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NOT TO BE MISSED

Clinical and Basic Research Papers – August 2008

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Bone Modeling, Remodeling and Repair

Akritopoulos P, Papaioannidou P, Hatzokos I, Haritanti A, Iosifidou E, Kotoula M, Mirtsou-Fidani V. Parecoxib has non-significant long-term effects on bone healing in rats when administered for a short period after fracture. *Arch Orthop Trauma Surg*. 2008 Aug 2; [Epub ahead of print] [Abstract]

Dimmen S, Nordsletten L, Engebretsen L, Steen H, Madsen JE. Negative effect of parecoxib on bone mineral during fracture healing in rats. *Acta Orthop*. 2008 Jun;79(3):438-44. [Abstract]

> *Two papers examining the same COX-2 selective NSAID on fracture repair, given for only 1 week after induction of fracture to mimic when patients may take such medications for pain relief. Both saw early negative effects that did not translate to altered mechanical union at late time points. These studies, and those before them, indicate it might be safe to use short courses of COX-2 inhibitors or other NSAIDs in the immediate post-fracture period for low risk fractures. Fractures at high risk of non-union might be another matter; this has yet to be properly tested. One study concludes the effects are non-significant and one tells us to avoid NSAIDs…confusion remains.* —DGL

Kolanczyk M, Kühnisch J, Kossler N, Osswald M, Stumpp S, Thurisch B, Kornak U, Mundlos S. Modelling neurofibromatosis type 1 tibial dysplasia and its treatment with lovastatin. *BMC Med*. 2008 Jul 31;6:21. [Abstract]

> *Pseudarthrosis of the tibia is a known severe complication of neurofibromatosis type 1 (NF1). Increases in Ras/MAPK activation have been associated with fibrous tissue formation rather than bone development in the healing NF1 skeleton. Using mice with conditionally inactivated neurofibromin (Nf1) in the developing limbs and cranium (Nf1Prx1), the effects of systemically applied lovastatin were explored in a drill hole metaphyseal bone healing model. In Nf1Prx1 mice, bone repair was delayed and characterized by the formation and the persistence of fibro-cartilaginous tissue and impaired extracellular matrix mineralization. High-dose treatment with systemic lovastatin accelerated new bone formation in Nf1Prx1 tibia. The bone anabolic effects correlated with a reduction of MAPK pathway hyper-activation in Nf1-deficient cells. This study is interesting as it utilizes the known bone anabolic effect of statins in a disease model where the specific action of the drug on the Ras/MAPK pathway is particularly beneficial. Statins are being trialled for other NF1-related pathology as well as bone.* —DGL

Miller MA, Bare SP, Recker RR, Smith SY, Fox J. Intratrabecular tunneling increases trabecular number throughout the skeleton of ovariectomized rhesus monkeys treated with parathyroid hormone 1-84. *Bone*. 2008 Jun;42(6):1175-83. [Abstract]

Daily treatment of ovariectomized (OVX) adult rhesus monkeys with human PTH 1-84 for 16 months increases trabecular bone volume (BV/TV), number (Tb.N) and connectivity at L3 and Th-10. At L3, tunneling frequency increased in PTH(1-84)-treated animals. Iliac crest biopsies showed time- and dose-related increases in tunnels. PTH(1-84) increased Tb.N, as well as BV/TV and bone formation rate. A modest but significant increase in trabecular thickness occurred only at the iliac crest. —ES

Cancer and Bone

Li ZG, Mathew P, Yang J, Starbuck MW, Zurita AJ, Liu J, Sikes C, Multani AS, Efstathiou E, Lopez A, Wang J, Fanning TV, Prieto VG, Kundra V, Vazquez ES, Troncoso P, Raymond AK, Logothetis CJ, Lin SH, Maity S, Navone NM. Androgen receptor-negative human prostate cancer cells induce osteogenesis in mice through FGF9-mediated mechanisms. *J Clin Invest*. 2008 Aug 1;118(8):2697-2710. [Abstract]

Development of resistance to androgen deprivation therapy has been an important problem in the treatment of advanced prostate cancer (PCa). The authors established human androgen receptor (AR)-negative PCa xenografts from a male patient with castration-resistant PCa. Using this xenograft model, they demonstrated that these tumors induced robust osteoblastic bone lesions. In addition, they found that FGF9 was overexpressed in the xenografts, and demonstrated that FGF9 induced new bone formation. Blockade of FGF9 by a neutralizing antibody reduced osteoblastic lesions, suggesting that FGF9 acts as a paracrine factor for the development of osteoblastic lesions. This xenograft model may contribute to the development of therapies targeting castration-resistant PCa. —TM

Clinical Studies and Drug Effects

Abdin-Mohamed M, Jameson K, Dennison EM, Cooper C, Arden NK; The Hertfordshire Cohort Study Group. Volumetric bone mineral density of the tibia is not increased in subjects with radiographic knee osteoarthritis. *Osteoarthritis Cartilage*. 2008 Aug 4; [Epub ahead of print] [Abstract]

Radiographic osteoarthritis of the knee is known to be associated with increased areal bone mineral density (BMD) at the hip and spine as measured by DXA. In this study, pQCT was used to assess vBMD, size and strength in a large population-based cohort. Knee radiographs were also available. In men, increasing OA grade was associated with increases in bone size but not vBMD. There were no significant associations of tibia bone area, BMD or strength with radiographic grade in women. The study suggests that increases in bone area and strength in OA in men is mediated by effects on size and not vBMD. The authors postulate that the increase in areal BMD demonstrated by DXA is likely to be artifactual. —DGL

Bolland MJ, Grey AB, Horne AM, Briggs SE, Thomas MG, Ellis-Pegler RB, Callon KE, Gamble GD, Reid IR. Effects of intravenous zoledronate on bone turnover and BMD persist for at least 24 months. *J Bone Miner Res*. 2008 Aug;23(8):1304-8. [Abstract]

Thirty-three HIV-infected men completed a randomized trial of 4 mg annual zoledronate or placebo and were studied for 12 months off treatment. Turnover markers remained suppressed and lower and BMD remained higher in the zoledronate group, suggesting zoledronate could be administered less frequently than annually. —ES

Cauley JA, Lacroix AZ, Wu L, Horwitz M, Danielson ME, Bauer DC, Lee JS, Jackson RD, Robbins JA, Wu C, Stanczyk FZ, LeBoff MS, Wactawski-Wende J, Sarto G, Ockene J, Cummings SR. Serum 25-hydroxyvitamin D concentrations and risk for hip fractures. *Ann Intern Med*. 2008 Aug 19;149(4):242-50. [Abstract]

> *For those not yet convinced of the importance of vitamin D in the prevention of fractures, this case-control, observational study confirms that each 25(OH)D decrease of 25 nmol/L is associated with a 33% increased risk of hip fractures among community-dwelling, post-menopausal women.* —SF

Cranney A, Wells GA, Yetisir E, Adami S, Cooper C, Delmas PD, Miller PD, Papapoulos S, Reginster JY, Sambrook PN, Silverman S, Siris E, Adachi JD. Ibandronate for the prevention of nonvertebral fractures: a pooled analysis of individual patient data. *Osteoporos Int*. 2008 Jul 29; [Epub ahead of print] [Abstract]

> *If you give the right dose of a bisphosphonate you get anti-fracture efficacy. If you don't, you don't. For ibandronate, annual cumulative exposure (ACE) of >/= 10.8 mg (150 mg once monthly, 3 mg i.v. quarterly, and 2 mg i.v. every 2 months) gives better non-vertebral fracture protection than ACE doses of 5.5 mg (HR 0.62 , 95% CI 0.396-0.974, p = 0.038).* —DGL

Frihagen F, Grotle M, Madsen JE, Wyller TB, Mowinckel P, Nordsletten L. Outcome after femoral neck fractures: A comparison of Harris Hip Score, Eq-5d and Barthel Index. *Injury*. 2008 Jul 24; [Epub ahead of print] [Abstract]

> *Harris Hip Score is validated as the best at distinguishing patients with complications from those who had no complications in this cohort.* —DGL

Gallego L, Junquera L. Consequence of therapy discontinuation in bisphosphonate-associated osteonecrosis of the jaws. *Br J Oral Maxillofac Surg*. 2008 Jul 16; [Epub ahead of print] [Abstract]

> *Case report of a patient with bisphosphonate-associated ONJ who developed pathological fractures of the upper and lower extremities after the suspension of treatment with bisphosphonates. The point is made that ceasing the BP doesn't change the management of ONJ and could be detrimental to the patient.* —DGL

Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Arch Intern Med*. 2008 Jun 9;168(11):1174-80. [Abstract]

> *Low levels of 25(OH)D are associated with higher risk of myocardial infarction. A nested case-control study was conducted in 18,225 men. During 10 years, 454 men developed nonfatal myocardial infarction or fatal coronary heart disease. Compared with controls (n = 900), men deficient in 25(OH)D (<or=15 ng/m) were at increased risk for MI compared with those considered to be sufficient in 25(OH)D (>or=30 ng/mL) (relative risk [RR], 2.42; 95% confidence interval [CI], 1.53-3.84; P < .001 for trend), and this remained significant after adjustment (RR, 2.09; 95% CI, 1.24-3.54; P = .02 for trend). Even men with intermediate 25(OH)D levels were at elevated risk relative to those with sufficient 25(OH)D levels (22.6-29.9 ng/mL: RR, 1.60 [95% CI, 1.10-2.32]; and 15.0-22.5 ng/mL: RR, 1.43 [95% CI, 0.96-2.13], respectively).* —ES

Lubbert PH, van der Rijt RH, Hoorntje LE, van der Werken C. Low-intensity pulsed ultrasound (LIPUS) in fresh clavicle fractures: A multi-centre double blind randomised controlled trial. *Injury*. 2008 Jul 24; [Epub ahead of print] [Abstract]

This study showed no effect of pulsed ultrasound treatment in a randomized trial of clavicle fractures. —DGL

Miller PD, Bolognese MA, Lewiecki EM, McClung MR, Ding B, Austin M, Liu Y, San Martin J, Amg Bone Loss Study Group. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. *Bone*. 2008 Aug;43(2):222-9. [Abstract]

The investigators report that effects of denosumab on bone turnover were fully reversible with discontinuation and restored with subsequent retreatment. The inferences are based on a study in postmenopausal women randomized to denosumab every 3 or 6 months or placebo or open-label alendronate weekly. After 24 months, patients receiving denosumab continued at 60 mg Q6M for an additional 24 months, discontinued, or discontinued for 12 months then re-initiated denosumab (60 mg Q6M) for 12 months. 262/412 (64%) patients completed 48 months. Continuous denosumab increased BMD at the spine (9.4% to 11.8%) and total hip (4.0% to 6.1%). Bone turnover markers were suppressed over 48 months. Discontinuation was associated with a BMD decrease of 6.6% at the spine and 5.3% at the total hip within 12 months. Retreatment increased spine BMD by 9.0% from original baseline values. —ES

Rutten S, Nolte PA, Korstjens CM, van Duin MA, Klein-Nulend J. Low-intensity pulsed ultrasound increases bone volume, osteoid thickness and mineral apposition rate in the area of fracture healing in patients with a delayed union of the osteotomized fibula. *Bone*. 2008 Aug;43(2):348-54. [Abstract]

Delayed unions (6 months) of the fibula were treated with ultrasound and then biopsied. Biopsies showed that in ultrasound-treated patients there was an increase in bone formation at the bone front with treatment. There were lesser effects on trabecular callus and no effects on cortical bone. The study demonstrates biological differences in humans with ultrasound treatment, but nowhere are we told if there were differences in union. —DGL

Genetics

Miyamoto Y, Shi D, Nakajima M, Ozaki K, Sudo A, Kotani A, Uchida A, Tanaka T, Fukui N, Tsunoda T, Takahashi A, Nakamura Y, Jiang Q, Ikegawa S. Common variants in DVWA on chromosome 3p24.3 are associated with susceptibility to knee osteoarthritis. *Nat Genet*. 2008 Aug;40(8):994-8. [Abstract]

Osteoarthritis is a common disorder, and is influenced by genetic factors. Associated genes such as FRZB, ASPN, and GDF5 have been identified. Here, using a genome-wide association study, the authors identified a new gene, DVWA, on chromosome 3p24.3 associated with knee osteoarthritis. DVWA encodes a protein with two regions corresponding to von Willebrand factor type A (VWA). Several DVWA SNPs are associated with knee osteoarthritis. DVWA protein binds to beta-tubulin, and the binding is associated with two missense SNPs in the VWA domain. Tubulin in cartilage is shown to be reduced in a rat model of osteoarthritis. These results suggest that DVWA affects osteoarthritis susceptibility by modulating the function of beta-tubulin. These findings will help to clarify pathogenetic mechanisms and to develop new therapeutic approaches against osteoarthritis. —TM

Varela I, Pereira S, Ugalde AP, Navarro CL, Suárez MF, Cau P, Cadiñanos J, Osorio FG, Foray N, Cobo J, de Carlos F, Lévy N, Freije JM, López-Otín C. Combined treatment with statins and

aminobisphosphonates extends longevity in a mouse model of human premature aging. *Nat Med*. 2008 Jul;14(7):767-72. [Abstract]

> *Accumulation at the nuclear envelope of farnesylated forms of truncated prelamin A has been shown to be a cause of several human progerias. Prelamin A is also altered in normal aging. Although farnesyltransferase inhibitors (FTIs) improve nuclear abnormalities associated with prelamin A accumulation, the authors demonstrate that prelamin A and its truncated form, progerin, undergo alternative prenylation by geranylgeranyltransferase in the presence of FTIs. They also show that a combination of statins and bisphosphonates efficiently inhibits both farnesylation and geranylgeranylation of prelamin A and progerin, and markedly improves aging-related phenotypes with substantial extension of longevity. Combined treatment with statins and bisphosphonates may open up a new therapeutic approach to slow down disease progression in children with progeroid syndromes associated with nuclear envelope abnormalities.* —TM

Molecular and Cell Biology

Chang MK, Raggatt LJ, Alexander KA, Kuliwaba JS, Fazzalari NL, Schroder K, Maylin ER, Ripoll VM, Hume DA, Pettit AR. Osteal tissue macrophages are intercalated throughout human and mouse bone lining tissues and regulate osteoblast function in vitro and in vivo. *J Immunol*. 2008 Jul 15;181(2):1232-44. [Abstract]

> *The role of osteoclasts in the induction of osteoblastogenesis is just beginning to be better understood. Through elegant immunohistochemistry analyses, this study identifies a population of bone resident macrophages, i.e., potentially osteoclast precursors, intercalated between lining osteoblasts and whose function is to promote osteoblast differentiation. These cells, called "OsteoMacs" by the authors, are also abundantly present in primary bone cell cultures from calvariae. In vitro co-culture experiments further show that macrophages support osteoblast mineralization, with the caveat that the very high extracellular calcium concentrations used here might prompt calcium precipitation*. —SF

Ogita M, Rached MT, Dworakowski E, Bilezikian JP, Kousteni S. Differentiation and proliferation of periosteal osteoblast progenitors are differentially regulated by estrogens and intermittent PTH administration. *Endocrinology*. 2008 Jul 10; [Epub ahead of print]

> *Due in part to experimental difficulties, studies on periosteal osteoblasts remain scarce. Hence the importance of this study, which demonstates that both PTH and dihydrotestosterone promote differentiation of periosteal osteoblasts, while estradiol inhibits PTH effects in vitro and in vivo. In contrast, estrogen favors proliferation and survival of periosteal osteoblast precursors, indicating the dual role of estrogen on the periosteum.* —SF

Ponce ML, Koelling S, Kluever A, Heinemann DE, Miosge N, Wulf G, Frosch KH, Schütze N, Hufner M, Siggelkow H. Coexpression of osteogenic and adipogenic differentiation markers in selected subpopulations of primary human mesenchymal progenitor cells. *J Cell Biochem*. 2008 Jul 1;104(4):1342-55. [Abstract]

> *Mesenchymal progenitor cells can differentiate to distinct osteoblasts and adipocytes. With the help of magnetic cell sorting and fluorescence activated cell sorting (FACS), the authors found that committed osteoblasts exhibit a greater adipogenic potential. They also observed that alkaline phosphatase negative cells differentiating to the mature osteoblastic phenotype was accompanied by increased expression of adipocytic gene*

markers. These results suggest that osteogenic and adipogenic differentiation in human mesenchymal progenitor cells might not be exclusively reciprocal, but rather, a parallel event until late during osteoblast development. —HWD

Shimada M, Greer PA, McMahon AP, Bouxsein ML, Schipani E. In vivo targeted deletion of calpain small subunit, Capn4, in cells of the osteoblast lineage impairs cell proliferation, differentiation, and bone formation. *J Biol Chem*. 2008 Jul 25;283(30):21002-10. [Abstract] [Full Text]

This study demonstrates that the calpain small subunit (Capn4) is essential for proper osteoblast activity and bone remodeling. Capn4 knockout mice had smaller bodies with shorter limbs, reduced trabecular bone with thinner cortices, and decreased osteoblast number. In vitro analysis confirmed that deletion of Capn4 in osteoblasts severely affected multiple osteoblast functions including proliferation, differentiation, and matrix mineralization. —HWD

Reviews, Perspectives and Editorials

Pinzone JJ, Hall BM, Thudi NK, Vonau M, Qiang YW, Rosol TJ, Shaughnessy Jr JD. The role of Dickkopf-1 in bone development, homeostasis and disease. *Blood*. 2008 Aug 7; [Epub ahead of Print]

Ralston SH, Langston AL, Reid IR. Pathogenesis and management of Paget's disease of bone. *Lancet*. 2008 Jul 12;372(9633):155-63. [Abstract]

Valtieri M, Sorrentino A. The mesenchymal stromal cell contribution to homeostasis. *J Cell Physiol*. 2008 Jul 9;217(2):296-300. [Abstract]

Other Studies of Potential Interest

Allan EH, Häusler KD, Wei T, Gooi JH, Quinn JM, Crimeen-Irwin B, Pompolo S, Sims NA, Gillespie MT, Onyia JE, Martin TJ. EphrinB2 regulation by PTH and PTHrP revealed by molecular profiling in differentiating osteoblasts. *J Bone Miner Res*. 2008 Aug;23(8):1170-81. [Abstract]

Boivin G, Bala Y, Doublier A, Farlay D, Ste-Marie LG, Meunier PJ, Delmas PD. The role of mineralization and organic matrix in the microhardness of bone tissue from controls and osteoporotic patients. *Bone*. 2008 Sep;43(3):532-8. [Abstract]

Brikowski TH, Lotan Y, Pearle MS. Climate-related increase in the prevalence of urolithiasis in the United States. *Proc Natl Acad Sci U S A*. 2008 Jul 15;105(28):9841-6. [Abstract] [Full Text]

D'Amelio P, Grimaldi A, Di Bella S, Brianza SZ, Cristofaro MA, Tamone C, Giribaldi G, Ulliers D, Pescarmona GP, Isaia G. Estrogen deficiency increases osteoclastogenesis up-regulating T cells activity: a key mechanism in osteoporosis. *Bone*. 2008 Jul;43(1):92-100. [Abstract]

El Hage F, Stroobant V, Vergnon I, Baurain JF, Echchakir H, Lazar V, Chouaib S, Coulie PG, Mami-Chouaib F. Preprocalcitonin signal peptide generates a cytotoxic T lymphocyte-defined tumor epitope processed by a proteasome-independent pathway. *Proc Natl Acad Sci U S A*. 2008 Jul 22;105(29):10119-24. [Abstract] [Full Text]

Guo R, Yamashita M, Zhang Q, Zhou Q, Chen D, Reynolds DG, Awad HA, Yanoso L, Zhao L, Schwarz EM, Zhang YE, Boyce BF, Xing L. Ubiquitin ligase Smurf1 mediates tumor necrosis

factor-induced systemic bone loss by promoting proteasomal degradation of bone morphogenetic signaling proteins. *J Biol Chem*. 2008 Aug 22;283(34):23084-92. [Abstract] [Full Text]

Lamothe B, Campos AD, Webster WK, Gopinathan A, Hur L, Darnay BG. The RING domain and first Zinc-finger of TRAF6 coordinate signaling by IL-1, LPS, and RANKL. *J Biol Chem*. 2008 Jul 10; [Epub ahead of print]

Mamillapalli R, Vanhouten J, Zawalich W, Wysolmerski J. Switching of G-protein usage by the calcium sensing receptor reverses its effect on PTHrP secretion in normal versus malignant breast cells. *J Biol Chem*. 2008 Jul 11; [Epub ahead of print]

Smerdel-Ramoya A, Zanotti S, Derogowski V, Canalis E. Connective tissue growth factor enhances osteoblastogenesis in vitro. *J Biol Chem*. 2008 Aug 15;283(33):22690-9. [Abstract] [Full Text]

Teplyuk NM, Galindo M, Teplyuk VI, Pratap J, Young DW, Lapointe D, Javed A, Stein JL, Lian JB, Stein GS, van Wijnen AJ. Runx2 regulates G-protein coupled signaling pathways to control growth of osteoblast progenitors. *J Biol Chem*. 2008 Jul 14; [Epub ahead of print]

Wang X, Allen MR, Burr DB, Lavernia EJ, Jeremić B, Fyhrie DP. Identification of material parameters based on Mohr-Coulomb failure criterion for bisphosphonate treated canine vertebral cancellous bone. *Bone*. 2008 Jun 10; [Epub ahead of print] [Abstract]

Zappone B, Thurner P, Adams J, Fantner GE, Hansma PK. Effect of Ca2+ ions on the adhesion and mechanical properties of adsorbed layers of human Osteopontin. *Biophys J*. 2008 Jun 27; [Epub ahead of print] [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. 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.