

AGE-RELATED CHANGES IN HIP GEOMETRIC PARAMETERS IN THE JAPANESE FEMALE POPULATION: CROSS-SECTIONAL AND LONGITUDINAL DATA FROM JPOS COHORT STUDY

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BACKGROUND: Hip geometric parameters are expected to improve hip fracture risk assessment conducted solely based on bone mineral density (BMD). However, their basic characteristics including relationship with age, body size and conventional BMD or longitudinal changes are still insufficiently described especially for Japanese.

METHODS: We randomly selected 2,600 Japanese women aged from 15 to 79 years from 4 areas throughout Japan at baseline, and analyzed 2,107 women who had no history of diseases liable to affect bone metabolism and had adequate DXA images (QDR4500A, Hologic) for hip geometry conducted with Hip Structure Analysis (HSA) program (Hologic). Participants of 3 study areas out of 4 were invited for follow-up surveys, and 1,033 women completed 10-year follow-up. HSA analysis yielded cross sectional area (CSA), cross sectional moment of inertia (CSMI), subperiosteal diameter (PD), endocortical diameter (ED), average cortical thickness (CT), section modulus (SM) and buckling ratio (BR) at the narrowest part of the neck (NN), intertrochanter (IT) and femoral shaft (FS). CV of the parameters ranged from 1.7% to 6.9%. T-scores for each HSA parameter were calculated using the reference mean and SD values obtained from present 654 subjects aged 20 through 39 years.

RESULTS: Cross-sectional patterns of age-specific values of CSA and CT were almost identical to that of BMD but those of CSMI, ED and SM were not (Fig. 1). Correlations between age and CSMI, SM or BR were significant even after adjusted for conventional BMD. CSA, CT and BR highly and CSMI, SM and ED moderately correlated with conventional BMD while PD did not. Magnitudes of longitudinal changes in the parameters at NN and IT were predominant in women in the menopausal transition as well as in late postmenopausal women while those at FS tended to increase with the increase in years since menopause (Fig. 2).

CONCLUSIONS: The patterns of change with aging in ED, CSMI and SM were quite different from that of conventional BMD. These parameters may improve conventional bone strength evaluation based on BMD.

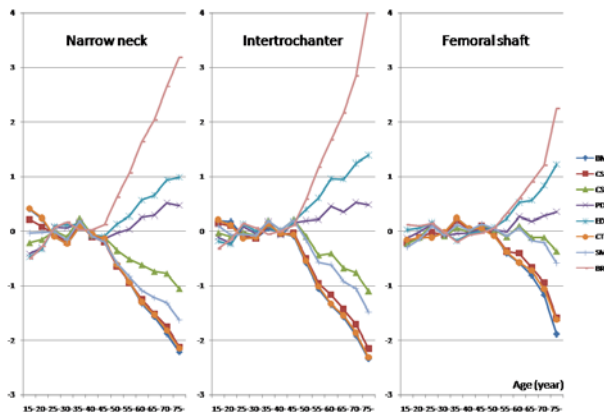


Fig. 1. Age-specific mean T-scores of HSA parameters in Japanese women. JPOS Study.

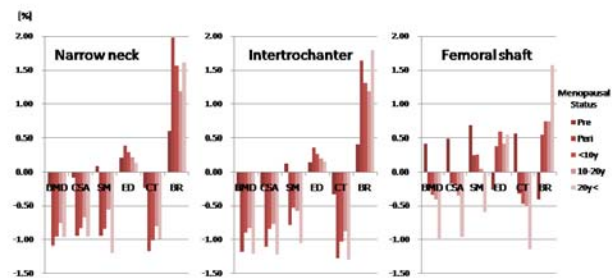


Fig. 2. Annual rates of changes in HSA parameters during 10-year follow-up of Japanese women grouped by menopausal status. JPOS Cohort Study.

Pre: premenopausal women at follow-up. Peri: women who entered menopause during the follow-up. <10y: Postmenopausal women with <10 years since menopause at baseline. 10-20y: Postmenopausal women with 10-20 years since menopause at baseline. 20y+: Postmenopausal women with 20+ years since menopause at baseline.

EFFECT OF MONTHLY IBANDRONATE ON HIP STRUCTURAL GEOMETRY IN MEN WITH LOW BONE DENSITY

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BACKGROUND: Hip fractures can be a devastating consequence of osteoporosis. Bone strength is dependent not only on bone mineral density (BMD) but also on microarchitecture and geometric properties. Hip structural analysis (HSA) of dual-energy X-ray absorptiometry (DXA) images can be used to evaluate changes in hip geometry in patients receiving osteoporosis therapy. The **STudy Researching Osteoporosis iN Guys (STRONG)** examined the efficacy and safety of 150-mg monthly oral ibandronate in men with low bone density. Men who received monthly ibandronate (n=85) demonstrated significant increases in lumbar spine and total hip BMD after 1 year compared with placebo (n=47) (3.52% vs 0.94% [difference 2.58%; $P<0.001$], and 1.82% vs -0.31% [difference 2.13%; $P<0.001$], respectively).¹ To examine the impact of monthly ibandronate on hip bone geometric properties in men with low bone density, we performed HSA on DXA images in a subset of STRONG participants.

METHODS: This prespecified subgroup analysis included men from the intent-to-treat population of STRONG with DXA data available for baseline and 12 months who had scans using Hologic scanners. Cross-sectional geometric parameters of the femoral shaft (FS), intertrochanteric region (ITR), and narrow neck (NN) were calculated from femoral DXA scans. All analyses were exploratory. Treatment differences were determined using analysis of covariance (ANCOVA) adjusting for baseline parameter value, testosterone level, and treatment.

RESULTS: HSA was performed on DXA scans from 89 men from STRONG (34 placebo; 55 monthly ibandronate). After 12 months, significant increases in average cortical thickness and cross sectional area and decreases (ie, improvements) in the buckling ratio were observed at the FS and ITR for ibandronate-treated men compared with placebo-treated men (**Table**). No significant differences were observed between ibandronate and placebo for any NN HSA parameters.

CONCLUSIONS: As determined by HSA, ibandronate treatment for 12 months was associated with trends toward improvement in hip geometry relative to placebo in men with low bone density.

¹Binkley N et al. 2009, J Bone Miner Res 24 (Suppl 1) Abstract A09002056.

Table. Treatment differences (ibandronate minus placebo) in mean percent changes from baseline to 12 months

Parameter	Treatment difference* (LSM and 95% CI)	P value
Femoral shaft		
Cross sectional area	1.7 (0.4, 3.1)	0.013
Average cortical thickness	3.1 (1.0, 5.2)	0.004
Endosteal diameter	-2.4 (-4.4, -0.3)	0.027
Outer diameter	-0.3 (-0.9, 0.4)	0.413
Buckling ratio	-3.6 (-6.0, -1.2)	0.004
Cross sectional moment of inertia	0.3 (-1.6, 2.2)	0.726
Section modulus	0.9 (-0.7, 2.4)	0.263
Intertrochanteric region		
Cross sectional area	2.1 (0.7, 3.5)	0.003
Average cortical thickness	2.7 (1.0, 4.3)	0.002
Endosteal diameter	-0.6 (-1.5, 0.2)	0.150
Outer diameter	-0.3 (-1.0, 0.4)	0.439
Buckling ratio	-2.9 (-4.8, -0.9)	0.006
Cross sectional moment of inertia	1.7 (-0.5, 3.9)	0.127
Section modulus	2.3 (0.1, 4.5)	0.042
LSM, least squares means		
*ANCOVA adjusted for baseline BMD, center, testosterone level, and treatment		

TRABECULAR ARCHITECTONIC FEATURES IN DIFFERENT ZONES OF HUMAN LUMBAR VERTEBRAE

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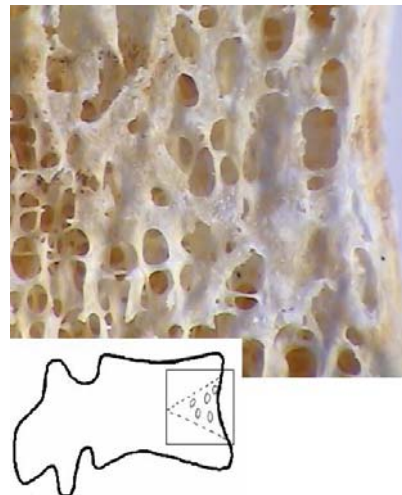
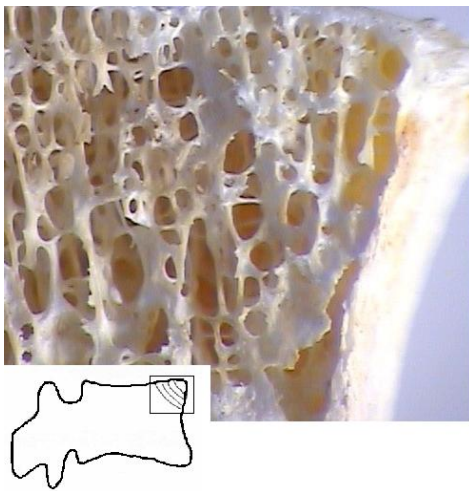
BACKGROUND: Recent researches prove that frequency of vertebral injuries had increased in 2-5 times last 30 years, often caused by raising (picking up) insignificant loads. In series of investigative studies it was established that age-associated changes in different parts of vertebra do not occur simultaneously. Detail research of relations in between compact and spongy bones of vertebral body, as well bone marrow filling of intertrabecular spaces will permit to create models of vertebral segments, predict their behavior under different mechanical stresses. That will help to estimate the risks of micro- and macro injuries, to bring better understanding of bone adaptation and remodeling. The purpose of this research was to establish trabecular architectonic features in different zones of human lumbar vertebra bodies.

METHODS: 62 specimens of 3rd lumbar vertebra (from cadavers 56-88 years old) were utilized. On the digital images of the sagittal sections shape, position, sizes of vertical and horizontal trabeculae, and width of intertrabecular spaces in 6 different zones were investigated.

RESULTS: The range of length for horizontal (1328.5 ± 112.5 microns) and vertical trabeculae (1053.7 ± 97.5 microns) for spongy bone of L3 vertebral body was found. In images of anterosuperior zone the specific trabeculae support for upper top corner of a vertebral body were observed (fig. 1). These fenestrated plates (thickness 213 ± 414 microns) locate under $24-35^\circ$ to a vertical and provide optimum redistribution of mechanical loading on lumbar vertebra front-upper edge. In anteromiddle zone triangle-like lamellae were found, with basis faced forward and top - to the vertebral centre (fig. 2). Large apertures (average 461×715 microns) communicate this space with roundish marrow cavities.

CONCLUSIONS: The height of vertebral bodies decreases in elderly age. The most interesting features were found in anterosuperior and anteromiddle zones. Further investigations of indicated zones of vertebral body are very important for prediction of microfractures.

Figure1. Light micrograph of a sagittal section of anterosuperior zone (x16). Figure2. Light micrograph of a sagittal section of anteromiddle zone (x16).



ESTABLISHMENT AND APPLICATION OF THE RAT TIBIAL THREE DIMENSIONAL FINITE ELEMENT ANALYSIS MODEL BASED ON THE MICROCT TECHNIQUE

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Background: Primary osteoporosis is the most common metabolic abnormality found in postmenopausal women. Increasing bone strength and preventing fragility fracture are of great importance. However, there is little of the study on non-invasive bone strength assay. Finite element analysis is a computer aided technique which is based on the scanning images and simulated the bone strength. Thus, we use this FEA model to evaluate the change of bone strength under different physical situation.

Objective: To establish the rat's tibial three-dimensional (3D) finite element analysis model and to evaluate the change of bone strength under different physical status.

Methods: A set of consecutive transactional microCT tomography images of 10-month-old rat's tibiae was selected. The scanning parameter was 16um, 70Kv. The scanning region started from the lowest point of the diaphysis. A proximal tibia 3D finite element analysis model was established by using software Mimics12.0. Appropriate pressure of the tibia and the orientation of load on the trabecular bone were applied to the model by using the software Abaqus6.8, to calculate the stress values of all nodes and units of each model. Moreover, the mechanical property of tibiae was assayed by compression test. Using the similar technique, we also established the 3D finite element analysis model of osteoporotic bone and compared the differences between the sham group and osteoporotic group.

Results: (1) The mechanical property of the rat tibiae evaluated using compression test. The results showed that the average BMD of the sham group is $0.302 \pm 0.03 \text{ g/cm}^2$, whereas for the osteoporotic (OP) group the average is $0.250 \pm 0.04 \text{ g/cm}^2$. The BMD of the OP group was significantly lower than that of the sham group ($P < 0.01$). From mechanical test, comparing the maximum load of the two groups, it was found that the maximum load of OP group is $108.85 \pm 9.63 \text{ N}$, however the sham group had a slightly higher value of $121.07 \pm 8.34 \text{ N}$.

(2) The mechanical property of the rat tibiae evaluated by FEA. The BMD of sham group was 1.132 g/cm^3 and of the OP group was 0.644 g/cm^3 . When subjected to compression fracture, the proportion of elements that exceeded yield strain in the OP groups significantly decreased 70%, especially in the region-I.

Conclusion: Our analysis showed that the stronger material properties are of better strengths of trabecular bone tissue. The results also indicated the 3D finite element analysis model is sensitive for bone strength, thus maybe a ideal surrogate biomarker.

MULTIPARAMETRIC IMAGING OF BONE ARCHITECTURE: A CADAVERIC STUDY

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BACKGROUND: Bone architecture is a major determinant of its strength. Currently, assessing trabecular architecture & the effectiveness of osteoporosis therapy by iliac crest biopsies is invasive. Imaging may be useful in such assessment, given that a - correlation between vertebral fractures and strength, and correlations between measures of microarchitectures across different sites in body (vertebrae, distal radii) and vertebral strength are assumed in the osteoporosis literature.

This study aims to examine such assumptions.

METHOD: Individual lumbar vertebra and radius of 14 formalin-fixed cadavers were dissected out after QCT scan, for μ CT & strength analysis.

QCT: Whole body multi detector CTs were performed with multiplanar reconstruction and were analyzed for bone mineral density (BMD), and fracture prevalence estimated as Spinal Deformity Index (sum of Genant scores of T9-L5 vertebrae).

μ CT: Structural analysis of lumbar vertebrae and distal radius included architecture parameters such as BV/TV, Conn.D, SMI, DA, BS/BV, marrow star volume, and trabecular thickness (TbTh), number (TbN) & separation (TbSp).

Strength: Each vertebra was placed between parallel plates and slowly compressed at 1/8 inch/min until the force needed to shorten the specimen decreased dramatically. The compressive force and the resulting specimen deformation were continuously recorded during. From above compiled and plotted data, the strength for each vertebra was calculated and log transformed for statistic analysis.

RESULTS: Subjects has median (range) of age 78 (39, 98) years and female:male ratio of 10:4. Mean \pm Std of vertebral strength (log transformed) was 6.01 \pm .66 for 11 subjects of mild fracture(SDI \leq 7); higher than that of 5.03 \pm .87 for the rest of 3 subjects with worse fracture. (p=.05). Vertebral strength and BMD shows + correlation(r=.87, p<.001). Correlations between vertebral strength (log transformed) and architectural parameters were summarized in table 1. A multivariate linear model showed the vertebral strength (log transformed) could be predicted by many radius architectural parameters and 90% of variability was explained by those predictors.

DISCUSSION: Vertebral strength was found associated to the fracture. Architectural parameters at both vertebra and radius were evaluated; some showed strong relationships to the vertebral strength. The finding could be clinically promising as it suggested architectural parameters at radius might be able to predict to vertebral strength and eventually the risk of osteoporotic fracture.

Table 1. Summary of Pearson correlation coefficient between Vertebral Strength (log transformed) and Architectural parameters at both vertebra and radius

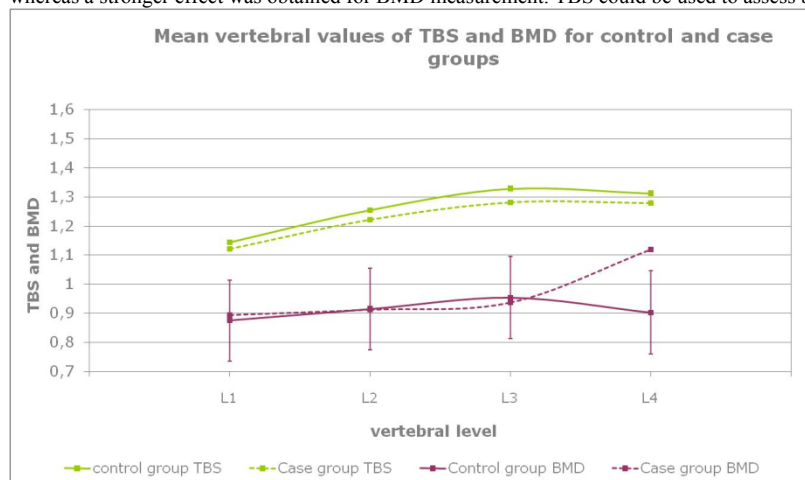
Architectural parameters	Statistics *significant	@ Vertebrae	@ Radius
bone volume fraction(BV/TV)	pearson correlation coefficient r (p-value)	0.75*(0.002)	0.70*(0.005)
connectivity density (Conn.D)	pearson correlation coefficient r (p-value)	0.81*(0.001)	0.24(0.408)
structural model index (SMI)	pearson correlation coefficient r (p-value)	-0.65*(0.012)	-0.74*(0.003)
trabecular number (TbN)	pearson correlation coefficient r (p-value)	0.74*(0.003)	0.63*(0.015)
trabecular thickness (TbTh)	pearson correlation coefficient r (p-value)	-0.22(0.455)	0.67*(0.009)
trabecular seperation (TbSp)	pearson correlation coefficient r (p-value)	-0.87*(<0.001)	-0.67*(0.009)
bone surface to volume (BS/BV)	pearson correlation coefficient r (p-value)	-0.18(0.548)	-0.71*(0.004)
degree of anisotropy (DA)	pearson correlation coefficient r (p-value)	0.27(0.356)	0.54*(0.048)
Marrow Star Volume	pearson correlation coefficient r (p-value)	-0.89*(<0.001)	-0.64*(0.014)

“Best Technologist Abstract”

SPINE OSTEO-ARTHROSIS HAS NO EFFECT ON TBS ASSESSMENT: A SITE MATCHED STUDY WITH BMD

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In the premenopausal population, spinal BMD predicts the risk of any fracture as well as hip BMD. In later life, however spine measurements are confounded by osteo-arthrosis. The latest guidelines published by the ISCD clearly states in case of osteo-arthrosis, it is accepted to exclude a vertebra when there is more than a 1.0 T-score difference between the vertebra in question and adjacent vertebrae. We know that osteo-arthrosis artificially increases DXA BMD measurement proportionally to its severity. TBS is a grey level texture parameter which characterizes micro-architecture status of bone independently of BMD. The objective of this study is to investigate the effect of the osteo-arthrosis on measurement of A-P lumbar spines TBS values using DXA imaging. We present a cross-sectional study on 390 Caucasian subjects. Study group was composed of 141 cases presenting arthrosis (according to ISCD definition) only at L4 vertebra with mean age and BMI of 66.0±8.3 years and 25.2.8±3.5 Kg/m² respectively and 249 control subjects free of arthrosis with mean age and BMI of 64.1±6.9 years and 24.5.8±3.4 Kg/m² respectively. Cases were stratified using severity of arthrosis defined by the differences between L3 and L4 expressed in standard deviation of T-score (severity ranges between 1 to 3.5 T-score). In order to validate control and case groups, a comparison between BMD and TBS data of these groups at L1-L3 was done. In addition, TBS values of control subject were compared with French TBS normative data at L1-L4. BMD and TBS were evaluated at AP Spine (L1-L4) with DXA prodigy (GE-Lunar) and TBS iNsight® (Med-Imaps). Absolute differences in percent between case and control groups at L1-L3 for BMD and TBS were 2.4 and 3.3% respectively. These differences were lower than their respective least significant change and did not show statistical significance. In addition, no significant differences were obtained between TBS values of the study group and French TBS normative data at L1-L3. At L4 vertebral level, differences between case and control groups for BMD and TBS were +19% and -3.2% respectively (see figure below). Difference obtained for TBS was lower than the LSC95 (4%) and statistically non significant. For BMD, highly significant difference was found. Correlations obtained between BMD or TBS and the severity of arthrosis were 0.626 and -0.161 respectively. Arthrosis and its severity had no significant effects on TBS whereas a stronger effect was obtained for BMD measurement. TBS could be used to assess bone microarchitecture even if in presence of arthrosis.



EFFECT OF CONTRAST SCALING MODE ON CONSISTENCY OF VERTEBRAL FRACTURE ASSESSMENT WITH NORLAND ILLUMINATUS-BASED SOFTWARE

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Because of the wide range of materials encountered by DXA in a vertebral fracture assessment, image contrast scaling is employed to bring out the structural detail in the study and aid in placement of the height cursors on the vertebrae. To establish a vertebral fracture assessment protocol this study examined the consistency of results using four Norland Illuminatus-based contrast scaling modes available to vertebral fracture assessment.

Three subjects underwent four evaluation of the thoracic and lumbar spine in decubitis recumbency on a Norland scanner fitted with dynamic filtration. These scans then underwent measurement of the posterior, mid and anterior vertebral body heights of all vertebrae from T-9 to L-4 using a linear, logarithmic, sin2 and square root contrast scaling mode to arrive at a vertebral fracture assessment.

Results of Measured Height Ratios				
	Lin	Log	Sin2	Sqrt
Ah/Ph	0.303	0.156	0.180	0.203
Mh/Ph	0.312	0.171	0.229	0.166
Ph/Ah	0.216	0.141	0.185	0.173
Mh/Ah	0.235	0.187	0.223	0.136
Sum	1.066	0.655	0.817	0.678

Results of measured height ratios were indexed against the average to calculate a ratio that reflected the consistency of measurements with the four contrast scaling modes. The review showed that the cumulative variation from the average in T-9 to L-4 region measurements ranged from 1.066 for studies using the Linear Contrast Scaling Mode to 0.655 for studies using the Logarithmic Contrast Scaling Mode.

Variation in Vertebral Fracture Assessment is minimized using the Logarithmic or Square Root Contrast Scaling Mode and is greatest using the Linear Contrast Scaling Mode. We therefore recommend not using the Linear Contrast Scaling Mode for Vertebral Fracture Assessment in the Norland scanner fitted with dynamic filtration.

RADIOGRAPHIC TEXTURE ANALYSIS (RTA) DURING TREATMENT WITH ALENDRONATE

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Background: RTA is a method for noninvasive assessment of bone structure through computerized analysis of the pattern of radiographic bone images. We have applied RTA to calcaneal images obtained using a portable densitometer and found that it differentiated subjects with and without vertebral fractures even when controlling for BMD and clinical risk factors. In the present study, we aimed to determine whether alendronate treatment produces changes in RTA that may be clinically useful for monitoring therapy.

Methods: We enrolled 36 postmenopausal women with T-score ≤ -2 or below at lumbar spine or proximal femur (femoral neck or total hip). All patients received 630 mg of elemental calcium and 400IU of vitamin D daily. Based on patients' preferences and the recommendation of their treating physician, the subjects either took 70 mg/week of alendronate, (Drug group) or did not (Control group). Bone mineral density (BMD) was measured at the lumbar spine and proximal femur using Prodigy (GE Medical Systems) every 6 months for 2 years. BMD and images of the calcaneus were obtained using PIXI (GE medical systems) at the same time points and additionally at 3 months. RTA of the heel images yielded features that characterized the trabecular pattern in terms of thickness (iRMS&sdRMS), spatial frequency (iFMP&minFMP), power spectrum (BETA) and fractal organization (Minkowski). Change over time and difference between groups was examined using ANOVA for repeated measures with month of study as within factor and group (Drug vs. Control) as between factor.

Results: There were 19 patients in the Drug and 17 in the Control group. Lumbar spine BMD increased in the Drug group ($p=0.009$) and did not change in the control group with a significant ($p=0.007$) difference in change over time (interaction term) between the groups. Femoral neck BMD decreased in Control group ($p=0.03$) with a trend towards difference between groups ($p=0.052$). Although total hip BMD did not change significantly in either group there was a difference between groups in change over time ($p=0.01$). There was no significant change over time or difference between groups for heel BMD or any of the texture features. Examination of the individual plots revealed that the texture features as well as heel BMD were remarkably stable over time.

Limitations: Changes in BMD observed in the study are relatively modest probably because patients who were included in the Active Drug group were more likely to have active bone loss while those who were in the control group were more likely to have stable BMD, thus diminishing the difference between groups.

Summary and Conclusion: Heel does not show changes in BMD or RTA during treatments which have mild effect on bone mass. It is possible that more potent treatment or more severe bone loss would be detected. Nevertheless, this study indicates that calcaneus is not suitable for evaluating changes during treatment.