NOT TO BE MISSED

Clinical and Basic Research Papers – March 2005 Selections

Ego Seeman, Clinical Editor
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Bone Modeling and Remodeling


The Karsenty group has previously focused on central control of bone formation; they now report that leptin stimulates bone resorption. The signaling pathway is the β-adrenergic nervous system and the cellular mechanism is activation of RANKL gene transcription by cAMP-dependent phosphorylation of activating transcription factor (ATF). Ovariectomy does not induce bone loss in β2-adrenergic receptor-null mice, suggesting that menopausal bone loss is centrally mediated – this will be controversial! An inhibitory arm of the central controller of bone resorption is also identified. CART (cocaine and amphetamine regulated transcript), a leptin-dependent hypothalamic neuropeptide, is the central mediator of this arm, but the peripheral effector is unknown. —GJS


Rho GTPases regulate the actin cytoskeleton, and vav proteins are guanine nucleotide exchange factors that enhance their actions. Removal of vav3 from mice produces a high bone mass phenotype in which osteoclast number is normal but bone resorption is decreased, and mice are protected from bone loss stimulated by PTH or RANKL. Signals by M-CSF and αvβ3 integrin to induce osteoclast polarization, spreading, and resorption are disrupted by removal of vav3. The signaling pathway involves the Syk tyrosine kinase upstream of Rac and vav3. —GJS


Interleukin 1 (IL-1) receptor-associated kinase M (IRAK-M) lacks kinase activity and functions as an endogenous dominant negative regulator of IL-1 signaling. Removal of the Irak-m gene from mice leads to increased osteoclastic bone resorption and severe osteoporosis. The detailed molecular basis of the increase in osteoclast activity is still cloudy, but the paper points up once more the need to understand more fully the relationships of RANKL, TNF-α and IL-1 in osteoclastogenesis. —GJS

Yoon BS, Ovchinnikov DA, Yoshii I, Mishina Y, Behringer RR, Lyons KM. Bmpr1a and Bmpr1b have overlapping functions and are essential for chondrogenesis in vivo. Proc Natl Acad Sci U S A. 2005 Apr 5;102(14):5062-7. [Abstract] [Full Text]

Although it is clear that bone morphogenetic proteins (BMPs) can induce chondrogenesis, removal of their individual receptors has a relatively mild phenotype.
Removal of both Bmpr1a and Bmpr1b from chondrocytes, however, eliminates most endochondral skeletal elements. The remainder of the skeleton is rudimentary, but patterning is intact. As suspected, no BMP, no cartilage. —GJS

Diagnosis

Abrahamsen B, Andersen I, Christensen SS, Madsen JS, Brixen K. Utility of testing for monoclonal bands in serum of patients with suspected osteoporosis: retrospective, cross sectional study. BMJ. 2005 Apr 9;330(7495):818. [Abstract] [Full Text]

Of 799 patients, 4.9% (18 of 366) with osteoporosis and 2.2% (nine of 408) without osteoporosis had a serum M band. Myeloma was diagnosed in three patients with osteoporosis (absolute risk, 0.8%). Relative risk of myeloma was 75 in patients presenting with osteoporosis. The M band had a positive predictive value of 17.6%. For each case diagnosed, 122 electrophoreses were carried out. All patients with multiple myeloma had a history of fracture. Monoclonal gammopathy of undetermined significance was diagnosed in 13 patients (3.6%) with osteoporosis and eight patients (2.0%) with normal BMD or osteopenia. Patients presenting with osteoporosis should be tested for M component in serum, because one in 20 patients with newly diagnosed osteoporosis had myeloma or monoclonal gammopathy of undetermined significance. —ES


Vertebral fractures are common, they predict further fractures and they are accompanied by increased morbidity and mortality. Despite this, patients with fractures remain underdiagnosed and undertreated. Of 2451 women, 789 (32%) had at least one vertebral fracture. A false-negative rate of 34% was observed because of adjudicated discrepancies (N = 350) between local and central readings caused by failed detection (68%) or equivocal terminology in the local report (32%). Underdiagnosis was observed in all regions (false-negatives: North America, 45.2%; Latin America, 46.5%; and Europe/South Africa/Australia, 29.5%). The false-positive rate was 5% globally. Underdiagnosis of vertebral fracture is a worldwide problem. —ES

Epidemiology


Osteoporosis in men is a neglected area of research. In this prospective case-cohort control study, the authors reported that, as in women, the combined use of densitometry and biochemical measures of bone remodeling assists in defining high-risk men to be targeted for therapy. In 151 elderly men followed for 6.3 years, high resorption, as assessed by serum cross-linked carboxyterminal telopeptide of type 1 collagen (S-ICTP), was independently associated with increased risk of fracture. Men in the highest quartile of S-ICTP had a 2.8-fold increased risk of fracture, compared with those in the lowest quartile. Incidence of fracture was 10 times higher in men with high S-ICTP and low femoral neck bone mineral density (FNBMD), compared with men with low S-ICTP and high FNBMD. Of the fracture risk in the population, 20% was attributable to high S-ICTP and low FNBMD, and S-ICTP contributed 17% to this increased risk. —ES

The authors reported that 12 of 266 patients (4.5%) with osteoporosis and six of 574 patients (1.0%) without osteoporosis tested positive by serology for celiac disease. Nine patients with osteoporosis and one patient without osteoporosis had positive biopsies. The prevalence of biopsy-proven celiac disease was 3.4% in the osteoporotic population and 0.2% in the nonosteoporotic population. All biopsy-positive patients tested positive by anti-tissue transglutaminase and anti-endomysial antibody. The prevalence of celiac disease in patients with osteoporosis (3.4%) is higher than that in patients without osteoporosis (0.2%) and justifies serologic screening for celiac disease in all patients with osteoporosis. —ES

Reviews, Perspectives, and Editorials


Other Studies of Potential Interest


