

NOT TO BE MISSED

Clinical and Basic Research Papers – April 2009

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Bone Modeling, Remodeling and Repair

◆Komatsu DE, Brune KA, Liu H, Schmidt AL, Han B, Zeng QQ, Yang X, Nunes JS, Lu Y, Geiser AG, Ma YL, Wolos JA, Westmore MS, Sato M. Longitudinal in vivo analysis of the region-specific efficacy of parathyroid hormone in a rat cortical defect model. *Endocrinology*. 2009 Apr;150(4):1570-9. [\[Abstract\]](#) [\[Full Text\]](#)

A paper examining the effect of hPTH1-38 at doses of 0, 3, 10 or 30 µg/kg/d on a drill hole defect model in rats. Histomorphometry revealed increased woven bone in the gap and intramedullary space but not the periosteum. Interestingly, the group concludes that “[t]he effects of PTH were kinetic, region specific, and most apparent at high doses that may not be entirely clinically relevant; therefore, clinical studies are necessary to clarify the therapeutic utility of PTH in bone healing.”—DGL

◆Krauss S, Fratzi P, Seto J, Currey JD, Estevez JA, Funari SS, Gupta HS. Inhomogeneous fibril stretching in antler starts after macroscopic yielding: Indication for a nanoscale toughening mechanism. *Bone*. 2009 Feb 21. [Epub ahead of print] [\[Abstract\]](#)

Antler is very tough, enabling it to fulfill its biological function as a weapon and defensive guard during combat between stags in the rutting season. Deformation at the nanoscale shows that fibrils are strained half as much as the whole tissue and the fibril strain increases linearly with tissue strain during elastic and inelastic deformation. Following yielding a straining of some fibrils equal to the macroscopic tissue strain is seen while other fibrils are hardly stretched at all. This behavior explains the extreme toughness of antler compared to normal bone. —ES

◆Morgan EF, Mason ZD, Bishop G, Davis AD, Wigner NA, Gerstenfeld LC, Einhorn TA. Combined effects of recombinant human BMP-7 (rhBMP-7) and parathyroid hormone (1-34) in metaphyseal bone healing. *Bone*. 2008 Dec;43(6):1031-8. [\[Abstract\]](#)

In this defect study in a rabbit model, a wedge-shaped metaphyseal defect was created and bridged by a fixator. The gap was filled with tricalcium phosphate (TCP) and treated with buffer, BMP-7, PTH(1-34) or a combination of BMP-7 and PTH(1-34). At 4 weeks, the combined groups had the most amount of bone, while BV/TV was relatively unchanged. BV/TV was lowest in the BMP-7 alone group. The combined and PTH groups showed an increase in compressive strength over BMP-7 alone, while only the combined group showed an increase in torsional rigidity. Remodeling seemed to be more coordinated and thus coupled in the PTH and combined groups, whereas some areas of uncontrolled resorption had occurred in the BMP-7 group. The authors conclude, with some justification, that while BMP-7 increased local stem cell recruitment and differentiation, PTH treatment increased specific bone cell differentiation and bone

production, as well as increased catabolism in a coupled fashion. These differences and synergies of combination therapies may be important in choosing the correct augmentation in different orthopedic circumstances. —DGL

Clinical Studies and Drug Effects

◆ Bischoff-Ferrari HA, Willett WC, Wong JB, Stuck AE, Staehelin HB, Orav EJ, Thoma A, Kiel DP, Henschkowski J. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. *Arch Intern Med.* 2009 Mar 23;169(6):551-61. [[Abstract](#)]

In case we needed more evidence concerning the benefits of vitamin D supplementation in reducing fracture risk, this new meta-analysis including the WHI and RECORD trials (which reported negative results), and estimating actual vitamin D intake according to compliance, confirms that in women older than 65, cholecalciferol at received doses higher than 482 IU/d reduced the risk of non-vertebral fractures by up to 23%. More interestingly, the study shows that the addition of calcium supplements adds no further benefit compared to vitamin D alone, that evidence is weak concerning the anti-fracture efficacy of ergocalciferol, whereas 1-alpha-derivatives may also reduce the risk of non-vertebral fractures, although in this case the evidence is weakened by a limited number of studies/subjects to date. —SF

◆ Harris ST, Reginster JY, Harley C, Blumentals WA, Poston SA, Barr CE, Silverman SL. Risk of fracture in women treated with monthly oral ibandronate or weekly bisphosphonates: The eValuation of IBandronate Efficacy (VIBE) database fracture study. *Bone.* 2009 Jan 9. [Epub ahead of print] [[Abstract](#)]

We had REAL and REALITY, now there is VIBE, comparing fracture incidence in patients from very large health care databases and prescribed either weekly alendronate, risedronate, or monthly ibandronate during the same period. Overall, that is in women older than 45 years and adherent to treatment for more than 3 months, ibandronate-treated patients had significantly fewer clinical vertebral fractures compared to alendronate and risedronate, and a similar proportion of non-vertebral and hip fractures. Sensitivity analyses, including in patients older than 65, did not markedly alter these results. Similar to the REAL and REALITY studies, these results are limited mainly by the low overall fracture rate (1.5% for all clinical fractures) and by the small proportion of subjects remaining in the observation after one year (mean follow-up of 7 months in this study). —SF

◆ Recker RR, Marin F, Ish-Shalom S, Mörnicke R, Hawkins F, Kapetanos G, de la Peña MP, Kekow J, Farrerons J, Sanz B, Oertel H, Stepan J. Comparative effects of teriparatide and strontium ranelate on bone biopsies and biochemical markers of bone turnover in postmenopausal women with osteoporosis. *J Bone Miner Res.* 2009 Apr 1. [Epub ahead of print] [[Abstract](#)]

Teriparatide (PTH1-34) remains the gold standard for bone anabolic agents for the treatment of osteoporosis. However, strontium ranelate (SR) has shown some potential effects, mostly in vitro, on osteoblast proliferation and/or activity. In this open label, randomized study, the effects of teriparatide (TPT) and SR were analyzed in 29 and 22 bone biopsies, respectively, obtained from postmenopausal women with osteoporosis after 6 months of therapy. Curiously, of 28 biopsies taken in the SR group, 6 were fragmented or insufficient, versus 0 in the TPT group. Histomorphometrical analyses showed greater endocortical mineralizing surfaces and cortical porosity in the TPT group compared to the SR group, as expected, but no differences in any other parameter of

bone formation nor in mineralization. No differences in either osteoclast number or surfaces between the two groups were found, however, the erosion surfaces were greater with SR, which is rather surprising considering that PTH, rather than SR, is known to activate osteoclasts and that bone turnover markers increased with TPT, but not SR. Finally, microarchitectural bone parameters were the same in both groups. These results suggest that despite obvious differences in their mode of action, TPT and SR may share some similarities at the tissue level, at least in the short-term. —SF

- ◆Scheper MA, Badros A, Chaisuparat R, Cullen KJ, Meiller TF. Effect of zoledronic acid on oral fibroblasts and epithelial cells: a potential mechanism of bisphosphonate-associated osteonecrosis. *Br J Haematol.* 2009 Mar;144(5):667-76. [\[Abstract\]](#)

Exposing human gingival fibroblast and keratinocyte cell lines to different concentrations of zoledronic acid (ZA) produced a dose-response effect on apoptosis and cell proliferation; both reversed using siRNA against caspase 3 or 9. Low concentrations of ZA affected the mucosa through a gene-regulated apoptotic process. —ES

Genetics

- ◆Cheung CL, Chan BY, Chan V, Ikegawa S, Kou I, Ngai H, Smith D, Luk KD, Huang QY, Mori S, Sham PC, Kung AW. Pre-B-cell leukemia homeobox 1 (PBX1) shows functional and possible genetic association with bone mineral density variation. *Hum Mol Genet.* 2009 Feb 15;18(4):679-87. [\[Abstract\]](#)

This pilot study applied a strategy combining traditional linkage and association with molecular studies in the identification of osteoporosis candidate genes. A fine mapping association analysis using 380 SNPs was conducted on chromosome 1q21–q23, an important quantitative trait locus underlying bone mineral density variation, and narrowed down the list of candidate genes to pre-B-cell leukemia homeobox 1 (PBX1). In vitro cellular studies revealed the functional role of PBX1 in osteoblast biology. —HWD

- ◆Xiong DH, Liu XG, Guo YF, Tan LJ, Wang L, Sha BY, Tang ZH, Pan F, Yang TL, Chen XD, Lei SF, Yerges LM, Zhu XZ, Wheeler VW, Patrick AL, Bunker CH, Guo Y, Yan H, Pei YF, Zhang YP, Levy S, Papasian CJ, Xiao P, Lundberg YW, Recker RR, Liu YZ, Liu YJ, Zmuda JM, Deng HW. Genome-wide association and follow-up replication studies identified ADAMTS18 and TGFBR3 as bone mass candidate genes in different ethnic groups. *Am J Hum Genet.* 2009 March;84(3):388-98. [\[Abstract\]](#)

An initial genome-wide association study, five follow-up replication studies, and functional evidence from an electrophoretic mobility shift assay demonstrate the importance of the ADAMTS18 (ADAM metalloproteinase with thrombospondin type 1 motif, 18) gene and the TGFBR3 (transforming growth factor, beta receptor III) gene for the genetic determination of bone mineral density. This study provides a background for future studies evaluating the contributions of these two genes to osteoporosis. —HWD

Molecular and Cell Biology

- ◆de Frutos CA, Dacquin R, Vega S, Jurdic P, Machuca-Gayet I, Nieto MA. Snail1 controls bone mass by regulating Runx2 and VDR expression during osteoblast differentiation. *EMBO J.* 2009 Mar 18;28(6):686-96. [\[Abstract\]](#)

Snail1 suppresses gene transcription of Runx2 and the VDR in osteoblasts. Snail1 expression is transiently enhanced during early osteoblast differentiation and is

downregulated during terminal differentiation. Snail1 transgenic mice exhibit deficient osteoblast differentiation with a severe inhibition of bone matrix mineralization, leading to osteomalacia. Osteoclastogenesis is also impaired in these mice due to a suppression of RANKL expression and enhancement of OPG expression by the loss of VDR signaling in osteoblasts. This study provides an important clue for understanding the mechanism of the complex temporal regulation of Runx2 action: the regulation of its expression by Snail1, along with the inhibition of transcriptional activity by Twist and protein degradation by Shnurri-3. —TM

- ◆ Ishii M, Egen JG, Klauschen F, Meier-Schellersheim M, Saeki Y, Vacher J, Proia RL, Germain RN. Sphingosine-1-phosphate mobilizes osteoclast precursors and regulates bone homeostasis. *Nature*. 2009 Mar 26;458(7237):524-8. [\[Abstract\]](#)

Osteoclast precursors can migrate to and from the bone surface, but differentiated osteoclasts must be attached to the bone surface. Here, sphingosine-1-phosphate (S1P) induces chemotaxis towards the blood circulation along an S1P gradient of osteoclast precursors expressing S1P1 receptors. CD11b-Cre conditional S1P1 knockout mice showed osteoporotic changes due to increased osteoclast attachment to the bone surface. An S1P1 agonist, FTY720, relieved ovariectomy-induced osteoporosis in mice by decreasing the number of osteoclasts on the bone surface. Thus, S1P controls the migratory behavior of osteoclast precursors in competition with chemotaxis towards CXCL12/SDF-1 secreted from stromal cells. The results provide a novel control point in osteoclastogenesis that may become a therapeutic target. —TM

Other Studies of Potential Interest

- ◆ Bénazet JD, Bischofberger M, Tiecke E, Gonçalves A, Martin JF, Zuniga A, Naef F, Zeller R. A self-regulatory system of interlinked signaling feedback loops controls mouse limb patterning. *Science*. 2009 Feb 20;323(5917):1050-3. [\[Abstract\]](#) [\[Full Text\]](#)
- ◆ Friedman MS, Oyserman SM, Hankenson KD. Wnt11 promotes osteoblast maturation and mineralization through R-spondin 2. *J Biol Chem*. 2009 Feb 12. [Epub ahead of print]
- ◆ Inui M, Kikuchi Y, Aoki N, Endo S, Maeda T, Sugahara-Tobinai A, Fujimura S, Nakamura A, Kumanogoh A, Colonna M, Takai T. Signal adaptor DAP10 associates with MDL-1 and triggers osteoclastogenesis in cooperation with DAP12. *Proc Natl Acad Sci U S A*. 2009 Mar 24;106(12):4816-21. [\[Abstract\]](#) [\[Full Text\]](#)
- ◆ Ishii KA, Fumoto T, Iwai K, Takeshita S, Ito M, Shimohata N, Aburatani H, Taketani S, Lelliott CJ, Vidal-Puig A, Ikeda K. Coordination of PGC-1beta and iron uptake in mitochondrial biogenesis and osteoclast activation. *Nat Med*. 2009 Mar;15(3):259-66. [\[Abstract\]](#)
- ◆ Kim HJ, Zhang K, Zhang L, Ross FP, Teitelbaum SL, Faccio R. The Src family kinase, Lyn, suppresses osteoclastogenesis in vitro and in vivo. *Proc Natl Acad Sci U S A*. 2009 Feb 17;106(7):2325-30. [\[Abstract\]](#) [\[Full Text\]](#)
- ◆ Mizoguchi T, Muto A, Udagawa N, Arai A, Yamashita T, Hosoya A, Ninomiya T, Nakamura H, Yamamoto Y, Kinugawa S, Nakamura M, Nakamichi Y, Kobayashi Y, Nagasawa S, Oda K, Tanaka H, Tagaya M, Penninger JM, Ito M, Takahashi N. Identification of cell cycle-arrested quiescent osteoclast precursors in vivo. *J Cell Biol*. 2009 Feb 23;184(4):541-54. [\[Abstract\]](#) [\[Full Text\]](#)
- ◆ McCarthy HS, Williams JH, Davie MW, Marshall MJ. Platelet-derived growth factor stimulates osteoprotegerin production in osteoblastic cells. *J Cell Physiol*. 2009 Feb;218(2):350-4. [\[Abstract\]](#)

◆Sheng MH, Amoui M, Stiffel V, Srivastava AK, Wergedal JE, Lau KH. Targeted transgenic expression of an osteoclastic transmembrane protein-tyrosine phosphatase in cells of osteoclastic lineage increased bone resorption and bone loss in male young adult mice. *J Biol Chem*. 2009 Feb 25. [Epub ahead of print]

◆Sugatani T, Hruska KA. Impaired micro-RNA pathways diminish osteoclast differentiation and function. *J Biol Chem*. 2009 Feb 13;284(7):4667-78. [\[Abstract\]](#) [\[Full Text\]](#)

Conflict of Interest: Dr. Ferrari reports that he receives research support from Amgen and is an advisory committee member and lectures occasionally at conference symposia for Merck Sharp & Dohme, the Alliance for Better Bone Health (Sanofi Aventis/P&G), Amgen, Eli Lilly (Switzerland), Servier (Switzerland), and Novartis (Switzerland). Dr. Little reports that he receives royalties, research funds and consultancy fees from Novartis Pharma, as well as research support from Stryker Biotech. 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. Matsumoto and Dr. Deng report no conflicts of interest.