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NOT TO BE MISSED

Clinical and Basic Research Papers – November 2009

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Bone Modeling, Remodeling, and Repair

Bergot C, Wu Y, Jolivet E, Zhou LQ, Laredo JD, Bousson V. The degree and distribution of cortical bone mineralization in the human femoral shaft change with age and sex in a microradiographic study. *Bone*. 2009 Sep;45(3):435-42. [Abstract]

> *Bergot et al. report that, in cortical bone from 193 femurs (from 99 females and 94 males), the degree of tissue mineralization (Tt.DMB-Al) decreased with age in females but not in males. Tt.DMB-Al was higher in females than males until 50 years of age but was lower in elderly females than elderly males. The first DMB-Al quartiles in osteons and interstitial tissue were not different between males and females, but the third quartile differed with greater heterogeneity in females than males.* —ES

Brouwers JE, Lambers FM, van Rietbergen B, Ito K, Huiskes R. Comparison of bone loss induced by ovariectomy and neurectomy in rats analyzed by in vivo micro-CT. *J Orthop Res*. 2009 Nov;27(11):1521-7. [Abstract]

> *This study compared bone loss in ovariectomized rats to bone loss in neurectomized (disuse) rats. At the same amount of induced bone loss, disuse led to more deteriorated bone structure and mechanical properties than estrogen deficiency.*
> —DGL

Histing T, Garcia P, Matthys R, Leidinger M, Holstein JH, Kristen A, Pohlemann T, Menger MD. An internal locking plate to study intramembranous bone healing in a mouse femur fracture model. *J Orthop Res*. 2009 Sep 24. [Epub ahead of print] [Abstract]

> *There has been concern that bisphosphonates and other anticatabolics, through osteoclast inhibition, could inhibit "primary bone healing". Primary bone healing is defined as exclusively lamellar bone formation through the Haversian system in humans or resorption cavities in mice. Secondary bone healing is either intramembranous via woven bone or endochondral in nature. If primary bone healing exists, it is osteoclast-dependent, whereas secondary bone healing is not. These authors could find no evidence of primary bone healing when femoral fractures were treated with locked plates in mice. Thus treatment with this type of locking plate does not require the presence or function of osteoclasts (although remodeling does).*
> —DGL

Manske SL, Boyd SK, Zernicke RF. Muscle and bone follow similar temporal patterns of recovery from muscle-induced disuse due to botulinum toxin injection. *Bone*. 2009 Oct 20. [Epub ahead of print] [Abstract]

The authors hypothesized that muscle cross-sectional area would return to baseline levels sooner than bone properties following botulinum toxin injection. They found that both returned similarly and that even small improvements in muscle function might be important. Return of BSA was not necessary for return of bone mass. —DGL

Shimono K, Morrison TN, Tung WE, Chandraratna RA, Williams JA, Iwamoto M, Pacifici M. Inhibition of ectopic bone formation by a selective retinoic acid receptor alpha-agonist: A new therapy for heterotopic ossification? *J Orthop Res*. 2009 Sep 1. [Epub ahead of print] [Abstract]

Heterotopic ossification (HO) is a large clinical problem, especially post-surgery and post-head injury. Most HO occurs via an endochondral pathway. This group confirms that BMP-mediated HO occurs via an endochondral pathway, and that a specific and potent retinoic acid receptor (RAR) alpha agonist suppresses ectopic bone formation. Side effect profiles are unknown, but as the current treatment is radiotherapy, a pharmaceutical-based treatment would be helpful. Intramembranous ossification seems unharmed, which is the major mode of healing in joint replacement surgery. —DGL

van der Jagt OP, van der Linden JC, Schaden W, van Schie HT, Piscaer TM, Verhaar JA, Weinans H, Waarsing JH. Unfocused extracorporeal shock wave therapy as potential treatment for osteoporosis. *J Orthop Res*. 2009 Nov;27(11):1528-33. [Abstract]

Extracorporeal shock wave (ESW) therapy has been suggested as a treatment for most things. Here its possible use in osteoporosis is examined. Although BV/TV was higher in the ESW group than controls in ovariectomized animals, there was still a 50% reduction in BV/TV over time, an unsatisfactory result. However, if ESW could be shown to affect cortical bone, its use in conjunction with therapies that protect trabecular but not long bone suites could be explored. —DGL

Clinical Studies and Drug Effects

Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, Orav JE, Stuck AE, Theiler R, Wong JB, Egli A, Kiel DP, Henschkowski J. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *BMJ*. 2009 Oct 1;339:b3692. [Abstract] [Full Text]

A meta-analysis of 8 randomized controlled trials (n=2426) of vitamin D suggests high dose vitamin D reduced fall risk by 19% (n=1921, 7 trials). Achieved serum 25(OH)D of 60 nmol/l or more was associated with a 23% fall reduction. Fewer falls were not observed with low dose vitamin D or serum 25 hydroxyvitamin D <60 nmol/l. Two randomized controlled trials (n=624) of active vitamin D reduced fall risk by 22%. —ES

Ma H, Leskinen T, Alen M, Cheng S, Sipilä S, Heinonen A, Kaprio J, Suominen H, Kujala UM. Long-term leisure time physical activity and properties of bone: a twin study. *J Bone Miner Res*. 2009 Aug;24(8):1427-33. [Abstract]

Ma et al. studied long-term leisure time physical activity (LTPA) in twin pairs discordant for LTPA for ~ 30 years in 16 middle-aged (50-74 years of age) same-sex twin pairs (7 monozygotic (MZ) and 9 dizygotic (DZ) pairs). Active members of MZ twin pairs had larger cortical bone cross-sectional area (intrapair difference: 8%, p = 0.006), thicker cortex (12%, p = 0.003), and greater moment of inertia (I(max), 20%, p = 0.024) at the tibia shaft than their inactive co-twins. At the distal tibia, trabecular BMD (12%, p = 0.050) and compressive strength index (18%, p = 0.038) were higher in the active MZ pair members than their inactive co-twins. —ES

Riches PL, McRorie E, Fraser WD, Determann C, van't Hof R, Ralston SH. Osteoporosis associated with neutralizing autoantibodies against osteoprotegerin. *N Engl J Med*. 2009 Oct 8;361(15):1459-65. [Abstract]

> *This case report of high bone turnover osteoporosis in a young man with auto-immune hypothyroidism and celiac disease identifies a new pathophysiological mechanism of rapid bone loss: auto-antibodies against osteoprotegerin. Of note is the excellent clinical response to zoledronic acid, indicating that bone resorption due to excessive RANKL activity can also be controlled by bisphosphonates, although in this case denosumab, i.e., the RANKL antagonist, would have been a more specifically targeted therapy.* —SF

Szulc P, Claustrat B, Delmas PD. Serum concentrations of 17beta-E and 25 hydroxycholecalciferol (25OHD) in relation to all-cause mortality in older men--the MINOS study. *Clin Endocrinol (Oxf)*. 2009 Oct;71(4):594-602. [Abstract]

> *Among 782 men followed for 10 years, 182 non-survivors were older, had more co-morbidities and lower physical performance. The lowest quartile of 25OHD predicted mortality (HR = 1.44, 1.03-2.03) for the first 3 years. 17β-E(2) predicted mortality after the third year (HR = 1.21 per 1 SD increase, 1.09-1.35). Low 25OHD may reflect poor health status; whether this is causal requires further study.* —ES

Genetics

Freedman BI, Bowden DW, Ziegler JT, Langefeld CD, Lehtinen AB, Rudock ME, Lenchik L, Hruska KA, Register TC, Carr JJ. Bone morphogenetic protein 7 (BMP7) gene polymorphisms are associated with inverse relationships between vascular calcification and BMD: the Diabetes Heart Study. *J Bone Miner Res*. 2009 Oct;24(10):1719-27. [Abstract]

> *Many studies have reported a strong association between osteoporosis and CVD, particularly the inverse relationship between low BMD and aortic calcifications. Bone fragility is also increased among diabetic patients. Yet the molecular determinants of this relationship remain unknown. This genetic association study in 920 European Americans from 374 families with type 2 diabetes provides evidence for an inverse association of 6 genotypes of BMP7 with BMD and vascular calcifications (assessed from CT scan images).* —SF

Gallois A, Lachuer J, Yvert G, Wierinckx A, Brunet F, Rabourdin-Combe C, Delprat C, Jurdic P, Mazzorana M. Genome-wide expression analyses establish dendritic cells as a new osteoclast precursor able to generate bone-resorbing cells more efficiently than monocytes. *J Bone Miner Res*. 2009 Sep 23. [Epub ahead of print] [Abstract]

> *This study compared dendritic cell (DC)-derived osteoclasts to monocyte-derived osteoclasts by transcriptomic profiling, and established DCs as a new osteoclast precursor able to generate osteoclasts more efficiently than monocytes. The results suggest that DCs can be used as target cells for functional studies for osteoclastogenesis.* —HWD

Rivadeneira F, Styrkársdottir U, Estrada K, Halldórsson BV, Hsu YH, Richards JB, Zillikens MC, Kavvoura FK, Amin N, Aulchenko YS, Cupples LA, Deloukas P, Demissie S, Grundberg E, Hofman A, Kong A, Karasik D, van Meurs JB, Oostra B, Pastinen T, Pols HA, Sigurdsson G, Soranzo N, Thorleifsson G, Thorsteinsdottir U, Williams FM, Wilson SG, Zhou Y, Ralston SH, van Duijn CM, Spector T, Kiel DP, Stefansson K, Ioannidis JP, Uitterlinden AG; Genetic Factors for

Osteoporosis (GEFOS) Consortium. Twenty bone-mineral-density loci identified by large-scale meta-analysis of genome-wide association studies. *Nat Genet*. 2009 Nov;41(11):1199-206. [Abstract]

Richards JB, Kavvoura FK, Rivadeneira F, Styrkársdóttir U, Estrada K, Halldórsson BV, Hsu YH, Zillikens MC, Wilson SG, Mullin BH, Amin N, Aulchenko YS, Cupples LA, Deloukas P, Demissie S, Hofman A, Kong A, Karasik D, van Meurs JB, Oostra BA, Pols HA, Sigurdsson G, Thorsteinsdottir U, Soranzo N, Williams FM, Zhou Y, Ralston SH, Thorleifsson G, van Duijn CM, Kiel DP, Stefansson K, Uitterlinden AG, Ioannidis JP, Spector TD; Genetic Factors for Osteoporosis Consortium. Collaborative meta-analysis: associations of 150 candidate genes with osteoporosis and osteoporotic fracture. *Ann Intern Med*. 2009 Oct 20;151(8):528-37. [Abstract]

> *Digging deeper into the sea of genetic variants associated with BMD...these two studies are both based on the merging of 5 cohort studies in which GWAS for osteoporosis traits had previously been reported. A greater number of subjects together, i.e., close to 19,000 here, and a meta-analytical approach means more power to detect associations between SNPs and the traits of interest. Thus the first study, a hypothesis-free approach, identifies a substantial number of new loci (15 for LS BMD, 13 for FN BMD), in addition to confirming previous ones (such as LRP5, ESR1, and the RANKL/OPG/RANK pathway). These SNPs together still explain less than 3% of BMD variance when applied to one of the study populations, and result in a minimally increased risk of vertebral, but not non-vertebral fractures. The second study focuses on a very large number of SNPs marking 150 candidate genes for osteoporosis. Very few (9) genes were confirmed to be associated with BMD and/or fractures (all in the list of genes by GWAS reported above), and some famous candidates were dismissed, such as VDR and MTHFR. So...much ado about...nothing?* —SF

Molecular and Cell Biology

Hamidouche Z, Fromigué O, Ringe J, Häupl T, Vaudin P, Pagès JC, Srouji S, Livne E, Marie PJ. Priming integrin alpha5 promotes human mesenchymal stromal cell osteoblast differentiation and osteogenesis. *Proc Natl Acad Sci U S A*. 2009 Nov 3;106(44):18587-91. [Abstract] [Full Text]

> *This study shows that the integrin α5 subunit (ITGA5), a fibronectin receptor, mediates osteoblast differentiation induced by dexamethasone in adult hMSCs. Using an anti-ITGA5 monoclonal antibody (SNAKA51) that primes and stimulates α5β1 integrin and promotes cell adhesion in fibroblasts, markers of osteoblastic differentiation (such as RUNX2 and ALP) were induced from MSCs, providing therapeutic potential for the induction of osteoblastogenesis by targeting ITGA5.* —SF

Yao Z, Xing L, Boyce BF. NF-kappaB p100 limits TNF-induced bone resorption in mice by a TRAF3-dependent mechanism. *J Clin Invest*. 2009 Oct;119(10):3024-34. [Abstract]

> *TNF can induce osteoclast formation directly from osteoclast precursors (OCPs), but fewer osteoclasts are formed by TNF than by RANKL. TNF increases inhibitory NF-kB p100 (NF-kB2). NIK enhances proteasomal degradation of NF-kB p100, and TRAF3 inhibits NIK activity. The authors demonstrate that TNF enhances the expression of TRAF3 which increases NF-kB p100 in OCPs, and that TNF robustly induces osteoclast formation in RANKL(-/-) and RANK(-/-) mice when they also lack NF-kB p100, suggesting a role for NF-kB p100 in limiting bone resorption under TNF excess such as in RA. Thus, TRAF3 or NF-kB p100 can become a new therapeutic target in inflammation-induced bone loss.* —TM

Yu S, Franceschi RT, Luo M, Fan J, Jiang D, Cao H, Kwon TG, Lai Y, Zhang J, Patrene K, Hankenson K, Roodman GD, Xiao G. Critical role of activating transcription factor 4 in the anabolic actions of parathyroid hormone in bone. *PLoS One*. 2009 Oct 23;4(10):e7583. [Abstract]

Kim MS, Kondo T, Takada I, Youn MY, Yamamoto Y, Takahashi S, Matsumoto T, Fujiyama S, Shirode Y, Yamaoka I, Kitagawa H, Takeyama K, Shibuya H, Ohtake F, Kato S. DNA demethylation in hormone-induced transcriptional derepression. *Nature*. 2009 Oct 15;461(7266):1007-12. [Abstract]

> *Two truly remarkable studies bringing some new insight into the molecular/intracellular mechanisms of action of PTH. The first study shows that the anabolic actions of PTH in bone are severely impaired in both growing and adult ovariectomized mice lacking bone-related activating transcription factor 4 (ATF4), and that PTH stimulates expression of osterix, a critical transcription factor for osteoblast differentiation, through the binding of ATF4 to the osterix promoter. The second study demonstrates that PTH exerts effects on epigenetic regulation of gene expression, i.e., induces demethylation of the cytochrome p450 27B1 (CYP27B1) gene, the final enzyme in vitamin D biosynthesis, in proximal kidney tubules.* —SF

Pathophysiology

Lu X, Wang Q, Hu G, Van Poznak C, Fleisher M, Reiss M, Massagué J, Kang Y. ADAMTS1 and MMP1 proteolytically engage EGF-like ligands in an osteolytic signaling cascade for bone metastasis. *Genes Dev*. 2009 Aug 15;23(16):1882-94. [Abstract]

> *The authors show that two distinct metalloproteinases, ADAMTS1 and MMP1, in breast cancer cells orchestrate a paracrine signaling cascade to enhance osteolytic bone metastasis. These metalloproteinases enhance proteolytic release of membrane-bound EGF-like growth factors from tumor cells, which suppress OPG expression in osteoblasts to potentiate osteoclastic bone resorption. Thus, these metalloproteinases in tumor cells can become new therapeutic targets against bone metastasis of breast cancer.* —TM

Reviews, Perspectives and Editorials

Chen JH, Liu C, You L, Simmons CA. Boning up on Wolff's Law: Mechanical regulation of the cells that make and maintain bone. *J Biomech*. 2009 Oct 7. [Epub ahead of print] [Abstract]

Kumar R. Pin1 regulates parathyroid hormone mRNA stability. *J Clin Invest*. 2009 Oct;119(10):2887-91. [Abstract]

Rizzoli R, Bruyere O, Cannata-Andia JB, Devogelaer JP, Lyritis G, Ringe JD, Vellas B, Reginster JY. Management of osteoporosis in the elderly. *Curr Med Res Opin*. 2009 Oct;25(10):2373-87. [Abstract]

> *A truly complete review, which also takes into account frailty, not only bone fragility, and interventions to prevent falls.* —SF

Schneider MR, Sibilia M, Erben RG. The EGFR network in bone biology and pathology. *Trends Endocrinol Metab*. 2009 Oct 9. [Epub ahead of print] [Abstract]

Other Studies of Potential Interest

Arabi A, Zahed L, Mahfoud Z, El-Onsi L, Nabulsi M, Maalouf J, Fuleihan Gel-H. Vitamin D receptor gene polymorphisms modulate the skeletal response to vitamin D supplementation in healthy girls. *Bone*. 2009 Dec;45(6):1091-7. [Abstract]

Bone HG, McClung MR, Roux C, Recker RR, Eisman JA, Verbruggen N, Hustad CM, Dasilva C, Santora AC, Ince BA. Odanacatib, a cathepsin-K inhibitor for osteoporosis: a two-year study in postmenopausal women with low bone density. *J Bone Miner Res*. 2009 Oct 29. [Epub ahead of print] [Abstract]

Chamoux E, Couture J, Bisson M, Morissette J, Brown JP, Roux S. The p62 P392L mutation linked to Paget's disease induces activation of human osteoclasts. *Mol Endocrinol*. 2009 Oct;23(10):1668-80. [Abstract]

Chen YJ, Wei YY, Chen HT, Fong YC, Hsu CJ, Tsai CH, Hsu HC, Liu SH, Tang CH. Osteopontin increases migration and MMP-9 up-regulation via alphavbeta3 integrin, FAK, ERK, and NF-kappaB-dependent pathway in human chondrosarcoma cells. *J Cell Physiol*. 2009 Oct;221(1):98-108. [Abstract]

Ge C, Xiao G, Jiang D, Yang Q, Hatch NE, Franceschi RT. Identification and functional characterization of extracellular-regulated kinase/MAPK phosphorylation sites in the Runx2 transcription factor. *J Biol Chem*. 2009 Sep 30. [Epub ahead of print]

Heywood HK, Lee DA. Low oxygen reduces the modulation to an oxidative phenotype in monolayer-expanded chondrocytes. *J Cell Physiol*. 2010 Jan;222(1):248-53. [Abstract]

King EM, Holden NS, Gong W, Rider CF, Newton R. Inhibition of NF-kappaB-dependent transcription by MKP-1: transcriptional repression by glucocorticoids occurring via p38 MAPK. *J Biol Chem*. 2009 Sep 25;284(39):26803-15. [Abstract] [Full Text]

Krossøy C, Ornsrud R, Wargelius A. Differential gene expression of bgp and mgp in trabecular and compact bone of Atlantic salmon (Salmo salar L.) vertebrae. *J Anat*. 2009 Oct 6. [Epub ahead of print] [Abstract]

Lee Y, Ha J, Kim HJ, Kim YS, Chang EJ, Song WJ, Kim HH. Negative-feedback inhibition of NFATc1 by DYRK1A regulates bone homeostasis. *J Biol Chem*. 2009 Oct 2. [Epub ahead of print]

Nechama M, Uchida T, Mor Yosef-Levi I, Silver J, Naveh-Many T. The peptidyl-prolyl isomerase Pin1 determines parathyroid hormone mRNA levels and stability in rat models of secondary hyperparathyroidism. *J Clin Invest*. 2009 Oct;119(10):3102-14. [Abstract]

Nelsen SM, Christian JL. Site-specific cleavage of BMP4 by furin, PC6, and PC7. *J Biol Chem*. 2009 Oct 2;284(40):27157-66. [Abstract] [Full Text]

Roberts MD, Santner TJ, Hart RT. Local bone formation due to combined mechanical loading and intermittent hPTH-(1-34) treatment and its correlation to mechanical signal distributions. *J Biomech*. 2009 Nov 13;42(15):2431-8. [Abstract]

Schiltz C, Prouillet C, Marty C, Merciris D, Collet C, de Vernejoul MC, Geoffroy V. Bone loss induced by Runx2 over-expression in mice is blunted by osteoblastic over-expression of TIMP-1. *J Cell Physiol*. 2010 Jan;222(1):219-29. [Abstract]

Schrauwen I, Ealy M, Fransen E, Vanderstraeten K, Thys M, Meyer NC, Cosgarea M, Huber A, Mazzoli M, Pfister M, Smith RJ, Van Camp G. Genetic variants in the RELN gene are associated with otosclerosis in multiple European populations. *Hum Genet*. 2009 Oct 22. [Epub ahead of print] [Abstract]

Tanaka S, Nakano H. NF-kappaB2 (p100) limits TNF-alpha-induced osteoclastogenesis. *J Clin Invest*. 2009 Oct;119(10):2879-81. [Abstract]

Tiedemann K, Hussein O, Sadvakassova G, Guo Y, Siegel PM, Komarova SV. Breast cancer derived factors stimulate osteoclastogenesis through the Ca2+/PKC and TGFbeta/MAPK signaling pathways. *J Biol Chem*. 2009 Sep 30. [Epub ahead of print]

Whyte LS, Ryberg E, Sims NA, Ridge SA, Mackie K, Greasley PJ, Ross RA, Rogers MJ. The putative cannabinoid receptor GPR55 affects osteoclast function in vitro and bone mass in vivo. *Proc Natl Acad Sci U S A*. 2009 Sep 22;106(38):16511-6. [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.