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NOT TO BE MISSED

Clinical and Basic Research Papers – January 2005 Selections

Ego Seeman, Clinical Editor
Gordon J. Strewler, Editor

Epidemiology

Nordstrom A, Karlsson C, Nyquist F, Olsson T, Nordstrom P, Karlsson M. Bone loss and fracture risk after reduced physical activity. *J Bone Miner Res.* 2005 20(2):202-7. [Abstract]

> *Whether exercise undertaken during growth reduces fractures in old age is unknown. In 55 young male athletes retired for five years, BMD was decreased, but remained higher than in controls. In 400 older and now retired athletes, fewer had fragility fractures than did controls (2.0% vs. 4.2%, respectively) and fewer had distal radius fractures (0.75% vs. 2.5%, respectively). —ES*

Genetics

Koller DL, Ichikawa S, Johnson ML, Lai D, Xuei X, Edenberg HJ, Conneally PM, Hui SL, Johnston CC, Peacock M, Foroud T, Econs MJ. Contribution of the LRP5 gene to normal variation in peak BMD in women. *J Bone Miner Res.* 2005 Jan;20(1):75-80. [Abstract]

> *Associations between single nucleotide polymorphisms (SNPs) in low-density lipoprotein receptor-related protein 5 (LRP5) and hip and spine BMD were detected in 1301 premenopausal women, but the genotyped SNPs accounted for 0.8% of the variation in femoral neck BMD and 1.1% of the variation in spine BMD. —ES*

Pathophysiology

Benet-Pages A, Orlik P, Strom TM, Lorenz-Depiereux B. An FGF23 missense mutation causes familial tumoral calcinosis with hyperphosphatemia. *Hum Mol Genet.* 2005 Feb 1;14(3):385-90. [Abstract]

> *In one family, tumoral calcinosis with hyperphosphatemia was associated with a missense mutation (S71G) in fibroblast growth factor 23 (FGF23). Full-length mutant FGF23 accumulates in the Golgi; inactive C-terminal fragments are secreted* in vitro *and accumulate in serum. The predominant form of familial tumoral calcinosis was recently associated with mutations in the* GALNT3 *gene, which encodes a Golgi-based galactosyl transferase; it seems likely that improper glycosylation of FGF23 is the explanation for hyperphosphatemia in both syndromes. —GJS*

Milne TA, Hughes CM, Lloyd R, Yang Z, Rozenblatt-Rosen O, Dou Y, Schnepp RW, Krankel C, Livolsi VA, Gibbs D, Hua X, Roeder RG, Meyerson M, Hess JL. Menin and MLL cooperatively regulate expression of cyclin-dependent kinase inhibitors. *Proc Natl Acad Sci U S A.* 2005 Jan 18;102(3):749-54. [Abstract] [Full Text]

> *How menin functions as a tumor suppressor in multiple endocrine neoplasia type 1 (MEN1) has been uncertain. Menin can activate transcription via binding to mixed lineage leukemia (MLL) family proteins in a histone methyltransferase complex. This paper shows that menin activates transcription of the cyclin-dependent kinase inhibitors* $p27^{Kip1}$ and

p18^{Ink4c} by recruiting MLL to their promoters. Expression of p27^{Kip1} is decreased in tumors in MEN1 patients, compared with normal neuroendocrine tissues. The results offer a plausible explanation of the proliferative advantage that is conferred on neuroendocrine cells by inactivating menin mutations. —GJS

Wei S, Kitaura H, Zhou P, Ross FP, Teitelbaum SL. IL-1 mediates TNF-induced osteoclastogenesis. *J Clin Invest.* 2005 Feb;115(2):282-90. [Abstract] [Full Text]

Interleukin 1 (IL-1) and tumor necrosis factor α (TNF-α) each plays a role in osteolysis associated with inflammatory disorders, such as arthritis. This paper reports that much of the induction of osteoclastogenesis by TNF-α is mediated by IL-1. TNF-α induces the expression of both IL-1 and its receptor, IL-1R1, in stromal cells and osteoclast precursors. In the absence of IL-1R1, osteoclast formation by TNF-α is abolished in vitro *and reduced by about 50% in calvaria of intact mice. IL-1 acts by inducing receptor activator of NF-κB ligand (RANKL) expression in stromal cells, and in the presence of permissive levels of RANKL, also stimulates macrophages directly to form osteoclasts. —GJS*

Physiology

Oh KW, Rhee EJ, Lee WY, Kim SW, Baek KH, Kang MI, Yun EJ, Park CY, Ihm SH, Choi MG, Yoo HJ, Park SW. Circulating osteoprotegerin and receptor activator of NF-kappaB ligand system are associated with bone metabolism in middle-aged males. *Clin Endocrinol (Oxf)*. 2005 Jan;62(1):92-8. [Abstract]

Hypogonadism results in bone loss in men, but whether this is the result of androgen or estrogen deficiency (or both) is unclear. In 80 Korean males (aged 42-70 years), there was a negative correlation between serum osteoprotegerin (OPG) and spine BMD. Only serum estradiol, not serum testosterone, predicted serum OPG or receptor activator of NF-κB ligand (RANKL) levels. The circulating OPG-RANKL system is likely to be associated with bone metabolism in males and may mediate the effects of estradiol in men. —ES

Qin L, Tamasi J, Raggatt L, Li X, Feyen JH, Lee DC, Dicicco-Bloom E, Partridge NC. Amphiregulin is a novel growth factor involved in normal bone development and in the cellular response to parathyroid hormone stimulation. *J Biol Chem.* 2005 Feb 4;280(5):3974-81. [Abstract] [Full Text]

The epidermal growth factor (EGF) family member amphiregulin was identified as a PTH-responsive osteoblast gene in profiling experiments. Here, it is shown that PTH induces the expression of amphiregulin in osteoblasts and that amphiregulin increases the proliferation and inhibits the differentiation of preosteoblasts. Removal of the amphiregulin gene causes a moderate reduction in trabecular number and thickness. It is proposed that amphiregulin functions as a feedback regulator of osteoblast formation. —GJS

Saito H, Maeda A, Ohtomo S, Hirata M, Kusano K, Kato S, Ogata E, Segawa H, Miyamoto K, Fukushima N. Circulating FGF-23 is regulated by 1alpha,25-dihydroxyvitamin D3 and phosphorus in vivo. *J Biol Chem.* 2005 Jan 28;280(4):2543-9. [Abstract] [Full Text]

In the rat, 1α,25-dihydroxyvitamin D_3 increases the serum level of fibroblast growth factor 23 (FGF23), and thyroparathyroidectomy plus manipulation of diet shows this to be independent of PTH or changes in serum phosphate. A high phosphate intake also

increases FGF23 levels in 5/6-nephrectomized rats. Thus, FGF23 undergoes feedback regulation by both of its downstream targets, phosphate and 1α,25-dihydroxyvitamin D_3. —GJS

Treatment and Drug Effects

Chen JR, Plotkin LI, Aguirre JI, Han L, Jilka RL, Kousteni S, Bellido T, Manolagas SC. Transient versus sustained phosphorylation and nuclear accumulation of ERKs underlie anti- versus pro-apoptotic effects of estrogens. *J Biol Chem.* 2005 Feb 11;280(6):4632-8. [Abstract] [Full Text]

Sex steroids are antiapoptotic on osteoblasts/osteocytes, but proapoptotic on osteoclasts; these effects involve activation of the extracellular signal-regulated kinases (ERKs). In contrast to its transient effect on ERK phosphorylation in osteocytes, estradiol-induced ERK phosphorylation in osteoclasts was sustained. Conversion of sustained to transient ERK phosphorylation abrogated the proapoptotic effect on osteoclasts. Prolongation of ERK activation in osteocytes converted the antiapoptotic effect of estradiol to a proapoptotic one. The kinetics of ERK phosphorylation and the length of time that phospho-ERKs are retained in the nucleus are responsible for the pro- versus antiapoptotic effects of estrogen on different cell types. —ES

Peacock M, Bilezikian JP, Klassen PS, Guo MD, Turner SA, Shoback D. Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism. *J Clin Endocrinol Metab.* 2005 Jan;90(1):135-41. [Abstract] [Full Text]

The results of this one-year randomized controlled clinical trial indicate that chronic treatment of primary hyperparathyroidism with a calcimimetic agent is feasible. Curiously, markers of bone turnover are increased, not decreased, in treated patients. Is this further evidence that the calcium receptor can regulate bone turnover in a tissue- or cell-autonomous fashion? —GJS

Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med.* 2005 Jan 13;352(2):154-64. [Abstract]

Hypogonadism is a risk factor of bone loss and bone fragility, and this study gives some idea of the increment of risk in men with prostate cancer. Of 50,613 men diagnosed with this condition, those surviving at least five years -- 19.4% of those receiving androgen deprivation therapy -- had a fracture, compared with 12.6% of those not receiving androgen deprivation therapy. Controls without prostate cancer or androgen deprivation therapy would have been informative. —ES

Reviews, Perspectives, and Editorials

Berenson JR. Recommendations for zoledronic acid treatment of patients with bone metastases. *Oncologist.* 2005 Jan;10(1):52-62. [Abstract]

Holick MF. Stay tuned to PXR: an orphan actor that may not be D-structive only to bone. *J Clin Invest.* 2005 Jan;115(1):32-4. [Abstract] [Full Text]

Murray TM, Rao LG, Divieti P, Bringhurst FR. Parathyroid hormone secretion and action: evidence for discrete receptors for the carboxyl-terminal region and related biological actions of carboxyl-terminal ligands. *Endocr Rev.* 2005 Feb;26(1):78-113. [Abstract] [Full Text]

Riggs BL, Parfitt AM. Drugs used to treat osteoporosis: the critical need for a uniform nomenclature based on their action on bone remodeling. *J Bone Miner Res.* 2005 Feb;20(2):177-84. [Abstract]

Roodman GD, Windle JJ. Paget disease of bone. *J Clin Invest.* 2005 Feb;115(2):200-8. [Abstract] [Full Text]

Stewart AF. Clinical practice. Hypercalcemia associated with cancer. *N Engl J Med.* 2005 Jan 27;352(4):373-9. [Info]

Tolar J, Teitelbaum SL, Orchard PJ. Osteopetrosis. *N Engl J Med.* 2004 Dec 30;351(27):2839-49. [Info]

Other Studies of Potential Interest

Alexopoulos LG, Williams GM, Upton ML, Setton LA, Guilak F. Osteoarthritic changes in the biphasic mechanical properties of the chondrocyte pericellular matrix in articular cartilage. *J Biomech.* 2005 Mar;38(3):509-17. [Abstract]

Andrew T, Antioniades L, Scurrah KJ, Macgregor AJ, Spector TD. Risk of wrist fracture in women is heritable and is influenced by genes that are largely independent of those influencing BMD. *J Bone Miner Res.* 2005 Jan;20(1):67-74. [Abstract]

Barrett-Connor E, Siris ES, Wehren LE, Miller PD, Abbott TA, Berger ML, Santora AC, Sherwood LM. Osteoporosis and fracture risk in women of different ethnic groups. *J Bone Miner Res.* 2005 Feb;20(2):185-94. [Abstract]

Bastepe M, Frohlich LF, Linglart A, Abu-Zahra HS, Tojo K, Ward LM, Juppner H. Deletion of the NESP55 differentially methylated region causes loss of maternal GNAS imprints and pseudohypoparathyroidism type Ib. *Nat Genet.* 2005 Jan;37(1):25-7. [Abstract]

Caballero-Alias AM, Loveridge N, Pitsillides A, Parker M, Kaptoge S, Lyon A, Reeve J. Osteocytic expression of constitutive NO synthase isoforms in the femoral neck cortex: A case-control study of intracapsular hip fracture. *J Bone Miner Res.* 2005 Feb;20(2):268-73. [Abstract]

Chevalley T, Rizzoli R, Hans D, Ferrari S, Bonjour JP. Interaction between calcium intake and menarcheal age on bone mass gain: an eight-year follow-up study from prepuberty to postmenarche. *J Clin Endocrinol Metab.* 2005 Jan;90(1):44-51. [Abstract] [Full Text]

Gross TS, King KA, Rabaia NA, Pathare P, Srinivasan S. Upregulation of osteopontin by osteocytes deprived of mechanical loading or oxygen. *J Bone Miner Res.* 2005 Feb;20(2):250-6. [Abstract]

Hashimoto K, Morishige K, Sawada K, Tahara M, Kawagishi R, Ikebuchi Y, Sakata M, Tasaka K, Murata Y. Alendronate inhibits intraperitoneal dissemination in in vivo ovarian cancer model. *Cancer Res.* 2005 Jan 15;65(2):540-5. [Abstract]

Hu J, McLarnon SJ, Mora S, Jiang J, Thomas C, Jacobson KA, Spiegel AM. A Region in the Seven-transmembrane domain of the human Ca2+ receptor critical for response to Ca2+. *J Biol Chem.* 2005 Feb 11;280(6):5113-20. [Abstract] [Full Text]

Javed A, Barnes GL, Pratap J, Antkowiak T, Gerstenfeld LC, van Wijnen AJ, Stein JL, Lian JB, Stein GS. Impaired intranuclear trafficking of Runx2 (AML3/CBFA1) transcription factors in breast

cancer cells inhibits osteolysis in vivo. *Proc Natl Acad Sci U S A.* 2005 Feb 1;102(5):1454-9. [Abstract] [Full Text]

Jiang Y, Zhao J, Geusens P, Liao EY, Adriaensens P, Gelan J, Azria M, Boonen S, Caulin F, Lynch JA, Ouyang X, Genant HK. Femoral neck trabecular microstructure in ovariectomized ewes treated with calcitonin: MRI microscopic evaluation. *J Bone Miner Res.* 2005 Jan;20(1):125-30. [Abstract]

Kitano M, Ogata A, Sekiguchi M, Hamano T, Sano H. Biphasic anti-osteoclastic action of intravenous alendronate therapy in multiple myeloma bone disease. *J Bone Miner Metab.* 2005;23(1):48-52. [Abstract]

Kizawa H, Kou I, Iida A, Sudo A, Miyamoto Y, Fukuda A, Mabuchi A, Kotani A, Kawakami A, Yamamoto S, Uchida A, Nakamura K, Notoya K, Nakamura Y, Ikegawa S. An aspartic acid repeat polymorphism in asporin inhibits chondrogenesis and increases susceptibility to osteoarthritis. *Nat Genet.* 2005 Feb;37(2):138-44. [Abstract]

Lai CF, Cheng SL. alphavbeta integrins play an essential role in BMP-2 induction of osteoblast differentiation. *J Bone Miner Res.* 2005 Feb;20(2):330-40. [Abstract]

Liu CJ, Chang E, Yu J, Carlson CS, Prazak L, Yu XP, Ding B, Lengyel P, Di Cesare PE. The interferon-inducible p204 protein acts as a transcriptional coactivator of Cbfa1 and enhances osteoblast differentiation. *J Biol Chem.* 2005 Jan 28;280(4):2788-96. [Abstract] [Full Text]

Mellstrom DD, Sorensen OH, Goemaere S, Roux C, Johnson TD, Chines AA. Seven years of treatment with risedronate in women with postmenopausal osteoporosis. *Calcif Tissue Int.* 2004 Dec;75(6):462-8. [Abstract]

Naito J, Kaji H, Sowa H, Hendy GN, Sugimoto T, Chihara K. Menin suppresses osteoblast differentiation by antagonizing the AP-1 Factor, JunD. *J Biol Chem.* 2005 Feb 11;280(6):4785-91. [Abstract] [Full Text]

Norvell SM, Alvarez M, Bidwell JP, Pavalko FM. Fluid shear stress induces beta-catenin signaling in osteoblasts. *Calcif Tissue Int.* 2004 Nov;75(5):396-404. [Abstract]

Okabe M, Graham A. The origin of the parathyroid gland. *Proc Natl Acad Sci U S A.* 2004 Dec 21;101(51):17716-9. [Abstract] [Full Text]

Pan W, Mathews W, Donohue JM, Ramnaraine ML, Lynch C, Selski DJ, Walsh N, Cassady AI, Clohisy DR. Analysis of distinct tartrate-resistant acid phosphatase promoter regions in transgenic mice. *J Biol Chem.* 2005 Feb 11;280(6):4888-93. [Abstract] [Full Text]

Pascussi JM, Robert A, Nguyen M, Walrant-Debray O, Garabedian M, Martin P, Pineau T, Saric J, Navarro F, Maurel P, Vilarem MJ. Possible involvement of pregnane X receptor-enhanced CYP24 expression in drug-induced osteomalacia. *J Clin Invest.* 2005 Jan;115(1):177-86. [Abstract] [Full Text]

Rogers MJ. From molds and macrophages to mevalonate: a decade of progress in understanding the molecular mode of action of bisphosphonates. *Calcif Tissue Int.* 2004 Dec;75(6):451-61. [Abstract]

Shimizu N, Dean T, Tsang JC, Khatri A, Potts JT Jr, Gardella TJ. Novel parathyroid hormone (PTH) antagonists that bind to the juxtamembrane portion of the PTH/PTH-related protein receptor. *J Biol Chem.* 2005 Jan 21;280(3):1797-807. [Abstract] [Full Text]

Verberckmoes SC, Behets GJ, Oste L, Bervoets AR, Lamberts LV, Drakopoulos M, Somogyi A, Cool P, Dorrine W, De Broe ME, D'Haese PC. Effects of strontium on the physicochemical characteristics of hydroxyapatite. *Calcif Tissue Int*. 2004 Nov;75(5):405-15. [Abstract]

Wang YH, Liu Y, Buhl K, Rowe DW. Comparison of the action of transient and continuous PTH on primary osteoblast cultures expressing differentiation stage-specific GFP. *J Bone Miner Res.* 2005 Jan;20(1):5-14. [Abstract]