NOT TO BE MISSED

Clinical and Basic Research Papers – January 2005 Selections

Ego Seeman, Clinical Editor
Gordon J. Strewler, Editor

Epidemiology


Whether exercise undertaken during growth reduces fractures in old age is unknown. In 55 young male athletes retired for five years, BMD was decreased, but remained higher than in controls. In 400 older and now retired athletes, fewer had fragility fractures than did controls (2.0% vs. 4.2%, respectively) and fewer had distal radius fractures (0.75% vs. 2.5%, respectively). —ES

Genetics


Associations between single nucleotide polymorphisms (SNPs) in low-density lipoprotein receptor-related protein 5 (LRP5) and hip and spine BMD were detected in 1301 premenopausal women, but the genotyped SNPs accounted for 0.8% of the variation in femoral neck BMD and 1.1% of the variation in spine BMD. —ES

Pathophysiology


In one family, tumoral calcinosis with hyperphosphatemia was associated with a missense mutation (S71G) in fibroblast growth factor 23 (FGF23). Full-length mutant FGF23 accumulates in the Golgi; inactive C-terminal fragments are secreted in vitro and accumulate in serum. The predominant form of familial tumoral calcinosis was recently associated with mutations in the GALNT3 gene, which encodes a Golgi-based galactosyl transferase; it seems likely that improper glycosylation of FGF23 is the explanation for hyperphosphatemia in both syndromes. —GJS


How menin functions as a tumor suppressor in multiple endocrine neoplasia type 1 (MEN1) has been uncertain. Menin can activate transcription via binding to mixed lineage leukemia (MLL) family proteins in a histone methyltransferase complex. This paper shows that menin activates transcription of the cyclin-dependent kinase inhibitors p27Kip1 and
p18Ink4c by recruiting MLL to their promoters. Expression of p27Kip1 is decreased in tumors in MEN1 patients, compared with normal neuroendocrine tissues. The results offer a plausible explanation of the proliferative advantage that is conferred on neuroendocrine cells by inactivating menin mutations. —GJS


Interleukin 1 (IL-1) and tumor necrosis factor α (TNF-α) each plays a role in osteolysis associated with inflammatory disorders, such as arthritis. This paper reports that much of the induction of osteoclastogenesis by TNF-α is mediated by IL-1. TNF-α induces the expression of both IL-1 and its receptor, IL-1R1, in stromal cells and osteoclast precursors. In the absence of IL-1R1, osteoclast formation by TNF-α is abolished in vitro and reduced by about 50% in calvaria of intact mice. IL-1 acts by inducing receptor activator of NF-κB ligand (RANKL) expression in stromal cells, and in the presence of permissive levels of RANKL, also stimulates macrophages directly to form osteoclasts. —GJS

Physiology


Hypogonadism results in bone loss in men, but whether this is the result of androgen or estrogen deficiency (or both) is unclear. In 80 Korean males (aged 42-70 years), there was a negative correlation between serum osteoprotegerin (OPG) and spine BMD. Only serum estradiol, not serum testosterone, predicted serum OPG or receptor activator of NF-κB ligand (RANKL) levels. The circulating OPG-RANKL system is likely to be associated with bone metabolism in males and may mediate the effects of estradiol in men. —ES


The epidermal growth factor (EGF) family member amphiregulin was identified as a PTH-responsive osteoblast gene in profiling experiments. Here, it is shown that PTH induces the expression of amphiregulin in osteoblasts and that amphiregulin increases the proliferation and inhibits the differentiation of preosteoblasts. Removal of the amphiregulin gene causes a moderate reduction in trabecular number and thickness. It is proposed that amphiregulin functions as a feedback regulator of osteoblast formation. —GJS


In the rat, 1α,25-dihydroxyvitamin D3 increases the serum level of fibroblast growth factor 23 (FGF23), and thyroparathyroidectomy plus manipulation of diet shows this to be independent of PTH or changes in serum phosphate. A high phosphate intake also
increases FGF23 levels in 5/6-nephrectomized rats. Thus, FGF23 undergoes feedback regulation by both of its downstream targets, phosphate and 1α,25-dihydroxyvitamin D₃.

—GJS

Treatment and Drug Effects


Sex steroids are antiapoptotic on osteoblasts/osteocytes, but proapoptotic on osteoclasts; these effects involve activation of the extracellular signal-regulated kinases (ERKs). In contrast to its transient effect on ERK phosphorylation in osteocytes, estradiol-induced ERK phosphorylation in osteoclasts was sustained. Conversion of sustained to transient ERK phosphorylation abrogated the proapoptotic effect on osteoclasts. Prolongation of ERK activation in osteocytes converted the antiapoptotic effect of estradiol to a proapoptotic one. The kinetics of ERK phosphorylation and the length of time that phospho-ERKs are retained in the nucleus are responsible for the pro- versus antiapoptotic effects of estrogen on different cell types. —ES


The results of this one-year randomized controlled clinical trial indicate that chronic treatment of primary hyperparathyroidism with a calcimimetic agent is feasible. Curiously, markers of bone turnover are increased, not decreased, in treated patients. Is this further evidence that the calcium receptor can regulate bone turnover in a tissue- or cell-autonomous fashion? —GJS


Hypogonadism is a risk factor of bone loss and bone fragility, and this study gives some idea of the increment of risk in men with prostate cancer. Of 50,613 men diagnosed with this condition, those surviving at least five years -- 19.4% of those receiving androgen deprivation therapy -- had a fracture, compared with 12.6% of those not receiving androgen deprivation therapy. Controls without prostate cancer or androgen deprivation therapy would have been informative. —ES

Reviews, Perspectives, and Editorials


❖ Holick MF. Stay tuned to PXR: an orphan actor that may not be D-structive only to bone. J Clin Invest. 2005 Jan;115(1):32-4. [Abstract] [Full Text]

Riggs BL, Parfitt AM. Drugs used to treat osteoporosis: the critical need for a uniform nomenclature based on their action on bone remodeling. *J Bone Miner Res.* 2005 Feb;20(2):177-84. [Abstract]


**Other Studies of Potential Interest**


Andrew T, Antioniades L, Scurrah KJ, Macgregor AJ, Spector TD. Risk of wrist fracture in women is heritable and is influenced by genes that are largely independent of those influencing BMD. *J Bone Miner Res.* 2005 Jan;20(1):67-74. [Abstract]


