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NOT TO BE MISSED

Clinical and Basic Research Papers – January 2011

Serge Ferrari, Editor-in-Chief
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Clinical Studies and Drug Effects

Ward LM, Rauch F, Whyte MP, D'Astous J, Gates PE, Grogan D, Lester EL, McCall RE, Pressly TA, Sanders JO, Smith PA, Steiner RD, Sullivan E, Tyerman G, Smith-Wright DL, Verbruggen N, Heyden N, Lombardi A, Glorieux FH. Alendronate for the treatment of pediatric osteogenesis imperfecta: a randomized placebo-controlled study. *J Clin Endocrinol Metab*. 2010 Nov 24. [Epub ahead of print] [Abstract]

> *Bisphosphonates are commonly used in children with osteogenesis imperfecta (OI) but no randomized trials have been done to examine whether fracture rates are reduced. 139 children (aged 4-19 yrs.) with type I, III, or IV OI were randomized to placebo (n = 30) or alendronate (ALN) (n = 109) for 2 yrs. ALN doses were 5 mg/d in children < 40 kg and 10 mg/d if > 40 kg. ALN increased spine BMD and decreased urinary N-telopeptide of collagen type I. Long-bone fracture incidence, average midline vertebral height, iliac cortical width, bone pain, and physical activity were similar between groups.* —ES

Cancer and Bone

Morgan GJ, Davies FE, Gregory WM, Cocks K, Bell SE, Szubert AJ, Navarro-Coy N, Drayson MT, Owen RG, Feyler S, Ashcroft AJ, Ross F, Byrne J, Roddie H, Rudin C, Cook G, Jackson GH, Child JA; National Cancer Research Institute Haematological Oncology Clinical Study Group. First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial. *Lancet*. 2010 Dec 11;376(9757):1989-99. [Abstract]

> *A 4 mg zoledronic acid infusion every 3-4 weeks (n = 981) was compared to 1600 mg oral clodronic acid daily (n = 979) in patients with multiple myeloma. Zoledronic acid reduced mortality by 16% (95% CI: 4-26) versus clodronic acid and extended median overall survival. Zoledronic acid also improved progression-free survival by 12% (95% CI: 2-20) versus clodronic acid and increased median progression-free survival. Zoledronic acid was associated with higher rates of osteonecrosis of the jaw (35 patients [4%]) than was clodronic acid (3 patients [<1%]).* —ES

Wilkinson GS, Baillargeon J, Kuo YF, Freeman JL, Goodwin JS. Atrial fibrillation and stroke associated with intravenous bisphosphonate therapy in older patients with cancer. *J Clin Oncol*. 2010 Nov 20;28(33):4898-905. [Abstract]

> *The authors matched 13,714 bisphosphonate nonusers to 6,857 bisphosphonate users on cancer type, age, sex, presence of bone metastases, and Surveillance, Epidemiology, and End Results (SEER) geographic region. Receipt of intravenous*

bisphosphonates was associated with an increased risk for atrial fibrillation (HR = 1.30, 95% CI: 1.18-1.43), all supraventricular tachycardia (SVT) (HR = 1.28, 95% CI: 1.19-1.38), and stroke (HR = 1.30, 95% CI: 1.09-1.54). The risk for all SVT increased 7% for each increase of five bisphosphonate dose equivalents (HR = 1.07; 95% CI: 1.02-1.12). —ES

Genetics

Guan Y, Ackert-Bicknell CL, Kell B, Troyanskaya OG, Hibbs MA. Functional genomics complements quantitative genetics in identifying disease-gene associations. *PLoS Comput Biol*. 2010 Nov 11;6(11):e1000991. [Abstract]

A team of bioinformaticians proposes a complementary approach to quantitative genetics (GWAS in humans and QTLs in mice) by mining the vast amount of high-throughput genomic data, including extracting protein function information, with a focus on the BMD phenotype. Thus, the authors experimentally validated two predicted genes (not observed in any previous GWAS/QTL studies) and found significant bone density defects for both Timp2- and Abcg8-deficient mice. The collaborators thus demonstrate that functional genomics can complement traditional quantitative genetic study by analyzing large collections of high throughput data with follow-up experiments. —DK

Zmuda JM, Yerges-Armstrong LM, Moffett SP, Klei L, Kammerer CM, Roeder K, Cauley JA, Kuipers A, Ensrud KE, Nestlerode CS, Hoffman AR, Lewis CE, Lang TF, Barrett-Connor E, Ferrell RE, Orwoll ES; for the Osteoporotic Fractures in Men (MrOS) Study Group. Genetic analysis of vertebral trabecular bone density and cross-sectional area in older men. *Osteoporos Int*. 2010 Dec 9. [Epub ahead of print] [Abstract]

Vertebral BMD and cross-sectional area (CSA) are important determinants of vertebral bone strength. Both are heritable phenotypes. Zmuda et al. measured volumetric bone mineral density (vBMD) and CSA by quantitative computed tomography in older men from the MrOS Study. They then tested for association between these phenotypes and 4,608 SNPs in 383 bone metabolism-related candidate genes. Using strict correction for multiple testing, none of the loci would surpass a "significant" threshold. Yet, they identified 11 SNPs in 10 genes as consistently associated with trabecular vBMD, and five SNPs in five genes consistently associated with CSA. These SNPs explain ~4% of the variance in vertebral trabecular vBMD and ~2% of the variance in vertebral CSA after controlling for covariates. Notably, none of the SNPs associated with trabecular vBMD were associated with CSA (it is unclear whether this should be expected since the phenotypic correlation between the two traits is not shown). —DK

Bone Modeling, Remodeling, and Repair

Allan CM, Kalak R, Dunstan CR, McTavish KJ, Zhou H, Handelsman DJ, Seibel MJ. Follicle-stimulating hormone increases bone mass in female mice. *Proc Natl Acad Sci U S A*. 2010 Dec 28;107(52):22629-34. [Abstract] [Full Text]

Transgenic female mice expressing human follicle-stimulating hormone (TgFSH) have increased tibial and vertebral trabecular bone volume in this study. TgFSH stimulated accrual of bone mass in hypogonadal mice lacking endogenous FSH and luteinizing hormone (LH) function. Higher TgFSH levels increased osteoblast surfaces in trabecular bone and stimulated de novo bone formation, filling marrow with woven rather than lamellar bone. Ovariectomy abolished TgFSH-induced bone formation,

proving that FSH effects on bone require an ovary-dependent pathway. No detectable FSH receptor mRNA in mouse bone or cultured osteoblasts or osteoclasts indicated that FSH did not directly stimulate bone. Contrary to proposed FSH-induced bone loss, the findings demonstrate that FSH has dose-dependent anabolic effects on bone via an ovary-dependent mechanism. —ES

Krause C, Korchynskyi O, de Rooij K, Weidauer SE, de Gorter DJ, van Bezooijen RL, Hatsell S, Economides AN, Mueller TD, Löwik CW, Ten Dijke P. Distinct modes of inhibition by sclerostin on bone morphogenetic protein and Wnt signaling pathways. *J Biol Chem*. 2010 Dec 31;285(53):41614-26. [Abstract] [Full Text]

Through cell culture studies and analysis of sclerostin KO mice, the authors conclude that sclerostin may exert its potent bone catabolic effects by antagonizing Wnt signaling in a paracrine and autocrine manner and antagonizing BMP signaling selectively in the osteocytes that synthesize simultaneously both sclerostin and BMP7 proteins. Thus the two previously competing theories that sclerostin acts as a BMP inhibitor or through Wnt/β-catenin may both be correct. —DGL

Miyagawa K, Kozai Y, Ito Y, Furuhama T, Naruse K, Nonaka K, Nagai Y, Yamato H, Kashima I, Ohya K, Aoki K, Mikuni-Takagaki Y. A novel underuse model shows that inactivity but not ovariectomy determines the deteriorated material properties and geometry of cortical bone in the tibia of adult rats. *J Bone Miner Metab*. 2010 Dec 3. [Epub ahead of print] [Abstract]

This novel study concludes that, in rats, lack of daily activity is detrimental to the strength and quality of cortical bone in the femur and tibia, while lack of estrogen is not. Estrogen loss affected cancellous parameters, but there were few truly additive effects of inactivity and ovariectomy. —DGL

Ominsky MS, Li C, Li X, Tan HL, Lee E, Barrero M, Asuncion FJ, Dwyer D, Han CY, Vlasseros F, Samadfam R, Jolette J, Smith SY, Stolina M, Lacey DL, Simonet WS, Paszty C, Li G, Ke HZ. Inhibition of sclerostin by monoclonal antibody enhances bone healing and improves bone density and strength of non-fractured bones. *J Bone Miner Res*. 2010 Dec 2. [Epub ahead of print] [Abstract]

Sclerostin antibody (Scl-Ab) was assessed in 2 models of bone healing: a closed femoral fracture model in rats and a fibular osteotomy model in cynomolgus monkeys. In the rat study, extensive timepoints and outcome measures were pursued, while in the monkey study only a long-term timepoint was able to be examined. In the rat study, all parameters of healing were increased with large increases in fracture strength. After ten weeks of healing in non-human primates, Scl-Ab treatment resulted in less callus cartilage and smaller fracture gaps containing more bone and less fibrovascular tissue. Bone strength was increased in the fractured and non-fractured bones. These studies pinpoint Scl-Ab as a possible therapeutic for fracture repair. While increases in bone parameters are understandable, the mechanisms for advancement of endochondral ossification require further elucidation. —DGL

van Oers RF, van Rietbergen B, Ito K, Hilbers PA, Huiskes R. A sclerostin-based theory for strain-induced bone formation. *Biomech Model Mechanobiol*. 2010 Nov 11. [Epub ahead of print] [Abstract]

Previous models of remodeling assumed that osteocytes secreted stimulatory factors in response to load. As it seems likely that the reverse is true – osteocytes decrease sclerostin and other factors in response to load – new models were created. Computer simulations showed that a sclerostin-based model is able to produce a load-aligned

trabecular architecture. When comparing the responses of the stimulatory and inhibitory models to loss of osteocytes, the authors found that the inhibitory pathway prevents the loss of trabeculae that is seen with the stimulatory model. With combined stimulatory/inhibitory models it is suggested that the two pathways can work side-by-side to achieve a load-adapted bone architecture. —DGL

Physiology and Metabolism

Ensrud KE, Ewing SK, Fredman L, Hochberg MC, Cauley JA, Hillier TA, Cummings SR, Yaffe K, Cawthon PM; Study of Osteoporotic Fractures Research Group. Circulating 25-hydroxyvitamin D levels and frailty status in older women. *J Clin Endocrinol Metab*. 2010 Dec;95(12):5266-73. [Abstract] [Full Text]

Sai AJ, Walters RW, Fang X, Gallagher JC. Relationship between vitamin D, parathyroid hormone, and bone health. *J Clin Endocrinol Metab*. 2010 Dec 15. [Epub ahead of print] [Abstract]

These 2 papers in JCEM focus on definition of the threshold below which serum 25(OH)D levels can be considered insufficient for musculoskeletal outcomes. Thus, in the 1st paper, lower vitamin D levels (15.0-19.9 ng/ml) among 6,307 women aged 69 years or older from the SOF study were associated with higher odds of frailty at baseline, and such low levels among non-frail women at baseline were associated with increased risk of incident frailty or death at a follow-up of 4.5 years. The lowest risk of frailty was among those with 20-29.9 ng/ml (referent group) vitamin D levels. More surprising was the finding that higher 25(OH)D levels were associated with higher odds of frailty at baseline. Therefore, there was proposed a U-shaped association between 25(OH)D levels and odds of frailty, with lower (< 20 ng/ml or 50 nmol/L) and higher (30 ng/ml or 75 nmol/L) levels associated with an increased risk of incident frailty or death at follow-up.

According to the second paper, by studying the relationship between serum 25(OH)D, PTH, and osteocalcin and 24-h urine N-telopeptides, vitamin D insufficiency should be defined as serum 25(OH)D less than 20 ng/ml (50 nmol/L) as it relates to bone health. —DK

Wang Y, Deluca HF. Is the vitamin D receptor found in muscle? *Endocrinology*. 2010 Dec 29. [Epub ahead of print] [Abstract]

The question whether the vitamin D receptor (VDR) is expressed in mature muscle cells has been debated but not settled. If a functional VDR is found in muscle, it would be a target of circulating vitamin D. The results from this investigation, which used a specific and sensitive immunohistochemical assay, show that the vitamin D receptor is undetectable in skeletal, as well as cardiac and smooth muscle, suggesting that the function of vitamin D on muscle is either of an indirect nature or does not involve this receptor. —DK

Reviews, Perspectives and Editorials

Olson LE, Ohlsson C, Mohan S. The role of GH/IGF-I-mediated mechanisms in sex differences in cortical bone size in mice. *Calcif Tissue Int*. 2010 Nov 27. [Epub ahead of print] [Abstract]

Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, Kovacs CS, Mayne ST, Rosen CJ, Shapses SA. The 2011

report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab*. 2010 Nov 29. [Epub ahead of print] [Abstract]

Other Studies of Potential Interest

Barsony J, Sugimura Y, Verbalis JG. Osteoclast response to low extracellular sodium and the mechanism of hyponatremia-induced bone loss. *J Biol Chem*. 2010 Dec 6. [Epub ahead of print] [Abstract]

Corallini F, Celeghini C, Rimondi E, di Iasio MG, Gonelli A, Secchiero P, Zauli G. TRAIL down-regulates the release of osteoprotegerin (OPG) by primary stromal cells. *J Cell Physiol*. 2010 Dec 6. [Epub ahead of print] [Abstract]

Djonic D, Milovanovic P, Nikolic S, Ivovic M, Marinkovic J, Beck T, Djuric M. Inter-sex differences in structural properties of aging femora: implications on differential bone fragility: a cadaver study. *J Bone Miner Metab*. 2010 Dec 4. [Epub ahead of print] [Abstract]

Hagihara M, Endo M, Hata K, Higuchi C, Takaoka K, Yoshikawa H, Yamashita T. Neogenin: A receptor for bone morphogenetic proteins. *J Biol Chem*. 2010 Dec 13. [Epub ahead of print] [Abstract]

Hsiao WK, Yew TL, Lai YL, Lee SY, Chen HL. Intramarrow BMP4 gene delivery improves local bone quality in femurs of ovariectomized rabbits. *J Periodontol*. 2010 Nov 23. [Epub ahead of print] [Abstract]

Klopocki E, Lohan S, Brancati F, Koll R, Brehm A, Seemann P, Dathe K, Stricker S, Hecht J, Bosse K, Betz RC, Garaci FG, Dallapiccola B, Jain M, Muenke M, Ng VC, Chan W, Chan D, Mundlos S. Copy-number variations involving the IHH locus are associated with syndactyly and craniosynostosis. *Am J Hum Genet*. 2010 Dec 16. [Epub ahead of print] [Abstract]

Korvala J, Hartikka H, Pihlajamäki H, Solovieva S, Ruohola JP, Sahi T, Barral S, Ott J, Ala-Kokko L, Männikkö M. Genetic predisposition for femoral neck stress fractures in military conscripts. *BMC Genet*. 2010 Oct 21;11:95. [Abstract]

Liedert A, Mattausch L, Röntgen V, Blakytny R, Vogele D, Pahl M, Bindl R, Neunaber C, Schinke T, Harroch S, Amling M, Ignatius A. Midkine-deficiency increases the anabolic response of cortical bone to mechanical loading. *Bone*. 2010 Dec 23. [Epub ahead of print] [Abstract]

McDonald MM, Morse A, Peacock L, Mikulec K, Schindeler A, Little DG. Characterization of the bone phenotype and fracture repair in osteopetrotic Incisors absent rats. *J Orthop Res*. 2010 Dec 3. [Epub ahead of print] [Abstract]

Quach JM, Walker EC, Allan E, Solano M, Yokoyama A, Gillespie MT, Kato S, Sims NA, Martin TJ. Zinc finger protein 467 is a novel regulator of osteoblast and adipocyte commitment. *J Biol Chem*. 2010 Dec 1. [Epub ahead of print] [Abstract]

Saito A, Ochiai K, Kondo S, Tsumagari K, Murakami T, Cavener DR, Imaizumi K. ER stress response mediated by the PERK-eIF2alpha-ATF4 pathway is involved in osteoblast differentiation induced by BMP2. *J Biol Chem*. 2010 Dec 6. [Epub ahead of print] [Abstract]

Sukumar D, Ambia-Sobhan H, Zurfluh R, Schlussel Y, Stahl T, Gordon C, Shapses S. Areal and volumetric bone mineral density and geometry at two levels of protein intake during caloric restriction: a randomized controlled trial. *J Bone Miner Res*. 2010 Dec 16. [Epub ahead of print] [Abstract]

Yates CJ, Bartlett MJ, Ebeling PR. An atypical subtrochanteric femoral fracture from pycnodysostosis - a lesson from nature. *J Bone Miner Res*. 2010 Dec 7. [Epub ahead of print] [Info]

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.