J Musculoskel Neuron Interact 2004; 4(1):1-11

Perspective Article

Hylonome

# Biomechanical background for a noninvasive assessment of bone strength and muscle-bone interactions

**G.R. Cointry[1], R.F. Capozza[1](ex-aequo), A.L. Negri[2], E.J.A. Roldάn[3], J.L. Ferretti[1]**

[1] Center for P-Ca Metabolism Studies (CEMFoC), National University of Rosario, Rosario;
[2] Postgraduate Dept of Osteology, Del Salvador University, Buenos Aires;
[3] Clinical Pharmacology Division, Gador SA, Buenos Aires, Argentina

**Abstract**

New concepts and methods of study in bone biomechanics defy the prevailing idea that bone strength is determined by a systemically-controlled "mineralized mass" which grows until reaching a peak and then is lost at individually-specific rates. In case of bones, "mass" represents actually the substratum of a structure, the stiffness of which does not depend on the mass, but on the intrinsic stiffness and the spatial distribution of the mineralized material. A feed-back system called "bone mechanostat" seems to orient the osteoblastic and osteoclastic processes of bone, modeling and remodeling, according to the sensing by osteocytes of strains caused in the structure by mechanical usage of the skeleton, in specific directions as determined principally by the customary contractions of regional muscles and impact forces. The endocrine-metabolic systems, crucial for the normal skeletal development, modulate the work of osteocytes, blasts and clasts in a systemic way (i.e., not related to a specific direction of the stimuli). Therefore, they tend actually to interact with, rather than contribute to, the biomechanical control of bone structure. Furthermore, no feed-back loop enabling a cybernetic relationship of those systems with bone is known. Instead of passively letting hormones regulate their "mass" in order to optimize their strength, bones would actively self-regulate their architecture following an *anisotropic* pattern in order to optimize their stiffness (the only known variable to be ever controlled in the skeleton) and strength "despite of" the endocrine systems. Three practical questions derive from those ideas: **1.** Osteoporoses are not "intense osteopenias" but "osteopenic fragilities". **2.** The diagnosis of osteopenia could be solved densitometrically; but that of bone fragility is a biomechanical problem which requires auxiliary resources for evaluating the stiffness and the spatial distribution of the mineralized material. **3.** Osteopenias and osteoporoses should be on time evaluated as related to the mass or strength of the regional muscles, respectively, in order to differentiate between the "primary" (intrinsic lesion of the mechanostat) or "secondary" (systemic) etiologies and the biomechanical origin (disuse) in each case, with important therapeutic implications.

**Keywords:** Osteopenia, Osteoporosis, Bone Mass, Bone Strength, Bone Fragility, Densitometry, Quantitative Computed Tomography, Bone Biomechanics, Muscle Mass, Muscle Strength, Muscle-bone Interactions

## Introduction

This article summarizes some new ideas about the biological determination of the mass and strength of bones; a proposed etiopathogenetic classification and differential diagnosis of osteopenias and osteoporoses, and some suggestions about how some of the determinants of bone strength could be evaluated non-invasively.

One prevalent concept holds that bone strength is determined by a "*mineralized mass*", *the growth of which is regulated by endocrine-metabolic mechanisms that determine a "peak" and a subsequent decline at different rates for different individuals*[1,2]. In another view, skeletons are mechanically-controlled structures, the non-invasive study of which requires use of some specialized technologies[3,4]. Recent studies failed to correlate the positive effects of some current therapies on DEXA-assessed bone "mass" (BMD) with a reduction of incidence of new fractures in osteopenic patients[5-7]. This suggested that bone mass measurements by DEXA might be inadequate to monitor effects on bone health[8-10]. In fact, DEXA determines

The authors have no conflict of interest.

*Corresponding author: José Luis Ferretti, MD, PhD, CEMFoC, National University of Rosario, Juan B. Justo 1427, 2000 Rosario (SF), Argentina, E-mail: jlferretti@arnet.com.ar*

*Accepted 2 September 2003*

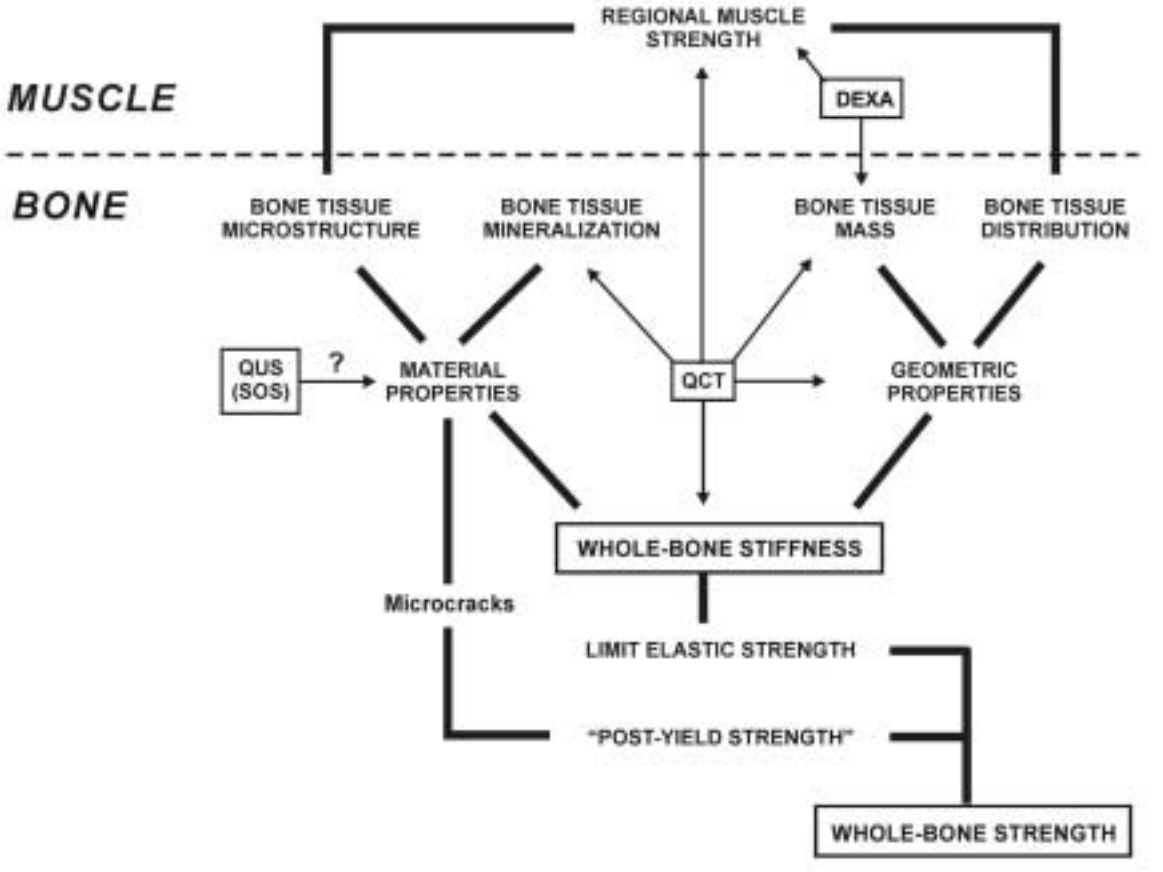


**Figure 1.** Biologic determinants of a bone's stiffness and strength, including the mechanical influence of muscles. The production of *anisotropy* (different stiffness / strength in different directions) at tissue and organ levels of structural complexity of bones derived from the *material* and *geometric* properties, respectively, is shown. The ability of some current methodologies (DEXA, QCT, and quantitative ultrasonometry-QUS/SOS of cortical bone-) to determine some suitable indicators of those properties is also indicated.

the mineral mass in the skeletal region with acceptable accuracy and precision and can describe its changes under different treatments[1,2]. However, the DEXA-assessed BMC and BMD data do not seem to provide information that can evaluate bone strength or reliably predict fracture incidence[3-7,10,11-13].

Newer ideas[14,15] reveal that:

a. osteoporoses are not "intense osteopenias" (i.e. very low BMC or BMD values)[1,2] but *osteopenias with a biomechanical compromise of bone structure*[3];
b. bone's resistance to strain and fracture is determined by many structural factors[4,16-18], most of which are beyond of the scope of DEXA technology but some of them are determinable by other methodologies[11-13], and
c. bone strength should be evaluated as a function of the mechanical usage of bones when that determines a bone's structural quality and design[19-22].

## I - Biologic determination of bone mass, structure and strength

Bones would not control their *mass* in order to optimize their *strength*. They would rather control their *architecture* in order to optimize their structural *stiffness*.

No solid structure fails without undergoing some tensile *strain* at some point[4,11]. Therefore, the chief skeletal property concerning body-weight bearing is stiffness (i.e. the relationship between the load on a bone and its deformation). A rigid material (mineralized collagen) seems to have developed during evolution for building bones. However, the mechanical efficiency of bones seemed not to depend on the mere *accumulation* of material but rather on the optimization of its *spatial distribution*[23]. Perhaps for this reason the architectural design of skeletal cortices and trabecular networks in all vertebrates is optimally oriented in order to avoid excessive deformation of bones under customary mechanical usage. This way bone strength can be optimized indirectly. The stiffness and strength of every bone are determined by two complementary factors, namely, the *intrinsic stiffness* of the mineralized tissue (unrelated to the bone's size and shape) and the spatial distribution of that tissue (the bone's design). Those features are usually referred to as bone's material and geometric properties, respectively[4,11] (Fig. 1). In this connection, the mechanical behavior of bone tissue and bones as organs shows a high degree of directionality determined by the spatial arrangement of their micro- and/or macro-structural components (tissue and bone *anisotropy*, respectively).

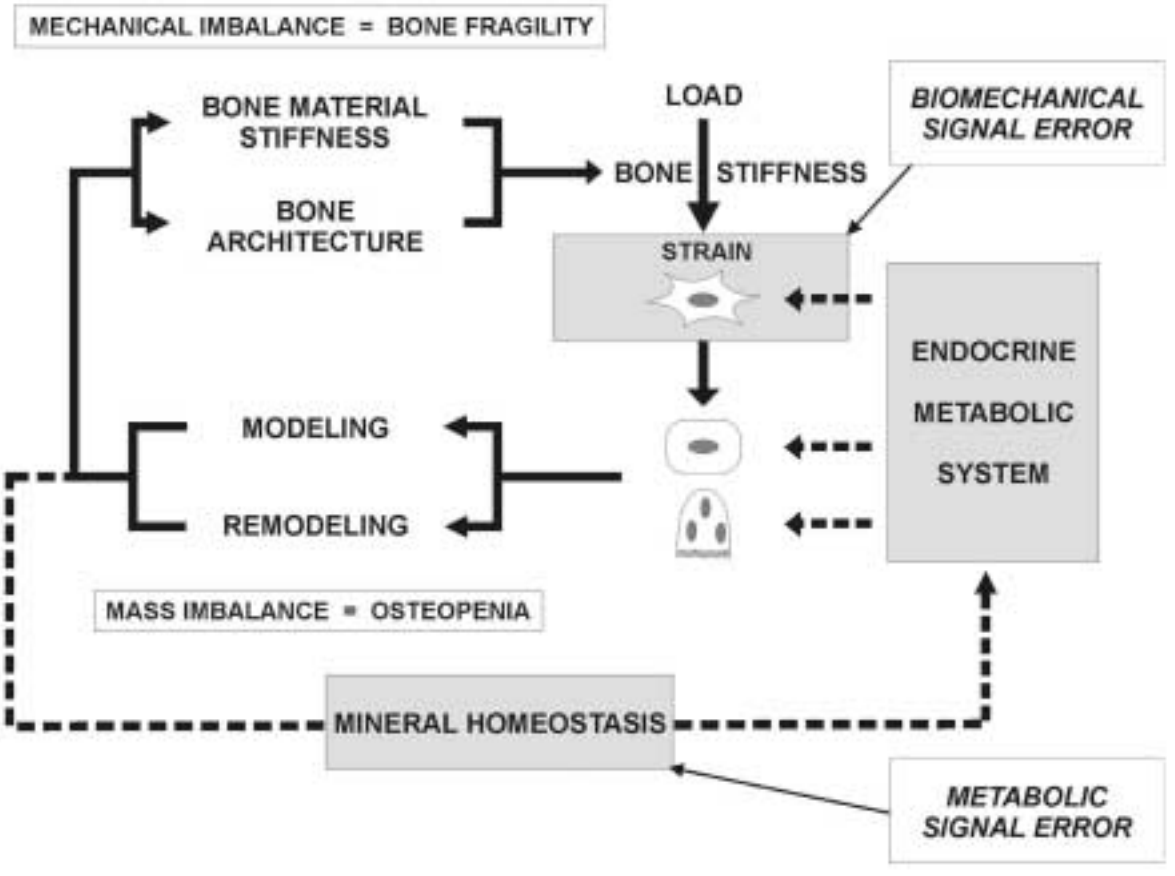


**Figure 2.** *Anisotropic* (i.e., sensitive to the direction of the stimuli) control of bone deformability by the bone's *mechanostat* based on the sensing of local strains produced by mechanical usage (solid arrows), and *isotropic* (systemic) interaction of the endocrine-metabolic systems with that control (dotted arrows), which affect the same effectors (osteoblasts, clasts) for controlling other, extraskeletal variables related to mineral homeostasis. The independence of the resulting, mass and mechanical balances is remarkable.

*Bone tissue's stiffness* is determined 1) by the degree of mineralization of the collagen matrix[24] and the microstructural disposition of crystalline elements on fibers; fibers in lamellae; lamellae in osteons, and osteons themselves within the "solid" tissue, and 2) by the density and distribution of microdamage produced by mechanical usage[16,18]. Many such factors which are unrelated to bone mineralization, determine the ability of bone tissue to avoid creeping and disruptions, expressed biomechanically as the bone's *toughness*.

*A bone's geometric properties* are determined in many different ways. In bone cortices, the distance of the compact tissue from the relevant axes for bending and torsion (evaluated by the *second moments of inertia* of the cross-sectional cortical bone area) is a critical factor[23]. In trabecular networks, some relevant geometric factors are their disposition along specific lines of force in different regions, and trabecular thickness and connectivity[25].

Bone development offers three mechanisms for adapting those properties, namely, 1) *growth in length* following either between surfaces (Howship's lacunae) or on the end ochondral pattern (null after the third decade in humans and thus out of interest here), 2) *modeling*, and 3) *remodeling*[26-28].

*Bone modeling* consists of a combination of independent osteoblastic apposition of new bone and osteoclastic resorption of pre-existing bone in different sites of a bone. Its general balance is usually positive and it declines in the second half of life. Modeling is the chief way to increase bone mass (i.e. to improve an osteopenia or osteoporosis)[29]. It can also modify bone geometry through changes in size and shape (growth in width) and trabecular thickening, and is thought to be an important mechanism of skeletal adaptation to mechanical needs, especially during growth.

*Bone remodeling* is a *coupled* process of osteoclastic resorption of tiny amounts of pre-existing bone which are then replaced totally ("conservative" mode) or partially ("disuse" mode) by osteoblastic formation at the same site. Remodeling seems to be a suitable mechanism to help to maintain mineral homeostasis, to replace old by new bone, and for microdamage repair. "Disuse" mode remodeling, especially important in the second half of life, is the way to decrease bone mass and it is the cause of all adult-acquired osteopenias and osteoporoses[28]. Bone remodeling can occur on endosteal and trabecular surfaces or on the intracortical surface (Haversian systems)[29]. Depending on its location, "disuse" mode remodeling can change bone geometry by thinning the cortex and also reducing the stiffness of compact bone by enhancing intracor-

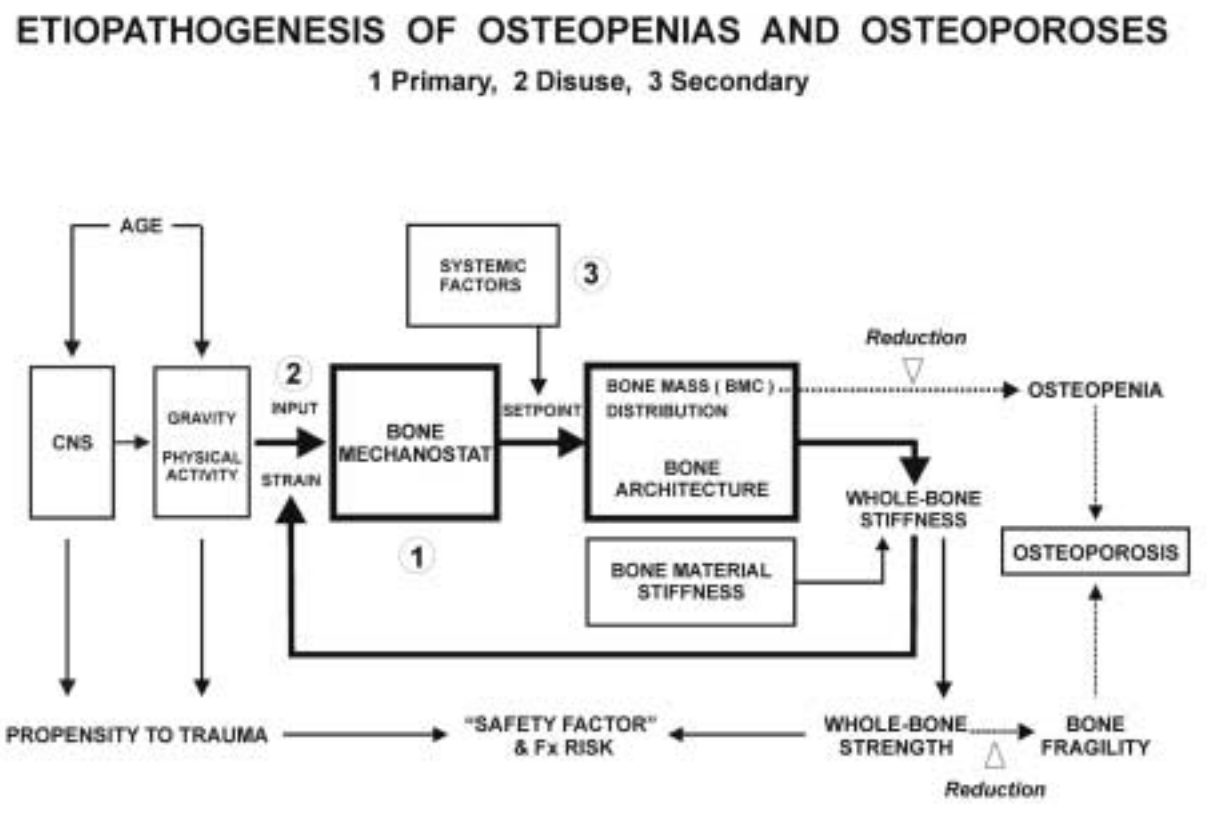


**Figure 3.** Etiopathogenesis of osteopenias and osteoporoses, focused on the role of the bone's *mechanostat* (indicated by thicker boxes and arrows) in the biological control of bone stiffness and strength schematized in **Fig. 2**. Osteoporoses involve a reduction in both bone mass (osteopenia) and bone strength (enhanced bone fragility, on time determined by the mass, quality and distribution of the mineralized tissue as shown in **Fig. 1**). Assuming a qualitative normality of the remaining mineralized tissue, osteopenias and osteoporoses could derive from either (**1**) a primary illness of bone cells with a direct impact on the bone's *mechanostat* function, (**2**) a lack of mechanical influences on bone tissue affecting the input of the bone's *mechanostat*, (**3**) or a systemic interaction of the endocrine-metabolic environment of bone cells with the *mechanostat* setpoints. Different combinations of those and other, extraskeletal factors determining fracture risk can be observed in senile individuals.

tical porosity (excessive haversianization).

Thus bones can *self-control* their structural stiffness, aided by the modeling and remodeling mechanisms[30]. They could achieve that control because osteocytes could sense the directions in which the usage-determined bone strains are usually determined[31,32]. This way osteocytes could *orient* their biological signals to local osteoblasts and osteoclasts, thus stimulating or inhibiting their formative or resorptive activity accordingly. That *functionally oriented* addition and removal of bone tissue would optimize the stiffness of bones as organs according to the strains produced by the customary mechanical usage, chiefly determined by contractions of the regional muscles[19,22] (Fig. 1).

That process determines two *independent* balances (Fig. 2), namely, a *mass balance* given by modeling-dependent gains and "disuse" remodeling-dependent losses of bone tissue, and a *mechanical balance* resulting from changes in bone's material and geometric properties[11].

The *mechanical balance* tends to control bone stiffness, the only skeletal property which seems to be under any feedback control[33,34]. The feedback system involved, known as *bone's mechanostat*[30], would keep customary strains in any skeletal region within a range of 1-2 / 1000 of the original length in the critical directions under maximal physiological efforts in vertebrates. This way bone strains would be kept far below the limit that could cause a bone fracture (approximately 20-25 / 1000 of that length). By controlling bone *stiffness*, the mechanostat would also determine bone *strength*[23,25].

The bone *mass balance* of that mechanism seems to be a side result, not related to any regulatory need. No biological system is known to measure bone mass, and what can not be measured can not be regulated. No known feedback mechanism can detect a bone *mass* change and inform an endocrine gland about it in order to correct some inadequacy.

## II - Etiopathogenesis and differential diagnosis of osteopenias and osteoporoses

A low bone *mass* balance can cause an *osteopenia* ("lack of bone within the bone"). A negative *mechanical* balance (from inadequate functioning of bone's *mechanostat*) can increase bone *fragility* (low resistance to fracture). To diagnose an

*osteoporosis* ("bone fragility resulting from an osteopenia") *both* negative balances have to be documented (Fig. 3). Osteoporoses are not "intense osteopenias" as suggested by the well-known, densitometric *t-score* scale[1,2]. The NIH recently redefined osteoporosis as "a disease in which bone strength is reduced"[3], which relates it to all other bone-weakening diseases. Rather than that, osteoporoses would be "osteopenic fragilities". The above arguments let us propose that any kind of osteoporosis (as well as every bone-weakening disease, too) could only result from some kind of failure of the *mechanostat* to control bone structural properties.

Physiologically, the *mechanostat* could control bone stiffness and strength[30,33,34]. However, mechanostat function depends on the normal state of all its *cells* (osteocytes, blasts and clasts), the customary mechanical usage of the skeleton (*input* of the system), and the endocrine-metabolic environment. The latter could be a critical factor. In fact, it can modify the osteocyte ability to detect any strain beyond the physiological range as an error. It can also modulate the osteoblast and osteoclast ability to respond to local stimulations or inhibitions. This would imply raising and lowering the *set-points* of the system for triggering local modeling-induced additions or "disuse"-mode remodeling-induced losses of mineralized mass, respectively (Fig. 3). This interaction of the endocrine environment with bone cell function may result either positive or negative in terms of bone mass, geometry, or structural properties. Therefore, particular kinds of disturbances in the above three critical requirements would determine a corresponding failure in the biomechanical control of bone structure. Accordingly, bone-weakening diseases can be classified into specific types[12,13,36] as follows:

***1.* "Primary" *diseases.*** An abnormal genetic constitution of the mechanostat, an intrinsic illness or the senile deterioration of its cells, transitory mechanisms that can accelerate bone remodeling regionally ("regionally acceleratory processes"), and other unknown factors ("idiopathic" cases) can cause osteopenias, osteoporoses, or bone weakness. "Primary" osteopenias and osteoporoses such as osteogenesis imperfecta and idiopathic osteoporosis, uncommon in practice, show characteristic features and none has a specific treatment.

***2.* "Secondary" *osteopenias and osteoporoses.*** Endocrine-metabolic systems provide a feedback control of the mineral balance of the internal *milieu*. Changes in the endocrine-metabolic environment of the mechanostat sensors (osteocytes) and effectors (osteoblasts and clasts) can modify the feedback control of bone structure in a systemic (i.e. *isotropic*) way. This interaction can affect either positively or negatively the *anisotropic* biomechanical control of bone structure exerted by the mechanostat[30] (Fig. 2). The higher biological hierarchy of the regulation of the mineral homeostasis of the body by evolutively older systems would subrogate the biomechanical control of bone structure to the metabolic control of mineral balance. This could interact with the *mechanostat* function by shifting the system's set-points, giving place to "secondary" osteopenias and osteoporoses and enhancing the risk of spontaneous fractures of the spine and traumatic fractures of the same and other parts of the skeleton[36]. Post-menopausal osteoporoses should be included into this group rather than regarded as a separate entity. These osteoporoses (most of daily cases in consulting office) may show a bone mass or strength *inadequately low for the mass or strength of the individual's muscles.* Their treatment requires the neutralization of the systemic disturbance, otherwise a non-hormonal, modeling-stimulator or remodeling-inhibitor drug has to be prescribed.

***3.* "Disuse" *osteopenias and osteoporoses.*** A reduced mechanical stimulation of the skeleton (low physical activity, immobilization, weight loss, weightlessness, etc.) will lower the mechanostat input (Fig. 2). The natural response of the system will be addressed to keep bone strength adequate to that lower level of mechanical requirement, i.e., *proportionate to muscle strength* and body weight. This situation can provide a reasonable skeletal strength regarding the relatively poor customary mechanical stimulation, yet not necessarily so for supporting maximal physiological efforts or loads. Oppositely to the "secondary" cases, "disuse" osteoporoses tend to affect predominantly cortical rather than trabecular bone, and the peripheral rather than axial skeleton[22,36]. Their treatment should aim just re-loading the unloaded skeleton, with no pharmacological additions provided that bone modeling and remodeling are normal.

***4.* "Senile" *osteopenias and osteoporoses.*** Senility implies the natural decay of many biological systems, including *neuromuscular coordination.* This may add to the natural causes of osteoporoses, that may combine in aging subjects, an increase in the tendency to fall as an important, extraskeletal determinant of fracture risk[12,13,36]. The currently prevalent distinction of these "combined" forms of osteoporoses as an opposed group to post-menopausal osteoporoses (the classic types "I" and "II" osteoporoses) ought to be disregarded.

## III - How to evaluate bone strength

The above relationships pose three diagnostic problems:

**1. Insufficiency of the DEXA determinations.** DEXA-assessment of BMC and BMD would provide the best (perhaps the only) available resource for diagnosing an *osteopenia*[1,2]. Regrettably, they can not provide a diagnosis of *osteoporosis* because they do not give any information on bone material and geometric properties[4-7,9-13] (Figs. 1, 3). The BMD is just a *surrogate* of bone strength. Therefore, the widely reported correlations between BMD and bone strength or fracture incidence afford no direct evidence that bone strength or its disease- or treatment-induced changes can be evaluated as a function of the induced variation in the "areal", projected mineral "density" of the bones.

**2. How to determine some mechanically meaningful indicators.** Suitable indicators of bone material and geometric properties should be determined for diagnosing a skeletal fragility[4,11-13,37,38] (Figs. 1, 3). Bones with a reduced mineral mass could be adequately strong provided that their calci-

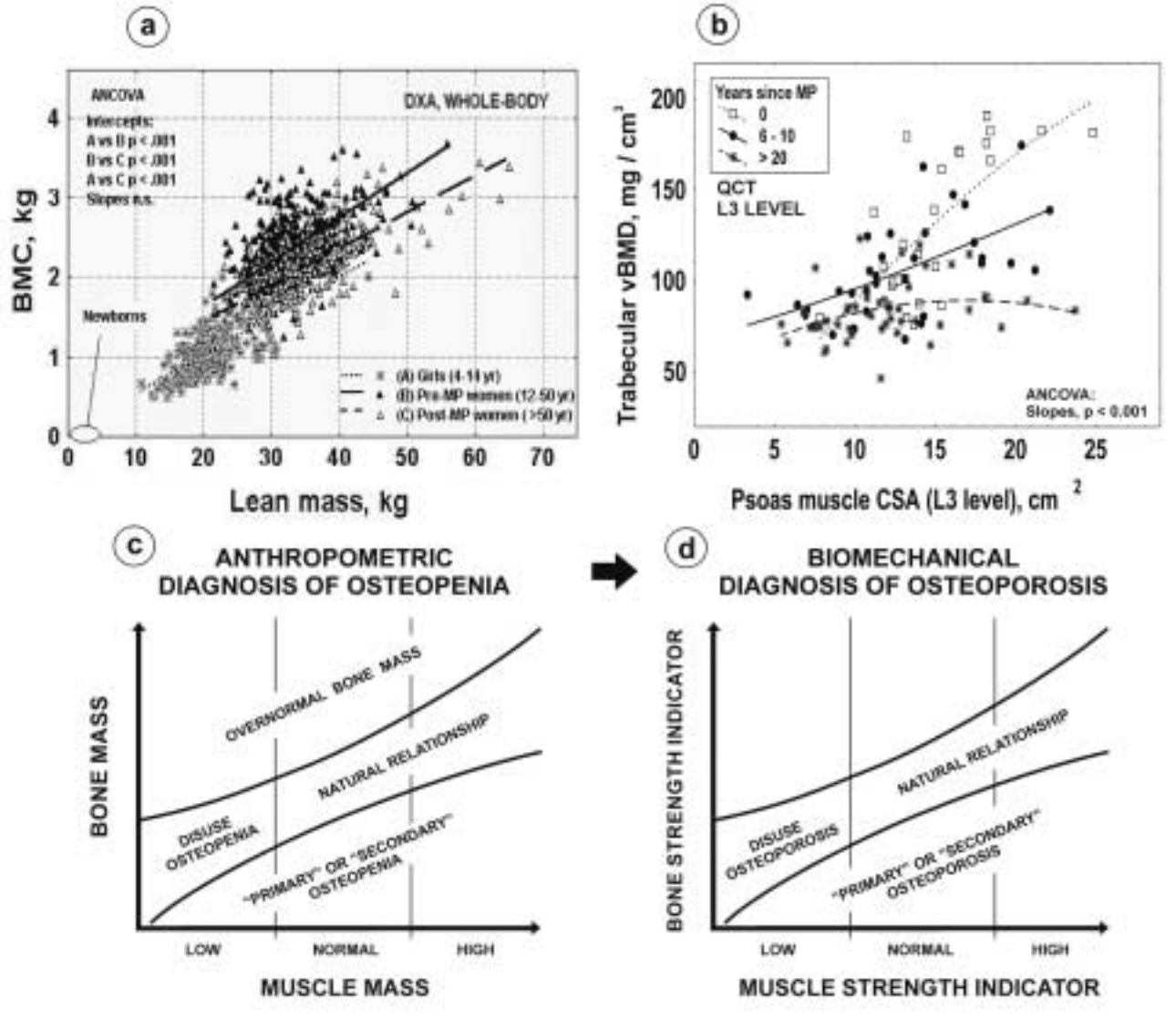


**Figure 4. a.** Correlations between DEXA data of bone mineral content (BMC) and lean mass of the whole body in 967 normal girls and pre- and post-menopausal females[56]. Parellelism of the curves (also evident in males) would indicate a common biomechanical control of bone structure (represented in this case by the bone mineral content) in the species. The intercept differences would reflect the (positive) interaction of sex hormones or related factors with that control.
**b.** Correlations between the volumetric BMD of the central core of trabecular bone of the L3 vertebrae and the cross-sectional area of psoas muscles in normal pre- and post-menopausal women[22,46]. The decreasing slopes of the curves describing the bone-muscle associations as affected by the lack of estrogen and time after menopause, in agreement with the intercept differences shown in (a), suggest that "*bones are as the (regional) muscles determine them to be, unless hormones think otherwise*":
**c,d.** Schematic representations of the above curves (**a,b**) indicating different distribution zones for cases in which the bone-muscle proportionality is or not normal. *Z-scored* versions of those graphs can be used as quantitative references for a differential diagnosis between osteopenias (mass relationships, left) or osteoporoses (strength relationships, right) derived from disuse (normal bone / muscle proportionality) and other etiologies (low bone / muscle proportionality).

fied tissue is stiff enough, or their design is architecturally efficient as to avoid a critical deformation in the directions of the customary loads supported.

The "mineral" component of bone tissue stiffness can be evaluated by measuring the *volumetric* (not "areal") mineral density (vBMD) of compact bone[24]. This can be done by several means, including quantitative computed tomography in its classic, "axial" (QCT, for the spine, hip, radius, etc.) and "peripheral" modes (pQCT, for radius, tibia, etc.)[12,13,38-41]. At present, the "microstructural" components of bone tissue stiffness are not measurable non-invasively.

Quantitative ultrasonometry could *indirectly* assess the stiffness of compact bone by measuring the propagation speed of sound (SOS) in tibiae, radius and phalanges[42,43], yet

its application still requires clinical validation.

The architectural design of cortical bone can be evaluated in tubular bones by pQCT, by determining the moments of inertia of the diaphyseal cross sections. These indicators vary with the distance of the compact tissue from the biomechanical axes for bending and torsion. Bones with thin walls and wide diameters may be stronger than others with thicker walls but smaller diameters, despite having the same or even less cross-sectional mineralized mass[12,13,38,40,44]. Nevertheless, bone mass indicators as the pQCT-measured cross-sectional area or mineral content of cortical bone[45,46] or even the DEXA-assessed BMC (not BMD) may result proportional to bone strength in some instances[47]. In vertebral bodies, which work predominantly in compression, the amount of cortical bone in the cross section may be mechanically more significant than the moments of inertia of that section[23].

The architectural arrangement of the trabecular network is more difficult to evaluate than the cortical design because it involves the mechanical efficiency of the distribution, thickness and connectivity of the horizontal and vertical struts. Some interesting attempts including "skeletonization" (lineal design of the cross-sectional image) of the trabecular network in axial QCT or MNR studies[48,49] and even tomographic assessment of the vBMD of the trabecular core of the vertebral bodies[45,46] have been reported.

An approach to a solution for the above problems could start from the idea that bone stiffness and strength could be proportional to a *product* of suitable indicators of bone's material and geometric properties[12,13,37,38,40,41,50]. We developed the first of such combined *Bone Strength Indices (BSI's)*[37,40,41,51]. Nevertheless, the regional and directional specificity of any BSI requires special calculations for every site in every bone and for each kind of deformation[52]. Despite this difficulty (which reflects the complexity of the mechanical problem), BSI's development seems to be one of the best currently available ways to evaluate bone strength non-invasively.

**3. How to evaluate the musculoskeletal interactions.** No attempt to evaluate bone mass or strength could be complete without correlating the bone data with indicators of strength of the *regional muscles* (Fig. 1). Otherwise, no distinction could be made between a "disuse" and other etiologies of the cases (Fig. 3), with the consequent therapeutic confusion. Two different approaches for this problem should be considered. **I.** Analysis of the relationship between the DEXA-assessed bone and regional muscle *masses* could provide a differential diagnosis of *osteopenias*. **II.** Analysis of the relationship between bone *strength* and regional muscle *strength* evaluated by other means could provide a differential diagnosis of *osteoporoses*.

***I. Differentiation of osteopenias by DEXA.*** A biomechanical complement to the DEXA assessment of bone mass (BMC) can be provided by DEXA by measuring the *lean mass* (LM)[53,54], which can be regarded as proportional to *muscle* mass within certain limits, in the whole body or in selected regions. Also the fat mass of the same regions can be determined by DEXA, providing an adjustment of the BMC data that corrects for the fat interference in mineral

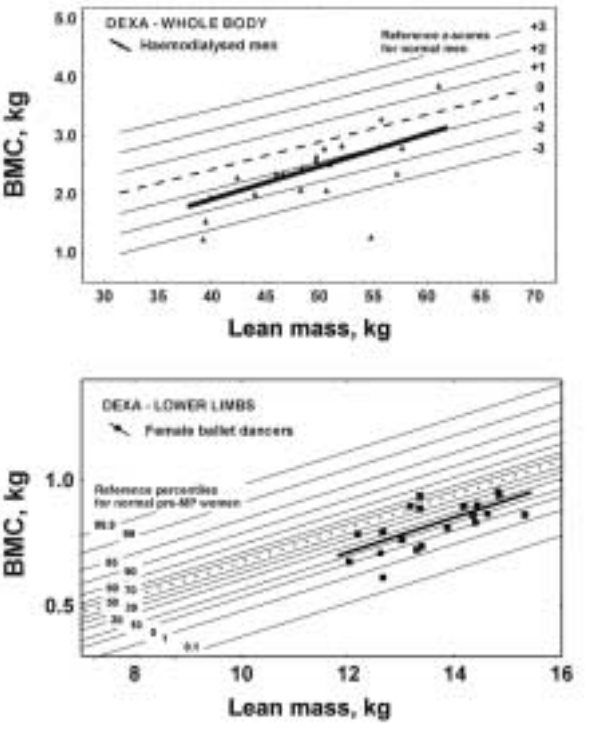


**Figure 5**. Applications of reference curves as schematized in **Fig. 4c** to the analysis of the muscle / bone mass proportions (DEXA-assessed BMC / lean mass) in the whole body of haemodialysed men (**top**)[59], in which the z-scores of that proportion were reduced because of the metabolic interference on bones' health, and in the lower limbs of female ballet dancers (**bottom**, reference values shown as percentiles in this case). In these women, bones could have been unable to reinforce their structure (mass) as a natural response to muscle development after training (high LM values) because of the enhanced renal losses of calcium and other disturbances derived from the impaired estrogen metabolism caused by leanness. In both instances the intercepts of the BMC / LM curves were lowered but the slopes were kept normal, revealing a metabolically-induced shift in the *mechanostat* setpoints with no other evident alteration of the system.

mass determination[55]. Those features of DEXA technology are little used by physicians[12,13,19,54,55].

We have shown close, linear relationships between BMC and LM in 1,450 normal Argentine boys / girls, men, and pre- and post-menopausal women[56]. The graphs for all the groups were parallel, regardless of age and reproductive status (Fig. 4a). This would reflect the biological control of bones by muscles through the bone mechanostat. However, the intercepts of the graphs differed between groups, growing in the order: boys / girls < post-MP women < men < pre-MP women. This would suggest a (positive) modulation of that control by sex hormones or related factors in each group.

These observations were confirmed for the whole body and extended to the lower and upper limbs in 3,000 normal Colombian men and women[57]. In the lower limbs, the variance of the BMC/LM relationship was substantially lower than it

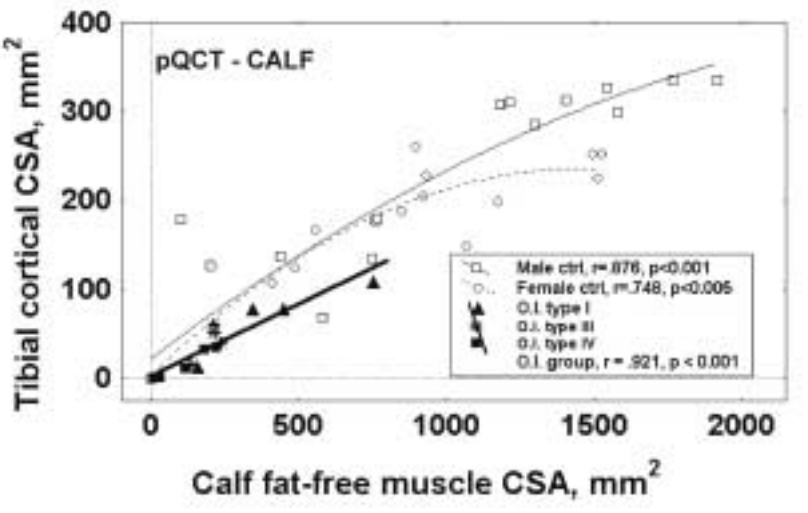


**Figure 6**. Analysis of the relationship between pQCT-assessed indicators of the bone strength (cortical bone area of the tibial cross-section) / muscle strength (cross-sectional area of the muscles) relationship in the calf of children with osteogenesis imperfecta compared with normal, age-matched controls of both genders[64].

was in the whole body. In the upper limbs, the curves for men plotted the highest. This gender-related regional difference became more evident after fat-adjustment of the BMC data, which suggests a different influence of gravity on bone structure in the lower and upper limbs in men and women.

These results allowed performing *z-scored* graphs, specific for gender, reproductive status, region studied, racial characteristics, and the type of DEXA equipment employed, suitable for evaluating the proportion between bone and muscle masses[58]. Such graphs may allow evaluating whether a given whole-body or regional BMC value, which may seem low, is adequately proportional to the individual's whole-body or regional muscle mass, as schematically shown in Fig. 4c. Disuse-related osteopenias should show a normal BMC / LM proportionality. This may also happen in small or lean, otherwise healthy and normally active individuals. In osteopenias caused by primary alterations of bone cells or by the secondary impact of changes in their endocrine-metabolic environment, BMC could be disproportionately low with respect to muscle mass. Such cases should be further studied in order to determine whether bone strength is or not affected; i.e. for establishing a differential diagnosis of osteoporosis as indicated in ( **II** ) below.

The analysis of these relationships let us quantify musculoskeletal disproportions in the whole body or limbs, secondary to endocrine unbalance in haemodialysis patients (in correlation with the time on dialysis and serum PTH activity; Fig. 5, top)[59]; in obese hyperinsulinemic euglycemic patients (in correlation with the body-mass index, fasting plasma insulin, and an insulin sensitivity index)[60]; in female ballet dancers (in correlation with calciuria, presumably enhanced by disturbed estrogen metabolism (Drnovsek et al, unpublished; Fig. 5, bottom)), and in hypopituitary men and women before and after treatment with growth hormone (in correlation with serum IGF-I levels)[61]. Those analyses would have been impossible to do by studying only their bones.

II. Differentiation of osteoporoses employing complementary resources. Analogously to the differentiation of osteopenias based on DEXA-assessed bone mass / muscle mass relationships described in (I), osteoporoses could be classified according to the bone strength / muscle strength relationships evaluated by other means. New methodologies are being developed for that purpose[62]. We have described the correlations between tomographic indicators of bone strength and muscle strength in normal individuals, employing QCT or pQCT. A single slope for the correlation between the tibial BSI and calf muscle cross-sectional area was observed for all boys / girls, men and pre-MP women, while a lower slope was observed for post-MP women[46]. Decreasing slopes for the correlation between the vBMD of the trabecular core of L3 vertebral bodies and the cross-sectional area of spinal muscles were obtained for menstruating women and women who were 10 to more than 20 years after menopause[22] (Fig. 4b). Those curves can also be z-scored and used as references for a differential diagnosis of osteoporoses as well as for evaluating the biomechanical relationships between muscles and bones in other bone-weakening diseases as schematized in Fig. 4d. Based on these data, we were able to show differences in the musculoskeletal alterations of men and women affected by celiac disease[63] and a lower than normal bone / muscle proportionality in children with osteogenesis imperfecta[64] (Fig. 6) which would have been impossible to reveal by employing only DEXA.

## Conclusion

More work is needed to achieve an effective differential diagnosis of osteopenias and osteoporoses in different clini-

cal conditions and in different skeletal regions. However, two procedures can seek a solution to the problem, namely, **1.** *describe structures* by means of volumetric densitometry and cross-sectional image analyses, rather than *measure amounts of mass* by projection densitometry, and **2.** analyze *muscles* and *bones* as functional units, rather than the skeleton alone. The first milestone in the road points out the concept that the strength of bones, rather than reflecting the passive result of a metabolic balance between formation and resorption of mineralized mass, represents the product of an adaptation of the quality and distribution of the hard tissue to its mechanical usage to optimize the structural deformability and strength.

*Acknowledgements*

*Most of the authors' investigations presented and cited were supported by grants from the Argentine National Research Council (CONICET), the Research Council of the National University of Rosario (CIUNR), and the Metabolic Research Foundation (FIM, Buenos Aires). Some of the presented data were obtained in collaboration with other groups as stated in the Reference list. Authors gratefully acknowledge Dr. Harold M Frost for reviewing this manuscript.*

## References

1. Kanis JA, Melton J, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. J Bone Miner Res 1994; 9:1137-1141.
2. Kanis JA, Devogelaer JP, Gennari C. Practical guide for the use of bone mineral measurements in the assessment of treatment of osteoporosis: A position paper of the European Foundation for Osteoporosis and Bone Disease. Osteoporosis Int 1996; 6:256-262.
3. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. JAMA 2001; 285:785-791.
4. Martin RB, Burr DB, Sharkey NA. Skeletal tissue mechanics. Springer; New York, 1998.
5. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. Br Med J 1996; 312:1254-1259.
6. Vilani P, Bondino-Riquier R, Bouvenot G. Fragilité des données acquises de la science. L'exemple du fluor dans l'osteoporose. Presse Med 1998; 27:361-362.
7. Wilkin T. Changing concepts in osteoporosis. Br Med J 1999; 318:862-865.
8. Faulkner KG. Bone matters: Are density increases necessary to reduce fracture risk? J Bone Miner Res 2000; 15:183-189.
9. Sandor T, Felsenberg D, Brown E. Comments on the hypotheses underlying fracture risk assessment in osteoporosis as proposed by the World Health Organization. Calcif Tissue Int 1999; 64:267-273.
10. Kanis JA, Prediction of fracture from low bone mineral density measurements overestimates risk. Bone 2000; 26:387-393.
11. Ferretti JL. Biomechanical properties of bone. In: Genant HK, Guglielmi G, Jergas M (eds). Bone Densitometry and Osteoporosis. Springer, Berlin; 1998:143-161.
12. Ferretti JL, Cointry GR, Capozza RF. Noninvasive analysis of bone mass, structure, and strength. In: An YH (ed) Orthopaedic Issues in Osteoporosis. CRC Press, Boca Raton, FL; 2002:145-167.
13. Ferretti JL, Frost HM. Osteopenias and osteoporoses. Muscle-bone interactions, absorptiometry, safety factors, and fracture risk. An overview. In: An YH (ed) Orthopaedic Issues in Osteoporosis. CRC Press, Boca Raton, FL; 2002:203-217.
14. Frost HM. The Utah paradigm of skeletal physiology: An overview of its insights for bone, cartilage and collagenous tissue organs. J Bone Miner Metab 2000; 18:305-309.
15. Frost HM. From Wolff's Law to the Utah paradigm: Insights about bone physiology and its clinical applications. Anat Rec 2001; 262:398-404.
16. Currey JD. The design of mineralised tissues for their mechanical functions. J Exp Biol 1999; 202:3285-3291.
17. Landis WJ. The strength of a calcified tissue depends in part on the molecular structure and organization of its constituent mineral crystals in their organic matrix. Bone 1995; 16:533-539.
18. Rho JY, Kuhn-Spearing L, Zioupos P. Mechanical properties and the hierarchical structure of bone. Med Eng Phys 1998; 20:92-102.
19. Frost HM, Ferretti JL, Jee WSS. Some roles of mechanical usage, muscle strength, and the mechanostat in skeletal physiology, disease, and research. Calcif Tissue Int 1998; 62:1-7.
20. Schönau E, Neu CM, Mokow E, Wassmer G, Manz F. Influence of puberty on muscle area and cortical bone area of the forearm in boys and girls. J Clin Endocrinol Metab 2000; 85:1095-1098.
21. Schönau E, Neu CM, Rauch F, Manz F. The development of bone strength at the proximal radius during childhood and adolescence. J Clin Endocrinol Metab 2001; 86:613-618.
22. Ferretti JL, Cointry GR, Capozza RF, Frost HM. Bone mass, bone strength, muscle-bone interactions, osteopenias and osteoporoses. Mech Aging Devel 2003; 124:269-279.
23. Wainwright SA, Biggs WD, Currey JD, Gossline JM. Mechanical design in organisms. London: Edward Arnold; 1976.
24. Currey JD. The effects of porosity and mineral content on the Young's modulus of elasticity of compact bone. J Biomech 1988; 21:131-140.
25. Compston JE. Connectivity of cancellous bone: Assessment and mechanical implications. Bone 1994; 15:463-469.

26. Frost HM. Intermediary Organization of the Skeleton. Vols. I & II. CRC Press, Boca Raton, FL; 1986.
27. Frost HM. Structural adaptations to mechanical usage (SATMU): 1. Redefining Wolff's Law: The bone modeling problem. Anat Rec 1990; 226:403-413.
28. Frost HM. Structural adaptations to mechanical usage (SATMU): 2. Redefining Wolff's Law: The bone remodeling problem. Anat Rec 1990; 226:414-422.
29. Jee WSS. Integrated bone tissue physiology: Anatomy and physiology. In: Cowin SC (ed) Bone Mechanics Handbook 2nd ed. CRC Press, Boca Raton, FL; 2001:1-16.
30. Frost HM. The mechanostat: A proposed pathogenetic mechanism of osteoporoses and the bone mass effects of mechanical and nonmechanical agents. Bone Miner 1987; 1:73-85.
31. Lanyon LE, Rubin CT, Raisz LE, Marotti G, Less H. Osteocytes, strain detection, bone modeling and remodeling. Calcif Tissue Int 1993; 53(Suppl 1):S102-107.
32. Marotti G. The osteocyte as a wiring transmission system, J Musculoskel Neuron Interact 2000; 1:133-139.
33. Lanyon LE. Functional strain in bone tissue as an objective, and controlling stimulus for adaptive bone remodeling. J Biomech 1987; 20:1083-1089.
34. Rubin CT, McLeod K, Bain S. Functional strains and cortical bone adaptation. Epigenetic assurance of skeletal integrity. J Biomech 1990; 23:43-49.
35. Fyhrie DP, Vashishth D. Bone stiffness predicts strength similarly for human vertebral cancellous bone in compression and for cortical bone in tension. Bone 2000; 26:169-175.
36. Frost HM. On defining osteopenias and osteoporoses: Problems! Another view (with insights from a new paradigm). Bone 1997; 20:385-391.
37. Ferretti JL, Capozza RF, Zanchetta JR. Mechanical validation of a tomographic (pQCT) index for the noninvasive measurement of rat femur bending strength. Bone 1996; 18:97-102.
38. Ferretti JL. Peripheral quantitative computed tomography (pQCT) for evaluating structural and mechanical properties of small bone. In: An YH, Draughn RA (eds). Mechanical Testing of Bone and the Bone-Implant Interface. CRC Press, Boca Raton, FL; 1999:385-406.
39. Augat P, Reeb H, Claes L. Prediction of fracture load at different skeletal sites by geometrical properties of the cortical shell. J Bone Miner Res 1996; 11:1356-1362.
40. Wilhelm G, Felsenberg D, Bogusch G, Willnecker J, Thaten J, Gummert P. Biomechanical examinations for validation of the Bone Strength-Strain Index SSI, calculated by peripheral quantitative computed tomography. In: Lyrithis GP (ed) Musculoskeletal Interactions. Vol II. Hylonome, Athens; 1999:105-111.
41. Schiessl H, Ferretti JL, Tysarczyk-Niemeyer G, Willnecker J. Noninvasive Bone Strength Index as analyzed by peripheral quantitative computed tomography (pQCT). In: Schönau E (ed). Pediatric Osteology. Elsevier, Amsterdam; 1996:141-145.
42. Mehta SS, Öz OK, Antich PP. Bone elasticity and ultrasound velocity are affected by subtle changes in the organic matrix. J Bone Miner Res 1998; 13:114-120.
43. Rho JY, Ashman RB, Turner CH. Young's modulus of trabecular and cortical bone material: Ultrasonic and microtensile measurements. J Biomech 1993; 26:111-117.
44. Zanchetta JR, Bogado CE, Ferretti JL, Wang O, Wilson MG, Sato M, Gaich GA, Dalsky GP, Myers SL. Effects of teriparatide [recombinant human parathyroid hormone (1-34)] on cortical bone in postmenopausal women with osteoporosis. J Bone Miner Res 2003; 18:339-343.
45. Hayes WC, Piazza SJ, Zysset PK. Biomechanics of fracture risk prediction of the hip and spine by quantitative computed tomography. Radiol Clin N Amer 1991; 29:1-12.
46. Ferretti JL, Capozza RF, Cointry GR, Capiglioni R, Roldάn EJ, Giménez CR, Zanchetta JR. Densitometric and tomographic analyses of musculoskeletal interactions in humans. J Musculoskel Neuron Interact 2000; 1:18-21.
47. Ortöft G, Mosekilde Li, Hasling C, Mosekilde Le. Estimation of vertebral body strength by dual photon absorptiometry in elderly individuals. Bone 1993; 14:667-673.
48. Chevallier F, Laval-Jeantet AM, Laval-Jeantet M, Bergot C. CT image analysis of the vertebral trabecular network *in vivo*. Calcif Tissue Int 1992; 51:8-14.
49. Majumdar S, Genant HK, Grampp S, Newitt DC, Truong V-H, Lin JC, Mathur A. Correlation of trabecular bone structure with age, bone mineral density, and ostreoporotic status: *In vivo* studies in the distal radius using high resolution magnetic resonance imaging. J Bone Miner Res 1997; 12:111-117.
50. Ahlborg HG, Johnell O, Turner CH, Rannevik G, Karlsson M. Bone loss and bone size after menopause. N Engl J Med 2003; 349:327-334.
51. Ferretti JL, Cointry GR, Capozza RF, Capiglioni R, Chiappe MA. Analysis of biomechanical effects on bone and on the bone-muscle interactions in small animal models. J Musculoskel Neuron Interact 2001; 1:263-272.
52. Schneider P, Reiners C, Cointry GR, Capozza RF, Ferretti JL. Bone quality parameters of the distal radius as assessed by pQCT in normal and fractured women. Osteopor Int 2001; 12:639-646.
53. Visser M, Fuerst T, Lang T, Salamone L, Harris T. Validity of fan-beam dual-energy X-ray absorptiometry for measuring the fat-free mass and leg muscle mass. J Appl Physiol 1999; 87:1513-1522.
54. Ferretti JL, Cointry GR, Capozza RF, Zanchetta JR. Dual-energy X-ray absorptiometry. In: Preedy VR, Peters TJ (eds). Skeletal muscle: Pathology, diagnosis and management of disease. Greenwich, London; 2001:451-458.
55. Ferretti JL, Schiessl H, Frost HM. On new opportuni-

ties for absorptiometry. J Clin Densitom 1998; 1:41-53.
56. Ferretti JL, Capozza RF, Cointry GR, García Sl, Plotkin H, Alvarez Filgueira ML Zanchetta JR. Gender-related differences in the relationships between densitometric values of whole-body bone mineral content and lean mass in humans between 2 and 87 years of age. Bone 1998; 22:683-690.
57. Cure-Cure C, Cure-Ramírez P, Cointry GR, Ferretti JL. Relationships between the densitometric mineral, fat and lean masses in the whole body and limbs of 3,000 normal Colombian men and pre- and postmenopausal women. J Musculoskel Neuron Interact 2002; 2:389.
58. Ferretti JL, García SL, Capozza RF, Cointry GR, Plotkin H, Roldάn EJ, Zanchetta JR. Percentilyzed BMC/LM curves for diagnosing "physiological" and "true" osteopenias in males and females of all ages. J Musculoskel Neuron Interact 2002; 2:377.
59. Negri AL, Cointry GR, Salica D, Zanchetta JR, Ferretti JL. Bone / lean mass relationships in peritoneally-dialysed and hemodialysed men and women. J Bone Miner Res 2001; 16(Suppl 1):S544.
60. Ulla MR, Stivala M, Noriega R, Cointry G, Ferretti JL. Altered relationships between mineral and lean masses in obese, euglycemic, hyperinsulinemic women. J Bone Miner Res 2001; 16(Suppl 1):S402.
61. Claus-Hermberg H, Fideleff H, Chervín A, Stalldecker G, Sinay I, Sobrado P, Cointry GR, Ferretti JL. Effects of GH on the mineral, lean, and fat masses in panhypopituitary men and women. J Bone Miner Res 2001; 16(Suppl 1):S403.
62. Rittweger J, Beller G, Ehrig J, Jung C, Koch U, Ramolla J, Schmidt F, Newitt D, Majumdar S, Schiessl H, Felsenberg D. Bone-muscle strength indices for the human lower leg. Bone 2000; 27:319-326.
63. Ferretti JL, Mazure R, Tanoue P, Marino A, Cointry G, Vάzquez H, Niveloni S, Pedreira S, Mauriño E, Zanchetta JR, Bai JC. Analysis of the structure and strength of bones in celiac disease patients. Amer J Gastroenterol 2003; 98:382-390.
64. Roldάn EJA, Ferretti JL, Cointry GR, Tau C. Bone structure and strength and muscle-bone interactions in 15 children with osteogenesis imperfecta. A pQCT study. J Bone Miner Res 2002; 17(S1):S379.