NOT TO BE MISSED

Clinical and Basic Research Papers – July 2009

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Clinical Studies and Drug Effects


The first study is a post-hoc analysis of the teriparatide versus placebo Fracture Prevention Trial, looking at the efficacy of treatment on non-vertebral fractures, clinical vertebral fractures and back pain as a function of time. Whereas the incidence of clinical vertebral fractures was diminished about 50% with TPT within the first 7 months of therapy, and virtually abolished thereafter, reduction of back pain as well as of non-vertebral fractures became apparent between 7 to 14 months of therapy and was maintained thereafter. Although these results are limited by the rather small number of events in each time interval, they may be of importance since they suggest that longer duration of teriparatide therapy may provide stronger clinical benefits while the incidence of other adverse events declines over time (improved tolerance).

The second study is a prolongation of a previously published study on the combination of alendronate and PTH, where the latter was administered either daily, or cyclically (three months on/three months off) for one year. Then, following one year on alendronate alone, patients at high risk resumed a one-year course of daily teriparatide. One-year gain of BMD at the spine was similar during retreatment as during the first course of administration, indicating that, when necessary, teriparatide can be readministered safely and efficiently after TPT and alendronate. There was, however, no apparent increase of hip BMD during retreatment. —SF


By comparing the effects of PTH with alendronate (ALN) or a cathepsin K inhibitor in growing ovariectomized mice, this study provides two really interesting observations. First, the cathepsin K inhibitor did not inhibit bone formation rate (BFR), as also previously seen in cathepsin K null mice, whereas ALN did. Second, PTH + cathepsin K inhibitor did not inhibit the increase of BFR induced by PTH, whereas ALN did, and PTH + cathepsin K inhibitor thereby exerted additive effects on trabecular bone volume. These observations support the notion that selective inhibition of bone resorbing activities may
occur without necessarily inhibiting osteoblastic functions. —SF

Genetics

Freedman BI, Bowden DW, Ziegler JT, Langefeld CD, Lehtinen AB, Rudock ME, Lenchik L, Hruska KA, Register TC, Carr JJ. Bone morphogenetic protein 7 (BMP7) gene polymorphisms are associated with inverse relationships between vascular calcification and bone mineral density: The Diabetes Heart Study. J Bone Miner Res. 2009 May 19. [Epub ahead of print] [Abstract]

Bone morphogenetic proteins (BMPs) are potential candidate genes that may mediate the inverse relationship between bone mineral density (BMD) and vascular calcification (VC). In 920 European Americans from 374 Diabetes Heart Study families, 762 with type 2 diabetes, variance components quantitative trait locus association analysis was computed using SOLAR software and a bivariate principal component analysis (PCA) assessed for genetic relationships between BMD and VC. The results suggest that polymorphisms in BMP7 are associated with inverse relationships between bone mineralization and vascular calcification in coronary, carotid and abdominal aorta.

—HWD


A genome-wide association study (GWAS) of 3700 cases with radio-opaque (hence mostly calcium) kidney stones and more than 40,000 controls reveals that subjects homozygous for a SNP in the gene coding for claudin 14, a transmembrane protein expressed in renal tubules and involved in regulation of cell permeability, have their risk of kidney stones increased by 64%, an unusually large effect for a single SNP. Furthermore, the SNPs also correlated to urinary calcium, serum PTH levels, and a decrease in hip and spine BMD. This study demonstrates that an unbiased, hypothesis-free approach can unveil unsuspected mechanisms for common disorders. —SF


This study reports a comprehensive association between volumetric bone density at the femoral neck and lumbar spine and 383 candidate genes. This study initially screened tagging and potentially functional SNPs and tested their associations among 862 community-dwelling old Caucasian men. The most promising SNP associations were validated in an additional 1156 Caucasian men. The genetic loci for volumetric bone density are to some extent skeletal site-specific. —HWD

Molecular and Cell Biology

Osterix (Osx) acts downstream of Runx2 and is an essential transcription factor for osteoblast differentiation and bone formation. Because Osx null mutants die immediately after birth, it has not been possible to examine the role of Osx in growing and adult bones. Thus, the authors generated conditional Osx knockout mice to inactivate the Osx gene in osteoblasts by Cre recombinase expression under the control of the 2.3-kb type I collagen promoter. Osx deficiency in osteoblasts resulted in delayed osteoblast maturation with an accumulation of immature osteoblasts, causing osteopenia in lumbar vertebra, thinner and more porous cortical bones, and reduced bone length. No functional defects were found in osteoclasts. The results show that Osx is a positive regulator of osteoblast differentiation with a significant role in longitudinal bone growth in growing and adult bone. —TM

◆ Mitchell J, Hong S, Nanes M, Lu X. Regulation of osterix (Osx, Sp7) and the Osx promoter by parathyroid hormone in osteoblasts. J Mol Endocrinol. 2009 Jun 8. [Epub ahead of print] [Abstract]

Continuous exposure to PTH not only results in an increased RANKL/OPG ratio leading to increased bone resorption and bone loss, at least in cortical bone, but is also characterized at the cell/tissue level by an inhibition of bone formation, again, at least on cortical surfaces, though the mechanisms remain largely unknown. This study indicates that PTH-stimulated cAMP signaling inhibits expression of the indispensable osteoblastic transcription factor osterix (Osx) and localizes the Osx promoter regions for PTH inhibition. —SF


This study extends our knowledge of the negative role of bone marrow adipocytes, which not only develop at the expense of and/or inhibit osteoblastogenesis, but are now shown to act as negative regulators of the hematopoietic stem cell niche. Hence, antagonizing/inhibiting ppar-gamma, which results in decreased adipogenesis and increased bone mass in mice, also favors engraftment of hematopoietic stem cells in the bone marrow. —SF

◆ Shim JH, Greenblatt MB, Xie M, Schneider MD, Zou W, Zhai B, Gygi S, Glimcher LH. TAK1 is an essential regulator of BMP signaling in cartilage. EMBO J. 2009 June 18. [Epub ahead of print] [Abstract]

TGFβ activated kinase 1 (TAK1), a member of the MAPKKK family, is a key regulator of MAPK kinase activation in the TGFβ and BMP signaling pathways. Because mutations in the TAK1 gene cause defects in developing embryos that are similar to those caused by Smad5 mutations, the authors generated mice with a conditional deletion of TAK1 driven by the collagen 2 promoter. These mice displayed severe chondrodysplasia with runting, impaired formation of secondary ossification centers, and joint abnormalities including elbow dislocation and tarsal fusion. Bone morphogenetic protein receptor (BMPR) signaling was markedly impaired in TAK1-deficient chondrocytes as evidenced by reduced phosphorylation of Smad1/5/8 in addition to defective p38/Jnk/Erk MAP kinase signaling. These results demonstrate that TAK1 is required for BMP signaling by acting as an upstream activating kinase for Smad1/5/8, and provide the first evidence that TAK1 is required for normal cartilage development. —TM
Pathophysiology


*These two papers report for the first time the clinical spectrum related to mutations in the IL1RN gene coding for an interleukin 1 receptor antagonist. Skeletal manifestations include osteopenia, lytic bone lesions, and abundant osteoclasts. —SF*


*Expression of the Jansen’s H223R constitutively active PTH/PTHrP receptor in osteoblasts, an elegant model of the effects of hyperparathyroidism on bone tissue, was shown years ago to increase osteoblast and osteoclast number, trabecular bone volume, and bone marrow fibrosis, while inhibiting periosteal mineral apposition, diminishing cortical thickness and inducing cortical porosity, an otherwise unknown feature in rodents (which lack spontaneous haversian bone remodeling). This study now shows that inhibition of osteoclasts by osteoprotegerin prevents cortical porosity and marrow fibrosis, whereas inhibition of bone resorption by BiPi does not. These results not only extend our appreciation of the unique effects of RANKL inhibition on bone remodeling but also suggest a direct role of osteoclasts and/or their products on the development of bone marrow fibrosis seen in hyperparathyroidism. Hence, they provide some rationale to test the effects of RANKL inhibitors in conditions where BiPi have either limited effects and/or are prohibited, such as fibrous dysplasia and some forms of renal osteodystrophy. —SF*

Other Studies of Potential Interest

**Amano S, Sekine K, Bonewald LF, Ohmori Y.** A novel osteoclast precursor cell line, 4B12, recapitulates the features of primary osteoclast differentiation and function: Enhanced transfection efficiency before and after differentiation. *J Cell Physiol.* 2009 Jun 2. [Epub ahead of print] [Abstract]


**Calloni GW, Le Douarin NM, Dupin E.** High frequency of cephalic neural crest cells shows coexistence of neurogenic, melanogenic, and osteogenic differentiation capacities. *Proc Natl Acad Sci U S A.* 2009 Jun 2;106(22):8947-52. [Abstract] [Full Text]


McKinstry WJ, Polekhina G, Diefenbach-Jagger H, Ho PW, Sato K, Onuma E, Gillespie MT, Martin TJ, Parker MW. Structural basis for antibody discrimination between two hormones that recognize the parathyroid hormone receptor. J Biol Chem. 2009 Jun 5;284(23):15557-63. [Abstract] [Full Text]

stimulates IL-6 release and inhibits osteoblastic differentiation through VPAC2 receptor in osteoblastic MC3T3 cells. J Cell Physiol. 2009 Jun 3. [Epub ahead of print] [Abstract]


Conflict of Interest: Dr. Ferrari reports that he receives research support from Amgen and is an advisory committee member and lectures occasionally at conference symposia for Merck Sharp & Dohme, the Alliance for Better Bone Health (Sanofi Aventis/P&G), Amgen, Eli Lilly (Switzerland), Servier (Switzerland), and Novartis (Switzerland). Dr. Little reports that he receives royalties, research funds and consultancy fees from Novartis Pharma, as well as research support from Stryker Biotech. 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. Dr. Matsumoto and Dr. Deng report no conflicts of interest.