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NOT TO BE MISSED

Clinical and Basic Research Papers – September 2008

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Bone Modeling, Remodeling and Repair

◆O'Brien CA, Plotkin LI, Galli C, Goellner JJ, Gortazar AR, Allen MR, Robling AG, Bouxsein M, Schipani E, Turner CH, Jilka RL, Weinstein RS, Manolagas SC, Bellido T. Control of bone mass and remodeling by PTH receptor signaling in osteocytes. *PLoS ONE*. 2008 Aug 13;3(8):e2942. [Abstract]

> *Transgenic mice expressing a constitutively active PTH receptor exclusively in osteocytes showed increased bone mass and remodeling. SOST expression was reduced, and Wnt signaling increased. Osteoclast number was increased, but deletion of the Wnt co-receptor LRP5 attenuated the bone mass phenotype but not the remodeling-related events. As the authors conclude, this would seem to indicate that PTH receptor signaling in osteocytes increases bone mass and the rate of bone remodeling through LRP5-dependent and -independent mechanisms, respectively. Exactly how the Wnt pathway overlays and interacts with well known pathways will be crucial to our future understanding.* —DGL

◆Siller-Jackson AJ, Burra S, Gu S, Xia X, Bonewald LF, Sprague E, Jiang JX. Adaptation of connexin 43-hemichannel prostaglandin release to mechanical loading. *J Biol Chem*. 2008 Sep 26;283(39):26374-82.

> *Bone tissues respond to mechanical loading/unloading by modeling and remodeling. Connexin (Cx) 43 hemichannels in osteocytes mediate the release of prostaglandin PGE2. Opening of hemichannels and release of PGE2 by shear stress is inhibited by an antibody blocking Cx43 hemichannels. A rest period enhances this response. Hemichannels close after continuous shear stress corresponding with reduced Cx43 expression, reducing negative effects of channels staying open.* —ES

Clinical Studies and Drug Effects

◆Cummings SR, Ettinger B, Delmas PD, Kenemans P, Stathopoulos V, Verweij P, Mol-Arts M, Kloosterboer L, Mosca L, Christiansen C, Bilezikian J, Kerzberg EM, Johnson S, Zanchetta J, Grobbee DE, Seifert W, Eastell R; LIFT Trial Investigators. The effects of tibolone in older postmenopausal women. *N Engl J Med*. 2008 Aug 14;359(7):697-708. [Abstract]

> 4538 women aged 60 to 85 years received daily tibolone (1.25 mg) or placebo. During a median of 34 months, treatment reduced the risk of vertebral fracture (70 vs. 126 cases per 1000 person-years, relative hazard 0.55; 95% CI, 0.41-0.74; P<0.001), nonvertebral fracture (122 vs. 166 cases per 1000 person-years, relative hazard 0.74; 95% CI, 0.58-0.93; P=0.01), invasive breast cancer (relative hazard, 0.32; 95% CI, 0.13-0.80; P=0.02)

and colon cancer (relative hazard, 0.31; 95% CI, 0.10-0.96; P=0.04) but increased risk of stroke (relative hazard, 2.19; 95% CI, 1.14-4.23; P=0.02) with no effect on risk of coronary heart disease or venous thromboembolism. —ES

Gutiérrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, Smith K, Lee H, Thadhani R, Jüppner H, Wolf M. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med*. 2008 Aug 7;359(6):584-92. [Abstract]

The authors examined mortality according to serum phosphate in a prospective cohort beginning hemodialysis, and analyzed FGF-23 levels in a nested case-control sample of 200 subjects who died and 200 who survived during the first year. Increased FGF-23 levels were associated with mortality independent of serum phosphate and other known risk factors. Serum FGF-23 levels may become a useful and sensitive biomarker to identify patients who may benefit from management of phosphate balance especially among early kidney disease patients without elevation in serum phosphate levels. It is unknown whether increased serum FGF-23 levels are in themselves toxic or are protective against other toxic factors. —TM

Melamed ML, Michos ED, Post W, Astor B. 25-hydroxyvitamin D levels and the risk of mortality in the general population. *Arch Intern Med*. 2008 Aug 11;168(15):1629-37. [Abstract]

Among 13,331 persons, age, female sex, nonwhite race, diabetes, smoking, and BMI were associated with higher odds of 25(OH)D deficiency. During a median of 8.7 years, the lowest quartile of 25(OH)D was associated with a 26% increased rate of all-cause mortality and an attributable risk of 3.1%. Association studies are difficult to interpret but I suspect randomized trials to test this association are unlikely. —ES

Genetics

Smith EP, Specker B, Bachrach BE, Kimbro KS, Li XJ, Young MF, Fedarko NS, Abuzzahab MJ, Frank GR, Cohen RM, Lubahn DB, Korach KS. Impact on bone of an estrogen receptor-alpha gene loss of function mutation. *J Clin Endocrinol Metab*. 2008 Aug;93(8):3088-96. [Abstract] [Full Text]

This study reported the first kindred that is the only known instance of a germ line loss of function mutation of estrogen receptor-α (ER-α). In the kindred identified via the propositus with a homozygous loss of function mutation, this study assessed the impact of the loss of function mutation on bone related phenotypes, e.g., bone volumetric density, bone geometry and skeletal growth, and adult height in an extended pedigree. This study provides substantial evidence for the important role played by ER-α in bone metabolism. —HWD

Steer C, Emmett P, Lewis S, Smith GD, Tobias J. The methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism is associated with spinal BMD in nine-year-old children. *J Bone Miner Res*. 2008 Aug 20; [Epub ahead of print] [Abstract]

This is the first study investigating associations between the C677T MTHFR polymorphism and bone phenotypes in children. By use of regression analyses in 3196 children aged 9.9 years from the Avon Longitudinal Study of Parents and Children (ALSPAC), strong association was detected between the C677T MTHFR polymorphism and spine BMD. There also was evidence that this genetic effect was stronger in boys compared to girls. Additionally, the association between the MTHFR genotype and spine BMD was attenuated particularly in girls by high maternal dietary intakes of vitamin B6 and folate during pregnancy, but not by child dietary intakes at 7 years. —HWD

Tranah GJ, Taylor BC, Lui LY, Zmuda JM, Cauley JA, Ensrud KE, Hillier TA, Hochberg MC, Li J, Rhees BK, Erlich HA, Sternlicht MD, Peltz G, Cummings SR; For the Study of Osteoporotic Fractures (SOF) Research Group. Genetic variation in candidate osteoporosis genes, bone mineral density, and fracture risk: The Study of Osteoporotic Fractures. *Calcif Tissue Int*. 2008 Sep;83(3):155-66. [Abstract]

> *Polymorphisms in 18 candidate genes were tested for their association with BMD and incidental fractures in 6500 postmenopausal women from the SOF cohort. This study is quite unique in this field because of its prospective design (14.5 yrs of follow-up) and assessment of radiologic vertebral fractures, a prototypic fragility fracture. BMP2 and ESR1 genotypes were significantly associated with a 51% and 64% increased risk of vertebral fractures, respectively; ALOX15 genotypes with a 33% increased risk of hip fracture; and MMP2 and PRL genotypes were also associated with fracture risk, whereas Col1A1 genotypes were not. This study represents one more step towards the implementation of genetic markers in prediction models of fracture risk.* —SF

Molecular and Cell Biology

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 Aug 22; [Epub ahead of print]

> *This in vitro study shows that applying bi-axial strain to CIMC-4 preosteoblastic cells activates β-catenins, followed by nuclear translocation and transcriptional activity, including that of COX-2, which is well known to induce synthesis of prostaglandins in response to mechanical stimulation. Since these effects were not inhibited by Dkk1 in the cell cultures, the authors conclude that mechanical strain activates β-catenin canonical signaling independent of LRP5.* —SF

Irie K, Ejiri S, Sakakura Y, Shibui T, Yajima T. Matrix mineralization as a trigger for osteocyte maturation. *J Histochem Cytochem*. 2008 Jun;56(6):561-7. [Abstract]

> *This simple study used etidronate to block mineralization in rats, noting decreased mineral deposition but no disturbance in matrix deposition. The osteocytes found in the unmineralized matrix were immature and failed to show immunoreactivity with anti-sclerostin antibody, whereas mature osteocytes in the mineralized matrix showed immunoreactivity in both control and HEBP groups. Mineralization of the matrix surrounding the osteocyte could be a major trigger for cytodifferentiation from a plump immature form to a mature osteocyte. The osteocyte appears to start secreting sclerostin only after it matures in the mineralized bone matrix.* —DGL

Kawatani M, Okumura H, Honda K, Kanoh N, Muroi M, Dohmae N, Takami M, Kitagawa M, Futamura Y, Imoto M, Osada H. The identification of an osteoclastogenesis inhibitor through the inhibition of glyoxalase I. *Proc Natl Acad Sci U S A*. 2008 Aug 19;105(33):11691-6. [Abstract] [Full Text]

> *This study demonstrats that methyl-gerfelin (M-GFN), the methyl ester of the natural product gerfelin, suppresses osteoclastogenesis by binding to the active site of glyoxalase I (GLO1) and inhibiting its activity. GLO1 appears to be required for osteoclastogenesis, because GLO1 knockdown by siRNA and a known GLO1 inhibitor, S-p-bromobenzylglutathione cyclopentyl diester, also inhibited osteoclastogenesis. A major function of the glyoxalase pathway is detoxification of α-ketoaldehydes, especially methylglyoxal (MG). The mechanism whereby the inhibition of GLO1 activity suppresses osteoclastogenesis remains to be clarified.* —TM

Physiology and Metabolism

Sitara D, Kim S, Razzaque MS, Bergwitz C, Taguchi T, Schüler C, Erben RG, Lanske B. Genetic evidence of serum phosphate-independent functions of FGF-23 on bone. *PLoS Genet*. 2008 Aug 8;4(8):e1000154. [Abstract]

> *FGF-23 KO mice have hyperphosphatemia, altered mineralization and high BMC. This study reports that double KO mice lacking both FGF-23 and the renal sodium/phosphate co-transporter NaPi2 have hypophosphatemia, hence proving the role of overexpressed NaPi2 in FGF-23 KO mice on phosphate retention. However, double KO mice maintain a high BMC, increased serum calcium and undetectable PTH levels, and exhibit a severe mineralization defect (increased osteoid), similar to FGF-23 KO mice, indicating that these alterations may be due to the absence of FGF-23, and not solely to altered phosphate levels.* —SF

Reviews, Perspectives and Editorials

Bouillon R, Carmeliet G, Verlinden L, van Etten E, Verstuyf A, Luderer HF, Lieben L, Mathieu C, Demay M. Vitamin D and human health: lessons from vitamin D receptor null mice. *Endocr Rev*. 2008 Aug 11; [Epub ahead of print]

Kuro-O M. Endocrine FGFs and Klothos: emerging concepts. *Trends Endocrinol Metab*. 2008 Sep;19(7):239-45. [Abstract]

Other Studies of Potential Interest

Alonso V, de Gortázar AR, Ardura JA, Andrade-Zapata I, Alvarez-Arroyo MV, Esbrit P. Parathyroid hormone-related protein (107-139) increases human osteoblastic cell survival by activation of vascular endothelial growth factor receptor-2. *J Cell Physiol*. 2008 Jul 23;217(3):717-27. [Abstract]

Amano K, Ichida F, Sugita A, Hata K, Wada M, Takigawa Y, Nakanishi M, Kogo M, Nishimura R, Yoneda T. Msx2 stimulates chondrocyte maturation by controlling Ihh expression. *J Biol Chem*. 2008 Aug 4; [Epub ahead of print]

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Ellis GK, Bone HG, Chlebowski R, Paul D, Spadafora S, Smith J, Fan M, Jun S. Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. *J Clin Oncol*. 2008 Aug 25; [Epub ahead of print] [Abstract]

Fukuda T, Kohda M, Kanomata K, Nojima J, Nakamura A, Kamizono J, Noguchi Y, Iwakiri K, Kondo T, Kurose J, Endo KI, Awakura T, Fukushi J, Nakashima Y, Chiyonobu T, Kawara A, Nishida Y, Wada I, Akita M, Komori T, Nakayama K, Nanba A, Maruki Y, Yoda T, Tomoda H, Yu PB, Shore EM, Kaplan FS, Miyazono K, Matsuoka M. Constitutively activated ALK2 and increased smad1/5 cooperatively induce BMP signaling in fibrodysplasia ossificans progressiva. *J Biol Chem*. 2008 Aug 6; [Epub ahead of print]

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healthy, young, pre-menopausal women from UK, France, Belgium and the USA. *J Bone Miner Res*. 2008 Jul 29; [Epub ahead of print] [Abstract]

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Kaufman JM, Ostertag A, Saint-Pierre A, Cohen-Solal M, Boland A, Van Pottelbergh I, Toye K, de Vernejoul MC, Martinez M. Genome-wide linkage screen of bone mineral density (BMD) in European pedigrees ascertained through a male relative with low BMD values: evidence for quantitative trait loci on 17q21-23, 11q12-13, 13q12-14 and 22q11. *J Clin Endocrinol Metab*. 2008 Jul 29; [Epub ahead of print]

Liu D, Fritz DT, Rogers MB, Shatkin AJ. Species-specific cis-regulatory elements in the 3'UTR direct alternative polyadenylation of bone morphogenetic protein 2 mRNA. *J Biol Chem*. 2008 Aug 14; [Epub ahead of print]

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]

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Medici D, Razzaque MS, Deluca S, Rector TL, Hou B, Kang K, Goetz R, Mohammadi M, Kuro-O M, Olsen BR, Lanske B. FGF-23-Klotho signaling stimulates proliferation and prevents vitamin D-induced apoptosis. *J Cell Biol*. 2008 Aug 11;182(3):459-65. [Abstract] [Full Text]

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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.