BoneKEy-Osteovision. 2006 July;3(7):1-5
http://www.bonekey-ibms.org/cgi/content/full/ibmske;3/7/1
DOI: 10.1138/20060219

NOT TO BE MISSED

Clinical and Basic Research Papers – June 2006 Selections

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

Bone Modeling and Remodeling

Sawakami K, Robling AG, Ai M, Pitner ND, Liu D, Warden SJ, Li J, Maye P, Rowe DW, Duncan RL, Warman ML, Turner CH. The WNT co-receptor LRP5 is essential for skeletal mechanotransduction, but not for the anabolic bone response to parathyroid hormone treatment. *J Biol Chem*. 2006 Jun 20; [Epub ahead of print]

> *It has been proposed that the Wnt-LRP5 pathway could mediate the effects of mechanical loading. This study now demonstrates that LRP5 KO mice have a markedly decreased bone formation rate (BFR) in response to in vivo loading of the ulna, whereas their anabolic response to intermittent PTH is preserved. Moreover, it shows that osteoblast numbers are normal at loaded sites in the absence of LRP5, but their capacity to synthesize specific proteins, in this case osteopontin, is affected.* —SF

Sigurdsson G, Aspelund T, Chang M, Jonsdottir B, Sigurdsson S, Eiriksdottir G, Gudmundsson A, Harris TB, Gudnason V, Lang TF. Increasing sex difference in bone strength in old age: The Age, Gene/Environment Susceptibility-Reykjavik study (AGES-REYKJAVIK). *Bone*. 2006 Jun 19; [Epub ahead of print] [Abstract]

> *Large-scale analyses of aging- and sex-related bone geometry changes are still rare. Using QCT in 1700 older men and women (67-93 yrs), this study shows that in the elderly, cross-sectional area of vertebrae, femur neck and shaft increases similarly in both sexes, whereas cortical thickness and trabecular volumetric bone density decline more prominently in females. This results in much larger indices of bending and compressive strength in males than females. Hence, in older age and contrarily to earlier ages, endocortical and trabecular bone loss rather than a deficit in periosteal bone expansion might explain the greater bone fragility in elderly women than men. Before these observations become a new paradigm for bone fragility in the oldest old, it awaits confirmation by longitudinal studies.* —SF

Tsukiyama K, Yamada Y, Yamada C, Harada N, Kawasaki Y, Ogura M, Bessho K, Li M, Amizuka N, Sato M, Udagawa N, Takahashi N, Tanaka K, Oiso Y, Seino Y. Gastric inhibitory polypeptide as an endogenous factor promoting new bone formation after food ingestion. *Mol Endocrinol*. 2006 Jul;20(7):1644-51. [Abstract] [Full Text]

> *Several gut hormones with incretin activity are thought to affect bone turnover. Here, gastric inhibitory peptide (GIP) (-/-) mice are shown to have decreased bone formation and increased bone resorption, with increased urinary deoxypyridinoline excretion, though overall effects on trabecular bone volume are small. GIP prevents osteoblast apoptosis. The postprandial rise in serum calcium is markedly exaggerated in knockout mice, suggesting that GIP functions in the assimilation of prandial calcium.* —GJS

Genetics

Ralston SH, Uitterlinden AG, Brandi ML, Balcells S, Langdahl BL, Lips P, Lorenc R, Obermayer-Pietsch B, Scollen S, Bustamante M, Husted LB, Carey AH, Diez-Perez A, Dunning AM, Falchetti A, Karczmarewicz E, Kruk M, van Leeuwen JP, van Meurs JB, Mangion J, McGuigan FE, Mellibovsky L, del Monte F, Pols HA, Reeve J, Reid DM, Renner W, Rivadeneira F, van Schoor NM, Sherlock RE, Ioannidis JP; GENOMOS Investigators. Large-scale evidence for the effect of the COLIA1 Sp1 polymorphism on osteoporosis outcomes: the GENOMOS study. *PLoS Med*. 2006 Apr;3(4):e90. Erratum in: *PLoS Med*. 2006 May;3(5):e90. [Abstract]

> *This is a pooled analysis of Col1A1 Sp1 polymorphism association with BMD and fractures in more than 20,000 individuals (mostly women) from multiple European centers, including 6,000 subjects with prevalent and/or incident fractures (vertebral and peripheral). Consistent with many prior single trials and meta-analysis, marginal but significant differences in hip and spine BMD were found. In contrast, no association with all fractures but a borderline association with vertebral fracture risk is reported. Thanks to these results, we now definitely ignore whether or not Col1A1 is associated with BMD and/or fractures. Did previous studies on Col1A1 alleles, including retrospective meta-analyses on fractures, lead to false positive results or is the current lack of association a false negative result due to genetic and/or phenotypic heterogeneity (mean age range from cohorts: 47-76 yrs; fracture prevalence: 13%-63%)?* —SF

Pathophysiology

Boucharaba A, Serre CM, Guglielmi J, Bordet JC, Clezardin P, Peyruchaud O. The type 1 lysophosphatidic acid receptor is a target for therapy in bone metastases. *Proc Natl Acad Sci U S A*. 2006 Jun 20;103(25):9643-8. [Abstract] [Full Text]

> *The naturally occurring bioactive lipid, lysophosphatidic acid (LPA), which is produced by activated blood platelets, inhibits bone metastasis [See Gillespie MT, Guise TA. BoneKEy-Osteovision. 2006 April;3(4):16-18]. Here, gene silencing of the LPA receptor is shown to reduce markedly the extent of osteolytic metastases from breast or ovarian cancer cells. A pharmacological inhibitor is also effective. This approach could be useful in clinical bone metastasis.* —GJS

Treatment and Drug Effects

Allen MR, Iwata K, Phipps R, Burr DB. Alterations in canine vertebral bone turnover, microdamage accumulation, and biomechanical properties following 1-year treatment with clinical treatment doses of risedronate or alendronate. *Bone*. 2006 Jun 8; [Epub ahead of print] [Abstract]

> *Microdamage density correlates with the degree of suppression of remodeling, but in this experiment, with doses equivalent to those used clinically, there were no compromises in vertebral strength.* —ES

Jackson RD, Wactawski-Wende J, LaCroix AZ, Pettinger M, Yood RA, Watts NB, Robbins JA, Lewis CE, Beresford SA, Ko MG, Naughton MJ, Satterfield S, Bassford T; Women's Health Initiative Investigators. Effects of conjugated equine estrogen on risk of fractures and BMD in postmenopausal women with hysterectomy: results from the Women's Health Initiative randomized trial. *J Bone Miner Res*. 2006 Jun;21(6):817-28. [Abstract]

Postmenopausal women 50-79 years of age with hysterectomy were randomized to CEE 0.625 mg daily (n = 5310) or placebo (n = 5429) followed for an average 7.1 years. CEE reduced the risk of hip (HR, 0.65; 0.45-0.94), clinical vertebral (HR, 0.64; 0.44-0.93), wrist/lower arm (HR, 0.58; 0.47-0.72), and total fracture (HR, 0.71; 0.64-0.80). —ES

Kulkarni NH, Onyia JE, Zeng Q, Tian X, Liu M, Halladay DL, Frolik CA, Engler T, Wei T, Kriauciunas A, Martin TJ, Sato M, Bryant HU, Ma YL. Orally bioavailable GSK-3alpha/beta dual inhibitor increases markers of cellular differentiation in vitro and bone mass in vivo. *J Bone Miner Res*. 2006 Jun;21(6):910-20. [Abstract]

Following on the discovery that Wnt-LRP5-β-catenin signaling is anabolic for bone, the race to discover new anabolic agents has reached olympic levels. A potential target is GSK3, an enzyme that is part of the β-catenin inactivation complex. Proof-of-concept that inhibition of GSK3 increases bone mass in both LRP5 KO and normal mice was previously shown using lithium chloride (Clement-Lacroix P, et al. Proc Natl Acad Sci U S A. 2005 Nov 29;102(48):17406-11). This study now shows that ovariectomized rats fed an oral small molecule GSK-3 inhibitor for 2 months completely maintained BMD and markedly improved microarchitecture compared to untreated animals. A story to be followed... —SF

Tracz MJ, Sideras K, Bolona ER, Haddad RM, Kennedy CC, Uraga MV, Caples SM, Erwin PJ, Montori VM. Testosterone use in men and its effects on bone health. A systematic review and meta-analysis of randomized placebo-controlled trials. *J Clin Endocrinol Metab*. 2006 Jun;91(6):2011-6. [Abstract] [Full Text]

A systematic review and meta-analysis of randomized placebo-controlled trials in men included 8 trials enrolling 365 patients. Compared with placebo, intramuscular testosterone was associated with an 8% gain in lumbar BMD and transdermal testosterone had no effect. Testosterone use was associated with a nonsignificant 4% gain in femoral neck BMD. No trials measured or reported the effect on fractures. —ES

Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, Bevers TB, Fehrenbacher L, Pajon ER Jr, Wade JL 3rd, Robidoux A, Margolese RG, James J, Lippman SM, Runowicz CD, Ganz PA, Reis SE, McCaskill-Stevens W, Ford LG, Jordan VC, Wolmark N; National Surgical Adjuvant Breast and Bowel Project (NSABP). Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial. *JAMA*. 2006 Jun 21;295(23):2727-41. [Abstract]

The incidence of invasive breast cancer did not differ by treatment. There were fewer cases of noninvasive breast cancer using tamoxifen than raloxifene (incidence, 1.51 vs 2.11 per 1000). There were 36 cases of uterine cancer with tamoxifen and 23 with raloxifene. No differences for other invasive cancer sites, ischemic heart disease, stroke, fractures or death were observed. Thromboembolic events and cataracts occurred less with raloxifene. Raloxifene is as effective as tamoxifen in reducing invasive breast cancer and has a lower risk of thromboembolic events and cataracts. —ES

Reviews, Perspectives and Editorials

Sambrook P, Cooper C. Osteoporosis. *Lancet*. 2006 Jun 17;367(9527):2010-8. Erratum in: *Lancet*. 2006 Jul 1;368(9529):28. [Abstract]

Other Studies of Potential Interest

Ahn JD, Dubern B, Lubrano-Berthelier C, Clement K, Karsenty G. Cart overexpression is the only identifiable cause of high bone mass in melanocortin 4 receptor deficiency. *Endocrinology*. 2006 Jul;147(7):3196-202. [Abstract] [Full Text]

Allison SJ, Baldock P, Sainsbury A, Enriquez R, Lee NJ, Lin EJ, Klugman M, During M, Eisman JA, Li M, Pan LC, Herzog H, Gardiner EM. Conditional deletion of hypothalamic Y2 receptors reverts gonadectomy-induced bone loss in adult mice. *J Biol Chem*. 2006 Jun 19; [Epub ahead of print]

Hecht J, Seitz V, Urban M, Wagner F, Robinson PN, Stiege A, Dieterich C, Kornak U, Wilkening U, Brieske N, Zwingman C, Kidess A, Stricker S, Mundlos S. Detection of novel skeletogenesis target genes by comprehensive analysis of a Runx2(-/-) mouse model. *Gene Expr Patterns*. 2006 Jun 6; [Epub ahead of print] [Abstract]

Hinoi E, Ueshima T, Hojo H, Iemata M, Takarada T, Yoneda Y. Upregulation of per mRNA expression by PTH through a PKA-CREB-dependent mechanism in chondrocytes. *J Biol Chem*. 2006 Jun 15; [Epub ahead of print]

James MJ, Jarvinen E, Wang XP, Thesleff I. Different roles of runx2 during early neural crest-derived bone and tooth development. *J Bone Miner Res*. 2006 Jul;21(7):1034-44. [Abstract]

Jeon EJ, Lee KY, Choi NS, Lee MH, Kim HN, Jin YH, Ryoo HM, Choi JY, Yoshida M, Nishino N, Oh BC, Lee KS, Lee YH, Bae SC. Bone morphogenetic protein-2 stimulates Runx2 acetylation. *J Biol Chem*. 2006 Jun 16;281(24):16502-11. [Abstract] [Full Text]

Lee YH, Rho YH, Choi SJ, Ji JD, Song GG. Meta-analysis of genome-wide linkage studies for bone mineral density. *J Hum Genet*. 2006;51(5):480-6. [Abstract]

Li J, Sarosi I, Cattley RC, Pretorius J, Asuncion F, Grisanti M, Morony S, Adamu S, Geng Z, Qiu W, Kostenuik P, Lacey DL, Simonet WS, Bolon B, Qian X, Shalhoub V, Ominsky MS, Zhu Ke H, Li X, Richards WG. Dkk1-mediated inhibition of Wnt signaling in bone results in osteopenia. *Bone*. 2006 May 24; [Epub ahead of print] [Abstract]

Liu Z, Tang Y, Qiu T, Cao X, Clemens TL. A dishevelled-1/Smad1 interaction couples WNT and bone morphogenetic protein signaling pathways in uncommitted bone marrow stromal cells. *J Biol Chem*. 2006 Jun 23;281(25):17156-63. [Abstract] [Full Text]

Matsumoto T, Shiraki M, Hagino H, Iinuma H, Nakamura T. Daily nasal spray of hPTH(1-34) for 3 months increases bone mass in osteoporotic subjects: a pilot study. *Osteoporos Int*. 2006 Jun 9; [Epub ahead of print] [Abstract]

Morvan F, Boulukos K, Clement-Lacroix P, Roman Roman S, Suc-Royer I, Vayssiere B, Ammann P, Martin P, Pinho S, Pognonec P, Mollat P, Niehrs C, Baron R, Rawadi G. Deletion of a single allele of the Dkk1 gene leads to an increase in bone formation and bone mass. *J Bone Miner Res*. 2006 Jun;21(6):934-45. [Abstract]

Pangrazio A, Poliani PL, Megarbane A, Lefranc G, Lanino E, Di Rocco M, Rucci F, Lucchini F, Ravanini M, Facchetti F, Abinun M, Vezzoni P, Villa A, Frattini A. Mutations in OSTM1 (grey

lethal) define a particularly severe form of autosomal recessive osteopetrosis with neural involvement. *J Bone Miner Res*. 2006 Jul;21(7):1098-105. [Abstract]

Spater D, Hill TP, O'sullivan RJ, Gruber M, Conner DA, Hartmann C. Wnt9a signaling is required for joint integrity and regulation of Ihh during chondrogenesis. *Development*. 2006 Aug;133(15):3039-49. [Abstract]

Xie L, Jacobson JM, Choi ES, Busa B, Donahue LR, Miller LM, Rubin CT, Judex S. Low-level mechanical vibrations can influence bone resorption and bone formation in the growing skeleton. *Bone*. 2006 Jul 4; [Epub ahead of print] [Abstract]

Yang M, Mailhot G, Birnbaum MJ, Mackay CA, Mason-Savas A, Odgren PR. Expression of and role for ovarian cancer G-protein coupled receptor 1 (OGR1) during osteoclastogenesis. *J Biol Chem*. 2006 Jun 19; [Epub ahead of print]

Conflict of Interest: Dr. Ferrari and Dr. Strewler report that no conflicts of interest exist. 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.