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NOT TO BE MISSED

Clinical and Basic Research Papers – August 2004 Selections

Ego Seeman, Clinical Editor
Gordon J. Strewler, Editor

Bone Modeling and Remodeling

Guo X, Day TF, Jiang X, Garrett-Beal L, Topol L, Yang Y. Wnt/beta-catenin signaling is sufficient and necessary for synovial joint formation. *Genes Dev*. 2004 Oct 1;18(19):2404-17.

> *Wnt genes, including* Wnt4*,* Wnt14*, and* Wnt16*, are expressed in developing synovial joints, where beta-catenin and transcription activity is upregulated. Ectopic expression of an activated form of beta-catenin or Wnt14 in differentiating chondrocytes induces ectopic joint formation, whereas removal of beta-catenin in chondrocytes leads to joint fusion. The Wnt/beta-catenin signaling pathway induces synovial joint formation. —ES*

Perez-Amodio S, Beertsen W, Everts V. (Pre-)osteoclasts induce retraction of osteoblasts before their fusion to osteoclasts. *J Bone Miner Res*. 2004 Oct;19(10):1722-31.

> *Osteoblast precursors induce formation of osteoclasts. Osteoclast precursors modulate osteoblast activity, too. Mononuclear cells attach to osteoblasts, which retract forming cell-free areas invaded by the mononuclear cells that fuse forming osteoclast-like cells. Inhibition of matrix metalloproteinase activity reduced retraction of the osteoblasts. —ES*

Recker R, Lappe J, Davies KM, Heaney R. Bone remodeling increases substantially in the years after menopause and remains increased in older osteoporosis patients. *J Bone Miner Res*. 2004 Oct;19(10):1628-33.

> *Bone remodeling rates doubled from 0.13/year to 0.24/year across menopause and strangely tripled 13 years after menopause and remained elevated. Values were not higher in patients with osteoporosis than in controls. The continued increase in remodeling rate surprised me, but the lack of difference in remodeling rate between fracture cases and controls was not surprising. To consider patients with fragility caused by excessive bone loss as a homogenous group is not wise. —ES*

Physiology and Metabolism

Harvey KB, Donahue SW. Bending properties, porosity, and ash fraction of black bear (Ursus americanus) cortical bone are not compromised with aging despite annual periods of disuse. *J Biomech*. 2004 Oct;37(10):1513-20.

> *Black bears maintain bone formation during hibernation, although bone resorption is increased. Cortical bending strength, bending modulus, fracture energy, porosity, and ash fraction are not compromised with age, despite annual disuse. A fascinating model. How does this occur? —ES*

Treatment and Drug Effects

Giraudo E, Inoue M, Hanahan D. An amino-bisphosphonate targets MMP-9-expressing macrophages and angiogenesis to impair cervical carcinogenesis. *J Clin Invest*. 2004 Sep;114(5):623-33.

> *Antitumor effects of bisphosphonates have been previously reported, but this study describes a novel mechanism of bisphosphonate action. The bisphosphonate zoledronic acid inhibits cervical cancer progression in a mouse model of papilloma virus oncogene-induced carcinogenesis. The matrix metalloprotease MMP-9 is implicated in the pathway of zoledronate affects by experiments showing that macrophage numbers, macrophage expression of MMP-9, and recruitment of vascular endothelial growth factor are reduced by zoledronate and that effects of zoledronate resemble those of MMP-9 removal. —GJS*

Leonard MB, Feldman HI, Shults J, Zemel BS, Foster BJ, Stallings VA. Long-term, high-dose glucocorticoids and bone mineral content in childhood glucocorticoid-sensitive nephritic syndrome. *N Engl J Med*. 2004 Aug 26;351(9):868-75.

> *Cases and controls differed in the proportion of males, females, blacks, distribution by Tanner stage, body composition, and height. The age at puberty and rates of growth of upper and lower body segments varied by race and sex. Even small imbalances in these covariates may influence the data, independent of corticosteroids, because growth is so rapid. These design issues warrant a randomized trial before the inference that corticosteroids are safe in children can be made with confidence. Statistical "adjustments" can't do everything. —ES*

Schlienger RG, Kraenzlin ME, Jick SS, Meier CR. Use of beta-blockers and risk of fractures. *JAMA*. 2004 Sep 15;292(11):1326-32.

> *This is an important issue. There must be strength in 30,601 fracture cases and 120,819 controls. Fracture risk reduction was 23% for current beta-blocker use, 20% for current thiazide use, and 19% for combined current use, all statistically significant. Several studies support these findings, others don't. Seems odd that the fractures were mostly not the type conventionally regarded as fragility fractures (12,837 hand/lower arm and 4627 foot). Nothing like a randomized trial to settle the issue. —ES*

Welt CK, Chan JL, Bullen J, Murphy R, Smith P, DePaoli AM, Karalis A, Mantzoros CS. Recombinant human leptin in women with hypothalamic amenorrhea. *N Engl J Med*. 2004 Sep 2;351(10):987-97.

> *Disruptions in hypothalamic-gonadal function related to energy deficits are associated with low leptin. Recombinant leptin treatment increased mean luteinizing hormone (LH), LH pulse frequency, follicular number and diameter, ovarian volume, estradiol levels, and ovulatory cycles in some women. —ES*

Reviews, Editorials, and Perspectives

Hamrick MW. Leptin, bone mass, and the thrifty phenotype. *J Bone Miner Res*. 2004 Oct;19(10):1607-11.

Liu PY, Swerdloff RS, Veldhuis JD. The rationale, efficacy and safety of androgen therapy in older men: future research and current practice recommendations. *J Clin Endocrinol Metab*. 2004 Oct;89(10):4789-96.

Pors Nielsen S. The biological role of strontium. *Bone*. 2004 Sep;35(3):583-8.

Tomlinson JW, Walker EA, Bujalska IJ, Draper N, Lavery GG, Cooper MS, Hewison M, Stewart PM. 11{beta}-Hydroxysteroid Dehydrogenase Type 1: A Tissue-Specific Regulator of Glucocorticoid Response. *Endocr Rev*. 2004 Oct;25(5):831-866.

Uitterlinden AG, Fang Y, Van Meurs JB, Pols HA, Van Leeuwen JP. Genetics and biology of vitamin D receptor polymorphisms. *Gene*. 2004 Sep 1;338(2):143-56.

Other Studies of Potential Interest

Conigrave AD, Mun HC, Delbridge L, Quinn SJ, Wilkinson M, Brown EM. L-amino acids regulate parathyroid hormone secretion. *J Biol Chem.* 2004 Sep 10;279(37):38151-9.

Dai S, Hirayama T, Abbas S, Abu-Amer Y. The IkappaB kinase (IKK) inhibitor, NEMO-binding domain peptide, blocks osteoclastogenesis and bone erosion in inflammatory arthritis. *J Biol Chem.* 2004 Sep 3;279(36):37219-22.

Les CM, Spence CA, Vance JL, Christopherson GT, Patel B, Turner AS, Divine GW, Fyhrie DP. Determinants of ovine compact bone viscoelastic properties: effects of architecture, mineralization, and remodeling. *Bone*. 2004 Sep;35(3):729-38.

Rangaswami H, Bulbule A, Kundu GC. Nuclear factor-inducing kinase plays a crucial role in osteopontin-induced MAPK/IkappaBalpha kinase-dependent nuclear factor kappaB-mediated promatrix metalloproteinase-9 activation. *J Biol Chem.* 2004 Sep 10;279(37):38921-35.

Winkler DG, Yu C, Geoghegan JC, Ojala EW, Skonier JE, Shpektor D, Sutherland MK, Latham JA. Noggin and sclerostin bone morphogenetic protein antagonists form a mutually inhibitory complex. *J Biol Chem.* 2004 Aug 27;279(35):36293-8.

Wu BT, Su YH, Tsai MT, Wasserman SM, Topper JN, Yang RB. A novel secreted, cell-surface glycoprotein containing multiple epidermal growth factor-like repeats and one CUB domain is highly expressed in primary osteoblasts and bones. *J. Biol Chem.* 2004 Sep 3;279(36):37485-90.

Zamurovic N, Cappellen D, Rohner D, Susa M. Coordinated activation of notch, Wnt, and transforming growth factor-beta signaling pathways in bone morphogenic protein 2-induced osteogenesis. Notch target gene Hey1 inhibits mineralization and Runx2 transcriptional activity. *J Biol Chem.* 2004 Sep 3;279(36):37704-15.