**NOT TO BE MISSED**

Clinical and Basic Research Papers – September 2005 Selections

Ego Seeman, Clinical Editor
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Bone Modeling and Remodeling


Dickkopf (Dkk) proteins antagonize Wnt signaling and can thereby block osteoblast proliferation. These two papers report that, unexpectedly, Dkk has an inhibitory effect on terminal osteoblast differentiation. Li et al. found that Dkk2-/- mice were osteopenic, with reduced osteoblast number and bone formation rates. Dkk2 is expressed in differentiating osteoblasts, its expression is enhanced by Wnt7b, and its expression in Dkk2-null osteoblasts rescues terminal differentiation. van der Horst et al. also found that Dkk1 and Dkk2 expression were upregulated in differentiating osteoblast lineage cells and that knockdown of Dkk2 with siRNA inhibited terminal differentiation and mineralization. Thus, Dkk may have opposite effects on early and late osteoblast development, complicating development of Dkk antagonists for treatment of osteoporosis. —GJS


PPARγ is converted to an antagonist of NFkB signaling in RAW264.7 macrophages by ligand-dependent SUMOylation (covalent modification at a lysine by a small ubiquitin-like modifier [SUMO] protein), which directs PPARγ to the promoters of NFkB-responsive genes, where it acts as a transcriptional repressor. This may offer a molecular explanation for the previously reported inhibition of osteoclast generation by PPAR agonists (Mbalaviele G, et al. J Biol Chem. 2000 May 12;275(19):14388-93 [Abstract]). —GJS

Epidemiology


Osteoporosis is known to be under treated and under diagnosed but what is not well appreciated is that more than one-half of women with incident fractures have...
osteopenia or normal BMD, not osteoporosis. Identifying these women that are at risk for fracture is a major challenge. The authors address this by reporting that among osteopenic women, age, prior fracture, and high remodeling markers independently predict fracture risk. A majority of incident fractures occurred in those with prior fractures, or bone alkaline phosphatase in the highest quartile. The 10-year probability of fracture in osteopenic women was 26% if at least one predictor was present. —ES

Treatment and Drug Effects


Prophylactic total thyroidectomy with parathyroid transplantation and lymph node dissection prevents the development of medullary thyroid carcinoma for at least five years in most patients with mutations in the RET oncogene that cause multiple endocrine neoplasia type 2A. Results appear better when thyroidectomy is carried out before age eight rather than at later ages (ages 9-19). —GJS

The three studies below are presented because of their simplicity and powerful messages. There is no substitute for good study design. Large costly studies can be avoided in some cases in which high risk, and often highly informative, patients can be studied and retention of subjects is achieved.


In a random and prospective study, AD patients were assigned to sunlight exposure (n = 132) or deprivation (n = 132) and followed for 1 year. The exposed group (3615 minutes/year) had fewer fractures. Eleven patients sustained fractures in the sunlight-deprived group, and three fractures occurred among the sunlight-exposed group (p = 0.0362; odds ratio = 3.7). —ES


Of 280 male patients 65 years or older with strokes, 140 received 2.5 mg risedronate and the other 140 received placebo daily. Ten patients sustained hip fractures in the placebo group, and 2 in the risedronate group, RR = 0.19 (0.04-0.89). —ES


500 women with Alzheimer disease were randomly assigned to 2.5 mg risedronate or a placebo plus1000 IU of ergocalciferol and 1200 mg of calcium for 18 months. At baseline, patients of both groups had 25-hydroxyvitamin D deficiency with hyperparathyroidism. Vertebral fractures occurred in 29 patients (24 hip fractures) in the control group and 8 patients (5 hip fractures) in the risedronate group, RR = 0.28 (0.13-0.59). —ES
Reviews, Perspectives, and Editorials


◆ de Crombrugghe B. Osteoblasts clock in for their day job. Cell. 2005 Sep 9;122(5):651-3. [Abstract]


Other Studies of Potential Interest


◆ Day TF, Guo X, Garrett-Beal L, Yang Y. Wnt/beta-catenin signaling in mesenchymal progenitors controls osteoblast and chondrocyte differentiation during vertebrate skeletogenesis. Dev Cell. 2005 May;8(5):739-50. [Abstract]


