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NOT TO BE MISSED

Clinical and Basic Research Papers – July 2004 Selections

Ego Seeman, Clinical Editor
Gordon J. Strewler, Editor

Bone Modeling and Remodeling

Tanck E, Van Donkelaar CC, Jepsen KJ, Goldstein SA, Weinans H, Burger EH, Huiskes R. The mechanical consequences of mineralization in embryonic bone. *Bone.* 2004 Jul;35(1):186-90. [Abstract]

> *Stiffness is an essential property of bone that is established by mineralization. Four-point bending studies were done on mouse ribs at 16 and 17 days of gestational age. Unmineralized specimens had a Young's modulus of 1.11 Mpa, and mineralized specimens had a value of 117 Mpa, an increase of two orders of magnitude in one day. The authors propose the novel notion that shielding hypertrophic chondrocytes from mechanical stress reduced their deformability, with subsequent resorption of calcified cartilage and expansion of the marrow cavity. —ES*

Pathophysiology

Akhter MP, Wells DJ, Short SJ, Cullen DM, Johnson ML, Haynatzki GR, Babij P, Allen KM, Yaworsky PJ, Bex F, Recker RR. Bone biomechanical properties in LRP5 mutant mice. *Bone*. 2004 Jul;35(1):162-9. [Abstract]

> *Transgenic mice expressing the glycine to valine substitution at amino acid residue 171 in the gene coding for low-density lipoprotein receptor-related protein 5 have the high bone mass phenotype, with greater structural and material strength and percent bone ash weight. Whether the denser and stiffer bones represent greater bone formation sensitivity to mechanical stimuli resulting in an overadaptation to loading remains to be determined. —ES*

Hikiji H, Ishii S, Shindou H, Takato T, Shimizu T. Absence of platelet-activating factor receptor protects mice from osteoporosis following ovariectomy. *J Clin Invest.* 2004 Jul;114(1):85-93. [Abstract] [Full Text]

> *Platelet-activating factor is a phospholipid mediator of platelet activation, bronchoconstriction, and increased vascular permeability that acts through the G-protein coupled receptor PAFR. Although the bones of PAFR-null mice are normal, absence of PAFR protects mice from osteoporosis following ovariectomy. PAFR is expressed in osteoclasts, but PAF is not a powerful stimulator of bone resorption, and the mechanism of protection remains to be clarified. —GJS*
>
> *Recommended. —ES*

Physiology and Metabolism

Arai F, Hirao A, Ohmura M, Sato H, Matsuoka S, Takubo K, Ito K, Koh GY, Suda T. Tie2/angiopoietin-1 signaling regulates hematopoietic stem cell quiescence in the bone marrow niche. *Cell.* 2004 Jul 23;118(2):149-61. [Abstract]

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Osteoblasts contribute to the stem cell niche in bone. Here it is shown that osteoblasts express angiopoietin, and hematopoietic stem cells (HSCs) from a side population express its receptor tie-2. Angiopoietin signaling induces adherence of HSCs to osteoblasts, quiescence of HSCs, and resistance of HSCs to cytotoxic chemotherapy. The induction of quiescence by adherence to osteoblasts could play a role in the induction of latency in bone metastases. —GJS

Kogler G, Sensken S, Airey JA, Trapp T, Muschen M, Feldhahn N, Liedtke S, Sorg RV, Fischer J, Rosenbaum C, Greschat S, Knipper A, Bender J, Degistirici O, Gao J, Caplan AI, Colletti EJ, Almeida-Porada G, Muller HW, Zanjani E, Wernet P. A new human somatic stem cell from placental cord blood with intrinsic pluripotent differentiation potential. *J Exp Med.* 2004 Jul 19;200(2):123-35. [Abstract]

A cultured population of cord blood cells has properties of somatic stem cells and differentiates to osteoblasts and chondrocytes, as well as to adipocytes and hematopoietic and neural cells, including astrocytes and neurons. They may be similar to cells previously described by Kusnetsov et al. *(J Cell Biol 2001 153(5):1133-40). —GJS*

Treatment and Drug Effects

Chesnut III CH, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A, Felsenberg D, Huss H, Gilbride J, Schimmer RC, Delmas PD; Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE). Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res.* 2004 Aug;19(8):1241-9. [Abstract]

A paper on the antifracture efficacy of intermittent ibandronate has finally been published. The incidence of vertebral fracture decreased by 50% after three years. Post hoc *analysis suggested that the daily regimen reduces the risk of nonvertebral fractures by 69% in a higher risk subgroup. —ES*

Dominici M, Pritchard C, Garlits JE, Hofmann TJ, Persons DA, Horwitz EM. Hematopoietic cells and osteoblasts are derived from a common marrow progenitor after bone marrow transplantation. *Proc Natl Acad Sci U S A.* 2004 Aug 10;101(32):11761-6. [Abstract] [Full Text]

Transplantation of nonadherent marrow cells into lethally irradiated mice reconstitutes the bone marrow of the recipient, but also contributes to the recipient's chondrocytes and osteoblast lineages (1% to 2% of total osteoblasts). PCR and Southern blotting establish that transplanted marrow cells and osteoblasts have a common progenitor, and cytogenetic studies exclude fusion events as the explanation. —GJS

Recommended. —ES

Ensrud KE, Barrett-Connor EL, Schwartz A, Santora AC, Bauer DC, Suryawanshi S, Feldstein A, Haskell WL, Hochberg MC, Torner JC, Lombardi A, Black DM; Fracture Intervention Trial Long-Term Extension Research Group. Randomized trial of effect of alendronate continuation versus discontinuation in women with low BMD: results from the Fracture Intervention Trial long-term extension. *J Bone Miner Res.* 2004 Aug;19(8):1259-69. [Abstract]

FLEX is the long-term extension of the Fracture Intervention Trial (FIT) of alendronate therapy. In this three-year interim analysis of FLEX, 1099 patients assigned to alendronate in FIT were rerandomized to alendronate 10 mg daily, alendronate 5 mg daily, or placebo. BMD continued to increase at the spine in patients continuing on alendronate 10 mg or 5 mg daily, with stable reduction in urinary N-telopeptide. Patients randomized to placebo experienced a small increase in N-telopeptide and a small

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decrease in BMD at the hip. Fracture data will be reported when the study has been completed and will be important for decision-making about long-term bisphosphonate treatment. —GJS

Komatsubara S, Mori S, Mashiba T, Li J, Nonaka K, Kaji Y, Akiyama T, Miyamoto K, Cao Y, Kawanishi J, Norimatsu H. Suppressed bone turnover by long-term bisphosphonate treatment accumulates microdamage but maintains intrinsic material properties in cortical bone of dog rib. *J Bone Miner Res.* 2004 Jun;19(6):999-1005. [Abstract]

Bisphosphonates are getting some bad press lately in the context of microdamage. One-year-old beagles given incadronate for three years had suppressed activation frequency and increased microdamage; however, structural mechanical properties were nevertheless increased after treatment, whereas intrinsic material properties were not changed. Whether microdamage in and of itself is deleterious to whole bone strength remains unproven. —ES

Rhee Y, Won YY, Baek MH, Lim SK. Maintenance of increased bone mass after recombinant human parathyroid hormone (1-84) with sequential zoledronate treatment in ovariectomized rats. *J Bone Miner Res.* 2004 Jun;19(6):931-7. [Abstract]

Whether antiresorptives should be given prior to, during, or after PTH is unclear. Sprague-Dawley rats were treated with PTH 25 weeks after ovariectomy, followed by nothing, PTH, 17β-estradiol, or zoledronate. This study supports the notion that effects are lost following withdrawal of PTH and are maintained by antiresorptives. —ES

Schaller S, Henriksen K, Sveigaard C, Heegaard AM, Helix N, Stahlhut M, Ovejero MC, Johansen JV, Solberg H, Andersen TL, Hougaard D, Berryman M, Shiodt CB, Sorensen BH, Lichtenberg J, Christophersen P, Foged NT, Delaisse JM, Engsig MT, Karsdal MA. The chloride channel inhibitor n53736 prevents bone resorption in ovariectomized rats without changing bone formation. *J Bone Miner Res.* 2004 Jul;19(7):1144-53. [Abstract]

The chloride channel inhibitor blocked osteoclastic resorption in vitro *and protected bone strength by 50%* in vivo. *Bone formation was not inhibited. Why was bone formation not inhibited? —ES*

Smith MR, Fallon MA, Lee H, Finkelstein JS. Raloxifene to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer: a randomized controlled trial. *J Clin Endocrinol Metab.* 2004 Aug;89(8):3841-6. [Abstract] [Full Text]

Raloxifene should reduce rates of bone loss in hypogonadal me. This paper tests the hypothesis in men in whom hypogonadism was induced pharmacologically to treat prostate cancer. Raloxifene treatment for 12 months significantly increased hip BMD, with a trend towards higher spinal BMD. —GJS

Reviews and Perspectives

Hofbauer LC, Schoppet M. Clinical implications of the osteoprotegerin/RANKL/RANK system for bone and vascular diseases. *JAMA.* 2004 Jul 28;292(4):490-5. [Abstract]

Parfitt AM What is the normal rate of bone remodeling? *Bone.* 2004 Jul;35(1):1-3. [Info]

Stewart AF. Translational implications of the parathyroid calcium receptor. *N Engl J Med.* 2004 Jul 22;351(4):324-6.

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Other Studies of Potential Interest

Boutahar N, Guignandon A, Vico L, Lafage-Proust MH. Mechanical strain on osteoblasts activates autophosphorylation of focal adhesion kinase and proline-rich tyrosine kinase 2 tyrosine sites involved in ERK activation. *J Biol Chem.* 2004 Jul 16;279(29):30588-99. [Abstract] [Full Text]

Chen C, Koh AJ, Datta NS, Zhang J, Keller ET, Xiao G, Franceschi RT, D'Silva NJ, McCauley LK. Impact of the mitogen-activated protein kinase pathway on parathyroid hormone-related protein actions in osteoblasts. *J Biol Chem.* 2004 Jul 9;279(28):29121-9. [Abstract] [Full Text]

Frew IJ, Sims NA, Quinn JM, Walkley CR, Purton LE, Bowtell DD, Gillespie MT. Osteopenia in Siah1a mutant mice. *J Biol Chem.* 2004 Jul 9;279(28):29583-8. [Abstract] [Full Text]

Jimi E, Aoki K, Saito H, D'Acquisto F, May MJ, Nakamura I, Sudo T, Kojima T, Okamoto F, Fukushima H, Okabe K, Ohya K, Ghosh S. Selective inhibition of NF-kappa B blocks osteoclastogenesis and prevents inflammatory bone destruction in vivo. *Nat Med.* 2004 Jun;10(6):617-24. [Abstract]

Matsuo K, Galson DL, Zhao C, Peng L, Laplace C, Wang KZ, Bachler MA, Amano H, Aburatani H, Ishikawa H, Wagner EF. Nuclear factor of activated T-cells (NFAT) rescues osteoclastogenesis in precursors lacking c-Fos. *J Biol Chem*. 2004 Jun 18;279(25):26475-80. [Abstract] [Full Text]

Mishina Y, Starbuck MW, Gentile MA, Fukuda T, Kasparcova V, Seedor JG, Hanks MC, Amling M, Pinero GJ, Harada S, Behringer RR. Bone morphogenetic protein type IA receptor signaling regulates postnatal osteoblast function and bone remodeling. *J Biol Chem.* 2004 Jun 25;279(26):27560-6. [Abstract] [Full Text]

Murphy CL, Polak JM. Control of human articular chondrocyte differentiation by reduced oxygen tension. *J Cell Physiol.* 2004 Jun;199(3):451-9. [Abstract]

Murshed M, Schinke T, McKee MD, Karsenty G. Extracellular matrix mineralization is regulated locally; different roles of two gla-containing proteins. *J Cell Biol.* 2004 Jun 7;165(5):625-30. [Abstract] [Full Text]

Ontiveros C, Irwin R, Wiseman RW, McCabe LR. Hypoxia suppresses runx2 independent of modeled microgravity. *J Cell Physiol.* 2004 Aug;200(2):169-76. [Abstract]

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Peng Y, Kang Q, Luo Q, Jiang W, Si W, Liu BA, Luu HH, Park JK, Li X, Luo J, Montag AG, Haydon RC, He TC. Inhibitor of DNA binding/differentiation helix-loop-helix proteins mediate bone morphogenetic protein-induced osteoblast differentiation of mesenchymal stem cells. *J Biol Chem.* 2004 Jul 30;279(31):32941-9. [Abstract] [Full Text]

Pischon N, Darbois LM, Palamakumbura AH, Kessler E, Trackman PC. Regulation of collagen deposition and lysyl oxidase by tumor necrosis factor-alpha in osteoblasts. *J Biol Chem.* 2004 Jul 16;279(29):30060-5. [Abstract] [Full Text]

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Xiao L, Naganawa T, Obugunde E, Gronowicz G, Ornitz DM, Coffin JD, Hurley MM. Stat1 controls postnatal bone formation by regulating fibroblast growth factor signaling in osteoblasts. *J Biol Chem.* 2004 Jun 25;279(26):27743-52. [Abstract] [Full Text]

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