

## **MEETING REPORT**

# **Meeting Report from the 29th Annual Meeting of the American Society for Bone and Mineral Research**

**September 16-19, 2007 in Honolulu, Hawaii, USA**

## **BONE IMAGING AND FINITE ELEMENT ANALYSIS**

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Finite element analysis (FEA) from bone imaging for bone biomechanical properties continued as a hot topic at this year's ASBMR meeting. The ultimate goal of bone imaging is to provide non-invasive measures of the likelihood of future fracture. Mechanical testing of machined bone specimens (1) and whole bones (2) have shown that the initial slope of the load-deformation curve is closely related to the material properties and bone architecture and can be estimated with FEA (3), while the breaking point is influenced by non-linear features and may differ by age, disease status, and other factors. Quantitative CT (QCT) can measure clinically relevant 3D volumetric BMD of the cortical and trabecular compartments. QCT BMD values of each bone voxel are converted into elastic modulus values using pre-determined correlations between the elastic modulus and QCT-derived BMD. FEA mechanically integrates geometrical and material property data from CT scans to provide measures and predictions of bone mechanical strength. FEA based on the distribution of the bone material and converting the CT-measured density values to local elastic modulus with a relationship that almost follows a square law (4) can better represent bone strength.

### **QCT FEA and Treatments for Osteoporotic Patients**

PTH (1-34) and alendronate were previously shown to have positive effects on vertebral strength as assessed by FEA of QCT (5). These studies were extended to include analysis of proximal femoral strength for a

simulated sideways fall. Total hip strength at 18 months significantly increased (5.9%) in the PTH (1-34) group and did not significantly change in the alendronate group. This significant biomechanical effect for PTH (1-34) was associated with a significant decrease in cortical density (-1%) and an increase in trabecular density (5.1%) (6). In another study, CT examination of the proximal femur indicated that 24 months of PTH (1-34) treatment improved bone strength of the proximal femur with regard to both bending and buckling, with larger protective effects in subjects at higher risk (7). In patients treated with PTH (1-34), DXA loses its ability to estimate bone strength, but QCT and CT image-derived bone structure maintain a high correlation with FEA bone strength (8). High resolution CT combined with FEA of the vertebra showed that bone apposition with PTH (1-34) treatment was not uniform, but directed to skeletal regions of local structural weakness, likely explained by the biomechanical concepts of bone tissue response to local strains, in accordance with Wolff's law and Frost's mechanostat (9).

Previously, a QCT-based nonlinear FEA was shown to predict vertebral strength, fracture sites and distribution of minimum principal strain (10). Now, L2 FEA of postmenopausal Japanese women with (n=29) or without (n=75) osteoporotic vertebral fracture showed that the optimal point on the ROC curve as vertebral fracture threshold was 1950 N with 76% sensitivity and 73% specificity. FEA showed a more sensitive response to alendronate therapy than DXA (11).

QCT scans of 36 unembalmed, previously frozen human cadaveric femora, and biomechanical testing that simulated a sideways fall at a rate of 100 mm/s, showed that most of the fracture lines propagated through the superoposterior region of the femoral neck. Hence the superoposterior region may be critical to the strength of the femoral neck as a key site of fracture initiation and propagation in sideways falls (12).

### **Micro CT, High Resolution Peripheral QCT, and FEA**

Micro CT examination continues to find application in the assessment of human bone biopsies, and in rodents *in vivo* and *in vitro*. High resolution (82  $\mu$ ) peripheral quantitative CT (HRpQCT) is not yet approved by the FDA, but is used as a research tool in examining the human distal radius and distal tibia.

Micro CT assessment of iliac crest biopsies from postmenopausal women treated with PTH (1-34) demonstrated an increase in both trabecular and cortical thickness, irrespective of whether subjects had received prior alendronate therapy (13). Micro CT examination of iliac crest biopsies at 8  $\mu$ m isotropic resolution demonstrated that risedronate reduced cortical porosity by reducing the birth rate of new osteons or by filling in the remodeling spaces in osteons that existed prior to treatment (14). FEA of non-linear tissue properties from micro CT scans of human iliac crest biopsies showed that deterioration of trabecular architecture directly affected both strength and bone toughness (15). Examination of cylinders of trabecular bone with micro CT indicated that partial volume, segmentation artifacts, and beam-hardening effects due to the polychromatic source could contribute to errors in micro CT-based measurement of degree of mineralization of bone (16).

Overall moderate relationships were found between comparable measures performed on iliac crest biopsies by 2D histomorphometry and 3D micro CT, and between most 2D as well as 3D parameters at the iliac crest and HRpQCT of the distal

radius, while parameters from distal tibia did not correlate well with biopsies (17).

HRpQCT and DXA examinations of 200 women showed that HRpQCT better discriminated fracture risk in osteopenic and osteoporotic patients, while the T-score seemed to underestimate fracture risk (18). FEA on HRpQCT images of the distal radius in 33 postmenopausal women who previously sustained a fragility fracture of the wrist and 33 age-matched controls demonstrated that the load distribution between cortical and trabecular bone seems promising for improving wrist fracture prediction, independent of BMD and microarchitecture (19).

HRpQCT measuring the ultradistal radius showed a significant 6.9% increase in BV/TV at 1 year post-treatment with PTH (1-34), similar in magnitude to the 5.7% change at the iliac crest in women treated for 3 years with PTH (20;21). Sustained increases in the more differentiated osteoprogenitor cells appear to be predictive of larger gains in trabecular bone volume assessed by HRpQCT (22).

HRpQCT of healthy girls without a prior history of fracture showed marked but transient decreases in cortical thickness during puberty, with no significant differences in trabecular parameters (23), which was a mirror image of the rise in distal forearm fractures in girls that peaks between ages 8 and 11, during the time of maximal pubertal growth (24). The trabecular parameters may be established very early in life, while the temporary cortical thinning may relate to increased calcium demands during maximal growth. Examination with pQCT and DXA showed that before and after menarche, bone growth in length and width were influenced differently by hormones and mechanical loading, with mechanical loading as the dominant factor throughout the pubertal period (25).

HRpQCT has various other applications. HRpQCT and QCT examination in men demonstrated that the prevalence of aortic calcification rapidly increased after age 50 and was correlated with lower vertebral and femur neck vBMD and with lower distal

radius BV/TV and trabecular thickness (26). HRpQCT scans of the radius and tibia in 8 premenopausal women with idiopathic osteoporosis showed fewer, more widely separated trabeculae of similar thickness, and decreased thickness (only in the tibia), compared to controls (n=9) (27). The loss of entire trabecular elements may underlie the more heterogeneous trabecular network. Examination of the distal radius and tibia in 103 European-Caucasian mother-daughter pairs demonstrated that heritability for BMD, cross-sectional area and trabecular thickness were more robust at weight-bearing sites, suggesting a genetic influence on the skeletal response to loading (28). HRpQCT examination of moderate chronic kidney disease and end-stage kidney disease demonstrated that lower eGFR was associated with both cortical and trabecular deterioration independent of gender and age, which may contribute to the increased susceptibility to fracture, due in part to the catabolic effects of secondary hyperparathyroidism (29).

#### **DXA, Controversial Hip Structural Analysis, and Other Imaging Modalities**

Current DXA strength calculations assume a linear relationship of density and elastic modulus and also assume a circular structure of the complex 3-D femoral neck structure from 2-D projection images with limited spatial resolution. Results might be improved by an appropriate assumption of a power-based relationship and non-circular structure, respectively (2). Cortical thickness, cross-sectional area, shape, cortical area, and section modulus measured directly from micro QCT images of postmortem specimens from 13 Caucasian females showed that the narrowest neck was not a constant referent predictive of the diverse structure of the femoral neck. Thus, use of DXA indirect estimates of femoral neck structure using hip structure analysis should be viewed with skepticism (30).

Precision may degrade in thicker subjects due to decreased x-ray flux and the effect of thicker tissue on edge detection. Lunar iDXA provided excellent precision for total body measurements, including BMD, BMC and

body composition, with root-mean-square standard deviation < 1% from obese subjects (31). Mid-body fat has been shown to be more predictive of cardiovascular risk factors than total body fat. Comparison of corresponding tape-measured and iDXA total body scan-analyzed body fat in android (abdominal) and gynoid (hip) regions in 37 postmenopausal overweight women with mean BMI 32 showed Pearson's correlation  $r$  ranging from 0.7 to 0.9 (32).

3D images constructed from helical CT scan (n=1280) and fluoroscopy images (n=2600) showed that the endplates of fractured vertebral bodies were irregular with multiple Schmorl's nodes and endplate perforations (33). CT would be better than conventional x-ray for fracture detection, and such changes may not be captured with morphometry.

Prolonged alendronate use (average duration of use of 7.3 years) may actually increase the risk of low energy subtrochanteric and shaft fractures, as x-rays of patients taking alendronate revealed a pattern of a simple or oblique fracture with cortical thickening and breaking of the cortex on one side (34). Examination of biopsies from osteoporotic women treated for 3 years with strontium ranelate (n=6) or placebo (n=6) using x-ray microanalysis of small selected areas (10 $\mu$ m~10  $\mu$ m) within individual bone packet areas revealed that Sr was present in a molar fraction up to 6%, exclusively in bone packets newly formed during strontium ranelate treatment (35).

A compact peripheral 1.0 T permanent magnet MRI system was used to perform trabecular bone micro-architectural assessment of the distal radius in 5 volunteers, with reproducibility 2-14% as the root mean square CV (36).

**Conflict of Interest:** None reported.

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