Bergot C, Wu Y, Jolivet E, Zhou LQ, Laredo JD, Bousson V. The degree and distribution of cortical bone mineralization in the human femoral shaft change with age and sex in a microradiographic study. Bone. 2009 Sep;45(3):435-42. [Abstract] Berkot et al. report that, in cortical bone from 193 femurs (from 99 females and 94 males), the degree of tissue mineralization (Tt.DMB-Al) decreased with age in females but not in males. Tt.DMB-Al was higher in females than males until 50 years of age but was lower in elderly females than elderly males. The first DMB-Al quartiles in osteons and interstitial tissue were not different between males and females, but the third quartile differed with greater heterogeneity in females than males. —ES

Brouwers JE, Lambers FM, van Rietbergen B, Ito K, Huiskes R. Comparison of bone loss induced by ovariectomy and neurectomy in rats analyzed by in vivo micro-CT. J Orthop Res. 2009 Nov;27(11):1521-7. [Abstract] This study compared bone loss in ovariectomized rats to bone loss in neurectomized (disuse) rats. At the same amount of induced bone loss, disuse led to more deteriorated bone structure and mechanical properties than estrogen deficiency. —DGL

Histing T, Garcia P, Matthys R, Leidinger M, Holstein JH, Kristen A, Pohlemann T, Menger MD. An internal locking plate to study intramembranous bone healing in a mouse femur fracture model. J Orthop Res. 2009 Sep 24. [Epub ahead of print] [Abstract] There has been concern that bisphosphonates and other anticatabolics, through osteoclast inhibition, could inhibit “primary bone healing”. Primary bone healing is defined as exclusively lamellar bone formation through the Haversian system in humans or resorption cavities in mice. Secondary bone healing is either intramembranous via woven bone or endochondral in nature. If primary bone healing exists, it is osteoclast-dependent, whereas secondary bone healing is not. These authors could find no evidence of primary bone healing when femoral fractures were treated with locked plates in mice. Thus treatment with this type of locking plate does not require the presence or function of osteoclasts (although remodeling does). —DGL

Manske SL, Boyd SK, Zernicke RF. Muscle and bone follow similar temporal patterns of recovery from muscle-induced disuse due to botulinum toxin injection. Bone. 2009 Oct 20. [Epub ahead of print] [Abstract]
The authors hypothesized that muscle cross-sectional area would return to baseline levels sooner than bone properties following botulinum toxin injection. They found that both returned similarly and that even small improvements in muscle function might be important. Return of BSA was not necessary for return of bone mass. —DGL


Heterotopic ossification (HO) is a large clinical problem, especially post-surgery and post-head injury. Most HO occurs via an endochondral pathway. This group confirms that BMP-mediated HO occurs via an endochondral pathway, and that a specific and potent retinoic acid receptor (RAR) alpha agonist suppresses ectopic bone formation. Side effect profiles are unknown, but as the current treatment is radiotherapy, a pharmaceutical-based treatment would be helpful. Intramembranous ossification seems unharmed, which is the major mode of healing in joint replacement surgery. —DGL


Extracorporeal shock wave (ESW) therapy has been suggested as a treatment for most things. Here its possible use in osteoporosis is examined. Although BV/TV was higher in the ESW group than controls in ovariectomized animals, there was still a 50% reduction in BV/TV over time, an unsatisfactory result. However, if ESW could be shown to affect cortical bone, its use in conjunction with therapies that protect trabecular but not long bone suites could be explored. —DGL

Clinical Studies and Drug Effects


A meta-analysis of 8 randomized controlled trials (n=2426) of vitamin D suggests high dose vitamin D reduced fall risk by 19% (n=1921, 7 trials). Achieved serum 25(OH)D of 60 nmol/l or more was associated with a 23% fall reduction. Fewer falls were not observed with low dose vitamin D or serum 25 hydroxyvitamin D <60 nmol/l. Two randomized controlled trials (n=624) of active vitamin D reduced fall risk by 22%. —ES


Ma et al. studied long-term leisure time physical activity (LTPA) in twin pairs discordant for LTPA for ~ 30 years in 16 middle-aged (50-74 years of age) same-sex twin pairs (7 monozygotic (MZ) and 9 dizygotic (DZ) pairs). Active members of MZ twin pairs had larger cortical bone cross-sectional area (intrapair difference: 8%, p = 0.006), thicker cortex (12%, p = 0.003), and greater moment of inertia (I(max), 20%, p = 0.024) at the tibia shaft than their inactive co-twins. At the distal tibia, trabecular BMD (12%, p = 0.050) and compressive strength index (18%, p = 0.038) were higher in the active MZ pair members than their inactive co-twins. —ES

This case report of high bone turnover osteoporosis in a young man with auto-immune hypothyroidism and celiac disease identifies a new pathophysiological mechanism of rapid bone loss: auto-antibodies against osteoprotegerin. Of note is the excellent clinical response to zoledronic acid, indicating that bone resorption due to excessive RANKL activity can also be controlled by bisphosphonates, although in this case denosumab, i.e., the RANKL antagonist, would have been a more specifically targeted therapy. —SF


Among 782 men followed for 10 years, 182 non-survivors were older, had more co-morbidities and lower physical performance. The lowest quartile of 25OHD predicted mortality (HR = 1.44, 1.03-2.03) for the first 3 years. 17beta-E(2) predicted mortality after the third year (HR = 1.21 per 1 SD increase, 1.09-1.35). Low 25OHD may reflect poor health status; whether this is causal requires further study. —ES

**Genetics**


Many studies have reported a strong association between osteoporosis and CVD, particularly the inverse relationship between low BMD and aortic calcifications. Bone fragility is also increased among diabetic patients. Yet the molecular determinants of this relationship remain unknown. This genetic association study in 920 European Americans from 374 families with type 2 diabetes provides evidence for an inverse association of 6 genotypes of BMP7 with BMD and vascular calcifications (assessed from CT scan images). —SF


This study compared dendritic cell (DC)-derived osteoclasts to monocyte-derived osteoclasts by transcriptomic profiling, and established DCs as a new osteoclast precursor able to generate osteoclasts more efficiently than monocytes. The results suggest that DCs can be used as target cells for functional studies for osteoclastogenesis. —HWD


Digging deeper into the sea of genetic variants associated with BMD...these two studies are both based on the merging of 5 cohort studies in which GWAS for osteoporosis traits had previously been reported. A greater number of subjects together, i.e., close to 19,000 here, and a meta-analytical approach means more power to detect associations between SNPs and the traits of interest. Thus the first study, a hypothesis-free approach, identifies a substantial number of new loci (15 for LS BMD, 13 for FN BMD), in addition to confirming previous ones (such as LRP5, ESR1, and the RANKL/OPG/RANK pathway). These SNPs together still explain less than 3% of BMD variance when applied to one of the study populations, and result in a minimally increased risk of vertebral, but not non-vertebral fractures. The second study focuses on a very large number of SNPs marking 150 candidate genes for osteoporosis. Very few (9) genes were confirmed to be associated with BMD and/or fractures (all in the list of genes by GWAS reported above), and some famous candidates were dismissed, such as VDR and MTHFR. So...much ado about...nothing? —SF

**Molecular and Cell Biology**


This study shows that the integrin α5 subunit (ITGA5), a fibronectin receptor, mediates osteoblast differentiation induced by dexamethasone in adult hMSCs. Using an anti-ITGA5 monoclonal antibody (SNAKA51) that primes and stimulates α5β1 integrin and promotes cell adhesion in fibroblasts, markers of osteoblastic differentiation (such as RUNX2 and ALP) were induced from MSCs, providing therapeutic potential for the induction of osteoblastogenesis by targeting ITGA5. —SF


TNF can induce osteoclast formation directly from osteoclast precursors (OCPs), but fewer osteoclasts are formed by TNF than by RANKL. TNF increases inhibitory NF-kB p100 (NF-kB2). NIK enhances proteasomal degradation of NF-kB p100, and TRAF3 inhibits NIK activity. The authors demonstrate that TNF enhances the expression of TRAF3 which increases NF-kB p100 in OCPs, and that TNF robustly induces osteoclast formation in RANKL(-/-) and RANK(-/-) mice when they also lack NF-kB p100, suggesting a role for NF-kB p100 in limiting bone resorption under TNF excess such as in RA. Thus, TRAF3 or NF-kB p100 can become a new therapeutic target in inflammation-induced bone loss. —TM
Two truly remarkable studies bringing some new insight into the molecular/intracellular mechanisms of action of PTH. The first study shows that the anabolic actions of PTH in bone are severely impaired in both growing and adult ovariectomized mice lacking bone-related activating transcription factor 4 (ATF4), and that PTH stimulates expression of osterix, a critical transcription factor for osteoblast differentiation, through the binding of ATF4 to the osterix promoter. The second study demonstrates that PTH exerts effects on epigenetic regulation of gene expression, i.e., induces demethylation of the cytochrome p450 27B1 (CYP27B1) gene, the final enzyme in vitamin D biosynthesis, in proximal kidney tubules. —SF

Pathophysiology

The authors show that two distinct metalloproteinases, ADAMTS1 and MMP1, in breast cancer cells orchestrate a paracrine signaling cascade to enhance osteolytic bone metastasis. These metalloproteinases enhance proteolytic release of membrane-bound EGF-like growth factors from tumor cells, which suppress OPG expression in osteoblasts to potentiate osteoclastic bone resorption. Thus, these metalloproteinases in tumor cells can become new therapeutic targets against bone metastasis of breast cancer. —TM

Reviews, Perspectives and Editorials

A truly complete review, which also takes into account frailty, not only bone fragility, and interventions to prevent falls. —SF

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Other Studies of Potential Interest


**Conflict of Interest:** Dr. Ferrari reports that he receives research support from Amgen and is an advisory committee member and lectures occasionally at conference symposia for Merck Sharp & Dohme, the Alliance for Better Bone Health (sanofi aventis/P&G), Amgen, Eli Lilly (Switzerland), Servier (Switzerland), and Novartis (Switzerland). Dr. Little reports that he receives royalties, research funds and consultancy fees from Novartis Pharma, as well as research support from Stryker Biotech. Dr. Seeman reports that he is an advisory committee member for sanofi-aventis, Eli Lilly, Merck Sharp & Dohme, Novartis, and Servier, and that he lectures occasionally at conference symposia for those companies. Dr. Matsumoto and Dr. Deng report no conflicts of interest.