

NOT TO BE MISSED

Clinical and Basic Research Papers – May 2005 Selections

Ego Seeman, Clinical Editor

Gordon J. Strewler, Editor

Bone Modeling and Remodeling

◆ Glass DA 2nd, Bialek P, Ahn JD, Starbuck M, Patel MS, Clevers H, Taketo MM, Long F, McMahon AP, Lang RA, Karsenty G. Canonical Wnt signaling in differentiated osteoblasts controls osteoclast differentiation. *Dev Cell*. 2005 May;8(5):751-64. [[Abstract](#)]

◆ Holmen SL, Zylstra CR, Mukherjee A, Sigler RE, Faugere MC, Bouxsein ML, Deng L, Clemens TL, Williams BO. Essential role of β -catenin in postnatal bone acquisition. *J Biol Chem*. 2005 Jun 3;280(22):21162-8. [[Abstract](#)] [[Full Text](#)]

These two papers use overlapping approaches to study Wnt signaling in osteoblasts. Both groups ablated the gene for β -catenin in osteoblasts, thereby disabling the canonical Wnt signaling pathway. This mutation produced severe osteoporosis, but it was primarily the result of increased osteoclast formation. Stabilization of β -catenin (by ablation of the APC gene or deletion of the phosphorylation sites in β -catenin) produced osteopetrosis. The transcription factor TCF-1 is downstream of β -catenin and both RANKL and OPG are targets of Wnt signaling. —GJS

◆ Li X, Zhang Y, Kang H, Liu W, Liu P, Zhang J, Harris SE, Wu D. Sclerostin binds to LRP5/6 and antagonizes canonical Wnt signaling. *J Biol Chem*. 2005 May 20;280(20):19883-7. [[Abstract](#)] [[Full Text](#)]

Sclerostin, the product of the SOST gene, is an inhibitor of osteoblast function, and inactivating mutations in SOST cause the osteosclerotic disorder sclerosteosis. Sclerostin was initially thought to be a bone morphogenetic protein (BMP) antagonist, but recent evidence suggests it is not ([Van Bezooijen et al. J. Exp. Med. 2004 199, 805–14](#)). This important paper provides evidence that sclerostin binds low-density lipoprotein receptor-related proteins 5 and 6 (LRP5 and 6) and inhibits canonical Wnt signaling, suggesting that increased Wnt signaling may be the mechanism of osteosclerosis. —GJS

Pathophysiology

◆ Diab T, Vashishth D. Effects of damage morphology on cortical bone fragility. *Bone*. 2005 Jul;37(1):96-102. [[Abstract](#)]

How fractures occur is not understood, nor is the relevance of microdamage. Microcracks may actually be a final defense against the less desirable alternative, complete fracture. The authors provide some insights into the compartmentalization and nature of microdamage on compressive and tensile surfaces to dissipate energy and resist fracture in progressive phases of loading. —ES

◆ Gensure RC, Makitie O, Barclay C, Chan C, Depalma SR, Bastepe M, Abuzahra H, Couper R, Mundlos S, Silience D, Ala Kokko L, Seidman JG, Cole WG, Juppner H. A novel COL1A1 mutation in infantile cortical hyperostosis (Caffey disease) expands the spectrum of collagen-related disorders. *J Clin Invest*. 2005 May;115(5):1250-7. [[Abstract](#)] [[Full Text](#)]

Infantile cortical hyperostosis (Caffey disease) is a disorder of subperiosteal new bone formation with inflammatory features that occurs in infants and has usually abated by age two. Positional cloning identifies the same mutation (R836C) in the triple-helical domain of the $\alpha 1(I)$ chain of type I collagen in several unrelated families. Affected children have a generalized disorder of connective tissues; susceptibility to injuries that detach the periosteum may underly the pathophysiology of the disorder. —GJS

◆Lynch CC, Hikosaka A, Acuff HB, Martin MD, Kawai N, Singh RK, Vargo-Gogola TC, Begtrup JL, Peterson TE, Fingleton B, Shirai T, Matrisian LM, Futakuchi M. MMP-7 promotes prostate cancer-induced osteolysis via the solubilization of RANKL. *Cancer Cell*. 2005 May;7(5):485-96. [\[Abstract\]](#)

A model of osteolysis was established by injection of mouse prostate carcinoma cells onto calvaria. The genes for matrix metalloproteinase 7 (MMP-7) and RANKL were expressed at high levels at the tumor-bone interface. MMP-7 was shown to convert RANKL to a soluble form. Osteolysis was markedly decreased when tumor cells were grown on the calvaria of MMP-7(-/-) mice. MMP-7 is an osteoclast product that enhances osteolysis by the processing of RANKL. —GJS

◆Qiu S, Sudhaker Rao D, Fyhrie DP, Palnitkar S, Parfitt AM. The morphological association between microcracks and osteocyte lacunae in human cortical bone. *Bone*. 2005 Jul;37(1):10-5. [\[Abstract\]](#)

Microcracks are more common and osteocytes are less common in interstitial bone than in osteons. There are also fewer osteocyte lacunae in interstitial bone in areas adjacent to microdamage. Microdamage and osteocyte deficiency occur in the same bone regions. Which comes first is not known. —ES

Treatment and Drug Effects

◆Chapurlat RD, Palermo L, Ramsay P, Cummings SR. Risk of fracture among women who lose bone density during treatment with alendronate. The Fracture Intervention Trial. *Osteoporos Int*. 2005 Jul;16(7):842-8. [\[Abstract\]](#)

The mechanisms responsible for lower fracture incidence in treated subjects than controls is not understood. Increased BMD accounts for only a small proportion of the 50% risk reduction of seen with most drugs. In the Fracture Intervention Trial women "losing" spine or hip BMD (0% to 4%) while on alendronate had a reduction of about 50-60% in vertebral fracture risk. Those who "gained" BMD (0% to 4%) had a similar reduction in risk. This was not observed for the few women who lost more than 4% at either site. Changes in BMD are not surrogates of anti-fracture efficacy. —ES

◆Porthouse J, Cockayne S, King C, Saxon L, Steele E, Aspray T, Baverstock M, Birks Y, Dumville J, Francis R, Iglesias C, Puffer S, Sutcliffe A, Watt I, Torgerson DJ. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. *BMJ*. 2005 Apr 30;330(7498):1003. [\[Abstract\]](#) [\[Full Text\]](#)

In an open randomized controlled trial of 3314 women aged 70 years and older, supplementation with calcium (1000 mg) and cholecalciferol (800 IU) was not associated with a lower risk of fracture, compared with controls, after a median of 25 months. Problems with compliance again limit the ability to make inferences. —ES

Reviews, Perspectives, and Editorials

- ◆Cleazardin P, Ebetino FH, Fournier PG. Bisphosphonates and cancer-induced bone disease: beyond their antiresorptive activity. *Cancer Res.* 2005 Jun 15;65(12):4971-4. [[Abstract](#)]
- ◆McClung MR. Osteopenia: to treat or not to treat? *Ann Intern Med.* 2005 May 3;142(9):796-7. [[Info](#)]
- ◆Melton LJ 3rd, Kanis JA, Johnell O. Potential impact of osteoporosis treatment on hip fracture trends. *J Bone Miner Res.* 2005 Jun;20(6):895-7. [[Info](#)]
- ◆Shaker JL, Lukert BP. Osteoporosis associated with excess glucocorticoids. *Endocrinol Metab Clin North Am.* 2005 Jun;34(2):341-56, viii-ix. [[Abstract](#)]
- ◆U.S. Preventive Services Task Force. Hormone therapy for the prevention of chronic conditions in postmenopausal women: recommendations from the U.S. Preventive Services Task Force. *Ann Intern Med.* 2005 May 17;142(10):855-60. [[Info](#)]

Other Studies of Potential Interest

- ◆Barbier JR, Gardella TJ, Dean T, MacLean S, Potetinova Z, Whitfield JF, Willick GE. Backbone-methylated analogues of the principle receptor binding region of human parathyroid hormone. Evidence for binding to both the N-terminal extracellular domain and extracellular loop region. *J Biol Chem.* 2005 Jun 24;280(25):23771-7. [[Abstract](#)] [[Full Text](#)]
- ◆Borah B, Ritman EL, Dufresne TE, Jorgensen SM, Liu S, Sacha J, Phipps RJ, Turner RT. The effect of risedronate on bone mineralization as measured by micro-computed tomography with synchrotron radiation: Correlation to histomorphometric indices of turnover. *Bone.* 2005 Jul;37(1):1-9. [[Abstract](#)]
- ◆Brown MA, Zhao Q, Baker KA, Naik C, Chen C, Pukac L, Singh M, Tsareva T, Parice Y, Mahoney A, Roschke V, Sanyal I, Choe S. Crystal structure of BMP-9 and functional interactions with pro-region and receptors. *J Biol Chem.* 2005 Jul 1;280(26):25111-8. [[Abstract](#)] [[Full Text](#)]
- ◆Buzza MS, Zamurs L, Sun J, Bird CH, Smith AI, Trapani JA, Froelich CJ, Nice EC, Bird PI. Extracellular matrix remodeling by human granzyme B via cleavage of vitronectin, fibronectin, and laminin. *J Biol Chem.* 2005 Jun 24;280(25):23549-58. [[Abstract](#)] [[Full Text](#)]
- ◆Dobnig H, Sipos A, Jiang Y, Fahrleitner-Pammer A, Ste-Marie LG, Gallagher JC, Pavo I, Wang J, Eriksen EF. Early Changes in Biochemical Markers of Bone Formation Correlate with Improvements in Bone Structure during Teriparatide Therapy. *J Clin Endocrinol Metab.* 2005 Jul;90(7):3970-7. (c) [[Abstract](#)] [[Full Text](#)]
- ◆Facchini A, Borzi RM, Marcu KB, Stefanelli C, Olivotto E, Goldring MB, Facchini A, Flamigni F. Polyamine depletion inhibits NF-kappaB binding to DNA and interleukin-8 production in human chondrocytes stimulated by tumor necrosis factor-alpha. *J Cell Physiol.* 2005 Sep;204(3):956-63. [[Abstract](#)]
- ◆Holick MF, Siris ES, Binkley N, Beard MK, Khan A, Katzer JT, Petruschke RA, Chen E, de Papp AE. Prevalence of Vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. *J Clin Endocrinol Metab.* 2005 Jun;90(6):3215-24. [[Abstract](#)] [[Full Text](#)]
- ◆Kalajzic I, Staal A, Yang WP, Wu Y, Johnson SE, Feyen JH, Krueger W, Maye P, Yu F, Zhao Y, Kuo L, Gupta RR, Achenie LE, Wang HW, Shin DG, Rowe DW. Expression profile of osteoblast

lineage at defined stages of differentiation. *J Biol Chem*. 2005 Jul 1;280(26):24618-26. [[Abstract](#)]
[[Full Text](#)]

◆ Kennell JA, MacDougald OA. Wnt signaling inhibits adipogenesis through beta-catenin-dependent and -independent mechanisms. *J Biol Chem*. 2005 Jun 24;280(25):24004-10. [[Abstract](#)] [[Full Text](#)]

◆ Kobayashi Y, Take I, Yamashita T, Mizoguchi T, Ninomiya T, Hattori T, Kurihara S, Ozawa H, Udagawa N, Takahashi N. Prostaglandin E2 receptors EP2 and EP4 are down-regulated during differentiation of mouse osteoclasts from their precursors. *J Biol Chem*. 2005 Jun 24;280(25):24035-42. [[Abstract](#)] [[Full Text](#)]

◆ Magee C, Nurminskaya M, Faverman L, Galera P, Linsenmayer TF. SP3/SP1 Transcription Activity Regulates Specific Expression of Collagen Type X in Hypertrophic Chondrocytes. *J Biol Chem*. 2005 Jul 8;280(27):25331-8. [[Abstract](#)] [[Full Text](#)]

◆ Miyata T, Iizasa H, Sai Y, Fujii J, Terasaki T, Nakashima E. Platelet-derived growth factor-BB (PDGF-BB) induces differentiation of bone marrow endothelial progenitor cell-derived cell line TR-BME2 into mural cells, and changes the phenotype. *J Cell Physiol*. 2005 Sep;204(3):948-55. [[Abstract](#)]

◆ Moali C, Font B, Ruggiero F, Eichenberger D, Rousselle P, Francois V, Oldberg A, Bruckner-Tuderman L, Hulmes DJ. Substrate-specific modulation of a multisubstrate proteinase. C-terminal processing of fibrillar procollagens is the only BMP-1-dependent activity to be enhanced by PCPE-1. *J Biol Chem*. 2005 Jun 24;280(25):24188-94. [[Abstract](#)] [[Full Text](#)]

◆ Niedermaier M, Schwabe GC, Fees S, Helmrich A, Brieske N, Seemann P, Hecht J, Seitz V, Stricker S, Leschik G, Schrock E, Selby PB, Mundlos S. An inversion involving the mouse Shh locus results in brachydactyly through dysregulation of Shh expression. *J Clin Invest*. 2005 Apr;115(4):900-9. [[Abstract](#)] [[Full Text](#)]

◆ Reed MJ, Bradshaw AD, Shaw M, Sadoun E, Han N, Ferrara N, Funk S, Puolakkainen P, Sage EH. Enhanced angiogenesis characteristic of SPARC-null mice disappears with age. *J Cell Physiol*. 2005 Sep;204(3):800-7. [[Abstract](#)]

◆ Saltman LH, Javed A, Ribadeneyra J, Hussain S, Young DW, Osdoby P, Amcheslavsky A, van Wijnen AJ, Stein JL, Stein GS, Lian JB, Bar-Shavit Z. Organization of transcriptional regulatory machinery in osteoclast nuclei: Compartmentalization of Runx1. *J Cell Physiol*. 2005 Sep;204(3):871-80. [[Abstract](#)]

◆ Uusi-Rasi K, Semanick LM, Zanchetta JR, Bogado CE, Eriksen EF, Sato M, Beck TJ. Effects of teriparatide [rhPTH (1-34)] treatment on structural geometry of the proximal femur in elderly osteoporotic women. *Bone*. 2005 Jun;36(6):948-58. [[Abstract](#)]

◆ Yamaguchi M, Ogata N, Shinoda Y, Akune T, Kamekura S, Terauchi Y, Kadowaki T, Hoshi K, Chung UI, Nakamura K, Kawaguchi H. Insulin receptor substrate-1 is required for bone anabolic function of parathyroid hormone in mice. *Endocrinology*. 2005 Jun;146(6):2620-8. [[Abstract](#)] [[Full Text](#)]

◆ Yu VW, Ambartsoumian G, Verlinden L, Moir JM, Prud'homme J, Gauthier C, Roughley PJ, St-Arnaud R. FIAT represses ATF4-mediated transcription to regulate bone mass in transgenic mice. *J Cell Biol*. 2005 May 23;169(4):591-601. [[Abstract](#)] [[Full Text](#)]