**NOT TO BE MISSED**

Clinical and Basic Research Papers – February 2005 Selections

Ego Seeman, Clinical Editor  
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**Bone modeling and remodeling**


Expression of Wnt10b in marrow adipocytes, using the FABP4 promoter, reduces marrow adiposity and dramatically increases bone mass. The effects of ovariectomy on bone mass are markedly blunted by transgene expression. Conversely, Wnt10b-null mice have osteopenia. Wnt10b expression inhibits peroxisome proliferator-activated receptor γ (PPARγ), potentially redirecting mesenchymal cells into the osteoblast lineage, and reduces fat mass, thereby decreasing leptin levels; as well as signaling directly in osteoblasts through the canonical wnt pathway.—GJS


C/EBP transcription factors regulate adipocyte differentiation. Osteoblasts and adipocytes share a common pluripotent progenitor in marrow. C/EBP transcription factors were disrupted in osteoblast lineage cells by overexpressing a dominant negative C/EBP isoform. All transgenic lines showed evidence of osteopenia and decreased mineral apposition and bone formation rates, reduced COL1A1 and osteocalcin mRNA levels, and increased BSP mRNA, consistent with an inhibition of terminal osteoblast differentiation. C/EBP transcription factors may be important determinants of osteoblast function and bone mass. —ES

**Pathophysiology**


Conditioned medium from two tumors associated with oncogenic osteomalacia has high levels of fibroblast growth factor 7 (FGF7) and much lower levels of FGF23. Inhibition of phosphate transport by conditioned medium is blocked by neutralizing antibodies to FGF7. Thus, FGF7 may be a second phosphaturic member of the FGF family. Assays of FGF7 in blood will be necessary to prove the point. —GJS


The protein kinase Rsk2 was recently shown to be required for osteoblast function (*Yang, X. et al. Cell, 117:387-398*). Here it is shown that Rsk2-null mice have osteopenia and
mild osteomalacia. Phex is absent from cortical bone, but phosphate-wasting does not occur. Osteosarcomas are induced in Rsk2(-/-) mice by a c-fos transgene, but grow very slowly. Rsk2 affects osteoblast matrix synthesis, mineralization, and osteosarcoma formation. —GJS

Treatment and Drug Effects


The adipocyte receptor PPARγ directs mesenchymal precursors preferentially into the adipocyte pathway. Treatment of Swiss Webster mice with the PPARγ agonist rosiglitizone reduces bone mass. This is associated with reductions in bone formation rate and wall thickness, without effects on osteoblast apoptosis. Negative rosiglitizone effects on osteoblasts have also been reported by others (Rzonca SO et al. Endocrinology 2004 145:401–406; Soroceanu et al. J Endocrinol 2004 183:203–216). Does diabetes treatment with thiazolidinediones have adverse effects on bone? —GJS


Antiresorptives reduce the remodeling rate, progression of cortical thinning and porosity, trabecular thinning, and loss of connectivity. The drugs allow more time for secondary mineralization, and thus, increased tissue mineral density. If treatment is prolonged, there is concern that tissue mineral density and homogeneity may increase “too much”, which may predispose to micro-damage production and progression, whereas reduced targeted remodeling may reduce removal of microdamage. There is evidence that greater remodeling suppression is associated with more microdamage; however evidence that reduced remodeling increases tissue mineral density which increases microdamage that leads to loss of antifracture efficacy, is not available. In this study, nine patients sustained spontaneous nonspinal fracture while receiving alendronate; while six of the patients had delayed or absent fracture healing. Histomorphometry showed suppressed bone formation. Matrix synthesis was markedly diminished, with absence of double-tetracycline label and absent or reduced single-tetracycline label in all patients. Whether there is a causal relationship between fracture and alendronate therapy is not proven in this study. —E


Greater suppression of remodeling, and thus greater gains in BMD, were reported with alendronate than risedronate. The unstated (but implied) inference is that the 1% to 2% difference in BMD between the drugs or the difference in remodeling suppression (50% vs. 35%, respectively) translates into fewer fracture events. If one drug is more “potent” than another, however, does this drug more greatly reduce activation frequency, reduce the volume of bone resorbed, increase the volume of bone deposited in each basic multicellular unit, or more greatly increase the degree of secondary mineralization? From these mechanistic differences, does alendronate more greatly reduce the appearance of cortical porosity; reduce the rate of progression of cortical thinning, trabecular thinning, and loss of connectivity; or more greatly reduce the removal of microdamage and...
increase microdamage production? Some features will be advantageous, others may be disadvantageous. It is therefore not possible to imply inferences about the relative antifracture efficacy of drugs, unless there is evidence of how many fewer patients need to be treated with one drug than another. Read more. —ES


Previous studies have shown a positive correlation between hip fracture and plasma homocysteine levels (N Engl J Med. 2004;350:2033–41; N Engl J Med. 2004;350:2042–49). Stroke patients are at high risk of hip fracture. Japanese patients with stroke (n = 628) were randomized to placebo or treatment with folic acid and mecobalamin to reduce homocysteine levels. Their homocysteine levels were high and fell with treatment. During two years of follow-up, 10 treated patients had a hip fracture, compared with 42 placebo-treated patients (adjusted relative risk, 0.20; 95% confidence interval, 0.08–0.50). —GJS

Reviews, Perspectives, and Editorials


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McLachlan RI, Allan CA. Defining the prevalence and incidence of androgen deficiency in aging men: where are the goal posts? *J Clin Endocrinol Metab.* 2004 Dec;89(12):5916-9. [Full Text]


Roth GS, Mattison JA, Ottinger MA, Chachich ME, Lane MA, Ingram DK. Aging in rhesus monkeys: relevance to human health interventions. *Science.* 2004 Sep 3;305(5689):1423-6. [Abstract] [Full Text]


Simkin PA. Hydraulically loaded trabeculae may serve as springs within the normal femoral head. *Arthritis Rheum.* 2004 Oct;50(10):3068-75. [Abstract]


**Other Studies of Potential Interest**


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