

NOT TO BE MISSED

Clinical and Basic Research Papers – April 2010

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Clinical Studies and Drug Effects

◆ Black DM, Kelly MP, Genant HK, Palermo L, Eastell R, Bucci-Rechtweg C, Cauley J, Leung PC, Boonen S, Santora A, de Papp A, Bauer DC; the Fracture Intervention Trial and HORIZON Pivotal Fracture Trial Steering Committees. Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. *N Engl J Med*. 2010 Mar 24. [Epub ahead of print] [\[Abstract\]](#)

This study examined the incidence of femoral shaft fractures in more than 14,000 patients previously enrolled in RCTs of alendronate (FIT and FLEX) and zoledronate (HORIZON). All fractures were adjudicated centrally in the original trials and further reviewed by a radiologist for the current analysis (although X-rays were rarely available, thereby precluding an actual analysis of the atypical features). Only 12 fractures of the subtrochanteric and/or diaphyseal femur sub-type were found, i.e., 2 in FIT, 4 in FLEX and 6 in HORIZON. The combined rate was therefore 2.3 per 10,000 patient-years, and their distribution was similar in bisphosphonate and placebo groups. Power was limited, particularly beyond 3-4 years of use. —SF

◆ Boonen S, Black DM, Colón-Emeric CS, Eastell R, Magaziner JS, Eriksen EF, Mesenbrink P, Haentjens P, Lyles KW. Efficacy and safety of a once-yearly intravenous zoledronic acid 5 mg for fracture prevention in elderly postmenopausal women with osteoporosis aged 75 and older. *J Am Geriatr Soc*. 2010 Feb 1;58(2):292-9. [\[Abstract\]](#)

By pooling the HORIZON Pivotal and Recurrent Fracture Trials, this post-hoc analysis was able to determine the antifracture efficacy of zoledronate 5 mg/yearly in nearly 4,000 women aged 75+ at baseline. The risk of all clinical and non-vertebral fractures was reduced by 35% and 27%, respectively, whereas the risk of hip fractures was non-significantly (18%) lower at 3 years. —SF

◆ Bubbear JS, Gall A, Middleton FR, Ferguson-Pell M, Swaminathan R, Keen RW. Early treatment with zoledronic acid prevents bone loss at the hip following acute spinal cord injury. *Osteoporos Int*. 2010 Apr 1. [Epub ahead of print] [\[Abstract\]](#)

Reductions in BMD after spinal cord injury (SCI) are rapid and are associated with a high fracture rate. Bone turnover markers suggest an early increase in resorption. In this randomized, open-label study of 14 patients with acute SCI, either IV zoledronic acid or a standard treatment approach was followed. After 12 months, there was a significant difference in BMD between the groups at the total hip (12.4%, $p = 0.005$), trochanter (13.4%, $p = 0.028$) and lumbar spine (2.7%, $p = 0.033$). In the treated group, bone resorption was reduced and remained reduced up to 12 months. Further research is needed to see if this maintenance of BMD also reduces fracture rates in this population. —DGL

- ◆Graw BP, Woolson ST, Huddleston HG, Goodman SB, Huddleston JI. Minimal incision surgery as a risk factor for early failure of total hip arthroplasty. *Clin Orthop Relat Res*. 2010 Mar 30. [Epub ahead of print] [\[Abstract\]](#)

Minimal incision total hip arthroplasty (MI THA) techniques were developed to decrease postoperative pain and recovery time. This small study issues a warning by reviewing 46 revision surgeries and finding the mean time to revision was 1.4 years for the MI patients compared with 14.7 years for the non-MI patients. Twelve of the 15 patients having MI THA required revision within 2 years of primary THA compared to 4 of the 31 patients without MI surgery (OR = 26.5, 95% CI 4.4-160.0). There were no differences between the groups with regard to age, gender, or body mass index. The most common reasons for revision in the MI THA group were intraoperative fracture and failure of femoral component osseointegration. —DGL

- ◆Iida K, Sudo A, Ishiguro S. Clinical and radiological results of calcium phosphate cement-assisted balloon osteoplasty for Colles' fractures in osteoporotic senile female patients. *J Orthop Sci*. 2010 Mar;15(2):204-9. [\[Abstract\]](#)

Building on concepts from balloon kyphoplasty in the spine, 11 Colles' type fractures (AO type A2, mean age 78 years) were treated with closed reduction and percutaneous pinning. The barrel of a disposable 1-ml syringe was inserted into the fracture site as a port through a small incision, facilitating pediatric uromatic balloon introduction into the fracture site. The balloon was inflated with contrast and calcium phosphate cement was injected with a cement gun through the port under an image intensifier. After a mean follow-up of 16 months all results were graded as excellent at the final follow-up. The average duration of immobilization was 4 weeks with a short forearm cast. Radial inclination and volar tilt showed no postoperative correction loss and the final volar tilt, radial inclination, and ulnar variance were comparable to those of the nonaffected side. An interesting technique that may become more common but needs thorough evaluation given the controversy over the efficacy of kyphoplasty. —DGL

- ◆Kanazawa I, Yamaguchi T, Yamauchi M, Yamamoto M, Kurioka S, Yano S, Sugimoto T. Serum undercarboxylated osteocalcin was inversely associated with plasma glucose level and fat mass in type 2 diabetes mellitus. *Osteoporos Int*. 2010 Feb 18. [Epub ahead of print] [\[Abstract\]](#)

- ◆Fernández-Real JM, Ortega F, Gómez-Ambrosi J, Salvador J, Frühbeck G, Ricart W. Circulating osteocalcin concentrations are associated with parameters of liver fat infiltration and increase in parallel to decreased liver enzymes after weight loss. *Osteoporos Int*. 2010 Mar 4. [Epub ahead of print] [\[Abstract\]](#)

Osteoporosis, obesity, and diabetes have each reached epidemic proportions in the Western world. Several human studies have previously reported that osteocalcin (OC) is lower in patients with established diabetes. The new study from Kanazawa et al. confirms that undercarboxylated OC is negatively associated with plasma glucose levels and fat mass in men with type 2 diabetes. Tantalizing findings that OC might be the active player in a bone-liver axis come from the study by Fernández-Real et al., who show that the circulating OC concentration was negatively associated with both alanine transaminase and aspartate transaminase levels at baseline and also during weight loss in obese subjects. These two studies provide additional evidence for OC being a marker not only of bone metabolism but also of glucose and lipid metabolism and obesity risk. —DK

- ◆Newcomb PA, Trentham-Dietz A, Hampton JM. Bisphosphonates for osteoporosis treatment are associated with reduced breast cancer risk. *Br J Cancer*. 2010 Mar 2;102(5):799-802.

[\[Abstract\]](#)

This population-based study compared the use of BPs among 2,936 women with incident invasive breast cancer and as many controls aged < 70 years. BP use was associated with a 33% reduction in breast cancer risk – is this at least some good news for BPs? Or is it one of those epidemiological biases in which women with the lowest residual estrogen levels are both at lower breast cancer risk and higher osteoporosis risk, and hence are more prone to BP therapy? —SF

- ◆Seeman E, Delmas PD, Hanley DA, Sellmeyer D, Cheung AM, Shane E, Kearns A, Thomas T, Boyd SK, Boutroy S, Bogado C, Majumdar S, Fan M, Libanati C, Zanchetta J. Microarchitectural deterioration of cortical and trabecular bone: Differing effects of denosumab and alendronate. *J Bone Miner Res.* 2010 Mar 10. [Epub ahead of print] [\[Abstract\]](#)

This is a randomized, double-blind, direct comparison study of alendronate, denosumab or placebo on bone microstructure at the distal radius and tibia, as evaluated by μ CT, in 247 postmenopausal women with low bone mass. At one year, both drugs prevented the loss of cortical and trabecular vBMD and improved cortical thickness (up to 5% at the tibia). Denosumab improved the polar moment of inertia, an estimate of bone strength, at the radius compared to alendronate. —SF

Genetics

- ◆Christiansen HE, Schwarze U, Pyott SM, AlSwaid A, Al Balwi M, Alrasheed S, Pepin MG, Weis MA, Eyre DR, Byers PH. Homozygosity for a missense mutation in SERPINH1, which encodes the collagen chaperone protein HSP47, results in severe recessive osteogenesis imperfecta. *Am J Hum Genet.* 2010 Mar 12;86(3):389-98. [\[Abstract\]](#)

Adding to a rapidly growing list of gene mutations causing OI, this study describes an autosomal-recessive missense mutation in a gene coding for a collagen chaperone-like protein that impairs the intracellular processing of collagen. —SF

- ◆Klopocki E, Hennig BP, Dathe K, Koll R, de Ravel T, Baten E, Blom E, Gillerot Y, Weigel JF, Krüger G, Hiort O, Seemann P, Mundlos S. Deletion and point mutations of PTHLH cause brachydactyly type E. *Am J Hum Genet.* 2010 Mar 12;86(3):434-9. [\[Abstract\]](#)

These must be the first mutations reported in the PTHrP gene, in this case loss-of-function mutations causing short hands and feet (brachydactyly) and short stature as a result of altered chondrocyte proliferation/differentiation, as previously observed in KO mice. —SF

- ◆Velasco J, Hernández JL, Pérez-Castrillón JL, Zarrabeitia MT, Alonso MA, González-Macías J, Riancho JA. Haplotypes of intron 4 of the estrogen receptor alpha gene and hip fractures: a replication study in Caucasians. *BMC Med Genet.* 2010 Jan 28;11:16. [\[Abstract\]](#)

- ◆Velasco J, Zarrabeitia MT, Prieto JR, Perez-Castrillon JL, Perez-Aguilar MD, Perez-Nuñez MI, Sañudo C, Hernandez-Elena J, Calvo I, Ortiz F, Gonzalez-Macias J, Riancho JA. Wnt pathway genes in osteoporosis and osteoarthritis: differential expression and genetic association study. *Osteoporos Int.* 2010 Jan;21(1):109-18. [\[Abstract\]](#)

In these 2 papers, Dr. Riancho's group used a genetic analysis approach to additionally validate whether the well-studied candidate genes for osteoporosis (OP) are contributing to the disease. Thus, in the first paper they found that polymorphisms

in exon 4/intron 4 of the ESR1 gene are associated with hip fractures in older men and women. They also obtained ESR1 expression in trabecular cores from the excised femoral necks in 42 fracture patients, however, they found no difference in gene expression by genotype. In their second study, the group studied dozens of SNPs and expression profiles of Wnt pathway genes in OP and hip or knee osteoarthritis (OA). Bone tissue samples came either from hip fracture patients or individuals with OA and primary osteoblasts were cultivated. Expression profiling of 86 genes suggested that genes in the Wnt pathway (BCL9, FZD5, DVL2, EP300, FRZB, LRP5, and TCF7L1) are upregulated in knee OA. This nice combination of a genetic association with study of differential expression adds new insights into the mechanisms of the above genes in subchondral and trabecular bone; it provides additional support to an old paradigm that OP and OA share etiologic factors that work in opposite directions. —DK

Public Health

◆ Bolland MJ, Grey A. Disparate outcomes from applying U.K. and U.S. osteoporosis treatment guidelines. *J Clin Endocrinol Metab.* 2010 Feb 10. [Epub ahead of print] [\[Abstract\]](#)

◆ Watts NB, Siris ES, Cummings SR, Bauer DC. Filtering FRAX. *Osteoporos Int.* 2010 Apr;21(4):537-41. [\[Info\]](#)

NOF guidelines for the management of osteoporosis are more generous than European ones as the former recommend to treat not only when FRAX[®] probability is above 20% (3% for hip) and when a fragility fracture has occurred, but also when BMD is < -2.5 T-score at the spine or hip. By applying those rules to a cohort of 1,471 healthy, community-dwelling women, mean age 74, who were followed for 4.4 years, the first paper reports that the FRAX[®]-based NOGG (UK) algorithm would recommend treating 21% of them, including 38% of hip fracture cases and 27% of osteoporotic cases. On another side, the NOF guidelines would recommend treating 48% of these women, including 63% of osteoporotic fracture cases and 76% of hip fracture cases. The second paper discusses the pros and cons of filtering FRAX[®] results out of DXA reports (as will be done in the US) when the T-score is < -2.5. The authors oppose their views about confusing and educating doctors when results from FRAX[®] and BMD are discordant. —SF

◆ Cooper C, Steinbuch M, Stevenson R, Miday R, Watts NB. The epidemiology of osteonecrosis: findings from the GPRD and THIN databases in the UK. *Osteoporos Int.* 2010 Apr;21(4):569-77. [\[Abstract\]](#)

792 cases of osteonecrosis (ON), mostly of the hip, were found in two major health care databases in the UK between 1989-2003. Incidence was low (< 5/100,000) but increased with age and in women more than men. Cases were matched to 6 controls (no ON) each and risk factors for ON were identified: besides the well-known risk factors of corticosteroids, fracture and cancer, osteoporosis itself was found as a risk factor (adjusted odds 2.1). Only 4.4% of ON cases were exposed to bisphosphonates within the previous 2 years, confirming that bisphosphonate use is not a major risk factor for ON (at least not for the hip, but not excluding ONJ). —SF

◆ Hodsmann AB, Leslie WD, Tsang JF, Gamble GD. 10-year probability of recurrent fractures following wrist and other osteoporotic fractures in a large clinical cohort: an analysis from the Manitoba Bone Density Program. *Arch Intern Med.* 2008 Nov 10;168(20):2261-7.

This very large epidemiological study including 1,225 women with a primary wrist

fracture provides compelling evidence that the risk of subsequent fractures, particularly at the hip, is increased less than two-fold and is therefore less than that observed after other fractures such as vertebral and humeral fractures. —SF

Bone Modeling, Remodeling, and Repair

◆Nazarian A, Pezzella L, Tseng A, Baldassarri S, Zurakowski D, Evans CH, Snyder BD. Application of structural rigidity analysis to assess fidelity of healed fractures in rat femurs with critical defects. *Calcif Tissue Int.* 2010 Mar 31. [Epub ahead of print] [\[Abstract\]](#)

This group has previously reported in vivo structural rigidity analysis (SRA) as a useful technique in predicting pathological fracture from metastases. In this animal study the technique was extended to μ CT of critical defects that healed with a broad range of measured mechanical properties. Strong correlations were found between measured torsional rigidity and computed torsional rigidity as calculated from both average ($R^2 = 0.63$) and minimum ($R^2 = 0.81$) structural rigidity data. Minimum torsional rigidity was a better descriptor of bone strength than previously described methods. —DGL

Molecular and Cell Biology

◆Li H, Hong S, Qian J, Zheng Y, Yang J, Yi Q. Crosstalk between the bone and immune systems: osteoclasts function as antigen-presenting cells and activate CD4+ and CD8+ T cells. *Blood.* 2010 Mar 19. [Epub ahead of print]

The role of immune cells, particularly T cells and dendritic/antigen-presenting cells, in the activation of osteoclastogenesis is increasingly recognized as playing a role not only in inflammation-induced bone loss but also in postmenopausal osteoporosis. This study takes the story one step further by showing that osteoclasts developing from monocytic precursors through the action of RANKL and M-CSF in turn display some properties of antigen-presenting cells, thereby directly activating T cells. Hence bone cells appear to play a role as immune cells as well. —SF

◆Raaijmakers MH, Mukherjee S, Guo S, Zhang S, Kobayashi T, Schoonmaker JA, Ebert BL, Al-Shahrour F, Hasserjian RP, Scadden EO, Aung Z, Matza M, Merckenschlager M, Lin C, Rommens JM, Scadden DT. Bone progenitor dysfunction induces myelodysplasia and secondary leukaemia. *Nature.* 2010 Mar 21. [Epub ahead of print] [\[Abstract\]](#)

Osterix-expressing mesenchymal cells of the osteoblast lineage initiate hematopoietic stem cell niche formation. Here the authors show that deletion of Dicer1, an RNase III endonuclease essential for microRNA biogenesis and RNA processing, in osterix-expressing mouse osteoprogenitors, but not in mature osteoblasts, disrupts the integrity of hematopoiesis, causing myelodysplasia and the propensity to develop acute myeloid leukemia. Dicer1 deletion in osteoprogenitors causes a reduction in the expression of Sbds, the gene mutated in Schwachman-Bodian-Diamond syndrome with bone marrow failure and a pre-leukemia condition. Sbds gene deletion in mouse osteoprogenitors recapitulates characteristics of Dicer1 deletion. These results demonstrate that primary stromal dysfunction can cause hematologic neoplasia. —TM

◆Romero G, Sneddon WB, Yang Y, Wheeler D, Blair HC, Friedman PA. Parathyroid hormone receptor directly interacts with dishevelled to regulate beta-catenin signaling and osteoclastogenesis. *J Biol Chem.* 2010 Mar 8. [Epub ahead of print]

A growing body of evidence links PTH to Wnt- β -catenin signaling. The cytoplasmic tail

of the PTH/PTHrP receptor has been implicated in a number of interactions with intracellular molecules, including β -arrestins, c-Src and NHERFs, to divert PTH signaling from the classical G protein signaling pathway to other pathways. The mutational approach used here identifies a region in the receptor C-terminus that directly interacts with Dishevelled, thereby allowing for β -catenin activation and translocation into the nucleus. —SF

- ◆Shi Y, Oury F, Yadav VK, Wess J, Liu XS, Guo XE, Murshed M, Karsenty G. Signaling through the M3 muscarinic receptor favors bone mass accrual by decreasing sympathetic activity. *Cell Metab.* 2010 Mar 3;11(3):231-8. [\[Abstract\]](#)

The authors previously demonstrated that sympathetic tone inhibits bone mass accrual. Using various mutant mice lacking four of the five muscarinic receptors that mediate parasympathetic activity, the authors show that the parasympathetic nervous system, via the M3 muscarinic receptor, is a positive regulator of bone mass accrual, increasing bone formation and decreasing bone resorption. These results reveal that the parasympathetic nervous system favors bone mass accrual, and that, unlike the sympathetic nervous system, it acts centrally and by decreasing the sympathetic tone. —TM

Cancer and Bone

- ◆David M, Wannecq E, Descotes F, Jansen S, Deux B, Ribeiro J, Serre CM, Grès S, Bendriss-Vermare N, Bollen M, Saez S, Aoki J, Saulnier-Blache JS, Clézardin P, Peyruchaud O. Cancer cell expression of autotaxin controls bone metastasis formation in mouse through lysophosphatidic acid-dependent activation of osteoclasts. *PLoS One.* 2010 Mar 17;5(3):e9741. [\[Abstract\]](#)

Autotaxin (ATX/NPP2) controls the level of lysophosphatidic acid (LPA) in the blood through its lysophospholipase D (lysoPLD) activity. ATX shows both oncogenic and pro-metastatic properties, and LPA promotes the progression of osteolytic bone metastases. The authors demonstrate that injection of human or mouse breast cancer cells expressing ATX to mice enhanced osteolytic bone metastasis formation. Silencing ATX expression inhibited the extent of osteolytic bone lesions. Addition of LPA restored the capacity of charcoal-treated serum to support RANKL/MCSF-induced osteoclastogenesis in vitro. This work demonstrates that LPA directly stimulates cancer growth and metastasis, and osteoclast differentiation. Targeting ATX/LPA may become a new therapeutic approach to overcome cancer metastases to bone. —TM

- ◆Vallet S, Mukherjee S, Vaghela N, Hideshima T, Fulciniti M, Pozzi S, Santo L, Cirstea D, Patel K, Sohani AR, Guimaraes A, Xie W, Chauhan D, Schoonmaker JA, Attar E, Churchill M, Weller E, Munshi N, Seehra JS, Weissleder R, Anderson KC, Scadden DT, Raje N. Activin A promotes multiple myeloma-induced osteolysis and is a promising target for myeloma bone disease. *Proc Natl Acad Sci U S A.* 2010 Mar 16;107(11):5124-9. [\[Abstract\]](#) [\[Full Text\]](#)

This study reveals that multiple myeloma (MM) cells induce activin A expression from bone marrow stromal cells in part via adhesion-mediated activation of the JNK pathway. Activin A, in turn, inhibits osteoblast differentiation via Smad2-dependent suppression of Dlx-5 expression. Inhibition of activin A signaling by a soluble decoy receptor rescues MM-induced impairment of osteoblast differentiation, resulting in amelioration of MM bone disease and inhibition of MM growth. Thus, activin A can become a therapeutic target in MM patients. —TM

Other Studies of Potential Interest

◆Haentjens P, Magaziner J, Colón-Emeric CS, Vanderschueren D, Milisen K, Velkeniers B, Boonen S. Meta-analysis: excess mortality after hip fracture among older women and men. *Ann Intern Med.* 2010 Mar 16;152(6):380-90. [[Abstract](#)]

◆Nagano M, Kimura K, Yamashita T, Ohneda K, Nozawa D, Hamada H, Yoshikawa H, Ochiai N, Ohneda O. Hypoxia responsive mesenchymal stem cells derived from human umbilical cord blood are effective for bone repair. *Stem Cells Dev.* 2010 Mar 26. [Epub ahead of print] [[Abstract](#)]

◆Xing Z, Lu C, Hu D, Yu YY, Wang X, Colnot C, Nakamura M, Wu Y, Miclau T, Marcucio RS. Multiple roles for CCR2 during fracture healing. *Dis Model Mech.* 2010 Mar 30. [Epub ahead of print] [[Abstract](#)]

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. Karasik report no conflicts of interest.