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NOT TO BE MISSED

Clinical and Basic Research Papers – January 2005 Selections

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

Bone Modeling and Remodeling

Garnero P, Borel O, Gineyts E, Duboeuf F, Solberg H, Bouxsein ML, Christiansen C, Delmas PD. Extracellular post-translational modifications of collagen are major determinants of biomechanical properties of fetal bovine cortical bone. *Bone*. 2005 Nov 2; [Epub ahead of print] [Abstract]

> *Type I collagen provides bone ductility and toughness. Fetal bovine cortical bone type I collagen cross-linking was modified by incubation, which increased type I collagen C-telopeptide isomerization. This decreased bending and compressive yield stress, and increased compressive post-yield energy absorption, independent of bone mineral density. The extent and nature of collagen cross-linking contribute to the mechanical properties of fetal bovine cortical bone.* —ES

Richard S, Torabi N, Franco GV, Tremblay GA, Chen T, Vogel G, Morel M, Cleroux P, Forget-Richard A, Komarova S, Tremblay ML, Li W, Li A, Gao YJ, Henderson JE. Ablation of the Sam68 RNA binding protein protects mice from age-related bone loss. *PLoS Genet*. 2005 Dec 16;1(6):e74; [Epub ahead of print] [Abstract]

> *Past 4 months of age, C57BL/6 mice lose a substantial amount of trabecular bone volume, but the reasons for these alterations remained unknown. Now it is shown that mice null for Sam68, a broadly expressed RNA binding protein, maintain their trabecular bone micro-architecture up to one year of age. Although Sam68 KO mice have lower leptin levels than wild type mice, histomorphometric and biochemical analyses do not show a decrease in bone remodeling in KO mice. In contrast, in vitro experiments suggest that osteoblast differentiation is increased whereas adipocyte differentiation is decreased in the absence of Sam68. It remains to be seen whether the expression of Sam68 is altered in the aging skeleton and whether it directly regulates expression of crucial osteoblastic transcription factors, such as Runx2 and Osx.* —SF

Steiglitz BM, Kreider JM, Frankenburg EP, Pappano WN, Hoffman GG, Meganck JA, Liang X, Hook M, Birk DE, Goldstein SA, Greenspan DS. Procollagen C proteinase enhancer 1 genes are important determinants of the mechanical properties and geometry of bone and the ultrastructure of connective tissues. *Mol Cell Biol*. 2006 Jan;26(1):238-49. [Abstract]

> *Pro-collagen C proteinase enhancer 1 (PCOLCE1) enhances the activity of pCP to cleave procollagen C propeptides. Mice null for PCOLCE1 were characterized by disorganized collagen fibrils in bone tissue resulting in altered bone material properties, as evaluated by predicted modulus from 4-point bending test of femora. Most interestingly, Pcolce null mice had greater cortical cross-sectional area and thickness*

resulting in improved structural mechanical integrity. This compensatory mechanism was more prominent in males than females, further indicating that gender-specific hormones and/or cytokines are involved in adapting bone geometry to material defects. —SF

Stevens HY, Meays DR, Yeh J, Bjursten LM, Frangos JA. COX-2 is necessary for venous ligation-mediated bone adaptation in mice. *Bone*. 2006 Jan;38(1):93-104. [Abstract]

This is a very elegant study demonstrating that fluid shear produces bone remodeling and does so in part through the induction of cyclooxygenase 2 (COX-2), an isozyme responsible for production of prostaglandins, local mediators of adaptive remodeling. Ligation of the femoral vein increases fluid shear stress and adapation without loading, unless there is no COX-2. Fluid-flow-mediated bone adaptation is COX-2 dependent. —ES

Diagnosis

Riggs BL, Melton LJ 3rd, Robb RA, Camp JJ, Atkinson EJ, Oberg AL, Rouleau PA, McCollough CH, Khosla S, Bouxsein ML. Population-based analysis of the relationship of whole bone strength indices and fall-related loads to age- and sex-specific patterns of hip and wrist fractures. *J Bone Miner Res*. 2006 Feb;21(2):315-23. [Abstract]

Understanding structure requires the study of structure, and not a two-dimensional shadow called 'BMD'. Riggs et al. lead the charge, assessing volumetric BMD (vBMD), cross-sectional geometry, and axial (EA) and flexural (EI) rigidities at the ultradistal radius and femoral neck. There are lots of goodies in this paper, in addition to the main themes. vBMD in young adults was similar by sex. Decreases in vBMD over life were also similar by sex at the ultradistal radius, and only somewhat greater in women at the femoral neck. Strength estimates were greater in men at the radius, and worsened over life less in men. Strength estimates were worsened less over life in men at the femoral neck. —ES

Epidemiology

Brophy S, John G, Evans E, Lyons RA. Methodological issues in the identification of hip fractures using routine hospital data: a database study. *Osteoporos Int*. 2005 Nov 25; [Epub ahead of print] [Abstract]

This paper is of interest because it identifies sources of error in shortcut attempts at defining the incidence of hip fractures using codes in hospital records. There is no substitute for counting fractures, and until this is done properly, differences in hip fracture incidence by sex, race, location, and epoch remain suspect. —ES

Genetics

Lau KH, Kapur S, Kesavan C, Baylink DJ. Upregulation of the WNT, estrogen receptor, insulin-like growth factor-I, and bone morphogenetic protein pathways in C57BL/6J osteoblasts as opposed to C3H/HeJ osteoblasts in part contributes to the differential anabolic response to fluid shear. *J Biol Chem*. 2006 Feb 3; [Epub ahead of print]

C3H and B6 mice present some striking differences in bone mass and structure, including an increased response to mechanical loading in B6. Primary osteoblasts

isolated from these mice were subjected to fluid shear stress and gene expression in these cells analyzed using "home-made" micro-arrays containing sequences for about 5500 genes. Among the several hundreds of genes that appeared to be differentially regulated in response to stress between C3H and B6 osteoblasts, the authors manually identified four pathways (BMP/TGF-ß, IGF-1, Wnt and estrogen) that were upregulated in B6 cells. Having confirmed differences in gene expression by RT-PCR, involvement of these pathways in cell proliferation and intracellular signaling in response to stress was confirmed using specific inhibitors. Quite remarkably, in vivo 4-point bending of C3H and B6 tibias for 2 weeks confirmed differential expression of several genes in these pathways. Although the nature of the arrays did not allow the investigators to identify all the genes implicated in the differences between C3H and B6 osteoblasts, these results may also help to identify candidate genes for specific skeletal traits within QTLs isolated in congenic B6 mice, for instance. —SF

Physiology and Metabolism

Hematopoietic stem cells live in a niche on the endosteum of bone that is defined by an association with osteoblasts. The three papers below discuss how hematopoietic stem cells find this niche and how they leave it. Both processes involve osteoblasts; the level of extracellular calcium also governs entry into the niche.

Adams GB, Chabner KT, Alley IR, Olson DP, Szczepiorkowski ZM, Poznansky MC, Kos CH, Pollak MR, Brown EM, Scadden DT. Stem cell engraftment at the endosteal niche is specified by the calcium-sensing receptor. *Nature*. 2006 Feb 2;439(7076):599-603. [Abstract]

After bone is mineralized, hematopoietic stem cells (HSCs) invade bone marrow and come to reside in an osteoblast-associated niche near the endosteum. To investigate the possibility that changes in extracellular calcium related to bone mineral govern the homing of HSCs to this niche, Adams et al. investigated the HSC niche in mice in which the parathyroid calcium receptor (CaR) had been inactivated. The CaR is expressed in HSCs. Fetal mice in which CaR had been inactivated have reduced HSC numbers in bone marrow but increased HSCs in spleen. In bone marrow transplantation experiments, CaR(-/-) *HSCs display defective homing to the endosteal niche, a trait that is associated with poor adhesion to type I collagen. Calcium release from mineralized bone may enhance the engraftment of hematopoietic cells to an osteoblast-associated niche.* —GJS

Kaplan RN, Riba RD, Zacharoulis S, Bramley AH, Vincent L, Costa C, MacDonald D, Jin DK, Shido K, Kerns SA, Zhu Z, Hicklin D, Wu Y, Port JL, Altorki N, Port R, Ruggero D, Shmelkov SV, Jensen KK, Rafii S, Lyden D. VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. *Nature*. 2005 Dec 8;438(7069):820-7. [Abstract]

In mouse models of tumor metastasis, hematopoietic progenitor cells (HPCs) are mobilized by the presence of tumor (Lewis lung carcinoma or B16 melanoma) and home to soft tissue niches that are the sites of subsequent metastases. Formation of premetastatic clusters can be blocked by preventing VEGF receptor-1 (Flt1) function. HPCs (and subsequently tumor cells) home to sites that are determined by fibronectin release from tissue fibroblasts stimulated by tumor-specific growth factors. Conditioned medium from melanoma cells is able to redirect the tissue-specific pattern of lung cancer metastasis, suggesting that patterns of fibronectin expression and HPC homing are what

dictate the organ specificity of metastasis. Does the presence of tumor release HPCs from an osteoblast-associated niche? —GJS

Katayama Y, Battista M, Kao WM, Hidalgo A, Peired AJ, Thomas SA, Frenette PS. Signals from the sympathetic nervous system regulate hematopoietic stem cell egress from bone marrow. *Cell*. 2006 Jan 27;124(2):407-21. [Abstract]

G-CSF releases hematopoietic stem and progenitor cells (HSPC) from bone marrow and is used for this purpose in bone marrow transplantation. G-CSF mobilization of stem cells is associated with a marked reduction in osteoblast activity (cell flattening, reduced runx2 and collagen gene expression) and reduced production of the chemokine CXCL12. Much of the suppression of osteoblasts by G-CSF is mediated by the adrenergic nervous system. Cytokines thus act partly through the sympathetic nervous system to inhibit osteoblast function and thereby release HSC from the osteoblast-associated stem cell niche. —GJS

Lindberg MK, Svensson J, Venken K, Chavoshi T, Andersson N, Moverare Skrtic S, Isaksson O, Vanderschueren D, Carlsten H, Ohlsson C. Liver-derived IGF-I is permissive for ovariectomy-induced trabecular bone loss. *Bone*. 2006 Jan;38(1):85-92. [Abstract]

The sex hormone-IGF-I connection is a story incompletely told. Liver-specific IGF-I(-/-) *mice don't lose bone after ovx and don't increase the number of T-cells in the marrow. In addition, they don't increase IL-7 mRNA or the RANKL/osteoprotegerin ratio, so no osteoclastogenesis takes place. Gorgeous stuff.* —ES

Razzaque MS, Sitara D, Taguchi T, St-Arnaud R, Lanske B. Premature aging-like phenotype in fibroblast growth factor 23 null mice is a vitamin D-mediated process. *FASEB J*. 2006 Jan 25; [Epub ahead of print]

Kurosu H, Ogawa Y, Miyoshi M, Yamamoto M, Nandi A, Rosenblatt KP, Baum MG, Schiavi S, Hu MC, Moe OW, Kuro-O M. Regulation of fibroblast growth factor-23 signaling by Klotho. *J Biol Chem*. 2006 Jan 25; [Epub ahead of print]

The phenotype of the FGF23(-/-) *and* klotho *mutations has been described as resembling premature aging. Razzaque et al. report that when vitamin D activation is prevented by ablation of vitamin D 1α-hydroxylase, soft tissue calcification, skin changes and pulmonary emphysema in* FGF23(-/-) *mice are reversed and their life span is increased. "Premature aging" is probably a consequence of combined hypercalcemia and hypophosphatemia. They also make the important new observation that* klotho *gene expression in the kidney is dependent on FGF23. Kurosu et al. show that the Klotho protein binds to FGF receptors and increases receptor binding and activation by FGF23. The new papers add considerably to our understanding of the relationship of Klotho and FGF23 as vitamin D-dependent partners in a new homeostatic axis (also see Strewler GJ. The Spinner Meets the Stone: Klotho and Mineral Metabolism. BoneKEy-Osteovision. 2005 November;2(11):29-33).*—GJS

Treatment and Drug Effects

Bauer DC, Garnero P, Hochberg MC, Santora A, Delmas P, Ewing SK, Black DM; for the Fracture Intervention Research Group. Pretreatment levels of bone turnover and the antifracture

efficacy of alendronate: the fracture intervention trial. *J Bone Miner Res*. 2006 Feb;21(2):292-9. [Abstract]

> *The higher the baseline risk for fracture, the lower the number needed to treat for a given level of efficacy of a drug. Most studies suggest that the relative risk reduction for fracture with a drug is no different in persons with high or low remodeling, only the absolute risk is higher in those with high remodeling (see Gonnelli S, et al. Calcif Tissue Int. 1999 Nov;65(5):359-64; Seibel MJ, et al. J Bone Miner Res. 2004 Feb;19(2):323-9; Civitelli R, et al. J Clin Invest. 1988 Oct;82(4):1268-74). This study is different, as it suggests that alendronate will reduce fracture risk to a greater extent in those with higher baseline remodeling. This is an interesting and important observation, if it is true. The only way we can find out is with a randomized trial of patients first stratified by remodeling rate, and then randomized to placebo versus treatment arms. This has never been done in this field.* —ES

Ensrud K, Riccardo Genazzani A, Geiger MJ, McNabb M, Dowsett SA, Cox DA, Barrett-Connor E. Effect of raloxifene on cardiovascular adverse events in postmenopausal women with osteoporosis. *Am J Cardiol*. 2006 Feb 15;97(4):520-7. [Abstract]

> *In post-menopausal women with osteoporosis, raloxifene decreased vertebral fracture risk (4 yrs study, MORE) and decreased breast cancer risk (MORE + 4 yrs follow-up, CORE). Retrospective analysis in a MORE subgroup with high risk of CV events further suggested that raloxifene might be protective for the CV system. In this report, the risk of CV events in the 3430 MORE participants who completed CORE are presented. Of note, both MORE and CORE inclusion criteria excluded patients at high risk of thrombo-embolic events. No significant differences in CV events were found between raloxifene and placebo over 8 yrs. In fact, hazard ratios for both cerebrovascular and coronary events subgroups all pointed towards an increased risk among raloxifene subjects, and this risk was nearly two-fold higher for raloxifene in a sub-group of women with anti-hypertensive medication.* —SF

Iida-Klein A, Hughes C, Lu SS, Moreno A, Shen V, Dempster DW, Cosman F, Lindsay R. Effects of cyclic versus daily hPTH(1-34) regimens on bone strength in association with BMD, biochemical markers, and bone structure in mice. *J Bone Miner Res*. 2006 Feb;21(2):274-82. [Abstract]

> *Anabolic treatment using PTH is expensive. In this experiment, the authors demonstrate less but comparable benefit, in terms of femoral bone strength, in animals given less drug. It's worth considering this finding together with a recent study published on cyclic PTH (Cosman F, et al. N Engl J Med. 2005 Aug 11;353(6):566-75).* —ES

Solomon DH, Avorn J, Katz JN, Finkelstein JS, Arnold M, Polinski JM, Brookhart MA. Compliance with osteoporosis medications. *Arch Intern Med.* 2005 Nov 14;165(20):2414-9. [Abstract]

> *This is not new, but it is an important study nonetheless. One year after initiating treatment for osteoporosis, 45.2% of 40,002 patients were not filling prescriptions. Factors predicting compliance were identified, but these accounted for only 6% of the variation in compliance. There are many challenges here. The higher fracture rates in noncompliers may have something to do with them, and not the lack of drug, because poor compliers to placebo have higher morbidity and mortality than compliers to placebo. (See Horwitz RI, et al. Lancet. 1990 Sep 1;336(8714):542-5 and New Engl J Med. 1980 Oct 30;303(18):1038-41).* —ES

Ste-Marie LG, Schwartz SL, Hossain A, Desaiah D, Gaich GA. Effect of teriparatide [rhPTH(1-34)] on BMD when given to postmenopausal women receiving hormone replacement therapy. *J Bone Miner Res*. 2006 Feb;21(2):283-91. [Abstract]

> *Compared with hormone replacement therapy alone, combined treatment produced greater increases in spine (14 vs 3%), total hip (5.2 vs 1.6%), and femoral neck (5.2 vs 2%) BMD. The implications are clear, but are they right? Sequential or combined use of a bone forming agent to combat reduced bone formation and an anti-resorptive to combat increased bone resorption has appeal. However, comparative trials with structural analysis and anti-fracture efficacy are unavailable – can we accept surrogate changes such as BMD? The BMD increase after an anti-resorptive is a poor predictor of fracture risk reduction. Antiresorptives shrink the remodeling space (remodeling sites active before treatment complete remodeling with bone formation, primary then more complete mineralization of this and older bone). PTH deposits new bone, increasing thickness of trabeculae and cortex. Whether the greater increase in BMD after PTH or combined treatment equates with a greater fracture risk reduction than the lesser increase in BMD after bisphosphonates will remain unknown until fracture endpoints are used.* —ES

Trout AT, Kallmes DF, Kaufmann TJ. New fractures after vertebroplasty: adjacent fractures occur significantly sooner. *AJNR Am J Neuroradiol*. 2006 Jan;27(1):217-23. [Abstract]

> *In this, the largest retrospective study to date, vertebroplasty was strongly associated with early fractures of adjacent vertebrae. These data sound a cautionary note about vertebroplasty and emphasize the vital importance of randomized, prospective clinical trials of the procedure.* —GJS

Watts NB, Geusens P, Barton IP, Felsenberg D. Relationship between changes in BMD and nonvertebral fracture incidence associated with risedronate: reduction in risk of nonvertebral fracture is not related to change in BMD. *J Bone Miner Res*. 2005 Dec;20(12):2097-104. [Abstract]

> *This study drives home once again the lack of association between change in BMD and fracture risk reduction. The incidence of nonvertebral fractures in risedronate-treated patients was no different in patients whose spine BMD decreased (7.8%) or increased (6.4%). The changes in BMD explained 7-12% of nonvertebral fracture efficacy. This is the reason why repeating BMD measurement has no scientific basis. If changes in BMD were predictors, why would we need randomized trials with fracture endpoints? Why would we need control groups?* —ES

Reviews, Perspectives and Editorials

Andress DL. Vitamin D in chronic kidney disease: a systemic role for selective vitamin D receptor activation. *Kidney Int*. 2006 Jan;69(1):33-43. [Abstract]

Arjmand N, Shirazi-Adl A. Biomechanics of changes in lumbar posture in static lifting. *Spine*. 2005 Dec 1;30(23):2637-48. [Abstract]

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Viguet-Carrin S, Garnero P, Delmas PD. The role of collagen in bone strength. *Osteoporos Int*. 2005 Dec 9; [Epub ahead of print] [Abstract]

Wada T, Nakashima T, Hiroshi N, Penninger JM. RANKL-RANK signaling in osteoclasto-genesis and bone disease. *Trends Mol Med*. 2006 Jan;12(1):17-25.

Westendorf JJ. Transcriptional co-repressors of Runx2. *J Cell Biochem*. 2006 Jan 26; [Epub ahead of print] [Abstract]

Other Studies of Potential Interest

Bauer DC, Garnero P, Bilezikian JP, Greenspan SL, Ensrud KE, Rosen CJ, Palermo L, Black DM. Short-term changes in bone turnover markers and bone mineral density response to parathyroid hormone in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab*. 2006 Jan 31; [Epub ahead of print]

Brouwers JE, van Donkelaar CC, Sengers BG, Huiskes R. Can the growth factors PTHrP, Ihh and VEGF, together regulate the development of a long bone? *J Biomech*. 2005 Nov 17; [Epub ahead of print] [Abstract]

Chen YL, Law PY, Loh HH. Sustained activation of phosphatidylinositol 3-kinase/AKT/nuclear factor kappaB signaling mediates G protein-coupled delta-opioid receptor gene expression. *J Biol Chem*. 2006 Feb 10;281(6):3067-74. [Abstract] [Full Text]

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Ichikawa S, Johnson ML, Koller DL, Lai D, Xuei X, Edenberg HJ, Hui SL, Foroud TM, Peacock M, Econs MJ. Polymorphisms in the bone morphogenetic protein 2 (BMP2) gene do not affect bone mineral density in white men or women. *Osteoporos Int*. 2006 Jan 24; [Epub ahead of print] [Abstract]

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Kim YJ, Kim HN, Park EK, Lee BH, Ryoo HM, Kim SY, Kim IS, Stein JL, Lian JB, Stein GS, van Wijnen AJ, Choi JY. The bone-related Zn finger transcription factor Osterix promotes proliferation of mesenchymal cells. *Gene*. 2006 Jan 17;366:145-51. [Abstract]

Kornak U, Ostertag A, Branger S, Benichou O, de Vernejoul MC. Polymorphisms in the CLCN7 gene modulate bone density in postmenopausal women and in patients with autosomal dominant osteopetrosis type II. *J Clin Endocrinol*. *Metab*. 2005 Dec 20; [Epub ahead of print]

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Ofek O, Karsak M, Leclerc N, Fogel M, Frenkel B, Wright K, Tam J, Attar-Namdar M, Kram V, Shohami E, Mechoulam R, Zimmer A, Bab I. Peripheral cannabinoid receptor, CB2, regulates bone mass. *Proc Natl Acad Sci U S A*. 2006 Jan 17;103(3):696-701. [Abstract] [Full Text]

Oshima S, Onodera S, Amizuka N, Li M, Irie K, Watanabe S, Koyama Y, Nishihira J, Yasuda K, Minami A. Macrophage migration inhibitory factor-deficient mice are resistant to ovariectomy-induced bone loss. *FEBS Lett*. 2006 Feb 20;580(5):1251-6. [Abstract]

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Zhong N, Gersch RP, Hadjiargyrou M. Wnt signaling activation during bone regeneration and the role of Dishevelled in chondrocyte proliferation and differentiation. *Bone*. 2006 Feb 2; [Epub ahead of print] [Abstract]

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.