**Citation:** IBMS BoneKEy **11,** Article number: 606 (2014) | doi:10.1038/bonekey.2014.101

**www.nature.com/bonekey**

# Plenary Presentations

**Selected abstracts from the 7th International Conference on Osteoporosis and Bone Research, 2014**
**16–19 October 2014, Xiamen, China**

**Organizers: Chinese Medical Association (CMA), Chinese Society of Osteoporosis and Bone Mineral Research (CSOBMR), International Bone and Mineral Society (IBMS), and International Chinese Musculoskeletal Research Society (ICMRS).**

## PL1
## Parathyroid Hormone Applications in Licensed and Unlicensed Diseases

***Liao Eryuan***
Institute of Endocrinology and Metabolism, Second Xiangya Hospital of Central South University, Changsha, Hunan, China

Osteoporosis is a condition of impaired bone strength that results in an increased risk of fracture. As a result of its unique mechanism of action, parathyroid hormone (PTH), the only approved anabolic therapy for bone, produces larger increases in bone mass than those seen with antiresorptive therapies in postmenopausal osteoporosis (PMOP). PTH treatment first stimulates bone formation and subsequently stimulates both bone resorption and formation; the balance remains positive for formation even in this latter phase of PTH treatment. The growth of new bone with PTH permits restoration of bone microarchitecture, including improved trabecular connectivity and enhanced cortical thickness. Bone formation may also be induced on the outer periosteal surface, possibly affecting bone size and geometry, with additional beneficial effects on bone strength.
Hypoparathyroidism is normally treated by calcium supplements and activated vitamin D analogues. Although plasma calcium is normalized in response to conventional therapy, quality of life (QoL) seems impaired and patients are at increased risk of renal complications. A number of studies have suggested subcutaneous injections with PTH as an alternative therapy. By replacement with the missing hormone, urinary calcium may be lowered and QoL improved. PTH replacement therapy possesses, nevertheless, a number of challenges. If PTH is injected only once a day, fluctuations in calcium levels may occur resulting in hypercalcemia in the hours following an injection. Twice-a-day injections seem to cause less fluctuation in plasma calcium but do stimulate bone turnover to above normal level. Most recently, continuous delivery of PTH by pump has appeared as a feasible alternative to injections. Plasma calcium levels do not fluctuate, urinary calcium is lowered, and bone turnover is only stimulated modestly.
Studies on PTH indications are growing and is being tried virtually in any situations that require bone growth. Teriparatide beyond the currently licensed indications is discussed like idiopathic/hypogonadal OP in men, GC-induced OP, fracture healing, dental stability, osteonecrosis of jaw, osseous defects in osteoarthritis and implant integration, etc.

## PL2
## Preosteoclasts Induce Angionenesis for Bone Formation

*Hui Xie[1,2], Zhuang Cui[1,3], Long Wang[1,4], Zhuying Xia[1,2], Yin Hu[1,2], Lingling Xian[1], Changjun Li[1], Liang Xie[1], Janet Crane[1], Mei Wan[1], Gehua Zhen[1], Qin Bian[1], Bin Yu[3], Weizhong Chang[1], Tao Qiu[1], Maureen Pickarski[5], Le Thi Duong[5], Jolene J. Windle[6], Xianghang Luo[2], Eryuan Liao[2],* ***Xu Cao[1]***
[1]Department of Orthopaedic Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [2]Institute of Endocrinology and Metabolism, Second Xiangya Hospital, Changsha, Hunan, China; [3]Department of Orthopedics and Trauma, Nan Fang Hospital, Southern Medical University, Guangzhou, Cuangdong, China; [4]Xiangya Hospital, Central South University; [5]Bone Biology, Merck Research Laboratories, West Point, PA, USA; [6]Department of Human and Molecular Genetics, Virginia Commonwealth University, Richmond, VA, USA

Bone size and shape is precisely modeled and remodeled throughout life to ensure the structure and integrity of the skeleton. Primary factors in temporally and spatially regulating bone remodeling have been characterized. Angiogenesis is coupled with bone formation in these processes. A recent study reveals a specific vessel subtype, $CD31^{hi}Emcn^{hi}$ vessel, couples angiogenesis and osteogenesis. However, the cellular and molecular regulation of angiogenesis in coupling osteogenesis remains elusive.
We generated $Csf1^{-/-}$ offspring and their wild-type littermates by crossing two heterozygote $Csf1^{op}$ strains. Hemizygous TRAP-Cre mice were crossed with $Pdgfb^{fl/fl}$ mice. The offspring were intercrossed to generate the following offspring: wild type mice, *TRAP-Cre* (mice expressing Cre recombinase driven by TRAP promoter), $Pdgfb^{fl/fl}$ (mice homozygous for *Pdgfb* flox allele are referred to as "$Pdgfb^{+/+}$" in the text), and *TRAP-Cre*; $Pdgfb^{fl/fl}$.
Osteogenesis during bone modeling and remodeling is coupled with angiogenesis. A recent study shows that the specific vessel subtype, strongly positive for CD31 and Endomucin ($CD31^{hi}Emcn^{hi}$), couples angiogenesis and osteogenesis. We found that preosteoclasts secrete platelet derived growth

factor-BB (PDGF-BB), inducing CD31$^{hi}$Emcn$^{hi}$ vessels during bone modeling and remodeling. Mice with depletion of PDGF-BB in tartrate-resistant acid phosphatase positive (TRAP$^{+}$) cell lineage (*Pdgfb*$^{-/-}$) show significantly lower trabecular and cortical bone mass, serum and bone marrow PDGF-BB concentrations, and CD31$^{hi}$Emcn$^{hi}$ vessels compared to wild-type mice. In the ovariectomized (OVX) osteoporotic mouse model, concentrations of serum and bone marrow PDGF-BB and CD31$^{hi}$Emcn$^{hi}$ vessels are significantly decreased. Inhibition of cathepsin K (CTSK) increases preosteoclast numbers, resulting in higher levels of PDGF-BB to stimulate CD31$^{hi}$Emcn$^{hi}$ vessels and bone formation in OVX mice.
Preosteoclasts secrete PDGF-BB during bone modeling and remodeling to induce angiogenesis for osteogenesis. Pharmacotherapies that increase PDGF-BB secretion from preosteoclasts offer a novel therapeutic target for osteoporosis to promote angiogenesis for bone formation.

**PL3**
**Why Bones Fail: Structure and Mechanics**
***Mark Forwood***
School of Medical Science, Griffith University, Gold Coast, Australia

Skeletal failure depends bone's energy absorption, and how much loading they experience. Our bones, must achieve an adequate safety factor while minimising the energy cost of movement: a trade off between strength and lightness. With age, our bone strength diminishes, reducing the safety factor so that daily activities can cause fracture. The robusticity of bones *per se* depends on their material properties, and the build of the whole bone structure. This offers three mechanisms to reduce their risk of fracture. First, increase bone mass, larger bones can resist greater loads. Second, distribute bone mass most effectively, strategic additions to bone mass can substantially increase bending and torsional strength. Third, improve bone material properties, make the bone matrix, itself, stronger or capable of absorbing more energy. Adding, or redistributing, bone mass influences structural properties, affecting the behaviour of bones as an organ. Alterations in the bone material are manifested in the mechanical properties of bone per unit volume, reflected in measures of stress, strain, modulus of elasticity and toughness. The influence of such factors that affect bone fragility, but are not accounted for by bone mass or quantity, has been termed bone quality. These variables explain the disparity between the change in BMD and the reduction in fracture risk in response to treatment. Although they are necessary to understand the risk of fracture, they are more inscrutable than mass to measure *in vivo*. Such factors include true mineral density, maturation and chemical composition; collagen structure and biochemistry; osteocyte viability; porosity, microdamage; and, micro-architecture. The technologies that measure bone quality to assess fracture risk are emerging, but embryonic. Greater understanding of the material properties of bone, and its interaction with structure, will ultimately improve the assessment of fracture risk and monitoring of patients being treated for metabolic bone disease.

**PL4**
**Cancer, Bone and Muscle: It's All About the Microenvironment**
*David Waning, Khalid Mohammad, Andrew R. Marks,*
***Theresa A. Guise***
Division of Endocrinology, Department of Medicine, Indiana University-Purdue University at Indianapolis, Indianapolis, Indiana, USA

Bone metastases are common in advanced breast, prostate and lung cancer and are associated with significant morbidity of bone pain, fracture, hypercalcemia and nerve compression syndromes. Tumor cells in the bone microenvironment disrupt normal bone remodeling to cause this morbidity as well as to promote tumor growth in bone. The molecular mechanisms of these tumor-bone interactions in the bone microenvironment are the basis for current bone-targeted therapy for bone metastases and will be discussed. Tumor metastases to bone are also associated with muscle weakness, which contributes to morbidity. Cancer-associated muscle weakness is a major paraneoplastic syndrome. In a mouse model of human breast cancer bone metastases there was profound skeletal muscle weakness that was absent in mice with primary breast cancer and no bone metastases, implicating a role for the tumor-bone microenvironment. TGFβ, released during tumor-induced bone destruction, upregulated NADPH oxidase 4 (Nox4) leading to oxidation of proteins required for contraction, including the ryanodine receptor/$Ca^{2+}$ channel (RyR1). Oxidized RyR1 was "leaky" and tetanic $Ca^{2+}$ release was reduced. Muscle function was restored by inhibiting RyR1 leak, blocking TGFβ signaling, or preventing osteoclastic bone resorption. Skeletal muscle from patients with bone metastases due to breast or lung cancer showed RyR1 oxidation indicating $Ca^{2+}$ leak. These data demonstrate: (1) muscle weakness occurs independent of reduced muscle mass in cancer; (2) products released from bone induce muscle weakness; (3) TGFβ induces muscle weakness via Nox4 leading to oxidation of RyR1 and intracellular calcium leak. Implications for therapy of bone metastases and associated muscle weakness will be discussed.

**PL5**
**Acidic Microenvironment Contributes to the Pathophysiology of Bone Pain Associated with Cancer Colonization**
***Toshiyuki Yoneda*[1,2]*, Masako Nakanishi*[2]*, Toshihiko Nishisyo*[2]*, Hiroki Wakabayshi*[2]*, Kenji Hata*[2]
[1]Division of Hematology/Oncology, Indiana University School of Medicine, Indianapolis, IN, USA; [2]Department of Biochemistry, Osaka University Graduate School of Dentistry, Suita, Osaka, Japan

Bone pain is one of the most common complications and major causes of morbidity and secondary death in cancer patients with bone metastasis. Our current understanding of the mechanism of cancer-associated bone pain is limited. The microenvironment of cancer-colonized bone is likely acidic due to increased proton release by bone-resorbing osteoclasts and elevated lactate/proton secretion by bone-colonizing cancer cells. Since protons are algogenic for primary afferent sensory neurons and bone is densely innervated by sensory neurons, we hypothesized that this pathological acidosis can activate

nociceptive sensory neurons innervating bone, leading to elicitation of bone pain.
We found calcitonin gene-related protein (CGRP)-positive sensory neurons innervating bone expressed the acid-sensing nociceptor, transient receptor potential channel-vanilloid subfamily member 1 (TRPV1). Cancer-bearing mice showed tactile hypersensitivity and thermal hyperalgesia with increased TRPV1 expression in cancer-colonized bone. The bisphosphonate zoledronic acid significantly alleviated these nociceptive behaviors. Moreover, the proton pump inhibitor bafilomycin A1 also reduced the nociceptive behaviors and blocked the development of acidosis in cancer-colonized bone, indicating a critical role of protons released by osteoclasts and cancer cells in evoking bone pain. Of note, thermal hyperalgesia and hind-limb lifting (flinching) were decreased in TRPV1-deficient ($TRPV^{-/-}$) cancer-bearing mice compared to wild-type cancer-bearing mice, demonstrating a crucial role of TRPV1 in cancer-associated bone pain.
Acidic conditions promoted calcium influx, TRPV1 phosphorylation and transcription activity of CREB and up-regulated CGRP production in the primary sensory neuron cells associated with bone *in vitro*. In contrast, acid failed to cause these events in the $TRPV^{-/-}$ sensory neuron cells.
Our results suggest that the activation of TRPV1 on the sensory neurons innervating bone by acidic microenvironment in cancer-colonized bone is critical to the pathophysiology of bone pain.

**PL6**
**Tumor and Bone**
***Xiao-lan Jin***
Chengdu Army General Hospital, Chengdu, China

The metastasis of cancer cell to the skeleton is a complication of malignancy that disrupts normal bone homeostasis and remodeling, weakens bone and results in pathological fracture, bone pain and hypercalcemia. 80–90% of patients with advanced cancer will develop bone metastases. The skeleton is the most common site of metastatic disease. It is also the most frequent site of first distant relapse in breast and prostate cancers. The “vicious cycle” coined by Dr. Gregory Mundy suggests a complex interaction between tumor cells that metastasize to bone, immune and stromal cells as well as osteoblast and osteoclast. Bone destruction, osteolytic factors produced by bone metastatic tumor cells such as PTHrP, RANKL, IL-8, RunX2 and MMPs are excellent targets in blocking osteolysis, but ET-1 and Wnt signaling pathway in osteoblastic lesion.
Bone metastases remain incurable. Bisphosphonate are the clinical standard of care and have been highly effective to reduce fractures and improve quality of life. Denosumab, a new treatment option, is a fully human monoclonal antibody against human RANKL.By binding to RANKL, denosumab disrupts the “vicious cycle” of bone destruction stimulated by the metastasized tumor cells. Denosumab inhibits the formation and activity of osteoclasts, which probably contributes to a larger inhibitory effect on bone resorption than what is achieved with bisphosphonates. TGF-β inhibitors(1D11 and SD-208), which can both inhibit tumor growth and improve bone quality, may be ideal drugs for bone metastases.
It is clear that more specific drugs are needed to target tumor growth in bone. Some current promising approaches include the histone deacetylase inhibitor vorinostat, which inhibits tumor growth in bone. Erlotinib, an inhibitor against epidermal growth factor receptor (EGF-R) tyrosine kinase, has been successfully tested in a preclinical model of non-small cell lung cancer metastasis to bone and effectively inhibited release of osteolytic factors such as PTHrT and IL-8.

**PL7**
**Reconsideration of the Relevance of Mild Wedge or Short Vertebral Height Deformities Across a Broad Age Distribution**
***Wei Yu****, Qiang Lin, Xiaohong Zhou, Hongyu Shao, Pengtao Sun*
Department of Radiology, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, China

Vertebral fractures, are the most common osteoporotic fracture and are strong predictors of future fracture. Proper vertebral fracture assessment is imperative for diagnosing osteoporotic fracture, and follow up. Radiographic assessment is limited by the inability to distinguish mild fractures from congenital mild wedge deformities or vertebrae of short vertebral height. We attempted to quantify the expected background prevalence of these deformities by measuring vertebral fracture prevalence across all age groups in a large hospital-based retrospective Chinese cohort.
We reviewed eligible lateral chest radiographs from patients admitted to Peking Union Medical College Hospital during 2011 using the Genant semiquantitative method for vertebral fracture assessment (T4-L2). We evaluated fracture prevalence among subjects by sex, 10-year age group, and fracture severity grades subjectively. We further analyzed characteristics of subjects with mild (grade I) fractures to estimate the relative contribution of congenital mild wedge deformities. A total of 10,720 subjects (5396 men and 5324 women) with lateral chest radiographs were evaluated. Subjects ranged in age from 0.5 to 97 years with a mean of 51.8±17.4 years (Men: 52.8±17.6 years; Women: 50.8±17.2 years). When stratified by 10-year age groups, the prevalence of vertebral fractures was relatively low until about 40 years of age, after which prevalence increased for both genders. Fractures (13 fractures for 9 males and 6 fractures for 5 females) seen in subjects younger than 40 years of age were almost exclusively mild grade fractures. No fractures were identified in subjects younger than 20 years of age.
Mild or wedged vertebral shape changes were rare among younger subjects, suggesting that when observed in older adults, they are less likely to be due to normal variation in vertebral body shape or congenital deformities. Our findings support current recommendations to treat mild wedged vertebral changes as osteoporosis or at least to consider it as a risk factor for osteoporotic fracture.

**PL8**

**Genetic Background of Rickets**

***Weibo Xia***
Peking Union Medical College Hospital, Chinese Academy of Medical Science, Beijing, China

Rickets and osteomalacia are a group of disorders characterized by impaired mineralization of bone and cartilage. Etiologies of rickets are various. Almost any factor interferes the bone mineralization can results in rickets, mainly including abnormal calcium-phosphate metabolism, vitamin D deficiency or abnormal metabolism, acidosis, abnormal bone matrix and mineralization inhibitors, etc. Nutrition deficiency rickets was the most prevalent cause of rickets in the past. However, with the improvement of living standards, and the use of vitamin D supplements and calcium-fortified food, nutrition deficiency rickets is now very rare. At present, rickets and osteomalacia are mainly associated with heredity, autoimmune disease, drug related, toxin or tumor induced, etc.

Here we focus on the hereditary rickets, of which hypophosphatemic rickets is most common. Hereditary forms of hypophosphatemic rickets include X-linked dominantly inherited hypophosphatemic rickets (XLH), autosomal dominant hypophosphatemic rickets (ADHR), autosomal recessivehypophosphatemia (ARHP) and autosomal recessive hypophosphatemia with hypercalciuria (HHRH), and the pathogenic genes responsible for the these diseases are PEX, FGF-23, DMP1/ENPP1/FM20C and SLC34A3, respectively. Impaired vitamin D metabolism is also the common cause of hereditary rickets. The two common types are pseudovitamin D-deficient rickets type I (PDDRI, which was previously called vitamin D-dependent rickets type I) due to inactivating mutations in the CYP27B1 gene,which encodes the 1-alpha hydroxylase, and pseudovitamin D-deficient rickets type II (PDDRII, which was previously called vitamin D-dependent rickets type II) due to mutations in the gene encoding the vitamin D receptor or the post-receptor signaling proteins. Few cases, caused by the mutations in the CYP2R1 gene, which encodes the 25 hydroxylase, have also been reported.

Mutations in genes encoding channel proteins or other regulatory proteins associated with ion transport in renal tubule can cause a defect in renal tubular reabsorption of calcium, phosphate, magnesium, amino acid, glucose or bicarbonate, and a defect in tubular secretion of hydrogen ion, resulting in Faconi's syndrome and metabolic acidosis, respectively, both of which can impair the bone mineralization and result in rickets.

**PL10**

**Current Concepts in Chronic Kidney Disease-Mineral and Bone Disorder**

***Seiji Fukumoto***
University of Tokyo Hospital, Tokyo, Japan

Chronic kidney disease–mineral and bone disorder (CKD-MBD) is defined as a systemic disease including deranged mineral and bone metabolism, abnormal hormone actions and ectopic calcification in patients with CKD. With declining glomerular filtration rate, serum 1,25-dihydroxyvitamin D [1,25D] starts to decrease, and hyperphosphatemia and hypocalcemia develop in the later stage of CKD. All these abnormalities stimulate the development of secondary hyperparathyroidism. Active vitamin D, phosphate binders and cinacalcet are used to correct these abnormalities and prevent the toxic effects of secondary hyperparathyroidism. Hyperphosphatemia has been shown to enhance vascular calcification and it is important to control phosphate levels in patients with CKD. Fibroblast growth factor 23 (FGF23) is a phosphaturic hormone produced mainly by osteocytes. FGF23 reduces serum phosphate by inhibiting proximal tubular phosphate reabsorption and also by inhibiting intestinal phosphate absorption through lowering 1,25D. In addition, FGF23 was shown to inhibit the production and secretion of parathyroid hormone. FGF23 binds to Klotho-FGF receptor complex and the expression of Klotho has been considered to determine the tissue-specific effects of FGF23. FGF23 level gradually increases with the deterioration of renal function. FGF23 contributes to lowering 1,25D and enhances urinary phosphate excretion in the early stage of CKD. On the other hand, FGF23 is sometimes extremely high in patients with end-stage renal disease. It has been shown that high FGF23 levels are associated with various adverse events including cardiovascular events, vascular calcification, left ventricular hypertrophy, fractures and progression of CKD. However, the mechanism of these associations is not clear. While FGF23 was shown to directly induce left ventricular hypertrophy in a Klotho-independent manner, it is not known whether Klotho-independent actions of FGF23 explain all these associations. Further studies are necessary to clarify whether lowering FGF23 levels has beneficial effects on patients with CKD.

**PL11**

**IGF1 in Skeletal Development, Remodeling, and Fracture Repair**

***Daniel D Bikle***, *Yongmei Wang, Tao Wang, Wenhan Chang*
Department of Medicine, VA Medical Center and University of California San Francisco, CA, USA

IGF signaling plays a critical role in all aspects of skeletal development, remodeling, and fracture repair. We studied the skeletal actions of IGF1 by deleting IGF1 or its receptor (IGF1R) from chondrocytes, osteoblasts of different maturities, and osteoclasts.

The global IGF1 knockout ($^{glo}$IGFKO) showed a marked decrease in chondrocyte proliferation with increased apoptosis and delayed differentiation and formation of the primary ossification centers. Specific deletion of IGF1R from chondrocytes reproduced many of these changes. When deleted post natally the mice demonstrated a similar disruption of endochondral bone formation during fracture repair. Deletion of IGF1R from osteochondroprogenitors using an osterix driven cre recombinase ($^{osx}$IGF1RKO) also affected growth plate development resulting in dwarfism with particular delay of the secondary ossification center. Deletion of IGF1R from mid maturity and mature osteoblasts/osteocytes with 2.3 col1a1 driven cre recombinase and osteocalcin driven cre recombinase, respectively, had little impact on growth but resulted in osteopenia, delayed fracture repair ($^{col1a1}$IGFRKO), and blunted anabolic response to skeletal loading ($^{ocn}$IGF1RKO). The $^{glo}$IGFKO that survived birth developed increased BV/TV secondary to decreased osteoclastogenesis. Osteoblasts

lacking IGF1 failed to stimulate osteoclastogenesis. Similarly osteoclast precursors lacking IGF1R failed to develop into osteoclasts, and these mice developed osteopetrosis. In seeking a mechanism by which IGF1 signaling mediates these cell-cell interactions we found that IGF1 induces ephrinB2 and ephB4 in chondrocytes and osteoblasts, and ephrinB2 in osteoclasts. Deletion of IGF1R from these cells leads to loss of their expression. Disruption of ephrinB2/ephB4 interactions or their expression blocks the ability of IGF1 to promote osteoblast and chondrocyte differentiation and their ability to stimulate osteoclastogenesis.
IGF1 signaling is crucial for the complex interactions between cells responsible for skeletal development, remodeling and fracture repair. These interactions require a number of signaling pathways of which ephrinB2/ephB4 plays a crucial role.

**PL13**
**Hyperkyphosis, an Age-Related Condition with Multiple Causes; What Role Does Osteoporosis Play, and What Are Recommended Treatments?**
***Deborah Kado***
Departments of Family Medicine and Internal Medicine, Stein Institute for Research on Aging, University of California, San Diego, La Jolla, CA, USA

Hyperkyphosis, or increased thoracic curvature, commonly affects older women and men, and osteoporosis is the most often cited cause. However, data from the Study of Osteoporotic Fractures, the Osteoporotic Fractures in Men (MrOS) Study and the Rancho Bernardo Study demonstrate that less than a third of those considered most kyphotic have evidence of underlying vertebral fractures. While each prevalent and incident vertebral fracture is associated with about a 3-4 degree increase in kyphosis angle, other important causes include low bone mineral density, bone density loss, weight loss, degenerative disc disease and a family history of hyperkyphosis. Although not definitively shown, low spinal muscle mass and general core muscle weakness are also likely contributing causes of accentuated kyphosis in older persons. Like osteoporosis, hyperkyphosis in older women and men is associated with worse health outcomes, including poor physical function, impaired pulmonary reserve, falls, fractures and an increased mortality risk. Women who have both osteoporosis and hyperkyphosis appear to be at greater risk of adverse health than those who have either vertebral fractures or increased thoracic curvature. But, unlike osteoporosis, there are no currently approved standard therapies to offer affected persons with hyperkyphosis, per se. This lecture will cover the common causes of hyperkyphosis, including potential underlying pathophysiological mechanisms, review any newly reported ill-effects on health, and discuss latest advances regarding treatment.

**PL14**
**Models for Fracture Prediction and Issues in Application to China**
***Kristine Ensrud[1,2]***
[1]University of Minnesota, Minneapolis, MN, USA; [2]VA Health Care System, Minneapolis, MN, USA

This review will outline tool components, tool development, presence or absence of external validation studies, transparency of fracture prediction models, tool performance (discrimination and calibration), and clinical utility of tools in the practice setting. FRAX, Garvan and QFracture tools will be discussed and findings from prospective studies conducted in Chinese populations evaluating performance of fracture prediction models will be presented. Results from studies evaluating the performance of a specific tool as compared with that of alternative fracture prediction models will be summarized.
Several tools for estimating fracture risk have been developed that have the potential to improve how clinicians assess a patient's risk of fracture. However, few tools have had adequate external validation and not all have provided transparent information on equations used to derive the prediction models. Discrimination of available tools to identify individuals who will or will not experience future fractures is moderate to good for hip fracture, but poorer for any major osteoporotic fracture. Few studies have assessed tool calibration and compared observed vs. predicted fracture risk as calculated by a tool. None of the available tools performs consistently better than others and simple tools do as well as more complex tools. Studies conducted in Chinese populations suggest that tools could be improved by incorporating information on fall-related risk factors. No studies have determined effectiveness of tools in selecting patients for drug treatment and improving fracture outcomes.
Fracture risk prediction is challenging. Randomized trials are needed in specific populations to evaluate comparative effectiveness of strategies based on fracture risk assessment tools in reducing fracture events prior to widespread adoption of these tools into clinical decision making.

**PL15**
**Diabetes, Treatments and Fracture Risk**
***Ann V. Schwartz***
Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California, USA

Osteoporotic fractures are an important health burden among older adults, and this population also has a high prevalence of type 2 diabetes (T2DM). Older adults with T2DM are on average overweight and have higher bone density than others of the same age. However, this higher bone mass does not confer protection against fractures. Indeed, the risk of hip fracture is increased by 40–70% in these individuals. Identification of those at higher risk of fracture among diabetic patients is a challenge. With the disparity between BMD and fracture risk, current clinical tools for assessing fracture risk, BMD T-score and FRAX, under-estimate risk in diabetic patients.
Factors that contribute to the increased fracture risk in diabetic patients include an increased frequency of falls and greater bone fragility. The underlying reasons for bone fragility

in diabetes are not clearly defined but some clues are emerging. Diabetic bone is less resistant to microindentation, suggesting that its material properties are compromised. Other characteristics of diabetic bone include reduced bone formation rate, increases in cortical porosity, and higher levels of advanced glycation endproducts.

While diabetes itself is associated with higher fracture risk, there is a growing appreciation that medications for treatment of diabetes may also have an effect on the skeleton. Thiazolidinediones increase fracture risk in women, and were the first class of antidiabetic therapy shown to affect bone. The more recently introduced incretin-based drugs are being investigated for possible beneficial effects on bone.

The optimal approach to osteoporosis prevention and treatment in diabetic patients has not been established. Maintaining adequate glycemic control may contribute to reduced fracture risk although study results are mixed. There is some limited evidence regarding the efficacy of osteoporosis therapies in diabetic patients, and this remains an important issue for future research.

**Disclosure:** Honoraria from Chugai Pharmaceutical Co and Merck; research support from GlaxoSmithKline.

**PL19**

**High Prevalence of Vitamin D Insufficiency and Deficiency Among Postmenopausal Women in China**

***Zhongjian Xie[1]***, *Zhenlin Zhang[2], Weibo Xia[3], Wen Wu[4], Chunyan Lu[5], Shuqing Tao[6], Lijun Wu[7], Julie Chandler[8], Senaka Peter[8], Ting Wu[9], Eryuan Liao[1]*

[1]Institute of Endocrinology and Metabolism, The Second Xiangya Hospital of Central South University, Changsha, Hunan, China; [2]Department of Osteoporosis and Bone Diseases, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China; [3]Department of Endocrinology, Key Laboratory of Endocrinology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China; [4]Department of Endocrinology, Guangdong General Hospital, Guangzhou, Guangdong, China; [5]Department of Endocrinology, West China Hospital, Sichuan University, Chengdu, Sichuan, China; [6]Department of Orthopedics, the Second Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, China; [7]Department of Rheumatism and Immunology, People's Hospital of Xinjiang Uygur Autonomous Region, Urumchi, Xinjiang, China; [8]EpidemiologyDepartment, Merck & Co., Inc., Whitehouse Station, NJ, USA; [9]Epidemiology Asia Pacific Unit, Merck Research Laboratories, MSD China, Beijing, China

Previous small studies exploring the prevalence of low serum 25-hydroxyvitamin D [25(OH)D] levels among postmenopausal women in China reported inconsistent findings. The aim of the present study was to determine the prevalence of low 25(OH)D levels in a large cohort of postmenopausal women in China.

This cross-sectional study recruited 1688 women with mean age of 65.4 years (55–93) from urban (N=848) and rural (N=840) areas of 7 geographically distinct regions during the summer (N=963) and winter (N=717) in China. Each woman was evaluated for total serum 25(OH)D levels using liquid chromatography-tandem mass spectrometry, fracture risk using Osteoporosis Self-Assessment Tool for Asians (OSTA), and bone mineral density (BMD) using dual energy X-ray absorptiometry. Serum parathyroid hormone (PTH) was evaluated. Serum cross-linked C-telopeptide of type I collagen (β-CTx) and aminoterminal propeptide of type I collagen (P1NP) were measured in a subgroup of women recruited in winter (N=360). Published definitions of vitamin D deficiency range from <10 ng/ml to < 20 ng/ml, and insufficiency from <20 ng/ml to <30 ng/ml in 25(OH)D. In the present study, the prevalence is reported using 25(OH)D cut-off points of <15 ng/ml, <20 ng/ml and <30 ng/ml.

Overall, 61.4 % of these postmenopausal women had a serum 25(OH)D<20 ng/ml. The overall prevalence was 91.2% for 25(OH)D< 30 ng/ml and 37.6% for 25(OH)D<15 ng/ml. Using a cut-off point of 25(OH)D<20 ng/ml, the prevalence was significantly higher among urban than rural dwellers (64.6% vs 57.3%, respectively), and among subjects recruited in winter than in summer (84.2% vs 43.6%, respectively). The prevalence of low vitamin D levels varied by region, but not necessarily by latitude, with lower prevalence (around 50%) found in the Middle and South regions, and higher prevalence (around 70%) in North and Southwest regions. PTH inversely correlated with 25(OH)D. There was no correlation of the prevalence of low vitamin D levels with fracture risk score determined by OSTA and femoral neck BMD. No correlation of 25(OH)D with β-CTx and P1NP was observed.

Our results suggest that the prevalence of vitamin D deficiency and insufficiency, by any definition, are common among postmenopausal women in China, and especially during winter and among those living in urban areas. Increased awareness of vitamin D deficiency and insufficiency among postmenopausal women in China is necessary, and dietary and other intervention strategies should be undertaken to correct this problem.

**Disclosure:** This study was supported by Merck Sharp & Dohme, Corp.

**PL21**

**The Gravity of Osteoporosis - Mechanobiology of Bone Loss in Space and Inactivity**

***Yi-Xian Qin***

Department of Biomedical Engineering, Stony Brook University, Stony Brook, NY, USA

Disuse osteopenia, i.e., during long term space mission, affects mineral density, microstructure and integrity of bone, which lead to increased risk of osteoporosis and fracture. Mechanotransduction has demonstrated potentials for tissue regeneration. A potential mechanism, by which bone cells may sense mechanotransductive signals, is through deformation and streaming of bone cells and their surface structures, to trigger osteogenesis. The purpose of this study was to evaluate the role of acoustic radiation force (ARF) in bone remodeling and osteogenesis, and biological responses of stem cells to induced fluid flow and mitigation of osteopenia.

Loading induced bone fluid flow (BFF) creates a pressure gradient that further influences the magnitude of the mechanotransductory signals, which can be elevated by ARF, which applied on multi-scale osteogenic potentials at cellular, mesenchymal stem cells (MSCs), and *in vivo* disuse plus fracture

model. (1) In an *in vitro* setting, Ad-HMSC cells were cultured in a 1D clinostat to simulate microgravity and treated with ARF at 30mW/cm$^2$ for 20 min/day. (2) In a separate *in vivo* setting, daily ARF was applied in femoral fracture rat model with disuse hindlimb suspension (HLS), in sham, and treatment groups.
(1) It has demonstrated that ARF significant increases in ALP, OSX, RANKL, RUNX2, and decreases in OPG in the treated cell cultures of MSC compared to non-treated groups. ARF exposure also restored OSX, RUNX2 and RANKL expression in osteoblast cells. (2) In the HLS model, while disuse delayed the callus healing, ARF has shown significance in promoting initial callus forming and mineralization (36%), and enhanced mechanical strength in fracture (48%).
Disuse conditions mitigate osteogenic potentials of MSCs, while disuse osteopenia delayed fraction mineralization. It is indicated that ARF induced fluid flow can regulate osteogenesis, MSCs turnover and enhance fracture healing.

**PL22**

## Age-Associated Changes in Body Composition and Diabetes: A Bone Disease?

*Holger Henneicke[1], Jingbao Li[1,2], Sylvia Gasparini[1], Markus J. Seibel[1,3],* ***Hong Zhou[1]***
[1]Bone Biology Program, ANZAC Research Institute, The University of Sydney, Sydney, Australia; [2]Key Laboratory for Space Bioscience & Biotechnology, Institute of Special Environmental Biophysics, Faculty of Life Sciences, Northwestern Polytechnical University, Shaanxi, China; [3]Department of Endocrinology and Metabolism, Concord Hospital, The University of Sydney, Sydney, Australia

The physiological aging process is associated with changes in body composition and metabolism, including central obesity, diabetes and osteoporosis. Since the osteoblast has recently been identified as a mediator of GC-induced metabolic dysfunction in mice,[1] we hypothesized a mechanistic link between increased GC signaling in the osteoblast and changes in body composition and fuel metabolism during aging.
To test this hypothesis, we investigated the aging phenotype of transgenic (tg) mice in which glucocorticoid signaling had been selectively disrupted in osteoblasts/osteocytes via targeted overexpression of the glucocorticoid-inactivating enzyme, 11ß-hydroxysteroid dehydrogenase type 2 ('11ßHSD2-tg' mice). Body weight and composition, insulin sensitivity and glucose tolerance, serum corticosterone (CS) and osteocalcin levels as well as hepatic gene expression were assessed in female 11ßHSD2-tg mice and litter-matched wild-type (WT) controls at 2 and 18 months of age. From 2 to 18 months of age, female WT mice gained more in body weight (WT: +32g vs tg: +16g, $P<0.01$) and overall fat mass (WT: +20.7g vs tg: +6.3g, $P<0.01$) than their tg littermates. 18 month-old WT mice exhibited reduced insulin sensitivity and hepatosteatosis, while insulin responsiveness and hepatic lipid deposition remained normal in their tg littermates. Hepatic mRNA expression of lipogenic and gluconeogenic pathways was higher in aged WT compared to aged tg mice (acetyl-coA-carboxylase, WT: 12.8 vs tg: 5.6 fold increase on respective young control, $P=0.051$ & glucose-6-phosphatase, WT: 8.1 vs tg: 3.3 fold increase on respective young control, $P=0.09$). Serum CS concentrations were similar in 18-month-old WT and tg mice and ~3-fold higher than in 2-month-old mice ($P<0.05$). Serum osteocalcin concentrations declined during aging in both genotypes but remained significantly higher in tg mice at all time points ($P<0.05$).
Our results indicate glucocorticoid signaling in osteoblasts is critically involved in the pathogenesis of age-related changes in glucose handling and body composition. Osteocalcin may act as a mediator of age-related metabolic dysfunction.

**Reference**

1. Brennan-Speranza. *J Clin Invest* 2012;122(11):4172–4189.

**PL23**

## The Role of Foxp Gene Family in the Osteogenesis and the Pathogenesis of Osteoporosis

***Xizhi Guo***
Bio-X Institutes, Shanghai Jiao Tong University, Shanghai, China

Osteoblast induction and differentiation in developing long bones is dynamically controlled by the opposing action of transcriptional activators and repressors. In contrast to the long list of activators that have been discovered over past decades, the network of repressors is not well-defined. Here we identify the expression of a Foxp1/2/4 protein complex, comprised of Forkhead-Box (Fox) transcription factors of the Foxp subfamily, in both skeletal progenitors at the perichondrium and proliferating chondrocytes during endochondral ossification. Enforced over-expression of Foxp1/2/4 in chondroctyes abrogated osteoblast formation and chondrocyte hypertrophy. Conversely, single or compound deficiency of Foxp1/2/4 in skeletal progenitors or chondrocytes resulted in premature osteoblast commitment and differentiation in the perichondrium, coupled with impaired chondrocyte proliferation, survival, and hypertrophy in the growth plate. We detected interactions between Foxp1/2/4 and Runx2 proteins which led to repression of transcriptional activity of Runx2 in heterologous cells, providing an explanation, at least in part, for the roles of the Foxp1/2/4 complex in bone formation. These observations reveal that Foxp1/2/4 controls osteogenesis and chondrocyte hypertrophy during endochondral ossification as a novel transcriptional repressor complex.
During postnatal bone mass accrual and maintenance, the differentiation preference of bone marrow mesenchymal stem cells (MSCs) progressively switches from osteoblast to adipocyte as the proceeding of aging. We detected that Foxp1 expression declined whereas p16INK4A expression underwent corresponding accrual as the aging of bone marrow MSCs. Foxp1-deficient MSCs appeared premature aging characteristics, and preferred to differentiate into adipocytes at the expense of osteoblasts in the conditional knockout mice by Nestin-Cre or Prx1-Cre. Conversely, over-expression of Foxp1 in C3H10T1/2 cells profoundly impaired adipocyte differentiation, accompanied by an increase of osteoblast differentiation. Molecularly, Foxp1 suppressed the transcriptional activation of the master adipogenic factor PPARg through directly interacting with and antagonizing Cebpβ/δ protein function, which are two important inducers for early adipogenic commitment. In addition, Foxp1 controlled the pace of MSC aging through directly repressing the expression of p16INK4A.
Taken together, Foxp1 regulates MSCs aging as a switch in cell fate commitment between osteoblast and adipocyte, providing novel cues for the therapy of age-related bone loss.