BoneKEy-Osteovision. 2007 September;4(9):231-235
http://www.bonekey-ibms.org/cgi/content/full/ibmske;4/9/231
DOI: 10.1138/20070270

NOT TO BE MISSED

Clinical and Basic Research Papers – August 2007 Selections

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

Bone Modeling and Remodeling

Cui W, Cuartas E, Ke J, Zhang Q, Einarsson HB, Sedgwick JD, Li J, Vignery A. CD200 and its receptor, CD200R, modulate bone mass via the differentiation of osteoclasts. *Proc Natl Acad Sci U S A*. 2007 Sep 4;104(36):14436-41. [Abstract] [Full Text]

> *The development of multinucleated osteoclasts occurs by fusion of macrophages under the action of M-CSF and RANKL. This paper demonstrates that RANKL induces expression of CD200 on macrophage surface. In turn, RANKL-stimulated osteoclastogenesis and signaling is diminished in CD200 KO mice. Moreover, osteoclast surfaces are decreased in these mice, BMD is increased, and trabecular bone volume is also increased, particularly as they age. However, the bone phenotypes remain moderate, indicating either that osteoclast fusion is not essential for bone remodeling and/or that redundant fusion mechanisms do exist.* —SF

Liu H, Fergusson MM, Castilho RM, Liu J, Cao L, Chen J, Malide D, Rovira II, Schimel D, Kuo CJ, Gutkind JS, Hwang PM, Finkel T. Augmented Wnt signaling in a mammalian model of accelerated aging. *Science*. 2007 Aug 10;317(5839):803-6. [Abstract] [Full Text]

> *The putative aging gene klotho binds and inhibits the actions of Wnts. Klotho mice have markedly increased Wnt signaling in skin and bone and increased trabecular bone mass. Adeno-klotho blocks signaling of a Wnt transgene in skin. Klotho mice have reduced stem cell populations in skin, bone marrow and other tissues; moreover, Wnt exposure induces the DNA damage repair pathway associated with cell senescence and cell senescence is blocked by klotho. The conclusion is that klotho increases longevity by blocking Wnt-induced senescence. The skin phenotype of klotho mice is partially rescued by removal of vitamin D; the relative importance of Wnt signaling and FGF23 signaling in klotho mice remains to be clarified.* —GJS

Nissen-Meyer LS, Jemtland R, Gautvik VT, Pedersen ME, Paro R, Fortunati D, Pierroz DD, Stadelmann VA, Reppe S, Reinholt FP, Del Fattore A, Rucci N, Teti A, Ferrari S, Gautvik KM. Osteopenia, decreased bone formation and impaired osteoblast development in Sox4 heterozygous mice. *J Cell Sci*. 2007 Aug 15;120(Pt 16):2785-95. [Abstract]

> *The triad Sox 5,6,and 9 are master genes for chondrocytes. Sox 4 is expressed in cartilage and bone, and deletion of the gene is embryonic lethal. Here the phenotype of bone in heterozygotes is described. Development is normal but an intrinsic osteoblast defect produces cortical and trabecular osteopenia. Proliferation, differentiation and mineralization of cultured osteoblasts is impaired. Sox 4 seems to act upstream of Osterix and independently of Runx2.* —GJS

BoneKEy-Osteovision. 2007 September;4(9):231-235
http://www.bonekey-ibms.org/cgi/content/full/ibmske;4/9/231
DOI: 10.1138/20070270

Epidemiology

Araujo AB, Esche GR, Kupelian V, O'donnell AB, Travison TG, Williams RE, Clark RV, McKinlay JB. Prevalence of symptomatic androgen deficiency in men. *J Clin Endocrinol Metab*. 2007 Aug 14; [Epub ahead of print]

> *Androgen deficiency is difficult to define. In 1,475 Black, Hispanic, and White Boston men between the ages of 30-79 years, 24% had total testosterone <300 ng/dL and 11% had free testosterone <5 ng/dL. Prevalence of symptoms were: low libido (12%), erectile dysfunction (16%), osteoporosis/fracture (1%), and two or more non-specific symptoms (20%). About 50% of men with low testosterone were asymptomatic. Prevalence of symptomatic androgen deficiency was 5.6%*. —ES

Treatment and Drug Effects

Bone HG, Kiel DP, Lindsay RS, Lewiecki EM, Bolognese MA, Leary ET, Lowe W, McClung MR. Effects of atorvastatin on bone in postmenopausal women with dyslipidemia: a double-blind, placebo-controlled, dose-ranging trial. *J Clin Endocrinol Metab*. 2007 Aug 28; [Epub ahead of print]

> *Remember a Science paper (Mundy G, et al. Science. 1999 Dec 3;286(5446):1946-9) showing that statins stimulate bone formation via BMP2, and numerous observational studies then reporting controversial results about the association of the use of statins with a decreased risk of fracture? These authors had the courage to perform a multicenter, RCT comparing atorvastatin (10 to 80 mg/d) in postmenopausal women with mildly elevated cholesterol levels but without osteoporosis. After one year, there were no effects of the statin on BMD nor on biochemical markers of bone turnover*. —SF

Huber C, Collishaw S, Mosley JR, Reeve J, Noble BS. Selective estrogen receptor modulator inhibits osteocyte apoptosis during abrupt estrogen withdrawal: implications for bone quality maintenance. *Calcif Tissue Int*. 2007 Aug;81(2):139-44. [Abstract]

> *In 24 juvenile female rats, the percentage of apoptotic osteocytes increased with OVX in the radius and ulna. Treatment with 17ß-estradiol or LY 117018 prevented these increases similarly*. —ES

Karam R, Camm J, McClung M. Yearly zoledronic acid in postmenopausal osteoporosis. *N Engl J Med*. 2007 Aug 16;357(7):712-3; author reply 714-5.

> *The HORIZON trial comparing zoledronate with PBO for postmenopausal osteoporosis reported anti-fracture efficacy but also a significantly increased risk of severe adverse events associated with atrial fibrillation (AF) in patients receiving zoledronate. Others reported similar results from the older FIT studies with alendronate. Is this a new class effect of bisphosphonates? In this letter, Karam and colleagues re-analyzed the incidence of AF, cerebrovascular accidents and cardiovascular death recorded in RCTs with risedronate. Including more than 15,000 patients in total, they found no increase in AF severe complications with risedronate, but rather a significant decrease of deadly cerebrovascular accidents. This result casts even more doubt on the causal relationship between bisphosphonate use and severe AF*. —SF

Morin S, Rahme E, Behlouli H, Tenenhouse A, Goltzman D, Pilote L. Effectiveness of antiresorptive agents in the prevention of recurrent hip fractures. *Osteoporos Int*. 2007 Jul 19; [Epub ahead of print] [Abstract]

In 20,644 patients, 6,779 filled a prescription for antiresorptive agents. There were 992 recurrent hip fractures. Patients exposed to antiresorptives had a 26% reduction in the rate of recurrent fractures (HR 0.74; 0.64-0.86) compared to patients who were not. Antiresorptive therapy reduces the risk of recurrent hip fractures in elderly patients. —ES

Vestergaard P, Jorgensen NR, Schwarz P, Mosekilde L. Effects of treatment with fluoride on bone mineral density and fracture risk – a meta-analysis. *Osteoporos Int*. 2007 Aug 15; [Epub ahead of print] [Abstract]

Fluoride is back. A daily dose of </=20 mg fluoride equivalents was associated with a reduction in vertebral (OR = 0.3, 95% CI: 0.1-0.9) and non-vertebral (OR = 0.5, 95% CI: 0.3-0.8) fracture risk. A daily dose >20 mg fluoride had no benefit in risk reduction. —ES

Wolf M, Shah A, Gutierrez O, Ankers E, Monroy M, Tamez H, Steele D, Chang Y, Camargo CA Jr, Tonelli M, Thadhani R. Vitamin D levels and early mortality among incident hemodialysis patients. *Kidney Int*. 2007 Aug 8; [Epub ahead of print] [Abstract]

Many patients are deficient in 25OHD, 1,25(OH)2D or both at the institution of hemodialysis. In a nested case-control study of 1000 patients, all-cause and cardiovascular 90-day mortality were strongly associated with vitamin D deficiency. Regardless of baseline 25OHD levels, active vitamin D therapy was associated with decreased mortality. The results accord with earlier studies showing an association of vitamin D therapy and survival among patients initiating hemodialysis. —GJS

Reviews, Perspectives and Editorials

Bianchi ML. Osteoporosis in children and adolescents. *Bone*. 2007 Oct;41(4):486-95. [Abstract]

Canalis E, Giustina A, Bilezikian JP. Mechanisms of anabolic therapies for osteoporosis. *N Engl J Med*. 2007 Aug 30;357(9):905-16. [Info]

Devuyst O, Pirson Y. Genetics of hypercalciuric stone forming diseases. *Kidney Int*. 2007 Aug 8; [Epub ahead of print] [Abstract]

Helms JA, Amasha RR, Leucht P. Bone voyage: An expedition into the molecular and cellular parameters affecting bone graft fate. *Bone*. 2007 Oct;41(4):479-85. [Abstract]

Kado DM, Prenovost K, Crandall C. Narrative review: hyperkyphosis in older persons. *Ann Intern Med*. 2007 Sep 4;147(5):330-8. [Abstract]

Sitges-Serra A, Bergenfelz A. Clinical update: sporadic primary hyperparathyroidism. *Lancet*. 2007 Aug 11;370(9586):468-70. [Info]

Other Studies of Potential Interest

Clarkin CE, Emery RJ, Pitsillides AA, Wheeler-Jones CP. Evaluation of VEGF-mediated signaling in primary human cells reveals a paracrine action for VEGF in osteoblast-mediated crosstalk to endothelial cells. *J Cell Physiol*. 2007 Aug 8; [Epub ahead of print] [Abstract]

Digirolamo DJ, Mukherjee A, Fulzele K, Gan Y, Cao X, Frank SJ, Clemens TL. Mode of growth hormone action in osteoblasts. *J Biol Chem*. 2007 Aug 13; [Epub ahead of print]

Hirbe AC, Rubin J, Uluçkan O, Morgan EA, Eagleton MC, Prior JL, Piwnica-Worms D, Weilbaecher KN. Disruption of CXCR4 enhances osteoclastogenesis and tumor growth in bone. *Proc Natl Acad Sci U S A*. 2007 Aug 28;104(35):14062-7. [Abstract] [Full Text]

Horsch K, de Wet H, Schuurmans MM, Allie-Reid F, Cato AC, Cunningham J, Burrin JM, Hough FS, Hulley PA. MKP-1/DUSP1 mediates glucocorticoid inhibition of osteoblast proliferation. *Mol Endocrinol*. 2007 Aug 30; [Epub ahead of print]

Ichikawa S, Imel EA, Kreiter ML, Yu X, Mackenzie DS, Sorenson AH, Goetz R, Mohammadi M, White KE, Econs MJ. A homozygous missense mutation in human KLOTHO causes severe tumoral calcinosis. *J Clin Invest*. 2007 Sep 4;117(9):2684-91.

Li X, Liu H, Qin L, Tamasi J, Bergenstock M, Shapses S, Feyen JH, Notterman DA, Partridge NC. Determination of parathyroid hormone's dual effects on skeletal gene expression in vivo by microarray and network analysis. *J Biol Chem*. 2007 Aug 9; [Epub ahead of print]

Li X, Qin L, Bergenstock M, Bevelock LM, Novack DV, Partridge NC. Parathyroid hormone stimulates osteoblastic expression of MCP-1 to recruit and increase the fusion of pre/osteoclasts. *J Biol Chem*. 2007 Aug 9; [Epub ahead of print]

McClung M, Recker R, Miller P, Fiske D, Minkoff J, Kriegman A, Zhou W, Adera M, Davis J. Intravenous zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. *Bone*. 2007 Jul;41(1):122-8. [Abstract]

Melton LJ, Riggs BL, Keaveny TM, Achenbach SJ, Hoffmann PF, Camp JJ, Rouleau PA, Bouxsein ML, Amin S, Atkinson EJ, Robb RA, Khosla S. Structural determinants of vertebral fracture risk. *J Bone Miner Res*. 2007 Aug 6; [Epub ahead of print] [Abstract]

Nakamura Y, Weidinger G, Liang JO, Aquilina-Beck A, Tamai K, Moon RT, Warman ML. The CCN family member Wisp3, mutant in progressive pseudorheumatoid dysplasia, modulates BMP and Wnt signaling. *J Clin Invest*. 2007 Sep 6; [Epub ahead of print]

Oz OK, Hajibeigi A, Howard K, Cummins CL, van Abel M, Bindels RJ, Word RA, Kuro-O M, Pak CY, Zerwekh JE. Aromatase deficiency causes altered expression of molecules critical for calcium reabsorption in the kidneys of female mice(A). *J Bone Miner Res*. 2007 Aug 20; [Epub ahead of print] [Abstract]

Richert L, Chevalley T, Manen D, Bonjour JP, Rizzoli R, Ferrari S. Bone mass in prepubertal boys is associated with a Gln223Arg amino acid substitution in the leptin receptor. *J Clin Endocrinol Metab*. 2007 Sep 4; [Epub ahead of print]

Schousboe JT, Taylor BC, Fink HA, Kane RL, Cummings SR, Orwoll ES, Melton LJ 3rd, Bauer DC, Ensrud KE. Cost-effectiveness of bone densitometry followed by treatment of osteoporosis in older men. *JAMA*. 2007 Aug 8;298(6):629-37. [Abstract]

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]

Vitovski S, Phillips JS, Sayers JR, Croucher PI. Investigating the interaction between osteoprotegerin and rankl or trail: Evidence for a pivotal role for osteoprotegerin in regulating two distinct pathways. *J Biol Chem*. 2007 Aug 15; [Epub ahead of print]

BoneKEy-Osteovision. 2007 September;4(9):231-235
http://www.bonekey-ibms.org/cgi/content/full/ibmske;4/9/231
DOI: 10.1138/20070270

Walkley CR, Shea JM, Sims NA, Purton LE, Orkin SH. Rb regulates interactions between hematopoietic stem cells and their bone marrow microenvironment. *Cell*. 2007 Jun 15;129(6):1081-95. [Abstract]

Windahl SH, Lagerquist MK, Andersson N, Jochems C, Kallkopf A, Håkansson C, Inzunza J, Gustafsson JA, van der Saag PT, Carlsten H, Pettersson K, Ohlsson C. Identification of target cells for the genomic effects of estrogens in bone. *Endocrinology*. 2007 Aug 30; [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.