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

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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
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\(^3,16-18\), most of which are beyond 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\(^10-22\).

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\(^11\). 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 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.
Bone tissue’s stiffness is determined 1) by the degree of mineralization of the collagen matrix 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. 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. In trabecular networks, some relevant geometric factors are their disposition along specific lines of force in different regions, and trabecular thickness and connectivity.

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 oechodral pattern (null after the third decade in humans and thus out of interest here), 2) modeling, and 3) remodeling.

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). 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. Bone remodeling can occur on endosteal and trabecular surfaces or on the intracortical surface (Haversian systems). 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-
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. The NIH recently redefined osteoporosis as "a disease in which bone strength is reduced," 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. 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 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 (Fig. 2). The higher biological hierarchy of the regulation of the mineral homeostasis of the body by evolutionally older systems would supplant 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. 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. 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. 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. Regrettably, they can not provide a diagnosis of osteoporosis because they do not give any information on bone material and geometric properties. 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. The higher biological hierarchy of the regulation of the mineral homeostasis of the body by evolutionally older systems would supplant 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. 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.

2. How to determine some mechanically meaningful indicators. Suitable indicators of bone material and geometric properties should be determined for diagnosing a skeletal fragility. Bones with a reduced mineral mass could be adequately strong provided that their calci-
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. 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.). 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, 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. Nevertheless, bone mass indicators as the pQCT-measured cross-sectional area or mineral content of cortical bone or even the DEXA-assessed BMC (not BMD) may result proportional to bone strength in some instances. 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.

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 and even tomo- graphic assessment of the vBMD of the trabecular core of the vertebral bodies 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. We developed the first of such combined Bone Strength Indices (BSI’s). Nevertheless, the regional and directional specificity of any BSI requires special calculations for every site in every bone and for each kind of deformation. 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), 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 mass determination. Those features of DEXA technology are little used by physicians.

We have shown close, linear relationships between BMC and LM in 1,450 normal Argentine boys / girls, men, and pre- and post-menopausal women. 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. In the lower limbs, the variance of the BMC/LM relationship was substantially lower than it
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. 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)

; in obese hyperinsulinemic euglycemic patients (in correlation with the body-mass index, fasting plasma insulin, and an insulin sensitivity index); 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). 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. 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. 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 (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 and a lower than normal bone / muscle proportionality in children with osteogenesis imperfecta (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.

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References

55. Ferretti JL, Schiess H, Frost HM. On new opportuni-


