**NOT TO BE MISSED**

Clinical and Basic Research Papers – July 2004 Selections

Ego Seeman, Clinical Editor
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**Bone Modeling and Remodeling**


* Stiffness is an essential property of bone that is established by mineralization. Four-point bending studies were done on mouse ribs at 16 and 17 days of gestational age. Unmineralized specimens had a Young's modulus of 1.11 Mpa, and mineralized specimens had a value of 117 Mpa, an increase of two orders of magnitude in one day. The authors propose the novel notion that shielding hypertrophic chondrocytes from mechanical stress reduced their deformability, with subsequent resorption of calcified cartilage and expansion of the marrow cavity. —ES

**Pathophysiology**


* Transgenic mice expressing the glycine to valine substitution at amino acid residue 171 in the gene coding for low-density lipoprotein receptor-related protein 5 have the high bone mass phenotype, with greater structural and material strength and percent bone ash weight. Whether the denser and stiffer bones represent greater bone formation sensitivity to mechanical stimuli resulting in an overadaptation to loading remains to be determined. —ES


* Platelet-activating factor is a phospholipid mediator of platelet activation, bronchoconstriction, and increased vascular permeability that acts through the G-protein coupled receptor PAFR. Although the bones of PAFR-null mice are normal, absence of PAFR protects mice from osteoporosis following ovariectomy. PAFR is expressed in osteoclasts, but PAF is not a powerful stimulator of bone resorption, and the mechanism of protection remains to be clarified. —GJS

**Recommended. —ES**

**Physiology and Metabolism**

Osteoblasts contribute to the stem cell niche in bone. Here it is shown that osteoblasts express angiopoietin, and hematopoietic stem cells (HSCs) from a side population express its receptor tie-2. Angiopoietin signaling induces adherence of HSCs to osteoblasts, quiescence of HSCs, and resistance of HSCs to cytotoxic chemotherapy. The induction of quiescence by adherence to osteoblasts could play a role in the induction of latency in bone metastases. —GJS


A cultured population of cord blood cells has properties of somatic stem cells and differentiates to osteoblasts and chondrocytes, as well as to adipocytes and hematopoietic and neural cells, including astrocytes and neurons. They may be similar to cells previously described by Kusnetsov et al. (J Cell Biol 2001 153(5):1133-40). —GJS

Treatment and Drug Effects


A paper on the antifracture efficacy of intermittent ibandronate has finally been published. The incidence of vertebral fracture decreased by 50% after three years. Post hoc analysis suggested that the daily regimen reduces the risk of nonvertebral fractures by 69% in a higher risk subgroup. —ES


Transplantation of nonadherent marrow cells into lethally irradiated mice reconstitutes the bone marrow of the recipient, but also contributes to the recipient’s chondrocytes and osteoblast lineages (1% to 2% of total osteoblasts). PCR and Southern blotting establish that transplanted marrow cells and osteoblasts have a common progenitor, and cytogenetic studies exclude fusion events as the explanation. —GJS

Recommended. —ES


FLEX is the long-term extension of the Fracture Intervention Trial (FIT) of alendronate therapy. In this three-year interim analysis of FLEX, 1099 patients assigned to alendronate in FIT were rerandomized to alendronate 10 mg daily, alendronate 5 mg daily, or placebo. BMD continued to increase at the spine in patients continuing on alendronate 10 mg or 5 mg daily, with stable reduction in urinary N-telopeptide. Patients randomized to placebo experienced a small increase in N-telopeptide and a small
BoneKEy-Osteovision. 2004 September;1(9):1-5
http://www.bonekey-ibms.org/cgi/content/full/ibmske;1/9/1
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*decrease in BMD at the hip. Fracture data will be reported when the study has been completed and will be important for decision-making about long-term bisphosphonate treatment.* —GJS


*Bisphosphonates are getting some bad press lately in the context of microdamage. One-year-old beagles given incadronate for three years had suppressed activation frequency and increased microdamage; however, structural mechanical properties were nevertheless increased after treatment, whereas intrinsic material properties were not changed. Whether microdamage in and of itself is deleterious to whole bone strength remains unproven.* —ES


*Whether antiresorptives should be given prior to, during, or after PTH is unclear. Sprague-Dawley rats were treated with PTH 25 weeks after ovariectomy, followed by nothing, PTH, 17β-estradiol, or zoledronate. This study supports the notion that effects are lost following withdrawal of PTH and are maintained by antiresorptives.* —ES


*The chloride channel inhibitor blocked osteoclastic resorption in vitro and protected bone strength by 50% in vivo. Bone formation was not inhibited. Why was bone formation not inhibited?* —ES


*Raloxifene should reduce rates of bone loss in hypogonadal me. This paper tests the hypothesis in men in whom hypogonadism was induced pharmacologically to treat prostate cancer. Raloxifene treatment for 12 months significantly increased hip BMD, with a trend towards higher spinal BMD.* —GJS

### Reviews and Perspectives


Other Studies of Potential Interest


