

NOT TO BE MISSED

Clinical and Basic Research Papers – September 2005 Selections

Ego Seeman, Clinical Editor
Gordon J. Strewler, Editor

Bone Modeling and Remodeling

◆ Li X, Liu P, Liu W, Maye P, Zhang J, Zhang Y, Hurley M, Guo C, Boskey A, Sun L, Harris SE, Rowe DW, Ke HZ, Wu D. Dkk2 has a role in terminal osteoblast differentiation and mineralized matrix formation. *Nat Genet.* 2005 Sep;37(9):945-52. [[Abstract](#)]

◆ van der Horst G, van der Werf SM, Farih-Sips H, van Bezooijen RL, Lowik CW, Karperien M. Downregulation of Wnt signaling by increased expression of Dickkopf-1 and -2 is a prerequisite for late-stage osteoblast differentiation of KS483 cells. *J Bone Miner Res.* 2005 Oct;20(10):1867-77. [[Abstract](#)]

Dickkopf (Dkk) proteins antagonize Wnt signaling and can thereby block osteoblast proliferation. These two papers report that, unexpectedly, Dkk has an inhibitory effect on terminal osteoblast differentiation. Li et al. found that Dkk2^{-/-} mice were osteopenic, with reduced osteoblast number and bone formation rates. Dkk2 is expressed in differentiating osteoblasts, its expression is enhanced by Wnt7b, and its expression in Dkk2-null osteoblasts rescues terminal differentiation. van der Horst et al. also found that Dkk1 and Dkk2 expression were upregulated in differentiating osteoblast lineage cells and that knockdown of Dkk2 with siRNA inhibited terminal differentiation and mineralization. Thus, Dkk may have opposite effects on early and late osteoblast development, complicating development of Dkk antagonists for treatment of osteoporosis. —GJS

◆ Pascual G, Fong AL, Ogawa S, Gamliel A, Li AC, Perissi V, Rose DW, Willson TM, Rosenfeld MG, Glass CK. A SUMOylation-dependent pathway mediates transrepression of inflammatory response genes by PPAR-gamma. *Nature.* 2005 Sep 29;437(7059):759-63. [[Abstract](#)]

*PPAR γ is converted to an antagonist of NF κ B signaling in RAW264.7 macrophages by ligand-dependent SUMOylation (covalent modification at a lysine by a small ubiquitin-like modifier [SUMO] protein), which directs PPAR γ to the promoters of NF κ B-responsive genes, where it acts as a transcriptional repressor. This may offer a molecular explanation for the previously reported inhibition of osteoclast generation by PPAR agonists (Mbalaviele G, et al. *J Biol Chem.* 2000 May 12;275(19):14388-93 [[Abstract](#)]). —GJS*

Epidemiology

◆ Sornay-Rendu E, Munoz F, Garnero P, Duboeuf F, Delmas PD. Identification of osteopenic women at high risk of fracture: The OFELY study. *J Bone Miner Res.* 2005 Oct;20(10):1813-9. [[Abstract](#)]

Osteoporosis is known to be under treated and under diagnosed but what is not well appreciated is that more than one-half of women with incident fractures have

osteopenia or normal BMD, not osteoporosis. Identifying these women that are at risk for fracture is a major challenge. The authors address this by reporting that among osteopenic women, age, prior fracture, and high remodeling markers independently predict fracture risk. A majority of incident fractures occurred in those with prior fractures, or bone alkaline phosphatase in the highest quartile. The 10-year probability of fracture in osteopenic women was 26% if at least one predictor was present. —ES

Treatment and Drug Effects

◆ Skinner MA, Moley JA, Dilley WG, Owzar K, Debenedetti MK, Wells SA Jr. Prophylactic thyroidectomy in multiple endocrine neoplasia type 2A. *N Engl J Med*. 2005 Sep 15;353(11):1105-13. [[Abstract](#)]

Prophylactic total thyroidectomy with parathyroid transplantation and lymph node dissection prevents the development of medullary thyroid carcinoma for at least five years in most patients with mutations in the RET oncogene that cause multiple endocrine neoplasia type 2A. Results appear better when thyroidectomy is carried out before age eight rather than at later ages (ages 9-19). —GJS

The three studies below are presented because of their simplicity and powerful messages. There is no substitute for good study design. Large costly studies can be avoided in some cases in which high risk, and often highly informative, patients can be studied and retention of subjects is achieved.

◆ Sato Y, Iwamoto J, Kanoko T, Satoh K. Amelioration of osteoporosis and hypovitaminosis D by sunlight exposure in hospitalized, elderly women with Alzheimer's disease: a randomized controlled trial. *J Bone Miner Res*. 2005 Aug;20(8):1327-33. [[Abstract](#)]

In a random and prospective study, AD patients were assigned to sunlight exposure (n = 132) or deprivation (n = 132) and followed for 1 year. The exposed group (3615 minutes/year) had fewer fractures. Eleven patients sustained fractures in the sunlight-deprived group, and three fractures occurred among the sunlight-exposed group (p = 0.0362; odds ratio = 3.7). —ES

◆ Sato Y, Iwamoto J, Kanoko T, Satoh K. Risedronate sodium therapy for prevention of hip fracture in men 65 years or older after stroke. *Arch Intern Med*. 2005 Aug 8-22;165(15):1743-8. [[Abstract](#)]

Of 280 male patients 65 years or older with strokes, 140 received 2.5 mg risedronate and the other 140 received placebo daily. Ten patients sustained hip fractures in the placebo group, and 2 in the risedronate group, RR = 0.19 (0.04-0.89). —ES

◆ Sato Y, Kanoko T, Satoh K, Iwamoto J. The prevention of hip fracture with risedronate and ergocalciferol plus calcium supplementation in elderly women with Alzheimer disease: a randomized controlled trial. *Arch Intern Med*. 2005 Aug 8-22;165(15):1737-42. [[Abstract](#)]

500 women with Alzheimer disease were randomly assigned to 2.5 mg risedronate or a placebo plus 1000 IU of ergocalciferol and 1200 mg of calcium for 18 months. At baseline, patients of both groups had 25-hydroxyvitamin D deficiency with hyperparathyroidism. Vertebral fractures occurred in 29 patients (24 hip fractures) in the control group and 8 patients (5 hip fractures) in the risedronate group, RR = 0.28 (0.13-0.59). —ES

Reviews, Perspectives, and Editorials

- ◆Cao X, Chen D. The BMP signaling and in vivo bone formation. *Gene*. 2005 Aug 29;357(1):1-8. [\[Abstract\]](#)
- ◆de Crombrughe B. Osteoblasts clock in for their day job. *Cell*. 2005 Sep 9;122(5):651-3. [\[Abstract\]](#)
- ◆Jan de Beur SM. Tumor-induced osteomalacia. *JAMA*. 2005 Sep 14;294(10):1260-7. [\[Abstract\]](#)

Other Studies of Potential Interest

- ◆Bai S, Kitaura H, Zhao H, Chen J, Muller JM, Schule R, Darnay B, Novack DV, Ross FP, Teitelbaum SL. FHL2 inhibits the activated osteoclast in a TRAF6-dependent manner. *J Clin Invest*. 2005 Oct 1;115(10):2742-51. [\[Abstract\]](#) [\[Full Text\]](#)
- ◆Bajayo A, Goshen I, Feldman S, Csernus V, Iverfeldt K, Shohami E, Yirmiya R, Bab I. Central IL-1 receptor signaling regulates bone growth and mass. *Proc Natl Acad Sci U S A*. 2005 Sep 6;102(36):12956-61. [\[Abstract\]](#) [\[Full Text\]](#)
- ◆Baldock PA, Sainsbury A, Allison S, Lin EJ, Couzens M, Boey D, Enriquez R, During M, Herzog H, Gardiner EM. Hypothalamic Control of Bone Formation: Distinct Actions of Leptin and Y2 Receptor Pathways. *J Bone Miner Res*. 2005 Oct;20(10):1851-57. [\[Abstract\]](#)
- ◆Chellaiah MA. Regulation of actin ring formation by rho GTPases in osteoclasts. *J Biol Chem*. 2005 Sep 23;280(38):32930-43. [\[Abstract\]](#) [\[Full Text\]](#)
- ◆Day TF, Guo X, Garrett-Beal L, Yang Y. Wnt/beta-catenin signaling in mesenchymal progenitors controls osteoblast and chondrocyte differentiation during vertebrate skeletogenesis. *Dev Cell*. 2005 May;8(5):739-50. [\[Abstract\]](#)
- ◆Frasor J, Danes JM, Funk CC, Katzenellenbogen BS. Estrogen down-regulation of the corepressor N-CoR: mechanism and implications for estrogen derepression of N-CoR-regulated genes. *Proc Natl Acad Sci U S A*. 2005 Sep 13;102(37):13153-7. [\[Abstract\]](#) [\[Full Text\]](#)
- ◆Gaur T, Lengner CJ, Hovhannisyan H, Bhat RA, Bodine PV, Komm BS, Javed A, van Wijnen AJ, Stein JL, Stein GS, Lian JB. Canonical WNT signaling promotes osteogenesis by directly stimulating Runx2 gene expression. *J Biol Chem*. 2005 Sep 30;280(39):33132-40. [\[Abstract\]](#) [\[Full Text\]](#)
- ◆Hall CL, Bafico A, Dai J, Aaronson SA, Keller ET. Prostate cancer cells promote osteoblastic bone metastases through Wnts. *Cancer Res*. 2005 Sep 1;65(17):7554-60. [\[Abstract\]](#)
- ◆Harvey KB, Drummer TD, Donahue SW. The tensile strength of black bear (*Ursus americanus*) cortical bone is not compromised with aging despite annual periods of hibernation. *J Biomech*. 2005 Nov;38(11):2143-50. [\[Abstract\]](#)
- ◆Hill TP, Spater D, Taketo MM, Birchmeier W, Hartmann C. Canonical Wnt/beta-catenin signaling prevents osteoblasts from differentiating into chondrocytes. *Dev Cell*. 2005 May;8(5):727-38. [\[Abstract\]](#)
- ◆Hilton MJ, Tu X, Cook J, Hu H, Long F. Ihh controls cartilage development by antagonizing Gli3, but requires additional effectors to regulate osteoblast and vascular development. *Development*. 2005 Oct;132(19):4339-51. [\[Abstract\]](#)

- ◆ Isidori AM, Giannetta E, Greco EA, Gianfrilli D, Bonifacio V, Isidori A, Lenzi A, Fabbri A. Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. *Clin Endocrinol (Oxf)*. 2005 Sep;63(3):280-93. [[Abstract](#)]
- ◆ Kassai Y, Munne P, Hotta Y, Penttila E, Kavanagh K, Ohbayashi N, Takada S, Thesleff I, Jernvall J, Itoh N. Regulation of mammalian tooth cusp patterning by ectodin. *Science*. 2005 Sep 23;309(5743):2067-70. [[Abstract](#)] [[Full Text](#)]
- ◆ Kim K, Kim JH, Lee J, Jin HM, Lee SH, Fisher DE, Kook H, Kim KK, Choi Y, Kim N. Nuclear Factor of Activated T Cells c1 Induces Osteoclast-associated Receptor Gene Expression during Tumor Necrosis Factor-related Activation-induced Cytokine-mediated Osteoclastogenesis. *J Biol Chem*. 2005 Oct 21;280(42):35209-16. [[Abstract](#)] [[Full Text](#)]
- ◆ Kugimiya F, Kawaguchi H, Kamekura S, Chikuda H, Ohba S, Yano F, Ogata N, Katagiri T, Harada Y, Azuma Y, Nakamura K, Chung UI. Involvement of Endogenous Bone Morphogenetic Protein (BMP) 2 and BMP6 in Bone Formation. *J Biol Chem*. 2005 Oct 21;280(42):35704-12. [[Abstract](#)] [[Full Text](#)]
- ◆ Miura Y, Miura M, Gronthos S, Allen MR, Cao C, Uveges TE, Bi Y, Ehrchiou D, Kortesis A, Shi S, Zhang L. Defective osteogenesis of the stromal stem cells predisposes CD18-null mice to osteoporosis. *Proc Natl Acad Sci U S A*. 2005 Sep 27;102(39):14022-7. [[Abstract](#)] [[Full Text](#)]
- ◆ Niida S, Kondo T, Hiratsuka S, Hayashi S, Amizuka N, Noda T, Ikeda K, Shibuya M. VEGF receptor 1 signaling is essential for osteoclast development and bone marrow formation in colony-stimulating factor 1-deficient mice. *Proc Natl Acad Sci U S A*. 2005 Sep 27;102(39):14016-21. [[Abstract](#)] [[Full Text](#)]
- ◆ Seemann P, Schwappacher R, Kjaer KW, Krakow D, Lehmann K, Dawson K, Stricker S, Pohl J, Ploger F, Staub E, Nickel J, Sebald W, Knaus P, Mundlos S. Activating and deactivating mutations in the receptor interaction site of GDF5 cause symphalangism or brachydactyly type A2. *J Clin Invest*. 2005 Sep 1;115(9):2373-81. [[Abstract](#)] [[Full Text](#)]
- ◆ Sun Y, Buki KG, Ettala O, Vaaraniemi JP, Vaananen HK. Possible role of direct Rac1-Rab7 interaction in ruffled border formation of osteoclasts. *J Biol Chem*. 2005 Sep 16;280(37):32356-61. [[Abstract](#)] [[Full Text](#)]
- ◆ van Abel M, Hoenderop JG, van der Kemp AW, Friedlaender MM, van Leeuwen JP, Bindels RJ. Coordinated control of renal Ca transport proteins by parathyroid hormone. *Kidney Int*. 2005 Oct;68(4):1708-21. [[Abstract](#)]