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NOT TO BE MISSED

Clinical and Basic Research Papers – April 2011

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Cancer and Bone

Fizazi K, Carducci M, Smith M, Damião R, Brown J, Karsh L, Milecki P, Shore N, Rader M, Wang H, Jiang Q, Tadros S, Dansey R, Goessl C. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet*. 2011 Mar 5;377(9768):813-22. [Abstract]

> *1,904 patients with castration-resistant prostate cancer and no previous exposure to intravenous bisphosphonate received denosumab (n = 950), a fully human monoclonal anti-RANKL antibody, or zoledronate (n = 951). Denosumab was better than zoledronate for prevention of skeletal-related events (HR = 0.82; 95% CI, 0.71-0.95; P = 0.008).* —PC

Henry DH, Costa L, Goldwasser F, Hirsh V, Hungria V, Prausova J, Scagliotti GV, Sleeboom H, Spencer A, Vadhan-Raj S, von Moos R, Willenbacher W, Woll PJ, Wang J, Jiang Q, Jun S, Dansey R, Yeh H. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol*. 2011 Mar 20;29(9):1125-32. [Abstract]

> *1,776 patients with advanced cancer and bone metastases (excluding breast and prostate) or myeloma received denosumab (n = 886) or zoledronate (n = 890) for delaying or preventing skeletal-related events. Denosumab was noninferior (trending to superiority) to zoledronate in preventing or delaying first on-study skeletal-related events in patients with advanced cancer metastatic to bone or myeloma (HR = 0.84; 95% CI, 0.71-0.98; P = .0007).* —PC

Tan W, Zhang W, Strasner A, Grivennikov S, Cheng JQ, Hoffman RM, Karin M. Tumour-infiltrating regulatory T cells stimulate mammary cancer metastasis through RANKL-RANK signalling. *Nature*. 2011 Feb 24;470(7335):548-53. [Abstract]

> *CD4+ CD25+ FOXP3+ regulatory T (Treg) cells are a major source of receptor activator of nuclear factor-κB (RANK) ligand (RANKL), which stimulates the metastatic spreading of RANK-expressing breast cancer cells in vivo by repressing the expression of the metastasis inhibitor maspin.* —PC

Genetics

Gordon CM, Gordon LB, Snyder BD, Nazarian A, Quinn N, Huh S, Giobbie-Hurder A, Neuberg D, Cleveland R, Kleinman M, Miller DT, Kieran MW. Hutchinson-Gilford progeria is a skeletal

dysplasia. *J Bone Miner Res*. 2011 Mar 28. [Epub ahead of print] [Abstract]

> *Classical Hutchinson-Gilford progeria syndrome (HGPS) is caused by mutations within exon 11 of LMNA, leading to an in-frame deletion of 50 amino acids. This rare, segmental, premature aging disorder affects bone and body composition, among other tissues. The current study investigated bone density and geometry in 26 prospectively enrolled children with HGPS (ages 3.1 to 16.2 years). In particular, pQCT revealed distinct abnormalities in bone structural geometry of the forearm in the HGPS patients compared to healthy controls. Thus, the authors found an unusual cross-sectional HGPS geometry: (i) a "star"-shaped cross-section for the radius and ulna at 20% distance from the distal growth plate, in comparison to the more elliptical cross-sections in the controls, and (ii) a "tailed" ulnar cross-section at a distance 66% from the distal growth plate, with the medullary cavity filled with bone. Notably, dietary intake in the children was adequate, and thus no malnutrition-induced bone loss is suspected to contribute to this unique skeletal dysplasia.*
>
> *This fascinating finding is not totally surprising: it is known that LMNA mutations cause striated muscle diseases with skeletal dysplasias. Thus, (a) homozygous Lmna knockout mice develop regional skeletal and cardiac muscle abnormalities within the first 2 months of life and (b) in a compound heterozygous subject for the LMNA R527H/V440M mutation, lack of muscle strength and decreased muscle tone has also been reported. This might suggest that there is a muscular component to the cross-sectional peculiarities of the HGPS distal appendicular skeleton.* —DK

Simpson MA, Irving MD, Asilmaz E, Gray MJ, Dafou D, Elmslie FV, Mansour S, Holder SE, Brain CE, Burton BK, Kim KH, Pauli RM, Aftimos S, Stewart H, Kim CA, Holder-Espinasse M, Robertson SP, Drake WM, Trembath RC. Mutations in NOTCH2 cause Hajdu-Cheney syndrome, a disorder of severe and progressive bone loss. *Nat Genet*. 2011 Mar 6;43(4):303-5. [Abstract]

Isidor B, Lindenbaum P, Pichon O, Bézieau S, Dina C, Jacquemont S, Martin-Coignard D, Thauvin-Robinet C, Le Merrer M, Mandel JL, David A, Faivre L, Cormier-Daire V, Redon R, Le Caignec C. Truncating mutations in the last exon of NOTCH2 cause a rare skeletal disorder with osteoporosis. *Nat Genet*. 2011 Mar 6;43(4):306-8. [Abstract]

> *Two back-to-back papers appear in Nature Genetics; both are dedicated to Hajdu-Cheney syndrome, a rare autosomal dominant skeletal disorder characterized by facial anomalies, acro-osteolysis and progressive bone loss. Both studies used an exome-sequencing strategy and identified frameshift mutations in NOTCH2, which acted in a gain-of-function manner. What makes these papers especially interesting is that NOTCH2 is a receptor for the ligand Jagged1, which is coded by the JAG1 gene. The latter was identified by a GWAS as a candidate gene for BMD and osteoporotic fractures (Kung et al. Am J Hum Genet. 2010 Feb 12;86(2):229-39). Taken together, the findings from these studies of rare diseases and GWAS further support a role for NOTCH2 signaling in the regulation of bone mass.* —DK

Yamaguchi T, Hosomichi K, Narita A, Shirota T, Tomoyasu Y, Maki K, Inoue I. Exome resequencing combined with linkage analysis identifies novel PTH1R variants in primary failure of tooth eruption in Japanese. *J Bone Miner Res*. 2011 Mar 14. [Epub ahead of print] [Abstract]

> *This group applied a combination of linkage, SNP and exome resequencing analyses to identify genes responsible for a very rare disease (primary failure of tooth eruption, PFE), a supposedly Mendelian disorder. First, linkage analyses of two families with eight affected individuals found ten loci with a LOD score ~1.5. Further, 4 affected individuals in one family were followed by massive parallel sequencing; 3 of 23*

discovered variants were considered as candidates for PFE. Among these 3 variants (in PTH1R, TGFBR2, and PROKR2), only one missense novel variant of the PTH1R gene was co-segregated in the first PFE family; the authors also identified other missense variants in PTH1R co-segregating in the second family and in the sporadic cases. These variants were not observed in 192 unrelated Japanese subjects. —DK

Bone Modeling, Remodeling, and Repair

Aro HT, Govender S, Patel AD, Hernigou P, Perera de Gregorio A, Popescu GI, Golden JD, Christensen J, Valentin A. Recombinant human bone morphogenetic protein-2: a randomized trial in open tibial fractures treated with reamed nail fixation. *J Bone Joint Surg Am*. 2011 Mar 31. [Epub ahead of print] [Abstract] [Full Text]

BMP-2 was previously shown to accelerate healing in open fractures in a pivotal trial (BESTT), which led to its approval for use in open tibia fractures. Since then, debate has raged about disproportional allocation in the randomization in the pivotal study between reamed and unreamed nails, with reamed nails purportedly having higher union rates.

This new randomized controlled trial examined only reamed nails, and standard of care treatment (SOC) was compared to SOC plus rhBMP-2 (12.0 mg) on an absorbable collagen sponge. The study was stopped prematurely because of increased infection in the rhBMP-2 group. The percentage of subjects with a healed fracture at thirteen and twenty weeks did not differ significantly between the treatment groups, nor was there a difference when analyzed by Gustilo-Anderson grade. There were no differences in the rate of secondary intervention. The number of infections, while being higher in the rhBMP-2 group (19%) than in the standard of care group (11%), did not reach significance ($p = 0.0645$). The rate of deep infection was 9% in the rh-BMP-2 group and 2% in the SOC group.

This study calls into question the use of rhBMP-2 in open fractures. In the absence of any further new evidence, rhBMP-2 is probably contraindicated in grade 1 and 2 fractures due to the possibility of increased infection risk and the lack of efficacy in the Aro et al. study. Further study of the effects of rhBMP-2 in high grade open fracture is warranted. (Also see an accompanying editorial in the same issue of J Bone Joint Surg Am. here). —DGL

Jerome C, Missbach M, Gamse R. Balicatib, a cathepsin K inhibitor, stimulates periosteal bone formation in monkeys. *Osteoporos Int*. 2011 Mar 5. [Epub ahead of print] [Abstract]

Deposition of bone upon the periosteal surface is a clever place to put it because this increases the resistance of bone to bending, more so than the deposition of a comparable amount of bone upon the endocortical surface. In this study, balicatib inhibited cathepsin K and reduced bone remodeling but unlike other resorption inhibitors, treatment increased periosteal bone formation rates as assessed using dynamic histomorphometry in ovariectomized monkeys. No data are available in studies in human subjects at this time. Animal studies also show this effect of anabolic agents, while this is not convincingly shown in studies in humans; the periosteal surface is a difficult terrain with little modeling or remodeling. —ES

Steck R, Ueno M, Gregory L, Rijken N, Wullschleger ME, Itoman M, Schuetz MA. Influence of internal fixator flexibility on murine fracture healing as characterized by mechanical testing and microCT imaging. *J Orthop Res*. 2011 Mar 15. [Epub ahead of print] [Abstract]

Using plates with locking screws that were either rigid or had a flexible component, this group shows that the mechanical environment can be nicely controlled in murine fractures. Larger calluses formed with flexible fixation, but given their cartilage component, they were less strong than intramembranous, smaller bridging calluses in rigid fixation. All mice had healed equivalently at 28 days. This system might allow better interrogation of genetic models in fracture healing. —DGL

Molecular and Cell Biology

Albers J, Schulze J, Beil FT, Gebauer M, Baranowsky A, Keller J, Marshall RP, Wintges K, Friedrich FW, Priemel M, Schilling AF, Rueger JM, Cornils K, Fehse B, Streichert T, Sauter G, Jakob F, Insogna KL, Pober B, Knobeloch KP, Francke U, Amling M, Schinke T. Control of bone formation by the serpentine receptor Frizzled-9. *J Cell Biol*. 2011 Mar 21;192(6):1057-72. [Abstract] [Full Text]

The authors show that Frizzled-9 (Fzd9) is the only Fzd family gene that is induced upon osteoblast differentiation, and that Fzd9(-/-) mice display low bone mass due to impaired bone formation. Canonical Wnt signaling was not impaired in the absence of Fzd9. Fzd9(-/-) osteoblasts differentiated normally but exhibited cell-autonomous defects in matrix mineralization. Gene chip analysis revealed that the expression of chemokines and interferon-regulated genes was reduced in Fzd9(-/-) osteoblasts. Among them, Isg15, which encodes a ubiquitin-like modifier protein, was identified as a mediator responsible for the reduced mineralization. These results reveal a previously unknown function of Fzd9 in the control of osteoblast function, which is independent of canonical Wnt signaling. —TM

Oury F, Sumara G, Sumara O, Ferron M, Chang H, Smith CE, Hermo L, Suarez S, Roth BL, Ducy P, Karsenty G. Endocrine regulation of male fertility by the skeleton. *Cell*. 2011 Mar 4;144(5):796-809. [Abstract]

There is no limit to the innovation from the Karsenty group. In male mice, bone regulates fertility. Using coculture assays, osteoblasts induce testosterone production by the testes, not estrogen production by the ovaries. Osteoblast-derived osteocalcin performs this function by binding to a G protein-coupled receptor expressed in Leydig cells. Osteocalcin regulates the expression of enzymes required for testosterone synthesis, promoting germ cell survival. The skeleton is an endocrine organ, now not only participating in energy metabolism and insulin sensitivity, but also in reproduction. —ES

Singbrant S, Russell MR, Jovic T, Liddicoat B, Izon DJ, Purton LE, Sims NA, Martin TJ, Sankaran VG, Walkley CR. Erythropoietin couples erythropoiesis, B lymphopoiesis, and bone homeostasis within the bone marrow microenvironment. *Blood*. 2011 Mar 18. [Epub ahead of print] [Abstract]

The authors found that erythropoietin (Epo) induced a rapid 26% loss of trabecular bone volume with an increase in osteoclastic bone resorption. Epo also impaired B lymphopoiesis without affecting hematopoietic stem cell populations within the bone marrow microenvironment. Bisphosphonate inhibited osteoclast activity and blocked the Epo-induced bone loss. Although Epo receptor expression was restricted to erythroid lineage cells, bisphosphonate also reduced the magnitude of the erythroid response to Epo, suggesting that bone remodeling is required for Epo-induced erythropoiesis. These data demonstrate a previously unrecognized regulatory network coordinating erythropoiesis, B lymphopoiesis and skeletal homeostasis by Epo. —TM

Public Health -- Epidemiology

Beaupre LA, Morrish DW, Hanley DA, Maksymowych WP, Bell NR, Juby AG, Majumdar SR. Oral bisphosphonates are associated with reduced mortality after hip fracture. *Osteoporos Int*. 2011 Mar;22(3):983-91. [Abstract]

> *Antiresorptive therapy is associated with prolonged survival independent of any effect of fracture prevention. A total of 101 (46%) patients started oral bisphosphonates and 65 (64%) remained on treatment; 24 (11%) died, 19 (9%) had new fractures, and 42 (20%) reached the composite outcome of death or fracture. Bisphosphonate exposure was associated with reduced mortality (17 [16%] vs. 7 [7%]; HR = 0.92 per month treated; 95% CI, 0.88-0.97). One explanation may be a healthy user effect – see below.* —ES

Curtis JR, Delzell E, Chen L, Black D, Ensrud K, Judd S, Safford MM, Schwartz AV, Bauer DC. The relationship between bisphosphonate adherence and fracture: Is it the behavior or the medication? Results from the placebo arm of the fracture intervention trial. *J Bone Miner Res*. 2011 Apr;26(4):683-8. [Abstract]

> *Among 3,169 women randomized to placebo, 82% had high compliance. Compared with women with lower placebo compliance, bone loss at the total hip was lower in compliant placebo-treated women (-0.43%/year vs. -0.58%/year; p = .04). Among placebo-treated women, there were 46 hip, 110 wrist, 77 clinical vertebral, and 492 total clinical fractures. Compared with women with lower placebo compliance, women with high placebo compliance had a reduced risk for hip fracture (adjusted HR = 0.67; 95% CI, 0.30-1.45). This trend was not observed for other fractures. Compliance may be a proxy for factors that confer benefit on reducing hip fracture independent of medication.* —ES

Lih A, Nandapalan H, Kim M, Yap C, Lee P, Ganda K, Seibel MJ. Targeted intervention reduces refracture rates in patients with incident non-vertebral osteoporotic fractures: a 4-year prospective controlled study. *Osteoporos Int*. 2011 Mar;22(3):849-58. [Abstract]

> *Failure to treat following a fracture is not acceptable because the risk of refracture following an incident fracture is high. Patients presenting with a non-vertebral fracture were identified and offered intervention or assigned to concurrent follow-up. Over 4 years, 10 of 246 patients (4.1%) fractured in the intervention group, while 31 of 157 patients (19.7%) fractured in the control group. Compared to the intervention group, the risk of refracture was 5.3-fold in the control group (95% CI, 2.8-12.2).* —ES

Steinvil A, Leshem-Rubinow E, Berliner S, Justo D, Finn T, Ish-shalom M, Birati EY, Shalev V, Sheinberg B, Rogowski O. Vitamin D deficiency prevalence and cardiovascular risk in Israel. *Eur J Clin Invest*. 2011 Mar;41(3):263-8. [Abstract]

Saliba W, Rennert HS, Kershenbaum A, Rennert G. Serum 25(OH)D concentrations in sunny Israel. *Osteoporos Int*. 2011 Mar 17. [Epub ahead of print] [Abstract]

> *These two studies assessed vitamin D status in large samples of Israelis (34,874 and 198,834 participants, respectively). Both agreed that the prevalence of the deficiency in Israel is similar to the prevalence found in less sunny regions. Thus, serum 25(OH)D levels <25 and <50 nmol/L are common in Israel with noted differences between Arabs and Jews (Saliba et al.) The relationship between 25(OH)D levels and age also differed among ethnic groups. In particular, Arab females were at high risk for 25(OH)D*

<50 nmol/L: 84.8% of them had low levels versus 48.1% of Jewish females (P < 0.0001). This finding might be attributed to dressing customs in Arab women where a greater surface of the skin is covered. —DK

Reviews, Perspectives and Editorials

Various authors. 50 years of research and discovery in chronic kidney disease and mineral & bone disorder: the central role of phosphate. *Kidney Int Suppl*. 2011 Apr;79(Suppl 121):S1-27. [Info]

Other Studies of Potential Interest

Gravenstein KS, Napora JK, Short RG, Ramachandran R, Carlson OD, Metter EJ, Ferrucci L, Egan JM, Chia CW. Cross-sectional evidence of a signaling pathway from bone homeostasis to glucose metabolism. *J Clin Endocrinol Metab*. 2011 Mar 9. [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*. 2011 Feb 18;286(7):5157-65. [Abstract] [Full Text]

Jemtland R, Holden M, Reppe S, Olstad OK, Reinholt FP, Gautvik VT, Refvem H, Frigessi A, Houston B, Gautvik KM. Molecular disease map of bone characterizing the postmenopausal osteoporosis phenotype. *J Bone Miner Res*. 2011 Mar 30. [Epub ahead of print] [Abstract]

Kawai M, Breggia AC, Demambro VE, Shen X, Canalis E, Bouxsein ML, Beamer WG, Clemmons DR, Rosen CJ. The heparin-binding domain of IGFBP-2 has IGF binding-independent biologic activity in the growing skeleton. *J Biol Chem*. 2011 Mar 3. [Epub ahead of print] [Abstract]

Koh JM, Kim BJ, Kim SY, Cho YS, Kim BJ, Han BG, Park EK, Lee SH, Kim HY, Kim GS, Lee JY. Association of Paraoxonase 1 (PON1) polymorphisms with osteoporotic fracture risk in postmenopausal Korean women. *Exp Mol Med*. 2011 Feb 28;43(2):71-81. [Abstract]

Parfitt M, Qiu S, Palnitkar S, Rao DS. Abnormal bone remodeling in patients with spontaneous painful vertebral fracture. *J Bone Miner Res*. 2011 Mar;26(3):475-85. [Abstract]

Rajalin AM, Aarnisalo P. Cross-talk between NR4A orphan nuclear receptors and beta-catenin signaling pathway in osteoblasts. *Arch Biochem Biophys*. 2011 Mar 6. [Epub ahead of print] [Abstract]

Ramamurthi K, Ahmad O, Engelke K, Taylor RH, Zhu K, Gustafsson S, Prince RL, Wilson KE. An in vivo comparison of hip structure analysis (HSA) with measurements obtained by QCT. *Osteoporos Int*. 2011 Mar 11. [Epub ahead of print] [Abstract]

Sato T, Kudo T, Ikehara Y, Ogawa H, Hirano T, Kiyohara K, Hagiwara K, Togayachi A, Ema M, Takahashi S, Kimata K, Watanabe H, Narimatsu H. Chondroitin sulfate N-acetylgalactosaminyltransferase 1 is necessary for normal endochondral ossification and aggrecan metabolism. *J Biol Chem*. 2011 Feb 18;286(7):5803-12. [Abstract] [Full Text]

Saxon LK, Jackson B, Sugiyama T, Lanyon LE, Price JS. Analysis of multiple bone responses to graded strains above functional levels, and to disuse, in mice in vivo show that the human G171V High Bone Mass mutation increases the osteogenic response to loading but that lack of Lrp5 activity reduces it. *Bone*. 2011 Mar 23. [Epub ahead of print] [Abstract]

Schmidt S, Nakchbandi I, Ruppert R, Kawelke N, Hess MW, Pfaller K, Jurdic P, Fässler R, Moser M. Kindlin-3-mediated signaling from multiple integrin classes is required for osteoclast-mediated bone resorption. *J Cell Biol*. 2011 Mar 7;192(5):883-97. [Abstract] [Full Text]

Shin MK, Jang YH, Yoo HJ, Kang DW, Park MH, Kim MK, Seo DS, Kim SD, Min G, Rhyu HK, Bae YS, Min DS. fMLP promotes osteoblast differentiation via the N-formyl peptide receptor 1-mediated signaling pathway in human mesenchymal stem cells from bone marrow. *J Biol Chem*. 2011 Mar 3. [Epub ahead of print] [Abstract]

Thaler R, Agsten M, Spitzer S, Paschalis EP, Karlic H, Klaushofer K, Varga F. Homocysteine suppresses the expression of the collagen cross-linker lysyl oxidase involving IL-6, Fli1, and epigenetic DNA methylation. *J Biol Chem*. 2011 Feb 18;286(7):5578-88. [Abstract] [Full Text]

Conflict of Interest: Dr. Clézardin reports receiving research support from Novartis (Basel, Switzerland) and honoraria for advisory work and speaking engagements from Novartis and Amgen. 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 reports that he is a member of the advisory board for Eli Lilly, and receives consultancy fees from Chugai, Astellas, Teijin, JT, and Daiichi-Sankyo. Dr. Karasik reports no conflicts of interest.