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NOT TO BE MISSED

Clinical and Basic Research Papers – February 2006 Selections

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

Pathophysiology

Lange PF, Wartosch L, Jentsch TJ, Fuhrmann JC. ClC-7 requires Ostm1 as a beta-subunit to support bone resorption and lysosomal function. *Nature*. 2006 Mar 9;440(7081):220-3.

> *Mutations in the CLCN7 (chloride channel) gene are found in autosomal dominant osteopetrosis type 2 (OPTA2) and malignant autosomal recessive osteopetrosis (OPTB1). OPTB1 may also be caused by "grey-lethal" mutations of the* OSTM1 *gene, and grey-lethal mice share with CLCN7 KO mice a similar osteopetrotic phenotype.* OSTM1 *encodes a membrane protein, but the precise function of this protein remained unknown. Through a series of elegant in vitro and in vivo experiments, this paper now co-localizes CLCN7 and OSTM1 in lysosomes, both in the CNS and the ruffled border of osteoclasts. It identifies OSTM1 as a β-subunit of the chloride channel complex and that loss of OSTM1 decreases CLC7 protein to pathogenic levels.* —SF

Liu S, Zhou J, Tang W, Jiang X, Rowe DW, Quarles LD. Pathogenic role of FGF23 in Hyp mice. *Am J Physiol Endocrinol Metab*. 2006 Jan 31; [Epub ahead of print]

> *To determine the cellular localization of FGF23 in bone and the relationship of FGF23 and Phex, green fluorescent protein (GFP) was knocked in in place of FGF23 and* FGF23*(+/-) mice were crossed with* Hyp *mice.* FGF23*(-/-)/*Hyp *mice have the phenotype of* FGF23*(-/-) – hyperphosphatemia rather than hypophosphatemia – and the dominance of this phenotype places FGF23 downstream of Phex – expression of the Phex phenotype requires FGF23. GFP as a marker of FGF23 is expressed mainly in osteocytes and venular endothelial cells in bone marrow and thymus, but is not found in osteoblasts, and expression is markedly increased in* FGF23 *(-/-) and Phex mice – this suggests that both vitamin D and hyperphosphatemia may regulate expression of FGF 23.* —GJS

Physiology and Metabolism

Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik S, Ochoa MT, Schauber J, Wu K, Meinken C, Kamen DL, Wagner M, Bals R, Steinmeyer A, Zugel U, Gallo RL, Eisenberg D, Hewison M, Hollis BW, Adams JS, Bloom BR, Modlin RL. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science*. 2006 Feb 23; [Epub ahead of print]

> *Vitamin D induces intracellular killing of M. tuberculosis by macrophages. This paper reports that both vitamin D 1-α-hydroxylase and the vitamin D receptor (VDR) are prominent among genes upregulated when the innate immune system in human macrophages is activated by ligands of Toll-like receptors (TLR). 1,25-dihydroxyvitamin D*

strongly upregulates synthesis of the defensin peptide cathelicidin and induction of cathelicidin by activation of TLR1/2 is blocked by a VDR antagonist. The level of 25-hydroxyvitamin D in Caucasian serum supports cathelicidin synthesis. Serum of African-Americans, with lower 25-hydroxyvitamin D levels, does not but cathelicidin synthesis can be induced by addition of 25OHD to the Caucasian level. The results suggest that vitamin D has a microbicidal role in granulomata and could explain, at least in part, the increased susceptability of Blacks to tuberculosis. —GJS

Treatment and Drug Effects

Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, Bassford T, Beresford SAA, Black HR, Blanchette P, Bonds DE, Brunner RL, Brzyski RG, Caan B, Cauley JA, Chlebowski RT, Cummings SR, Granek I, Hays J, Heiss G, Hendrix SL, Howard BV, Hsia J, Hubbell FA, Johnson KC, Judd H, Kotchen JM, Kuller LH, Langer RD, Lasser NL, Limacher MC, Ludlam S, Manson JE, Margolis KL, McGowan J, Ockene JK, O'Sullivan MJ, Phillips L, Prentice RL, Sarto GE, Stefanick ML, Van Horn L, Wactawski-Wende J, Whitlock E, Anderson GL, Assaf AR, Barad D, for the Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med.* 2006 Feb 16;354(7):669-83. [Abstract]

Finkelstein JS. Calcium plus vitamin D for postmenopausal women — bone appétit? *N Engl J Med*. 2006 Feb 16;354(7):750-2. [Info]

36,282 postmenopausal women aged 50 to 79 years were randomly assigned to 1000 mg calcium carbonate with 400 IU vitamin D3 daily or placebo for approximately 7 years. Hip BMD was 1.06% higher in the treated group than placebo (P<0.01). Intention-to-treat analysis indicated a hazard ratio of 0.88 for hip fracture (95%CI 0.72-1.08), 0.90 for clinical spine fracture (0.74-1.10), and 0.96 for total fractures (0.91-1.02). The risk of renal calculi increased (0.52 to 0.97). This study is not to be missed because everything that can go wrong in the design, execution and interpretation did. Over 80% of the sample were under 70 years of age. How can hip fracture prevention be studied? If the aim is to assess the effect of calcium, why allow the use of other drugs; 50% currently received hormone therapy? If the effect of vitamin D is to be assessed, why study replete women? How can any inference be made with a dropout rate of approximately 40%? Can a lower fracture rate in compliers to treatment be attributed to the treatment, if the principle of randomization that known and unknown covariates will be equally prevalent is no longer assured? Neither the null result by intent to treat, nor the positive result in compliers is interpretable. The only interpretable data is the high risk of kidney stones found in the intent to treat analysis. —ES

Jarjou LM, Prentice A, Sawo Y, Laskey MA, Bennett J, Goldberg GR, Cole TJ. Randomized, placebo-controlled, calcium supplementation study in pregnant Gambian women: effects on breast-milk calcium concentrations and infant birth weight, growth, and bone mineral accretion in the first year of life. *Am J Clin Nutr*. 2006 Mar;83(3):657-66.

This randomized, placebo-controlled supplementation study tested the hypothesis that calcium supplements (1500 mg/d calcium carbonate) given from week 20 to 36 of pregnancy to 125 Gambian women with a very low calcium intake (350 mg/d on average) could improve bone mineral mass in newborns. However, neither radius BMC (BMD) nor whole body BMC (available in a subset of infants) was improved by calcium supplements. Furthermore, BMC gain in the first year of life tended to be decreased in the offspring of supplemented mothers. Of note, birth weight, which has also been associated with bone

mass later in life, remained unaffected by calcium supplements. These results indicate that physiological mechanisms regulating calcium transfer from mothers to children in utero (including vitamin D metabolites and PTHrP) can cope with a large range of maternal calcium intake in order to provide the approximately 300-350 mg/d of calcium that are necessary for bone mineralization in the last trimester of pregnancy. Whether in contrast calcium supplements may have preserved the mother's skeleton from bone loss during this period is currently being investigated. —SF

McClung MR, Lewiecki EM, Cohen SB, Bolognese MA, Woodson GC, Moffett AH, Peacock M, Miller PD, Lederman SN, Chesnut CH, Lain D, Kivitz AJ, Holloway DL, Zhang C, Peterson MC, Bekker PJ; AMG 162 Bone Loss Study Group. Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med*. 2006 Feb 23;354(8):821-31.

Whyte MP. The long and the short of bone therapy. *N Engl J Med*. 2006 Feb 23;354(8):860-3.

Denosumab (AMG 162) is a humanized monoclonal antibody to RANKL that blocks osteoclast formation and function in vitro. Denosumab was administered for 12 months to postmenopausal women with T-score < 1.8, in one of three doses every three months or four doses every six months, and the effects were compared to alendronate, 70 mg weekly. Denosumab and alendronate treatment produced increases in BMD at the spine and hip that were comparable to alendronate, and denosumab produced greater suppression of bone turnover markers at the higher doses. No difference was noted in adverse event profiles. —GJS

Reviews, Perspectives and Editorials

Schiavi SC. Fibroblast growth factor 23: the making of a hormone. *Kidney Int*. 2006 Feb;69(3):425-7.

White KE, Larsson TM, Econs MJ. The roles of specific genes implicated as circulating factors involved in normal and disordered phosphate homeostasis: Frp-4, MEPE, and FGF23. *Endocr Rev*. 2006 Feb 7; [Epub ahead of print]

Other Studies of Potential Interest

Chen YX, Yan J, Keeshan K, Tubbs AT, Wang H, Silva A, Brown EJ, Hess JL, Pear WS, Hua X. The tumor suppressor menin regulates hematopoiesis and myeloid transformation by influencing Hox gene expression. *Proc Natl Acad Sci U S A*. 2006 Jan 24;103(4):1018-23. [Abstract] [Full Text]

Kelley GA, Kelley KS. Exercise and bone mineral density at the femoral neck in postmenopausal women: a meta-analysis of controlled clinical trials with individual patient data. *Am J Obstet Gynecol*. 2006 Mar;194(3):760-7.

Provot S, Kempf H, Murtaugh LC, Chung UI, Kim DW, Chyung J, Kronenberg HM, Lassar AB. Nkx3.2/Bapx1 acts as a negative regulator of chondrocyte maturation. *Development*. 2006 Feb;133(4):651-62. [Abstract]

Suzuki N, Ohneda O, Minegishi N, Nishikawa M, Ohta T, Takahashi S, Engel JD, Yamamoto M. Combinatorial Gata2 and Sca1 expression defines hematopoietic stem cells in the bone marrow niche. *Proc Natl Acad Sci U S A*. 2006 Feb 14;103(7):2202-7. [Abstract] [Full Text]

Wallace JM, Rajachar RM, Chen XD, Shi S, Allen MR, Bloomfield SA, Les CM, Robey PG, Young MF, Kohn DH. The mechanical phenotype of biglycan-deficient mice is bone- and gender-specific. *Bone*. 2006 Mar 6; [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.