

NOT TO BE MISSED

Clinical and Basic Research Papers – March 2005 Selections

Ego Seeman, Clinical Editor

Gordon J. Strewler, Editor

Bone Modeling and Remodeling

◆ Elefteriou F, Ahn JD, Takeda S, Starbuck M, Yang X, Liu X, Kondo H, Richards WG, Bannon TW, Noda M, Clement K, Vaisse C, Karsenty G. Leptin regulation of bone resorption by the sympathetic nervous system and CART. *Nature*. 2005 Mar 24;434(7032):514-20. [[Abstract](#)]

The Karsenty group has previously focused on central control of bone formation; they now report that leptin stimulates bone resorption. The signaling pathway is the β -adrenergic nervous system and the cellular mechanism is activation of RANKL gene transcription by cAMP-dependent phosphorylation of activating transcription factor (ATF). Ovariectomy does not induce bone loss in β 2-adrenergic receptor-null mice, suggesting that menopausal bone loss is centrally mediated – this will be controversial! An inhibitory arm of the central controller of bone resorption is also identified. CART (cocaine and amphetamine regulated transcript), a leptin-dependent hypothalamic neuropeptide, is the central mediator of this arm, but the peripheral effector is unknown. —GJS

◆ Faccio R, Teitelbaum SL, Fujikawa K, Chappel J, Zallone A, Tybulewicz VL, Ross FP, Swat W. Vav3 regulates osteoclast function and bone mass. *Nat Med*. 2005 Mar;11(3):284-290. [[Abstract](#)]

Rho GTPases regulate the actin cytoskeleton, and vav proteins are guanine nucleotide exchange factors that enhance their actions. Removal of vav3 from mice produces a high bone mass phenotype in which osteoclast number is normal but bone resorption is decreased, and mice are protected from bone loss stimulated by PTH or RANKL. Signals by M-CSF and α v β 3 integrin to induce osteoclast polarization, spreading, and resorption are disrupted by removal of vav3. The signaling pathway involves the Syk tyrosine kinase upstream of Rac and vav3. —GJS

◆ Li H, Cuartas E, Cui W, Choi Y, Crawford TD, Ke HZ, Kobayashi KS, Flavell RA, Vignery A. IL-1 receptor-associated kinase M is a central regulator of osteoclast differentiation and activation. *J Exp Med*. 2005 Apr 4;201(7):1169-77. [[Abstract](#)]

Interleukin 1 (IL-1) receptor-associated kinase M (IRAK-M) lacks kinase activity and functions as an endogenous dominant negative regulator of IL-1 signaling. Removal of the Irak-m gene from mice leads to increased osteoclastic bone resorption and severe osteoporosis. The detailed molecular basis of the increase in osteoclast activity is still cloudy, but the paper points up once more the need to understand more fully the relationships of RANKL, TNF- α and IL-1 in osteoclastogenesis. —GJS

◆ Yoon BS, Ovchinnikov DA, Yoshii I, Mishina Y, Behringer RR, Lyons KM. Bmpr1a and Bmpr1b have overlapping functions and are essential for chondrogenesis in vivo. *Proc Natl Acad Sci U S A*. 2005 Apr 5;102(14):5062-7. [[Abstract](#)] [[Full Text](#)]

Although it is clear that bone morphogenetic proteins (BMPs) can induce chondrogenesis, removal of their individual receptors has a relatively mild phenotype.

Removal of both Bmpr1a and Bmpr1b from chondrocytes, however, eliminates most endochondral skeletal elements. The remainder of the skeleton is rudimentary, but patterning is intact. As suspected, no BMP, no cartilage. —GJS

Diagnosis

◆ Abrahamsen B, Andersen I, Christensen SS, Madsen JS, Brixen K. Utility of testing for monoclonal bands in serum of patients with suspected osteoporosis: retrospective, cross sectional study. *BMJ*. 2005 Apr 9;330(7495):818. [[Abstract](#)] [[Full Text](#)]

Of 799 patients, 4.9% (18 of 366) with osteoporosis and 2.2% (nine of 408) without osteoporosis had a serum M band. Myeloma was diagnosed in three patients with osteoporosis (absolute risk, 0.8%). Relative risk of myeloma was 75 in patients presenting with osteoporosis. The M band had a positive predictive value of 17.6%. For each case diagnosed, 122 electrophoreses were carried out. All patients with multiple myeloma had a history of fracture. Monoclonal gammopathy of undetermined significance was diagnosed in 13 patients (3.6%) with osteoporosis and eight patients (2.0%) with normal BMD or osteopenia. Patients presenting with osteoporosis should be tested for M component in serum, because one in 20 patients with newly diagnosed osteoporosis had myeloma or monoclonal gammopathy of undetermined significance. —ES

◆ Delmas PD, van de Langerijt L, Watts NB, Eastell R, Genant H, Grauer A, Cahall DL; for the IMPACT Study Group. Underdiagnosis of Vertebral Fractures Is a Worldwide Problem: The IMPACT Study. *J Bone Miner Res*. 2005 Apr;20(4):557-63. [[Abstract](#)]

Vertebral fractures are common, they predict further fractures and they are accompanied by increased morbidity and mortality. Despite this, patients with fractures remain underdiagnosed and undertreated. Of 2451 women, 789 (32%) had at least one vertebral fracture. A false-negative rate of 34% was observed because of adjudicated discrepancies (N = 350) between local and central readings caused by failed detection (68%) or equivocal terminology in the local report (32%). Underdiagnosis was observed in all regions (false-negatives: North America, 45.2%; Latin America, 46.5%; and Europe/South Africa/Australia, 29.5%). The false-positive rate was 5% globally. Underdiagnosis of vertebral fracture is a worldwide problem. —ES

Epidemiology

◆ Meier C, Nguyen TV, Center JR, Seibel MJ, Eisman JA. Bone resorption and osteoporotic fractures in elderly men: the dubbo osteoporosis epidemiology study. *J Bone Miner Res*. 2005 Apr;20(4):579-87. [[Abstract](#)]

Osteoporosis in men is a neglected area of research. In this prospective case-cohort control study, the authors reported that, as in women, the combined use of densitometry and biochemical measures of bone remodeling assists in defining high-risk men to be targeted for therapy. In 151 elderly men followed for 6.3 years, high resorption, as assessed by serum cross-linked carboxyterminal telopeptide of type 1 collagen (S-ICTP), was independently associated with increased risk of fracture. Men in the highest quartile of S-ICTP had a 2.8-fold increased risk of fracture, compared with those in the lowest quartile. Incidence of fracture was 10 times higher in men with high S-ICTP and low femoral neck bone mineral density (FNBMD), compared with men with low S-ICTP and high FNBMD. Of the fracture risk in the population, 20% was attributable to high S-ICTP and low FNBMD, and S-ICTP contributed 17% to this increased risk. —ES

- ◆Stenson WF, Newberry R, Lorenz R, Baldus C, Civitelli R. Increased prevalence of celiac disease and need for routine screening among patients with osteoporosis. *Arch Intern Med*. 2005 Feb 28;165(4):393-9. [[Abstract](#)]

The authors reported that 12 of 266 patients (4.5%) with osteoporosis and six of 574 patients (1.0%) without osteoporosis tested positive by serology for celiac disease. Nine patients with osteoporosis and one patient without osteoporosis had positive biopsies. The prevalence of biopsy-proven celiac disease was 3.4% in the osteoporotic population and 0.2% in the nonosteoporotic population. All biopsy-positive patients tested positive by anti-tissue transglutaminase and antiendomysial antibody. The prevalence of celiac disease in patients with osteoporosis (3.4%) is higher than that in patients without osteoporosis (0.2%) and justifies serologic screening for celiac disease in all patients with osteoporosis. —ES

Reviews, Perspectives, and Editorials

- ◆Chlebowski RT. Bone health in women with early-stage breast cancer. *Clin Breast Cancer*. 2005 Feb;5 Suppl 2:S35-40. [[Abstract](#)]
- ◆Gralow J. Evolving role of bisphosphonates in women undergoing treatment for localized and advanced breast cancer. *Clin Breast Cancer*. 2005 Feb;5 Suppl 2:S54-62. [[Abstract](#)]
- ◆Guise TA, Kozlow WM, Heras-Herzig A, Padalecki SS, Yin JJ, Chirgwin JM. Molecular mechanisms of breast cancer metastases to bone. *Clin Breast Cancer*. 2005 Feb;5 Suppl 2:S46-53. [[Abstract](#)]
- ◆Mosekilde L. Vitamin D and the elderly. *Clin Endocrinol (Oxf)*. 2005 Mar;62(3):265-81. [[Abstract](#)]
- ◆Ott SM. Long-term safety of bisphosphonates. *J Clin Endocrinol Metab*. 2005 Mar;90(3):1897-9. [[Full Text](#)]
- ◆Paterson AH. Evaluating bone mass and bone quality in patients with breast cancer. *Clin Breast Cancer*. 2005 Feb;5 Suppl 2:S41-5. [[Abstract](#)]
- ◆Provot S, Schipani E. Molecular mechanisms of endochondral bone development. *Biochem Biophys Res Commun*. 2005 Mar 18;328(3):658-65. [[Abstract](#)]
- ◆Shanahan CM. Mechanisms of vascular calcification in renal disease. *Clin Nephrol*. 2005 Feb;63(2):146-57. [[Abstract](#)]
- ◆Silver J, Levi R. Cellular and molecular mechanisms of secondary hyperparathyroidism. *Clin Nephrol*. 2005 Feb;63(2):119-26. [[Abstract](#)]
- ◆Theriault RL. Strategies to prevent chemotherapy-induced bone loss in women with breast cancer. *Clin Breast Cancer*. 2005 Feb;5 Suppl 2:S63-70. [[Abstract](#)]
- ◆Wan M, Cao X. BMP signaling in skeletal development. *Biochem Biophys Res Commun*. 2005 Mar 18;328(3):651-7. [[Abstract](#)]

Other Studies of Potential Interest

- ◆ Atkins GJ, Kostakis P, Welldon KJ, Vincent C, Findlay DM, Zannettino AC. Human trabecular bone-derived osteoblasts support human osteoclast formation in vitro in a defined, serum-free medium. *J Cell Physiol.* 2005 Jun;203(3):573-82. [[Abstract](#)]
- ◆ Ferrari SL, Pierroz DD, Glatt V, Goddard DS, Bianchi EN, Lin FT, Manen D, Bouxsein ML. Bone response to intermittent parathyroid hormone is altered in mice null for {beta}-Arrestin2. *Endocrinology.* 2005 Apr;146(4):1854-62. [[Abstract](#)] [[Full Text](#)]
- ◆ Garcia Palacios V, Robinson LJ, Borysenko CW, Lehmann T, Kalla SE, Blair HC. Negative Regulation of RANKL-induced Osteoclastic Differentiation in RAW264.7 Cells by Estrogen and Phytoestrogens. *J Biol Chem.* 2005 Apr 8;280(14):13720-7. [[Abstract](#)] [[Full Text](#)]
- ◆ Healy KD, Vanhooke JL, Prael JM, Deluca HF. Parathyroid hormone decreases renal vitamin D receptor expression in vivo. *Proc Natl Acad Sci U S A.* 2005 Mar 29;102(13):4724-8. [[Abstract](#)] [[Full Text](#)]
- ◆ Ito H, Koefoed M, Tiyapatanaputi P, Gromov K, Goater JJ, Carmouche J, Zhang X, Rubery PT, Rabinowitz J, Samulski RJ, Nakamura T, Soballe K, O'keefe RJ, Boyce BF, Schwarz EM. Remodeling of cortical bone allografts mediated by adherent rAAV-RANKL and VEGF gene therapy. *Nat Med.* 2005 Mar;11(3):291-297. [[Abstract](#)]
- ◆ Kobayashi Y, Mizoguchi T, Take I, Kurihara S, Udagawa N, Takahashi N. Prostaglandin E2 enhances osteoclastic differentiation of precursor cells through protein kinase A-dependent phosphorylation of TAK1. *J Biol Chem.* 2005 Mar 25;280(12):11395-403. [[Abstract](#)] [[Full Text](#)]
- ◆ Leclerc N, Noh T, Khokhar A, Smith E, Frenkel B. Glucocorticoids inhibit osteocalcin transcription in osteoblasts by suppressing Egr2/Krox20-binding enhancer. *Arthritis Rheum.* 2005 Mar;52(3):929-39. [[Abstract](#)]
- ◆ Maalouf NM, Shane E. Osteoporosis after solid organ transplantation. *J Clin Endocrinol Metab.* 2005 Apr;90(4):2456-65. [[Abstract](#)] [[Full Text](#)]
- ◆ Mansukhani A, Ambrosetti D, Holmes G, Cornivelli L, Basilico C. Sox2 induction by FGF and FGFR2 activating mutations inhibits Wnt signaling and osteoblast differentiation. *J Cell Biol.* 2005 Mar 28;168(7):1065-76. [[Abstract](#)] [[Full Text](#)]
- ◆ Nielsen-Marsh CM, Richards MP, Hauschka PV, Thomas-Oates JE, Trinkaus E, Pettitt PB, Karavanic I, Poinar H, Collins MJ. Osteocalcin protein sequences of Neanderthals and modern primates. *Proc Natl Acad Sci U S A.* 2005 Mar 22;102(12):4409-13. [[Abstract](#)] [[Full Text](#)]
- ◆ Samad TA, Rebbapragada A, Bell E, Zhang Y, Sidis Y, Jeong SJ, Campagna JA, Perusini S, Fabrizio DA, Schneyer AL, Lin HY, Brivanlou AH, Attisano L, Woolf CJ. DRAGON, a Bone Morphogenetic Protein Co-receptor. *J Biol Chem.* 2005 Apr 8;280(14):14122-9. [[Abstract](#)] [[Full Text](#)]
- ◆ Schmidt K, Schinke T, Haberland M, Priemel M, Schilling AF, Mueldner C, Rueger JM, Sock E, Wegner M, Amling M. The high mobility group transcription factor Sox8 is a negative regulator of osteoblast differentiation. *J Cell Biol.* 2005 Mar 14;168(6):899-910. [[Abstract](#)] [[Full Text](#)]
- ◆ Shen H, Liu Y, Liu P, Recker RR, Deng HW. Nonreplication in genetic studies of complex diseases--lessons learned from studies of osteoporosis and tentative remedies. *J Bone Miner Res.* 2005 Mar;20(3):365-76. [[Abstract](#)]

- ◆Silva MJ, Brodt MD, Ko M, Abu-Amer Y. Impaired marrow osteogenesis is associated with reduced endocortical bone formation but does not impair periosteal bone formation in long bones of SAMP6 mice. *J Bone Miner Res.* 2005 Mar;20(3):419-27. [[Abstract](#)]
- ◆Syme CA, Friedman PA, Bisello A. Parathyroid hormone receptor trafficking contributes to the activation of extracellular signal-regulated kinases but is not required for regulation of cAMP signaling. *J Biol Chem.* 2005 Mar 25;280(12):11281-8. [[Abstract](#)] [[Full Text](#)]
- ◆Tsuji T, Kunieda T. A loss-of-function mutation in natriuretic peptide receptor 2 (Npr2) gene is responsible for disproportionate dwarfism in cn/cn mouse. *J Biol Chem.* 2005 Apr 8;280(14):14288-92. [[Abstract](#)] [[Full Text](#)]
- ◆Vertino AM, Bula CM, Chen JR, Almeida M, Han L, Bellido T, Kousteni S, Norman AW, Manolagas SC. Nongenotropic, Anti-Apoptotic Signaling of 1{alpha},25(OH)2-Vitamin D3 and Analogs through the Ligand Binding Domain of the Vitamin D Receptor in Osteoblasts and Osteocytes: MEDIATION BY Src, PHOSPHATIDYLINOSITOL 3-, AND JNK KINASES. *J Biol Chem.* 2005 Apr 8;280(14):14130-7. [[Abstract](#)] [[Full Text](#)]
- ◆Wada T, Nakashima T, Oliveira-Dos-Santos AJ, Gasser J, Hara H, Schett G, Penninger JM. The molecular scaffold Gab2 is a crucial component of RANK signaling and osteoclastogenesis. *Nat Med.* 2005 Apr;11(4):394-9. [[Abstract](#)]
- ◆Wang YC, Ferguson EL. Spatial bistability of Dpp-receptor interactions during Drosophila dorsal-ventral patterning. *Nature.* 2005 Mar 10;434(7030):229-34. [[Abstract](#)]
- ◆Woods A, Wang G, Beier F. RhoA/ROCK signaling regulates Sox9 expression and actin organization during chondrogenesis. *J Biol Chem.* 2005 Mar 25;280(12):11626-34. [[Abstract](#)] [[Full Text](#)]
- ◆Yogesha SD, Khapli SM, Wani MR. Interleukin-3 and granulocyte-macrophage colony-stimulating factor inhibits tumor necrosis factor (TNF)-alpha-induced osteoclast differentiation by down-regulation of expression of TNF receptors 1 and 2. *J Biol Chem.* 2005 Mar 25;280(12):11759-69. [[Abstract](#)] [[Full Text](#)]
- ◆Yu HM, Jerchow B, Sheu TJ, Liu B, Costantini F, Puzas JE, Birchmeier W, Hsu W. The role of Axin2 in calvarial morphogenesis and craniosynostosis. *Development.* 2005 Apr;132(8):1995-2005. [[Abstract](#)]