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NOT TO BE MISSED

Clinical and Basic Research Papers – November 2007 Selections

Serge Ferrari, Associate Editor
Ego Seeman, Clinical Editor
Gordon J. Strewler, Editor

Bone Modeling and Remodeling

Wan Y, Chong LW, Evans RM. PPAR-gamma regulates osteoclastogenesis in mice. *Nat Med*. 2007 Dec;13(12):1496-503. [Abstract]

> *Clinically, the risk of long bone fractures is increased in women taking the PPAR-γ activators rosiglitazone or pioglitazone. Both drugs push mesenchymal cells away from the osteoblast pathway into the adipocyte lineage, as do genetic manipulations of PPAR-γ expression. This paper reports that osteoclasts are involved as well, with mild osteopetrosis in mice in which PPAR-γ was removed from hematopoietic cells with Tie2/cre. Mechanism? PPAR-γ induces cfos transcription in osteoclasts, as do thiazolidinediones, and cfos expression rescues the phenotype. Thiazolidinediones may be a double whammy for bone.* —GJS

You L, Temiyasathit S, Lee P, Kim CH, Tummala P, Yao W, Kingery W, Malone AM, Kwon RY, Jacobs CR. Osteocytes as mechanosensors in the inhibition of bone resorption due to mechanical loading. *Bone*. 2007 Sep 26; [Epub ahead of print] [Abstract]

> *Osteocytes support osteoclast formation and activation when co-cultured with osteoclast precursors. Mechanical stimulation of MLO-Y4 osteocyte-like cells decreases their osteoclastogenic-support potential when co-cultured with RAW264.7 monocyte osteoclast precursors. Soluble factors released by stimulated MLO-Y4 cells inhibit osteoclastogenesis induced by ST2 bone marrow stromal cells or MLO-Y4 cells. Soluble RANKL and OPG were released by MLO-Y4 cells and the expressions of both were mechanically regulated. Loading decreases the osteocyte's potential to induce osteoclast formation by direct cell-cell contact. Mechanically stimulated osteocytes release soluble factors that can inhibit osteoclastogenesis induced by marrow stromal cells. Osteocytes may function as mechanotransducers by regulating local osteoclastogenesis via soluble signals.* —ES

Epidemiology

Mackey DC, Lui LY, Cawthon PM, Bauer DC, Nevitt MC, Cauley JA, Hillier TA, Lewis CE, Barrett-Connor E, Cummings SR; Study of Osteoporotic Fractures (SOF) and Osteoporotic Fractures in Men Study (MrOS) Research Groups. High-trauma fractures and low bone mineral density in older women and men. *JAMA*. 2007 Nov 28;298(20):2381-8. [Abstract]

Khosla S. High-trauma fractures and bone mineral density. *JAMA*. 2007 Nov 28;298(20):2418-9. [Info]

> *A fracture is a fracture, i.e., it is the hallmark of bone fragility: what seems so trivial is in fact a small revolution in the osteoporosis field. Using prospective data from SOF and MrOs, this study shows that the prevalence of osteoporosis in older women and men with*

a high trauma fracture is significantly higher compared to controls with no fractures and very similar to those who suffer from low trauma fractures. Moreover, the probability of re-fracture was as high among those with high trauma as among those with low trauma. Although these results may at least partly reflect our inability to correctly classify the nature of the traumatic event a posteriori, the consequences of these observations in terms of clinical evaluation and pharmacological interventions are important. —SF

Robbins J, Aragaki AK, Kooperberg C, Watts N, Wactawski-Wende J, Jackson RD, LeBoff MS, Lewis CE, Chen Z, Stefanick ML, Cauley J. Factors associated with 5-year risk of hip fracture in postmenopausal women. *JAMA*. 2007 Nov 28;298(20):2389-98. [Abstract]

From the WHI cohort, 11 factors were identified to be associated with the risk of incidental hip fractures. An additive model score was developed based on the observational arm of WHI, then validated in the intervention arms, while BMD was available in a subset of about 10,000 subjects. The ROC for the risk factors model was quite good, actually not significantly different from BMD alone. Yet only 30 out of 80 women who had BMD and a hip fracture would have been identified by either BMD<-2.5 or a high clinical score, indicating that models allowing for a continuous evaluation of hip fracture probability, rather than dichotomous models, will be required. —SF

Physiology and Metabolism

Ben-Dov IZ, Galitzer H, Lavi-Moshayoff V, Goetz R, Kuro-O M, Mohammadi M, Sirkis R, Naveh-Many T, Silver J. The parathyroid is a target organ for FGF23 in rats. *J Clin Invest*. 2007 Dec 3;117(12):4003-8. [Abstract] [Full Text]

FGF23 signals through FGF receptors (FGFRs) bound by the transmembrane protein Klotho as a coreceptor. Most tissues express FGFR, so expression of Klotho determines FGF23 target organs. The parathyroid expresses Klotho and 2 FGFRs. Recombinant FGF23 increased parathyroid Klotho levels and activated the MAPK pathway through ERK1/2 phosphorylation and suppressed PTH secretion and gene expression. PTH secretion was prevented by a MAPK inhibitor. FGF23 acts directly on the parathyroid through the MAPK pathway to decrease serum PTH. —ES

Weinman EJ, Biswas RS, Peng Q, Shen L, Turner CL, E X, Steplock D, Shenolikar S, Cunningham R. Parathyroid hormone inhibits renal phosphate transport by phosphorylation of serine 77 of sodium-hydrogen exchanger regulatory factor-1. *J Clin Invest*. 2007 Nov;117(11):3412-20. [Abstract] [Full Text]

PTH induces phosphaturia by promoting removal of the sodium-phosphate transporter NaPi2 from the apical brush border membrane of proximal tubule cells. This paper reports that PTH phosphorylates the adaptor protein NHERF1 on ser77 – acting through both PKA and PKC – and thereby promotes dissociation of a NHERF1-NaPi2 complex in the apical membrane of renal tubule cells – as evidenced by effects of expressing various NHERF1 peptides, phosphorylatable or not, in tubule cells. —GJS

Treatment and Drug Effects

Nieves JW, Barrett-Connor E, Siris ES, Zion M, Barlas S, Chen YT. Calcium and vitamin D intake influence bone mass, but not short-term fracture risk, in Caucasian postmenopausal women from the National Osteoporosis Risk Assessment (NORA) study. *Osteoporos Int*. 2007 Nov 13; [Epub ahead of print] [Abstract]

The impact of calcium and vitamin D intake on BMD and fracture incidence was assessed in 76,507 postmenopausal Caucasian women completing a dietary questionnaire including childhood, adult, and current consumption of dairy products. BMD was measured at the forearm, finger or heel. About 3 years later, 36,209 participants returned a questionnaire about new fractures. Higher lifetime calcium intake was associated with reduced odds of osteoporosis (peripheral BMD T-score </=-2.5; OR = 0.80; 95% CI 0.72,0.88), as was a higher current calcium (OR = 0.75; (0.68, 0.82)) or vitamin D intake (OR = 0.73; 95% CI 0.66, 0.81). Women reported 2,205 new fragility fractures. The 3-year risk of any fracture combined or separately was not associated with intake of calcium or vitamin D. —ES

Saag KG, Shane E, Boonen S, Marín F, Donley DW, Taylor KA, Dalsky GP, Marcus R. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. *N Engl J Med*. 2007 Nov 15;357(20):2028-39. [Abstract]

Sambrook PN. Anabolic therapy in glucocorticoid-induced osteoporosis. *N Engl J Med*. 2007 Nov 15;357(20):2084-6. [Info]

In an 18-month randomized, double-blind, controlled trial, 214 patients received 20 microg of teriparatide daily, and 214 received 10 mg of alendronate daily. BMD at the spine increased more in the teriparatide than alendronate group (7.2+/-0.7% vs. 3.4+/-0.7%, P<0.001). At 12 months, total hip BMD increased more in the teriparatide group. Fewer new vertebral fractures occurred in the teriparatide than alendronate group (0.6% vs. 6.1%, P=0.004); the incidence of nonvertebral fractures did not differ (5.6% vs. 3.7%, P=0.36). —ES

Reviews, Perspectives and Editorials

Corr M, Lane NE. FRZB: A bone and joint connection. *Arthritis Rheum*. 2007 Nov 29;56(12):3881-3. [Info]

Delmas PD, Siris ES. NICE recommendations for the prevention of osteoporotic fractures in postmenopausal women. *Bone*. 2007 Nov 12; [Epub ahead of print] [Info]

Ebeling PR, Burr DB. Editorial - Positive effects of intravenous zoledronic acid on bone remodelling and structure: Are different effects on osteoblast activity to other oral bisphosphonates responsible? *J Bone Miner Res*. 2007 Nov 6; [Epub ahead of print] [Info]

Kearns AE, Khosla S, Kostenuik P. RANKL and OPG regulation of bone remodeling in health and disease. *Endocr Rev*. 2007 Dec 5; [Epub ahead of print]

Mitka M. Study probes best choice of drug to reduce phosphate in patients on dialysis. *JAMA*. 2007 Nov 7;298(17):1995-6. [Info]

Rizzoli R, Boonen S, Brandi ML, Burlet N, Delmas P, Reginster JY. The role of calcium and vitamin D in the management of osteoporosis. *Bone*. 2007 Oct 22; [Epub ahead of print] [Abstract]

Other Studies of Potential Interest

Grundberg E, Lau EM, Lorentzson M, Karlsson M, Holmberg A, Groop L, Mellström D, Orwoll E, Mallmin H, Ohlsson C, Ljunggren O, Akesson K. Large-scale association study between two

coding LRP5 gene polymorphisms and bone phenotypes and fractures in men. *Osteoporos Int*. 2007 Nov 17; [Epub ahead of print] [Abstract]

Lamour V, Detry C, Sanchez C, Henrotin Y, Castronovo V, Bellahcène A. Runx2- and histone deacetylase 3-mediated repression is relieved in differentiating human osteoblast cells to allow high bone sialoprotein expression. *J Biol Chem*. 2007 Dec 14;282(50):36240-9. [Abstract] [Full Text]

Li X, Liu H, Qin L, Tamasi J, Bergenstock M, Shapses S, Feyen JH, Notterman DA, Partridge NC. Determination of dual effects of parathyroid hormone on skeletal gene expression in vivo by microarray and network analysis. *J Biol Chem*. 2007 Nov 9;282(45):33086-97. [Abstract] [Full Text]

Maiti A, Hait NC, Beckman MJ. Extracellular calcium sensing receptor activation induces vitamin D receptor levels in proximal kidney HK-2G cells by a mechanism that requires phosphorylation of p38alpha MAPK. *J Biol Chem*. 2007 Nov 1; [Epub ahead of print]

Patra D, Xing X, Davies S, Bryan J, Franz C, Hunziker EB, Sandell LJ. Site-1 protease is essential for endochondral bone formation in mice. *J Cell Biol*. 2007 Nov 19;179(4):687-700. [Abstract] [Full Text]

Peng J, Bencsik M, Louie A, Lu W, Millard S, Nguyen P, Burghardt A, Majumdar S, Wronski TJ, Halloran B, Conklin BR, Nissenson RA. Conditional expression of a Gi-coupled receptor in osteoblasts results in trabecular osteopenia. *Endocrinology*. 2007 Nov 29; [Epub ahead of print]

Ulsamer A, Ortuño MJ, Ruiz S, Susperregui AR, Osses N, Rosa JL, Ventura F. BMP-2 induces osterix expression through upregulation of DLX5 and its phosphorylation by p38. *J Biol Chem*. 2007 Dec 3; [Epub ahead of print]

Viguet-Carrin S, Farlay D, Bala Y, Munoz F, Bouxsein ML, Delmas PD. An in vitro model to test the contribution of advanced glycation end products to bone biomechanical properties. *Bone*. 2007 Sep 19; [Epub ahead of print] [Abstract]

Yamada C, Yamada Y, Tsukiyama K, Yamada K, Udagawa N, Takahashi N, Tanaka K, Drucker DJ, Seino Y, Inagaki N. The murine Glp1r is essential for control of bone resorption. *Endocrinology*. 2007 Nov 26; [Epub ahead of print]

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. Dr. Strewler reports that no conflict of interest exists.