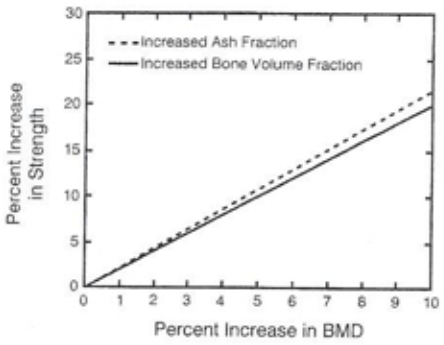

Figure P-10

bone strength and BMD therefore does not appear to be modified by increased ash fraction. Our previous study suggested that small increases in ash fraction improve bone strength more than similar increases in bone volume fraction. This analysis suggests that the separate effects of bone volume fraction and ash fraction on bone strength are accounted for by BMD measures. We suggest that it is unlikely that mineralization induced increases in bone strength are responsible for any unexpectedly large changes in fracture incidence during bisphosphonate treatment.

P-11

42. ### Implications for Understanding Fluid Flow Dynamics During Functional Loading: Application of Regional Microstructural Heterogeneity in the Turkey Ulna

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It has been suggested that the mechano-sensitivity of osteocytes is mediated by fluid-flow through bone's lacunar-canalicular porosity. This idea has been examined in an analytical model of the turkey ulna [Srinivasan & Gross, Med. Eng. & Phys., 2000]. During normal loading, this bone experiences circumferential strain gradients that are highest along the neutral axis, which typically traverses the cranial-caudal cortices. Regional differences in fluid-flow dynamics within the turkey ulna have also been described. Intercortical and transcortical pressure gradients and fluid flux are largely dependent on matrix porosity. We speculate that heterogeneities in osteocyte lacuna density and non-lacuna porosity, in addition to other material characteristics, might be important considerations in understanding fluid-flow and related strain dynamics. A transverse segment was cut at mid-diaphysis of 11 skeletally mature domestic turkeys, and four 200X backscattered electron images (two endocortical and two pericortical; excluding circumferential lamellae) were obtained from cortical octants: D, D-Cr, Cr, D-Cd, Cd, V-Cd, V, V-Cr (D = dorsal, Cr = cranial, Cd = caudal, V=ventral). These images were examined for osteocyte lacuna population densities and non-lacuna porosity (primary and secondary canals, vascular channels). Secondary osteon population densities were quantified in cortical quadrants (D, V, Cr, Cd). Octant comparisons demonstrated more lacunae in the Cr and Cd cortices compared to the other locations ($p<0.001$) [Means: Cr 1,316.6/mm^2; Cd 1,388.0; range in other regions: D-Cd 966.7 to V-Cr 1,100.1]. There was relatively greater porosity in Cd, V-Cd, and D-Cd regions ($p<0.05$). However, non-lacuna porosity and lacuna density were not correlated ($r=0.008$). Quadrant comparisons showed significantly more secondary osteons in the caudal cortex. Previous data have shown that this region has significantly greater thickness and lower mineralization (%ash). Pericortical-endocortical comparisons showed more lacunae in the pericortical region (1,234.4 vs. 1,170.1, $p=0.05$) and greater non-lacunar porosity in the endocortical region ($p=0.06$). These data demonstrate significant regional microstructural heterogeneity. In the context of fluid-flow analyses, it is important to recognize that regional variations in lacuna and non-lacuna porosities might not be correlated. These are important considerations in analytical models examining strains and fluid flow. An important clinical challenge is to understand fluid-flow dynamics so that we can ultimately comprehend the mechanisms that mediate bone maintenance and adaptation for applications in disease prevention.

P-12

A Murine Model of Postmenopausal Osteoporosis and Estrogen Replacement Therapy: Assessments of Volumetric BMD Using pQCT and of Three-Dimensional Trabecular Microstructure Using mCT

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Because of the recent wide availability of various genetically altered mice in genomics research and for drug discovery and development, there is an unprecedented new interest in developing a murine model for investigating osteoporosis. The purpose of this study was to characterize volumetric BMD and the three-dimensional (3D) trabecular bone and microstructure of a murine model of osteoporosis induced by estrogen deprivation and effects of hormone replacement therapy (HRT) on the model using computed tomography (CT), a non-destructive advanced image technique. Seventy 3-month-old Swiss Webster mice were equally divided into 7 groups: baseline, sham surgery received placebo (sham, 2 groups), ovariectomy received placebo (OVX, 2 groups), ovariectomy received 17β-estradiol at 250 μg/kg/week s.c. (HRT, 2 groups). One group of the animals from sham, OVX, and HRT were sacrificed at 5 weeks post-surgery, and the rest were sacrificed at 13 weeks post-surgery. The distal femur was scanned using a pQCT (Stratec, Germany), and scanned with a μCT scanner (Scanco, Switzerland) with isotropic resolution of 9 μm^3. 3D μCT trabecular structure, including structure model index (SMI) and degree of anisotropy (DA) in the secondary spiongiosa were directly measured without stereological model assumption. Serum osteocalcin and NTx were measured as indicators of bone turnover. Compared to sham animals, OVX led to significant reductions in BMD at 5 and 13 weeks post-OVX. These reductions were apparent at 5 weeks in the distal femur by pQCT (-16%). μCT showed that at 5 weeks post-surgery, there was a significant change in BV (-50%), Tb.N (-29%), Tb.Th (-8%), Tb.Sp (+54.38%), SMI (+14%), and DA (-10%) in OVX compared with those in sham. These changes were similar at 13 weeks post-surgery, and no further bone loss was observed. HRT prevented OVX-induced changes up to the sham level. OVX increased bone turnover at 5 weeks post-surgery. These data indicate that OVX induces short-term high-turnover accelerated deterioration of 3D trabecular structure in the Swiss Webster mouse. The trabeculae become more rod-like and more isotropic after OVX. HRT only prevented OVX-induced bone loss without anabolic effect at this dose.

P-13

L-Type Calcium Channels Mediate Mechanically Induced Bone Adaptation *In Vivo*

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Introduction: Calcium channel antagonists have been found to alter the intracellular calcium response to a variety of stimuli in bone cells *in vitro*. It has been hypothesized that activation of mechano-sensitive calcium channels activate Long-lasting (L-) type voltage sensitive calcium channels (VSCC) that, in turn, trigger chemical signals in the signal cascade from applied load to cell response in bone tissue. In the present study, we investigated whether L-type VSCC mediate mechanically induced bone adaptation *in vivo* using two L-type VSCC antagonists, verapamil and nifedipine.

Materials and Methods: Twenty-four adult rats were divided into three groups: control, verapamil treated and nifedipine treated. Verapamil and nifedipine were orally administered by using gavage once at a dose of 100mg/kg. One bout of loading was carried out 90 minutes after administration of verapamil or 30 minutes after administration of nifedipine. The control animals were loaded 30 minutes after administration of polyethylene glycerol vehicle. The right tibia of each animal was externally loaded with 64 N peak force for 360 cycles at 2 Hz in a four-point bending device, and the left tibia was used as a nonloaded control.