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NOT TO BE MISSED

Clinical and Basic Research Papers – August 2010

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Clinical Studies and Drug Effects

Genant HK, Engelke K, Hanley DA, Brown JP, Omizo M, Bone HG, Kivitz AJ, Fuerst T, Wang H, Austin M, Libanati C. Denosumab improves density and strength parameters as measured by QCT of the radius in postmenopausal women with low bone mineral density. *Bone*. 2010 Jul;47(1):131-9. [Abstract]

> *Early postmenopausal women (n=332) with spine BMD T-scores between −1.0 and −2.5 received denosumab 60 mg or placebo (PBO) every 6 months during this 24-month study. QCT measurements were made at the distal radius using a whole-body computed tomography scanner. vBMD declined 1% to 2% in all 3 regions of the radius in the PBO group, but increased 1% to 3.5% with denosumab, a significant difference vs. PBO. More specifically, cortical vBMD and thickness decreased in the PBO group but were kept unchanged in the denosumab group, providing further evidence that inhibition of bone turnover preserves cortical bone mass and structure at this site. The improvements observed in this analysis of radial bone density measured by QCT are consistent with DXA results previously reported from the same study (the DEFEND trial), in which aBMD (measured by DXA) increased by 1.4% at the one-third radius following denosumab treatment and decreased by 2.1% with PBO. The authors engage in a fair discussion about the limitations (limited resolution and precision) of QCT for these measurements.* —SF

Keaveny TM, Kopperdahl DL, Melton LJ 3rd, Hoffmann PF, Amin S, Riggs BL, Khosla S. Age-dependence of femoral strength in white women and men. *J Bone Miner Res*. 2010 May;25(5):994-1001. [Abstract]

> *This cross-sectional study evaluated hip BMD and strength by QCT and finite element analysis in Caucasian men and women aged between 21 to 89 years. Peak strength estimates are greater in men, start to decline later (i.e., above 55 yrs. compared to 45 yrs. of age in women), and continue to decline at a lower rate, particularly in the oldest group – 2.8%/yr. in women and 1.7%/yr in men aged 85 years. Thus, by age 80, virtually 90% of women, but about 50% of men, had reached a femoral neck strength < 3000 Newtons, which was estimated to be the fracture threshold (in another study in men [MrOS]).* —SF

Shiraki M, Kuroda T, Shiraki Y, Tanaka S, Higuchi T, Saito M. Urinary pentosidine and plasma homocysteine levels at baseline predict future fractures in osteoporosis patients under bisphosphonate treatment. *J Bone Miner Metab*. 2010 May 11. [Epub ahead of print] [Abstract]

> *Previous reports indicated a close relationship between non-enzymatic collagen cross-links (pentosidine) in bone and plasma homocysteine (Hcys) levels, which have been*

associated with fracture risk independent of age and BMD. This prospective study in 251 elderly Japanese women (incl. 6% diabetics) starting alendronate or risedronate for treatment of osteoporosis evaluated the contribution of urinary pentosidine and plasma Hcys levels to incident, morphometric vertebral fractures (VFx) over several years. It found that mean pentosidine and Hcys levels at baseline were significantly higher in the group with incident VFx (n=61), whereas urinary NTx and sBAP were not different. The vast majority of patients in the highest pentosidine or Hcys tertile suffered a VFx during follow-up (up to 8 yrs.), whereas less than 20% of those in the lowest tertile had such fractures. These results were independent of baseline BMD, age and prevalent fractures. —SF

Genetics

Kapur K, Johnson T, Beckmann ND, Sehmi J, Tanaka T, Kutalik Z, Styrkarsdottir U, Zhang W, Marek D, Gudbjartsson DF, Milaneschi Y, Holm H, Diiorio A, Waterworth D, Li Y, Singleton AB, Bjornsdottir US, Sigurdsson G, Hernandez DG, Desilva R, Elliott P, Eyjolfsson GI, Guralnik JM, Scott J, Thorsteinsdottir U, Bandinelli S, Chambers J, Stefansson K, Waeber G, Ferrucci L, Kooner JS, Mooser V, Vollenweider P, Beckmann JS, Bochud M, Bergmann S. Genome-wide meta-analysis for serum calcium identifies significantly associated SNPs near the calcium-sensing receptor (CASR) gene. *PLoS Genet*. 2010 Jul 22;6(7):e1001035. [Abstract]

Results of the first meta-analysis of a genome-wide association study of serum calcium are reported. The study integrates data from four cohorts with a total of 12,865 individuals of European and Indian descent. Unsurprisingly, the meta-analysis shows that serum calcium concentrations are strongly associated with variants in or near the calcium-sensing receptor (CASR) gene on 3q13, with a missense variant (rs1801725) explaining 1.26% of the variance in serum calcium. Furthermore, the CASR was shown to replicate in an independent Icelandic cohort (deCODE, with 4,126 individuals). The investigators also tested whether rs1801725 was also involved with calcium-related outcomes, including osteoporosis, however, they did not find any evidence for such an association. —DK

Bone Modeling, Remodeling, and Repair

Allen MR, Turek JJ, Phipps RJ, Burr DB. Greater magnitude of turnover suppression occurs earlier after treatment initiation with risedronate than alendronate. *Bone*. 2010 Jul 15. [Epub ahead of print] [Abstract]

In the test tube, it has been demonstrated that differences exist in the mineral binding affinity and FPP synthase inhibitory potency among amino-bisphosphonates. Whether or not this relates to clinical differences between these drugs is difficult to know since the clinically administered doses and/or mode of administration differ so much. In this rabbit model, subcutaneous administration of doses of risedronate or alendronate "equivalent" to the 35 mg and 70 mg weekly regimen, respectively, led to a faster and more profound inhibition of bone turnover at the tissue level with risedronate, which is consistent with its proposed mechanism of action, i.e., a lesser affinity but higher FPPS inhibitory potency, compared to alendronate. Again, whether these observations are clinically relevant in humans is unknown. —SF

Molecular and Cell Biology

Rauch A, Seitz S, Baschant U, Schilling AF, Illing A, Stride B, Kirilov M, Mandic V, Takacz A, Schmidt-Ullrich R, Ostermay S, Schinke T, Spanbroek R, Zaiss MM, Angel PE, Lerner UH, David

JP, Reichardt HM, Amling M, Schütz G, Tuckermann JP. Glucocorticoids suppress bone formation by attenuating osteoblast differentiation via the monomeric glucocorticoid receptor. *Cell Metab*. 2010 Jun 9;11(6):517-31. [Abstract]

> *Using a Cre-transgenic mouse line, the authors demonstrate that the repression of bone formation by glucocorticoids (GCs) requires glucocorticoid receptor (GR) expression in osteoblasts. In the absence of GR, osteoblasts become refractory to GC-induced apoptosis, inhibition of proliferation and differentiation. GCs still reduce bone formation in mice with disruption of GR dimerization, resulting in bone loss in vivo, with enhanced apoptosis and suppressed differentiation in vitro. The monomeric GR interacts with the AP-1 site on the interleukin (IL)-11 promoter and inhibits its transcription. Thus, the inhibitory GC effects on osteoblasts can be explained by a suppression of cytokines, such as IL-11, via interaction of the monomeric GR with AP-1, but not NF-κB.* —TM

Shiozawa Y, Jung Y, Ziegler AM, Pedersen EA, Wang J, Wang Z, Song J, Wang J, Lee CH, Sud S, Pienta KJ, Krebsbach PH, Taichman RS. Erythropoietin couples hematopoiesis with bone formation. *PLoS One*. 2010 May 27;5(5):e10853. [Abstract]

> *Hematopoietic stem cells (HSCs), after acute bleeding, regulate osteoblast differentiation from marrow stromal cells by producing BMP2 and BMP6. In this study, the authors demonstrate that erythropoietin (Epo) activates Jak-Stat signaling pathways in HSCs, which leads to the production of BMPs. Epo also directly activates mesenchymal cells to form osteoblasts in vitro and enhances bone formation in vivo. Epo first enhances osteoclast formation without affecting osteoclastic bone resorption, which is followed by osteoblastogenesis. These data demonstrate that Epo not only regulates erythropoiesis but also bone formation via both direct and indirect mechanisms, suggesting the presence of a link between hematopoiesis and osteogenesis in the marrow.* —TM

Wei W, Wang X, Yang M, Smith LC, Dechow PC, Wan Y. PGC1beta mediates PPARgamma activation of osteoclastogenesis and rosiglitazone-induced bone loss. *Cell Metab*. 2010 Jun 9;11(6):503-516. [Abstract]

> *Using mouse models with genetically altered PPARγ, PGC1β, or ERRα, the authors show that PGC1β is required for the potentiation by rosiglitazone of RANKL-mediated enhancement of osteoclast differentiation. Rosiglitazone activation of PPARγ, in cooperation with RANKL, indirectly induces PGC1β expression by down-regulating β-catenin protein, which represses the expression of c-jun that activates the PGC1β promoter. PGC1β, in turn, functions as a PPARγ coactivator to stimulate osteoclast differentiation. PPARγ also induces ERRα expression, which coordinates with PGC1β to enhance mitochondrial biogenesis and osteoclast function. Thus, PGC1β mediates PPARγ stimulation of osteoclastogenesis by activating both PPARγ- and ERRα-mediated transcriptional programs. These results may help develop new PPARγ modulators that do not have detrimental effects on bone but retain insulin-sensitizing effects.* —TM

Pathophysiology

Vikulina T, Fan X, Yamaguchi M, Roser-Page S, Zayzafoon M, Guidot DM, Ofotokun I, Weitzmann MN. Alterations in the immuno-skeletal interface drive bone destruction in HIV-1 transgenic rats. *Proc Natl Acad Sci U S A*. 2010 Aug 3;107(31):13848-53. [Abstract] [Full Text]

This model of HIV-1 infection allows for the demonstration that infected lymphocytic B cells produce an excess of RANKL over OPG, thereby promoting osteoclastogenesis and bone loss. A molecular mechanism for AIDS-related osteoporosis and bone fragility is thereby revealed. —SF

Physiology and Metabolism

DuSell CD, Nelson ER, Wang X, Abdo J, Mödder UI, Umetani M, Gesty-Palmer D, Javitt NB, Khosla S, McDonnell DP. The endogenous selective estrogen receptor modulator 27-hydroxycholesterol is a negative regulator of bone homeostasis. *Endocrinology*. 2010 Aug;151(8):3675-85. [Abstract]

The bone-sparing effects of SERMs are well-known and thought to be mediated by their tissue-specific estrogen-like activities through the estrogen receptors (ERs). 27-hydroxycholesterol (27HC) is an early product of cholesterol bile acid metabolism. It binds to estrogen receptors and its relative agonist/antagonist activity differs between cells, making it a potential endogenous SERM. This study now shows that high levels of 27HC are associated with low BMD in mice, probably acting as an estradiol antagonist on ERs, but also by ER-independent pathways. Interestingly, RANKL, a primary mediator of osteoclastogenesis, was strongly induced by 27HC. —SF

Ferron M, Wei J, Yoshizawa T, Del Fattore A, DePinho RA, Teti A, Ducy P, Karsenty G. Insulin signaling in osteoblasts integrates bone remodeling and energy metabolism. *Cell*. 2010 Jul 23;142(2):296-308. [Abstract]

Fulzele K, Riddle RC, DiGirolamo DJ, Cao X, Wan C, Chen D, Faugere MC, Aja S, Hussain MA, Brüning JC, Clemens TL. Insulin receptor signaling in osteoblasts regulates postnatal bone acquisition and body composition. *Cell*. 2010 Jul 23;142(2):309-19. [Abstract]

These two seminal papers demonstrate independently that the production of uncarboxylated osteocalcin by osteoblasts – previously shown to be a regulator of insulin secretion by pancreatic islet cells and glucose tolerance systemically – is under the control of insulin signaling in osteoblasts, and furthermore depends on osteoclastic activity, i.e., bone resorption (Ferron et al.). Osteoblast-specific insulin receptor-deficient mice in particular accumulate less trabecular bone due to a failure of osteoblast maturation and decreased bone formation (Fulzele et al.). With age, these mice develop marked peripheral adiposity and insulin resistance accompanied by decreased circulating undercarboxylated osteocalcin, whereas targeted deletion of the IGF1 receptor in osteoblasts does not impact fat mass. These experiments close the loop of energy metabolism control by the skeleton. Also see the related editorial by Rosen and Motyl, who raise an intriguing question: according to the data from Ferron et al., could anti-resorptives promote insulin resistance and diabetes? —SF

Reviews, Perspectives and Editorials

Manolagas SC. From estrogen-centric to aging and oxidative stress: a revised perspective of the pathogenesis of osteoporosis. *Endocr Rev*. 2010 Jun;31(3):266-300. [Abstract]

The most enduring theory of aging stipulates that oxidative stress resulting from mitochondrial metabolism and the resulting increase in intracellular reactive oxygen species (ROS) is the major determinant of aging and lifespan. This review provides ample evidence that the age-related increase in ROS is a likely culprit for osteoporosis. Indeed, the same mechanisms of oxidative defense (e.g., by the FoxO transcription

factors) work in bone cells as in other tissues. A beneficial effect of resveratrol and sirtuins on bone health might be linked to their antioxidant activity. On the other hand, estrogen (and androgen) deficiency reduces defense against oxidative stress in bone, and thus is a secondary factor in bone resorption etiology. The author advocates for a reappraisal of our traditional ideas about age-related osteoporosis; specifically, he proposes a paradigm shift from the "estrogen-centric" idea of the pathogenesis of osteoporosis to one emphasizing the general process of aging, similar to what occurs in other organs and tissues such as the ovaries, kidneys, or muscles. —DK

Other Studies of Potential Interest

Alves de Oliveira EC, Szejnfeld VL, Pereira da Silva N, Coelho Andrade LE, Heldan de Moura Castro C. Intermittent PTH1–34 causes DNA and chromosome breaks in osteoblastic and nonosteoblastic cells. *Calcif Tissue Int*. 2010 Jul 17. [Epub ahead of print] [Abstract]

Greenblatt MB, Shim JH, Zou W, Sitara D, Schweitzer M, Hu D, Lotinun S, Sano Y, Baron R, Park JM, Arthur S, Xie M, Schneider MD, Zhai B, Gygi S, Davis R, Glimcher LH. The p38 MAPK pathway is essential for skeletogenesis and bone homeostasis in mice. *J Clin Invest*. 2010 Jul 1;120(7):2457-73. [Abstract]

Lapunzina P, Aglan M, Temtamy S, Caparrós-Martín JA, Valencia M, Letón R, Martínez-Glez V, Elhossini R, Amr K, Vilaboa N, Ruiz-Perez VL. Identification of a frameshift mutation in Osterix in a patient with recessive osteogenesis imperfecta. *Am J Hum Genet*. 2010 Jul 9;87(1):110-4. [Abstract]

Lionikas A, Cheng R, Lim JE, Palmer AA, Blizard DA. Fine-mapping of muscle weight QTL in LG/J and SM/J intercrosses. *Physiol Genomics*. 2010 Jul 13. [Epub ahead of print] [Abstract]

Mantila Roosa SM, Liu Y, Turner CH. Gene expression patterns in bone following mechanical loading. *J Bone Miner Res*. 2010 Jul 23. [Epub ahead of print] [Abstract]

Söderström K, Stein E, Colmenero P, Purath U, Müller-Ladner U, de Matos CT, Tarner IH, Robinson WH, Engleman EG. Natural killer cells trigger osteoclastogenesis and bone destruction in arthritis. *Proc Natl Acad Sci U S A*. 2010 Jul 20;107(29):13028-33. [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.