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NOT TO BE MISSED

Clinical and Basic Research Papers – September 2007 Selections

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

Bone Modeling and Remodeling

Nakamura T, Imai Y, Matsumoto T, Sato S, Takeuchi K, Igarashi K, Harada Y, Azuma Y, Krust A, Yamamoto Y, Nishina H, Takeda S, Takayanagi H, Metzger D, Kanno J, Takaoka K, Martin TJ, Chambon P, Kato S. Estrogen prevents bone loss via estrogen receptor alpha and induction of Fas ligand in osteoclasts. *Cell*. 2007 Sep 7;130(5):811-23. [Abstract]

> *Despite the importance of estrogen for bone, the mechanism of estrogen's protection against bone loss remains uncertain. This important study finds that when the estrogen receptor-α is removed from osteoclasts, trabecular bone loss occurs in female but not male mice, but further bone loss post-OVX is prevented, even though the expected OVX-induced cytokine surge occurs. Estrogen protects against bone loss by cell-autonomously decreasing the lifespan of osteoclasts through effects on Fas ligand. Mice were followed for only two weeks post-OVX, leaving open the possibility that cytokines influence osteoclast function further out. The paper is discussed in a BoneKEy Commentary.* —GJS

Sato S, Hanada R, Kimura A, Abe T, Matsumoto T, Iwasaki M, Inose H, Ida T, Mieda M, Takeuchi Y, Fukumoto S, Fujita T, Kato S, Kangawa K, Kojima M, Shinomiya K, Takeda S. Central control of bone remodeling by neuromedin U. *Nat Med*. 2007 Oct;13(10):1234-40. [Abstract]

> *Neuromedin U (NMU) is an anorexigenic neuropeptide that acts independently of leptin. NMU null mice not only have increased trabecular bone volume fraction, similar to leptin-deficient mice, but also increased cortical thickness, and this effect predominates in males. Osteoblast proliferation and BFR is increased in these mice. Central administration of NMU decreased fat mass and trabecular bone volume in NMU null mice and to a lesser extent in leptin null mice, indicating that NMU regulates bone mass centrally and independently (in fact downstream) of leptin. Interestingly, central administration of leptin increased bone formation and bone volume in NMU null mice, contrary to its effects in wild-type mice. Further experiments indeed showed that NMU may mediate the negative effects of leptin through the molecular clock genes*. —SF

Yeo H, Beck LH, Thompson SR, Farach-Carson MC, McDonald JM, Clemens TL, Zayzafoon M. Conditional dysruption of calcineurin B1 in osteoblasts increases bone formation and reduces bone resorption. *J Biol Chem*. 2007 Sep 19; [Epub ahead of print]

> *Inhibition of calcineurin (Cn) increases osteoblast and bone mass. Mice lacking Cnb1 (Cn regulatory subunit) in osteoblasts (Cnb1OB) have increases in bone mass, mineral apposition rate (67%), bone volume (32%), trabecular thickness (29%) and osteoblast numbers (68%), and a 40% decrease in osteoclast numbers. Osteoblasts missing Cnb1 differentiated and mineralized rapidly. Deletion of Cnb1 increased expression of*

osteoprotegerin and decreased expression of RANKL. Co-culturing Cnb1-deficient osteoblasts with wild type osteoclasts failed to support osteoclast differentiation. Inhibition of Cnb1 in osteoblasts increases bone mass by increasing osteoblast differentiation and decreasing osteoclastogenesis. —ES

Genetics

Kiel DP, Demissie S, Dupuis J, Lunetta KL, Murabito JM, Karasik D. Genome-wide association with bone mass and geometry in the Framingham Heart Study. *BMC Med Genet*. 2007 Sep 19;8 Suppl 1:S14. [Abstract]

The first 100K genome-wide association study of bone mass has been published. In up to 1141 phenotyped persons from the Framingham cohort, heritability estimates for all bone phenotypes ranged from 30–66%. Of the 40 top SNPs with the greatest numbers of significantly associated BMD traits (including femoral neck, trochanter, and lumbar spine), one-half to two-thirds were in or near genes that have not previously been studied for osteoporosis. Pleiotropic associations between BMD and bone geometric traits were uncommon, suggesting that BMD and geometric traits are governed by distinct gene variants. The study will need replication with 500K markers. —GJS

Treatment and Drug Effects

Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 2007 Sep 10;167(16):1730-7. [Abstract]

In 18 randomized controlled trials (n = 57,311), 4777 deaths occurred during a trial size-adjusted mean of 5.7 years. Daily doses of vitamin D varied from 300 to 2000 IU giving a mean daily dose of 528 IU. The relative risk for mortality was 0.93 (95% confidence interval, 0.87-0.99). There was neither heterogeneity nor publication bias. Intake of ordinary doses of vitamin D supplements seems to be associated with decreases in total mortality rates. —ES

Lyles KW, Colón-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, Hyldstrup L, Recknor C, Nordsletten L, Moore KA, Lavecchia C, Zhang J, Mesenbrink P, Hodgson PK, Abrams K, Orloff JJ, Horowitz Z, Eriksen EF, Boonen S; the HORIZON Recurrent Fracture Trial. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med*. 2007 Sep 26; [Epub ahead of print]

Here comes the second large RCT of annual injection of zoledronate vs placebo on fracture prevention, only this time patients were included within 3 months after a hip fracture. Significant reduction of clinical vertebral and non-vertebral fractures was demonstrated, although the reduction of hip fracture risk did not reach statistical significance. Most importantly, this study shows for the first time a reduction of overall mortality in patients treated with a bisphosphonate, hence providing a proof-of-concept that osteoporosis treatment in high risk patients can spare lives. A word of caution: the number of patients followed drops sharply beyond one year because the study was stopped early at the time of occurrence of about 200 new fractures, and not because of a compliance problem. —SF

Reid IR, Bolland MJ, Grey AB. Is bisphosphonate-associated osteonecrosis of the jaw caused by soft tissue toxicity? *Bone*. 2007 Sep;41(3):318-20. [Abstract]

A really interesting perspective that reminds us of some previously published papers indicating a possible toxicity of bisphosphonates on epithelial cells, and that speculates on whether this could participate in the pathophysiology of ONJ. —SF

Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet*. 2007 Aug 25;370(9588):657-66. [Abstract]

In 17 trials, n = 52,625, treatment was associated with a 12% risk reduction in all fractures (risk ratio 0.88, 95% CI 0.83-0.95; p=0.0004). In trials that reported bone-mineral density as an outcome (23 trials, n=41,419), treatment was associated with a reduced rate of bone loss of 0.54% (0.35-0.73; p<0.0001) at the hip and 1.19% (0.76-1.61%; p<0.0001) in the spine. The fracture risk reduction was greater (24%) in trials with high compliance (p<0.0001). The treatment effect was better with calcium doses of 1200 mg or more than with doses less than 1200 mg (0.80 vs 0.94; p=0.006), and with vitamin D doses of 800 IU or more than with doses less than 800 IU (0.84 vs 0.87; p=0.03). Evidence supports the use of calcium alone or in combination with vitamin D in people aged 50 years or older. For best therapeutic effect, the authors recommend minimum doses of 1200 mg of calcium, and 800 IU of vitamin D (for combined calcium plus vitamin D supplementation). —ES

Reviews, Perspectives and Editorials

Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. *Osteoporos Int*. 2007 Oct;18(10):1319-28. [Abstract]

Lekkerkerker F, Kanis JA, Alsayed N, Bouvenot G, Burlet N, Cahall D, Chines A, Delmas P, Dreiser RL, Ethgen D, Hughes N, Kaufman JM, Korte S, Kreutz G, Laslop A, Mitlak B, Rabenda V, Rizzoli R, Santora A, Schimmer R, Tsouderos Y, Viethel P, Reginster JY; Group for the Respect of Ethics and Excellence in Science (GREES). Adherence to treatment of osteoporosis: a need for study. *Osteoporos Int*. 2007 Oct;18(10):1311-7. [Abstract]

Silverman SL, Cummings SR, Watts NB; For the Consensus Panel of the ASBMR, ISCD and NOF. Recommendations for the clinical evaluation of agents for treatment of osteoporosis: consensus of an expert panel representing the American Society for Bone and Mineral Research (ASBMR), the International Society for Clinical Densitometry (ISCD), and the National Osteoporosis Foundation (NOF). *J Bone Miner Res*. 2007 Sep 24; [Epub ahead of print] [Abstract]

Other Studies of Potential Interest

Bi Y, Ehirchiou D, Kilts TM, Inkson CA, Embree MC, Sonoyama W, Li L, Leet AI, Seo BM, Zhang L, Shi S, Young MF. Identification of tendon stem/progenitor cells and the role of the extracellular matrix in their niche. *Nat Med*. 2007 Oct;13(10):1219-27. [Abstract]

Darling EM, Topel M, Zauscher S, Vail TP, Guilak F. Viscoelastic properties of human mesenchymally-derived stem cells and primary osteoblasts, chondrocytes, and adipocytes. *J Biomech*. 2007 Sep 5; [Epub ahead of print] [Abstract]

De Luca A, Carotenuto A, Rachiglio A, Gallo M, Maiello MR, Aldinucci D, Pinto A, Normanno N. The role of the EGFR signaling in tumor microenvironment. *J Cell Physiol*. 2007 Sep 25; [Epub ahead of print] [Abstract]

Dixon N, Pali T, Kee TP, Ball S, Harrison MA, Findlay JB, Nyman J, Väänänen K, Finbow ME, Marsh D. Interaction of spin-labelled inhibitors of the vacuolar H+-ATPase with the transmembrane Vo-sector. *Biophys J*. 2007 Sep 14; [Epub ahead of print] [Abstract]

Fox J, Miller MA, Newman MK, Recker RR, Turner CH, Smith SY. Effects of daily treatment with parathyroid hormone 1-84 for 16 months on density, architecture and biomechanical properties of cortical bone in adult ovariectomized rhesus monkeys. *Bone*. 2007 Sep;41(3):321-30. [Abstract]

Gazzerro E, Smerdel-Ramoya A, Zanotti S, Stadmeyer L, Durant D, Economides AN, Canalis E. Conditional deletion of gremlin causes a transient increase in bone formation and bone mass. *J Biol Chem*. 2007 Oct 26;282(43):31549-57. [Abstract] [Full Text]

Gil-Henn H, Destaing O, Sims NA, Aoki K, Alles N, Neff L, Sanjay A, Bruzzaniti A, De Camilli P, Baron R, Schlessinger J. Defective microtubule-dependent podosome organization in osteoclasts leads to increased bone density in Pyk2(-/-) mice. *J Cell Biol*. 2007 Sep 10;178(6):1053-64. [Abstract] [Full Text]

Héroux M, Hogue M, Lemieux S, Bouvier M. Functional calcitonin gene-related peptide receptors are formed by the asymmetric assembly of a calcitonin receptor-like receptor homo-oligomer and a monomer of receptor activity-modifying protein-1. *J Biol Chem*. 2007 Oct 26;282(43):31610-20. [Abstract] [Full Text]

Lambert C, Oury C, Dejardin E, Chariot A, Piette J, Malaise M, Merville MP, Franchimont N. Further insights in the mechanisms of interleukin-1beta stimulation of osteoprotegerin in osteoblast-like cells. *J Bone Miner Res*. 2007 Sep;22(9):1350-61. [Abstract]

Lewiecki EM, Miller PD, McClung MR, Cohen SB, Bolognese MA, Liu Y, Wang A, Siddhanti S, Fitzpatrick LA; for the AMG 162 Bone Loss Study Group. Two-year treatment with denosumab (AMG 162) in a randomized phase 2 study of postmenopausal women with low bone mineral density. *J Bone Miner Res*. 2007 Aug 20; [Epub ahead of print] [Abstract]

Mozar A, Haren N, Chasseraud M, Louvet L, Mazière C, Wattel A, Mentaverri R, Morlière P, Kamel S, Brazier M, Mazière JC, Massy ZA. High extracellular inorganic phosphate concentration inhibits RANK-RANKL signaling in osteoclast-like cells. *J Cell Physiol*. 2007 Sep 25; [Epub ahead of print] [Abstract]

Ogata N, Kawaguchi H, Chung UI, Roth SI, Segre GV. Continuous activation of G alpha Q in osteoblasts results in osteopenia through impaired osteoblast differentiation. *J Biol Chem*. 2007 Sep 5; [Epub ahead of print]

Pang M, Martinez AF, Fernandez I, Balkan W, Troen BR. AP-1 stimulates the cathepsin K promoter in RAW 264.7 cells. *Gene*. 2007 Nov 15;403(1-2):151-8. [Abstract]

Wang B, Bisello A, Yang Y, Romero GG, Friedman PA. NHERF1 regulates parathyroid hormone receptor membrane retention without affecting recycling. *J Biol Chem*. 2007 Sep 19; [Epub ahead of print]

Wang Y, McNamara LM, Schaffler MB, Weinbaum S. A model for the role of integrins in flow induced mechanotransduction in osteocytes. *Proc Natl Acad Sci U S A*. 2007 Oct 2;104(40):15941-6. [Abstract] [Full Text]

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Wu S, Flint JK, Rezvani G, De Luca F. Nuclear factor-kappa B p65 facilitates longitudinal bone growth by inducing growth plate chondrocyte proliferation and differentiation and by preventing apoptosis. *J Biol Chem*. 2007 Sep 19; [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.