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NOT TO BE MISSED

Clinical and Basic Research Papers – December 2010

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Clinical Studies and Drug Effects

Burghardt AJ, Issever AS, Schwartz AV, Davis KA, Masharani U, Majumdar S, Link TM. High-resolution peripheral quantitative computed tomographic imaging of cortical and trabecular bone microarchitecture in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab*. 2010 Nov;95(11):5045-55. [Abstract] [Full Text]

> *Female patients (aged 62.9 ± 7.7 yrs.) with T2DM (n = 19) compared to age- and height-matched controls (n = 19) had 10% higher trabecular volumetric BMD (P < 0.05) adjacent to the cortex and higher trabecular thickness in the tibia (13.8%; P < 0.05). Cortical porosity differences alone were consistent with impaired bone strength and were significant in the radius (> +50%; P < 0.05), whereas pore volume approached significance in the tibia (+118%; P = 0.1). The higher trabecular density may reflect trabecularization of the cortex.* —ES

Yu EW, Neer RM, Lee H, Wyland JJ, de la Paz AV, Davis MC, Okazaki M, Finkelstein JS. Time-dependent changes in skeletal response to teriparatide: Escalating vs. constant dose teriparatide (PTH 1-34) in osteoporotic women. *Bone*. 2010 Nov 24. [Epub ahead of print] [Abstract]

> *An original scheme of TPT administration – 20 μg/d for 6 months, then 30 μg/d for 6 months, then 40 μg/d for 6 months – seemed to overcome the potential desensitization of PTH effects on bone turnover markers, however, without providing a significantly greater BMD gain compared to a 20 μg/d fixed-dose group.* —SF

Public Health – Epidemiology

Goliasch G, Blessberger H, Azar D, Heinze G, Wojta J, Bieglmayer C, Wagner O, Schillinger M, Huber K, Maurer G, Haas M, Wiesbauer F. Markers of bone metabolism in premature myocardial infarction (≤ 40 years of age). *Bone*. 2010 Nov 13. [Epub ahead of print] [Abstract]

> *In this prospective study, 102 myocardial infarction (MI) patients younger than 40 years of age and 200 controls, matched on gender and age, were included. The study used baseline laboratory measurements for the acute phase and measurements from one-year follow-up visits (stable phase). In both the acute and stable phases, elevated levels of 25(OH) vitamin D_3 and 1,25$(OH)_2$ vitamin D_3 were positively associated with premature MI (for 25(OH) vitamin D_3, acute phase: OR = 2.02, 95% CI: 1.13-3.58; stable phase: OR = 4.07, 95% CI: 1.8-9.2; for 1,25$(OH)_2$ vitamin D_3, acute phase: OR = 2.82, 95% CI: 1.7-4.7; stable phase: OR = 4.57, 95% CI: 2.31- 9.05). Conversely, osteocalcin levels were inversely associated with premature MI (acute phase: OR =*

0.53, 95% CI: 0.28-1.03; stable phase: OR = 0.26, 95% CI: 0.12-0.6). —DK

Yang S, Nguyen ND, Center JR, Eisman JA, Nguyen TV. Association between beta-blocker use and fracture risk: The Dubbo Osteoporosis Epidemiology Study. *Bone*. 2010 Nov 1. [Epub ahead of print] [Abstract]

Among 3,488 participants, 262 (20%) men and 411 (19%) women received β-blockers (BB). In men, BB use was associated with higher BMD at the femoral neck (0.96 versus 0.92 g/cm^2, P < 0.01), higher lumbar spine BMD (1.32 vs. 1.25 g/cm^2, P < 0.01), and lower fracture risk (odds ratio = 0.49, 95% CI: 0.32-0.75) than those not on BB. In women, BB users also had higher femoral neck BMD (0.83 vs. 0.81g/cm^2, P < 0.01), higher lumbar spine BMD (1.11 vs. 1.06 g/cm^2, P < 0.01), and lower risk of fracture (odds ratio = 0.68, 95% CI: 0.53-0.87) than non-users. This risk reduction is large. Whether there are confounders present remains to be determined. —ES

Cancer and Bone

Stopeck AT, Lipton A, Body JJ, Steger GG, Tonkin K, de Boer RH, Lichinitser M, Fujiwara Y, Yardley DA, Viniegra M, Fan M, Jiang Q, Dansey R, Jun S, Braun A. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol*. 2010 Nov 8. [Epub ahead of print] [Abstract]

Patients were randomly assigned to denosumab 120 mg and placebo (n = 1,026) or zoledronic acid 4 mg (n = 1,020) every 4 weeks. Denosumab was superior to zoledronic acid in delaying time to first skeletal-related event (SRE) (hazard ratio = 0.82, 95% CI: 0.71-0.95) and time to first and subsequent (multiple) on-study SREs (rate ratio = 0.77, 95% CI: 0.66-0.89). Reduction in turnover markers was greater with denosumab. Overall survival, disease progression, and rates of adverse events (AEs) and serious AEs were similar. An excess of renal AEs and acute-phase reactions occurred with zoledronic acid; hypocalcemia occurred more often with denosumab. Osteonecrosis of the jaw occurred infrequently (2.0%, denosumab; 1.4%, zoledronic acid; P = .39). —ES

Genetics

Harsløf T, Tofteng CL, Husted LB, Nyegaard M, Børglum A, Carstens M, Stenkjær L, Brixen K, Eiken P, Jensen JE, Mosekilde L, Rejnmark L, Langdahl BL. Polymorphisms of the peroxisome proliferator-activated receptor γ (PPARγ) gene are associated with osteoporosis. *Osteoporos Int*. 2010 Nov 23. [Epub ahead of print] [Abstract]

Harsløf T, Husted LB, Nyegaard M, Carstens M, Stenkjær L, Brixen K, Eiken P, Jensen JE, Børglum AD, Mosekilde L, Rejnmark L, Langdahl BL. Polymorphisms in the ALOX12 gene and osteoporosis. *Osteoporos Int*. 2010 Nov 23. [Epub ahead of print] [Abstract]

These two studies from the same group show somewhat puzzling results: both used two Danish cohorts from the same population yet found different genetic associations. The two cohorts studied were the AROS cohort, a case-control population comprising 809 individuals (osteoporotic patients, 360 women and 102 men, and normal controls, 262 women and 74 men) and the DOPS cohort, comprising 1,716 initially perimenopausal women, followed for 5-10 years. The authors postulated that, since stimulation of PPARγ with ALOX enzymes drives mesenchymal stem cells in an adipocyte direction at the expense of an osteoblast pool, variations in PPARγ and ALOX genes are informative. Thus they chose 10 polymorphisms in each gene for

association with BMD and incidental fractures. SNPs in PPARγ predicted an increased risk of vertebral fractures (OR = 1.48-1.76, p = 0.005-0.04) in AROS. SNPs in ALOX12 were associated with lumbar spine BMD (p = 0.02-0.06) and an increased risk of vertebral fractures (p < 0.05) in AROS but not in DOPS. Importantly, an interaction between PPARγ SNPs and diet or body weight was found on BMD. These cohort-specific gene-environment interactions and different cohort designs could explain the discrepancies between these Danish samples. —DK

Mantila Roosa SM, Liu Y, Turner CH. Alternative splicing in bone following mechanical loading. *Bone*. 2010 Nov 20. [Epub ahead of print] [Abstract]

This study used the rat forelimb loading model to evaluate the extent of alternative splicing in a bone under mechanical loading. Animals were subjected to loading sessions every day, and ulnae were sampled at 11 time points, from 4 hours to 32 days since loading started. The authors identified multiple alternatively spliced genes encoding cytokines, ion channels, solute carriers, and notably, muscle-related genes. Among the alternatively spliced genes, five (Akap12, Fn1, Pcolce, Sfrp4, and Tpm1) were selected based on a bioinformatic algorithm and validated with qPCR. The authors concluded that mechanical loading induces alternative splicing in bone. —DK

Bone Modeling, Remodeling, and Repair

Agholme F, Li X, Isaksson H, Ke HZ, Aspenberg P. Sclerostin antibody treatment enhances metaphyseal bone healing in rats. *J Bone Miner Res*. 2010 Nov;25(11):2412-8. [Abstract]

Male rats had a screw inserted in the proximal tibia and were given 25 mg/kg of sclerostin antibody or control twice a week subcutaneously for 2 or 4 weeks. Sclerostin antibody increased the pull-out force by almost 50% compared with controls after 2 and 4 weeks. Micro-computed tomography showed a 30% increase in bone volume fraction in a region surrounding the screw. There also was an increase in trabecular thickness in cancellous bone. —ES

Wegrzyn J, Roux JP, Arlot ME, Boutroy S, Vilayphiou N, Guyen O, Delmas PD, Chapurlat R, Bouxsein ML. Role of trabecular microarchitecture and its heterogeneity parameters in the mechanical behavior of ex vivo human L3 vertebrae. *J Bone Miner Res*. 2010 Nov;25(11):2324-31. [Abstract]

Among 21 human L(3) vertebrae, BMD explained up to 44% of the variability in vertebral mechanical behavior, bone volume fraction (BV/TV) up to 53%, and trabecular architecture up to 66%. BMD or BV/TV with microarchitecture and its heterogeneity improved the prediction of vertebral mechanical behavior, together explaining up to 86% of the variability in failure load. —ES

Molecular and Cell Biology

Geng S, Zhou S, Glowacki J. Effects of 25-hydroxyvitamin D3 on proliferation and osteoblast differentiation of human marrow stromal cells require CYP27B1/1α-hydroxylase. *J Bone Miner Res*. 2010 Nov 23. [Epub ahead of print] [Abstract]

By studying human mesenchymal cell lines expressing different levels of 1α-hydroxylase, this study demonstrates the role of vitamin D metabolites in arresting human marrow stromal cell (hMSC) proliferation while promoting osteoblast differentiation, hence broadening the role of vitamin D in the regulation of bone and

mineral homeostasis. —SF

Medici D, Shore EM, Lounev VY, Kaplan FS, Kalluri R, Olsen BR. Conversion of vascular endothelial cells into multipotent stem-like cells. *Nat Med*. 2010 Nov 21. [Epub ahead of print] [Abstract]

Fibrodysplasia ossificans progressiva (FOP) is a disease with heterotopic ossification caused by activating mutations of an activin-like kinase-2 (ALK2) receptor. The authors showed that, in lesions from FOP patients or from transgenic mice expressing constitutively active ALK2, chondrocytes and osteoblasts expressed endothelial markers. Lineage tracing using a Tie2-Cre construct in mice also suggested an endothelial origin of these cells. Expression of constitutively active ALK2 in endothelial cells, or treatment of untransfected endothelial cells with transforming growth factor-β2 (TGF-β2) or bone morphogenetic protein-4 (BMP4) caused endothelial-to-mesenchymal transition and acquisition of a stem cell-like phenotype. These findings may provide a new approach to tissue engineering. —TM

Moreaux J, Hose D, Kassambara A, Reme T, Moine P, Requirand G, Goldschmidt H, Klein B. Osteoclast-gene expression profiling reveals osteoclast-derived CCR2-chemokines promoting myeloma cell migration. *Blood*. 2010 Nov 19. [Epub ahead of print] [Abstract]

Multiple myeloma (MM) cells enhance osteoclastic bone resorption, and grow near active resorption sites. In order to elucidate the mechanism of the osteoclastic support of MM cell survival, the authors performed microarray analysis and identified genes encoding four CCR2-targeting chemokines and MM cell growth factors (IGF-1, APRIL). An anti-CCR2 MoAb blocked osteoclast chemoattractant activity for MM cells. CCR2-chemokines also promote MAPK activation for MM cell growth. An anti-IGF-1 receptor MoAb completely blocked the osteoclast-induced survival of MM cells. These results suggest that CCR2 and/or IGF-1 targeting strategies can be a new therapeutic approach against MM. —TM

Ta HM, Nguyen GT, Jin HM, Choi J, Park H, Kim N, Hwang HY, Kim KK. Structure-based development of a receptor activator of nuclear factor-kappaB ligand (RANKL) inhibitor peptide and molecular basis for osteopetrosis. *Proc Natl Acad Sci U S A*. 2010 Nov 23;107(47):20281-6. [Abstract] [Full Text]

Based on a molecular pharmacology approach and ligand-receptor interaction modeling, peptide inhibitors designed to mimic Loop3 of RANK blocked the RANKL-induced differentiation of osteoclast precursors. This work may provide the basis for a non-denosumab inhibition of the RANKL pathway and bone resorption. —SF

Vanleene M, Saldanha Z, Cloyd KL, Jell G, Bou-Ghairos G, Bassett JH, Williams GR, Fisk NM, Oyen ML, Stevens MM, Guillot PV, Shefelbine SJ. Transplantation of human fetal blood stem cells in the osteogenesis imperfecta mouse leads to improvement in multi-scale tissue properties. *Blood*. 2010 Nov 18. [Epub ahead of print] [Abstract]

The authors have previously shown that intrauterine transplantation of blood fetal stem/stromal cells in osteogenesis imperfecta (OI) mice significantly reduced bone fracture. Here, the authors examined the cellular mechanisms and modifications in mechanical properties of bone after transplantation. Femoral fractures decreased by 84% in transplanted OI mice. Fetal blood stem cells engrafted in bones, differentiated into mature osteoblasts, expressed osteocalcin, and produced Col1a2 protein absent in OI mice. The formation of normal collagen altered apatite crystal structure, increased bone matrix stiffness, and reduced bone brittleness. Thus, fetal blood stem

cell transplantation can improve the mechanical integrity of bone, and may become a new therapeutic approach against OI. —TM

Physiology and Metabolism

Mavalli MD, DiGirolamo DJ, Fan Y, Riddle RC, Campbell KS, van Groen T, Frank SJ, Sperling MA, Esser KA, Bamman MM, Clemens TL. Distinct growth hormone receptor signaling modes regulate skeletal muscle development and insulin sensitivity in mice. *J Clin Invest*. 2010 Nov 1;120(11):4007-20. [Abstract]

This is a seminal piece of work in which GH is shown to induce myoblast production of IGF-1, and this IGF-1, in turn, stimulates myoblast proliferation and fusion in vitro through an autocrine mechanism. Targeted deletion of the IGF-1 and GH receptors in skeletal muscle demonstrates that GH signaling directly regulates muscle development and metabolism. In GH receptor-deficient mice, insulin sensitivity was also reduced, resulting in increased peripheral adiposity. IGF-1 receptor KO mice were phenocopies of the muscular defects seen in GH receptor KOs, however, they did not display similar metabolic abnormalities (no insulin resistance nor adiposity), pointing to both shared and specific functions of GH and IGF-1 in muscle. —SF

Pathophysiology

Heiland GR, Zwerina K, Baum W, Kireva T, Distler JH, Grisanti M, Asuncion F, Li X, Ominsky M, Richards W, Schett G, Zwerina J. Neutralisation of Dkk-1 protects from systemic bone loss during inflammation and reduces sclerostin expression. *Ann Rheum Dis*. 2010 Dec;69(12):2152-9. [Abstract]

In a transgenic mouse model overexpressing TNF-α – a non-specific model of inflammation-induced bone loss – Dkk1-Ab prevented the inhibition of osteoblast markers and bone formation more efficiently than infliximab – a TNF inhibitor – whereas both drugs inhibited osteoclast numbers similarly. Dkk1-Ab allowed for the preservation of BV/TV. Results also suggest that increased Sost expression could participate in TNF-induced bone loss and, conversely, Dkk1-Ab effects. —SF

Reviews, Perspectives and Editorials

Karsenty G, Oury F. The central regulation of bone mass, the first link between bone remodeling and energy metabolism. *J Clin Endocrinol Metab*. 2010 Nov;95(11):4795-801. [Abstract] [Full Text]

Ralston SH, Uitterlinden AG. Genetics of osteoporosis. *Endocr Rev*. 2010 Oct;31(5):629-62. [Abstract]

Rizzoli R, Akesson K, Bouxsein M, Kanis JA, Napoli N, Papapoulos S, Reginster JY, Cooper C. Subtrochanteric fractures after long-term treatment with bisphosphonates: a European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, and International Osteoporosis Foundation Working Group Report. *Osteoporos Int*. 2010 Nov 18. [Epub ahead of print] [Abstract]

Teitelbaum SL, Seton MP, Saag KG. Should bisphosphonates be used for long-term treatment of glucocorticoid-induced osteoporosis? *Arthritis Rheum*. 2010 Nov 8. [Epub ahead of print] [Info]

Teti A, Eastell R, eds. Central role of the skeleton in chronic diseases. *Arch Biochem Biophys*.

2010 Nov 1;503(1):1-160.

- *We draw your attention to this series of review articles published in Archives of Biochemistry and Biophysics, covering topics like fat and bone, the immune system and bone, cardiovascular disease and bone, and many others.*

Other Studies of Potential Interest

Agueda L, Velázquez-Cruz R, Urreizti R, Yoskovitz G, Sarrion P, Jurado S, Güerri R, Garcia-Giralt N, Nogués X, Mellibovsky L, Díez-Pérez A, Marie PJ, Balcells S, Grinberg D. Functional relevance of the BMD-associated polymorphism rs312009: novel involvement of Runx2 in LRP5 transcriptional regulation. *J Bone Miner Res*. 2010 Nov 18. [Epub ahead of print] [Abstract]

Arthur A, Zannettino A, Panagopoulos R, Koblar SA, Sims NA, Stylianou C, Matsuo K, Gronthos S. EphB/ephrin-B interactions mediate human MSC attachment, migration and osteochondral differentiation. *Bone*. 2010 Nov 5. [Epub ahead of print] [Abstract]

Clifton-Bligh RJ, Nguyen TV, Au A, Bullock M, Cameron I, Cumming R, Chen JS, March LM, Seibel MJ, Sambrook PN. Contribution of a common variant in the promoter of the 1-α-hydroxylase gene (CYP27B1) to fracture risk in the elderly. *Calcif Tissue Int*. 2010 Nov 25. [Epub ahead of print] [Abstract]

Giroux S, Elfassihi L, Clément V, Bussières J, Bureau A, Cole DE, Rousseau F. High-density polymorphisms analysis of 23 candidate genes for association with bone mineral density. *Bone*. 2010 Nov;47(5):975-81. [Abstract]

Gregson CL, Hollingworth P, Williams M, Petrie KA, Bullock AN, Brown MA, Tobias JH, Triffitt JT. A novel ACVR1 mutation in the glycine/serine-rich domain found in the most benign case of a fibrodysplasia ossificans progressiva variant reported to date. *Bone*. 2010 Oct 29. [Epub ahead of print] [Info]

Liu LF, Shen WJ, Zhang ZH, Wang LJ, Kraemer FB. Adipocytes decrease Runx2 expression in osteoblastic cells: roles of PPARγ and adiponectin. *J Cell Physiol*. 2010 Nov;225(3):837-45. [Abstract]

Mrak E, Guidobono F, Moro G, Fraschini G, Rubinacci A, Villa I. Calcitonin gene-related peptide (CGRP) inhibits apoptosis in human osteoblasts by β-catenin stabilization. *J Cell Physiol*. 2010 Nov;225(3):701-8. [Abstract]

Paternoster L, Lorentzon M, Vandenput L, Karlsson MK, Ljunggren O, Kindmark A, Mellstrom D, Kemp JP, Jarett CE, Holly JP, Sayers A, St. Pourcain B, Timpson NJ, Deloukas P, Davey Smith G, Ring SM, Evans DM, Tobias JH, Ohlsson C. Genome-wide association meta-analysis of cortical bone mineral density unravels allelic heterogeneity at the RANKL locus and potential pleiotropic effects on bone. *PLoS Genet*. 2010 Nov;6(11):e1001217. [Abstract]

Venegas KR, Gómez MA, Eisman JA, Sánchez AG, Dader MJ, Hernández MA. Pharmacogenetics of osteoporosis-related bone fractures: moving towards the harmonization and validation of polymorphism diagnostic tools. *Pharmacogenomics*. 2010 Sep;11(9):1287-303. [Abstract]

Conflict of Interest: Dr. Ferrari reports that he receives research support from Amgen and Merck Sharp & Dohme, and is an advisory committee member and lectures occasionally at conference symposia for the Alliance for Better Bone Health (sanofi aventis/P&G), Amgen, Merck Sharp & Dohme, Eli Lilly, Servier, and Novartis. Dr. Little reports that he receives royalties, research funds and consultancy fees from Novartis Pharma, as well as research support from Stryker Biotech.

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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. Karasik report no conflicts of interest.