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NOT TO BE MISSED

Clinical and Basic Research Papers – June 2010

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Clinical Studies and Drug Effects

Gray SL, LaCroix AZ, Larson J, Robbins J, Cauley JA, Manson JE, Chen Z. Proton pump inhibitor use, hip fracture, and change in bone mineral density in postmenopausal women: results from the Women's Health Initiative. *Arch Intern Med*. 2010 May 10;170(9):765-71. [Abstract]

> *In the Women's Health Initiative (WHI), with a mean (SD) follow-up of 7.8 (1.6) years, among 130,487 women, 1,500 hip fractures, 4,881 forearm or wrist fractures, 2,315 clinical spine fractures, and 21,247 total fractures occurred. The OR for current PPI use was 1.00 (95% CI, 0.71-1.40) for hip fracture, 1.47 (95% CI, 1.18-1.82) for clinical spine fracture, 1.26 (95% CI, 1.05-1.51) for forearm or wrist fracture, and 1.25 (95% CI, 1.15-1.36) for total fractures.* —ES

Liu XS, Cohen A, Shane E, Yin PT, Stein EM, Rogers H, Kokolus SL, McMahon DJ, Lappe JM, Recker RR, Lang T, Guo XE. Bone density, geometry, microstructure and stiffness: Relationships between peripheral and central skeletal sites assessed by DXA, HR-pQCT, and cQCT in premenopausal women. *J Bone Miner Res*. 2010 Apr 30. [Epub ahead of print] [Abstract]

> *The authors compared aBMD, vBMD, and bone geometry of the lumbar spine, proximal femur, distal radius and distal tibia, assessed by DXA, pQCT, and central QCT, to the stiffness measured by a finite element (FE) model. The study population consisted of premenopausal women. Many findings of interest are provided: aBMD and vBMD agreed well at the lumbar spine (r=0.79) and proximal femur (r=0.77); vBMD, microstructure and stiffness measured by HR-pQCT at the distal radius and tibia corresponded nicely to stiffness of the lumbar spine and proximal femur. The authors write that "[i]t is intriguing that aBMD of lumbar spine and total hip were strong indicators of stiffness of all four skeletal sites." It is difficult to agree with this statement, since aBMD by DXA proves its value for prediction of bone strength time and again.*
> —DK

Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, Nicholson GC. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA*. 2010 May 12;303(18):1815-22. [Abstract]

> *Vitamin D insufficiency is purported to cause or be associated with a huge number of seemingly unrelated illnesses and repletion is purported to be the cure – a bit like bloodletting in the early and even middle of the last century. In this double-blind, placebo-controlled study, the authors report that a single annual dose of 500,000 IU of cholecalciferol given orally to 2,256 community-dwelling women, aged 70 years or older, for 3 to 5 years was associated with more falls and fractures than in the placebo group: 171 fractures vs. 135 in the placebo group; 837 women in the vitamin D group*

fell 2,892 times (rate, 83.4 per 100 person-years) while 769 women in the placebo group fell 2,512 times (rate, 72.7 per 100 person-years; RR for falls, 1.15, 95% CI, 1.02-1.30; P = .03). The RR for fracture in the vitamin D group was 1.26 (95% CI, 1.00-1.59; P = .047) vs. the placebo group (rates per 100 person-years, 4.9 vitamin D vs. 3.9 placebo). This doesn't fit the current fashion; it will mess up all the meta-analyses; it must be wrong of course and more research is needed until the data fits our preconceived ideas. —ES

Genetics

Albagha OM, Visconti MR, Alonso N, Langston AL, Cundy T, Dargie R, Dunlop MG, Fraser WD, Hooper MJ, Isaia G, Nicholson GC, del Pino Montes J, Gonzalez-Sarmiento R, di Stefano M, Tenesa A, Walsh JP, Ralston SH. Genome-wide association study identifies variants at CSF1, OPTN and TNFRSF11A as genetic risk factors for Paget's disease of bone. *Nat Genet*. 2010 Jun;42(6):520-4. [Abstract]

Paget's disease of bone (PDB) is a late-onset metabolic bone disease characterized by focal areas of increased bone remodeling affecting ~ 8% and ~ 5% of older men and women, respectively. It's etiology is due primarily to increased activity of osteoclasts. The only mutated gene reported and replicated to date is SQSTM1, which encodes the protein sequestosome-1/p62. This GWA study therefore was excluding PDB cases with any SQSTM1 mutations. GWA analysis thus discovered, in an impressive sample of cases and controls (and replicated in an independent set), three top genes: CSF1, which encodes macrophage colony-stimulating factor (M-CSF); OPTN, which encodes optineurin (which had been linked to glaucoma!); and TNFRSF11A – which encodes RANK, a critical agent in osteoclast differentiation and function. It was not stated, however, how much of the total variance in PDB risk is explained by these novel genes. —DK

Bone Modeling, Remodeling, and Repair

Zebaze RM, Ghasem-Zadeh A, Bohte A, Iuliano-Burns S, Mirams M, Price RI, Mackie EJ, Seeman E. Intracortical remodelling and porosity in the distal radius and post-mortem femurs of women: a cross-sectional study. *Lancet*. 2010 May 15;375(9727):1729-36. [Abstract]

The present study used high-resolution (HR)-pQCT at the distal radius to evaluate the loss of volumetric bone density (mg of hydroxyapatite, mgHA) in the cortical and trabecular region in a cross-sectional sample of women aged 27 to 98 years, and used scanning electron microscopy on post-mortem bone specimens from 24 women aged 29-99 years to evaluate pores. It shows that two thirds (68%) of bone density lost at the distal radius between 50 and 80 years of age is cortical, most being lost after 65 years of age. The analysis of post-mortem bone specimens showed that the remodeling surfaces within the cortex increased tremendously with age, eventually representing far more than remodeling trabecular surfaces, thereby explaining the disproportionate loss of cortical bone with age and challenging the notion that cortical bone represents 80% of bone mass but only 20% of remodeling surfaces. This study also showed that enlarging pores erupting on the endocortical surface leave cortical remnants that look like trabeculae – wherefrom an underestimation of trabecular bone loss with age – and contribute to apparent cortical thinning. —SF

Molecular and Cell Biology

Ito Y, Teitelbaum SL, Zou W, Zheng Y, Johnson JF, Chappel J, Ross FP, Zhao H. Cdc42

regulates bone modeling and remodeling in mice by modulating RANKL/M-CSF signaling and osteoclast polarization. *J Clin Invest*. 2010 Jun 1;120(6):1981-93. [Abstract]

> *The authors examined mice with osteoclast-specific loss-of-function of Cdc42 and mice with universal gain-of-function of Cdc42 by a deletion of Cdc42Gap. Cdc42 loss-of-function mice were osteopetrotic and resistant to ovariectomy-induced bone loss, while gain-of-function animals were osteoporotic. Cdc42 enhanced osteoclast precursor proliferation via stimulation of cyclin D expression and Rb phosphorylation by activating the PI3K-Akt pathway. Cdc42 protected against apoptosis by a suppression of Bim expression and the caspase-9/3 pathway. Cdc42 also enhanced osteoclast differentiation by MITF activation and NFATc1 expression via phosphorylation of p38/JNK. Furthermore, Cdc42 was a component of the Par3/Par6/atypical PKC complex to enhance polarization of osteoclasts. Thus, Cdc42 regulates osteoclast formation and function and may become a new therapeutic target against bone loss.* —TM

Sohaskey ML, Jiang Y, Zhao JJ, Mohr A, Roemer F, Harland RM. Osteopotentia regulates osteoblast maturation, bone formation, and skeletal integrity in mice. *J Cell Biol*. 2010 May 3;189(3):511-25. [Abstract] [Full Text]

> *Osteoblasts respond to high metabolic demand by active expansion of their rough endoplasmic reticulum (rER) and increased synthesis of type I collagen. The authors show that mutagenesis of the osteopotentia (Opt) gene in mice disrupts osteoblast function and postnatal skeletal development. Opt encodes an rER-localized integral membrane protein containing a conserved SUN (Sad1/Unc-84 homology) domain. Mice lacking Opt develop acute onset skeletal defects including impaired bone formation and spontaneous fractures, which result in part from a posttranscriptional decline in type I collagen synthesis and a failure of osteoblast maturation. These results identify Opt as a crucial regulator of bone formation, and uncover a rER-mediated control in osteoblast function.* —TM

Weinert S, Jabs S, Supanchart C, Schweizer M, Gimber N, Richter M, Rademann J, Stauber T, Kornak U, Jentsch TJ. Lysosomal pathology and osteopetrosis upon loss of H+-driven lysosomal Cl- accumulation. *Science*. 2010 Jun 11;328(5984):1401-3. [Abstract] [Full Text]

> *During lysosomal acidification, proton pump currents are thought to be shunted by a Cl- channel, ClC-7, but recent data suggest that ClC-7 mediates Cl-/H+-exchange. The authors generated mice with a point mutation converting ClC-7 into an uncoupled Cl-conductor (Clcn7(unc/unc)). Despite maintaining lysosomal conductance and normal lysosomal pH, Clcn7(unc/unc) mice showed lysosomal storage disease like ClC-7(-/-) mice. However, Clcn7(unc/unc) mice showed milder osteopetrosis and brown instead of gray coat color. Thus only some roles of ClC-7 Cl-/H+-exchange can be taken over by a Cl- conductance. Because Clcn7(-/-) and Clcn7(unc/unc) mice accumulated less Cl- in lysosomes than WT mice, lowered lysosomal chloride may underlie their common phenotypes.* —TM

Muscle and Bone

Gullett NP, Hebbar G, Ziegler TR. Update on clinical trials of growth factors and anabolic steroids in cachexia and wasting. *Am J Clin Nutr*. 2010 Apr;91(4):1143S-1147S. [Abstract]

Kung T, Springer J, Doehner W, Anker SD, von Haehling S. Novel treatment approaches to cachexia and sarcopenia: highlights from the 5th Cachexia Conference. *Expert Opin Investig Drugs*. 2010 Apr;19(4):579-85. [Abstract]

Two recent reviews might be of interest to those of us who are working at the bone-muscle interface. Both deal with novel treatment approaches to cachexia and sarcopenia, providing insights into the Phase I and Phase II-III clinical trials. Thus, Gullett et al. focus on effects of growth hormone, ghrelin, testosterone and progesterone derivatives, to prevent muscle (and adipose) wasting. Kung et al. report highlights from the 5th Cachexia Conference in Barcelona, Spain, including presentations on melanocortin-4 receptor antagonists, myostatin inhibition, β-blockers, IL-6 antagonism, and vitamin D. —DK

Perrini S, Laviola L, Carreira MC, Cignarelli A, Natalicchio A, Giorgino F. The GH/IGF1 axis and signaling pathways in the muscle and bone: mechanisms underlying age-related skeletal muscle wasting and osteoporosis. *J Endocrinol*. 2010 Jun;205(3):201-10. [Abstract]

Both loss of muscle mass (sarcopenia) and osteoporosis/osteopenia are increasing with aging. Recent experimental evidence suggests that an age-dependent decline in GH and IGF1 serum levels and the impairment in their post-receptor signaling machinery may contribute to both processes of age-related muscle-and-bone mass wasting. This review paper discusses interesting molecular links between growth hormone and reduced insulin sensitivity, as well as links between reduced intracellular GH signaling and action observed in subjects with central obesity, which is attributed to free fatty acid levels. Molecular mechanisms of impaired GH and IGF1 signaling are cataloged. —DK

Reviews, Perspectives and Editorials

Translational Endocrinology & Metabolism: Osteoporosis Update. Volume I, Number 1, 2010. Editor-in-Chief: R. Paul Robertson, Guest editor: Sundeep Khosla. [PDF]

This new monograph series was developed by the editors of Endocrine Reviews, "to represent the collective expertise of the Endocrine Society." It is symbolic that the very first volume of the series is dedicated to osteoporosis – its biology, assessment, and treatment. It provides an overview and highlights by experts in the field, including the following chapters: "Clinical Management of the Patient with Osteoporosis" by Tamara Vokes and Murray Favus; "Pathogenesis of Osteoporosis" by Sundeep Khosla; "Bone Biology Underlying Therapeutic Approaches" by Lorenz Hofbauer and Michael Schoppet; and "Genetics of Osteoporosis" by Charles Farber and Clifford Rosen.

The latter chapter provides historical perspective on identifying osteoporosis genes and genome-wide association studies, and most importantly, provides a forecast for the future role of genetics in the evaluation of patients and in the management of osteoporosis. There is a case study, which makes the chapter of interest to a CME audience. Yet, pharmacogenetic and pharmacogenomic aspects could be developed in more detail, although this reflects a limitation of current knowledge of the genetic treatment of osteoporosis. —DK

Ralston SH, Uitterlinden AG. Genetics of osteoporosis. *Endocr Rev*. 2010 Apr 29. [Epub ahead of print] [Abstract]

Xu XH, Dong SS, Guo Y, Yang TL, Lei SF, Papasian CJ, Zhao M, Deng HW. Molecular genetic studies of gene identification for osteoporosis: The 2009 update. *Endocr Rev*. 2010 Mar 31. [Epub ahead of print] [Abstract]

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Other Studies of Potential Interest

Bosetti M, Leigheb M, Brooks RA, Boccafoschi F, Cannas M. Regulation of osteoblast and osteoclast functions by FGF-6. *J Cell Physiol*. 2010 May 10. [Epub ahead of print] [Abstract]

Gabbay KH, Bohren KM, Morello R, Bertin T, Liu J, Vogel P. The ascorbate synthesis pathway: Dual role of ascorbate in bone homeostasis. *J Biol Chem*. 2010 Apr 21. [Epub ahead of print] [Abstract]

Guezguez A, Prodhomme V, Mouska X, Baudot A, Blin-Wakkach C, Rottapel R, Deckert M. 3BP2 adapter protein is required for RANKL-induced osteoclast differentiation of RAW264.7 cells. *J Biol Chem*. 2010 May 3. [Epub ahead of print] [Abstract]

McCormick WD, Atkinson-Dell R, Campion KL, Mun HC, Conigrave AD, Ward DT. Increased receptor stimulation elicits differential calcium-sensing receptor(T888) dephosphorylation. *J Biol Chem*. 2010 May 7;285(19):14170-7. [Abstract] [Full Text]

Qiu W, Hu Y, Andersen TE, Jafari A, Li N, Chen W, Kassem M. Tumor necrosis factor receptor superfamily member 19 (TNFRSF19) regulates differentiation fate of human mesenchymal (stromal) stem cells through canonical Wnt signaling and C/EBP. *J Biol Chem*. 2010 May 7;285(19):14438-49. [Abstract] [Full Text]

Stein K, Csiki Z, Rogers KC, Weishampel DB, Redelstorff R, Carballido JL, Sander PM. Small body size and extreme cortical bone remodeling indicate phyletic dwarfism in Magyarosaurus dacus (Sauropoda: Titanosauria). *Proc Natl Acad Sci U S A*. 2010 May 18;107(20):9258-63. [Abstract] [Full Text]

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. 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.