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Absorptiometric assessment of muscle–bone relationships in humans: reference, validation, and application studies

Abstract This report summarizes some preliminary absorptiometric (DXA, QCT/pQCT) studies from our laboratory, supporting the following assumptions. 1. In *Homo sapiens* at all ages, natural proportionality between DXA-assessed bone mineral mass (bone mineral content, BMC) and muscle mass (lean mass, LM) of the whole body or limbs is specific for ethnicity, gender, and reproductive status, but not for body weight, height, or body mass index. 2. This proportionality is sensitive to many kinds of endocrine-metabolic perturbations. 3. Percentilized or Z-scored charts of the BMC/LM correlations as determined in large samples of healthy individuals can provide a diagnostic reference for evaluating proportionality in different conditions. 4. Employing exclusively DXA, this methodology can be applied to discriminate between "disuse-related" and "metabolic" osteopenias based on the finding of normal or low BMC/LM percentiles or Z-scores respectively, with important therapeutic and monitoring implications.

Key words DXA · Osteopenia · Osteoporosis · Muscle mass · Lean mass

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Introduction

Whole-bone strength is determined not only by the mass, but also by the intrinsic stiffness, the spatial distribution, and the density of cracks inside the microstructure of the mineralized material (material, geometric, and fatigue properties, respectively) [1,2]. The earlier interpretation by the medical community of osteoporosis as "intense osteopenia" (WHO [3]) is now shifting to be understood as "bone-weakening osteopenia" (NIH) [4,5]. Accordingly, the current diagnosis of osteoporosis involves the assessment of both bone mass *and* strength [6].

Bone "mechanostat" theory proposes that bone geometric properties are strongly influenced by the directional modulation of bone modeling and remodeling performed by osteoblasts and osteoclasts [7,8]. Because the osteocytes have the ability to sense bone strains produced by daily mechanical usage of the skeleton [8,9] (Fig. 1, left), it is thought that the directionality of that modulation, as well as the rate at which bone tissue self-repairs microdamage, is determined by local osteocytes in each skeletal site in biological communication with neighbor osteoblasts and clasts. This way, bones can adapt to peak forces produced by the regional muscles under physiological conditions [7].

Bone mechanostat removes and adds bone material at different skeletal locations, with different mechanical impact, following the strain gradients sensed by osteocytes. Endocrine-metabolic factors may affect that control systemically by shifting its setpoint in the whole skeleton, i.e., nondirectionally [8]. This shift involves additional influences on the same osteocytes, blasts, and clasts. This mechanism explains (1) the independence between daily balances in bone mass (from which an osteopenia may develop) and strength (from which bone fragility may increase) in each skeletal region (Fig. 1, left), and (2) why endocrine-metabolic factors are a frequent cause of osteopenias and osteoporoses [10]. According to this concept, we propose the following three different etiologies of all osteopenias and bone-weakening diseases: primary, disuse, and systemic [11–13].

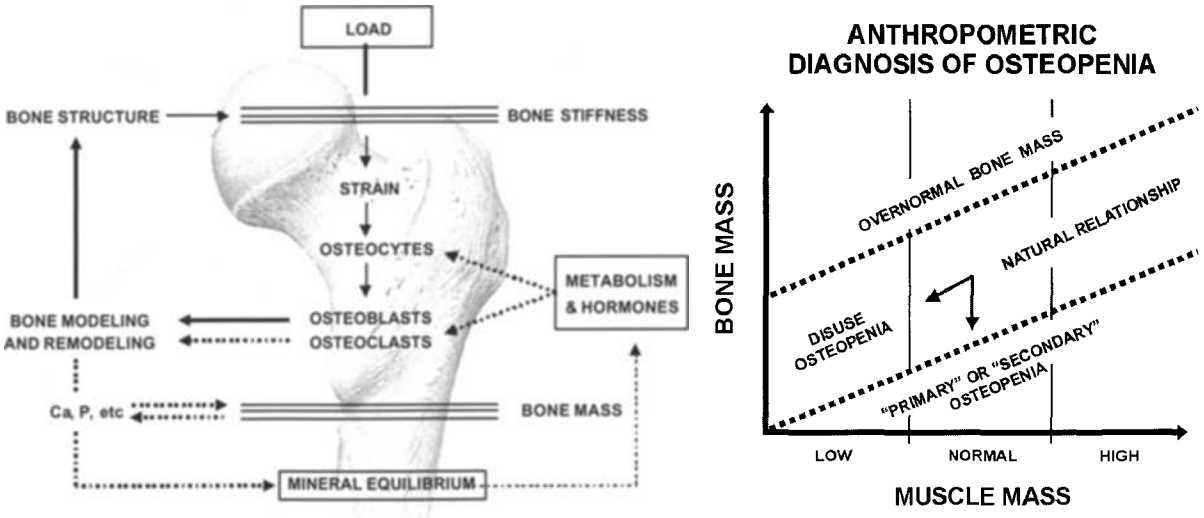

Fig. 1. *Left.* Schematic representation of the directional, biomechanical control of bone structural stiffness (and, indirectly, of strength) by the bone mechanostat (*plain arrows*), and the modulation induced by endocrine-metabolic factors (*dotted arrows*) through the involvement of the same receptors (bone cells) for controlling more vital variables related to the mineral equilibrium of the internal milieu. The independence between the resulting balances of bone strength (controlled) and mass (uncontrolled) is clearly shown. *Right.* Schematic representation of the rationale for the application of the bone mineral content–lean mass (BMC–LM) percentiles or Z-scores for assessing the bone–muscle proportionality to distinguish between the "disuse" and "metabolic" (primary or secondary) etiologies of an osteopenia

This new perspective calls into question the current criteria for noninvasive diagnosis of osteopenias and osteoporoses. Noninvasive diagnosis should consider relevant (1) evaluating bone structural strength rather than merely measuring bone mineralized mass; (2) assessing the biomechanical proportionality between bones and muscles, and (3) determining whether an osteopenia is related to disuse or to an endocrine-metabolic shift of the mechanostat setpoint [12]. These problems apply to the current application of standard bone densitometry, dual-energy X-ray aborptiometry (DXA), and to the axial and peripheral modalities of quantitative computed tomography (QCT and pQCT, respectively).

Bone mineral content and areal density as determined by DXA (BMC, aBMD) are the best available parameters to measure mineralized bone mass and diagnose osteopenias [3], but they do not assess bone strength [2]. Therefore, despite the aBMD T-score scales acknowledged by the WHO [3], DXA could not diagnose osteoporosis as a single methodology according to the NIH criterion [4]. This limitation would explain the lack of correlation observed between some positive drug effects on DXA aBMD and fracture incidence in recent studies in osteoporotic women [14–17].

This apparent paradox can be explained by two main reasons. (1) The aBMD data are often extrapolated to the biomechanical field without biophysical consideration [2,6,12,18–22]. (2) The mechanically significant role of muscle mass/strength in determining bone mass/strength, which we have contributed to demonstrating [5,7,23–25], is often disregarded. As a consequence, BMC and aBMD data are usually adjusted to other confounding factors such as age, body height, weight, or body mass index (BMI), which have only an indirect influence on bone strength variance [23,24].

An interesting feature of DXA technology is its ability to measure lean mass (LM) as a valid surrogate of muscle mass or strength [6,12,19,20,26]. This little-used application could contribute to quantifying the relative participation of disuse and metabolic factors in the etiology of many osteopenias [19].

Axial QCT and pQCT can provide some mechanically meaningful indicators of bone material and geometric properties as well as muscle strength [6,18,21,24,25]. For example, the volumetric BMD (vBMD) of cortical bone varies closely with the degree of mineralization of the bone matrix, which is often proportional to bone material stiffness (elastic modulus) [27]. Trabecular vBMD of the vertebral bodies and distal radius is proportional to compression strength [21,28]. Cross-sectional and polar moments of inertia (MIs) of tubular bones describe their bending or torsional strength [21,29]. Suitable bone strength indices (BSIs) for long bone bending or torsion strength can be calculated by simply multiplying cortical vBMD and an MI [2,6,18,30]. This article analyzes some preliminary studies in which we have measured BMC and LM with DXA in healthy individuals (reference studies) [23,31], patients with different endocrine-metabolic pathologies (validation studies) [32–35], and women with fractures (application study). Additional QCT and pQCT studies of muscle–bone relationships in healthy individuals [12] are also reported as a biomechanically stronger reference of the muscle–bone interrelation involved in the DXA analysis.

We hypothesized that the BMC–LM relationship assessed by DXA in the reference studies (1) will vary as a function of metabolic indicators to the severity of each dis-

ease in the validation studies and (2) will help to detect the metabolic nature of fractures in typically osteoporotic sites in postmenopausal (post-MP) women but not in healthy premenopausal (pre-MP) women in the application study (Fig. 1, right).

The collected evidence suggests that DXA-assessed bone–muscle (BMC–LM) relationships could provide a differential diagnosis between osteopenias with disuse etiology and osteopenias with metabolic etiology following the current biomechanical criteria and with important implications concerning treatment and monitoring.

Material and methods

Densitometric determinations

Both whole-body and lower-limb BMC and LM were determined by DXA with either an XR-26 (Norland, Cranbury, NJ, USA) [23] or a DPX Plus (GE Lunar, Madison, WI, USA) device as follows [31].

Reference studies

Reference, percentilized, and Z-scored charts of the BMC–LM (y/x) relationships were obtained from 545 healthy children (2–14 years), 535 men (13–87 years), 1083 pre-MP women (12–55 years), and 1799 post-MP women (45–85 years) of Caucasian (n = 1450) [23] or Hispanic ethnicity (n = 2512) [31]. The charts were made specifically for ethnicity, gender, reproductive status, and type of densitometer, but not so for age, time since menopause, body weight, body height, or BMI, so long as multiple regression tests showed nonsignificant independent impacts of all these variables on BMC variance [23,31]. An original software was developed for automatic calculation of individual percentiles and Z-scores from those curves. This software was applied in the following studies.

Validation studies

Individual percentiles or Z-score of the whole-body BMC–LM relationship were calculated as indicated above in 21 healthy Caucasian women, professional ballet dancers with large muscle development and extreme body leanness, in whom daily urinary excretion of calcium was measured (Drnovsek and Ercolano, unpublished data); 37 men (51.5 ± 12.5 years), and 24 pre-MP (36.2 ± 10.6 years) and 47 post-MP (55.0 ± 10.8 years) Caucasian women undergoing chronic peritoneal dialysis or hemodialysis, for whom the time on dialysis and serum parathyroid hormone (PTH) activity were determined [34]; 24 obese, normoglycemic Caucasian pre-MP and post-MP women (19–60 years) with hyperinsulinemia because of insulin resistance, whose BMI, plasma fasting insulin, and the HOMA insulin sensitivity index were evaluated [32]; 14 Caucasian men and 15 Caucasian women with insufficient growth hormone (GH) secretion, both before and after 1 year treatment with recombinant human GH (rhGH), whose plasma msulin-like growth factor (IGF-1) activity was assessed [33]; and 208 Belarussian children who had been thyroparathyroidectomized because of thyroid carcinoma developed after the Chernobyl disaster chronically supplemented with Ca and AT-10, in whom serum PTH activity and plasma P concentration were measured [35].

Application study

The same individual BMC–LM Z-scores were also calculated in healthy Hispanic women, 140 pre-MP and 483 post-MP, who had suffered a fracture in a typically "osteoporotic" site (n = 396) or in other regions of the skeleton (n = 227) within 18 months before the study.

Tomographic studies

The following QCT and pQCT determinations were performed in healthy adults as a complement to the DXA reference studies [12].

QCT scans at L3 level

The vBMD of the trabecular core of the L3 vertebral body and the perispinal cross-sectional muscle area of the same 1-cm-thick scan were determined with a Somatron Plus '98 machine (Siemens, Munich, Germany) in healthy 25 men, 25 pre-MP women, and 90 post-MP women with 6–10 (n = 30), 10–20 (n = 30), or >20 (n = 30) years since menopause (YSMP).

Calf pQCT scans

The vBMD, area, and bending MI (xMI) of the cortical bone and the calf muscle area were determined in scans taken at a site located 66% of the tibial length, proximal to the articular surface of the ankle, with a pQCT XCT-2000 (Stratec, Germany) in 18 children, 14 men, 25 pre-MP women, and 50 post-MP women. A stress-strain index (SSI = f [cortical vBMD, xMI]) was calculated as a tibial bending strength indicator [12,30,36].

Statistical analyses

Simple correlations were analyzed between BMC (y) and LM (x) in all the DXA studies; between the trabecular vBMD of the central core (y) and the perispinal muscle area (x) in the QCT study; and between the cross-sectional cortical area, xMI or the SSI (y) and the calf muscle area (x) in the pQCT study. Percentilized or Z-scored charts of the DXA BMC–LM relationships were performed from the data collected in the reference studies, specifically for ethnicity, gender, reproductive status, and type of DXA device. Individual percentiles or Z-scores of the DXA BMC–LM relationships calculated as per the corresponding reference charts (y) were correlated with the different metabolic indicators (x) determined in the validation

studies, and were discriminated accordingly with the type of fracture in the application study. Differences between slopes and intercepts of the curves were tested by analysis of covariance (ANCOVA) [37].

Results

Reference studies

The DXA BMC–LM curves were parallel in all cases (ANCOVA, all $P > 0.05$), but their intercepts increased in the order: children < men < post-MP women < pre-MP women (ANCOVA, $P < 0.001$). Percentilized or Z-scored reference charts were performed for comparison purposes and for calculation of individual percentiles or Z-scores in the following studies.

1. The QCT-assessed trabecular vBMD of the L3 vertebral bodies correlated significantly with the cross-sectional area of the perispinal muscles in all groups ($P < 0.01$), but the slopes of the regression curves decreased significantly in the order: men > pre-MP women > post-MP women [0–10 YSMP] > [10–20 YSMP] > [>20 YSMP] (ANCOVA, $P < 0.01$).
2. The pQCT-assessed cortical bone area, xMI, and SSI correlated positively with the calf muscle area ($P < 0.01$), showing a common slope for children, men, and pre-MP women and a significantly lower slope for the post-MP women in every instance (ANCOVA, $P < 0.01$).

Validation studies

The BMC–LM curves obtained from the different groups of patients were always parallel to the reference curves, specifically for ethnicity, gender, and reproductive status (ANCOVA, $P > 0.05$). However, their intercepts (and hence the individual BMC–LM percentiles or Z-scores) differed from the reference (ANCOVA, $P < 0.01$) in correlation with the specific metabolic indicators studied in each case. In the female ballet dancers, the BMC–LM Z-scores decreased proportionally to urinary Ca excretion ($r = -0.562$, $P < 0.01$). In women undergoing dialysis, the scores decreased in proportion with time on dialysis and serum PTH activity ($r = -0.429$, $P < 0.01$; $r = -0.628$, $P < 0.001$). In obese insulin-resistant adults, the scores decreased proportionally with BMI ($r = -0.483$, $P < 0.05$), fasting plasma insulin activity ($r = -0.521$, $P < 0.01$), and HOMA insulin sensitivity index ($r = -0.510$, $P < 0.01$). In hypopituitary men and women, scores ranked always within the normal range, either before or after rhGH treatment, but after-treatment scores correlated with serum IGF-I activity ($r = -0.423$, $P < 0.05$). In thyroparathyroidectomized children, scores decreased in both genders proportionally with serum PTH activity ($r = -0.325$, $P < 0.01$), but increased only in the Ca + AT10-supplemented boys as a function of serum P concentration ($r = 0.233$, $P < 0.001$).

Application study

In pre-MP women with any type of fracture, and in post-MP women with fractures in nonosteoporotic sites, the slopes and intercepts of the BMC–LM curves were similar to the reference (ANCOVA, $P > 0.05$). In contrast, post-MP women with fractures in osteoporotic sites showed non-linear BMC–LM relationships, with BMC–LM Z-scores rapidly decreasing toward the lower end of the LM range.

Discussion

Reference studies

On one hand, the parallelism of the DXA BMC–LM curves may reflect not only the natural, anthropometric proportionality between bones and muscles, but also the common biomechanical control of bone structure as a function of the daily mechanical usage of the skeleton (bone mechanostat theory) [5,7,8]. The same applies to the QCT/pQCT-assessed muscle–bone relationships in the spinal and calf regions, which show similar associations between more direct indicators of muscle–bone biomechanical relationships [5,6,12,18,24,25]. On the other hand, differences in the intercepts of the curves in the DXA studies, as well as those in the slopes of the curves in QCT/pQCT studies (always related to the gender and reproductive status of the groups) may show the modulation of that control by sex hormones [2,8,12,13].

Therefore, the percentilized or Z-score charts of the DXA BMC–LM curves can be used as standard references for testing both biomechanical and metabolic influences on the mass-to-mass muscle–bone relationships in different clinical conditions, as suggested in Fig. 1 (right).

Validation studies

The parallelism observed between all the DXA BMC–LM curves studied and the specific reference charts used for comparisons show that the natural trend of bone structure to follow muscle changes was maintained in every studied instance. However, significant differences observed in the intercepts of all the curves may reflect some systemic interaction of the metabolic perturbations studied with the bone-to-muscle anthropometric/biomechanical proportionality [8,12,13]. The significant correlations observed between the BMC–LM percentiles or Z-scores and the metabolic indicators studied in all cases strongly suggest the metabolic nature of such modulation.

These results support our hypothesis that the ordinates of the BMC–LM relationships, or the derived percentiles or Z-scores, should be sensitive to changes in the endocrine-metabolic environment of the musculoskeletal system [8,12,13]. If so, then the little-used ability of DXA technology to measure the LM in whole body and limbs [38] could provide a quantitative approach to a differential diagnosis between metabolic and disuse-related osteopenias

[19,20] (see Fig. 1 right). In disuse osteopenias, the bone–muscle proportionality would be maintained regardless of the bone mass (BMC) status [11], as indicated by a low BMC–LM percentile or Z-score. In metabolic osteopenias, the bone–muscle proportionality would be impaired by either a primary disease of bone cells or a secondary bone perturbation (a systemically induced shift of the mechanostat setpoint [11]), as indicated by a low BMC–LM percentile or Z-score.

Application study

Based on the foregoing criteria, this study showed that post-MP women had more fractures associated with metabolic than disuse osteopenias compared with pre-MP women, in whom the former were practically absent. However, it also showed that in post-MP women the metabolic etiology tended to predominate as the LM decreased. This phenomenon may support the idea that the lack of estrogen reduces the sensitivity of bone cells to mechanical stimuli, although this is still a matter of controversy [39–41].

Final remarks

The reported studies show that this novel use of DXA could differentiate between osteopenias that require different treatments (mainly a physical intervention in "disuse-related" cases, versus pharmacological treatment for "systemic" cases), thus allowing monitoring the therapeutic effects according to biomechanical criteria. Nevertheless, the BMC–LM proportionality alone cannot distinguish between individuals more or less exposed to fractures in any instance. DXA cannot be used as a single methodology to diagnose osteoporosis defined as an "osteopenic fragility" of the skeleton [4].

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