
Bone remodeling is under β-adrenergic control. Low (0.1 mg/kg/day), medium (5 mg/kg/day) or high (20 mg/kg/day) doses of propranolol were given 5 days per week for 10 weeks in ovariectomized (OVX) rats. The low dose prevented OVX-induced bone loss by increasing bone formation (+30%) and decreasing bone resorption (-52% of osteoclast surface). Consequently, rats receiving 0.1 mg/kg/day of propranolol displayed higher stress (+27%), intrinsic energy (+28.7%) and Young's Modulus in compression, compared to placebo. No significant effects on heart hemodynamic parameters were found. Medium and high doses of propranolol had a negative effect on heart functions but no protective effects on bone mass. These results suggest that low doses of β-blockers may have a therapeutic utility. —ES


After previously optimizing the amount of zoledronic acid in a polymer through in vitro assays, zoledronic acid-coated K wires were used to fixate femoral fractures. Increases in radiographic scores and mechanical properties without any deficit in healing were noted with zoledronic acid-coated K wires as compared to polymer-coated or uncoated controls. In this model, local dosing was feasible. —DGL


This study evaluated the impact of oral calcitonin on bone collagen maturation (the ratio between degradation products of newly synthesized C-telopeptides of type I collagen (non-isomerized ααCTX) and mature isomerized ββCTX) in 168 postmenopausal women treated with placebo, 0.15, 0.4, 1, or 2.5 mg of calcitonin per day. Calcitonin dose-dependently inhibited resorption but the ααCTX to ββCTX ratio remained unchanged, in contrast to other anti-resorptive therapies. —ES
Clinical Studies and Drug Effects


Further evidence that in the elderly, displaced intracapsular hip fractures are best treated with arthroplasty in a real-world setting. —DGL


Although the BONE RCT showed significant reduction of vertebral fractures in postmenopausal women receiving daily ibandronate, direct evidence of an effect on non-vertebral and specifically femoral neck fractures is lacking. The present study used QCT and DXA, and finite element analysis (FEA) of QCT data and HSA of DXA data, to evaluate structural effects of ibandronate at the hip and spine. This small-scale, randomized, placebo-controlled study in postmenopausal women with T-scores below -2 provides indirect and encouraging results for a potentially bone-strengthening effect of monthly oral ibandronate, in particular at the femoral neck. FEA indeed indicated 5.9% and 4.1% greater femoral strength and strength-to-density ratio, respectively, in IBN vs PBO, that is a maintenance of estimated bone strength in treated subjects, whereas a significant loss occurred among PBO subjects. Statistical analysis was performed by the sponsor (GSK). —SF


In this study, patients who had undergone vertebroplasty/kyphoplasty had a greater risk of new vertebral compression fractures (VCFs) compared to patients with prior VCFs who did not undergo either procedure. —DGL


This study of a large Medicare cohort shows that operation for non-union is rare (0.4%) but the relative risk is doubled after exposure to bisphosphonates. This association does not equal causation, but gives further pause for thought. The diaphyseal nature of humerus fractures may be a different environment from that of hip fractures, where the administration of zoledronic acid did not significantly increase non-union. Confirmation from other databases is required, as is further research on the timing of administration and the mechanism. —DGL
Genetics


LRP5 has received much attention from geneticists as an important candidate gene for osteoporosis-related phenotypes, but some studies have reported inconsistent results. The work presented here helps to clarify this situation by providing consistent evidence for the importance of LRP5 to bone. —HWD


Numerous quantitative trait loci (QTLs) affecting bone traits have been identified in the mouse, however, few of the underlying genes have been discovered. This study introduces a novel approach that integrates multiple lines of evidence to pinpoint promising candidate genes in plausible QTLs. The approach includes linkage analysis, expression QTL (eQTL) mapping, causality modeling and genetic association in outbred mice. Application of this method to C57BL/6J x C3H/HeJ (BXH) F2 mice provides strong support for Wnt9a, Rasd1 or both underlying the Bmd11 QTL. This study proposes that integration of multiple genetic and genomic data sets can substantially improve the efficiency of QTL fine-mapping and candidate gene identification. —HWD


Levels of vitamin B12 have been implicated in a number of chronic disorders, from anemia to osteoporosis. The common view is that insufficient intake and/or gastrointestinal malabsorption are the cause of vitamin B12 deficiency. Through genome-wide association study (GWAS) looking at 500k polymorphic markers in 1658 women and replication in a thousand women from the Nurse's Health Study, the authors identified a non-synonymous (coding) SNP in the gene FUT2 coding for α1,2-fucosyltransferase, which was associated with plasma vitamin B12. The proposed mechanism is that FUT2 alleles influence the attachment of H. pylori to the gastric mucosa, leading to gastritis, atrophy, and deficiency in the secretion of intrinsic factor. This study therefore beautifully illustrates the strength of hypothesis-free approaches such as GWAS to identify previously unsuspected genetic mechanisms for interindividual variations in common traits. It also shows its current limitations by the lack of analysis of FUT2 interactions with B12 intake. —SF


Mutations in NPT2a and NPT2c have been identified as causes for hereditary hypophosphatemic rickets with nephro lithiasis, with increased serum 1,25(OH)2D and absorptive hypercalciuria. However, most patients with renal phosphate leak with hypercalciuria and nephrolithiasis do not carry these mutations. The authors sequenced the sodium-hydrogen exchanger regulatory factor 1 (NHERF1) gene in patients with low
TmP/GFR and nephrolithiasis or bone demineralization, and identified 3 distinct mutations in 7 patients. NHERF1 is a PDZ-domain protein that interacts with the C-terminus of NPT2a and 2c, and plays an important role in the trafficking of these transporters. NHERF1 also interacts with the PTH type 1 receptor. Although serum PTH levels were normal in these patients, they had increased urinary cAMP, suggesting that responsiveness to PTH is increased by the mutation in NHERF1, causing hyperphosphaturia with hypophosphatemia, increased serum 1,25(OH)2D and hypercalciuria. —TM


This paper reports the first GWAS of hip bone size (BS), one of the key measurable risk factors for hip fractures (HF). Out of the studied 380,000 SNPs genotyped in 1,000 Caucasians, the PLCL1 (phospholipase c-like 1) gene had four SNPs associated with hip BS at, or approaching, a genomewide significance level. A SNP of the PLCL1 gene achieved a p value of 7.66×10^-3 (odds ratio = 0.26) for association with HF in a Chinese sample. The biological relevance supporting the role of PLCL1 in BS is also discussed. This study provides persuasive evidence for the importance of PLCL1 to BS and thus to the risk of HF. —SF


Frizzled homolog 1 (FZD1) acts as a WNT co-receptor and initiates WNT signal transduction. This study reports interesting associations of two SNPs of the FZD1 promoter (rs2232157, rs2232158) with femoral neck areal BMD, bone size and strength-strain index (an indicator of bone’s ability to withstand torsion) in 1084 men of African ancestry. Subsequent functional experiments showed that the minor C allele in rs2232158 creates a binding site for the transcription factor Egr1. This study indicates that a cis-regulatory polymorphism in the FZD1 promoter region may have a functional role in determining bone structural geometry. —HWD

Molecular and Cell Biology


This work provides further evidence concerning the role of NFATc1 in mediating RANKL-induced osteoclastogenesis by showing that conditional NFATc1 KO mice have osteopetrosis. Most importantly, it reveals that RANKL induces OPG production by osteoclast progenitors in the absence of NFATc1, thereby conferring to the OC lineage the ability to self-regulate its differentiation. —SF

The authors used a proteomics approach to show that brain-type cytoplasmic creatine kinase (Ckb) is greatly increased during osteoclastogenesis. Ckb siRNA or inhibition of its enzymatic activity by an inhibitor, cyclocreatine, suppressed actin ring formation, RhoA GTPase activity and vacuolar ATPase activity, and inhibited the bone-resorbing activity of osteoclasts in vitro. Functions of osteoclasts obtained from Ckb(-/-) mice were similarly affected. Ckb(-/-) mice were protected from bone loss induced by ovariectomy or inflammatory cytokines. Administration of cyclocreatine or adenoviruses harboring Ckb shRNA attenuated bone loss in rats and mice in vivo. These results clearly demonstrate that Ckb plays an important role in the bone-resorbing function of osteoclasts. Unless an inhibition of Ckb causes any adverse effects in tissues other than bone, Ckb can become a new molecular target for the development of anti-resorptive drugs.

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Secreted frizzled related protein-1 (sFRP1) expression is robust in brain, skeleton, kidney, eye, spleen, abdomen, heart and somites in early embryos. sFRP1 gene inactivation in these tissues did not endanger normal embryonic and post-natal development. Calvarial osteoblasts from neonatal sFRP1(-/-) mice exhibited a 20% increase in cell proliferation and differentiation at the early stages of osteoblast maturation. In pre- and post-natal development, sFRP1 is localized to the mineralizing front in the skeleton. sFRP1 inhibition could be a strategy for enhancement in bone anabolism. —DGL

Pathophysiology


Did you already think there were too many cytokines critically involved in bone erosions in rheumatoid arthritis? Using intraarticular injection of methylated BSA (antigen-induced arthritis (AIA) model) in mice lacking the TNF receptor superfamily member DR3, this work demonstrates a general absence of synovial hyperplasia, a lack of pannus formation, and no evidence of bone erosion compared to WT mice. In contrast, intraarticular injection of TL1A, the DR3 ligand, exacerbates joint destruction. This research further shows that this TNF pathway promotes RANKL-mediated osteoclastogenesis. Local injections of a TL1A antibody reduced joint inflammation in both the AIA and systemic, collagen-induced arthritis (CIA) models, providing some evidence for a potentially new therapeutic approach. —SF


Continuous excess of PTH is associated with increased bone resorption and bone loss. PTH acts via stromal cells (SCs) to enhance osteoclastic bone resorption. The authors demonstrate that continuous PTH infusion fails to induce osteoclast formation, bone resorption and cortical bone loss in mice lacking T cells. T cells support the proliferation and survival of SCs, and sensitize SCs to PTH through CD40 ligand (CD40L) that
induces CD40 signaling in SCs. Deletion of T cells or CD40L on T cells blunts bone-resorptive effects of PTH by decreasing SC number, the RANKL/OPG ratio and osteoclastogenic activity. These results demonstrate that T cells play an essential permissive role in the enhancement of osteoclastic bone resorption induced by continuous PTH excess, by influencing SC proliferation, life span and function through CD40L. This pathway may become a new therapeutic target by modifying the balance between bone resorption and bone formation under PTH excess. —TM

Public Health

Iglesias CP, Manca A, Torgerson DJ. The health-related quality of life and cost implications of falls in elderly women. Osteoporos Int. 2008 Oct 10; [Epub ahead of print] [Abstract]

The largest impact on health-related quality of life in this study was fear of falling, and the authors conclude that better efforts to reduce this fear will have the greatest impact on health-related quality of life. Costs of falls were estimated in the UK system to be 1000 pounds for a fall, 15,000 pounds for a hip fracture, and 2,000 pounds for a wrist fracture. —DGL


The FRAX® tool computes the 10-year risk of fractures from clinical risk factors with or without femoral BMD. In this study, fracture probabilities were calibrated to the epidemiology of fracture and death in the UK. An intervention threshold was set by age in men based on the fracture probability equivalent to that of women with a history of a prior fracture. Treatment was cost-effective at all ages when the 10-year probability of fracture exceeded 7%. The intervention threshold at 50 years corresponded to a 10-year probability of a major fracture of 7.5%. This rose with age to 30% at 80 years, so that intervention was cost-effective at all ages. Assessment thresholds for testing with BMD (6-9% at the age of 50 years) also rose with age (18-36% at the age of 80 years). The use of these thresholds in case-finding identifies 6-20% of women as eligible for BMD testing and 23-46% as eligible for treatment, depending on age. The same threshold can be used in men. —ES

Cochrane Reviews


Gamma nails and other cephalocondylar nails have gained popularity for the treatment of intertrochanteric fractures. This study finds no advantage, and some disadvantages, to those nails compared to the standard sliding hip screw and plate. —DGL

Other Studies of Potential Interest

Bai S, Zha J, Zhao H, Ross FP, Teitelbaum SL. TRAF6 is an intranuclear transcriptional co-activator in osteoclasts. J Biol Chem. 2008 Sep 3; [Epub ahead of print]


Lavoie JF, Biernaskie JA, Chen Y, Bagli D, Alman B, Kaplan DR, Miller FD. Skin-derived precursors differentiate into skeletogenic cell types and contribute to bone repair. *Stem Cells Dev.* 2008 Oct 3; [Epub ahead of print] [Abstract]


**Conflict of Interest:** Dr. Ferrari reports that he receives research support from Amgen and consultancy/speaker's fees from Merck Sharp & Dohme, Eli Lilly, and Amgen. 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.