Hylonome

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BONE MARKERS IN PATIENTS WITH RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS

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Background: The characteristics of rheumatoid arthritis (RA) and osteoarthritis (OA) are inflammation and joint degradation. Bone markers are good parameters which picture bone metabolism. Helical peptides (HP) are new sensitive markers of bone degradation.

Objectives: The aim of this study was to assess, compare and correlate IL-1 and HP levels in patients with RA and knee OA.

Methods: The blood and urine were collected from 35 RA patients and 21 OA patients. The serum IL-1 and urine HP levels were determined using ELISA.

Results: The average value of IL-1 and HP in the group patients with RA were $16,3 \pm 19,5$ pg/ml, $161,37 +/- 84,14$ μg/mmol creatinine, respectively and in the group patients with OA were $13,77 \pm 4,68$ pg/m, $120,81 \pm 33,58$ μg/mmol creatinine, respectively. Further analysis showed that the average values of HP in RA patients were significantly higher compared to the average values in OA patients $p < 0,001$, but between average IL-1 levels were not significantly difference between groups. In RA patients, the value of IL-1 correlated with HP ($r = 0,502$; $p = 0,002$) and also in OA patients, the value of IL-1 correlated with HP ($r = 0,622$; $p = 0,003$).

Conclusion: Our results confirmed that the increased values of HP point to the present increased bone degradation, which can predict future bone loss in both patients. The correlation of HP and IL-1 values in patients with RA and OA indicate correlation between inflammation and bone degradation and showed the significance of determining HP in urine as the marker of bone degradation in patients with different arthritis.

CORRELATION OF RADIAL pQCT WITH FEMORAL DEXA MEASUREMENTS IN RHEUMATOID ARTHRITIS PATIENTS

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Aim: The correlation of radial peripheral quantitative computed tomography (pQCT) with femoral DEXA in rheumatoid arthritis (RA) patients.

Material: Twenty-three RA postmenopausal women 46-65 years old (mean $\pm$ SD 57, $95 \pm 5,4$), with active disease (DAS28 = $3,65 \pm 1.5$) stageII-III were measured at the distal radius by pQCT- Stratec XCT- 2000 scanner and with Lunar DPX-L at the non dominant hip.

Method: Comparisons of A) femoral Trochanter T-score (Troch-T score) with Trabecular density T-score(Trab-T score) and B) femoral Total T-score with radius Total density T score were done by linear regression analysis.

Results: A) $y = 0,9919x - 0,6812$, $R^2 = 0,8482$ B) $y = 0,391x - 2,338$, $R^2 = 0,6862$
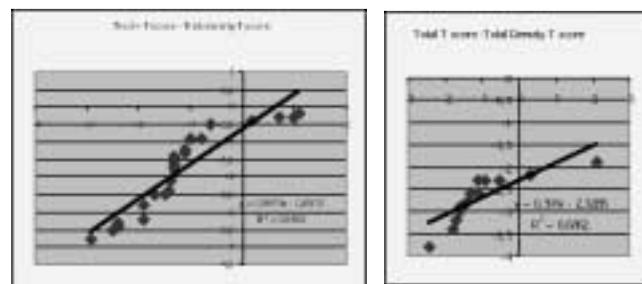
Conclusions: Although previous reports in postmenopausal woman with low bone mineral density (BMD) have shown a poor correlation of radial pQCT values with femoral BMD as assessed by DEXA, our results in RA group shows a very good correlation between these two methods.

THERAPEUTIC EFFICACT OF RISEDRONATE IN MEN WITH RHEUMATOID ARTHRITIS. TWO YEARS CONTROL STUDY

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Background: Osteoporosis (OP) is a common metabolic bone disease characterized by bone fragility and high fracture risk, due to deterioration of bone mineralization. Osteoporosis has been frequently seen in rheumatoid arthritis (RA) patients. 1/3 of all the hip osteoporotic fracture occurred in men. Clinical trials of the oral bisphosphonates have demonstrated fracture risk reduction in osteoporotic patients.

Methods: The were two control comparative groups (61 men) with (OP) and (RA). 39 patients with RA and OP treated with 35mg risedronate weekly, and daily 500 mg Ca plus 400iu Vit.D for two years. And 32 patients with RA and OP without any medication for osteoporosis. Diagnosis of RA and OP were confirmed by the 1987 American College Rheumatology revised criteria for diagnosis RA and Word Health Organization Criteria for diagnosis of OP. T-score lumbar spine (ls) < -2.5 SD (WHO criteria) BMD measurement has been done on (LS) by dual energy X-ray

absorptiometry (DEXA).

Results: Patients whose received risedronate plus calcium and Vit D have increased lumbar BMD by 3.9% (P<0.005) compared baseline in group without any therapy for osteoporosis BMD decreased by 0.6% compared baseline (p<0.005). All patients completed the study and drugs have been well tolerated by our patients.

Conclusion: We concluded that risedronate 35mg weekly is efficient and safe and could increase BMD in men patients with osteoporosis and RA.

HIGHER PREVALENCE OF DECREASED BONE MASS IN SCHIZOPHRENIC PATIENTS

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Aim: Schizophrenia affects about 8 individuals in 1,000 during their lifetimes, and also causes a higher rate of physical morbidity. Several recent studies have suggested that schizophrenia patients have a higher prevalence of decreased bone mass, possibly related to prolactin elevation, a side effect of antipsychotic medications. The aim of the study is to evaluate the prevalence of decreased bone mass among schizophrenic patients.

Material: Bone mineral density (BMD) was measured in 27 male (mean age 43) and 36 female schizophrenic patients (mean age 53) and in 9 healthy males (mean age 42) and 25 healthy females (mean age 51).

Method: Subjects filled out a questionnaire regarding gender, height, weight, and risk factors for osteoporosis; schizophrenic subjects provided information about antipsychotic medications. BMD was measured in the lumbar spine (L2-L4) and both hips using the Lunar Prodigy Bone X-ray absorptiometer (DEXA). Osteoporosis was defined as a T score of $\leq$-2.5, and osteopenia between -1 and -2.5.

Results-Conclusions: Among males, the prevalence of either osteoporosis or osteopenia was 70.4% in schizophrenic patients vs. 22.2% in control subjects (p=0.02). Among females, 61.1% of the schizophrenic patients had either osteoporosis or osteopenia vs. 40% of the control subjects (p=0.12). Using a logistic regression model, the age, gender, and BMI adjusted odds ratio for osteoporosis/osteopenia was 4.04 (schizophrenic vs. control subjects). No statistically significant difference in the prevalence of osteoporosis/osteopenia was found between patients receiving prolactin elevating and non-prolactin elevating antipsychotic medications. Screening of BMD should be considered in this population.

DENSITOMETRIC ANALYSES OF MUSCULOSKELETAL INTERACTIONS IN HUMANS

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The Mechanostat Theory [*Frost, 1987*] proposes that the available compact tissue (cortical "mass") would be spatially distributed tending to compensate for differences in its intrinsic stifness as required by the customary mechanical usage of the skeleton, in order to optimize the stiffness/strength of long bones. pQCT can determine indicators of cortical tissue mass (CSA, BMC), stiffness (vCtBMD, proportional to tissue elastic modulus), and distribution (moments of inertia, xMI, pMI). In order to assess the proposed homeostatic relationships and their impact on the estimated bone strength (Bone Strength Index, BSI = MI.vCtBMD), pQCT scans were taken 66% and 38% proximally to the distal ends of nondominant radius and tibia, respectively, of 50 men, 80 pre-MP women and 120 post-MP women aged 25-85 yr, all fracture-free, healthy Caucasians.

Data were generally congruent for radii and tibiae. Men showed higher CSA, BMC, MIs and BSI values and lower vCtBMD values than pre-MP women. The MIs (*y*) grew linearly with CSA or BMC (*x*; "distribution/mass", *d/m* curves) showing higher slopes and ordinates for men than for pre-MP women. Negative, hyperbolic relationships were shown between MIs (*y*) and vCtBMD (*x*; "distribution/quality" or "distribution/density", *d/d* curves), with higher ordinates for men than pre-MP women. After MP, women lose CSA, BMC and vCtBMD rather than MIs, thus showing similar MI values for progressively lower CSA, BMC or vCBMtD values compared with pre-MP women (shift to the left in all graphs). Graphs for men and pre-MP women were Z-scored as normal references for comparative evaluation. A special software was developed for automatic calculation of individual Z-scores for this and other studies. Calculated Z-scores for post-MP women became progressively higher than normal for the positive *d/m* curves and lower than normal for the negative *d/d* curves as a function of time since MP. The post-MP decay in BSI was less significant than that observed in cortical vBMD, CSA, or BMC.

In addition to support the above hypothesis, results show that 1. men priorize naturally the architectural design and strength of bones, while pre-MP women rather tend to achieve a denser cortical tissue, with less impact on bone strength, and 2. post-MP women tend to maintain bone design despite the bone mass loss, thus minimizing its impact on bone strength. The standarized *d/m* and *d/q* curves, Z-scores and software are proposed as comparative reference tools for evaluation of cortical tissue distribution as a function of its availability and mechanical quality, respectively, in clinical studies. These novel diagnostic tools can not only describe the functional condition of bone mechanostat, but also detect and quantify the interaction of any treatment with the homeostatic control exerted by that system on bone structure.

The elastic modulus of cortical tissue varies proportionally to matrix mineralization and intracortical porosity. The pQCT-assessed cortical vBMD (vCtBMD) captures both these factors; thus, it could reflect bone material's quality. The vCtBMD distribution in long bone diaphyses can be affected by mechanical forces (proposedly coming from regional muscles rather than gravity) acting directionally on modeling and remodeling. Systemic agents as sex hormones may modulate these effects nondirectionally. This study aimed to analyze the eventual effects of gender and gravity on vCtBMD distribution in tibial and radial diaphyses of 250 normal men and women.

Scans were taken 66% of the ulna length proximal to the wrist joint and 38% of the tibial length proximal to the ankle joint in 50 men, 80 pre-MP and 120 post-MP women aged 25-85 years. Specific high- and low-vCtBMD ROIs were defined with voxels showing attenuation values >1.0 cm^{-1} (HD), and 0.4-1.0 cm^{-1} (LD), respectively. Pixels with lesser attenuation values were ignored.

Tibial and radial data were generally coherent. Both %HD and %LD areas were similar in men and pre-MP women, but the %HD area was lower and the %LD area was higher in post-MP than pre-MP women. The HD area decreased with years since MP (YSMP). A single relationship between %HD (y) and %LD (x) areas of all the bones was observed, showing distribution zones with decaying values of the HD/LD relationship for [men] >[pre-MP women] >[post-MP women with up to 7-9 YSMP] >[post-MP women with more YSMP]. The proportion between %HD and %LD areas decayed significantly with YSMP. The loss of HD area after MP determined a mechanically meaningful, geometrical discontinuity of the ROI.

Congruence of tibial and radial data suggests little or no interaction of gravity with the mechanical effects of regional muscle contractions on vCtBMD distribution. The interdependence between %HD and %LD areas was reflected by the negative relationships observed between those variables in either forearms or legs when male and female bones were studied together. These curves provide reference charts for evaluating bone (cortical) material deterioration (which can be assumed to be similar in different skeletal regions of the same individual) as shifts toward the lower-right region of the graphs, in closer connection with bone strength than that observed for DXA BMC/aBMD data.

ESTIMATION FROM EARLY CHANGES OF SERUM PROCOLLAGEN TYPE I AMINOTERMINAL PROPEPTIDE OF THE LUMBAR BMD GAIN AFTER 2 YEARS IN CHILDREN SUFFERING FROM SEVERE OSTEOGENESIS IMPERFECTA

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Three-day intravenous (IV) pamidronate every 3 months has become a classical therapy of severe osteogenesis imperfecta (OI) in children. However, this therapy is rather heavy, and a rapid determination of its future efficacy

should be welcome. We have therefore determined whether the measurement of changes of serum procollagen type I aminoterminal propeptide (PINP), a biological marker of bone formation, between day 0 and day +3 could help to foresee the BMD response after 2 years.

We have treated 11 patients [M, 9; F, 2; aged 10.4 (3.7 SD)] suffering from severe OI with IV pamidronate. sPINP was measured on day 0 and +3, by radioimmunoassay (Orion Corporation Espoo, Finland). The results were expressed as a percentage value of day 0 and day 3. Lumbar-BMD (L1-L4-BMD) was measured by DXA (QDR 4500 Elite, Hologic Inc, Bedford MA) at time 0 and at time +24 months. On average, after 3 days of therapy, PINP value decreased from 398 (251) to 194 (193) mg/l (-52%, $p<0.001$) and L1-L4-BMD increased from 0.454 (0.134) at time 0 to 0.648 (0.155) g/cm^2 (+43%, $p<0.001$) after 24 months. A significant inverse correlation was observed between PINP changes (0-3 days) and L1-L4-BMD (0-24 months) [r=-0.60 (p=0.05)].

In conclusion, a significant decrease of PINP between day 0 and day 3 during a 3-day IV pamidronate therapy is accompanied by a significant increase of L-BMD after two years. The PINP measurements could constitute a promising biological measurement leading to a better compliance to therapy.

BONE IN BONE IMAGE AFTER TREATMENT WITH INTRAVENOUS INFUSIONS OF DISODIUM PAMIDRONATE IN TWIN CHILDREN SUFFERING FROM OSTEOGENESIS IMPERFECTA

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Two twin boys aged 12 suffering from osteogenesis imperfecta, complicated by several peripheral and thoracic vertebral fractures were treated by intravenous infusions of disodium pamidronate (1 mg/kg per infusion), 3 consecutive days every 3 months for 2 years. Their BMD measured by DXA increased from 0.416 to 0.600 g/cm^2 at the (L1-L4) lumbar spine and from 0.590 to 0.804 g/cm^2 at the total hip after 4 years. In the same time, they grew 16 cm. The views of the postero-anterior DXA scan of the lumbar spine obtained 2 years after the last course of therapy demonstrated the presence of "arrest lines" close to the plateaus of the vertebral bodies. X-ray films confirmed that this aspect was attributable to a "bone in bone image" due to bisphosphonate therapy, a well-known radiological aspect in growing children treated by cyclical intermittent bisphosphonates[1]. This DXA aspect corresponding to the radiological image should be recognized, because part of the bone gain can be explained by it.

Reference

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THERE ARE CHANGES IN BONE MINERAL DENSITY IN PATIENTS WITH HYPERLIPIDEMIA TREATED WITH STATIN

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Background: Osteoporosis (OP) is a disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and an increase in fracture risk. HMG-CoA reductase inhibitor (statin) treatment is frontline therapy for lowering plasma cholesterol levels in patients with hyperlipidemia. In a few case studies, analysis of clinical data has revealed a decreased risk of fracture in patients on statin therapy.

Objectives: In this study, we examined the effect of statin treatment in patients with hyperlipidemia and osteoporosis.

Materials and methods: The study included 70 postmenopausal women (the mean age of the women was 63.2 years, range 48-75 years) they had established osteoporosis according to the WHO (Spine osteoporosis was diagnosed if DEXA T-score (L1-L4) was below to -2,5) Patients do not have osteoporotic fracture. There were two controls comparative groups with osteoporosis. The first group were 40 women with osteoporosis and the

second were 30 women with osteoporosis and hyperlipidemia (total clolesterol >220 mmol/l MD 350 +/-100, triglycerides >150 mmol/l MD 280 +/-120) treated with atorvastatin calcium daily.

Results: There was no difference between the two groups with osteoporosis, only group lumbar BMD T-score -2.9+/-0.4 and the second group with osteoporosis and hyperlipidemia lumbar BMD T-score -2.8 +/-0.3.

Conclusions: The results of this study indicate that there was no statistical significant difference about BMD (p<0.8) between the two comparative groups.

BODY COMPOSITION IN SPINAL CORD INJURED MEN

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Aim: Spinal cord injured subjects lose lean tissue mass and bone but gain body fat. There is a need to quantify the magnitude of these changes in body composition because there are associated skeletal and cardiovascular health risks.

Method and material: Sixty four men were included in this study (mean age 32,3 years). 31 had complete traumatic spinal cord injury (ASIA A) in chronic stage (>1,5 years), Thoracic (T)4-T 12 neurological level of injury (group A), in comparison with 33 able bodied subjects as control group (C) of similar age, height, and weight. None of the subjects was given bone acting drugs. Whole body dual X-ray absorptiometry NORLAND was used to study subjects with SCI and controls for estimates of regional and total body BMC (g), lean and fat tissue mass (kg) and percent. In all measurements head is excluded.

Results - Conclusions: In group A from the measured parameters BMC and Lean mass, were statistically decreased and Fat mass statistically increased in comparison with controls in lower limbs,abdomen and total body composition (p=0,0005 and p=0,05 respectively).We didn't found any diference between groups in upper limbs and trunk BMC (p=N.S.).These results suggest the development of significant alterations in body composition of chronic paraplegic men. The lower limbs and regions below the level of injury were more affected. Whole body DXA gives to the clinician valuable informations for the assesssment of body composition changes in paraplegia.

BONE STRUCTURE CHANGES INDUCED BY MECHANICAL AND BIOLOGICAL AGENTS

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Abstract: Bone remodelling is dynamic process and occurs normally during bone growth and includes the sensing of environmental changes, the formation of new bone and the bone resorption, i.e. the removal of existing old bone.

Aim: Mathematical formulation of three stages of bone remodelling processes: **1.** bone resorption based on the osteoclast activity, **2.** bone deposition based on the osteoblast activity and **3.** bone growth control established on RANK/RANKL/OPG pathway - RANKL/OPG balance.

Method: On the bone remodelling model there is explained the well known tight coupling between osteoblasts (OB) and osteoclasts (OC) and control of the new bone growth. The destructive mechanism of the imbalance of the RANKL/OPG ratio is influenced by the two recently recognized genetic defects - mutations in RANKL/RANK/OPG cytokine system that cause familial expansile osteolysis (TNFRSF11A) and idiopatic hyperphosphatasia,

called juvenile Paget disease (TNFRSF11B). Remodelling disorders start with the uncontrolled activity of OC caused by these mutations and/or similarly by other known disorders of bone metabolism, e.g. different forms of osteoporosis, osteopetrosis, rickets (osteomalatia), inflammatory bone diseases, malignant bone tumours, etc. All these aspects are included in the presented bio-mechanical concept of bone remodelling.
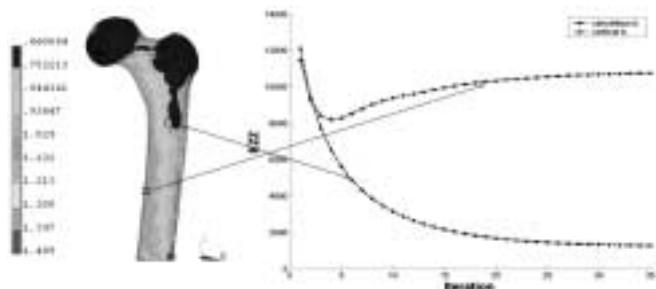

Figure 1.

Results-Conclusions: The numerical simulation shows, the concentration of a new bone substantially depends on the history and intensity of loading and/or nutrition and medical treatment. As example the influence of dynamic mechanical loading is shown in Figure 1. The differentiation of density of cancellous bone and corticalis is evident.

GLUCOCORTICOIDS REGULATE THE mGluR5, EAAT1 AND GS EXPRESSION IN MG-63 OSTEOBLAST-LIKE HUMAN OSTEOSARCOMA CELLS

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Aim: The presence of components of the glutamatergic (Glu) bioregulation system in bone cells has provided new evidence for its possible role in bone patho/physiology. Therefore, we have investigated the regulation of certain components of the Glu system, such as the metabotropic glutamate receptor 5 (mGluR5), the Glu transporter EAAT1 and the glutamine synthetase (GS), which metabolize Glu to glutamine, by glucocorticoids in MG-63 osteoblast-like cells, in vitro.

Material: We have characterized the presence of glucocorticoid receptor (GR) in MG-63 cells, consequently we analyzed the time-dependent and dose-dependent effects of dexamethasone (Dexa; up to 48hr and up to 100nM) on the expression of the mGluR5, the EAAT1 and the GS in MG-63 cells.

Method: We used relative quantitative RT-PCR and Western blot analysis for mRNA and protein analysis. The 18S RNA and the GAPDH protein were used as internal standards for the mRNAs and proteins quantitations, respectively.

Results - Conclusions: We detected the significant increase of GS at both the mRNA and protein level by Dexa (maximum effect at 48 hr and with 100nM: up to 6.6-fold and 7.5-fold respectively). In addition, we documented the expression of the mGluR5 and EAAT1, as well as the ability of Dexa to upregulate modestly the expression of the (i) mGluR5 (1.7-fold increase for mRNA and 1.4-fold for protein), and (ii) EAAT1 (no significant regulation at mRNA level, whereas an increase 2.8-fold at protein level) in the MG-63 cells. Our data suggest that glucocorticoids regulate Glu system in MG-63 osteoblast-like cells.

THE DIFFERENTIAL EXPRESSION OF OPG AND RANKL IN A CO-CULTURE SYSTEM CONTAINING PC-3 PROSTATE CANCER CELLS AND MG-63 OSTEOBLAST-LIKE CELLS

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Aim: RANKL is a protein which interacts with RANK, to promote osteoclastogenesis. OPG, is a decoy receptor which binds to RANKL to prevent RANKL activated osteoclastogenesis. Prostate cancer cells commonly metastasize to bone and produce osteoblastic lesions. The aim of our study was to co-culture PC-3 and MG-63 and to evaluate the expression of OPG and RANKL.

Material and method: Three-dimensional gels prepared by rapidly mixing cells with type I collagen. We created the co-culture by placing gels containing PC-3 in flasks containing MG-63 and vice versa. As control we used gels containing PC-3 and MG-63 in empty flasks and simple cultures in flasks. Total RNA was extracted from gels and flasks and the expression and evaluation of related genes was assessed using the quantitative reverse transcription-polymerase chain reaction.

Results: In both the monolayer cultures and 3-D co-culture system, we detected the expression of OPG and RANKL in MG-63. In PC-3 we detected only the expression of OPG. We noted a modest but significant reduction (40%) of the expression of OPG and RANKL in MG-63 cells when co-cultured with PC-3 cells, and a significant increase (6-fold) of the expression of OPG in PC-3 when co-cultured with MG-63 cells.

Conclusions: The detection of the expression of OPG in the prostate cancer cells and especially, the significant increase in the presence of osteoblast-like cells indicate that the expression of OPG may contribute in the inhibition of osteoclastogenesis in bone metastasis from prostate cancer, resulting in the blastic nature of such lesions.

DIFFERENTIAL DISTRIBUTION OF GLUCOCORTICOID AND ESTROGEN RECEPTOR ISOFORMS: LOCALIZATION OF GRBETA AND ERALPHA IN NUCLEOLI AND GRALPHA AND ERBETA IN THE MITOCHONDRIA OF HUMAN OSTEOSARCOMA SAOS-2 AND HEPATOCARCINOMAEPATOCARCINOMA HEPG2 CELL LINES

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The presence of steroid hormone receptors in mitochondria of mammalian cells has been well documented. The localization of glucocorticoid and estrogen receptors alpha (GRalpha, ERalpha) and beta (GRbeta, ERbeta) in osteosarcoma SaOS-2 and hepatocarcinoma HepG2 cells was studied by immunofluorescence labelling and confocal laser scanning microscopy, as well as by subcellular fractionation and immunoblotting of the proteins of the fractions with respective antibodies. In HepG2 and SaOS-2 cells GRbeta and ERalpha were localized mainly in the nucleus, particularly concentrated on nuclear structures, which on the basis of their staining with antibody against C23-nucleolin, were characterized as nucleoli. A faint, diffuse GRbeta and ERalpha staining was also observed in the cytoplasm. GRalpha and ERbeta were specifically enriched at the site of cell mitochondria, visualized by labelling with the vital dye CMX. Immunoblotting experiments corroborated the immunofluorescence labelling distribution of glucocorticoid and estrogen receptor isoforms in the cell lines studied. These findings support the concept of a direct action of steroid/thyroid hormones on mitochondrial functions by way of their cognate receptors and also suggest a direct involvement of GRbeta and ERalpha in nucleolar-related processes in HepG2 and SaOS-2 cells.

HCN ION CHANNELS REGULATE BONE FORMATION AND RESORPTION IN VITRO AND IN VIVO

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The identification of "neuronal" signalling mechanisms in bone led us to determine the role in bone of the Hyperpolarization-activated Cation Nonselective channel family (HCNs) that regulate synaptic membrane potential and ion trafficking. We determined expression of mRNA and protein for HCNs1-4 in bone, and their functions. All 4 HCNS were

detectable at mRNA and protein levels in mouse bone extracts, and LM and EM immunolocalisations revealed highly specific expression patterns. HCN-1 was expressed predominantly in the ruffled border of osteoclasts, while HCN-4 was more generally expressed in osteoclasts. HCN-2 was detectable in mononuclear cells near bone surfaces. HCN-3 was expressed by bone forming osteoblasts and some marrow cells. Electrophysiological studies showed that the HCN antagonist ZD7288 abolished inward currents in osteoclasts in response to voltage steps and increased resting membrane potential by 90% (P<0.01). In marrow cultures, inhibition of HCN-2 function with selective doses of ZD7288 reduced osteoblastic differentiation by over 80% (p<0.01).

To determine the role of HCN-2 *in vivo*, we analysed bones from HCN-2 null mice that are reduced in size compared with wild-types but otherwise grossly normal. After correction for size, there were significant differences in cortical and trabecular BMD and area measured by pQCT and microCT. Mechanical testing revealed that bones of the HCN-2 null mice were 20% weaker in bending than WT bones, which would be consistent with reduced osteoblastic differentiation and bone formation. Together, these results suggest that HCN ion channels have important regulatory functions in bone formation and resorption.

REPOSITION OF BONE MASSES IN THE LATERAL DIRECTION AT DIAPHYSES AS THE BIOCHEMICAL RESPONSE TO EXCESSIVE STRESS/STRAIN STATES

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Reconstruction of diaphyses during the lateral drift is a typical example of the bone tissue adaptation to external mechanical effects. During the lateral drift, a key part is played by volume changes of molecular mixtures which, during the tissue reconstruction, predetermine its quality, i.e. regulate in it the processes connected with its resorption or with its apposition. The presented research is focused on the elimination (or substantially reduction) of the current extreme stresses/strains during the lateral drift. The decisive influence on the dynamics of the bone tissue apposition in its compressed area is exerted by positive changes in compressive stresses with regard to stresses that correspond to the ideal equilibrium state p_e. The bone tissue apposition is slowed down by negative changes in compressive stresses. The decisive influence on the dynamics of the bone tissue resorption in its tensioned area is exerted by negative changes in tensile stresses, whereas positive changes in tensile stresses function as decelerators of the bone tissue resorption. Logarithmic decrement δ of the inhibition of resorption (thinning) of the bone tissue in its tensile area (or in its element) indicates the decrease of the old (original) bone tissue. During the inhibition, when changes in stresses fluctuate above and below value $\Delta p=0$, resorption/apposition in the assumed tensile/ compressive area of the bone tissue is almost terminated. Similarly, logarithmic decrement δ of the inhibition of apposition (thickening) of the bone tissue in its compressive area (or in its element) indicates the increase in the bone tissue. *The logarithmic decrements δ of the reconstruction inhibitions indicate the lateral shift of cortical bone*. The long-term existence of the living tissue is determined by the stability of oscillation of current stresses p in the proximity of p_e. The bone tissue is then in *a relatively weakly steady state* which will last until this state is disrupted, i.e. until the new remodelling processes are initiated. (Acknowledgement: This research has been supported by grant of the MSK CR-No.:6840770012.)

ASSOCIATION BETWEEN BONE MINERAL DENSITY AND MUSCLE MASS IN POSTMENOPAUSAL WOMEN

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Introduction: Reduced physical activity and muscle mass have been

associated with a decrease of bone mineral density (BMD). The theory of the "mechanostat" refers to the impact of muscle force on the bone on which it is exerted.

Aim: To investigate the correlation of the extremities' muscle mass to the local and total body BMD.

Subjects-Methods: In 37 postmenopausal women [(age 54.6±4, age at menopause 49±2.7, BMI 28.3±2.9 Kg/m², (mean±1 SD)] whole body composition and BMD measurements were performed by DXA. None of the women had ever received any medication with known influence on bone metabolism, neither had been an athlete or was immobilized for more than one week. The head was excluded from all measurements. The upper and lower extremities were evaluated independently in respect to their lean mass (EX-LM) [heavier (H) and lighter (L)]. The EX-LM was considered identical to the extremity's muscle mass.

Results: The upper H extremity's EX-LM tended to be significantly higher than the L's (p=0.08). Only in the same extremity a significant positive correlation was detected between EX-LM and local BMD (EX-BMD) (r=0.44, p<0.05). No other significant differences were observed between the H and L extremities in respect to their EX-LM or EX-BMD. Total body BMD (TO-BMD) and total lean mass (TO-LM) were significantly positively correlated (r=0.40, p<0.05). No significant correlation was detected between TO-LM or TO-BMD and any EX-LM. On the contrary, TO-BMD was significantly positively correlated with all EX-BMDs (r=0.35-0.84, p<0.05).

Conclusions: Total body bone mineral density seems to be positively correlated rather to total than the local extremities' lean mass. The association of physical activity to the total body or the extremities' local lean mass needs to be demonstrated. The positive correlation between the local bone density and lean mass of the upper extremities, enforces the "mechanostat" theory.

KINETIC PARAMETERS IN PRE- AND POSTMENOPAUSAL WOMEN

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Aim: The treatment of osteoporosis which focuses only on bones ignores muscle function and balance elements directed connected with this disease, the prevention of falls and fractures. Our purpose was to study differences in kinetic parameters of pre and postmenopausal women which influence balance and muscle function.

Material and methods: One houndred twenty eight women were included in the study separated in three groups: Group A included 38 osteoporotic postmenopausal taken antiosteoporotic drugs and calcium/vitamin D supplementation (mean age 65±9,6 years), group B consisted of 57 healthy postmenopausal women (mean age 62,9±9,8 yrs), in comparison with 33 healthy (group C) premenopausal women (mean age 35±7,6 yrs). For the measurement of objective parameters of movement we used the mechanography system in Leonardo platform (Novotec, Pforzheim, Germany) which measures forces, calculates through acceleration the vertical velocity of centre of gravity and also using force and velocity it calculates power of vertical movements. After explaining in all participants the process, they jumped on the platform (two leg jump) .Weight was recorded on the platform before the jump and height was measured with a wall-mounted ruler.

Results-Conclusions: The anthropometric values and the kinetic parameters of the study population are presented in the following table.

COUNTING PARAMETERS	GROUP A (n=38)	GROUP B (n=57)	GROUP C (n=33)	Anova p value
weight Kg	63.74±9.90***	67.3±9.70***	60.5±10.10	0.008
height cm	160±4.00**	162±5.00	166±4.00	<0.0005
BMI Kg/m²	24.78±4.20***	25.7±3.69***	21.76±3.70	<0.0005
force max KN	1.14±0.21**	1.15±0.31**	1.35±0.24	0.001
velocity m/sec	1.21±0.42***	1.09±0.53***	1.79±0.49	<0.0005
power N/m²	1.07±0.45***	1.05±0.54***	1.78±0.52	<0.0005
power/weight N×Kg/m²	17.47±7.9***	15.75±8.38***	30.41±11.45	<0.0005
jump height m	0.14±0.08***	0.16±0.06***	0.25±0.11	<0.0005
***p<0.0005, **p<0.005, *p<0.05 vs Group B (Bonferroni post-hoc)				

In groups A,B all kinetic parameters were statistically decreased in comparison with group C. Height decreased significant with age .The results suggest that in all postmenopausal women a decline in the kinetic parameters is expected. Jumping mechanography gives to the clinician additional informations in order to prevent falls and fractures in postmenopausal women.

MARKERS OF BONE METABOLISM DURING ENDURANCE CYCLING EXERCICE IN MALE ATHLETES: ACUTE EFFECTS AF AN ORAL CALCIUM LOAD

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Although sport and physical activity are generally considered as positive factors for bone metabolism some endurance trainings such as running and bicycling have few or no beneficial or even deleterious effects on bone mineral density. The present study was designed to investigate the acute effect of an intensive endurance cycling exercise on biochemical bone markers. Furthermore, the effect of the oral intake of 1g calcium load just prior to the exercise was checked. Twelve well-trained elite male triathletes aged 23-37y were explored. The serum concentrations of calcium, phosphate, bone alkaline phosphatase (BALP), as a biochemical marker of bone formation, and C-terminal cross-linking telopeptide of type I collagen (CTX), as a biochemical maker of bone resorption, were measured before, during and after a 60 min 80% VO_2max cycle ergometer exercise. When the exercise was performed without calcium load serum CTX concentrations began to increase progressively 30 min after the start of the exercise and were still significantly elevated, by 50%, 2h after the end of the exercise. By contrast serum concentrations of BALP fluctuated and showed no significant difference with or without calcium load. The significant increase in CTX observed after exercise was completely suppressed by the ingestion of calcium. The present study demonstrates that the burst of osteoclastic activity acutely induced by an intensive endurance cycling exercise can be suppressed by the previous intake of a calcium load.

QUALITY OF BONE DENSITY - ACCELERATION OF THE BONE THICKENING

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The bone thickening/thinning are regulated biochemically (genetically) and biomechanically. The rates (speeds) of biochemical reactions (i.e. the speeds of intense metabolic processes) depend on *the volume changes of molecular mixtures and on the stress changes in a bone element*. The paper is focused on *analysing the molecular dynamics of metabolic processes related to thickening of the cortical bone*. The main objective is to formulate exactly the fundamental theorems related to the influence of mechanical/ biomechanical stress changes on accelerating/retarding the bone thickening. The complex project has been aimed at the efficient use of presented conclusions in the clinical practice. The rate of thickening in the tissue in the jth biochemical reaction initiated by volume change $n_{jch} < 0$, influenced by primary chemical effects, or $\eta_{jm} < 0$, influenced by primary mechanical effects is the *exponential function of stress changes* $dp=p-p_e$ in the examined bone tissue element. Thickening in the bone tissue will be retarded (reduced) when the stress changes (load changes) $dp < 0$ declines. When the stress changes (load changes) $dp > 0$, i.e. $p > pe$ increases, the thickening process in the bone will be accelerated. *The application of medicaments supporting the bone tissue thickening is dominantly effective only in cases of dynamic loading* (dynamic stress) of a skeleton (or its examined location). Acknowledgement: This research has been supported by the Grant of GACR, No.: 106/06/0761.

MALE MICE HETEROZYGOUS FOR THE pH-SENSING RECEPTOR OGR1 SHOW A MILD BONE PHENOTYPE AT SKELETAL MATURITY

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The discovery of pH-sensing G protein-coupled receptors has raised the question about their potential role in bone metabolism. A link between metabolic acidosis and increased bone resorption is well documented. Bone mineralization, on the other hand, occurs under conditions of locally alkaline pH. The pH-sensing receptor OGR1 (Ovarian cancer G protein-coupled receptor 1; GPR68) is preferentially expressed in osteoblasts and osteocytes, but is also detected in osteoclasts. Here we describe the bone phenotype of bl6 OGR1+/- mice. Mice are apparently healthy and fertile. At skeletal maturity (4 months) male OGR1+/- mice show normal body weight and bone length but reduced bone mineral density at peak bone mass. The reduction in BMD is explained by a decrease in cortical thickness (CtTh). The trabecular bone volume (BV/TV) is also reduced due to a decrease in trabecular thickness (TbTh) with no change in trabecular number (TbN). Material density is normal at 4 months but the SMI (Structure Model Index) is increased, indicating that male OGR+/- mice have a more rod-like trabecular structure compared to wild-type (WT) animals. This bone phenotype is less pronounced in female animals. During ageing to 5 and 6 months, BV/TV and TbN decrease linearly in WT but not OGR1+/- mice. Cortical thinning is also visible over time in WT mice while CtTh continues to increase in OGR+/- mice due to endocortical bone apposition.

The weak bone phenotype observed in male OGR+/- mice seen at skeletal maturity may result from a mild impairment in their osteoblast function which delays trabecular thickening that normally occurs during the conversion of primary to secondary spongiosa. The same impairment may delay the naturally occurring endocortical modelling drift during bone growth resulting in the decrease in cortical thickness at 4 months. Continuous endocortical apposition in OGR1+/- mice and prevention of the age-related decrease in TbN which is seen in WT-mice may be compensatory mechanisms aimed at adjusting mechanical competence of the structure of male OGR1+/- mice to the 'normal' level of WT-mice. The pH-sensing receptor OGR1 may have a mild modulatory role on osteoblast function.

SAFETY AND QUALITY OF LIFE PATIENTS WITH OSTEOPOROSIS AND LUMBAR FRACTURES AFTER 18 MONTHS WITH TERIPARATIDE TREATMENT

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Background: A vertebral fractures causes acute pain and disturbs physical functions. The existence of more vertebral fractures is often associated with chronic pain and disability. Patients with low bone mineral density (BMD) have high risk of future fractures.

Methods and material: This study examined 25 patients, 16 women, age 65 +/-10 years and 9 men age 61 +/-8,2 years. We examined: a) efficacy and safety, b) the degree to which improvement, quality of life patients with osteoporosis, after 18 months treatments with 20 mg/d teriparatide. There were two controls comparative groups patients with osteoporosis one before and one after treatment. Osteoporosis as defined by low B.M.D. T-score lumbar spine (l.s) <-2.5 S.D (W.H.O. criteria). B.M.D. measurement has been done on l.s. by dual energy X-ray absorbtiometry, (DEXA). Osteoporosis were treated with 20 mg/d teriparatide and 500 mg Ca plus 400 iu Vit.D. daily. All patients had more than one fractures of l.s. Osteoporosis quality of life questionnaire (OQLQ) was used to assess the symptoms, physical function, activities of daily living, emotional functional and social domains in patient for each domain. The mean score was calculated as a sum of items in domain dividing with the number of items. Functional status was measured by questionnaire score running from 0 (worse) to 10 (best) before and 18 months later.

Results: All patients completed the study and drugs were well tolerated by our patients.

OQLQ	Begging	18 M later	P
Physical function	3.93 +/- 1.7	7.01 +/- 1.5	<0.005
Emotional functional	4.01 +/- 1.35	7.8 +/- 1.3	<0.005
Activities of daily living	4.58 +/- 1.58	6.9 +/- 1.8	<0.005
Symptoms	3.51 +/- 1.30	7.5 +/- 1.25	<0.005
Leisure/social	3.8 +/- 1.53	7.7 +/- 1.35	<0.005

Conclusion: We conclude that teriparatide is safe and effective in reducing associated back pain increasing physical function and improving quality of life.

THE PREVALENCE OF OSTEOPOROSIS IN THE POPULATION OF TIRANA, ALBANIA

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Purpose: The aim of the study was to establish the prevalences of osteoporosis and osteopenia in the population of Tirana, in general and separately for females and males. The study evaluated the prevalence of osteoporosis and osteopenia in women after 50 years old.

Material and method: Our study was prospective, epidemiologic, cross-sectional. The study included 1084 subjects, 670 females and 414 males. Were chosen 1 in every 80 habitants from 4 different Primary Ambulatory Centers. Bone Mineral Density was measured in every subject using a heel ultrasound bone densitometer (Pegasus type). For each subject height and weight were documented. A detailed questionnaire was compiled for every subject. The data gathered were analyzed using STATA program. The criteria of osteoporosis were those of WHO; T-score less then -2.5 SD.

Results: The prevalence of osteoporosis in the population of Tirana was 7.28%. Osteopenia was found in 33.1% of total population over 20 years old. Osteoporosis was more frequent in women, 9.6 % compared with only 3.6 % in men. Osteoporosis was significantly more common in women after 50 years old 15.2%. Osteoporosis was found more frequent in men after 65 years old, 8.1%.

Conclusions: Osteoporosis is a frequent disease in our population. Women are affected more then men with a ratio 2.66:1. Women are affected more after 50 years old and men after the sixties.

LOCAL ANAESTHESIA BALOON KYPHOPLASTY IN THE TREATMENT OF OSTEOPOROTIC VERTEBRAL FRACTURES

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Aim: The purpose of the study was the evaluation of the early results of balloon kyphoplasty under local anaesthesia for vertebral osteoporotic fractures in our department during the last year.

Patients and Methods: 26 patients (58 levels) unterwent kyphoplasty in one (1) to five (5) levels per patient. Indications were recent or older osteoporotic vertebral fractures).

Bilateral transpedicular approach (two balloons) was used in lumbar and lower thoracic spine and simple transpedicular or extrapedicular approach (one balloon) in upper thoracic. All patients underwent the procedure under local anesthesia and simple C-arm control.

Visual Analogue Pain Scale and Oswestry Disability Index were evaluated pre- and postoperatively in 6 weeks, 3 months and 6 months after.

Results: All patients were mobilized immediately postoperatively without any cast. There was marked improvement of pain (VAS and reduction of opiate-base analgesics) immediately postoperatively. ODI was also improved 56% in tree months. Six months postoperatively all patients stopped opiates, returned to previous activities of daily living. There were no serious complications. In two patients during the trocar insertion through the skin, they felt ache and pins and needles at the lower limb which they mentioned and which improved immediately by changing the approach.

Conclusions: Kyphoplasty under local anaesthesia is an aggressive but rewarding treatment for osteoporotic and osteolytic lesions. It is easier and time saving procedure which markedly improves pain and mobility. The continuous communication and neurological evaluation of the patient due to the local anaesthesia helps avoid major complications.

ORAL SALMON CALCITONIN REDUCES THE LEQUESNE'S FUNCTIONAL INDEX AND DECREASES THE URINARY AND SERUM LEVELS OF BIOMARKERS OF JOINT METABOLISM IN KNEE OSTEOARTHRITIS

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Objective: To evaluate the effects of oral sCT on the Lequesne's algofunctional index and on biomarkers of joint metabolism in knee osteoarthritis.

Methods: In this randomized, double-blind trial, patients received daily either a placebo (n=18), 0.5 mg sCT (n=17) or 1 mg sCT (n=18) for 84 days. Biomarkers included type II collagen C-telopeptide (CTX-II), type II collagen neoepitope C2C, collagenases (MMP-1, MMP-8 and MMP-13), stromelysin (MMP-3), tissue inhibitors of MMPs (TIMP-1 and TIMP-2) and hyaluronan (HA). Statistical analysis included nonparametric tests.

Results: The number of patients who completed the study was 13 in the 0.5 mg sCT group and 14 in the 2 other groups. While, at day 84, the placebo group and 1 mg sCT group both exhibited a similar significant decrease in pain score (>-30%; P<0.01), a significant reduction of the function score (>-25%; P<0.01) was only observed in the 2 sCT groups. At day 84, there was no significant decrease in biomarkers levels of the placebo group whereas the 2 sCT groups had a significant reduction (P<0.05) in their levels of both MMP-3 (>-15%) and HA (>-20%), and the 1 mg sCT group exhibited a significant decrease in its levels of CTX-II (-20%), C2C (-16%) and MMP-13 (-20%).

Conclusions: By improving functional disability and by reducing levels of biomarkers which are thought to predict joint space narrowing, and thus cartilage loss, 1 mg oral sCT might be a useful pharmacologic agent in human knee OA.

TOMOGRAPHIC ASSESSMENT OF MUSCLE-BONE INTERACTIONS IN NORMAL HUMANS

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A standardization of methods, sites, variables, data management, analyses and interpretation of pQCT determinations is urgently required. Aiming to offer some reference for that purpose, pQCT indicators of bone mass (total, cortical and trabecular BMC, cortical CSA, trabecular vBMD), mineralization (cortical vBMD), design (CSMI's), and strength (BSI's, pSSI), and muscle CSA (MCSA) were determined in forearms (4% and 66% sites) and legs (4%, 14%, 38%, and 66% sites) of 250 normal volunteers (40 men, 60 pre-MP women, 150 post-MP women) aged 20-86 years. Correlations of every bone indicator with age, menoage and MCSA were analyzed. A specially-developed software allowed 1. massive storage and analysis of data employing single databases, Z-scorization of any obtained correlation curve, and individual Z-score calculation, specifically for gender and reproductive status.

Little or no correlation of bone data with age was observed in men and pre-MP women. Some significant, negative influence of menoage on bone variables was detected, with decreasing significance for mineralization >mass >strength >design indicators. Highly significant, linear correlations between bone mass, design and strength indicators (tibial 38% site, radial 66% site, y) and MCSA (66% sites, x) were observed for men and pre-MP women together. The relationship between cortical [tibia+fibula] CSA and MCSA showed a 0.05 slope comprising the origin, as predicted by biomechanical considerations. Plotted on the Z-scored charts of the muscle-bone relationships for pre-MP women, post-MP women data shifted significantly to the lower-right regions. Negative associations between the Z-scores of these relationships for post-MP women and menoage were observed for bone mass and strength (not design) indicators.

Results show that regional muscle strength influences bone mass, design and strength more significantly than age or menoage. A larger negative influence of menoage on cortical mineralization than on diaphyseal design was observed, suggesting the persistence of some directional control of cortical modeling by bone mechanostat after MP. However, this would have not compensated for the progressive loss of cortical vBMD (stiffness) and strength. The obtained Z-scored graphs of the muscle-bone relationships provide suitable references for a differential diagnosis between mechanical

The resistance of a long bone to uniaxial compression is linearly proportional to the amount of mineralized tissue (ToBMC) in the perpendicular cross-section. The structure of the human tibia varies largely along its longitudinal axis. Standard pQCT scans show a predominance of trabecular bone at the 4% site; a narrower, approximately round section with only cortical bone at the 14% site, and a trend to adapt a triangular shape with a thicker cortex (38% site) and to show increasing diameters and a more complex profile with a thinner cortex (66% site). This variability can be mechanically predicted. Particularly, the ToBMC should show a minimal value at the 14% site; it should be approximately 1.5 times larger than that at both the 4% site (where the whole structure would be 66% as efficient in uniaxial compression as the cortical shell is at the 14% site) and the 38% site (at which a complex pattern of compression, bending and torsional forces applies).

Aiming to show some evidence of that predictable proportionality, we measured ToBMC at the 4%, 14% and 38% sites in the nondominant tibia of 40 men, 60 pre-MP women and 150 post-MP women aged 20-86 years, all normal, healthy Caucasians without fractures. Correlation between values at the 4% site (y) and at the 14% or 38% sites (x) showed single, close linear relationships for men and pre-MP women together (for the 14% site, y=-0.45+1.54x, r=-0.657, R^2=0.432, p<0.001; for the 38% site, y=-0.31+1.08x, r=0.903, R^2=0.815, p<0.001) comprising statistically the origin of the graphs. Z-scored charts of those relationships provided ± 1, 2, and 3 SD's reference intervals for comparative purposes. Analyzed against that reference, post-MP women showed similar Z-scores for the 14% site and significantly lower than that for the 38% site. No correlation was found between the Z-scores of post-MP women for any of those correlations and time since menopause.

The slopes of the adjusting equations, close to 1.50 and 1.00, respectively, confirmed the predicted proportionalities. The Z-scored charts may provide useful references for assessment of the proportionality between trabecular bone (only present at the 4% sites) and cortical bone mass as determined at two sites (14 and 38%) with different mechanical environment. A relative reduction of trabecular bone according to any of the proposed comparisons (as shown for some of the the post-MP women at the 38% site in this study) may correspond to either a metabolic or a mechanical osteopenia. The clinical history of the patient should afford the complementary information for the corresponding differential diagnosis. The charts are also suitable for monitoring purposes following biomechanical criteria.