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NOT TO BE MISSED

Clinical and Basic Research Papers – September 2006 Selections

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

Bone Modeling and Remodeling

Nyman JS, Roy A, Acuna RL, Gayle HJ, Reyes MJ, Tyler JH, Dean DD, Wang X. Age-related effect on the concentration of collagen crosslinks in human osteonal and interstitial bone tissue. *Bone*. 2006 Sep 7; [Epub ahead of print] [Abstract]

> *Interstitial bone between osteons is older and less remodeled, has higher tissue mineral density, more micro-damage, and more empty osteocytic lacunae. Cracks propagate more readily through this homogenously mineralized tissue than through the lamellar structure of osteons. Additional abnormalities occur, as reported in this study. In 40 human cadaveric femurs, concentration of enzymatic crosslinks and a non-enzymatic crosslink indicate age- and sex-specific effects on the crosslinks in the osteons that differ from those in the interstitial bone. Non-enzymatic crosslinking may increase, while enzymatic crosslinking may decrease, with age and reduce the quality of the bone tissue.* —ES

Epidemiology

Clark EM, Ness AR, Bishop NJ, Tobias JH. Association between bone mass and fractures in children: a prospective cohort study. *J Bone Miner Res*. 2006 Sep;21(9):1489-95. [Abstract]

> *A number of observational and some longitudinal studies have reported that childhood fractures are associated with lower bone mass, including at peak, compared to non-fractured children, indicating that fractures during growth are not just a hallmark of risky behavior but of bone fragility too. Considering the large contribution of peak bone mass to osteoporosis risk later in life, it has been suggested that fractures in childhood should be considered as a risk factor for osteoporosis. Now this study: 2-year longitudinal fracture risk in boys and girls again is shown to be positively associated with lower BMD at 9.9 years, even more so after adjustment for height and weight (a so-called estimate of vBMD). This may not sound very new, but since 6213 children were studied here, i.e., a whole population (from Avon in the UK), this study may still be the ultimate proof that fractures in childhood, although extremely common, mean something must be urgently done to improve bone mass acquisition in these children. Will someone listen now?* —SF

Genetics

Feng JQ, Ward LM, Liu S, Lu Y, Xie Y, Yuan B, Yu X, Rauch F, Davis SI, Zhang S, Rios H, Drezner MK, Quarles LD, Bonewald LF, White KE. Loss of DMP1 causes rickets and osteomalacia and identifies a role for osteocytes in mineral metabolism. *Nat Genet*. 2006 Oct 8; [Epub ahead of print] [Abstract]

Lorenz-Depiereux B, Bastepe M, Benet-Pages A, Amyere M, Wagenstaller J, Muller-Barth U, Badenhoop K, Kaiser SM, Rittmaster RS, Shlossberg AH, Olivares JL, Loris C, Ramos FJ, Glorieux F, Vikkula M, Juppner H, Strom TM. DMP1 mutations in autosomal recessive hypophosphatemia implicate a bone matrix protein in the regulation of phosphate homeostasis. *Nat Genet*. 2006 Oct 8; [Epub ahead of print] [Abstract]

> *Dentin matrix protein 1 (DMP1) is a non-collagenous acidic phosphoprotein secreted by odontoblasts that plays a crucial role in dentinogenesis (also see a recent review by Macdougall et al. Molecular basis of human dentin diseases. Am J Med Genet A. 2006 Sep 5; [Epub ahead of print]). A few years ago, DMP1 was also shown to be present in osteocytes, however, its role has remained elusive to this day. Now the authors show that DMP1 KO mice develop urinary phosphate wasting and rickets after birth, with elevated FGF23 levels, similar to the situation seen in human XLH and HYP mice. Most remarkably, the authors identified some families with a recessive form of hypo-phosphatemic rickets whose probands carry homozygous mutations in DMP1. Hence, not only does the family of phosphate-regulating molecules have a new baby, but the study also suggests that the osteocyte and the osteoblast are part of this regulatory loop through the production of FGF23. This raises the interesting question whether DMP1 may be a mediator of bone mineralization consecutive to mechanical stimulation.* —SF

Scillitani A, Guarnieri V, Battista C, De Geronimo S, Muscarella LA, Chiodini I, Cignarelli M, Minisola S, Bertoldo F, Francucci CM, Malavolta N, Piovesan A, Lucia Mascia M, Muscarella S, Hendy GN, D'Agruma L, Cole DE. Primary hyperparathyroidism and the presence of kidney stones are associated with different haplotypes of the calcium-sensing receptor. *J Clin Endocrinol Metab*. 2006 Oct 3; [Epub ahead of print]

> *Is there a genetic susceptibility to develop PHPT, and when the disorder is present, are some patients more susceptible than others to develop complications – in this particular case, kidney stones? This study of a rather large series of PHPT patients (n=237) and controls (n=433) suggests that allelic variation in the calcium-sensing receptor (CASR) could be implicated in this susceptibility. To be verified independently, of course, but intriguing also regarding the possibility that CASR genotypes could determine the course of latent (normocalcemic) PHPT to develop in overt disease?* – SF

Topaz O, Indelman M, Chefetz I, Geiger D, Metzker A, Altschuler Y, Choder M, Bercovich D, Uitto J, Bergman R, Richard G, Sprecher E. A deleterious mutation in SAMD9 causes normophosphatemic familial tumoral calcinosis. *Am J Hum Genet*. 2006 Oct;79(4):759-64. [Abstract]

> *Each issue brings its load of gene(s) with newly discovered functions in bone and/or mineral homeostasis. Here is SAMD9, a large protein of unknown function (so far), bearing little homology with other known proteins, but widely expressed in many tissues and species. Here it is shown that a point-mutation in SAMD9 is related to a non-hyperphosphatemic form of malignant calcinosis of soft tissues present in 5 families of Jewish Yemenite origin. Remember that the hyperphosphatemic forms of tumoral calcinosis were recently shown to be caused by loss-of-function mutations in FGF23 and GALNT3. Future studies need to elucidate whether the underlying mechanisms of heterotopic calcifications in SAMD9 mutations are due to localized inflammatory-like processes in the skin (as seen in dystrophic calcinosis), altered permeability and/or transport of calcium and/or phosphate through the endothelium of skin capillaries (where SAMD9 is expressed), and/or whether SAMD9 acts as an inhibitor of mineral nucleation or growth.* —SF

Pathophysiology

Liao J, Schneider A, Datta NS, McCauley LK. Extracellular calcium as a candidate mediator of prostate cancer skeletal metastasis. *Cancer Res*. 2006 Sep 15;66(18):9065-73. [Abstract]

> *High bone turnover predisposes to skeletal metastasis. This paper reports that stimulation of the calcium-sensing receptor in PC3 prostate cancer cells activates their proliferation, survival and attachment, suggesting that cancer cells can sense and respond to calcium released during bone resorption and thereby target adjacent sites. The calcium-sensing receptor plays a similar role in the homing of hematopoietic stem cells (HSCs) to their endosteal niche (see http://www.bonekey-ibms.org/cgi/content/full/ibmske;3/3/5). The results of Laio et al. raise the possibility that cancer stem cells occupy the HSC niche or an adjacent, overlapping niche (see http://www.bonekey-ibms.org/cgi/content/full/ibmske;3/5/19). —*GJS

Physiology and Metabolism

Inoue K, Mikuni-Takagaki Y, Oikawa K, Itoh T, Inada M, Noguchi T, Park JS, Onodera T, Krane SM, Noda M, Itohara S. A crucial role for MMP-2 in osteocytic canalicular formation and bone metabolism. *J Biol Chem*. 2006 Sep 7; [Epub ahead of print]

> *Mutations of the gene encoding matrix metalloproteinase (MMP)-2 produce an impaired osteocytic canalicular network. Aged but not young Mmp2(-/-) mice had calvarial sclerosis with osteocyte death. Transplantation of wild-type periosteum restored the osteocytic canalicular networks. MMP-2 plays a role in forming and maintaining the osteocytic canalicular network. —*ES

Treatment and Drug Effects

Winzenberg T, Shaw K, Fryer J, Jones G. Effects of calcium supplementation on bone density in healthy children: meta-analysis of randomised controlled trials. *BMJ*. 2006 Oct 14;333(7572): 775. [Abstract] [Full Text]

> *The beauty of a myth is that, with time, it takes on a life of its own but remains immortal, irrespective of accumulating evidence of its mythological status. For example, a meta-analysis of 19 studies involving 2859 children found no effect of calcium supplementation on BMD at the femoral neck or spine. Read two other papers: Kanis et al. Osteoporos Int. 2005 Jul;16(7):799-804 and Lanou et al. Pediatrics. 2005 Mar;115(3):736-43. If you are in love you will find fault in all three. It's time for a properly designed trial. —*ES

Reid IR, Mason B, Horne A, Ames R, Reid HE, Bava U, Bolland MJ, Gamble GD. Randomized controlled trial of calcium in healthy older women. *Am J Med*. 2006 Sep;119(9):777-85. [Abstract]

> *The same myth applies to calcium in adulthood. This is the third of three papers this year failing to support a role for calcium in fracture prevention. (See Jackson et al. N Engl J Med. 2006 Feb 16;354(7):669-83 and Prince et al. Arch Int Med. 2006 Apr 24;166(8):869-75). However, poor compliance confounds interpretation of all three. In 1471 postmenopausal women over 5 years, compliance was 55%. A benefit in BMD (intention-to-treat analysis) ascribed to calcium was about 1-2% between groups. No anti-fracture efficacy was documented, but in the per-protocol analysis, forearm fracture risk was*

reduced, as was height loss. Whether this is attributable to the calcium is a matter of opinion. —ES

Reviews, Perspectives and Editorials

Balogh K, Racz K, Patocs A, Hunyady L. Menin and its interacting proteins: elucidation of menin function. *Trends Endocrinol Metab*. 2006 Sep 22; [Epub ahead of print] [Abstract]

Bauss F, Dempster DW. Effects of ibandronate on bone quality: Preclinical studies. *Bone*. 2006 Sep 20; [Epub ahead of print] [Abstract]

Beer TM, Myrthue A. Calcitriol in the treatment of prostate cancer. *Anticancer Res*. 2006 Jul-Aug;26(4A):2647-51. [Abstract]

Compston JE, Seeman E. Compliance with osteoporosis therapy is the weakest link. *Lancet*. 2006 Sep 16;368(9540):973-4. [Info]

Cui Y, Rohan TE. Vitamin D, calcium, and breast cancer risk: a review. *Cancer Epidemiol Biomarkers Prev*. 2006 Aug;15(8):1427-37. [Abstract]

de Groot JW, Links TP, Plukker JT, Lips CJ, Hofstra RM. RET as a diagnostic and therapeutic target in sporadic and hereditary endocrine tumors. *Endocr Rev*. 2006 Aug;27(5):535-60. [Abstract] [Full Text]

Flanagan JN, Young MV, Persons KS, Wang L, Mathieu JS, Whitlatch LW, Holick MF, Chen TC. Vitamin D metabolism in human prostate cells: implications for prostate cancer chemoprevention by vitamin D. *Anticancer Res*. 2006 Jul-Aug;26(4A):2567-72. [Abstract]

Grant WB. Epidemiology of disease risks in relation to vitamin D insufficiency. *Prog Biophys Mol Biol*. 2006 Sep;92(1):65-79. [Abstract]

Hazenberg JG, Taylor D, Lee TC. The role of osteocytes and bone microstructure in preventing osteoporotic fractures. *Osteoporos Int.* 2006 Sep 14; [Epub ahead of print] [Abstract]

Holick MF. Vitamin D: its role in cancer prevention and treatment. *Prog Biophys Mol Biol*. 2006 Sep;92(1):49-59. [Abstract]

Krause R, Matulla-Nolte B, Essers M, Brown A, Hopfenmuller W. UV radiation and cancer prevention: what is the evidence? *Anticancer Res*. 2006 Jul-Aug;26(4A):2723-7. [Abstract]

Kricker A, Armstrong B. Does sunlight have a beneficial influence on certain cancers? *Prog Biophys Mol Biol*. 2006 Sep;92(1):132-9. [Abstract]

Peterlik M, Cross HS. Dysfunction of the vitamin D endocrine system as common cause for multiple malignant and other chronic diseases. *Anticancer Res*. 2006 Jul-Aug;26(4A):2581-8. [Abstract]

Ralston SH, de Crombrugghe B. Genetic regulation of bone mass and susceptibility to osteoporosis. *Genes Dev*. 2006 Sep 15;20(18):2492-506. [Abstract]

Siffert RS, Kaufman JJ. Ultrasonic bone assessment: "The time has come." *Bone*. 2006 Aug 31; [Epub ahead of print] [Info]

Trump DL, Muindi J, Fakih M, Yu WD, Johnson CS. Vitamin D compounds: clinical development as cancer therapy and prevention agents. *Anticancer Res*. 2006 Jul-Aug;26(4A):2551-6. [Abstract]

Van Poznak C, Estilo C. Osteonecrosis of the jaw in cancer patients receiving IV bisphosphonates. *Oncology (Williston Park)*. 2006 Aug;20(9):1053-62; discussion 1065-6. [Abstract]

van Staa TP. The pathogenesis, epidemiology and management of glucocorticoid-induced osteoporosis. *Calcif Tissue Int*. 2006 Sep;79(3):129-37. [Abstract]

Other Studies of Potential Interest

Eriksson AL, Lorentzon M, Mellstrom D, Vandenput L, Swanson C, Andersson N, Hammond GL, Jakobsson J, Rane A, Orwoll ES, Ljunggren O, Johnell O, Labrie F, Windahl SH, Ohlsson C. SHBG gene promoter polymorphisms in men are associated with serum SHBG, androgen and androgen metabolite levels and hip BMD. *J Clin Endocrinol Metab*. 2006 Aug 22; [Epub ahead of print]

Flores MV, Lam EY, Crosier P, Crosier K. A hierarchy of Runx transcription factors modulate the onset of chondrogenesis in craniofacial endochondral bones in zebrafish. *Dev Dyn*. 2006 Sep 29;235(11):3166-76. [Abstract]

Irwin R, Lapres JJ, Kinser S, McCabe LR. Prolyl-hydroxylase inhibition and HIF activation in osteoblasts promotes an adipocytic phenotype. *J Cell Biochem*. 2006 Oct 9; [Epub ahead of print] [Abstract]

Janzen V, Forkert R, Fleming HE, Saito Y, Waring MT, Dombkowski DM, Cheng T, Depinho RA, Sharpless NE, Scadden DT. Stem-cell ageing modified by the cyclin-dependent kinase inhibitor p16INK4a. *Nature*. 2006 Sep 28;443(7110):421-6. [Abstract]

Khan A, Hyde RK, Dutra A, Mohide P, Liu P. Core binding factor beta (CBFB) haploinsufficiency due to an interstitial deletion at 16q21q22 resulting in delayed cranial ossification, cleft palate, congenital heart anomalies, and feeding difficulties but favorable outcome. *Am J Med Genet A*. 2006 Oct 4; [Epub ahead of print] [Abstract]

Kvist AJ, Johnson AE, Morgelin M, Gustafsson E, Bengtsson E, Lindblom K, Aszodi A, Fassler R, Sasaki T, Timpl R, Aspberg A. Chondroitin sulfate perlecan enhances collagen fibril formation - implications for perlecan chondrodysplasias. *J Biol Chem*. 2006 Sep 5; [Epub ahead of print]

Samadfam R, Xia Q, Goltzman D. Cotreatment of parathyroid hormone with osteoprotegerin or alendronate increases its anabolic effect on the skeleton of oophorectomized mice. *J Bone Miner Res*. 2006 Oct 2; [Epub ahead of print] [Abstract]

Streeten EA, McBride DJ, Pollin TI, Ryan K, Shapiro J, Ott S, Mitchell BD, Shuldiner AR, O'Connell JR. Quantitative trait loci for BMD identified by autosome-wide linkage scan to chromosomes 7q and 21q in men from the Amish Family Osteoporosis Study. *J Bone Miner Res*. 2006 Sep;21(9):1433-42. [Abstract]

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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.