A genome-wide association study of BMD and related traits was performed in children from a large population-based cohort in which BMD was assessed by total DXA. The results were compared to a scan of adults with extreme high or low hip BMD. Associations with BMD were identified in an area of chromosome 12 containing the Osterix (SP7) locus in both cohorts. A meta-analysis of studies with similar association with adult BMD revealed strong association between SNPs in the Osterix region and adult lumbar BMD. Genotyping of additional individuals confirmed the association with whole body BMD in children as well. All SNPs were related to height in children, but not weight or body mass index. These results demonstrate that genetic variants in the Osterix region are associated with BMD in children and adults probably through primary effects on growth. —TM

MCP-1 and -3 bind to their receptor, CCR2, and enhance RANK expression in preosteoclasts. Ovariectomy (OVX) leads to an increase in CCR2 expression in preosteoclasts. OVX upregulates MCP-1 expression on CD3+ T cells, but does not upregulate the other bone resorptive chemokines. CCR2(-/-) mice exhibit increased bone mass due to impaired osteoclast development and function resulting from suppressed RANK expression, and are protected from OVX-induced increases in bone resorption or BMD loss. This study unveils a hitherto unrecognized mechanism of estrogen deficiency-induced bone loss occurring through upregulation of RANK expression in preosteoclasts via enhanced CCR2 signaling. Thus, targeting the CCR2 pathway to inhibit only the pathological bone resorptive process may become a new modality of therapy for postmenopausal osteoporosis. —TM

PGC-1β, but not PGC-1α, expression is induced during osteoclastogenesis. PGC-1β is a regulator of mitochondrial biogenesis, and mitochondrial DNA/protein content increases in parallel with PGC-1β. The PGC-1β gene promoter contains CREB binding sites, and reactive oxygen species (ROS) enhance PGC-1β gene transcription by CREB. Iron demands increase along with mitochondrial biogenesis, which enhances transferrin receptor 1 (TIRF1) expression and cellular heme content during osteoclastogenesis. Transferrin enhances osteoclastogenesis, mitochondrial gene expression, ROS production, CREB phosphorylation, and PGC-1β expression. Thus, there is a positive feedback loop between iron uptake and PGC-1β, thereby accelerating osteoclastogenesis. —TM


RANKL inhibitors, such as OPG and specific antibodies, have been proven efficient in preventing osteoclastogenesis and bone resorption in pre-clinical models and in humans. Considering the impact of the RANKL/RANK pathway on immune functions (see recent Perspective by Ferrari-Lacraz et al.), alternate strategies to block RANK signaling specifically in osteoclast (precursors) have some appeal. This study demonstrates the ability of a cell-permeable RANK inhibitor targeting a specific RANK cytoplasmic motif to do so. —SF

Pathophysiology


While focusing on Wnt-LRP5/LRP6-β-catenin signaling as a major pathway for bone formation, we should not forget that Wnts also have a major impact on the oncogenic process. Wnt inhibitory factor 1 (WIF1) was found to be epigenetically silenced in 5 human osteosarcoma cell lines, including SaOS2. In turn, WIF1 induced osteoblast cell differentiation and suppressed osteosarcoma tumor cell growth in vitro. In the adult mouse, Wif1 was highly expressed in the skeleton and a limited range of additional tissues, but bone mass was not significantly altered in Wif 1-deleted mice. However, some of these mice developed osteosarcoma, either spontaneously or in response to radiation. Whether or not these findings should raise further concerns with regard to the development of pharmacological agonists of the Wnt pathway for bone remains to be seen, considering that SOST KO mice, for instance, were not reported to develop osteosarcoma spontaneously. —SF

Physiology and Metabolism


It is not about bone, but fat, more precisely metabolically active brown adipose tissue, a major source of energy expenditure, which was supposed to vanish quickly after birth. The common message from these studies is that brown adipose tissue is present and active in adult humans, and its presence and activity are inversely associated with BMI, adiposity and indexes of the metabolic syndrome. One can only start to think about its potential influence on bone homeostasis as well. —SF


This study describes a new role for oxytocin, beyond lactation: the direct stimulation of osteoblast differentiation and the complex modulation of osteoclastogenesis and activity. Oxytocin and oxytocin receptor KO mice have markedly reduced trabecular bone volume and a decline in osteoblast number and bone formation, whereas haploinsufficient mice also have a trabecular bone defect. Central injections of oxytocin did not modify bone turnover, indicating that its effects on bone are peripheral. —SF

Public Health


Since osteoporosis treatment has shown clear limitations in reducing non-vertebral fractures, clinicians should be aware of concomitant strategies to reduce falls in order to prevent peripheral fractures. This state-of-the-art review and meta-analysis identifies exercise, Tai Chi, cataract surgery and withdrawal of psychotropic medications as significantly reducing falls. Overall vitamin D did not, but could potentially in vitamin D-deficient subjects. Subtle differences are identified between reducing risk of falls, and reducing or not reducing risk of falling. —SF

Reviews, Perspectives and Editorials


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.

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