of bones, this relationship is valid within a wide range of values, comprising virtually all the geometric and absorptiometric characteristics of most long bones' diaphyses. Thus, within some obvious limitations, the structural stiffness of a bone diaphysis could be approximated non-invasively by the product of two tomographic indicators, the vCtD and the corresponding MI[27,34]. Although, this does not imply that the separate influences of each of the two factors (which represent different bone properties) should keep a similar proportionality in any kind of bones, individuals, or circumstances. Interestingly, significant correlations were reported between the product E*MI and the BMC or the bone width of the ulna, but different influences of each factor on the product were observed in younger and older healthy women[38].

In rat femurs, employing pQCT and mechanical testing, we have shown that the mid-diaphyseal MI's were negatively correlated with the vCtD ("distribution/quality" (d/q) relationships[39-41]). The same relationship was recently shown also in humans[42]. Many other authors have reported reciprocal variations of MI's or similar variables and vCtD[3,29,33,43-49], but they did not refer that finding as a physiological association or as a biomechanical d/q relationship as we did[42]. The curves describing the d/q relationships always show a hyperbolic-like shape, as would be expected for transfer functions of feed-back regulated variables[4,42], and for which the product of the two coordinates ($x*y$) of every point tends to give a constant value. As a further evidence of that point, we have also demonstrated that the product of the bending MI and the vCtD of rat femur mid-diaphysis correlated linearly with the real, mechanically measured bending fracture load of the same bones, much more significantly than the separate MI and vCtD values did[27]. Accordingly, we coined the term "Bone Strength Index" (BSI) to describe that product, MI*vCtD and proposed it as probably the first non-invasive indicator of bone strength. Lately the same index was also validated in canine femora[33] and in human radii and tibiae[50-52].

Analogously to our BSI, a standardized index known as "Stress-Strength Index" (SSI)[53,54] was calculated as the product of the vCtD divided by a theoretical, maximal value of 1.20 $mg/mm^3$, and the torsion MI divided by the maximal radius of the bone cross section. The pQCT-assessed BSIs and SSI (and analogous determinations) were and are nowadays widely applied in experimental and clinical studies[1,11,14,17,36,38,43,50,52,55-68] and recommended as diagnostic indicators for osteoporosis or related bone-weakening diseases[3,12,34,61,65,69-71].

It must be acknowledged that the components (factors) of the indices do not exactly represent the abovementioned bone properties in every kind of circumstances[34]. The following reasons can be proposed both to explain and partially neutralize those inconveniencies.

**a.** As a mineralized tissue stiffness estimator, the vCtD disregards the role of many other, microstructural determinants of that property (collagen quality, crystallinity, micro-porosity, etc.[1,72,73]) and their different and variable impacts on both bone material stiffness and toughness[74,75]. Nevertheless, the use of vCtD to evaluate all tissue stiffness, yield stress or ultimate strength is supported by compelling evidence[8,37,76-81]. In fact, it could be regarded as acceptable, provided that the other determinants of bone stiffness do not vary too much as to affect the aims of the study.

**b.** The so called "strength" indices are more likely estimates of "flexural stiffness" rather than of *strength* of some long bones, disregarding all the determinants of bone *toughness*, which can have a high impact on bone strength[1,34,72,82-85]. Anyway, it was frequently observed that, in long bones, structural stiffness and strength are highly correlated[86], provided that there is no perturbation of bone toughness. In any case, the correlations we originally proposed to support BSI calculation concerned always to bone structural strength, not stiffness, and disregarded bone toughness. However, their statistical performance was always quite acceptable[3,34].

**c.** The BSI validation after 3-point bending tests of geometrically regular, rat femur mid-diaphyses[27], could not be extrapolated to bones with differently-shaped cross-sections, or related to other types of deformation[51,87]. At any rate, a number

of studies in which the BSIs or the SSI were determined in different bones have reported quite clear mechanical correlates[3,34].

**d.** The natural variation of the vCtD (expressed as CV values) is by comparison much smaller than that of the MI's[2,3,5,13,14,19]. Thus, in consonance with (a,b) above, *the variation of the indices could not reflect the relative mechanical impact of the variation of their determinant factors, vCtD and MIs in adequate proportions*. In other words, beyond their obvious mathematical contribution to the numerical value of the product (BSIs, SSI), each factor (vCtD, MIs) should afford some independent, complementary biomechanical translation of the status of some relevant bone property to bone strength determination[1,3] that could not be reflected by the index value in different individuals or circumstances.

Furthermore, both vCtD and MIs (which depend on different biological determinants) may vary either in dependence or in independence of each other[35,61], and if they are dependent, then this could either be directly, i.e. mechanically-physiologically, or indirectly through other "epidemiological" factor (e.g. gender, menopausal state, physical activity, etc)[3,42,88]. Thus, even taking into account all the values of the indicators and those of their factors in a given study as independent entities, *the evaluation of the relative contribution of the vCtD or the MIs to bone stiffness/strength may become difficult, and it could even be impossible to compare in different individuals and circumstances*.

In this study, we aimed to eliminate this problem. To that purpose, we determined the vCtD and the A-P bending and torsion MI's in tibia scans of healthy men and pre- and post-MP women, expressed in SD of the means calculated for each group to neutralize the influence of their different ranges of natural variation. Then we calculated the corresponding BSIs and SSI, and analyzed the independent influence of 1 SD unit of variation of each factor on that of the indices, as expressed by their partial regression coefficients ($\beta_p$) determined in multiple correlation analyses, in each of the studied groups, with different comparative criteria.

Our working hypothesis was that, beyond the mathematical identity of the calculation of the indices in all the groups, some significant inter-group differences ought to be found, not only in the values of the indices and/or their determinants, but also, and specially, in the calculated $\beta_p$ coefficients for each determinant. The specific goals of the study were to define: 1. which of the two biological determinants (vCtD, MIs, which represent the influence of intra-cortical remodeling and cortical modeling on structural bone strength, respectively) has a larger independent impact (i.e. a larger $\beta_p$ coefficient) on the indices' values in the different groups, and 2. if the impacts of the factors on the indices show or not some relationship with the gender or the reproductive status (pre-/post-menopausal) of the individuals studied. Additionally, we also measured the cortical BMC (CtBMC) and cross-sectional area (CtA) of the same bones as indicators of the cortical bone "mass" and analyzed their influence on the indices as "third factors" upon that of the vCtD and MIs.

## Materials and methods

*The study participants*

Forty seven men aged 25-80 years, 70 pre-menopausal (pre-MP) women aged 25-50 years, and 122 post-MP women aged 50-80 years were recruited and included in the study. All were healthy and underwent normal physical activities. None had a history of fractures or diseases, smoking or drinking, or treatments affecting the skeleton, and none of the women had a history of menstrual disorders. Body weight and height, age an years since menopause (YMP) were registered for each individual.

Informed consent was obtained from each individual before inclusion in the study. The study had been approved by the Hospital's Ethics Committee (Application # 83, *Comité de Ética del Hospital Provincial del Centenario*, Rosario, Argentina).

*pQCT Measurements*

An XCT-2000 scanner (*STRATEC, Germany*) was used to scan the right tibia of each individual at 38% of the total tibia length proximal to the tibio-talar joint line previously determined by a scout-view procedure. The X-ray beam generated by the *XCT-2000* scanner has a thickness of 2.5 mm, and the pixel edge size was set to 0.5 mm. All image analyses were done with the integrated XCT software in its version 5.50. In particular, the following parameters were applied for all sectional images: *contmode 2, peelmode 2, and cortmode 1*. Threshold values for total and cortical bone were selected at 398.5 and 700.0 $mg \cdot cm^{-3}$, respectively.

The following indicators[89] were obtained from each scan.

*1. Cortical bone mineral content (CtC)*, in mg/cm of slice thickness.

*2. Cortical bone area (CtA)*: area covered by pixels identified as "cortical" by the software, in $mm^2$.

*3. Volumetric mineral density of cortical bone (vCtD= CtC/CtA)*, in $mg/mm^3$: amount of mineral per unit of cortical bone volume including the pores (apparent volumetric density). It is a direct correlate of the degree of calcification of the bone matrix, which is known to vary proportionally with the intrinsic stiffness (elastic modulus, here regarded as the "material quality") of cortical bone tissue[8,37,80,81].

*4. Second moments of inertia of the cross-sectional cortical area (MIs)*: integrated sums of products of the area of every pixel in the defined cortical image by their squared perpendicular distance to the neutral bone axes passing through the center of mass of the bone image, namely: the lateral-medial axis (anterior-posterior (A-P) bending MI, *xMI*), and the longitudinal axis (polar or torsion MI, *pMI*) in $mm^4$. These measures express the architectural efficiency of the cross-sectional design of the cortical shell (bone tissue "distribution") to resist A-P bending and torsional, respectively[3,4,85].

*5. Moment of resistance of the cortical area (MR= pMI/$D_{max}$*, in $mm^3$, being $D_{max}$ the distance from the center of mass of the bone image to the farthest pixel of the cortical image, in mm). It is a geometrically standardized form of expression of the pMI, with a similar correlate with the architectural efficiency of cross-sectional bone design concerning torsional strength.

| Model | y | $x_1$ | $x_2$ | $x_3$ | $x_4$ | $x_5$ | $x_6$ | Global R values | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Men | PreMP | PostMP |
| A-1 | xBSI | xMI | Age/TMP | B. weight | B. height | | | 0.999 | 0.999 | 0.999 |
| A-2 | pBSI | pMI | Age/TMP | B. weight | B. height | | | 0.999 | 0.999 | 0.999 |
| A-3 | SSI | MR | Age/TMP | B. weight | B. height | | | 0.973 | 0.990 | 0.980 |
| B-1 | xBSI | xMI | vCtD | Age/TMP | B. weight | B. height | | 0.999 | 0.999 | 0.999 |
| B-2 | pBSI | pMI | vCtD | Age/TMP | B. weight | B. height | | 0.999 | 0.999 | 0.999 |
| B-3 | SSI | MR | vCtD | Age/TMP | B. weight | B. height | | 0.983 | 0.998 | 0.999 |
| C-1 | xBSI | xMI | vCtD | CtBMC | Age/TMP | B. weight | B. height | 0.999 | 0.963 | 0.943 |
| C-2 | pBSI | pMI | vCtD | CtBMC | Age/TMP | B. weight | B. height | 0.999 | 0.936 | 0.999 |
| C-3 | SSI | MR | vCtD | CtBMC | Age/TMP | B. weight | B. height | 0.983 | 0.998 | 0.999 |

**Table I.** Complete set of multiple regression tests performed, showing the 3 different ways (Models) of selection of the proposed determinant factors ($x_{1-6}$) of the 3 selected indices (xBSI, pBSI, SSI - y -) according to the aim and scope of the study. The global correlation coefficients (R) of each multiple correlation Model are indicated in the extreme right columns. In addition to the selected confounders (Age or TMP, body weight, body height), Model A includes only one of the two factors of the indices as bone indicators (namely, the "distribution" indicators, MIs or MR, which were found always the most significant determinants at all); Model B includes both factors of the indices (the MIs or MR and the vCtD) as bone indicators; and Model C includes also one bone "mass" indicator (CtBMC) in addition to the two factors selected for Model B.

| | MEN | | | PRE-MP WOMEN | | | POST-MP WOMEN | | |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | CV | Mean | SD | CV | Mean | SD | CV |
| Age, yr | 46.5 | 14.4 | — | 32.4 | 11.4 | — | 58.9 | 8.9 | — |
| YMP | — | — | — | — | — | — | 12.3 | 9.0 | — |
| Body weight, g | 76.3 | 11.1 | 14.6% | 58.6 | 8.6 | 14.6% | 69.9 | 11.5 | 16.4% |
| Body height, cm | 175. | 6 7.1 | 4.0% | 163.1 | 7.1 | 4.4% | 158.1 | 7.0 | 4.4% |
| Cortical BMC, mg/cm | 3.93 | 0.58 | 14.7% | 2.88 | 0.37 | 13.0% | 2.69 | 0.35 | 13.1% |
| Cortical area, $mm^2$ | 351 | 51.9 | 14.8% | 248 | 38.6 | 15.6% | 240 | 34.2 | 14.2% |
| Cortical vBMD, $mg/cm^3$ | 1119 | 29.1 | 2.6% | 1152 | 29.3 | 2.6% | 1112 | 44.5 | 3.9% |
| xMI, $mm^4$ | 34902 | 7874 | 22.6% | 18755 | 4864 | 25.9% | 19391 | 4011 | 20.7% |
| pMI, $mm^4$ | 53374 | 11459 | 21.5% | 29369 | 7436 | 25.3% | 29981 | 6131 | 20.4% |
| MR, $mm^3$ | 2231 | 442 | 19.8% | 1391 | 289 | 20.8% | 1392 | 244 | 17.5% |
| xBSI, mg*mm | 39.0 | 8.56 | 22.0% | 21.6 | 5.38 | 24.9% | 21.5 | 4.33 | 20.1% |
| pBSI, mg*mm | 59.6 | 12.4 | 20.9% | 33.8 | 8.18 | 24.2% | 33.3 | 6.63 | 19.9% |
| SSI, $mm^3$ | 2083 | 401 | 19.3% | 1295 | 224 | 17.3% | 1337 | 268 | 20.1% |

**Table II.** Means, SDs and CVs of age, YMP, body weight and height, and pQCT data of all groups studied.

*6. Bone Strength Indices (xBSI= vCtD * xMI, or pBSI= vCtD * pMI)*: estimates of bone strength (actually, bone structural stiffness) in A-P bending (*xBSI*) or torsion (*pBSI*), in mg*mm units.

*7. Stress-Strain Index (SSI= MR * vCtD/$vCtD_{max}$*, in $mm^3$ units, being vCtDmax a constant, maximal theoretical value for vCtD of 1.2 $g/cm^3$). It is a standardized form of expression of the pBSI from both the geometrical (MR is used instead of the pMI) and "quality" (vCtD is related to a fixed, maximal value) points of view.

*Statistical analyses*

Means and SD's of all the variables determined (expressed in crude values) were calculated for each studied group. Multiple regression tests *[STATISTICA (data analysis software system), version 8.0, 2008: StatSoft, inc., USA, www.statsoft.com]* were then performed for each of the 3 groups studied, according to 3 different Models of analysis, as described in Table I, in which the corresponding, global R values are indicated.

The partial regression ($\beta_p$) coefficients between the xBSI, pBSI or SSI values (as determined variables) and the vCtD, or the xMI, pMI or MR values, as well as the vCtBMC, CtA, age or TMP, and body weight and height (as determinant variables) were then calculated and compared between groups. The $\beta_p$ coefficients obtained described the relationships between the increases of each determined variable (*y*) and those of each of their possible determinant factors (*x*) by separate, expressed in SD(y)/SD(x) units, each of them being calculated independently of the variation of any other determinant or confounder

| BONE STRENGTH INDICATOR (y) | ANALYTICAL MODEL (A, B, C) | "QUALITY" OR "DISTRIBUTION" DETERMINANT FACTOR ($x_1$, $x_2$) | MEN $\beta_p \pm S\beta_p$ | PRE-MP WOMEN $\beta_p \pm S\beta_p$ | POST-MP WOMEN $\beta_p \pm S\beta_p$ |
|---|---|---|---|---|---|
| **xBSI** | **A** | **xMI ($x_1$)** | 0.983±0.020 (p<0.001) | 0.995±0.021 (p<0.001) | 0.978±0.016 (p<0.001) |
| | **B** | **xMI ($x_1$)** | 1.021±0.005 (p<0.001) | 1.010±0.006 (p<0.001) | 1.027±0.005 (p<0.001) |
| | **B** | **vCtD ($x_2$)** | 0.095±0.004 (p<0.001) | 0.086±0.004 (p<0.001) | 0.156±0.005 (p<0.001) |
| **pBSI** | **A** | **pMI ($x_1$)** | 0.998±0.020 (p<0.001) | 0.972±0.020 (p<0.001) | 0.977±0.018 (p<0.001) |
| | **B** | **pMI ($x_1$)** | 1.024±0.005 (p<0.001) | 1.021±0.007 (p<0.001) | 1.022±0.006 (p<0.001) |
| | **B** | **vCtD ($x_2$)** | 0.100±0.004 (p<0.001) | 0.099±0.005 (p<0.001) | 0.174±0.005 (p<0.001) |
| **SSI** | **A** | **MR ($x_1$)** | 0.937±0.050 (p<0.001) | 0.965±0.027 (p<0.001) | 0.965±0.025 (p<0.001) |
| | **B** | **MR ($x_1$)** | 0.968±0.036 (p<0.001) | 1.009±0.013 (p<0.001) | 1.007±0.006 (p<0.001) |
| | **B** | **vCtD ($x_2$)** | 0.108±0.011 (p<0.001) | 0.130±0.009 (p<0.001) | 0.220±0.006 (p<0.001) |

**Table III.** Partial regression coefficients ($\beta_p$) and their SD's ($S\beta_p$) of the regression analyses calculated between the tomographic strength indices (xBSI, pBSI, SSI - y -) and their "distribution" (xMI, pMI, MR - $x_1$ -) and "quality" (vCtD - $x_2$ -) determinant factors, as described by the analytical Models A and B in Table I (the influences of the other confounders were found nonsignificant). In each case, the $\beta_p$ coefficients express the relationship between 1 SD increase in the ordinate (y) per unit of SD variation of the abscissa ($x_1$, $x_2$, as determined by the corresponding Model), calculated as $\beta_p = \Delta SD_y/\Delta SD_x$, while all other proposed determinants included in the Model are kept constant. The $\beta_p \pm S\beta_p$ values and their statistical significances (p values) are indicated.

as described by the Models selected for analysis (Table I), for each group. The SD values corresponding to each $\beta_p$ value ($S\beta_p$) were also calculated to assess the variance of the $\beta_p$'s about the calculated regression line in each instance. Statistical significance was assumed when $p<0.05$.

## Results

Table II shows the means, SDs and CVs of age, YMP, body weight and height, and pQCT data of all groups studied.

As expected, all the tomographic indicators which are known to be allometrically associated to body weight (CtBMC, CtA, MIs BSIs, SSI) showed significantly higher values in men than women (ANOVA, always $p<0.001$) and non-significant differences between pre- and post-MP women. These gender-related differences were especially evident for the MI's. Instead, the bone "quality" indicator, vCtD, was significantly higher in the pre-MP women than in men and post-MP women (ANOVA, $p<0.05$), with no statistical differences between the two latter groups.

Also as expected, much larger CVs were found for the MIs and the MR than for the vCtD, in all instances.

Table III shows the partial $\beta_p$ and $S\beta_p$ values calculated for the multiple correlations analyzed between the tomographic strength indices, xBSI, pBSI, SSI ($y_i$) and their two kinds of direct determinant factors, the corresponding "distribution" indicators, xMI, pMI, MR ($x_1$), and the "quality" indicator, vCtD ($x_2$) as per the analytical Models A & B described in Table I. The partial regression coefficients $\beta_p$ of the analyzed correlations indicate the relationship between the increments observed in the ordinate values (in SD units) per unit SD of variation of the abscissae values, calculated for every instance of comparison between each of the selected indices (xBSI, pBSI, SSI; *y*) and each of their selected skeletal determinants (xMI, pMI, MR, vCtD; *x*) by separate. These values were calculated independently of any within-group variation of the non-selected determinants and in age or YPM, body weight or body height.

Table IV shows the results of adding one "mass" indicator (CtBMC in this case) to the analyses, as described by Model C. In general terms, this procedure had almost no effect on the determinant power of the two direct factors of the indices, the "distribution" and "quality" indicators assayed, and likewise showed only little influence of the "mass" idicator itself. Similar results (not shown) were obtained by including the "mass" indicator CtA instead of CtBMC into the analyses, following the same Model C.

In general terms, results showed differences in the behavior of the coefficients derived from the kind of determinants or indices selected, and from sex-related variations, as follows.

*a. Variations related to the selected determinants*

Highly significant differences were encountered between the coefficients of the selected determinants, including the MIs or MR as the only bone indicators (Model A, Tables I & III), showed that, in those analytical conditions, most of the influence on the variance of the indices was accounted for by the "distribution" indicators. The determinant power of the other selected variables (age or TMP, body weight, body height; not shown) was found non-significant. The inclusion of both, "distribution" indicators and vCtD in the analysis (Model B (Tables I & III) demonstrated that both kinds of indicators were significant determinants of the indices, yet their quantitative influences were mostly contributed by the MIs or MR, even if

| INDICATOR | DETERMINANTS | $\beta_p$ | SE | p |
|---|---|---|---|---|
| **Men** | | | | |
| **xBSI** | **xMI ($x_1$)** | **0.946518** | **0.148775** | **0.000001** |
| | **vCtD ($x_2$)** | **0.076996** | **0.068935** | **0.027141** |
| | CtBMC ($x_3$) | 0.052893 | 0.141058 | 0.709881 |
| **pBSI** | **pMI ($x_1$)** | **1.008588** | **0.009955** | **0.000001** |
| | **vCtD ($x_2$)** | **0.095841** | **0.004613** | **0.000001** |
| | CtBMC ($x_3$) | 0.016377 | 0.009439 | 0.091272 |
| **SSI** | **MR ($x_1$)** | **0.885158** | **0.094838** | **0.000001** |
| | **vCtD ($x_2$)** | **0.092246** | **0.043943** | **0.042873** |
| | CtBMC ($x_3$) | 0.11634 | 0.089919 | 0.203964 |
| **PreMP women** | | | | |
| **xBSI** | **xMI ($x_1$)** | **1.026461** | **0.106848** | **0.000001** |
| | **vCtD ($x_2$)** | **0.153788** | **0.049409** | **0.002919** |
| | CtBMC ($x_3$) | 0.027993 | 0.087855 | 0.75119 |
| **pBSI** | **pMI ($x_1$)** | **1.045126** | **0.009972** | **0.000001** |
| | **vCtD ($x_2$)** | **0.097345** | **0.004611** | **0.000001** |
| | CtBMC ($x_3$) | -0.001744 | 0.008199 | 0.83236 |
| **SSI** | **MR ($x_1$)** | **1.001884** | **0.083122** | **0.000001** |
| | **vCtD ($x_2$)** | **0.143201** | **0.038438** | **0.000455** |
| | CtBMC ($x_3$) | 0.058333 | 0.068346 | 0.397024 |
| **PostMP women** | | | | |
| **xBSI** | **xMI ($x_1$)** | **1.057205** | **0.061258** | **0.000001** |
| | **vCtD ($x_2$)** | **0.141475** | **0.052532** | **0.008301** |
| | **CtBMC ($x_3$)** | **-0.123026** | **0.06243** | **0.05153** |
| **pBSI** | **pMI ($x_1$)** | **1.008205** | **0.008025** | **0.000001** |
| | **vCtD ($x_2$)** | **0.161753** | **0.006882** | **0.000001** |
| | CtBMC ($x_3$) | 0.018596 | 0.008178 | 0.025116 |
| **SSI** | **MR ($x_1$)** | **0.781901** | **0.046428** | **0.000001** |
| | **vCtD ($x_2$)** | **0.176463** | **0.039815** | **0.000024** |
| | **CtBMC ($x_3$)** | **0.209688** | **0.047317** | **0.000024*** |

**Table IV.** Partial regression coefficients ($\beta_p$) and their SE's and p values calculated from the multiple regression analyses performed as per Model C (addition of CtBMC to Model B as a potentially determinant factor). Significant results are marked in bold. The influences of the other confounders tested (age or TMP, body weight, body height) on the indices were found to be non-significant. Inclusion of CtA as an alternative bone "mass" indicator (not shown) yielded very similar results.

expressed in SD units. In general terms, the $\beta_p$ coefficients of any of the "distribution" indicators (MI's, MR) were between 4.6 and 10.7 times higher than those obtained for the density indicator (vCtD), regardless of gender and menstrual state. Nevertheless, the addition of vCtD to the analysis improved the value and reduced the variance of the coefficients calculated for the "distribution" indicators. Model C showed that the inclusion of CtBMC (Tables I & IV) or CtA (not shown) as a bone "mass" indicator added little significant influence as determinants over that exerted by the "direct" factors of the indices, vCtD and MIs or MR. However, the inclusion of either CtBMC or CtA into the analyses *for post-MP women* (only) contributed to enhance the assessed impact of vCtD and reduced that of the MIs or MR as determinants of the indices. The global R values (Table I) were quite high in all instances, with a maximum range for Model B (0.983-0.999) and a minimum one for Model C (0.936 to 0.999).

These findings suggest the convenience to focus the following analyses mostly on results of Model B Tables I & III).

*b. Variations related to the selected strength index*

Model B showed also some differences between the coefficients of both "distribution" (geometric) and "quality" (density) determinants which were specific of the selected index. Concerning the "distribution" determinants, larger mean values of the coefficients were calculated for the xBSI (range of variation= 1.010-1.027 for the different groups) or the pBSI (range= 1.021-1.024) than for the SSI (range= 0.968-1.009) (ANOVA, $p<0.01$). As per the vCtD determinant, the mean coefficient values increased as calculated for the xBSI (range= 0.076-0.156), the pBSI (range= 0.099-0.174) and the SSI (range= 0.108-0.220) (ANOVA, $p<0.001$) in all groups (Table III). In general

terms, the global R values of the Models (Table I) were slightly lower for the SSI (0.936-0.999) than for the other indices.

*c. Sex-related variation*

The analysis of Model B also demonstrated that the relationships shown by the strength indices with their "distribution" determinants and with the vCtD were distinctly affected by the gender and the menstrual status of the individuals (Table III).

The coefficients calculated for the correlation between the strength indices and the "distribution" determinants were similar in all groups, with average $\beta_p$ values ranging between 1.010 and 1.027 for the BSIs vs the MIs, and between 0.968 and 1.009 for the SSI vs the MR, with no significant differences between groups for each of the indices.

By contrast, the coefficients calculated for the relationships between the strength indices and the vCtD varied significantly between groups. In general terms, coefficients were about 69-106% larger for the post-MP women (range= 0.156-0.220) than for pre-MP women (range= 0.078-0.130), and 64-103% larger than for men (range= 0.095-0.108) (ANOVA, $p<0.001$).

Accordingly, the differences between the mean coefficient values calculated for "distribution" and density determinants were significantly smaller in post-MP women (4.6- to 6.6-fold) than in pre-MP women (7.7- to 13.4-fold) or in men (8.9- to 10.7-fold). The global R values of the Models (Table I) did not show any gender-related distribution.

## Discussion

It is widely acknowledged that bone tissue mineralization and distribution are independent predictors of bone strength, and that combining data of indicators of both of those properties improves the estimation of bone strength and fracture risk[2,3,15,29,30,34,35]. Hence, it can be proposed that "the concept of screening susceptible individuals by noninvasive estimates of bone density depends on a reliable correlation of the density and geometry of bone with susceptibility to fracture"[1]. In this study we report a quantitative evaluation of the relative participation of tomographic indicators of each of these properties in the determination of the pQCT-assessed BSI's and SSI as indices of the structural stiffness/strength of human long bones according to three different analytical criteria. Stress was put on the relative importance of the selected determinants, the selected indices, and the influences of the sex of the individuals. As a side result, the influences of other, potentially important determinants of the indices (as some bone "mass" indicators), or confounding factors like age (or TMP), body weight, or body height, showed little or no significant effects in the studied conditions.

Results confirmed the expected, very much larger CV values observed for the MIs' and MR's values ("extensive" variables which usually show very strong allometric associations) compared to those shown by the vCtD (an "intensive" indicator of bone "quality", for which there is virtually no reason to show any allometric relationship). Accordingly, and far beyond their obvious mathematical associations between the three bone strength indices selected for study and their "quality" and "distribution" determinants, the multiple correlations assayed showed quite variable relationships between indices and factors in the different groups and instances studied. The described results could be interpreted as follows.

*1. Absolute and relative variations of the independent impacts of the MIs or MR and vCtD values on the calculated indices (BSIs, SSI)*

The impacts of the variation of the "distribution" (MIs or the MR) and "quality" (vCtD) determinants on the variation of the strength indices, all expressed in SD terms, differed substantially. A 1-SD variation of any of the MIs or the MR induced a much larger change on any of the indices than 1-SD variation of the vCtD did. Results also showed that the addition of vCtD to the analyses did not improve the statistical power of the corresponding Models (global R values, Table I) over that shown for the inclusion of the "distribution" factors alone. These findings point out the importance of the geometric adaptation of bones to their mechanical environtment, in agreement with many other authors[23-25]. Interestingly, the coefficients for the "distribution" indicators were improved, rather than impaired, after inclusion of the vCtD into the analysis (i.e. when this second factor of the indices was taken into account and kept constant; Model B). This highly suggests that the "quality" (vCtD) and "distribution" (MIs, MR) indicators analyzed in this investigation should not be taken as mutual confounders, but rather as real and constructive constituents (i.e. agonists with a "trade-off" in statistical terms) for the determination of the structural bone bending or torsion stiffness (and, very likely, strength). This interpretation is congruent with our "*distribution/quality* concept"[42], from which the "*BSI* concept" was originally derived[27].

In general terms, all the above differences and effects were more evident in men and pre-MP women than in post-MP women. These results deserve a separate analysis of the independent influences of the MIs or MR and the vCtD on bone strength.

*2. Independent impact of the "distribution" determinants (MIs, MR) on the strength indices*

The significant, independent impact of the variations of bone "distribution" indicators on the estimated whole-bone strength as assessed in this study (slightly larger on the BSIs than on the SSI) was unaffected by the gender or the reproductive status of the individual. This gender-independence would have been expected, as far as the naturally strong mechanical relationships between cortical bone mass (BMC, CSA) or cross-sectional geometry (MI's, MR) with the whole-bone strength in adults usually show a constant behavior for the species[1,34] as well as for animals[5], on which no hormonal influence is known. Results also show that the relative impact of bone "mass" indicators (CtBMC, CtA - Model C - in this particular case) on the determination of the indices was clearly lower than that shown by both the bone "distribution" (chiefly) and "quality" indicators in the assayed conditions. Whether

this important effect of the "directional" indicators of bone geometry is or not related to their particularly wide range of physiological variation is a matter of discussion[1].

*3. Independent impact of the vCtD on the strength indices, and gender-related influences*

In general terms, the significant, independent impact of the variations of the bone material "quality" indicator, vCtD on the indices, was lower than that exerted by changes in bone tissue "distribution", yet it was significantly higher than that shown for the bone "mass" indicators assayed (CtBMC and CtA, Model C). In particular, the impact of vCtD changes on the values of the strength indices was statistically more evident for the post-MP women than for the other groups (in congruence with others' findings, and with the report of a greater mechanical impact on bone toughness in post- than in pre-MP women[72,90]). This effect was more evident when the selected index for analysis was the SSI. A possible explanation for that finding is that in post-MP women the vCtD not only was significantly lower but also showed a 50% larger CV than that of the other groups, reflecting both a loss and a wider range of variation of cortical density after menopause. The vCtD loss in post-MP women can easily be explained by estrogen withdrawal and its known effects on intra-cortical Haversian remodeling[3,91]. These relationships can help to evaluate the different impacts of changes in vCtD and the MIs in post-MP women[29,35,92-94].

*4. Changes after the inclusion of "mass" indicators into the analyses (Model C)*

The added influence of either CtBMC or CtA on the indices (Model C) was generally much less significant than that of the original candidates, i.e. vCtD and MIs or MR. This could have been expected, perhaps not as a physiological finding, but rather because the "mass" indicators, CtBMC and CtA did not integrate the calculations of the indices. Anyway, the beta coefficients calculated for the vCtD and the MIs or MR in these new approaches were generally little affected by the higher complexity or comprehensiveness of the analytical model (as assessed by the global correlation coefficients, R). Although in some instances for post-MP women some significant contribution of CtBMC and CtA was observed, this corresponded either to quite low or even negative (i.e. erratic) values of the beta coefficients.

The only interesting exception observed was the mild but significant influences of either or both, CtBMC (shown) and CtA (not shown) on the SSI after menopause. Interestingly, the inclusion of either CtBMC or CtA into the analyses for post-MP women strengthened the assessed impact of vCtD and reduced that of the MIs or MR as determinants of the indices. This may reflect that, in these particular analytical circumstances, the contribution of cortical porosity to bone strength is more evident if, in addition to the "distribution" indicators, also the cortical "mass" indicators are kept artificially constant. The restriction of this observation to only the post-MP women is congruent with what is known concerning the natural enhancement of cortical porosity after menopause[86], a relevant factor to the impairment of bone strength through a deterioration of bone toughness. The fact that only the SSI index was able to detect this finding could possibly be explained because the standardization of the SSI as per the maximal cross-sectional diameter to obtain the MR could have produced a more sensitive indicator of bone distribution than the "raw" MIs in cases where the CtBMC or CSA are reduced, as they are in the post-MP women.

*General interpretation of the findings*

In general terms, the collected evidence suggests that the mechanical impact of an anti-osteoporotic treatment on structural bone strength, expressed by unit SD of variation, should be larger when it improves the architectural efficiency of bone design (involving an improvement of the spatial coordination of bone modeling and remodeling, possibly as a result of a more effective control of bone structure by the bone *mechanostat*) than when it enhances the mechanical quality of the mineralized tissue (through a reduction of intra-cortical micro-porosity by a modulation of Haversian cortical bone remodeling), or just increase the bone mineralized mass. This agrees with some reported clinical evidence[2,31]. In fact, determinations of the relative risk (RR) of fracture in human studies have reported changes of -1.5 (0.9 to -2.69) in RR for each 1 SD variation in vCtD, and of -3.8 (-1.6 to -9.1) for the same in the MI[3]. These observations may apply specially to old women, in which the bone loss is predominantly cortical, with a high mechanical impact[95-97], and the reduced vCtD (or the excessive cortical thinning) in long bones can still be compensated (mildly but significantly) by increases in the MIs[19,42,98].

It could be also proposed that, *prima facie*, the SSI should be a little more reliable indicator of bone strength than the BSIs for the assayed model of study.

In particular, and in agreement with others' observations[72], the study also suggests that the independent mechanical impact of any positive or negative effect exerted by a treatment on intra-cortical remodeling (as described by the method, and expressed per unit SD of variation) should be more relevant to bone structural stiffness (as assessed by the indices) for post-MP women than for men or for pre-MP women.

In brief, the reported findings provide evidence of: 1. the relatively greater importance of "distribution" over "mass" indicators in bone strength analysis, 2. the "trade-off" nature of the participation of the assayed bone properties (material "quality" and "distribution") in the hypothetically servo-controlled regulation of the structural stiffness of the whole bones, and 3. the possibility that the inclusion of "mass" indicators in the analyses help to detect or to quantify the particular impact of cortical porosity as a determinant of cortical bone weakness (very likely derived from a low bone tissue toughness) in post-MP women.

At any rate, the analysis of the participation of these and other "mass" indicators as putative independent determinants of structural bone stiffness or strength as assessed by the assayed or similar indices deserves a deeper investigation em-

ploying specifically-designed models, and as such it must be regarded as an open question.

*Limitations of the study*

The above interpretation is restricted: 1. by the characteristics of the tomographic methodology employed, including its unability to distinguish between matrix mineralization and micro-porosity and to assess bone toughness; 2. by the well-known site-specificity of the biological determinants of the structural bone strength; 3. by the high directionality of the mechanical vectors involved in the stress/strain relationships, and 4. by the unavoidable limitations imposed by the analytical Models selected for the study.

The elastic modulus E of bone tissue was shown to vary as a function of the cube of the Ca content[8,34,80]. However, sometimes the relationship looks linear within the physiological range[37,75,81]. To clarify this apparent ambiguity, we re-calculated all the beta coefficients in this study following the Model B but taking the cubed vCtD values instead of the raw ones. Results (not shown) did not differ statistically from those reported here. Regardless of the mathematical form of the adjusting equations, this could mean that the way the data are expressed (standardized as Z-scores) neutralizes any difference coming from that possible source of error. For practical purposes, we prefer to use the raw vCtD data as reported here as a reference, because this way of expression looks more familiar to clinicians than cubed values in unusual units do.

*Perspectives of clinical application*

The study aims at a better interpretation of both the natural and pharmacologically-induced variations of the tomographic vCtD and MIs of MR data as indicators of different aspects ("material quality" and "distribution", respectively) of what is being currently regarded as "(whole-)bone quality" (structural bone strength) in clinical practice, with interesting therapeutic derivations.

Further, specifically designed studies will allow establish: 1. whether the expression of the values or changes of vCtD and MIs or MR in SD terms ($vCtD_{SD}$, $xMI_{SD}$, $pMI_{SD}$, $MR_{SD}$) as related to pre-defined reference values should or should not be regarded as adequate to monitor the effects of a treatment on bone strength and/or fracture risk in different skeletal sites, and 2. If so, whether the interpretation criteria for comparative assessments made in men, pre-MP women and post-MP women should or should not differ as proposed here.

Practically speaking, results of this study (and related ones) will thus help to understand whether and where pharmaceutical and other interventions interfere with mechanostat-like regulation of bone structural design.

*Acknowledgements*

*This study was supported by the research grants PICT 0695/08 of the Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT, Argentina) and PIP 0476/09 of the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET, Argentina). Authors are gratefully acknowledged to Drs Sara Feldman (LABOATEM, National University of Rosario), Roberto Tozzini and Mario Morosano (Servicio de Menopausia & Osteoporosis, Hospital Provincial del Centenario, Rosario) for providing many of the cases and data for study. Drs JLF, RFC and GRC are Members of the Research Career, CONICET; Drs PSR and LMN are fellowships of the CONICET and ANPCyT, respectively.*

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