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NOT TO BE MISSED

Clinical and Basic Research Papers – August 2006 Selections

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

Bone Modeling and Remodeling

Hernandez CJ, Gupta A, Keaveny TM. A biomechanical analysis of the effects of resorption cavities on cancellous bone strength. *J Bone Miner Res*. 2006 Aug;21(8):1248–55. [Abstract]

> *Resorption cavities created during bone remodeling may produce stress risers predisposing to micro-cracks. The authors add cavities by finite element modeling. For a given bone volume fraction, stiffness and yield strength were reduced more with cavities targeted to regions of high strain than with nontargeted cavities. The authors infer that resorption cavities may influence strength and stiffness independent of bone volume.* —ES

Li J, Sarosi I, Cattley RC, Pretorius J, Asuncion F, Grisanti M, Morony S, Adamu S, Geng Z, Qiu W, Kostenuik P, Lacey DL, Simonet WS, Bolon B, Qian X, Shalhoub V, Ominsky MS, Zhu Ke H, Li X, Richards WG. Dkk1-mediated inhibition of Wnt signaling in bone results in osteopenia. *Bone*. 2006 Oct;39(4):754-66.

> *Dkk1 is an inhibitor of Wnt-LRP5 signaling that in adult mice is almost excusively expressed in bone, more precisely in osteocytes, osteoblasts and the growth plate. Interestingly, this study also shows that PTH (more precisely a long-lasting PTH-derived molecule, PTH-Fc) dose-dependently increases Dkk1 expression in bone, raising the question of what role Dkk1 plays in coupling/uncoupling PTH response to the Wnt/LRP5 pathway (note that a recent paper by Sawakami et al. showed that the anabolic activity of intermittent PTH was not altered in LRP5 KO mice). By overexpressing Dkk1 in osteoblasts, the authors demonstrate that an excess of Dkk1 decreases bone formation/mineralization and causes osteopenia in all bone compartments, whereas broader over-expression also causes limb defects, similar to LRP5 and/or LRP6 knockouts. However, trabecular bone micro-architecture and periosteal expansion shows a disproportionate alteration compared to BMD. While adding to the evidence of the role of Wnt-LRP5 signaling on the modeling/remodeling of the skeleton, these results also raise the question whether overproduction of Dkk1 could be directly involved in the pathophysiology of osteoporosis.* —SF

Windahl SH, Galien R, Chiusaroli R, Clement-Lacroix P, Morvan F, Lepescheux L, Nique F, Horne WC, Resche-Rigon M, Baron R. Bone protection by estrens occurs through non-tissue-selective activation of the androgen receptor. *J Clin Invest*. 2006 Sep;116(9):2500-9. [Abstract] [Full Text]

Neill US. You say estren, I say estrogen. Let's call the whole replacement off! *J Clin Invest*. 2006 Sep;116(9):2327-9. [Abstract] [Full Text]

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In contrast to earlier reports, estrens protect against bone loss by reducing bone turnover, and their effects are primarily mediated by the androgen receptor. In addition, estren-α induces an increase in uterine weight in female mice and an increase in seminal vesicle weight in male mice. There was no evidence of a truly anabolic response to estren-α. The accompanying editorial stresses that there were differences, albeit small, between this and the earlier experiments and the proof of the pudding is in the effects of estrens in humans, which have yet to be reported. —GJS

Zaman G, Jessop HL, Muzylak M, De Souza RL, Pitsillides AA, Price JS, Lanyon LL. Osteocytes use estrogen receptor alpha to respond to strain but their ERalpha content is regulated by estrogen. *J Bone Miner Res*. 2006 Aug;21(8):1297–306. [Abstract]

The authors suggest that bone loss of estrogen deficiency is a consequence of reduction in ERα number/activity reducing the effectiveness of cells' anabolic response to strain. Ovariectomy decreased ERα protein expression per osteocyte, and strain had a small positive effect, except medially where loading stimulated reversal of resorption to formation. Strain, not estrogen, induces discrete membrane localization of ERα. Bone cells' responses to strain and estrogen involve ERα. —ES

Zhao C, Irie N, Takada Y, Shimoda K, Miyamoto T, Nishiwaki T, Suda T, Matsuo K. Bidirectional ephrinB2-EphB4 signaling controls bone homeostasis. *Cell Metab*. 2006 Aug;4(2):111-21. [Abstract]

Mundy GR, Elefteriou F. Boning up on ephrin signaling. *Cell*. 2006 Aug 11;126(3):441-3. [Abstract]

Osteoclastic bone resorption must somehow attract osteoblast precursors to the resorption site and instruct them to lay down new bone. Ephrins and their receptors are bidirectional signaling transducers that are important in neural, vascular and bone development. Zhao et al. report that osteoclasts express the NFAT target ephrinB2 and osteoblasts express its receptor EphB4. Exposure of osteoclasts to EphB4 suppresses osteoclast differentiation by "reverse" signaling. Forward signaling through EphB4 enhances osteoblast differentiation in cultured cells, and forced expression of EphB4 increases bone formation rates and bone mass in transgenic mice. Knockout of EphB4 does not produce a strong bone phenotype, suggesting redundancy of ephrin signaling. It remains to be shown directly that ephrins are the coupling factor that is critical to bone remodeling, but they are strong candidates. —GJS

Epidemiology

Jadoul M, Albert JM, Akiba T, Akizawa T, Arab L, Bragg-Gresham JL, Mason N, Prutz KG, Young EW, Pisoni RL. Incidence and risk factors for hip or other bone fractures among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. *Kidney Int*. 2006 Aug 23; [Epub ahead of print] [Abstract]

Available data on bone fractures in hemodialysis (HD) patients are scarce. This study analyzes the fracture incidence in a very large population of hemodialysis patients (n=12,782) from around the world. The prevalence and incidence of hip or any fractures was high (9 and 25 per 1000 patient-years, respectively), and corresponds to the incidence of hip fractures among a general population older by 10-20 years. Besides the usual risk factors for osteoporotic fractures, this study identified some specific risk factors for this population, such as prior kidney transplant, low albumin levels, high PTH, and a

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number of drugs, including narcotics. Although it remains difficult to know whether patients with CRF have osteoporosis superimposed upon renal osteodystrophy and how to treat them if they do, this large observational study has the merit of reminding us that we can hardly remain passive with regard to fracture prevention in HD patients. —SF

Genetics

Yang SH, Meta M, Qiao X, Frost D, Bauch J, Coffinier C, Majumdar S, Bergo MO, Young SG, Fong LG. A farnesyltransferase inhibitor improves disease phenotypes in mice with a Hutchinson-Gilford progeria syndrome mutation. *J Clin Invest*. 2006 Aug;116(8):2115-21. [Abstract] [Full Text]

Hutchinson-Gilford progeria syndrome is a rare disorder that recapitulates at an early age many of the changes that normally occur in the very old, including osteoporosis and fractures. The mutation responsible for this disorder is known: it involves a defect of the processing of prelamin A to mature lamin by farnesylation and cleavage. The authors generated a transgenic mouse overexpressing the mutant protein, inducing severe skeletal alterations, such as kyphosis of the spine, osteolytic lesions in the ribs, and spontaneous fractures. Unfortunately, the cellular alterations leading to this bone phenotype were not analyzed in detail here. However, the authors demonstate that administration of a farnesyltransferase inhibitor mislocalizes the aberrant protein (progerin) from its target (the nuclear membrane), partially preventing the bony and other defects. This is one of the rare examples of a genetic defect that can be at last partially corrected by administration of a chemical compound, and also opens the hypothesis that the approach could be of use for osteoporosis treatment in the very elderly. —SF

Treatment and Drug Effects

Delmas PD, Licata AA, Reginster JY, Crans GG, Chen P, Misurski DA, Wagman RB, Mitlak BH. Fracture risk reduction during treatment with teriparatide is independent of pretreatment bone turnover. *Bone*. 2006 Aug;39(2):237–43. [Abstract]

'Common sense' suggests that anti-resorptives should be more effective in individuals with high than low remodeling and PTH (1-34) more effective in low than high remodeling states. Not so. In this study, as with other studies using anti-resorptives, the absolute fracture risk reduction is higher in persons with high remodeling because more patients sustain fractures in higher risk groups, but the relative risk reduction with PTH or anti-resorptives is no different in patients with high or low baseline remodeling rates. —ES

Reviews, Perspectives and Editorials

Johnson ML, Rajamannan N. Diseases of Wnt signaling. *Rev Endocr Metab Disord*. 2006 Aug 31; [Epub ahead of print] [Abstract]

Norman AW. Vitamin D Receptor (VDR): New assignments for an already busy receptor. *Endocrinology*. 2006 Aug 31; [Epub ahead of print]

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Other Studies of Potential Interest

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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.

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