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NOT TO BE MISSED

Clinical and Basic Research Papers – December 2007 Selections

Serge Ferrari, Editor-in-Chief
Ego Seeman, Clinical Editor

Bone Modeling and Remodeling

McGee ME, Maki AJ, Johnson SE, Nelson OL, Robbins CT, Donahue SW. Decreased bone turnover with balanced resorption and formation prevent cortical bone loss during disuse (hibernation) in grizzly bears (Ursus arctos horribilis). *Bone*. 2007 Oct 25; [Epub ahead of print] [Abstract]

> *Disuse uncouples bone formation from resorption, leading to increased porosity and decreased bone geometrical properties. Black bears have decreased cortical bone turnover during hibernation with balanced formation and resorption in femurs. Hibernating grizzly bear femurs were less porous and more mineralized, and did not demonstrate any changes in cortical bone geometry or whole bone mechanical properties compared to active grizzly bear femurs. The activation frequency of intracortical remodeling was 75% lower during hibernation than during periods of physical activity, but the normalized mineral apposition rate was unchanged. Bone turnover decreases during hibernation, but osteons continue to refill at normal rates. There were no changes in regional variation of porosity, geometry, or remodeling indices in femurs from hibernating bears.* —ES

Epidemiology

Finkelstein JS, Brockwell SE, Mehta V, Greendale GA, Sowers MR, Ettinger B, Lo JC, Johnston JM, Cauley JA, Danielson ME, Neer RM. Bone mineral density changes during the menopause transition in a multi-ethnic cohort of women. *J Clin Endocrinol Metab*. 2007 Dec 26; [Epub ahead of print]

> *Does peri- and post-menopausal bone loss differ by race? This large, multi-ethnic cohort study shows that bone loss is indeed greater in Asians than Caucasians and lowest in African-Americans. Most interestingly, however, most of these differences could be accounted for by differences in weight, the BMD decline being 30-50% less in the heaviest women*. —SF

Pathophysiology

Lories RJ, Peeters J, Bakker A, Tylzanowski P, Derese I, Schrooten J, Thomas JT, Luyten FP. Articular cartilage and biomechanical properties of the long bones in Frzb-knockout mice. *Arthritis Rheum*. 2007 Dec;56(12):4095-103. [Abstract]

> *Polymorphisms in the FRZB gene, a secreted WNT antagonist, is associated with osteoarthritis. Targeted deletion of the Frzb gene in mice increased articular cartilage loss during arthritis triggered by instability, enzymatic injury, or inflammation. Cartilage damage in Frzb(-/-) mice was associated with increased WNT signaling and matrix metalloproteinase 3 (MMP-3) expression and activity. Frzb(-/-) mice had increased cortical thickness and density, stiffness, and periosteal anabolic response to mechanical loading. Loss of Frzb may contribute to cartilage damage by increasing the expression and activity of MMPs, in a WNT-dependent and WNT-independent manner. This may*

contribute to the development of osteoarthritis by producing increased strain on the articular cartilage during normal locomotion but may protect against osteoporosis. —ES

Yuan B, Takaiwa M, Clemens TL, Feng JQ, Kumar R, Rowe PS, Xie Y, Drezner MK. Aberrant Phex function in osteoblasts and osteocytes alone underlies murine X-linked hypophosphatemia. *J Clin Invest*. 2008 Jan 2; [Epub ahead of print]

Recent studies have started to highlight the role played by osteoblastic cells in the regulation of phosphate metabolism. Whether an osteoblast-specific defect in some component of the phosphate regulatory pathway is sufficient to cause hypophosphatemia, however, remains unclear. The authors generated both a global and osteoblast-specific KO mouse of Phex. Their findings indicate very similar phenotypes in both KO mice and in Hyp mice, including an increase of bone and circulating FGF-23, a decreased expression of the NaPi II renal transporter, and osteomalacia. Hence osteoblastic PHEX seems both necessary and sufficient to regulate phosphate homeostasis by phosphatonins. —SF

Treatment and Drug Effects

Bonnelye E, Chabadel A, Saltel F, Jurdic P. Dual effect of strontium ranelate: stimulation of osteoblast differentiation and inhibition of osteoclast formation and resorption in vitro. *Bone*. 2008 Jan;42(1):129-38. [Abstract]

Considering the ongoing controversy about the mode of action of strontium ranelate (SrR) on bone, this paper is of interest as it consistently demonstrates, through the use of standard laboratory procedures, dual effects of the drug in mouse primary cells. Hence expression of osteoblast differentiation markers and nodule mineralization was increased whereas osteoclastogenesis and bone resorbing activity in vitro was decreased dose-dependently by SrR. One may only regret the absence of calcium in the control group. —SF

Boonen S, Marin F, Obermayer-Pietsch B, Simões ME, Barker C, Glass EV, Hadji P, Lyritis G, Oertel H, Nickelsen T, McCloskey EV; for the EUROFORS Investigators. Effects of prior antiresorptive therapy on the bone mineral density response to two years of teriparatide treatment in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab*. 2007 Dec 26; [Epub ahead of print]

Whether PTH effects on bone turnover and BMD will be similar in the actual clinical setting of patients previously treated with anti-resorptives and in treatment-naive patients, as included in the pivotal PTH studies, remains unclear. The common practice of a "drug holiday" between antiresorptives and PTH also remains empirical. This prospective, open-label study clarifies some of these issues by demonstrating that in postmenopausal women with established osteoporosis and previously treated with an anti-resorptive, mainly a bisphosphonate, for at least 12 months, PINP nearly doubled within 1 month of teriparatide therapy, whereas spine BMD increased progressively from 6 to 24 months, eventually reaching 9 to 13% above baseline. However, this study also confirms that BMD at the hip decreases early after initiation of teriparatide, which could be due to a reversal of the higher degree of mineralization induced by anti-resorptives once bone turnover is accelerated by PTH. —SF

Cartsos VM, Zhu S, Zavras AI. Bisphosphonate use and the risk of adverse jaw outcomes: a medical claims study of 714,217 people. *J Am Dent Assoc*. 2008 Jan;139(1):23-30. [Abstract]

This analysis concerning the risk of ONJ in 714,217 patients with osteoporosis or cancer (breast, lung, prostate and myeloma) was performed on a large healthcare database of 15 million members in the US and based on ICD diagnostic codes for inflammatory conditions of the jaw (incl. ONJ); for major jaw surgery necessitated by necrotic or inflammatory indications; and for jaw surgeries necessitated by a malignant process. The design of this study is similar to some recent analyses of the effects of corticosteroids or beta-blockers on fracture risk, and analyses of drug effectiveness in osteoporosis (the REAL study). Here, odds ratios for ONJ and Co. were increased 4- to 8-fold among both patients with osteoporosis, and those with cancer, receiving intravenous bisphosphonates, but reduced up to 35% in those receiving oral bisphosphonates for osteoporosis. On the other hand, the pivotal zoledronate trials did not report an increased risk of ONJ over three years. Hence the jury is still out... —SF

Lekander I, Borgström F, Ström O, Zethraeus N, Kanis JA. Cost effectiveness of hormone therapy in women at high risks of fracture in Sweden, the US and the UK-Results based on the Women's Health Initiative randomised controlled trial. *Bone*. 2007 Oct 23; [Epub ahead of print] [Abstract]

The cost-effectiveness of estrogen treatment in 50-year-old women was assessed based on a societal perspective and evidence in the Women's Health Initiative (WHI) trials. Hormone therapy (HT) compared to no treatment was cost-effective for most sub-groups of hysterectomized women, whereas for women with an intact uterus without a previous fracture, HT was dominated by no treatment. Fracture risks were the single most important determinant of cost-effectiveness. HT is cost-effective in women with a hysterectomy irrespective of prior fracture status. In women with an intact uterus, opposed HT was cost-effective in those with a prior vertebral fracture, but cost-ineffective in women without a prior vertebral fracture. Even though HT is found cost-effective for a selection of osteoporotic women, it is unlikely to be considered for first-line therapy for osteoporosis because bisphosphonates have shown a similar reduction in fracture risks but without an increased risk of adverse events. —ES

Recker RR, Delmas PD, Halse J, Reid IR, Boonen S, García-Hernandez PA, Supronik J, Lewiecki EM, Ochoa L, Miller P, Hu H, Mesenbrink P, Hartl F, Gasser J, Eriksen EF. Effects of intravenous zoledronic acid once yearly on bone remodeling and bone structure. *J Bone Miner Res*. 2008 Jan;23(1):6-16. [Abstract]

Cross-sectional analysis of quite a large number of iliac crest bone biopsies (n=152) obtained after 3 years of zoledronate treatment or placebo indicates improvement of bone microarchitecture and the expected decrease of bone turnover indices, without evidence of a defect in osteoid formation or mineralization. Rather, mineral apposition rate was significantly higher in ZOL compared to PBO, an intriguing and quite novel observation regarding bisphosphonate therapy. —SF

Reviews, Perspectives and Editorials

Greenspan SL. Approach to the prostate cancer patient with bone disease. *J Clin Endocrinol Metab*. 2008 Jan;93(1):2-7. [Abstract] [Full Text]

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Other Studies of Potential Interest

Adami S, San Martin J, Muñoz-Torres M, Econs MJ, Xie L, Dalsky GP, McClung M, Felsenberg D, Brown JP, Brandi ML, Sipos A. Effect of raloxifene after recombinant teriparatide [hPTH(1-34)] treatment in postmenopausal women with osteoporosis. *Osteoporos Int*. 2008 Jan;19(1):87-94. [Abstract]

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Conflict of Interest: Dr. Ferrari reports that he receives research support from Amgen and consultancy/speaker's fees from Merck Sharp & Dohme, Eli Lilly, and Amgen. Dr. Seeman reports that he is an advisory committee member for Sanofi-Aventis, Eli Lilly, Merck Sharp & Dohme, Novartis, and Servier, and that he lectures occasionally at conference symposia for those companies.