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NOT TO BE MISSED

Clinical and Basic Research Papers – October 2008

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Bone Modeling, Remodeling and Repair

Bonnet N, Benhamou CL, Malaval L, Goncalves C, Vico L, Eder V, Pichon C, Courteix D. Low dose beta-blocker prevents ovariectomy-induced bone loss in rats without affecting heart functions. *J Cell Physiol*. 2008 Dec;217(3):819-27. [Abstract]

> Bone remodeling is under β-adrenergic control. Low (0.1 mg/kg/day), medium (5 mg/kg/day) or high (20 mg/kg/day) doses of propranolol were given 5 days per week for 10 weeks in ovariectomized (OVX) rats. The low dose prevented OVX-induced bone loss by increasing bone formation (+30%) and decreasing bone resorption (-52% of osteoclast surface). Consequently, rats receiving 0.1 mg/kg/day of propranolol displayed higher stress (+27%), intrinsic energy (+28.7%) and Young's Modulus in compression, compared to placebo. No significant effects on heart hemodynamic parameters were found. Medium and high doses of propranolol had a negative effect on heart functions but no protective effects on bone mass. These results suggest that low doses of β-blockers may have a therapeutic utility. —ES

Greiner SH, Wildemann B, Back DA, Alidoust M, Schwabe P, Haas NP, Schmidmaier G. Local application of zoledronic acid incorporated in a poly(D,L-lactide)-coated implant accelerates fracture healing in rats. *Acta Orthop*. 2008 Oct;79(5):717-25. [Abstract]

> *After previously optimizing the amount of zoledronic acid in a polymer through in vitro assays, zoledronic acid-coated K wires were used to fixate femoral fractures. Increases in radiographic scores and mechanical properties without any deficit in healing were noted with zoledronic acid-coated K wires as compared to polymer-coated or uncoated controls. In this model, local dosing was feasible.* —DGL

Karsdal MA, Byrjalsen I, Leeming DJ, Delmas PD, Christiansen C. The effects of oral calcitonin on bone collagen maturation: implications for bone turnover and quality. *Osteoporos Int*. 2008 Sep;19(9):1355-61. [Abstract]

> *This study evaluated the impact of oral calcitonin on bone collagen maturation (the ratio between degradation products of newly synthesized C-telopeptides of type I collagen (non-isomerized ααCTX) and mature isomerized ββCTX) in 168 postmenopausal women treated with placebo, 0.15, 0.4, 1, or 2.5 mg of calcitonin per day. Calcitonin dose-dependently inhibited resorption but the ααCTX to ββCTX ratio remained unchanged, in contrast to other anti-resorptive therapies.* —ES

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Clinical Studies and Drug Effects

Gjertsen JE, Vinje T, Lie SA, Engesaeter LB, Havelin LI, Furnes O, Fevang JM. Patient satisfaction, pain, and quality of life 4 months after displaced femoral neck fractures: a comparison of 663 fractures treated with internal fixation and 906 with bipolar hemiarthroplasty reported to the Norwegian Hip Fracture Register. *Acta Orthop*. 2008 Oct;79(5):594-601. [Abstract]

> *Further evidence that in the elderly, displaced intracapsular hip fractures are best treated with arthroplasty in a real-world setting.* —DGL

Lewiecki EM, Keaveny TM, Kopperdahl D, Genant HK, Engelke K, Fuerst T, Kivitz A, Davies RY, Fitzpatrick LA. Once-monthly oral ibandronate improves biomechanical determinants of bone strength in women with postmenopausal osteoporosis. *J Clin Endocrinol Metab*. 2008 Oct 7; [Epub ahead of print]

> *Although the BONE RCT showed significant reduction of vertebral fractures in post-menopausal women receiving daily ibandronate, direct evidence of an effect on non-vertebral and specifically femoral neck fractures is lacking. The present study used QCT and DXA, and finite element analysis (FEA) of QCT data and HSA of DXA data, to evaluate structural effects of ibandronate at the hip and spine. This small-scale, randomized, placebo-controlled study in postmenopausal women with T-scores below -2 provides indirect and encouraging results for a potentially bone-strengthening effect of monthly oral ibandronate, in particular at the femoral neck. FEA indeed indicated 5.9% and 4.1% greater femoral strength and strength-to-density ratio, respectively, in IBN vs PBO, that is a maintenance of estimated bone strength in treated subjects, whereas a significant loss occurred among PBO subjects. Statistical analysis was performed by the sponsor (GSK).* —SF

Mudano AS, Bian J, Cope JU, Curtis JR, Gross TP, Allison JJ, Kim Y, Briggs D, Melton ME, Xi J, Saag KG. Vertebroplasty and kyphoplasty are associated with an increased risk of secondary vertebral compression fractures: a population-based cohort study. *Osteoporos Int*. 2008 Sep 17; [Epub ahead of print] [Abstract]

> *In this study, patients who had undergone vertebroplasty/kyphoplasty had a greater risk of new vertebral compression fractures (VCFs) compared to patients with prior VCFs who did not undergo either procedure.* —DGL

Solomon DH, Hochberg MC, Mogun H, Schneeweiss S. The relation between bisphosphonate use and non-union of fractures of the humerus in older adults. *Osteoporos Int*. 2008 Oct 9; [Epub ahead of print] [Abstract]

> *This study of a large Medicare cohort shows that operation for non-union is rare (0.4%) but the relative risk is doubled after exposure to bisphosphonates. This association does not equal causation, but gives further pause for thought. The diaphyseal nature of humerus fractures may be a different environment from that of hip fractures, where the administration of zoledronic acid did not significantly increase non-union. Confirmation from other databases is required, as is further research on the timing of administration and the mechanism.* —DGL

Genetics

Agueda L, Bustamante M, Jurado S, Garcia-Giralt N, Ciria M, Saló G, Carreras R, Nogués X, Mellibovsky L, Díez-Pérez A, Grinberg D, Balcells S. A haplotype-based analysis of the LRP5 gene in relation to osteoporosis phenotypes in Spanish postmenopausal women. *J Bone Miner Res*. 2008 Aug 6; [Epub ahead of print] [Abstract]

> *LRP5 has received much attention from geneticists as an important candidate gene for osteoporosis-related phenotypes, but some studies have reported inconsistent results. The work presented here helps to clarify this situation by providing consistent evidence for the importance of LRP5 to bone.* —HWD

Farber CR, van Nas A, Ghazalpour A, Aten JE, Doss S, Sos B, Schadt EE, Ingram-Drake L, Davis RC, Horvath S, Smith DJ, Drake TA, Lusis AJ. An integrative genetics approach to identify candidate genes regulating bone density: combining linkage, gene expression and association. *J Bone Miner Res*. 2008 Sep 3; [Epub ahead of print] [Abstract]

> *Numerous quantitative trait loci (QTLs) affecting bone traits have been identified in the mouse, however, few of the underlying genes have been discovered. This study introduces a novel approach that integrates multiple lines of evidence to pinpoint promising candidate genes in plausible QTLs. The approach includes linkage analysis, expression QTL (eQTL) mapping, causality modeling and genetic association in outbred mice. Application of this method to C57BL/6J X C3H/HeJ (BXH) F2 mice provides strong support for Wnt9a, Rasd1 or both underlying the Bmd11 QTL. This study proposes that integration of multiple genetic and genomic data sets can substantially improve the efficiency of QTL fine-mapping and candidate gene identification.* —HWD

Hazra A, Kraft P, Selhub J, Giovannucci EL, Thomas G, Hoover RN, Chanock SJ, Hunter DJ. Common variants of FUT2 are associated with plasma vitamin B12 levels. *Nat Genet*. 2008 Oct;40(10):1160-2. [Abstract]

> *Levels of vitamin B12 have been implicated in a number of chronic disorders, from anemia to osteoporosis. The common view is that insufficient intake and/or gastro-intestinal malabsorption are the cause of vitamin B12 deficiency. Through genome-wide association study (GWAS) looking at 500k polymorphic markers in 1658 women and replication in a thousand women from the Nurse's Health Study, the authors identified a non-synonymous (coding) SNP in the gene FUT2 coding for a,1,2-fucosyltransferase, which was associated with plasma vitamin B12. The proposed mechanism is that FUT2 alleles influence the attachment of H. pylori to the gastric mucosa, leading to gastritis, atrophy, and deficiency in the secretion of intrinsic factor. This study therefore beautifully illustrates the strength of hypothesis-free approaches such as GWAS to identify previously unsuspected genetic mechanisms for interindividual variations in common traits. It also shows its current limitations by the lack of analysis of FUT2 interactions with B12 intake.* —SF

Karim Z, Gérard B, Bakouh N, Alili R, Leroy C, Beck L, Silve C, Planelles G, Urena-Torres P, Grandchamp B, Friendlander G, Prié D. NHERF1 mutations and responsiveness of renal parathyroid hormone. *N Engl J Med*. 2008 Sept 11;359(11):1128-35. [Abstract]

> *Mutations in NPT2a and NPT2c have been identified as causes for hereditary hypophosphatemic rickets with nephrolithiasis, with increased serum 1,25(OH)2D and absorptive hypercalciuria. However, most patients with renal phosphate leak with hypercalciuria and nephrolithiasis do not carry these mutations. The authors sequenced the sodium-hydrogen exchanger regulatory factor 1 (NHERF1) gene in patients with low*

TmP/GFR and nephrolithiasis or bone demineralization, and identified 3 distinct mutations in 7 patients. NHERF1 is a PDZ-domain protein that interacts with the C-terminus of NPT2a and 2c, and plays an important role in the trafficking of these transporters. NHERF1 also interacts with the PTH type 1 receptor. Although serum PTH levels were normal in these patients, they had increased urinary cAMP, suggesting that responsiveness to PTH is increased by the mutation in NHERF1, causing hyperphosphaturia with hypophosphatemia, increased serum 1,25(OH)2D and hypercalciuria. —TM

Liu YZ, Wilson SG, Wang L, Liu XG, Guo YF, Li J, Yan H, Deloukas P, Soranzo N, Chinnapen-Horsley U, Cervino A, Williams FM, Xiong DH, Zhang YP, Jin TB, Levy S, Papasian CJ, Drees BM, Hamilton JJ, Recker RR, Spector TD, Deng HW. Identification of PLCL1 gene for hip bone size variation in females in a genome-wide association study. *PLoS ONE*. 2008 Sep 8;3(9):e3160. [Abstract]

This paper reports the first GWAS of hip bone size (BS), one of the key measurable risk factors for hip fractures (HF). Out of the studied 380,000 SNPs genotyped in 1,000 Caucasians, the PLCL1 (phospholipase c-like 1) gene had four SNPs associated with hip BS at, or approaching, a genomewide significance level. A SNP of the PLCL1 gene achieved a p value of 7.66×10^{-3} (odds ratio = 0.26) for association with HF in a Chinese sample. The biological relevance supporting the role of PLCL1 in BS is also discussed. This study provides persuasive evidence for the importance of PLCL1 to BS and thus to the risk of HF. —SF

Yerges LM, Zhang Y, Cauley JA, Kammerer CM, Nestlerode CS, Wheeler VW, Patrick AL, Bunker CH, Moffett SP, Ferrell RE, Zmuda JM. Functional characterization of genetic variation in the Frizzled 1 (Fzd1) promoter and association with bone phenotypes: more to the Lrp5 story? *J Bone Miner Res*. 2008 Aug 20; [Epub ahead of print] [Abstract]

Frizzled homolog 1 (FZD1) acts as a WNT co-receptor and initiates WNT signal transduction. This study reports interesting associations of two SNPs of the FZD1 promoter (rs2232157, rs2232158) with femoral neck areal BMD, bone size and strength-strain index (an indicator of bone's ability to withstand torsion) in 1084 men of African ancestry. Subsequent functional experiments showed that the minor C allele in rs2232158 creates a binding site for the transcription factor Egr1. This study indicates that a cis-regulatory polymorphism in the FZD1 promoter region may have a functional role in determining bone structural geometry. —HWD

Molecular and Cell Biology

Aliprantis AO, Ueki Y, Sulyanto R, Park A, Sigrist KS, Sharma SM, Ostrowski MC, Olsen BR, Glimcher LH. NFATc1 in mice represses osteoprotegerin during osteoclastogenesis and dissociates systemic osteopenia from inflammation in cherubism. *J Clin Invest*. 2008 Oct 9; [Epub ahead of print] [Abstract]

This work provides further evidence concerning the role of NFATc1 in mediating RANKL-induced osteoclastogenesis by showing that conditional NFATc1 KO mice have osteopetrosis. Most importantly, it reveals that RANKL induces OPG production by osteoclast progenitors in the absence of NFATc1, thereby conferring to the OC lineage the ability to self-regulate its differentiation. —SF

Chang EJ, Ha J, Oerlemans F, Lee YJ, Lee SW, Ryu J, Kim HJ, Lee Y, Kim HM, Choi JY, Kim JY, Shin CS, Pak YK, Tanaka S, Wieringa B, Lee ZH, Kim HH. Brain-type creatine kinase has a crucial role in osteoclast-mediated bone resorption. *Nat Med*. 2008 Sept;14(9):966-72. [Abstract]

The authors used a proteomics approach to show that brain-type cytoplasmic creatine kinase (Ckb) is greatly increased during osteoclastogenesis. Ckb siRNA or inhibition of its enzymatic activity by an inhibitor, cyclocreatine, suppressed actin ring formation, RhoA GTPase activity and vacuolar ATPase activity, and inhibited the bone-resorbing activity of osteoclasts in vitro. Functions of osteoclasts obtained from Ckb(-/-) mice were similarly affected. Ckb(-/-) mice were protected from bone loss induced by ovariectomy or inflammatory cytokines. Administration of cyclocreatine or adenoviruses harboring Ckb shRNA attenuated bone loss in rats and mice in vivo. These results clearly demonstrate that Ckb plays an important role in the bone-resorbing function of osteoclasts. Unless an inhibition of Ckb causes any adverse effects in tissues other than bone, Ckb can become a new molecular target for the development of anti-resorptive drugs. —TM

Trevant B, Gaur T, Hussain S, Symons J, Komm BS, Bodine PV, Stein GS, Lian JB. Expression of secreted frizzled related protein 1, a Wnt antagonist, in brain, kidney, and skeleton is dispensable for normal embryonic development. *J Cell Physiol*. 2008 Oct;217(1):113-26. [Abstract]

Secreted frizzled related protein-1 (sFRP1) expression is robust in brain, skeleton, kidney, eye, spleen, abdomen, heart and somites in early embryos. sFRP1 gene inactivation in these tissues did not endanger normal embryonic and post-natal development. Calvarial osteoblasts from neonatal sFRP1(-/-) mice exhibited a 20% increase in cell proliferation and differentiation at the early stages of osteoblast maturation. In pre- and post-natal development, sFRP1 is localized to the mineralizing front in the skeleton. sFRP1 inhibition could be a strategy for enhancement in bone anabolism. —DGL

Pathophysiology

Bull MJ, Williams AS, Mecklenburgh Z, Calder CJ, Twohig JP, Elford C, Evans BA, Rowley TF, Slebioda TJ, Taraban VY, Al-Shamkhani A, Wang EC. The Death Receptor 3-TNF-like protein 1A pathway drives adverse bone pathology in inflammatory arthritis. *J Exp Med*. 2008 Sep 29; [Epub ahead of print]

Did you already think there were too many cytokines critically involved in bone erosions in rheumatoid arthritis? Using intraarticular injection of methylated BSA (antigen-induced arthritis (AIA) model) in mice lacking the TNF receptor superfamily member DR3, this work demonstrates a general absence of synovial hyperplasia, a lack of pannus formation, and no evidence of bone erosion compared to WT mice. In contrast, intraarticular injection of TL1A, the DR3 ligand, exacerbates joint destruction. This research further shows that this TNF pathway promotes RANKL-mediated osteoclastogenesis. Local injections of a TL1A antibody reduced joint inflammation in both the AIA and systemic, collagen-induced arthritis (CIA) models, providing some evidence for a potentially new therapeutic approach. —SF

Gao Y, Wu X, Terauchi M, Li JY, Grassi F, Galley S, Yang X, Weitzmann MN, Pacifici R. T cells potentiate PTH-induced cortical bone loss through CD40L signaling. *Cell Metab*. 2008 Aug; 8(2):132-45. [Abstract]

Continuous excess of PTH is associated with increased bone resorption and bone loss. PTH acts via stromal cells (SCs) to enhance osteoclastic bone resorption. The authors demonstrate that continuous PTH infusion fails to induce osteoclast formation, bone resorption and cortical bone loss in mice lacking T cells. T cells support the proliferation and survival of SCs, and sensitize SCs to PTH through CD40 ligand (CD40L) that

induces CD40 signaling in SCs. Deletion of T cells or CD40L on T cells blunts bone-resorptive effects of PTH by decreasing SC number, the RANKL/OPG ratio and osteoclastogenic activity. These results demonstrate that T cells play an essential permissive role in the enhancement of osteoclastic bone resorption induced by continuous PTH excess, by influencing SC proliferation, life span and function through CD40L. This pathway may become a new therapeutic target by modifying the balance between bone resorption and bone formation under PTH excess. —TM

Public Health

Iglesias CP, Manca A, Torgerson DJ. The health-related quality of life and cost implications of falls in elderly women. *Osteoporos Int*. 2008 Oct 10; [Epub ahead of print] [Abstract]

The largest impact on health-related quality of life in this study was fear of falling, and the authors conclude that better efforts to reduce this fear will have the greatest impact on health-related quality of life. Costs of falls were estimated in the UK system to be 1000 pounds for a fall, 15,000 pounds for a hip fracture, and 2,000 pounds for a wrist fracture. —DGL

Kanis JA, McCloskey EV, Johansson H, Strom O, Borgstrom F, Oden A; National Osteoporosis Guideline Group. Case finding for the management of osteoporosis with FRAX--assessment and intervention thresholds for the UK. *Osteoporos Int*. 2008 Oct;19(10):1395-408. [Abstract]

The FRAX® tool computes the 10-year risk of fractures from clinical risk factors with or without femoral BMD. In this study, fracture probabilities were calibrated to the epidemiology of fracture and death in the UK. An intervention threshold was set by age in men based on the fracture probability equivalent to that of women with a history of a prior fracture. Treatment was cost-effective at all ages when the 10-year probability of fracture exceeded 7%. The intervention threshold at 50 years corresponded to a 10-year probability of a major fracture of 7.5%. This rose with age to 30% at 80 years, so that intervention was cost-effective at all ages. Assessment thresholds for testing with BMD (6-9% at the age of 50 years) also rose with age (18-36% at the age of 80 years). The use of these thresholds in case-finding identifies 6-20% of women as eligible for BMD testing and 23-46% as eligible for treatment, depending on age. The same threshold can be used in men. —ES

Cochrane Reviews

Parker MJ, Handoll HH. Gamma and other cephalocondylic intramedullary nails versus extramedullary implants for extracapsular hip fractures in adults. *Cochrane Database Syst Rev*. 2008 Jul 16;(3):CD000093. [Abstract]

Gamma nails and other cephalocondylic nails have gained popularity for the treatment of intertrochanteric fractures. This study finds no advantage, and some disadvantages, to those nails compared to the standard sliding hip screw and plate. —DGL

Other Studies of Potential Interest

Bai S, Zha J, Zhao H, Ross FP, Teitelbaum SL. TRAF6 is an intranuclear transcriptional co-activator in osteoclasts. *J Biol Chem*. 2008 Sep 3; [Epub ahead of print]

Bentzen H, Bergland A, Forsén L. Risk of hip fractures in soft protected, hard protected, and unprotected falls. *Inj Prev*. 2008 Oct;14(5):306-10. [Abstract]

Case N, Ma M, Sen B, Xie Z, Gross TS, Rubin J. beta-catenin levels influence rapid mechanical responses in osteoblasts. *J Biol Chem*. 2008 Oct 24;283(43):29196-205. [Abstract] [Full Text]

Cheung AM, Tile L, Lee Y, Tomlinson G, Hawker G, Scher J, Hu H, Vieth R, Thompson L, Jamal S, Josse R. Vitamin K supplementation in postmenopausal women with osteopenia (ECKO trial): a randomized controlled trial. *PLoS Med*. 2008 Oct 14;5(10):e196. [Abstract]

Cui M, Klopot A, Jiang Y, Fleet JC. The effect of differentiation on 1,25 dihydroxyvitamin D-mediated gene expression in the enterocyte-like cell line, Caco-2. *J Cell Physiol*. 2008 Aug 25; [Epub ahead of print] [Abstract]

Fleischer J, Stein EM, Bessler M, Della Badia M, Restuccia N, Olivero-Rivera L, McMahon DJ, Silverberg SJ. The decline in hip bone density after gastric bypass surgery is associated with extent of weight loss. *J Clin Endocrinol Metab*. 2008 Oct;93(10):3735-40. [Abstract] [Full Text]

Jehan F, Gaucher C, Nguyen TM, Walrant-Debray O, Lahlou N, Sinding C, Déchaux M, Garabédian M. Vitamin D receptor genotype in hypophosphatemic rickets as a predictor of growth and response to treatment. *J Clin Endocrinol Metab*. 2008 Sep 30; [Epub ahead of print]

Kartsogiannis V, Sims NA, Quinn JM, Ly C, Cipetic M, Poulton IJ, Walker EC, Saleh H, McGregor NE, Wallace ME, Smyth MJ, Martin TJ, Zhou H, Ng KW, Gillespie MT. Osteoclast inhibitory lectin (OCIL), an immune cell product that is required for normal bone physiology in vivo. *J Biol Chem*. 2008 Sep 8; [Epub ahead of print]

Kashima TG, Nishiyama T, Shimazu K, Shimazaki M, Kii I, Grigoriadis AE, Fukayama M, Kudo A. Periostin, a novel marker of intramembranous ossification, is expressed in fibrous dysplasia and in c-Fos-overexpressing bone lesions. *Hum Pathol*. 2008 Sep 15; [Epub ahead of print] [Abstract]

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Moore CM, Leonardi-Bee J. The prevalence of pain and disability one year post fracture of the distal radius in a UK population: A cross sectional survey. *BMC Musculoskelet Disord*. 2008 Sep 29;9(1):129. [Abstract]

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Quinn JM, Sims NA, Saleh H, Mirosa D, Thompson K, Bouralexis S, Walker EC, Martin TJ, Gillespie MT. IL-23 inhibits osteoclastogenesis indirectly through lymphocytes and is required for the maintenance of bone mass in mice. *J Immunol*. 2008 Oct 15;181(8):5720-9. [Abstract]

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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.