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NOT TO BE MISSED

Clinical and Basic Research Papers – October 2007 Selections

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

Bone Modeling and Remodeling

Galusca B, Zouch M, Germain N, Bossu C, Frere D, Lang F, Lafage-Proust MH, Thomas T, Vico L, Estour B. Constitutional thinness: unusual human phenotype of low bone quality. *J Clin Endocrinol Metab*. 2007 Oct 23; [Epub ahead of print]

> *One of the strongest areas of debate concerning low bone mass associated with low body size/underweight at a younger age is whether bone mass in this case is well adapted and/or whether it is a hallmark of bone fragility. This paper is of interest because it compares BMD and microstructure as determined by high-resolution QCT at distal radius and tibia in young women with constitutional leaness (BMI < 16.5) and no hormonal disturbances to women with anorexia nervosa and controls. BMD and microstructural parameters were similarly decreased in lean women and those with long-standing anorexia nervosa, and the calculated breaking strength was also decreased. These observations strongly argue against adjustment of BMD for body mass, i.e., against a "pseudo-normalization" of low bone mass in lean individuals.* —SF

Riggs BL, Melton LJ, Robb RA, Camp JJ, Atkinson EJ, McDaniel L, Amin S, Rouleau PA, Khosla S. A population-based assessment of rates of bone loss at multiple skeletal sites: evidence for substantial trabecular bone loss in young adult women and men. *J Bone Miner Res*. 2007 Oct 15; [Epub ahead of print] [Abstract]

> *The notion that there is a period of stability in bone mass without bone loss after completion of growth is almost certainly incorrect. Trabecular bone loss occurs before midlife in both sexes. Given that the remodeling rate is slow before menopause, it is possible that this early loss of bone reduces bone strength to a lesser degree than bone loss later in life. The authors report cortical bone loss began in the peri-menopause in women and later in life in men. However, total and medullary areas were not measured so cortical bone loss may have occurred from the endocortical surface in young adulthood with continued (possibly) independent periosteal apposition accounting for the lack of net cortical bone loss.* —ES

Takada I, Mihara M, Suzawa M, Ohtake F, Kobayashi S, Igarashi M, Youn MY, Takeyama K, Nakamura T, Mezaki Y, Takezawa S, Yogiashi Y, Kitagawa H, Yamada G, Takada S, Minami Y, Shibuya H, Matsumoto K, Kato S. A histone lysine methyltransferase activated by non-canonical Wnt signalling suppresses PPAR-gamma transactivation. *Nat Cell Biol*. 2007 Nov;9(11):1273-85. [Abstract]

> *Activation of the transcription factor Pparγ leads mesenchymal stem cells towards adipogenesis, while restraining osteoblastogenesis. This paper now demonstrates the role of Wnt signaling therein. Whereas the β-catenin-mediated canonical pathway is essential for bone formation, Wnt signaling through a non-canonical, calcium/calmodulin-dependent protein kinase (CaMK) pathway leads to the assembly of a chromatin-*

associated complex, which through histone methylation prevents Pparγ from activating its target promoters while favoring transcription of Cbfa1/Runx2 target genes. Of note, whereas Pparγ haploinsufficient mice have decreased bone marrow adipocytes together with increased bone mass, Wnt5a heterozygous mice presented the opposite phenotype, whereas Wnt3a heterozygous mice had a restricted phenotype (bone but not fat). —SF

Uzan B, Villemin A, Garel JM, Cressent M. Adrenomedullin is anti-apoptotic in osteoblasts through CGRP1 receptors and MEK-ERK pathway. *J Cell Physiol*. 2007 Oct 16; [Epub ahead of print] [Abstract]

Adrenomedullin (ADM) stimulates the proliferation of osteoblasts in vitro and promotes bone growth in vivo by anti-apoptotic effects through CGRP1 receptors. In mouse MC3T3-E1 cells that express ADM and ADM receptors, ADM blunted apoptosis, an effect abolished by the subtype-1 CGRP receptor antagonist, CGRP(8-37). Both ADM and its specific receptor antagonist, the (22-52) ADM fragment, exhibited a similar anti-apoptotic effect. Neutralization of endogenous ADM enhanced apoptosis. An inhibitor of MAPK kinase (MEK), PD98059, abolished the apoptosis protective effect of ADM and prevented ADM activation of ERK1/2. ADM acts as a survival factor in osteoblastic cells via a CGRP1 receptor-MEK-ERK pathway. —ES

Pathophysiology

Chiodini I, Mascia ML, Muscarella S, Battista C, Minisola S, Arosio M, Santini SA, Guglielmi G, Carnevale V, Scillitani A. Subclinical hypercortisolism among outpatients referred for osteoporosis. *Ann Intern Med*. 2007 Oct 16;147(8):541-8. [Abstract]

Nieman LK. Screening for reversible osteoporosis: is cortisol a culprit? *Ann Intern Med*. 2007 Oct 16;147(8):582-4. [Info]

219 consecutive patients who were referred for osteoporosis and were without clinical evidence of Cushing's Syndrome were screened with a dexamethasone suppression test. Cortisol excess was confirmed with 2 day dexamethasone suppression, 24 hr. urinary cortisol and midnight cortisol assays. Seven of 65 patients with T-scores of -2.5 or less and vertebral fractures had subclinical hypercortisolism (prevalence, 10.8% [95% CI, 3.23% to 18.31%]). The prevalence was 4.8% (CI, 1.32% to 8.20%) among all patients with osteoporosis. Most had adrenal adenomas. The surprisingly high prevalence of cortisol excess in this cross-sectional study accords with an unexpectedly high prevalence reported by others in patients with diabetes mellitus, hypertension and adrenal adenomas. If this result is confirmed, should we begin routine screening for subclinical Cushing's in osteoporosis clinics? —GJS

Physiology and Metabolism

Bodyak N, Ayus JC, Achinger S, Shivalingappa V, Ke Q, Chen YS, Rigor DL, Stillman I, Tamez H, Kroeger PE, Wu-Wong RR, Karumanchi SA, Thadhani R, Kang PM. Activated vitamin D attenuates left ventricular abnormalities induced by dietary sodium in Dahl salt-sensitive animals. *Proc Natl Acad Sci U S A*. 2007 Oct 23;104(43):16810-5. [Abstract] [Full Text]

Vitamin D metabolites seem to have wide medicinal properties. Left ventricular (LV) structural and functional abnormalities are associated with mortality in hemodialyzed patients. Compared with Dahl salt-sensitive (DSS) rats fed a high salt 6% (HS) diet for 6 weeks, HS + paricalcitol (PC), an activated vitamin, was associated with lower heart and lung weights, LV mass, posterior wall thickness and end diastolic pressures, and

increased fractional shortening. Plasma brain natriuretic peptide and cardiac mRNA expression of brain natriuretic peptide, atrial natriuretic factor, and renin were reduced. In a retrospective study of hemodialysis patients, PC-treated subjects had improved diastolic function and a reduction in LV septal and posterior wall thickness. —ES

Sacchetti B, Funari A, Michienzi S, Di Cesare S, Piersanti S, Saggio I, Tagliafico E, Ferrari S, Robey PG, Riminucci M, Bianco P. Self-renewing osteoprogenitors in bone marrow sinusoids can organize a hematopoietic microenvironment. *Cell*. 2007 Oct 19;131(2):324-36. [Abstract]

The stromal stem cell has been elusive. This paper reports that cells capable of supporting formation of bone and bone marrow when transplanted to hydroxyapatite matrices are CD146$^+$. In bone marrow, CD146$^+$ cells are reticular cells in a perisinusoidal location that express high levels of HSC niche-related transcripts (Jagged-1, N-cadherin, CXCL12 and Ang-1). They can direct the assembly of pseudovascular structures, suggesting that they function in the recruitment and assembly of bone marrow sinusoids. CD146$^+$ cells are capable of self-renewal during several passages through hydroxyapatite matrices. These cells may be components of the HSC niche; indeed, most previous results implicating osteoblasts in the HSC niche could be explained by the presence of CD146$^+$ preosteoblasts. —GJS

Wang Y, McNamara LM, Schaffler MB, Weinbaum S. A model for the role of integrins in flow induced mechanotransduction in osteocytes. *Proc Natl Acad Sci U S A*. 2007 Oct 2;104(40): 15941-6. [Abstract] [Full Text]

Tissue strains which are usually under 0.1% caused by locomotion are too small to initiate signaling in osteocytes. To reconcile the proposed function of osteocytes in mechanotransduction, amplification mechanisms may exist that are sufficient to initiate adaptation. The authors report that a cell level strain amplification system is achieved by integrins that attach osteocyte processes to the canalicular wall. Tensile forces on the integrins are <15 pN. Axial strains caused by sliding of actin microfilaments about the fixed integrin attachment are an order of magnitude larger than radial strains and two orders of magnitude greater than whole tissue strains, and are large enough to open stretch-activated cation channels. —ES

Treatment and Drug Effects

Chiu YC, Huang TH, Fu WM, Yang RS, Tang CH. Ultrasound stimulates MMP-13 expression through p38 and JNK pathway in osteoblasts. *J Cell Physiol*. 2007 Oct 16; [Epub ahead of print] [Abstract]

Ultrasound (US) stimulation increases the secretion of MMP-13 in cultured rat osteoblasts, and increases mRNA of MMP-13, c-Fos, and c-Jun. The p38 inhibitor, SB203580, and JNK inhibitor, SP600125, attenuated the US-induced MMP-13, c-Fos, and c-Jun expression. US stimulation enhanced binding of c-Fos and c-Jun to the AP-1 element on the MMP-13 promoter and enhanced AP-1 luciferase activity. US stimulation increases MMP-13 expression through p38 and JNK signaling to regulate bone remodeling. —ES

Rubin CT, Capilla E, Luu YK, Busa B, Crawford H, Nolan DJ, Mittal V, Rosen CJ, Pessin JE, Judex S. Adipogenesis is inhibited by brief, daily exposure to high-frequency, extremely low-magnitude mechanical signals. *Proc Natl Acad Sci U S A*. 2007 Nov 6;104(45):17879-84. [Abstract] [Full Text]

We knew from previous work from these authors that high-frequency, low-amplitude mechanical stimulation favors bone formation. Now they show that 9 weeks of low-magnitude mechanical signals on mice conversely reduces adipose tissue/fat mass. By using an ingenious tool, i.e., transplantation of GFP-labeled bone marrow cells, they further show that the fate of these cells towards becoming peripheral adipocytes is decreased upon mechanical stimulation. Moreover, the IGF-1 and Pparγ-dependent adipocytic phenotype of congenic 6T mice was improved by mechanical stimulation. Conclusion: let's shake our bodies! —SF

Reviews, Perspectives and Editorials

Body JJ, Bergmann P, Boonen S, Boutsen Y, Devogelaer JP, Goemaere S, Reginster JY, Rozenberg S, Kaufman JM. Management of cancer treatment-induced bone loss in early breast and prostate cancer -- a consensus paper of the Belgian Bone Club. *Osteoporos Int*. 2007 Nov;18(11):1439-50. [Abstract]

Devuyst O, Pirson Y. Genetics of hypercalciuric stone forming diseases. *Kidney Int*. 2007 Nov;72(9):1065-72. [Abstract]

Hamrick MW, Ferrari SL. Leptin and the sympathetic connection of fat to bone. *Osteoporos Int*. 2007 Oct 9; [Epub ahead of print] [Abstract]

Reid IR. Relationships between fat and bone. *Osteoporos Int*. 2007 Oct 27; [Epub ahead of print] [Abstract]

Szulc P, Kaufman JM, Delmas PD. Biochemical assessment of bone turnover and bone fragility in men. *Osteoporos Int*. 2007 Nov;18(11):1451-61. [Abstract]

Other Studies of Potential Interest

Adami S, San Martin J, Muñoz-Torres M, Econs MJ, Xie L, Dalsky GP, McClung M, Felsenberg D, Brown JP, Brandi ML, Sipos A. Effect of raloxifene after recombinant teriparatide [hPTH(1-34)] treatment in postmenopausal women with osteoporosis. *Osteoporos Int*. 2007 Oct 16; [Epub ahead of print] [Abstract]

Arlot ME, Jiang Y, Genant HK, Zhao J, Burt-Pichat B, Roux JP, Delmas PD, Meunier PJ. Histomorphometric and mu-CT analysis of bone biopsies from postmenopausal osteoporotic women treated with strontium ranelate. *J Bone Miner Res*. 2007 Oct 8; [Epub ahead of print] [Abstract]

Cosman F, Nieves JW, Zion M, Barbuto N, Lindsay R. Effect of prior and ongoing raloxifene therapy on response to PTH and maintenance of BMD after PTH therapy. *Osteoporos Int*. 2007 Oct 11; [Epub ahead of print] [Abstract]

Ferdous Z, Wei VM, Iozzo RV, Höök M, Grande-Allen KJ. Decorin-TGF beta interaction regulates matrix organization and mechanical characteristics of 3-D collagen matrices. *J Biol Chem*. 2007 Oct 17; [Epub ahead of print]

Hayashi M, Maeda S, Aburatani H, Kitamura K, Miyoshi H, Miyazono K, Imamura T. Pitx2 prevents osteoblastic trans-differentiation of myoblasts by bone morphogenetic proteins. *J Biol Chem*. 2007 Oct 20; [Epub ahead of print]

Hiraoka S, Furuichi T, Nishimura G, Shibata S, Yanagishita M, Rimoin DL, Superti-Furga A, Nikkels PG, Ogawa M, Katsuyama K, Toyoda H, Kinoshita-Toyoda A, Ishida N, Isono K, Sanai Y, Cohn DH, Koseki H, Ikegawa S. Nucleotide-sugar transporter SLC35D1 is critical to chondroitin sulfate synthesis in cartilage and skeletal development in mouse and human. *Nat Med*. 2007 Nov;13(11):1363-7. [Abstract]

Kawamura N, Kugimiya F, Oshima Y, Ohba S, Ikeda T, Saito T, Shinoda Y, Kawasaki Y, Ogata N, Hoshi K, Akiyama T, Chen WS, Hay N, Tobe K, Kadowaki T, Azuma Y, Tanaka S, Nakamura K, Chung UI, Kawaguchi H. Akt1 in osteoblasts and osteoclasts controls bone remodeling. *PLoS ONE*. 2007 Oct 24;2(10):e1058. [Abstract]

Makita N, Sato J, Rondard P, Fukamachi H, Yuasa Y, Aldred MA, Hashimoto M, Fujita T, Iiri T. Human Gsalpha mutant causes pseudohypoparathyroidism type Ia/neonatal diarrhea, a potential cell-specific role of the palmitoylation cycle. *Proc Natl Acad Sci U S A*. 2007 Oct 30;104(44):17424-9. [Abstract] [Full Text]

Moffatt P, Thomas G, Sellin K, Bessette MC, Lafreniere F, Akhouayri O, St-Arnaud R, Lanctot C. Osteocrin is a specific ligand of the natriuretic peptide clearance receptor that modulates bone growth. *J Biol Chem*. 2007 Oct 19; [Epub ahead of print]

Shanmugarajan S, Irie K, Musselwhite C, Key L Jr, Ries W, Reddy S. Transgenic mice with OIP-1/hSca overexpression targeted to the osteoclast lineage develop an osteopetrosis bone phenotype. *J Pathol*. 2007 Dec;213(4):420-8. [Abstract]

Conflict of Interest: Dr. Ferrari reports that he receives research support from Amgen and consultancy/speaker's fees from Merck Sharp & Dohme, Eli Lilly, and Amgen. 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. Strewler reports that no conflict of interest exists.