BoneKEy-Osteovision. 2007 March;4(3):88-93
http://www.bonekey-ibms.org/cgi/content/full/ibmske;4/3/88
DOI: 10.1138/20070252

NOT TO BE MISSED

Clinical and Basic Research Papers – February 2007 Selections

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

Bone Modeling and Remodeling

Bassett JH, O'shea PJ, Sriskantharajah S, Rabier B, Boyde A, Howell PG, Weiss RE, Roux JP, Malaval L, Clement-Lacroix P, Samarut J, Chassande O, Williams GR. Thyroid hormone excess rather than TSH deficiency induces osteoporosis in hyperthyroidism. *Mol Endocrinol*. 2007 Feb 27; [Epub ahead of print]

> *The skeletal phenotypes of removal of two thyroid hormone receptors, TRα(0/0) and TRβ(-/-), are reported here. TRα(0/0) mice have normal thyroid hormone and TSH concentrations but display delayed ossification and osteosclerosis in adults. TRβ(-/-) mice, by contrast, have high levels of thyroid hormone and TSH (peripheral resistance to thyroid hormone). They have accelerated ossification and display osteopenia in adults that is attributable to increased osteoclastic bone resorption. Thus TRα is the important thyroid hormone receptor in bone. Bone loss in hyperthyroidism is mediated by TRα and occurs in mice with markedly elevated TSH concentrations. This suggests, by contrast with the interpretation of the phenotype of the TSH(-/-) mouse, that thyroid hormone, not TSH suppression, is predominantly responsible for increased bone resorption and bone loss in hyperthyroidism.* —GJS

Liu X, Bruxvoort KJ, Zylstra CR, Liu J, Cichowski R, Faugere MC, Bouxsein ML, Wan C, Williams BO, Clemens TL. Lifelong accumulation of bone in mice lacking Pten in osteoblasts. *Proc Natl Acad Sci U S A*. 2007 Feb 13;104(7):2259-64. [Abstract] [Full Text]

> *The phosphatidylinositol 3-kinase (PI3K) is downstream of growth factor receptors in a pathway that increases cell proliferation and prevents apoptosis. PI3K is negatively regulated by PTEN. PTEN deletions are common in cancers, indicating that removal of its inhibitory effect promotes cancer cell growth and survival. Liu et al. removed the PTEN gene from osteoblasts to produce a phenotype of spectacularly exuberant osteoblast activity, with massive overgrowth of cortical and trabecular bone. Deletion of PTEN markedly reduces apoptosis of osteoblasts and also increases their differentiation and proliferation. What pathways downstream of PI3K are responsible for increased osteoblast survival and function remains to be determined.* —GJS

McGee ME, Miller DL, Auger J, Black HL, Donahue SW. Black bear femoral geometry and cortical porosity are not adversely affected by ageing despite annual periods of disuse (hibernation). *J Anat*. 2007 Feb;210(2):160-9. [Abstract]

> *Cross-sectional geometric properties increase with age, but porosity and resorption cavity density do not change in skeletally immature male and female bears. Porosity showed minimal variations between quadrants and radial positions. Black bears possess a biological mechanism to prevent disuse osteoporosis.* —ES

BoneKEy-Osteovision. 2007 March;4(3):88-93
http://www.bonekey-ibms.org/cgi/content/full/ibmske;4/3/88
DOI: 10.1138/20070252

Epidemiology

Hillier TA, Stone KL, Bauer DC, Rizzo JH, Pedula KL, Cauley JA, Ensrud KE, Hochberg MC, Cummings SR. Evaluating the value of repeat bone mineral density measurement and prediction of fractures in older women: the study of osteoporotic fractures. *Arch Intern Med*. 2007 Jan 22;167(2):155-60. [Abstract]

> *In 4124 women, during 5 years following a repeat BMD measure taken approximately 8 years after the initial measurement, fracture risk was no better predicted by the repeat measurement. Areas under the receiver operating characteristic curves revealed no differences in discriminating fractures using models with initial BMD, repeat BMD, or initial BMD plus change in BMD. Repeating a measurement of BMD provides little additional value over the initial BMD measurement for predicting fractures.* —ES

Kanis JA, Oden A, Johnell O, Johansson H, De Laet C, Brown J, Burckhardt P, Cooper C, Christiansen C, Cummings S, Eisman JA, Fujiwara S, Gluer C, Goltzman D, Hans D, Krieg MA, La Croix A, McCloskey E, Mellstrom D, Melton LJ 3rd, Pols H, Reeve J, Sanders K, Schott AM, Silman A, Torgerson D, van Staa T, Watts NB, Yoshimura N. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. *Osteoporos Int*. 2007 Feb 24; [Epub ahead of print] [Abstract]

> *Fracture probability increases as BMD decreases, and also in the presence of distinct risk factors. Now the authors have calculated the gradient of risk (i.e. RR/SD) for BMD and for a risk factor's score, and validated this combined approach in a large sample of international cohorts. The risk score performed pretty well, although not as good as BMD alone, but the gradients of risk were not multiplicative. In particular, adding risk factors to BMD in 70+ women barely improved the prediction of BMD alone. Now that the exercise appears completed, it remains to be seen how it will be possible to integrate it into clinical practice.* —SF

Genetics

Cabral WA, Chang W, Barnes AM, Weis M, Scott MA, Leikin S, Makareeva E, Kuznetsova NV, Rosenbaum KN, Tifft CJ, Bulas DI, Kozma C, Smith PA, Eyre DR, Marini JC. Prolyl 3-hydroxylase 1 deficiency causes a recessive metabolic bone disorder resembling lethal/severe osteogenesis imperfecta. *Nat Genet*. 2007 Mar;39(3):359-65. [Abstract]

> *Hydroxylation of a specific prolyl residue in collagen fibrils is critical in order to achieve the proper quality of bone matrix. Recently, mutations in CRTAP, a cartilage-associated protein that is a member of the collagen hydroxylation complex of molecules, have been associated with the clinical spectrum of recessive osteogenesis imperfecta (OI), including the type II and VII forms (see a recent BoneKEy Commentary by Stephen M. Krane). This paper now describes mutations in LEPRE1, coding for prolyl 3-hydroxylase 1 (the actual collagen hydroxylation enzyme), as a cause of recessive forms of OI.* —SF

Mani A, Radhakrishnan J, Wang H, Mani A, Mani MA, Nelson-Williams C, Carew KS, Mane S, Najmabadi H, Wu D, Lifton RP. LRP6 mutation in a family with early coronary disease and metabolic risk factors. *Science*. 2007 Mar 2;315(5816):1278-82. [Abstract] [Full Text]

> *Deficiency of LRP6, a homologue of the LDL receptor-related protein 5 gene (LRP5), has a skeletal phenotype in mice, and fracture risk is increased among carriers of LRP6 as well as LRP5 polymorphisms. This study now reports a large family of Iranian origin with*

an extreme clustering of the metabolic syndrome and coronary artery disease (CAD) of early onset, predominantly in males. Moreover, three men in this family had severe osteoporosis and a hip fracture at an early age. The disease segregated with an autosomal dominant pattern of inheritance. Linkage to chromosome 12p and direct sequencing of LRP6 therein identified a unique LRP6 mutation (R611C, missense). This finding may provide a molecular basis for the epidemiological association of osteoporosis with CAD. —SF

Pathophysiology

Schauber J, Dorschner RA, Coda AB, Buchau AS, Liu PT, Kiken D, Helfrich YR, Kang S, Elalieh HZ, Steinmeyer A, Zugel U, Bikle DD, Modlin RL, Gallo RL. Injury enhances TLR2 function and antimicrobial peptide expression through a vitamin D-dependent mechanism. *J Clin Invest*. 2007 Mar 1;117(3):803-11. [Abstract] [Full Text]

Vitamin D was recently shown to be necessary for the production of antimicrobial peptides after activation of the innate immune system in macrophages (Liu PT, et al. Science. 2006 Mar 24;311(5768):1770–3). A similar story is now told about the epidermis. Wounding of skin induces a marked increase in Toll-like receptor-2 (TLR2) and in the antimicrobial peptide cathelicidin. Both responses are amplified by 1,25(OH)$_2$D, synthesis of which is triggered by wounding the skin. Functioning of the innate immune system is vitamin D-dependent in both macrophages and the skin. —GJS

Treatment and Drug Effects

Follet H, Li J, Phipps RJ, Hui S, Condon K, Burr DB. Risedronate and alendronate suppress osteocyte apoptosis following cyclic fatigue loading. *Bone*. 2007 Apr;40(4):1172-7. [Abstract]

Fatigue loading induces micro-damage and causes osteocyte apoptosis. The mechanism of action of bisphosphonates in reducing fracture risk remains incompletely understood. The authors demonstrate that risedronate or alendronate suppressed osteocyte apoptosis induced by fatigue loading of the ulna in rats and do so equally effectively and within 3 days. —ES

Reviews, Perspectives and Editorials

Chavassieux P, Seeman E, Delmas PD. Insights into material and structural basis of bone fragility from diseases associated with fractures: how determinants of the biomechanical properties of bone are compromised by disease. *Endocr Rev*. 2007 Feb 23; [Epub ahead of print]

Cramer JA, Gold DT, Silverman SL, Lewiecki EM. A systematic review of persistence and compliance with bisphosphonates for osteoporosis. *Osteoporos Int*. 2007 Feb 17; [Epub ahead of print] [Abstract]

Gronthos S, Zannettino AC. The role of the chemokine CXCL12 in osteoclastogenesis. *Trends Endocrinol Metab*. 2007 Feb 20; [Epub ahead of print] [Abstract]

Hofbauer LC, Brueck CC, Shanahan CM, Schoppet M, Dobnig H. Vascular calcification and osteoporosis-from clinical observation towards molecular understanding. *Osteoporos Int*. 2007 Mar;18(3):251-9. [Abstract]

Xian CJ. Roles of epidermal growth factor family in the regulation of postnatal somatic growth. *Endocr Rev*. 2007 Feb 23; [Epub ahead of print]

Other Studies of Potential Interest

Bhat BM, Allen KM, Liu W, Graham J, Morales A, Anisowicz A, Lam HS, McCauley C, Coleburn V, Cain M, Fortier E, Bhat RA, Bex FJ, Yaworsky PJ. Structure-based mutation analysis shows the importance of LRP5 beta-propeller 1 in modulating Dkk1-mediated inhibition of Wnt signaling. *Gene*. 2007 Apr 15;391(1-2):103-12. [Abstract]

Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. *Kidney Int*. 2007 Mar;71(5):438-41. [Abstract]

Chellaiah MA, Kuppuswamy D, Lasky L, Linder S. Phosphorylation of a WASP-associated signal complex is critical in osteoclast bone resorption. *J Biol Chem*. 2007 Feb 5; [Epub ahead of print]

Chung I, Karpf AR, Muindi JR, Conroy JM, Nowak NJ, Johnson CS, Trump DL. Epigenetic silencing of CYP24 in tumor-derived endothelial cells contributes to selective growth inhibition by calcitriol. *J Biol Chem*. 2007 Mar 23;282(12):8704-14. [Abstract] [Full Text]

Cottrell GS, Padilla B, Pikios S, Roosterman D, Steinhoff M, Grady EF, Bunnett NW. Post-endocytic sorting of calcitonin receptor-like receptor and receptor activity-modifying protein 1. *J Biol Chem*. 2007 Feb 19; [Epub ahead of print]

David V, Martin A, Lafage-Proust MH, Malaval L, Peyroche S, Jones DB, Vico L, Guignandon A. Mechanical loading down regulates PPARgamma in bone marrow stromal cells and favours osteoblastogenesis at the expense of adipogenesis. *Endocrinology*. 2007 Feb 22; [Epub ahead of print]

Ge C, Xiao G, Jiang D, Franceschi RT. Critical role of the extracellular signal-regulated kinase-MAPK pathway in osteoblast differentiation and skeletal development. *J Cell Biol*. 2007 Feb 26;176(5):709-18. [Abstract] [Full Text]

Genetos DC, Kephart CJ, Zhang Y, Yellowley CE, Donahue HJ. Oscillating fluid flow activation of gap junction hemichannels induces atp release from MLO-Y4 osteocytes. *J Cell Physiol*. 2007 Feb 14; [Epub ahead of print] [Abstract]

Gutierrez J, Paredes R, Cruzat F, Hill DA, van Wijnen AJ, Lian JB, Stein GS, Stein JL, Imbalzano AN, Montecino M. Chromatin remodeling by SWI/SNF results in nucleosome mobilization to preferential positions in the rat osteocalcin gene promoter. *J Biol Chem*. 2007 Feb 1; [Epub ahead of print]

Harper KD, Krege JH, Marcus R, Mitlak BH. Osteosarcoma and teriparatide? *J Bone Miner Res*. 2007 Feb;22(2):334. [Info]

Harper RP, Fung E. Resolution of bisphosphonate-associated osteonecrosis of the mandible: possible application for intermittent low-dose parathyroid hormone [rhPTH(1-34)]. *J Oral Maxillofac Surg*. 2007 Mar;65(3):573-80. [Info]

Im HJ, Muddasani P, Natarajan V, Schmid TM, Block JA, David F, van Wijnen AJ, Loeser RF. Basic fibroblast growth factor stimulates matrix metalloproteinase-13 via the molecular cross-talk between the mitogen activated protein kinases and protein kinase c delta pathways in human adult articular chondrocytes. *J Biol Chem*. 2007 Feb 20; [Epub ahead of print]

Jasuja R, Ge G, Voss NG, Lyman-Gingerich J, Branam AM, Pelegri FJ, Greenspan DS. Bone morphogenetic protein 1 prodomain specifically binds and regulates signaling by bone morphogenetic proteins 2 and 4. *J Biol Chem*. 2007 Mar 23;282(12):9053-62. [Abstract] [Full Text]

Javelaud D, Mohammad KS, McKenna CR, Fournier P, Luciani F, Niewolna M, Andre J, Delmas V, Larue L, Guise TA, Mauviel A. Stable overexpression of Smad7 in human melanoma cells impairs bone metastasis. *Cancer Res*. 2007 Mar 1;67(5):2317-24. [Abstract]

Johnson J, Albarani V, Nguyen M, Goldman M, Willems F, Aksoy E. Protein kinase C alpha is involved in IRF-3 activation and type I IFN-beta synthesis. *J Biol Chem*. 2007 Feb 12; [Epub ahead of print]

Keaveny TM, Donley DW, Hoffmann PF, Mitlak BH, Glass EV, San Martin JA. Effects of teriparatide and alendronate on vertebral strength as assessed by finite element modeling of QCT scans in women with osteoporosis. *J Bone Miner Res*. 2007 Jan;22(1):149-57. [Abstract]

Lazarenko OP, Rzonca SO, Hogue WR, Swain FL, Suva LJ, Lecka-Czernik B. Rosiglitazone induces decreases in bone mass and strength that are reminiscent of aged bone. *Endocrinology*. 2007 Mar 1; [Epub ahead of print]

Park M, Yong Y, Choi SW, Kim JH, Lee JE, Kim DW. Constitutive RelA activation mediated by Nkx3.2 controls chondrocyte viability. *Nat Cell Biol*. 2007 Mar;9(3):287-98. [Abstract]

Saita Y, Takagi T, Kitahara K, Usui M, Ezura Y, Nakashime K, Kurosawa H, Ishii S, Noda M. Lack of schnurri-2 expression associates with reduced bone remodeling and osteopenia. *J Biol Chem*. 2007 Feb 20; [Epub ahead of print]

Sapkota G, Alarcon C, Spagnoli FM, Brivanlou AH, Massague J. Balancing BMP signaling through integrated inputs into the Smad1 linker. *Mol Cell*. 2007 Feb 9;25(3):441-54. [Abstract]

Sato A, Hirai T, Imura A, Kita N, Iwano A, Muro S, Nabeshima Y, Suki B, Mishima M. Morphological mechanism of the development of pulmonary emphysema in klotho mice. *Proc Natl Acad Sci U S A*. 2007 Feb 13;104(7):2361-5. [Abstract] [Full Text]

van Donkelaar CC, Janssen XJ, de Jong AM. Distinct developmental changes in the distribution of calcium, phosphorus and sulphur during fetal growth-plate development. *J Anat*. 2007 Feb;210(2):186-94. [Abstract]

Xu K, Zhang Y, Ilalov K, Carlson CS, Febg JQ, Di Cesare PE, Liu CJ. COMP associates with gep and potentiates gep-stimulated chondrocyte proliferation. *J Biol Chem*. 2007 Feb 26; [Epub ahead of print]

Yu JK, Satou Y, Holland ND, Shin-I T, Kohara Y, Satoh N, Bronner-Fraser M, Holland LZ. Axial patterning in cephalochordates and the evolution of the organizer. *Nature*. 2007 Feb 8;445(7128):613-7. [Abstract]

BoneKEy-Osteovision. 2007 March;4(3):88-93
http://www.bonekey-ibms.org/cgi/content/full/ibmske;4/3/88
DOI: 10.1138/20070252

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.