IBMS BoneKEy. 2009 September;6(9):307-310
http://www.bonekey-ibms.org/cgi/content/full/ibmske;6/9/307
doi: 10.1138/20090394

NOT TO BE MISSED

Clinical and Basic Research Papers – September 2009

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Clinical Studies and Drug Effects

Kallmes DF, Comstock BA, Heagerty PJ, Turner JA, Wilson DJ, Diamond TH, Edwards R, Gray LA, Stout L, Owen S, Hollingworth W, Ghdoke B, Annesley-Williams DJ, Ralston SH, Jarvik JG. A randomized trial of vertebroplasty for osteoporotic spinal fractures. *N Engl J Med*. 2009 Aug 6;361(6):569-79. [Abstract]

Buchbinder R, Osborne RH, Ebeling PR, Wark JD, Mitchell P, Wriedt C, Graves S, Staples MP, Murphy B. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *N Engl J Med*. 2009 Aug 6;361(6):557-68. [Abstract]

> *Long-awaited and very difficult to perform, here are two RCTs comparing the effects of vertebroplasty with sham procedures for pain reduction following osteoporotic, vertebral crush fractures. The results of the first study carry both bad and good news for the tenants of this procedure: no differences in disability score at one month, but a trend towards better reduction in clinically meaningful pain at 1 month and more crossover from controls to vertebroplasty at 3 months. Although limited by the rather small number of subjects included (78), the second study also shows no differences in pain and functional scores at 1 and 6 months. Altogether these data do not suggest a clear short-term benefit of vertebroplasty for painful vertebral fractures. Long-term results remain to be investigated.* —SF

Lenart BA, Neviaser AS, Lyman S, Chang CC, Edobor-Osula F, Steele B, van der Meulen MC, Lorich DG, Lane JM. Association of low-energy femoral fractures with prolonged bisphosphonate use: a case control study. *Osteoporos Int*. 2009 Aug;20(8):1353-62. [Abstract]

> *In a retrospective case-control study from 2000 to 2007, 41 subtrochanteric and femoral shaft fracture cases were matched to one intertrochanteric and femoral neck fracture each. Bisphosphonate use was observed in 15 of the 41 subtrochanteric/shaft cases, compared to 9 of the 82 intertrochanteric/femoral neck controls (OR 4.44, 95% CI: 1.77-11.35, P = 0.002). A common X-ray pattern in ten of the 15 subtrochanteric/shaft cases on a bisphosphonate was associated with bisphosphonate use (OR, 15.33, 95% CI: 3.06-76.90; P < 0.001). Duration of bisphosphonate use was longer in subtrochanteric/shaft cases compared to both hip fracture controls groups.*
> —ES

Smith MR, Egerdie B, Hernández Toriz N, Feldman R, Tammela TL, Saad F, Heracek J, Szwedowski M, Ke C, Kupic A, Leder BZ, Goessl C; Denosumab HALT Prostate Cancer Study Group. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med*. 2009 Aug 20;361(8):745-55. [Abstract]

Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, Delmas P, Zoog HB, Austin M, Wang A, Kutilek S, Adami S, Zanchetta J, Libanati C, Siddhanti S, Christiansen C; FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009 Aug 20;361(8):756-65. [Abstract]

> *In a double-blind, multicenter study from Smith et al., patients received denosumab 60 mg subcutaneously every 6 months or placebo (734 patients in each group). At 24 months, spine BMD increased by 5.6% with denosumab and decreased 1.0% with placebo (P < 0.001). Denosumab increased BMD at the total hip, femoral neck, and distal third of the radius. Denosumab reduced new vertebral fractures at 36 months (1.5% vs. 3.9% with placebo) (RR, 0.38; 95% CI: 0.19 to 0.78; P = 0.006). —ES*
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> *In the second study from Cummings et al., 7868 women between 60 and 90 years of age with a T score of less than -2.5 at the spine or total hip were randomly assigned to 60 mg of denosumab or placebo subcutaneously every 6 months for 36 months. Denosumab reduced new vertebral fractures; 2.3% versus 7.2% in the placebo group (RR, 0.32; 95% CI: 0.26 to 0.41; P < 0.001) – a decrease of 68%. Denosumab reduced the risk of hip fracture, 0.7% versus 1.2% in the placebo group (HR, 0.60; 95% CI: 0.37 to 0.97; P = 0.04) – a decrease of 40%. Denosumab also reduced the risk of nonvertebral fractures, 6.5% versus 8.0% in the placebo group (HR, 0.80; 95% CI: 0.67 to 0.95; P = 0.01) – a decrease of 20%. —ES*
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> *Serious infectious occurred in 4.1% and 3.4% of women and 5.9% and 4.6% of men treated with denosumab and placebo, respectively, the difference pertaining to significantly more cases of severe cellulitis in women with denosumab, and to some rare cases of diverticulitis and lobar pneumonia in men with denosumab.* —SF

Genetics

Barr R, Macdonald H, Stewart A, McGuigan F, Rogers A, Eastell R, Felsenberg D, Glüer C, Roux C, Reid DM. Association between vitamin D receptor gene polymorphisms, falls, balance and muscle power: results from two independent studies (APOSS and OPUS). *Osteoporos Int*. 2009 Jul 24. [Epub ahead of print] [Abstract]

> *The vitamin D receptor (VDR) gene is a well-studied candidate gene for osteoporosis. Fall prevention is another key strategy for reducing osteoporotic fractures. This study investigated the association between VDR polymorphisms and reported falls in postmenopausal women. Bsm1 polymorphisms of the VDR gene were associated with falls, balance and muscle power measurements.* —HWD

Yerges LM, Klei L, Cauley JA, Roeder K, Kammerer CM, Ensrud KE, Nestlerode CS, Lewis C, Lang TF, Barrett-Connor E, Moffett SP, Hoffman AR, Ferrell RE, Orwoll ES, Zmuda JM; for the Osteoporotic Fractures in Men (MrOS) Study Group. Candidate gene analysis of femoral neck trabecular and cortical volumetric bone mineral density in older men. *J Bone Miner Res*. 2009 Jul 20. [Epub ahead of print] [Abstract]

> *This study tested 4608 tagging and potentially functional single nucleotide polymorphisms (SNPs) in 383 bone metabolism candidate genes for association with trabecular and cortical volumetric bone mineral density (vBMD) at the femoral neck in 822 Caucasian men. Promising SNP associations were then tested for replication in an additional 1155 men. SNPs in 5 genes were robustly associated with cortical vBMD and SNPs in 9 genes were robustly associated with trabecular vBMD.* —HWD

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Molecular and Cell Biology

Almeida M, Ambrogini E, Han L, Manolagas SC, Jilka RL. Increased lipid oxidation causes oxidative stress, increased PPARgamma expression and diminished pro-osteogenic Wnt signaling in the skeleton. *J Biol Chem*. 2009 Aug 5. [Epub ahead of print]

> *An increase in 4-hydroxynonenal (4-HNE), a product of lipid oxidation, with age and increased expression of lipoxygenase and peroxisome proliferator-activated receptor-gamma (PPARγ) is reported in the skeletons of mice. These changes, and decreased Wnt signaling, are reproduced in 4-month-old mice bearing a high expressing allele of the lipoxygenase Alox15. Adding 4-HNE to osteoblastic cells increases oxidative stress and diverts β-catenin from T-cell specific transcription factors (TCF) to Forkhead box O (FoxO) transcription factors attenuating the suppressive effect of β-catenin on PPARγ gene expression. Oxidized lipids promote binding of PPARγ to β-catenin and reduce the latter, and attenuate Wnt3a-stimulated proliferation and osteoblast differentiation. Oxidized lipids and 4-HNE stimulate osteoblastic cell apoptosis.* —ES

Kramer I, Loots GG, Studer A, Keller H, Kneissel M. Parathyroid hormone (PTH) induced bone gain is blunted in SOST overexpressing and deficient mice. *J Bone Miner Res*. 2009 Jul 13. [Epub ahead of print] [Abstract]

Luiz de Freitas PH, Li M, Ninomiya T, Nakamura M, Ubaidus S, Oda K, Udagawa N, Maeda T, Takagi R, Amizuka N. Intermittent PTH administration stimulates pre-osteoblastic proliferation without leading to enhanced bone formation in osteoclast-less c-fos(-/-) mice. *J Bone Miner Res*. 2009 Sep;24(9):1586-97. [Abstract]

> *Despite the fact that the anabolic effects of intermittent PTH on bone are well-recognized and that PTH-derived molecules are commonly used for osteoporosis treatment, the molecular mechanisms by which PTH exerts its effects on the skeleton remain a subject of major interest. These two studies indicate on one side that PTH inhibition of sclerostin expression is central to its bone-forming effects even though PTH effects on osteoclasts are maintained in SOST-deficient or overexpressing mice; on another side that osteoclasts are required for PTH anabolic effects, since PTH failed to induce bone formation in osteopetrotic, c-fos-deficient mice, despite the fact it led to proliferation of pre-osteoblasts. Based on electron microscopy and immunohistochemical analyses, the latter study further suggests that osteoblast-osteoclast cross-talk through the ephrin-ephrin receptor system could explain the role of osteoclasts in supporting PTH-stimulated bone formation. These results, however, are limited to histomorphometrical analyses of the metaphyseal region, i.e., they do not consider PTH effects on bone modeling surfaces, and by the fact that c-fos expression in osteoblasts also affects their differentiation and function.* —SF

Reviews, Perspectives and Editorials

Ali T, Lam D, Bronze MS, Humphrey MB. Osteoporosis in inflammatory bowel disease. *Am J Med*. 2009 Jul;122(7):599-604. [Abstract]

Nakashima T, Takayanagi H. Osteoimmunology: crosstalk between the immune and bone systems. *J Clin Immunol*. 2009 Sep;29(5):555-67. [Abstract]

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Other Studies of Potential Interest

Alvarez-Díaz S, Valle N, García JM, Peña C, Freije JM, Quesada V, Astudillo A, Bonilla F, López-Otín C, Muñoz A. Cystatin D is a candidate tumor suppressor gene induced by vitamin D in human colon cancer cells. *J Clin Invest*. 2009 Aug;119(8):2343-58. [Abstract]

Borgström F, Ström O, Coelho J, Johansson H, Oden A, McCloskey EV, Kanis JA. The cost-effectiveness of risedronate in the UK for the management of osteoporosis using the FRAX(R). *Osteoporos Int*. 2009 Jun 30. [Epub ahead of print] [Abstract]

Huang H, Song TJ, Li X, Hu L, He Q, Liu M, Lane MD, Tang QQ. BMP signaling pathway is required for commitment of C3H10T1/2 pluripotent stem cells to the adipocyte lineage. *Proc Natl Acad Sci U S A*. 2009 Aug 4;106(31):12670-5. [Abstract] [Full Text]

Kim MH, Ryu SY, Choi JS, Min YK, Kim SH. Saurolactam inhibits osteoclast differentiation and stimulates apoptosis of mature osteoclasts. *J Cell Physiol*. 2009 Aug 3. [Epub ahead of print] [Abstract]

Niziolek PJ, Murthy S, Ellis SN, Sukhija KB, Hornberger TA, Turner CH, Robling AG. Rapamycin impairs trabecular bone acquisition from high-dose but not low-dose intermittent parathyroid hormone treatment. *J Cell Physiol*. 2009 Jul 28. [Epub ahead of print] [Abstract]

Pioszak AA, Parker NR, Gardella TJ, Xu HE. Structural basis for parathyroid hormone-related protein binding to the parathyroid hormone receptor and design of conformation-selective peptides. *J Biol Chem*. 2009 Aug 12. [Epub ahead of print]

Yang CM, Hsieh HL, Yao CC, Hsiao LD, Tseng CP, Wu CB. PKC-delta transactivates PDGFR-alpha in mechanical strain induced collagenase 3 (MMP-13) expression by osteoblast-like cells. *J Biol Chem*. 2009 Jul 24. [Epub ahead of print]

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.