Ludwig Boltzmann Institute
Osteology

ANNUAL REPORT

Inhaltsverzeichnis

0 Abbreviations - Abkürzungen

ADH	Autosomal Dominant Hypoparathyroidism
ALN	Alendronat
ALP	Alkaline Phosphatase
APS	Anti-Phospholipid Syndrome
ATR-FTIR	Attenuated Total Reflectance Fourier Transform Infrared
BA	Bone Area
BMD	Bone Mineral Density
BMDD	Bone Mineralization Density Distribution
BMP1	Bone Morphogenic Protein-1
Brtl	Knock-In Model for Moderately Severe Osteogenesis imperfecta
BV/TV	Bone Volume per Trabecular Volume
Ca	Calcium
CaMean	mittlere Ca-Konzentration
CaPeak	häufigste auftretende Ca-Konzentration
CaSR	Calcium Sensing Receptor
CaWidth	Peak-Breite der Knochenmineralisationsdichteverteilung
CKD	Chronic Kidney Disease
CLSM	Confocal Laser Scanning Microscopy
COL1A1	Collagen Type I alpha 1
COL1A2	Collagen Type I alpha 2
COPD	Chronic Obstructive Pulmonary Disease
CT	Computertomographie
DNA	Deoxyribonucleic Acid
DXA	Dual Energy X-Ray Absorptiometry
ECD	Erdheim-Chester Disease
ECM	Extracellular Matrix
EDX	Energy-Dispersive X-Ray Spectroscopy
ER	Endoplasmatic Reticulum
EV	Extracellular Vesicle
FGF23	Fibroblast Growth Factor 23
FTIR	Fourier Transform Infrared
FTIRI	Fourier Transform Infrared Imaging
FWF	Fonds zur Förderung der wissenschaftlichen Forschung (Austrian Science Fund)
GAG	Glycosaminoglycan
HFE	High Iron Fe
IBD	Inflammatory Bowel Disease
IFITM5	Interferon Induced Transmembrane Potein 5
IgG4-RD	Immunoglobulin G4 – Related Disease
KLF10	Kruppel-like factor 10
ko	Knockout
MAP2K1	dual specificity mitogen-activated protein kinase kinase 1
MC3T3-E1	Mouse Osteoblastic Cell Line
MCP	Metacarpophalangeal
MLO-A5	Mouse Postosteoblast/Preosteocyte-Like Cell Line
MMC	Mineral/Maturity/Crystallinity
Mn	Manganese
mRNA	messenger RNA
MRT	Magnetresonanztomographie
NIH	National Institutes of Health

OI	Osteogenesis imperfecta
OLCN	Osteocyte Lacuna Canaliculi Network
OLS	Osteocyte Lacunae Section
OVX	Ovariektomized
P3H1	Prolyl 3-Hydroxylase
PEDF	(also SERPINF1) Pigment Epithelium-Derived Factor
PHEX	Phosphate Regulating Endopeptidase Homolog, X-Linked
PLS3	Plastin 3
PPIase	Peptidyl-Prolyl-cis-trans-Isomerase
PPIB	Peptidylprolyl Isomerase B (Cyclophilin B
pQCT	peripheral Quantitative Computed Tomography
PS	Postsurgical Hypoparathyroidism
PTH	Parathyroid Hormone
qBEI	quantitative Backscattered Electron Imaging
RA	Rheumatoid Arthritis
RANKL	Receptor Activator of NFkappa-B Ligand
RNA	Ribonucleic Acid
Runx2	Runt-related transcription factor 2
Saa3	Serum Amyloid A
SAM	Scanning Acoustic Microscope
SASAM	Saarland Scanning Acoustic Microscopy
SAXS	Small Angle X-Ray Scattering
SERPINF1	(also PEDF) Pigment Epithelium-Derived Factor
SHAM	Placebo Surgery
SIK	Salt-inducible kinase
TA	Tissue Area
TNF	Tumor Necrosis Factor
TPTD	Teriparatide
TRAP5b	serum band 5 tartrate-resistant acid phosphatase
TREM2	Triggering Receptor Expressed on Myeloid Cells 2
TYROBP	TYRO Protein Tyrosine Kinase Binding Protein
VEH	Vehicle
WNT1	Wnt family member 1
WT	Wild type
XLH	X-Linked Hypophosphatemia
ZOL	Zoledronic Acid

1 Overview of the Institute

The Ludwig Boltzmann Institute of Osteology (LBIO) was founded in 1991 through a partnership agreement between Austrian Workers' Compensation Board (AUVA), Vienna Health Insurance Fund (WGKK) and Ludwig Boltzmann Gesellschaft (LBG) at the Hanusch Hospital and the Trauma Centre Meidling, with Klaus Klaushofer, MD, serving as the Scientific and Administrative Head. A board oversees the scientific and administrative activities of the LBIO with board members of the partner institutions (AUVA, WGKK, LBG). Special emphasis was placed on the organization and performance of multidisciplinary basic and clinical research in bone and mineral metabolism with the main focus on **translational** medicine. Thus the LBIO serves as the scientific core center within a multidisciplinary clinical network located at the two hospitals targeting diagnosis and treatment of bone and joint diseases.

1.1 Mission Statement

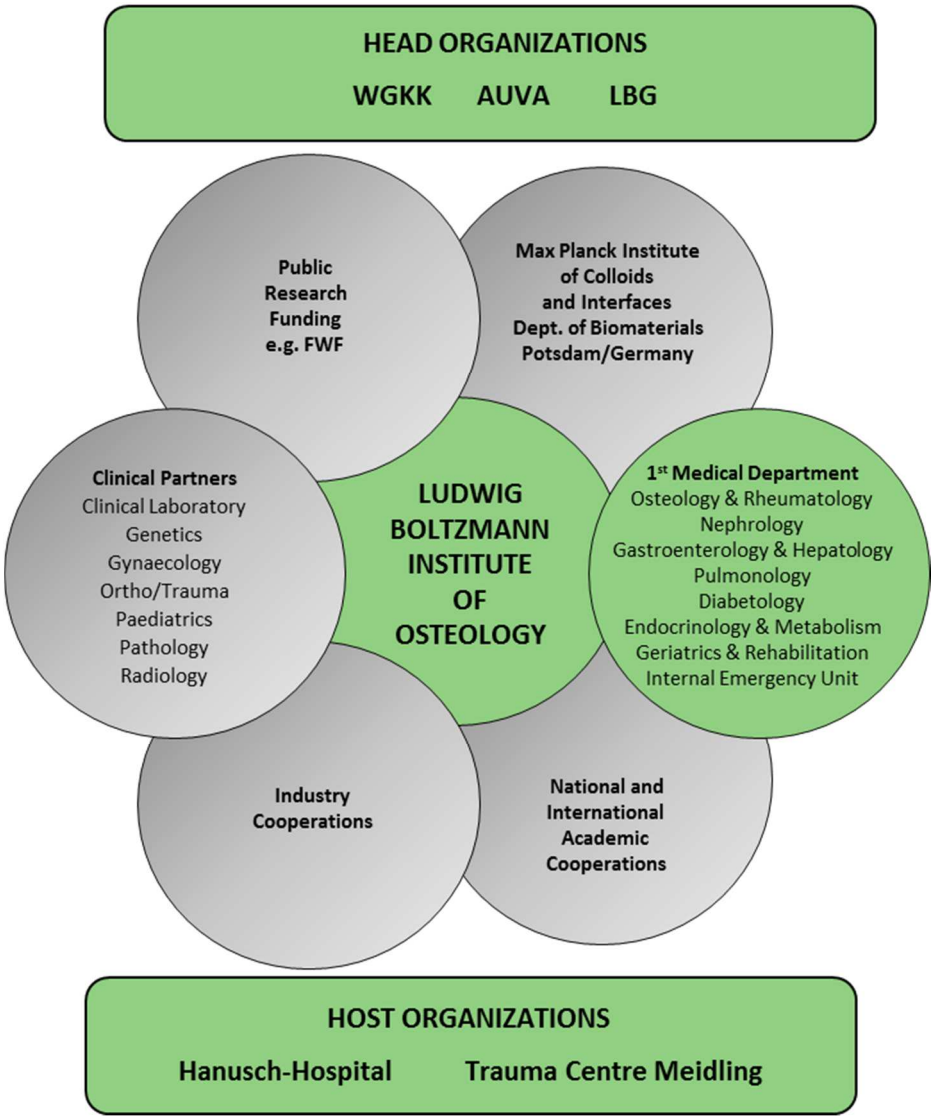
LBIO's **mission** is to achieve the highest level of scientific excellence through basic and clinical research, as well as the training of young scientists in clinical and experimental Osteology and the gender-neutral development of their careers.

LBIO's **goal** is the improvement of patient care. Towards this goal, the study of bone is undertaken at all hierarchical levels through a combination of techniques, unique worldwide.

The **aim** is the elucidation of the mechanisms underlying the basic function of bone, and musculoskeletal diseases, leading to the discovery and development of effective strategies for diagnosis, prevention, and treatment.

To **achieve** the stated goal, LBIO basic scientists and clinicians in tandem with scientists of the Department of Biomaterials of the Max Planck Institute of Colloids and Interfaces, Potsdam, Germany, as well as national and international collaborators and industry, are utilizing in partnerships the globally unparalleled LBIO expertise and available combination of analytical approaches to study bone at all hierarchical levels. The existing combination of instrumental capabilities allows analyses to be performed from a clinical, cell & molecular biology, physical chemical, and material science perspective.

1.2 Organization



Board members:
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2 Cooperations

2.1 Partners

Allgemeine Unfallversicherungsanstalt und Unfallkrankenhaus Meidling

Wiener Gebietskrankenkasse

Hanusch-Krankenhaus

Ludwig Boltzmann Gesellschaft

2.2 Ongoing scientific cooperations

Baylor College of Medicine, Department of Molecular and Human Genetics, Houston, USA (Dr. Erica Homan, Dr. Brendan Lee)

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Medical University of Vienna, Department of Forensic Medicine, Vienna, Austria (Prof. Andrea Berzlanovich)

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Orthopaedic Hospital Vienna-Speising, Department of Pediatric Orthopaedics, Deformity Correction, Neuroorthopaedics and Adult Foot and Ankle Surgery (Prof. Rudolf Ganger)

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3 Infrastructure/Methods

TECHNIQUE	OUTCOME
Cellular & Molecular Biology	Culture of primary cells and established cell lines. Techniques for studying gene expression including gene transfection and reporter gene assay. Cloning and recombinant protein techniques. Isolation and characterization of extracellular vesicles. Shear flow analysis using cultured bone forming cells.
Light Microscopy/ Histomorphometry	Structural parameters, parameters of static bone formation and resorption, dynamic bone formation. Pathohistological, diagnostic evaluation of bone biopsies.
Confocal Laser Scanning Microscopy	3-D fluorescence imaging of labeled bone tissue, cellular structures & cytoskeletal architecture. Imaging of resorption lacunae in *in-vitro* assays. Immunofluorescence microscopy of cultured cells.
qBEI (quantitative backscattered electron imaging)	Bone mineral density distribution (BMDD) in a spatially resolved manner at the µm-range.
EDX (energy dispersive X-ray micro-analysis)	Elemental composition of bone (sensitivity of quantification 0.1%)
HR-BEI (high resolution backscatter electron imaging)	Visualization of bone matrix in nm-range (limit 4nm)
Osteocyte lacunae section (OLS) characteristics	Analysis of qBEI images (pixel resolution 0.88 µm) resulting in characteristics of osteocyte lacunae in 2D-images. Parameters obtained are: OLS porosity (%), OLS density (number/mm^2), OLS area (µm^2), OLS perimeter (µm), and OLS aspect ratio
Scanning SAXS (Small-angle X-ray scattering) in coop. with P. Fratzl	Information of bone mineral crystallites characteristics in a spatially resolved manner at the nanometer range.
Nanoindentation in coop. with P. Fratzl	Spatial distribution of elastic properties of bone composite.
SASAM (Saarland scanning acoustic microscopy)	Spatially resolved acoustic properties of bone material at the µm-range.
FTIRI (Fourier transform infrared imaging)	Spatial distribution of mineral crystallite maturity Spatial distribution of collagen cross-link ratio at the 6.3 µm spatial level
ATR-FTIR (Attenuated total reflectance Fourier transform infrared)	Attenuated total reflectance FTIR spectroscopy coupled to a flow through chamber for real-time analysis of extracellular matrix in *in situ* cell cultures.
RAMAN	Spatial distribution of mineral characteristics at the 0.6-1 µm spatial level Mineral crystallite and collagen fiber orientation Nanoporosity Spatial distribution of pyridinoline collagen cross-link content Lipids AGEs Pyrophosphate Proteoglycans
Conventional X-ray	Clinical diagnosis; classification and characterization of patients

DXA, CT, MRT, bone scan	with bone diseases
Micro-computed tomography (micro-CT) instrument shared with H. Redl	Architecture/structure of mineralized bone sample

4 Closed projects and published manuscripts

4.1 Hypophosphatemia, severe bone pain, gait disturbance, and fatigue fractures after iron substitution in inflammatory bowel disease: a case report

Intravenous infusions of different iron formulations are recognized as a cause of hypophosphatemia. Chronic hypophosphatemia can alter bone metabolism and bone material structure. As a consequence, osteomalacia may develop and lead to bone fragility. Herein, we report a patient with Crohn's disease presenting with persistent hypophosphatemia and insufficiency fractures while receiving regular iron infusions due to chronic gastrointestinal bleeding. Previously, the patient regularly received vitamin D and also zoledronic acid. The patient underwent bone biopsy of the iliac crest that showed typical signs of osteomalacia with dramatically increased osteoid volume and decreased bone formation. Analysis of the bone mineralization density distribution (BMDD) revealed a more complex picture: On the one hand, there was a shift to higher matrix mineralization, presumably owing to low bone turnover; on the other hand, a broadening of the BMDD indicating more heterogeneous mineralization due to osteomalacia was also evident. This is the first report on changes of bone histomorphometry and bone matrix mineralization in iron-induced osteomalacia.

J Bone Miner Res 33:534-9 IF 6.314 (1415 + 1416)

4.2 Novel familial mutation of LRP5 causing high bone mass: Genetic analysis, clinical presentation, and characterization of bone matrix mineralization

The Wnt signalling pathway is a critical regulator of bone mass and quality. Several heterozygous mutations in the LRP5 gene, a Wnt co-receptor, causing high bone mass (LRP5-HBM) have been described to date. The pathogenic mechanism is thought to be a gain-of-function caused by impaired inhibition of the canonical Wnt signalling pathway, thereby leading to increased bone formation. We report the cases of two affected family members, a 53-year-old mother and her 23-year-old daughter, with high bone mass (T-scores mother: lumbar spine 11.4, femoral neck 10.5; T-scores daughter: lumbar spine 5.4, femoral neck 8.7), increased calvarial thickness, and thickened cortices of the long bones but no history of fractures. Whereas the mother did not show any indications of the mutation, the daughter suffered from congenital hearing impairment resulting in cochlear implantation, recurrent facial palsy, and migraine. In addition, she had stenosis of the foramen magnum. In both individuals, we detected a novel heterozygous duplication of six basepairs in the LRP5 gene, resulting in an insertion of two amino acids, very likely associated with a gain-of-function. When the daughter had part of the occipital bone surgically removed, the bone sample was used for the visualization of bone lamellar structure and bone cells as well as the measurement of bone mineralization density distribution (BMDD). The bone sample revealed two distinctly different regions: an intra-cortical region with osteonal remodeling, typical osteonal lamellar orientation, associated with relatively higher heterogeneity of bone matrix mineralization, and another periosteal region devoid of bone remodeling, with parallel bone lamellae and lower heterogeneity of mineralization. In conclusion, we present data on bone tissue and material level from an LRP5-HBM patient with a novel mutation in the LRP5 gene. Our findings indicate normal morphology of osteoclasts and osteoblasts as well as normal mineralization in skull bone in LRP5-HBM.

Bone 107:154-60 IF 4.455 (1417)

4.3 Chronic arsenicosis and cadmium exposure in wild snowshoe hares (Lepus americanus) breeding near Yellowknife, Northwest Territories (Canada), part 2: Manifestation of bone abnormalities and osteoporosis

Various bone abnormalities, including osteoporosis, have been associated with chronic arsenic and cadmium exposure in experimental animal models, but information regarding the bone

pathology of wild population of small mammals breeding in contaminated environment is limited. This present study was conducted to comparatively assess the prevalence and pattern of skeletal abnormalities in free ranging snowshoe hares inhabiting an area heavily contaminated by arsenic and other trace metals, near the vicinity of the abandoned Giant mine, and in a reference location approximately 20km from the city of Yellowknife, Northwest Territories, Canada. The femur and vertebrae of snowshoe hares from the mine area and reference location were subjected to bone densitometry examination and biomechanical testing using dual energy X-ray absorptiometry (DXA) and 3-point bending test. t-test results indicated that femoral densitometry parameters such as bone mineral density (BMD) ($p=0.5$), bone mineral content (BMC) ($p=0.675$), bone area (BA) ($p=0.978$) and tissue area (TA) ($p=0.549$) were not significantly different between locations. All densitometry parameters of the vertebrae (BMD, BA and TA) differed between locations ($p<0.05$), except for BMC ($p=0.951$) which showed no significant difference between the two locations. Vertebrae from the mine area also showed relatively lower BA and TA compared to the reference location. A constellation of skeletal abnormalities were also observed along the axial and appendicular bones respectively. Specifically, growth defects, osteoporosis, cortical fractures, sclerosis, and cyst like changes were commonly observed in the femurs and vertebrae of hares from both locations. With respect to biomechanical properties, only bone stiffness and peak load tended to be relatively reduced in specimens from the mine area, whereas work to failure was notably increased in specimens from the reference site compared to those from the mine area. Taken together, the results of this preliminary study suggest that chronic concomitant exposure to arsenic and cadmium may be involved in the etiology of various bone abnormalities, including osteoporosis in wild population of snowshoe hares from the Yellowknife area. The result presented in this study represent the first evaluation of osteological effects in free-ranging furbearers (snowshoe hares) diagnosed with arsenicosis, and concomitantly exposed to environmental levels of cadmium.

Sci Total Environ 612:1559-67 IF 4.610 (1418)

4.4 Proteomics to predict the response to tumour necrosis factor-α inhibitors in rheumatoid arthritis using a supervised cluster-analysis based protein score

OBJECTIVE:

In rheumatoid arthritis (RA), it is of major importance to identify non-responders to tumour necrosis factor-α inhibitors (TNFi) before starting treatment, to prevent a delay in effective treatment. We developed a protein score for the response to TNFi treatment in RA and investigated its predictive value.

METHOD:

In RA patients eligible for biological treatment included in the BiOCURA registry, 53 inflammatory proteins were measured using xMAP® technology. A supervised cluster analysis method, partial least squares (PLS), was used to select the best combination of proteins. Using logistic regression, a predictive model containing readily available clinical parameters was developed and the potential of this model with and without the protein score to predict European League Against Rheumatism (EULAR) response was assessed using the area under the receiving operating characteristics curve (AUC-ROC) and the net reclassification index (NRI).

RESULTS:

For the development step (n = 65 patient), PLS revealed 12 important proteins: CCL3 (macrophage inflammatory protein, MIP1a), CCL17 (thymus and activation-regulated chemokine), CCL19 (MIP3b), CCL22 (macrophage-derived chemokine), interleukin-4 (IL-4), IL-6, IL-7, IL-15, soluble cluster of differentiation 14 (sCD14), sCD74 (macrophage migration inhibitory factor), soluble IL-1 receptor I, and soluble tumour necrosis factor receptor II. The protein score scarcely improved the AUC-ROC (0.72 to 0.77) and the ability to improve classification and reclassification (NRI = 0.05). In validation (n = 185), the model including protein score did not improve the AUC-ROC (0.71 to 0.67) or the reclassification (NRI = -0.11).

CONCLUSION:

No proteomic predictors were identified that were more suitable than clinical parameters in distinguishing TNFi non-responders from responders before the start of treatment. As the results of previous studies and this study are disparate, we currently have no proteomic predictors for the response to TNFi.

Scand J Rheumatol 47:12-21 IF 3.021 (1419)

4.5 Digital PCR: a sensitive and precise method for KIT D816V quantification in mastocytosis

BACKGROUND:
The analytically sensitive detection of KIT D816V in blood and bone marrow is important for diagnosing systemic mastocytosis (SM). Additionally, precise quantification of the KIT D816V variant allele fraction (VAF) is relevant clinically because it helps to predict multilineage involvement and prognosis in cases of advanced SM. Digital PCR (dPCR) is a promising new method for sensitive detection and accurate quantification of somatic mutations.
METHODS:
We performed a validation study of dPCR for KIT D816V on 302 peripheral blood and bone marrow samples from 156 patients with mastocytosis for comparison with melting curve analysis after peptide nucleic acid-mediated PCR clamping (clamp-PCR) and allele-specific quantitative real-time PCR (qPCR).
RESULTS:
dPCR showed a limit of detection of 0.01% VAF with a mean CV of 8.5% and identified the mutation in 90% of patients compared with 70% for clamp-PCR ($P < 0.001$). Moreover, dPCR for KIT D816V was highly concordant with qPCR without systematic deviation of results, and confirmed the clinical value of KIT D816V VAF measurements. Thus, patients with advanced SM showed a significantly higher KIT D816V VAF (median, 2.43%) compared with patients with indolent SM (median, 0.14%; $P < 0.001$). Moreover, dPCR confirmed the prognostic significance of a high KIT D816V VAF regarding survival ($P < 0.001$).
CONCLUSIONS:
dPCR for KIT D816V provides a high degree of precision and sensitivity combined with the potential for interlaboratory standardization, which is crucial for the implementation of KIT D816V allele burden measurement. Thus, dPCR is suitable as a new method for KIT D816V testing in patients with mastocytosis.

Clin Chem 64:547-55 IF 8.008 (1420)

4.6 A randomized controlled trial-based algorithm for insulin-pump therapy in hyperglycemic patients early after kidney transplantation

Treating hyperglycemia in previously non-diabetic individuals with exogenous insulin immediately after kidney transplantation reduced the odds of developing Posttransplantation Diabetes Mellitus (PTDM) in our previous proof-of-concept clinical trial. We hypothesized that insulin-pump therapy with maximal insulin dosage during the afternoon would improve glycemic control compared to basal insulin and standard-of-care. In a multi-center, randomized, controlled trial testing insulin isophane for PTDM prevention, we added a third study arm applying continuous subcutaneous insulin lispro infusion (CSII) treatment. CSII was initiated in 24 patients aged 55±12 years, without diabetes history, receiving tacrolimus. The mean daily insulin lispro dose was 9.2±5.2 IU. 2.3±1.1% of the total insulin dose were administered between 00:00 and 6:00, 19.5±11.6% between 6:00 and 12:00, 62.3±15.6% between 12:00 and 18:00 and 15.9±9.1% between 18:00 and 24:00. Additional bolus injections were necessary in five patients. Mild hypoglycemia (52-60 mg/dL) occurred in two patients. During the first post-operative week glucose control in CSII patients was overall superior compared to standard-of-care as well as once-daily insulin isophane for fasting and post-supper glucose. We present an algorithm for CSII treatment in kidney transplant

recipients, demonstrating similar safety and superior short-term efficacy compared to standard-of-care and once-daily insulin isophane.

PLoS One 13:e0193569 IF 3.540 (1421)

4.7 Use of biological disease modifying antirheumatic drugs in rheumatoid arthritis in Austria from 2008 to 2011: A retrospective analysis of 72% of the population

BACKGROUND:
Rheumatoid arthritis (RA) is the most prevalent chronic inflammatory joint disease. On a national level in Austria, there are currently no data available on how often and which biological disease modifying antirheumatic drugs (bDMARDs) are prescribed in patients with RA. The aim of the present study was to explore prescription patterns of bDMARDs in RA in Austria with a focus on drug survival.
METHODS:
A retrospective data analysis of bDMARD courses of individual patients with RA that were extracted from the databases of nine Austrian health insurance funds covering 6.1 million (72%) insured people in a 4-year observation period from January 2008 to December 2011. Only patients with first prescriptions of bDMARDs were included. All patients with diagnoses other than RA were excluded.
RESULTS:
A total of 2906 first prescriptions of bDMARDs were included in the present analysis and 19.35% of RA patients were on bDMARDs in Austria taking into account a prevalence of RA of 0.5%. Tocilizumab showed the longest drug survival after 1 year (73.2%), followed by abatacept which had the longest drug survival after 2 (68.2%) and 3 years (65.2%). The most frequent second bDMARDs switched to were adalimumab (n = 109, 26%), tocilizumab (n = 83, 20%) and etanercept (n = 82, 20%) and 37% of biological DMARDs were prescribed as monotherapy (ranging from 33% with infliximab to 46% with tocilizumab).
CONCLUSIONS:
Our analysis is based on the largest health care database available in Austria. Tocilizumab and abatacept showed the longest drug survival. Adalimumab, tocilizumab and etanercept were the most frequent DMARDs switched to. Of interest was the high number of bDMARD monotherapies.

Wien Klin Wochenschr 130:230-7 IF 1.003 (1422)

4.8 Somatic activating mutations in MAP2K1 cause melorheostosis

Melorheostosis is a sporadic disease of uncertain etiology characterized by asymmetric bone overgrowth and functional impairment. Using whole exome sequencing, we identify somatic mosaic MAP2K1 mutations in affected, but not unaffected, bone of eight unrelated patients with melorheostosis. The activating mutations (Q56P, K57E and K57N) cluster tightly in the MEK1 negative regulatory domain. Affected bone displays a mosaic pattern of increased p-ERK1/2 in osteoblast immunohistochemistry. Osteoblasts cultured from affected bone comprise two populations with distinct p-ERK1/2 levels by flow cytometry, enhanced ERK1/2 activation, and increased cell proliferation. However, these MAP2K1 mutations inhibit BMP2-mediated osteoblast mineralization and differentiation in vitro, underlying the markedly increased osteoid detected in affected bone histology. Mosaicism is also detected in the skin overlying bone lesions in four of five patients tested. Our data show that the MAP2K1 oncogene is important in human bone formation and implicate MEK1 inhibition as a potential treatment avenue for melorheostosis.

Nat Commun 9:1390 IF 12.353 (1423)

4.9 Cardiac, bone and growth plate manifestations in hypocalcemic infants: revealing the hidden body of the vitamin D deficiency iceberg

BACKGROUND:

Whilst hypocalcemic complications from vitamin D deficiency are considered rare in high-income countries, they are highly prevalent among Black, Asian and Minority Ethnic (BAME) group with darker skin. To date, the extent of osteomalacia in such infants and their family members is unknown. Our aim was to investigate clinical, cardiac and bone histomorphometric characteristics, bone matrix mineralization in affected infants and to test family members for biochemical evidence of osteomalacia.
CASE PRESENTATION:
Three infants of BAME origin (aged 5-6 months) presented acutely in early-spring with cardiac arrest, respiratory arrest following seizure or severe respiratory distress, with profound hypocalcemia (serum calcium 1.22-1.96 mmol/L). All infants had dark skin and vitamin D supplementation had not been addressed during child surveillance visits. All three had severely dilated left ventricles (z-scores + 4.6 to + 6.5) with reduced ejection fraction (25-30%; normal 55-70), fractional shortening (7 to 15%; normal 29-40) and global hypokinesia, confirming hypocalcemic dilated cardiomyopathy. They all had low serum levels of 25 hydroxyvitamin D (25OHD < 15 nmol/L), and elevated parathyroid hormone (PTH; 219-482 ng/L) and alkaline phosphatase (ALP; 802-1123 IU/L), with undiagnosed rickets on radiographs. One infant died from cardiac arrest. At post-mortem examination, his growth plate showed a widened, irregular zone of hypertrophic chondrocytes. Histomorphometry and backscattered electron microscopy of a trans-iliac bone biopsy sample revealed increased osteoid thickness (+ 262% of normal) and osteoid volume/bone volume (+ 1573%), and extremely low bone mineralization density. Five of the nine tested family members had vitamin D deficiency (25OHD < 30 nmol/L), three had insufficiency (< 50 nmol/L) and 6/9 members had elevated PTH and ALP levels.
CONCLUSIONS:
The severe, hidden, cardiac and bone pathology described here exposes a failure of public health prevention programs, as complications from vitamin D deficiency are entirely preventable by routine supplementation. The family investigations demonstrate widespread deficiency and undiagnosed osteomalacia in ethnic risk groups and call for protective legislation.

BMC Pediatr 18:183 IF 2.042 (1424)

4.10 Late stages of mineralization and their signature on the bone mineral density distribution

PURPOSE:
Experimental measurements of bone mineral density distributions (BMDDs) enable a determination of secondary mineralization kinetics in bone, but the maximum degree of mineralization and how this maximum is approached remain uncertain. We thus test computationally different hypotheses on late stages of bone mineralization by simulating BMDDs in low-turnover conditions.
MATERIALS AND METHODS:
An established computational model of the BMDD that accounts for mineralization and remodeling processes was extended to limit mineralization to various maximum calcium capacities of bone. Simulated BMDDs obtained by reducing turnover rate from the reference trabecular BMDD under different assumptions on late stage mineralization kinetics were compared with experimental BMDDs of low-turnover bone.
RESULTS:
Simulations show that an abrupt stopping of mineralization near a maximum calcium capacity induces a pile-up of minerals in the BMDD statistics that is not observed experimentally. With a smooth decrease of mineralization rate, imposing low maximum calcium capacities helps to match peak location and width of simulated low-turnover BMDDs with peak location and width of experimental BMDDs, but results in a distinctive asymmetric peak shape. No tuning of turnover rate and maximum calcium capacity was able to explain the differences found in experimental BMDDs between trabecular bone (high turnover) and femoral cortical bone (low turnover).
CONCLUSIONS:

Secondary mineralization in human bone does not stop abruptly, but continues slowly up to a calcium content greater than 30 wt% Ca. The similar mineral heterogeneity seen in trabecular and femoral cortical bones at different peak locations was unexplained by the turnover differences tested.

Connect Tissue Res 59(sup1):74-80 IF 2.608 (1425)

4.11 Mutations that alter the carboxy-terminal-propeptide cleavage site of the chains of type I procollagen are associated with a unique osteogenesis imperfecta phenotype

Osteogenesis imperfecta (OI) is a genetic bone disorder characterized by fractures, low bone mass, and skeletal fragility. It most commonly arises from dominantly inherited mutations in the genes COL1A1 and COL1A2 that encode the chains of type I collagen. A number of recent reports have suggested that mutations affecting the carboxyl-terminal propeptide cleavage site in the products of either COL1A1 or COL1A2 give rise to a form of OI characterized by unusually dense bones. We have assembled clinical, biochemical, and molecular data from 29 individuals from 8 families with 7 different mutations affecting the C-propeptide cleavage site. The phenotype was generally mild: The median height was ~33th centile. Eighty percent of subjects had their first fracture by the age of 10 years, and one-third had a femoral or tibial fracture by the age of 25 years. Fractures continued into adulthood, though rates varied considerably. Healing was normal and rarely resulted in long bone deformity. One-third of subjects older than 15 years had scoliosis. The teeth and hearing were normal in most, and blue sclerae were not observed. Other features noted included fibro-osseous dysplasia of the mandible and Achilles tendon calcification. The mean spinal bone mineral density Z-score was +2.9 (SD 2.1) compared with -2.2 (0.7) in subjects with COL1A1 haploinsufficiency mutations. Bone mineral density distribution, assessed by quantitative backscattered electron imaging in bone showed higher levels of mineralization than found in any other disorder. Bone histology showed high trabecular volume and increased cortical thickness, with hyperosteoidosis and delayed mineralization. In vitro studies with cultured skin fibroblasts suggested that these mutations interfere with processing of the chain in which the sequence alteration occurs, but the C-propeptide is eventually cleaved (and detectable in blood), suggesting there are alternative sites of cleavage. The precise mechanism of the bony pathology is not yet clear.

J Bone Miner Res 33:1260-71 IF 6.314 (1426)

4.12 Performance of the 2012 Systemic Lupus International Collaborating Clinics classification criteria versus the 1997 American College of Rheumatology classification criteria in adult and juvenile systemic lupus erythematosus. A systematic review and meta-analysis

OBJECTIVE:

To evaluate the performance in classifying systemic lupus erythematosus by the 2012 Systemic Lupus International Collaborating Clinics criteria (SLICC'12), versus the revised American College of Rheumatology criteria from 1997 (ACR'97) in adult and juvenile SLE patients.

METHODS:

A systematic literature search was conducted in PubMed and Embase for studies comparing SLICC'12 and ACR'97 with clinical diagnosis. A meta-analysis was performed to estimate the sensitivity and specificity of SLICC'12 and ACR'97. To assess classification earlier in the disease by either set, sensitivity and specificity were compared for patients with disease duration <5years. Sensitivity and specificity of individual criteria items were also assessed.

RESULTS:

In adult SLE (nine studies: 5236 patients, 1313 controls), SLICC'12 has higher sensitivity (94.6% vs. 89.6%) and similar specificity (95.5% vs. 98.1%) compared to ACR'97. For juvenile SLE (four studies: 568 patients, 339 controls), SLICC'12 demonstrates higher sensitivity (99.9% vs. 84.3%)

than ACR'97, but much lower specificity (82.0% vs. 94.1%). SLICC'12 classifies juvenile SLE patients earlier in disease course. Individual items contributing to diagnostic accuracy are low complement, anti-ds DNA and acute cutaneous lupus in SLICC'12, and the immunologic and hematologic disorder in ACR'97.
CONCLUSION:
Based on sensitivity and specificity SLICC'12 is best for adult SLE. Following the view that higher specificity, i.e. avoidance of false positives, is preferable, ACR'97 is best for juvenile SLE even if associated with lower sensitivity. Our results on the contribution of the individual items of SLICC'12 and ACR´97 may be of value in future efforts to update classification criteria.

Autoimmun Rev 17:316-22 IF 8.745 (1427)

4.13 Homozygosity for CREB3L1 premature stop codon in first case of recessive osteogenesis imperfecta associated with OASIS-deficiency to survive infancy

BACKGROUND:
Mutations of the endoplasmic reticulum (ER)-stress transducer OASIS (encoded by CREB3L1), cause severe recessive osteogenesis imperfecta (OI) not compatible with surviving the neonatal period, as has been shown in two unrelated families through a whole gene deletion vs. a qualitative alteration of OASIS. Heterozygous carriers in the described families have exhibited a mild phenotype. OASIS is a transcription factor highly expressed in osteoblasts, and OASIS-/- mice exhibit severe osteopenia and spontaneous fractures. Here, we expand the clinical spectrum by a detailed phenotypic characterization of the first case of OASIS-associated OI surviving the neonatal period, with heterozygous family members being unaffected.
METHODS:
All OI-associated genes were sequenced. Primary human osteoblast-like cell (hOB) and fibroblast (FB) cultures were obtained for qPCR, and steady-state collagen biochemistry. FB, hOB and skin biopsies were ultrastructurally analysed. Bone was analysed by µCT, histomorphometry, quantitative backscattered electron imaging (qBEI), and Raman microspectroscopy.
RESULTS:
The proband, a boy with severe OI, had blue sclera and tooth agenesis. A homozygous CREB3L1 stop codon mutation was detected by sequencing, while several family members were heterozygotes. Markedly low levels of CREB3L1 mRNA were confirmed by qPCR in hOBs (16%) and FB (21%); however, collagen I levels were only reduced in hOBs (5-10%). Electron microscopy of hOBs showed pronounced alterations, with numerous myelin figures and diminished RER vs. normal ultrastructure of FB. Bone histomorphometry and qBEI were similar to collagen I OI, with low trabecular thickness and mineral apposition rate, and increased bone matrix mineralization. Raman microspectroscopy revealed low level of glycosaminoglycans. Clinical response to life-long bisphosphonate treatment was as expected in severe OI with steadily increasing bone mineral density, but despite this the boy suffered repeated childhood fractures.
CONCLUSIONS:
Deficiency of OASIS can cause severe OI compatible with surviving the neonatal period. A marked decrease of collagen type I transcription was noted in bone tissue, but not in skin, and ultrastructure of hOBs was pathological. Results also suggested OASIS involvement in glycosaminoglycan secretion in bone.

Bone 114:268-77 IF 4.455 (1428)

4.14 RNA sequencing to predict response to TNF-α inhibitors reveals possible mechanism for nonresponse in smokers

BACKGROUND:
Several studies have employed microarray-based profiling to predict response to tumor necrosis factor-alpha inhibitors (TNFi) in rheumatoid arthritis (RA); yet efforts to validate these targets have failed to show predictive abilities acceptable for clinical practice.

METHODS:
The eighty most extreme responders and nonresponders to TNFi therapy were selected from the observational BiOCURA cohort. RNA sequencing was performed on mRNA from peripheral blood mononuclear cells (PBMCs) collected before initiation of treatment. The expression of pathways as well as individual gene transcripts between responders and nonresponders was investigated. Promising targets were technically replicated and validated in n = 40 new patients using qPCR assays.
RESULTS:
Before therapy initiation, nonresponders had lower expression of pathways related to interferon and cytokine signaling, while also showing higher levels of two genes, GPR15 and SEMA6B ($p = 0.02$). The two targets could be validated, however, additional analyses revealed that GPR15 and SEMA6B did not independently predict response, but were rather dose-dependent markers of smoking ($p < 0.0001$).
CONCLUSIONS:
The study did not identify new transcripts ready to use in clinical practice, yet GPR15 and SEMA6B were recognized as candidate explanatory markers for the reduced treatment success in RA smokers.

Expert Rev Clin Immunol 14:623-33 IF 3.436 (1429)

4.15 Attaining the optimal flange for intrascleral intraocular lens fixation

We describe a technique for making an optimal flange in intraocular lenses (IOLs) used for flanged intrascleral IOL fixation. The flange shape varies in poly(methyl methacrylate) (PMMA) haptics of different IOLs of different manufacturers. We identified the distance between the forceps grip of the haptic and the end of the haptic during heating with a cauter as a critical factor for the optimal flange shape in 5 PMMA haptics but not in 2 polyvinylidene fluoride haptics.

J Cataract Refract Surg S0886-3350(18)30669-2 IF 2.680 (1430)

4.16 Novel PLS3 variants in X-linked osteoporosis: Exploring bone material properties

BACKGROUND:
Idiopathic Juvenile Osteoporosis (IJO) refers to significantly lower than expected bone mass manifesting in childhood with no identifiable aetiology. IJO classically presents in early pubertal period with multiple fractures including metaphyseal and vertebral crush fractures, and low bone-mass.
METHODS:
Here we describe two patients and provide information on their clinical phenotype, genotype and bone material analysis in one of the patients.
RESULTS:
Patient 1: 40-year old adult male diagnosed with IJO in childhood who re-presented with a hip fracture as an adult. Genetic analysis identified a pathogenic PLS3 hemizygous variant, c.1765del in exon 16. Patient 2: 15-year old boy with multiple vertebral fractures and bone biopsy findings suggestive of IJO who also has a diagnosis of autism spectrum disorder. Genetic analysis identified a maternally inherited PLS3 pathogenic c.1295T>A variant in exon 12. Analyses of the transiliac bone sample revealed severe reduction of trabecular volume and bone turnover indices and elevated bone matrix mineralisation.
DISCUSSION:
We propose that genetic testing for PLS3 should be undertaken in patients presenting with a current or previous history of IJO as this has implications for genetic counselling and cascade screening. The extensive evaluation of the transiliac biopsy sample of Patient 2 revealed a novel bone phenotype.
CONCLUSION:

This report includes a review of IJO and genetic causes of osteoporosis, and suggests that existing cases of IJO should be screened for PLS3. Through analysis of bone material properties in Patient 2, we can conclude that PLS3 does have a role in bone mineralisation.

Am J Med Genet A 176:1578-86 IF 2.264 (1431)

4.17 A randomized, first-in-human, healthy volunteer trial of sutimlimab, a humanized antibody for the specific inhibition of the classical complement pathway

Aberrant activation of the classical complement pathway is the common underlying pathophysiology of orphan diseases such as bullous pemphigoid, antibody-mediated rejection of organ transplants, cold agglutinin disease, and warm autoimmune hemolytic anemia. Therapeutic options for these complement-mediated disorders are limited and sutimlimab, a humanized monoclonal antibody directed against complement factor C1s, may be potentially useful for inhibition of the classical complement pathway. A phase I, first-in-human, double-blind, randomized, placebo-controlled, dose-escalation trial of single and multiple doses of sutimlimab or placebo was conducted in 64 volunteers to evaluate safety, tolerability, pharmacokinetic, and pharmacodynamic profiles. Single and multiple infusions of sutimlimab were well tolerated without any safety concerns. sutimlimab exhibited a steep concentration-effect relationship with a Hill coefficient of 2.4, and an IC90 of 15.5 µg/mL. This study establishes the foundation for using sutimlimab as a highly selective inhibitor of the classical complement pathway in different diseases.

Clin Pharmacol Ther 104:655-63 IF 6.544 (1432)

4.18 Schmid's type of metaphyseal chondrodysplasia: diagnosis and management

OBJECTIVES:
There are several types of metaphyseal chondrodysplasia and various clinical types have been differentiated. The Schmid type of metaphyseal chondrodysplasia is the most common. Diffuse metaphyseal flaring, irregularity, and growth plate widening, which are most severe in the knees, are the most striking radiological features of this disease. The Schmid type of metaphyseal dysostosis is characterized by failure of normal mineralization of the zone of provisional calcification, leading to widened physes and enlarged knobby metaphyses, effectively causing shortening of the tubular bones, splaying of the metaphyses, coxa vara, and bow legs. Orthopaedic interventions were primarily performed on the lower extremities.
METHODS:
Twelve children (seven girls and five boys) aged 7-10 years were enrolled in this study. Moderate short stature was a uniform feature associated with predominant involvement of the proximal femora and bow legs resulted in the development of angular deformities. A waddling gait was a consequence of coxa vara in eight children. Valgus osteotomy of the proximal femur was planned after physeal closure for the group of children with coxa vara. Hemiepiphysiodesis was performed to re-align the genu varum in three children.
RESULTS:
Other forms of metaphyseal dysostosis were ruled based on full clinical and radiographic phenotypes, with confirmation through molecular pathology. Mutations in the COL10A1 gene located on chromosome 6q21-q22.3 were confirmed. Re-alignment was accomplished in our group of patients.
CONCLUSION:
The most striking clinical features of Schmid metaphyseal chondrodysplasia which appear within the first 2-3 years of life are: moderate short limbs and short stature, a waddling gait, and increasing shortness of stature with age. The Schmid type of metaphyseal chondrodysplasia is a disorder that arises from defective type X collagen, which is typically found in the hypertrophic zone of the physes. Moderate short stature and a waddling gait associated with pain are the most

common clinical presentations. Osteotomies to correct bow legs are sometimes combined with lengthening procedures. Recurrence of the deformities with growth is not uncommon; therefore, hemiepiphysiodesis or stapling might be indicated in some cases.

Orthop Surg 10:241-6 IF 1.147 (1433)

4.19 Hypophosphatasia: from diagnosis to treatment

PURPOSE OF REVIEW:
Hypophosphatasia (HPP) is a rare genetic disorder caused by mutations of the ALPL gene. ALPL encodes the tissue-non-specific isoenzyme of alkaline phosphatase (TNSALP). Consequently, bone mineralization is decreased leading to fractures, arthralgia, and extra-skeletal manifestations including tissue calcification, respiratory failure, and neurological complications. This review summarizes the most important clinical findings, diagnosis, and treatment options for HPP.
RECENT FINDINGS:
Asfotase alfa is a recombinant human alkaline phosphatase, used as treatment for the underlying cause of HPP. Asfotase alfa enhances the survival in life-threatening HPP and improves bone mineralization, muscle strength, and pulmonary function. However, discontinuation of asfotase alfa leads to reappearance of bone hypomineralization. Due to its varied manifestations, HPP often mimics rheumatological and other bone diseases, thereby delaying its diagnosis. Asfotase alfa, a recombinant alkaline phosphatase, is available for the long-term enzyme replacement therapy in patients with pediatric-onset HPP to treat the bone manifestations of the disease.

Curr Rheumatol Rep 20:69 IF 3.079 (1434)

4.20 An evidence-based approach to pre-pregnancy counselling for patients with systemic lupus erythematosus

Patients with SLE are often young females of childbearing age and a pregnancy wish in this patient group is common. However, SLE patients are at high risk for adverse pregnancy outcomes that require adequate guidance. It is widely acknowledged that pre-pregnancy counselling is the pivotal first step in the management of SLE patients with a wish to become pregnant. Next, management of these patients is usually multidisciplinary and often requires specific expertise from the different physicians involved. Very recently a EULAR recommendation was published emphasizing the need for adequate preconception counselling and risk stratification. Therefore the present review specifically addresses the issue of pre-pregnancy counselling for SLE patients with an evidence-based approach. The review summarises data retrieved from recently published, high-quality cohort studies that have contributed to a better understanding and estimation of pregnancy-related risks for SLE patients. The present review categorizes risks from a patient-oriented point of view, that is, the influence of pregnancy on SLE, of SLE on pregnancy, of SLE on the foetus/neonate and of SLE-related medication. Lastly, pre-pregnancy counselling of SLE patients with additional secondary APS is reviewed. Collectively these data can guide clinicians to formulate appropriate preventive strategies and patient-tailored monitoring plans during pre-pregnancy counselling of SLE patients.

Rheumatology (Oxford) 57:1707-20 IF 5.245 (1435)

4.21 Impaired osteocyte maturation in the pathogenesis of renal osteodystrophy

Pediatric renal osteodystrophy is characterized by skeletal mineralization defects, but the role of osteoblast and osteocyte maturation in the pathogenesis of these defects is unknown. We evaluated markers of osteocyte maturation and programmed cell death in iliac crest biopsy samples from pediatric dialysis patients and healthy controls. We evaluated the relationship between numbers of fibroblast growth factor 23 (FGF23)-expressing osteocytes and histomorphometric parameters of skeletal mineralization. We confirmed that chronic kidney disease (CKD) causes intrinsic changes in bone cell maturation using an in vitro model of primary osteoblasts from patients with CKD and healthy controls. FGF23 co-localized with the early

osteocyte marker E11/gp38, suggesting that FGF23 is a marker of early osteocyte maturation. Increased numbers of early osteocytes and decreased osteocyte apoptosis characterized CKD bone. Numbers of FGF23-expressing osteocytes were highest in patients with preserved skeletal mineralization indices, and packets of matrix surrounding FGF23-expressing osteocytes appeared to have entered secondary mineralization. Primary osteoblasts from patients with CKD retained impaired maturation and mineralization characteristics in vitro. Addition of FGF23 did not affect primary osteoblast mineralization. Thus, CKD is associated with intrinsic changes in osteoblast and osteocyte maturation, and FGF23 appears to mark a relatively early stage in osteocyte maturation. Improved control of renal osteodystrophy and FGF23 excess will require further investigation into the pathogenesis of CKD-mediated osteoblast and osteocyte maturation failure.

Kidney Int 94:1002-12 IF 8.429 (1436)

4.22 Functional consultation and exercises improve grip strength in osteoarthritis of the hand - a randomised controlled trial

BACKGROUND:

Evidence for non-pharmacological interventions in hand osteoarthritis is promising but still scarce. Combined interventions are most likely to best cover the clinical needs of patients with hand osteoarthritis (OA). The aim of this study was to evaluate the effect of a combined, interdisciplinary intervention feasible in both primary and specialist care compared to routine care plus placebo in patients with hand OA.

METHODS:

This was a randomised, controlled 2-month trial with a blinded assessor. In the combined-intervention group, rheumatology-trained health professionals from different disciplines delivered a one-session individual intervention with detailed information on functioning, activities of daily living, physical activity, nutrition, assistive devices, instructions on pain management and exercises. Telephone follow up was performed after 4 weeks. The primary outcome was grip strength after 8 weeks. Secondary outcomes were self-reported pain, satisfaction with treatment, health status, two of the Jebsen-Taylor Hand Function subtests and the total score of the Australian/Canadian Hand Osteoarthritis Index (AUSCAN). Statistical significance was calculated by Student's t test or the Mann-Whitney U test depending on data distribution. Binominal logistic regression models were fitted, with the primary outcome being the dependent and the group allocation being the independent variable.

RESULTS:

There were 151 participating patients (74 in the combined-intervention and 77 in the routine-care-plus-placebo group) with 2-month follow-up attendance of 84% (n = 128). Grip strength significantly increased in the combined-intervention group and decreased in the routine-care group (dominant hand, mean 0.03 bar (SD 0.11) versus - 0.03 (SD 0.13), p value = 0.001, baseline corrected values) after 8 weeks.

CONCLUSION:

The combined one-session individual intervention significantly improved grip strength and self-reported satisfaction with treatment in patients with hand OA. It can be delivered by different rheumatology-trained health professionals and is thus also feasible in primary care.

Arthritis Res Ther 20:253 IF 4.269 (1437)

4.23 HFE hemochromatosis screening in patients with severe hip osteoarthritis: A prospective cross-sectional study

OBJECTIVE:

Despite the high frequency of HFE gene mutations in Western Europe, widespread screening for HFE hemochromatosis is not recommended due to its variable phenotype. Joint pain and a premature osteoarthritis-like disease including the hip joints are the most frequent manifestation in

patients with HFE hemochromatosis and iron overload. Therefore, screening of patients with severe osteoarthritis of the hip could identify patients with HFE hemochromatosis.
METHODS:
In this prospective cross-sectional study, 940 patients aged <70 years with end-stage osteoarthritis of the hip undergoing elective joint replacement surgery were screened for HFE hemochromatosis and compared to age- and sex-matched controls.
RESULTS:
No greater prevalence of C282Y homozygosity mutation or elevated serum ferritin or transferrin saturation levels was found in the study cohort with severe osteoarthritis of the hip than in controls from the general population.
CONCLUSION:
Our screening approach could not identify an increased prevalence of HFE gene mutations and iron overload in younger patients with severe osteoarthritis of the hip.

PLoS One 13:e0207415 IF 2.766 (1438)

4.24 mineral content and volume in cortical and trabecular bone of Iliac crest: A comparison of infrared imaging with X-ray-based bone assessment techniques

Teriparatide increases bone mass primarily through remodeling of older or damaged bone and abundant replacement with new mineralizing bone. This post hoc analysis investigated whether dual-energy X-ray absorptiometric (DXA) areal bone mineral density (aBMD) measurement adequately reflects changes of mineral and organic matrix content in cortical and trabecular bone. Paired biopsies and aBMD measurements were obtained before and at end of 2 years of teriparatide treatment from postmenopausal women with osteoporosis who were either alendronate pretreated (mean, 57.5 months) or osteoporosis-treatment naive. Biopsies were assessed by micro-computed tomography (μCT) to calculate mean cortical width (Ct.Wi), cortical area (Ct.Ar), and trabecular bone volume fraction (BV/TV). Fourier transformed infrared imaging (pixel size $\sim 6.3 \times 6.3\,\mu m2$) was utilized to calculate mineral and organic matrix density (mean absorption/pixel), as well as total mineral and organic contents of cortical and cancellous compartments (sum of all pixels in the compartment). Effect of pretreatment over time was analyzed using mixed model repeated measures. μCT derived Ct.Wi and BV/TV increased, accompanied by similar increases in the overall mineral contents of their respective bone compartments. Mineral density did not change. Marked increases in the total content of both mineral and organic matrix associated with volumetric growth in both compartments consistently exceeded those of aBMD. Increases in organic matrix exceeded increases in mineral content in both cortical and trabecular compartments. For percent changes, only change in Ct.Wi correlated to change in femoral neck aBMD ($r = .38$, $p = 0.043$), whereas no other significant correlations of Ct.Wi or BV/TV with lumbar spine, total hip, or femoral neck aBMD were demonstrable. These data indicate that 2 years of teriparatide treatment leads to an increased bone organic matrix and mineral content in the iliac crest. The magnitude of these increases in the iliac crest were not detected with conventional aBMD measurements at other skeletal sites.

J Bone Miner Res 33:2230-5 IF 6.314 (1439)

4.25 Morphine interaction with Aspirin: a double-blind, crossover trial in healthy volunteers

Aspirin is a cornerstone in the antiplatelet therapy for acute coronary syndromes. Coadministration of morphine may potentially influence the intestinal absorption, pharmacokinetics, and pharmacodynamics, as seen with $P2Y_{12}$ inhibitors. In this trial, healthy volunteers were randomized to receive morphine (5 mg, i.v. bolus injection) at one of seven different time points before, after, or with aspirin (162 mg, p.o.) in a double-blind, placebo-controlled fashion. After a 14-day washout, subjects received placebo instead of morphine. Pharmacokinetics were determined by liquid chromatography, and aspirin's effects were measured by platelet function tests (whole-blood

platelet aggregation: multiplate, platelet plug formation: PFA-100). Morphine increased the total acetylsalicylic acid exposure by 20% compared with placebo when given simultaneously with aspirin, whereas C_{max} and t_{max} were not altered. Morphine had no significant effect on aspirin-induced platelet inhibition. In contrast to coadministration with $P2Y_{12}$ inhibitors, morphine appears to have negligible interaction with aspirin.

J Pharmacol Exp Ther 365:430-6 IF 3.706 (1440)

4.26 Galectin-9 is an easy to measure biomarker for the interferon signature in systemic lupus erythematosus and antiphospholipid syndrome

OBJECTIVE:
The interferon (IFN) signature is related to disease activity and vascular disease in systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) and represents a promising therapeutic target. Quantification of the IFN signature is currently performed by gene expression analysis, limiting its current applicability in clinical practice. Therefore, the objective of this study was to establish an easy to measure biomarker for the IFN signature.
METHODS:
Serum levels of galectin-9, CXCL-10 (IP-10) and tumour necrosis factor receptor type II (TNF-RII) were measured in patients with SLE, SLE+APS and primary APS (PAPS) and healthy controls (n=148) after an initial screening of serum analytes in a smaller cohort (n=43). Analytes were correlated to measures of disease activity and the IFN signature. The performance of galectin-9, CXCL-10 and TNF-RII as biomarkers to detect the IFN signature was assessed by receiver operating characteristic curves.
RESULTS:
Galectin-9, CXCL-10 and TNF-RII were elevated in patients with SLE, SLE+APS and PAPS ($p<0.05$) and correlated with disease activity and tissue factor expression. Galectin-9 correlated stronger than CXCL-10 or TNF-RII with the IFN score ($r=0.70$, $p<0.001$) and was superior to CXCL-10 or TNF-RII in detecting the IFN signature (area under the curve (AUC) 0.86). Importantly, in patients with SLE(±APS), galectin-9 was also superior to anti-dsDNA antibody (AUC 0.70), or complement C3 (AUC 0.70) and C4 (AUC 0.78) levels in detecting the IFN signature.
CONCLUSION:
Galectin-9 is a novel, easy to measure hence clinically applicable biomarker to detect the IFN signature in patients with systemic autoimmune diseases such as SLE and APS.

Ann Rheum Dis 77:1810-4 IF 12.350 (1441)

4.27 Is attention deficit/hyperactivity disorder (ADHD) a diagnosis or a symptom complex? Experience from pediatric orthopedic practice

Objective: Attention deficit hyperactivity disorder (ADHD) is a group of behavioral symptoms that include hyperactivity and impulsiveness. The etiological understanding is somehow controversial. We aimed to study the etiological understanding in a remarkable number of children and adults with various orthopedic problems in which (ADHD) was the earliest feature and was considered as a diagnosis.
Material and Methods: 47 children and adolescent (5 females and 42 males) of age range of (7-17 years) were sought in our departments from the period of 1998-2012. Prior to the development of variable forms of bone disorders, ADHD was the earliest feature. Clinical examination of parents and multigenerational family tree analyses was fundamental. Eventually phenotypic and genotypic correlation was the baseline tool of documentation. Results: ADHD was a symptom complex rather than a diagnosis in all patients we sought and a number of serious heritable disorders such as; hamartoneoplastic disorders (neurofibromatosis type I, NF-I) in 34 patients(72.3%), syndromic craniosynostosis (3MC, hypophosphataemic rickets) in 3 patients (6.4%) , mucopolysaccharidosis type II (Hunter syndrome) and type III (Sanfilippo syndrome) in one patient (2.1%) and 2 patients

(4,3 %) respectively, and in 7 adult patients with XXY syndrome (14,9 %) were diagnosed accordingly.
Conclusion: The term ADHD is classically used as a diagnostic entity in accordance and as defined by DSM-5. We wish to underline that these children were not referred to our departments on the premise that they were ADHD patients. The referral was because they starting to develop a diversity of skeletal deformities. Our task was to categorize these children in accordance with their phenotypic and genotypic correlation. Therefore, the usage of stimulant drugs should not be issued, unless a complete clinical documentation is established and the etiological understanding is reached. Our findings confirm the continuity of ADHD beyond the adolescent as a symptom complex rather than a diagnosis

WJPMR 4:122-31 IF 4.639 (1442)

4.28 Bilateral coxa vara and tibia vara associated with severe short stature in a girl manifesting a constellation of bone lesions with exclusive involvement of the lower limbs

In most instances, a toddler is seen with unilateral varus of the tibia, usually the deformity appearing slightly more distal than the knee joint. Radiographs of the focal fibrocartilaginous dysplasia show a characteristic abrupt varus at the metaphyseal — diaphyseal junction of the tibia. Cortical sclerosis is in and around the area of the abrupt varus on the medial cortex. A radiolucency may appear just proximal to the area of cortical sclerosis. The aetiology of such defects and the pathogenesis of the deformity are mostly unknown. Many of the associated factors suggest that the condition at least partly results from a mechanical overload of the medioproximal tibial physis.
The evaluation of a child with suspected pathologic tibia vara begins with a thorough history. A complete birth and developmental history should include the age at which the child begun walking. The medical history should identify any renal disease, endocrinopathies, or known skeletal dysplasia. The physical examination also should include the child's overall lower extremity alignment and symmetry, hip and knee motion, ligamentous hyperlaxity, and tibial torsion.
We describe on a 17 year-old-girl who manifests severe short stature associated with multiple orthopaedic abnormalities, namely, bilateral coxa vara and tibia vara. Radiographic documentation showed bilateral and symmetrical involvement of the lower limbs with the extensive form of fibrocartilaginous dysplasia, osteoporosis, and osteolytic lesions. The constellation of the malformation complex of osteolytic lesions, fibrocartilaginous changes and the polycystic like fibromas are not consistent to any previously published reports of fibrocartilaginous dysplasia. To the best of our knowledge, it seems that fibrocartilaginous changes are part of a novel type of skeletal dysplasia.

Pediatric Traumatology, Orthopaedics and Reconstructive Surgery 6:63-9 IF 0.388 (1443)

4.29 Turning the backbone into an ankylosed concrete-like structure: Case report

RATIONALE:
Progressive restriction of the spinal bio-mechanics is not-uncommon deformity encountered in spine clinics. Congenital spinal fusion as seen in Klippel-Feil-anomaly, progressive non-infectious anterior vertebral fusion, and progressive spinal hyperostosis secondary to ossification of the anterior longitudinal spinal ligament are well delineated and recognized.
PATIENT CONCERNS:
A 24-year-old girl has history of osteoporosis since her early childhood, associated with multiple axial and appendicular fractures and scoliosis. Recently she presented with episodes of severe back pain, spinal rigidity/stiffness with total loss of spine biomechanics.
DIAGNOSES:
She was provisionally diagnosed as having osteogenesis imperfecta and was investigated for COL1A1/A2 mutations which have been proven to be negative. Autosomal recessive type of

osteogenesis imperfecta was proposed as well, no mutations have been encountered. A homozygous for CTSA gene mutation, the gene associated with Galactosialidosis was identified via whole exome sequencing (Next-Generation Sequencing projects) has been identified.
INTERVENTIONS:
Early in her life she had a history of frequent fractures of the long bones since she was 4 years which was followed by vertebral fractures at the age of 12 years. She manifested lower serum 25OH-D levels and were associated with lower LS-aBMD Z-scores with higher urinary bone turnover indexes (urinary NTX/Cr).
OUTCOMES:
Lysosomal storage diseases (LSD) have a strong correlation with the development of osteoporosis. LSD causes skeletal abnormalities results from a lack of skeletal remodeling and ossification abnormalities owing to abnormal deposition of GAGs (impaired degradation of glycosaminoglycans) in bone and cartilage. 3D reconstruction CT scan of the spine showed diffuse hyperostosis of almost the entire spine (begins at the level of T4- extending downwards to involve the whole thoraco-lumbar and upper part of the sacrum) with total diffuse fusion of the pedicles, the transverse and articular processes, the laminae and the spinous processes.
LESSONS:
This is the first clinical report of adult patient with a history of osteoporosis and fractures with the late diagnosis of Galactosialidosis. Osteogenesis imperfecta (autosomal dominant and recessive) were the first given diagnoses which proven negative. The pathophysiology of the spine ankylosis in our current patient and its correlation with LSD, antiresorptive medications, vitamin D3 and supplemental calcium is not fully understood. Therefore, further studies are needed to elucidate this sort of correlation.

Medicine (Baltimore) 97:e0278 IF 2.028 (1444)

4.30 Increased B-cell activating factor (BAFF)/B-lymphocyte stimulator (BLyS) in primary antiphospholipid syndrome is associated with higher adjusted global antiphospholipid syndrome scores

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterised by antiphospholipid antibodies (aPL), thrombosis and pregnancy morbidity in patients with rheumatic diseases.
BAFF/BLyS is a key cytokine in systemic lupus erythematosus (SLE) and targeting BAFF by belimumab is used to treat patients with SLE.
BAFF levels are elevated in patient with primary APS (PAPS) and correlate with higher adjusted global antiphospholipid syndrome scores.
In SLE, but not in APS, the expression of BAFF receptors is altered on peripheral blood B cells.
Similar to SLE, both mRNA and serum levels of BAFF are elevated in PAPS, in particular in patients with PAPS with higher adjusted global antiphospolipid syndrome score (aGAPSS), which are at higher risk for thrombotic events. As the treatment response to belimumab in patients with SLE is associated with higher serum levels of BAFF, belimumab might be a therapeutic option in a subset of patients with PAPS with increased BAFF levels

RMD Open 4:e000693 (1445)

4.31 Confocal laser scanning microscopy-a powerful tool in bone research

The confocal laser scanning microscope (CLSM) enables the collection of images picturing selected planes in depth of thick samples, thus giving 3D information while keeping the sample intact. In this article we give an overview of our CLSM applications in bone research: (i) the characterization of osteoblasts and osteoclasts properties in cell biology, (ii) the visualization of the three dimensional (3D) osteocyte lacunar canalicular network in undemineralized plastic-embedded bone samples, (iii) the observation of tetracycline labels in bone biopsy samples from patients in combination with information on the mineralization density from quantitative backscatter

electron imaging, which enables the time course of mineral accumulation in newly formed bone to be followed, (iv) the precise measurement of the thickness of thin ground bone sections, a prerequisite for the mapping of local mechanical properties by scanning acoustic microscopy.

Wien Med Wochenschr 168:314-21 (1446)

5 Aktivitäten in Wissenschafts-Organisation und Administration

5.1 Kongressorganisation, Tagungsleitungen und Fortbildung

5.1.1 Fortbildung

Vom 1.-3. März fand die bereits traditionelle gemeinsame Klausurtagung des LBI für Osteologie und des MPI für Kolloid- und Grenzflächenforschung in Zurndorf/Burgenland statt. Das Programm umfasste Vorträge und Diskussionen zu vielen laufenden Projekten und bot Gelegenheit zur Besprechung und Planung künftiger Kooperationen.

Im Rahmen der ärztlichen Fortbildung im Hanusch-Krankenhaus hielt N. Fratzl-Zelman im Mai einen Vortrag über “Osteogenesis imperfecta”.

G. Hedjazi nahm vom 1.-4. September an einem PhD Trainingskurs der ECTS in den Niederlanden teil.

P. Keplinger, S. Lueger und P. Messmer besuchten am 19. Oktober den Fortbildungskurs „Elektronenmikroskopie in Medizin und Biologie“ von biomed austria.

P. Messmer nimmt vom 14. Oktober bis 14. April 2019 an einem E-Learning Kurs „Communicating in the world of biomedical scientists” teil.

5.1.2 Kongressorganisation

K. Klaushofer war Vorsitzender der Jury für den International Research Prize und Mitglied des Organizing Committees der Austrian Bone Conference (ehemals International Conference on Progress in Bone and Mineral Research), die vom 23.-24. November 2018 stattfand.

5.2 Aktivitäten in nationalen und internationalen wissenschaftlichen Gesellschaften

K. Klaushofer ist Ehrenmitglied der Österreichischen Gesellschaft für Knochen und Mineralstoffwechsel (ÖGKM), Vorstandsmitglied der Elsbeth Bonhoff Stiftung, Deutschland, Mitglied des Wissenschaftlichen und Künstlerischen Beirates des Theodor-Körner-Fonds, des Obersten Sanitätsrates, des Onkologiebeirates, des Beirates für Altersmedizin sowie der Ärzteausbildungskommission im Bundesministerium für Gesundheit, des Wissenschaftlichen Beirates des Austrian Inpatient Quality Indicators Project (AIQI), der Heilmittel-Evaluierungs-Kommission (HEK) des Hauptverbandes der österreichischen Sozialversicherungsträger, der Nationalen Koordinationsstelle für Seltene Erkrankungen (NKSE) der Gesundheit Österreich GmbH und der Ludwig-Heilmeyer-Gesellschaft (Gesellschaft für Fortschritte in der Inneren Medizin), Deutschland sowie Beratender Arzt des Hauptverbandes der österreichischen Sozialversicherungsträger.

A. Al Kaissi ist Mitglied der Royal Society of Medicine, London, UK.

M. Behanova ist Mitglied der Österreichischen Gesellschaft für Public Health (ÖGPH) sowie der Slovak Public Health Association (SAVEZ).

P. Fratzl ist korrespondierendes Mitglied der Österreichischen Akademie der Wissenschaften und Mitglied der Berlin-Brandenburgischen Akademie der Wissenschaften.

E. Zwettler ist ordentliches Mitglied im Landessanitätsrat für Wien.

J. Zwerina ist Vorstandsmitglied der Österreichischen Gesellschaft für Rheumatologie & Rehabilitation sowie der Österreichischen Gesellschaft für Knochen und Mineralstoffwechsel (ÖGKM).

N. Fratzl-Zelman und R. Kocijan sind Mitglieder des wissenschaftlichen Beirates der Österreichischen Gesellschaft für Knochen und Mineralstoffwechsel (ÖGKM).

5.3 Tagungsaktivitäten

Die MitarbeiterInnen des Instituts nahmen an zahlreichen nationalen und internationalen wissenschaftlichen Tagungen teil, wie zum Beispiel: Annual European Calcified Tissue Society (ECTS) Congress in Valencia, Endocrine Society's Annual Meeting (ENDO) in Chicago, Annual Meeting of the American Society for Bone and Mineral Research (ASMBR) in Montreal, Osteologie 2018 in Dresden und Osteoporose Forum in St. Wolfgang. Details unter 7.1.2 Abstracts (1452 – 1482) und 7.1.3 Invited talks (V581 – V583).

5.4 Lehrtätigkeit

K. Klaushofer hielt im Sommersemester 2018 sowie im Wintersemester 2018/19 die Vorlesung “Ausgewählte Kapitel aus der klinischen und experimentellen Osteologie” (2 SSt) an der Medizinischen Universität Wien.

P. Roschger hielt die Blockvorlesung “Knochen und Bindegewebe” (1 SSt) an der Montanuniversität Leoben.

J. Zwerina hielt im Sommersemester 2018 sowie im Wintersemester 2018/2019 die Vorlesungen „Osteoimmunologie: Experimentielle und klinische Aspekte“ (2 SSt) und „Vaskulitis“ (2 SSt) an der Universität Erlangen und ist Lektor an der Medizinischen Universität Wien.

T. Dechat hielt im Rahmen des Masterstudiums „Molecular Biotechnologies“ am FH-Campus Wien im Sommersemester 2018 einen Stammzellenkurs (3 SSt). Im Juli hielt er für die Junge Uni Krems an der IMC Fachhochschule Krems den Vortrag „DNA, Zellen und das Alter“ sowie den Workshop „Geheimschleim“.

Im Rahmen der „Basic Lectures of Bone and Joint Regeneration“ (2 SSt) hielten P. Roschger, S. Blouin und B. Misof im Wintersemester 2017/2018 an der Medizinischen Universität Wien die Vorlesung „Bone Material Quality“.

N. Fratzl-Zelman hielt im Rahmen der „Basic Lectures of Bone and Joint Regeneration“ (2 SSt) im Wintersemester 2017/2018 die Vorlesung „Osteoblasts and Osteocytes: Essentials and Methods“ und ein Practical Seminar. Im Sommersemester 2018 die Vorlesung „Osteogenesis imperfecta“ sowie jeweils einen Journal Club im Rahmen des Studienlehrgangs N790 der Medizinischen Universität Wien.

T. Dechant betreute drei BachelorstudentInnen der Uni Wien (Studium Biologie mit Schwerpunkt Mikrobiologie) und eine Bachelorstudentin der FH Campus Wien (Studium Molekulare Biotechnologie).

R. Fritsch-Stork hielt im Sommersemester 2018 die Vorlesungen „Autoimmunität und Rheumatologie“ (0,5 SSt) und „Autoimmunität“ (0,5 SSt) sowie das Praktikum „Physikalische Untersuchung des Bewegungsapparates“ (0,5 SSt). Im Wintersemester 2018/2019 dasselbe

Programm plus eine Anamnese Blockvorlesung und Klinische Fallbesprechung für den Masterstudiengang (insgesamt jeweils 3 SSt).

R. Fritsch-Stork (Rheumatologie) und G. Uyanik (medizinische Genetik) halten Lehrstühle an der Sigmund Freud Privatuniversität Wien.

5.5 Reviewertätigkeit

A. Al Kaissi ist Mitglied des Editorial Boards von *BMJ Case Reports*.

E. Paschalis ist Mitglied der Editorial Boards von *Journal of Bone and Mineral Research* und *Bone* und Associate Editor des *Journal of Musculoskeletal and Neuronal Interactions*.

E. Paschalis und P. Roschger sind Mitglieder des Editorial Boards von *Calcified Tissue International*.

J. Zwerina ist Mitglied des Editorial Boards von *Arthritis & Rheumatism*.

T. Dechat ist Academic Collection Editor für die Topical Collection "Lamins and Laminopathies" bei *Cells*

S. Blouin ist Review Editor von *Frontiers in Endocrinology*.

K. Klaushofer, P. Roschger, N. Fratzl-Zelman, B. Misof und E. Paschalis sind Mitglieder von F1000 Medicine.

K. Klaushofer ist Begutachter des Theodor Körner Fonds zur Förderung von Wissenschaft und Kunst.

K. Klaushofer ist stellvertretender Vorsitzender des Kuratoriums der Elsbeth Bonhoff Stiftung, Berlin.

Darüber hinaus wurden Peer Reviews für zahlreiche wissenschaftliche Journale und Forschungsförderungs Fonds von MitarbeiterInnen des LBIO verfasst.

5.6 Beteiligung an Projekten

- 3D and 2D Distribution of Trace Elements in Pathological Human Bone and in Histological Transition Zones – An Approach with Micro and Nano Resolution Elemental Imaging by Synchrotron XRF
  FWF-Projekt P-27715-N20
  Projektleitung: C. Streli, Atominstitut, Technische Universität Wien
  Co-Investigators: P. Roschger, J. Hofstätter
  01.04.2015 – 31.03.2018
- Metaflammation in Childhood Obesity: Pathogenetic Mechanisms and Novel Biomarkers
  Medizinisch-Wissenschaftlicher Fonds des Bürgermeisters der Bundeshauptstadt Wien, 15215
  Projektleitung: M. Mayerhofer
  01.12.2016 – 31.03.2018
- Untersuchung von klinischen, serologischen und genetischen Faktoren der lgG4 – Related Disease
  Medizinisch-Wissenschaftlicher Fonds des Bürgermeisters der Bundeshauptstadt Wien, 15069
  Projektleitung: J. Zwerina
  01.08.2015 – 31.12.2019
- The Influence of the Coordination of Cross-Links on the Mechanical Properties of Polymers
  Projektleitung: M. Hartmann
  01.09.2015 – 31.08.2019
  Das ursprünglich an der Universität Wien gestartete Projekt wurde mit dem Wechsel von M. Hartmann an das LBIO an dieses übertragen.
- Occult Bone Disease in Sudden Childhood Death: a Post-Mortem Study
  Kooperation mit Birmingham Women's & Children's NHS Foundation Trust
  Projektleitung: W. Högler
  Projektkoordination LBIO: N. Fratzl-Zelman
  01.01.2018 – 31.12.2022

5.7 Preise und Nominierungen

M. Blank erhielt den ImmunoTools Award 2018 im Wert von € 5.000,- in Form von Antikörpern.

5.8 Personelle Daten

5.8.1 Neueintritte

Dr. Martina Behanova übernahm am 15. März die Position für Epidemiologie und Biostatistik.

Seit 1. Mai ist Ghazal Hedjazi, MSc. als PhD Studentin im Labor im UKH Meidling tätig.

Mit 14. Mai kehrte Univ.Doz. DI Dr. Paul Roschger aus der Pension zurück, um im Rahmen einer Teilzeitanstellung weiterhin das Labor in Meidling zu leiten und die Übergabe an seinen Nachfolger vorzubereiten.

Mag. Dr. Thomas Dechat übernahm per 1. Juni die Leitung der Support Facility Cell Biology.

Seit 1. September verstärkt PD Dr. Markus Hartmann die Programmlinie Material Science – Mineral, Structure, Function, deren Leitung er mit Juni 2019 übernehmen soll.

5.8.2 Austritte

Dr. Wolfgang Brozek verließ per 31. Jänner das LBIO, um sich beruflich neu zu orientieren.

Univ.Doz. DI Dr. Paul Roschger trat mit 1. April die Pension an.

Martha Blank, MSc. verließ mit 30. Juni das Institut, um ihr Studium in Melbourne weiter zu führen und mit einem PhD abzuschließen.

Dr. Johann Bartko wechselte mit 1.1.2019 in die 1. Medizinische Abteilung des Hanusch-Krankenhauses.

5.8.3 Diverses

Univ.Prof. Dr. Klaus Klaushofer ging mit 1. September als Leiter der 1. Medizinischen Abteilung im Hanusch-Krankenhaus in Pension und Ende des Jahres auch als Leiter des LBI für Osteologie.

PD Dr. Jochen Zwerina wurde per 1. September zum Primarius der 1. Medizinischen Abteilung des Hanusch-Krankenhauses ernannt. Mit 1.1.2019 löste er Univ.Prof. Dr. Klaus Klaushofer auch als Leiter des LBI für Osteologie ab.

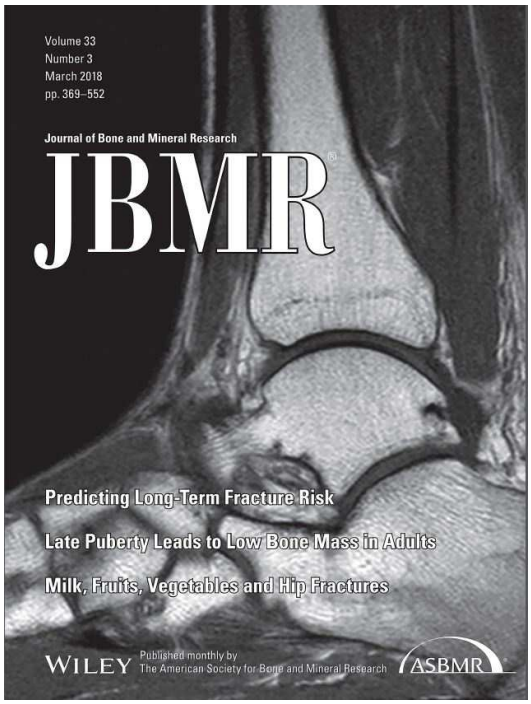
6 Publications and oral presentations

6.1 Publications of the year 2018

6.1.1 Original papers

1415. Bartko J, Roschger P, Zandieh S, Brehm A, Zwerina J, Klaushofer K 2018 Hypophosphatemia, severe bone pain, gait disturbance, and fatigue fractures after iron substitution in inflammatory bowel disease: a case report. J Bone Miner Res 33:534-9
IF 6.314

1416. Bartko J, Roschger P, Zandieh S, Brehm A, Zwerina J, Klaushofer K 2018 Reply: Hypophosphatemia, severe bone pain, gait disturbance, and fatigue fractures after iron substitution in inflammatory bowel disease: a case report. J Bone Miner Res 33:546
IF 6.314



An MRI picture of this article was featured on the cover page of JBMR's March issue.

1417. Roetzer KM, Uyanik G, Brehm A, Zwerina J, Zandieh S, Czech T, Roschger P, Misof BM, Klaushofer K 2018 Novel familial mutation of LRP5 causing high bone mass: Genetic analysis, clinical presentation, and characterization of bone matrix mineralization. Bone 107:154-60
IF 4.455

1418. Amuno S, Al Kaissi A, Jamwal A, Niyogi S, Quenneville CE 2018 Chronic arsenicosis and cadmium exposure in wild snowshoe hares (Lepus americanus) breeding near Yellowknife, Northwest Territories (Canada), part 2: Manifestation of bone abnormalities and osteoporosis. Sci Total Environ 612:1559-67
IF 4.610

1419. Cuppen B, Fritsch-Stork R, Eekhout I, de Jager W, Marijnissen AC, Bijlsma J, Custers M, van Laar JM, Lafeber F, Welsing P; all Society for Rheumatology Research Utrecht (SRU) investigators 2018 Proteomics to predict the response to tumour necrosis factor-α inhibitors in rheumatoid arthritis using a supervised cluster-analysis based protein score. Scand J Rheumatol 47:12-21
IF 3.021

1420. Greiner G, Gurbisz M, Ratzinger F, Witzeneder N, Simonitsch-Klupp I, Mitterbauer-Hohendanner G, Mayerhofer M, Müllauer L, Sperr WR, Valent P, Hoermann G 2018 Digital PCR: a sensitive and precise method for KIT D816V quantification in mastocytosis. Clin Chem 64:547-55
IF 8.008

1421. Werzowa JM, Säemann MD, Mohl A, Bergmann M, Kaltenecker CC, Brozek W, Thomas A, Haidinger M, Antlanger M, Kovarik JJ, Kopecky C, Song PXK, Budde K, Pascual J, Hecking M 2018 A randomized controlled trial-based algorithm for insulin-pump therapy in hyperglycemic patients early after kidney transplantation. PLoS One 13:e0193569
IF 3.540

1422. Stamm TA, Reichardt B, Zwerina J, Ritschl V, Nell-Duxneuner V 2018 Use of biological disease modifying antirheumatic drugs in rheumatoid arthritis in Austria from 2008 to 2011: A retrospective analysis of 72% of the population. Wien Klin Wochenschr 130:230-7
IF 1.003

1423. Kang H, Jha S, Deng Z, Fratzl-Zelman N, Cabral WA, Ivovic A, Meylan F, Hanson EP, Lange E, Katz J, Roschger P, Klaushofer K, Cowen EW, Siegel RM, Marini JC, Bhattacharyya T 2018 Somatic activating mutations in MAP2K1 cause melorheostosis. Nat Commun 9:1390
IF 12.353

1424. Uday S, Fratzl-Zelman N, Roschger P, Klaushofer K, Chikermane A, Saraff V, Tulchinsky T, Thacher TD, Marton T, Högler W 2018 Cardiac, bone and growth plate manifestations in hypocalcemic infants: revealing the hidden body of the vitamin D deficiency iceberg. BMC Pediatr 18:183
IF 2.042

1425. Buenzli PR, Lerebours C, Roschger A, Roschger P, Weinkamer R 2018 Late stages of mineralization and their signature on the bone mineral density distribution 2018 Connect Tissue Res 59(sup1):74-80
IF 2.608

1426. Cundy T, Dray M, Delahunt J, Hald JD, Langdahl B, Li C, Szybowska M, Mohammed S, Duncan EL, McInerney-Leo AM, Wheeler PG, Roschger P, Klaushofer K, Rai J, Weis M, Eyre D, Schwarze U, Byers PH 2018 Mutations that alter the carboxy-terminal-Propeptide cleavage site of the chains of type I procollagen are associated with a unique osteogenesis imperfecta phenotype. J Bone Miner Res 33:1260-71
IF 6.314

1427. Hartman EAR, van Royen-Kerkhof A, Jacobs JWG, Welsing PMJ, Fritsch-Stork RDE 2018 Performance of the 2012 Systemic Lupus International Collaborating Clinics classification criteria versus the 1997 American College of Rheumatology classification criteria in adult and juvenile systemic lupus erythematosus. A systematic review and meta-analysis. Autoimmun Rev 17:316-22 Review
IF 8.745

1428. Lindahl K, Åström E, Dragomir A, Symoens S, Coucke P, Larsson S, Paschalis E, Roschger P, Gamsjaeger S, Klaushofer K, Fratzl-Zelman N, Kindmark A 2018 Homozygosity for CREB3L1 premature stop codon in first case of recessive osteogenesis imperfecta associated with OASIS-deficiency to survive infancy. Bone 114:268-77
IF 4.455

1429. Cuppen BVJ, Rossato M, Fritsch-Stork RDE, Concepcion AN, Linn-Rasker SP, Bijlsma JWJ, van Laar JM, Lafeber FPJG, Radstake TR; all SRU investigators 2018 RNA sequencing to predict response to TNF-α inhibitors reveals possible mechanism for nonresponse in smokers. Expert Rev Clin Immunol 14:623-33
IF 3.436

1430. Kronschläger M, Blouin S, Roschger P, Varsits R, Findl O 2018 Attaining the optimal flange for intrascleral intraocular lens fixation. J Cataract Refract Surg S0886-3350(18)30669-2
IF 2.680

1431. Balasubramanian M, Fratzl-Zelman N, O'Sullivan R, Bull M, Peel NFA, Pollitt RC, Jones R, Milne E, Smith K, Roschger P, Klaushofer K, Bishop NJ 2018 Novel PLS3 variants in X-linked osteoporosis: exploring bone material properties. Am J Med Genet A 176:1578-86
IF 2.264

1432. Bartko J, Schoergenhofer C, Schwameis M, Firbas C, Beliveau M, Chang C, Marier JF, Nix D, Gilbert JC, Panicker S, Jilma B 2018 A randomized, first-in-human, healthy volunteer trial of sutimlimab, a humanized antibody for the specific inhibition of the classical complement pathway. Clin Pharmacol Ther 104:655-63
IF 6.544

1433. Al Kaissi A, Ghachem MB, Nabil NM, Kenis V, Melchenko E, Morenko E, Grill F, Ganger R, Kircher SG 2018 Schmid's type of metaphyseal chondrodysplasia: diagnosis and management. Orthop Surg 10:241-6
IF 1.147

1434. Simon S, Resch H, Klaushofer K, Roschger P, Zwerina J, Kocijan R 2018 Hypophosphatasia: from diagnosis to treatment. Curr Rheumatol Rep 20:69
IF 3.079

1435. Teng YKO, Bredewold EOW, Rabelink TJ, Huizinga TWJ, Eikenboom HCJ, Limper M, Fritsch-Stork RDE, Bloemenkamp KWM, Sueters M 2018 An evidence-based approach to pre-pregnancy counselling for patients with systemic lupus erythematosus. Rheumatology (Oxford) 57:1707-20
IF 5.245

1436. Pereira RC, Salusky IB, Roschger P, Klaushofer K, Yadin O, Freymiller EG, Bowen R, Delany AM, Fratzl-Zelman N, Wesseling-Perry K 2018 Impaired osteocyte maturation in the pathogenesis of renal osteodystrophy. Kidney Int 94:1002-12
IF 8.429

1437. Stoffer-Marx MA, Klinger M, Luschin S, Meriaux-Kratochvila S, Zettel-Tomenendal M, Nell-Duxneuner V, Zwerina J, Kjeken I, Hackl M, Öhlinger S, Woolf A, Redlich K, Smolen JS, Stamm TA 2018 Functional consultation and exercises improve grip strength in osteoarthritis of the hand - a randomised controlled trial. Arthritis Res Ther 20:253
IF 4.269

1438. Oppl B, Husar-Memmer E, Pfefferkorn S, Blank M, Zenz P, Gollob E, Wurnig C, Engel A, Stadlmayr A, Uyanik G, Brozek W, Klaushofer K, Zwerina J, Datz C 2018 HFE hemochromatosis screening in patients with severe hip osteoarthritis: A prospective cross-sectional study. PLoS One 13:e0207415
IF 2.766

1439. Paschalis EP, Krege JH, Gamsjaeger S, Eriksen EF, Burr DB, Disch DP, Stepan JJ, Fahrleitner-Pammer A, Klaushofer K, Marin F, Pavo I 2018 Teriparatide treatment increases mineral content and volume in cortical and trabecular bone of iliac crest: A comparison of infrared imaging with X-ray-based bone assessment techniques. J Bone Miner Res 33:2230-5
IF 6.314

1440. Bartko J, Schoergenhofer C, Schwameis M, Wadowski P, Kubica J, Jilma B, Hobl EL 2018 Morphine interaction with Aspirin: a double-blind, crossover trial in healthy volunteers. J Pharmacol Exp Ther 365:430-6
IF 3.706

1441. van den Hoogen LL, van Roon JAG, Mertens JS, Wienke J, Lopes AP, de Jager W, Rossato M, Pandit A, Wichers CGK, van Wijk F, Fritsch-Stork RDE, Radstake TRDJ 2018 Galectin-9 is an easy to measure biomarker for the interferon signature in systemic lupus erythematosus and antiphospholipid syndrome. Ann Rheum Dis 77:1810-4
IF 12.350

1442. Al Kaissi A, Ben Chehida F, Kenis V, Brozek W, Grill F, Ganger R, Kircher SG 2018 Is attention deficit/hyperactivity disorder (ADHD) a diagnosis or a symptom complex? Experience from pediatric orthopedic practice. WJPMR 4:122-31
IF 4.639

1443. Al Kaissi A, Grill F, Ganger R, Kircher SG 2018 Bilateral coxa, vara and tibia vara associated with severe short stature in a girl manifesting a constellation of bone lesions with exclusive involvement of the lower limbs. Pediatric Traumatology, Orthopaedics and Reconstructive Surgery 6:63-9
IF 0.388

1444. Al Kaissi A, Ben Chehida F, Frill F, Ganger R, Kircher SG 2018 Turning the backbone into an ankylosed concrete-like structure: Case report. Medicine (Baltimore) 97:e0278
IF 2.028

1445. van den Hoogen LL, Palla G, Bekker CPJ, Fritsch-Stork RDE, Radstake TRDJ, van Roon JAG 2018 Increased B-cell activating factor (BAFF)/B-lymphocyte stimulator (BLyS) in primary antiphospholipid syndrome is associated with higher adjusted global antiphospholipid syndrome scores. RMD Open 4:e000693

1446. Blouin S, Roschger A, Varga F, Misof B, Spitzer S, Roschger P, Klaushofer K. 2018 Confocal laser scanning microscopy-a powerful tool in bone research. Wien Med Wochenschr 168:314-21

1447. Rauner M, Buttgereit F, Distler J, Garbe AI, Herrmann M, Hofbauer L, Hoffmann M, Jessberger R, Kornak U, Krönke G, Mundlos S, Spies C, Tuckermann J, Zwerina J 2018 Osteoimmunology-IMMUNOBONE: Regulation of bone by inflammation. Z Rheumatol 77(Suppl 1):12-5
IF 0.697

1448. Al Kaissi A, Grill F, Ganger R, Kircher SG 2018 Carpal fusion in Ellis-Van Creveld Syndrome. Letter to the Editor, Orthop Spine Sports Med 2:010

1449. Kocijan R 2018 Glukokortikoidinduzierte Osteporose. Fakten der Rheumatologie 04/2018

1450. Blank M 2018 Investigation of the mineralization process in normal and cancer cells and the influence of matrix vesicles on bone tissue. (Master Thesis)

1451. Heugl T 2018 Does notch signaling induced by co-cultured leukemia cells modulate differentiation of osteoblasts? (Master Thesis)

6.1.2 Abstracts

1452. Jha S, Kang H, Deng Z, Fratzl-Zelman N, Cabral WA, Ivovic A, Meylan F, Hanson E, Lange E, Katz J, Roschger P, Klaushofer K, Cowen EW, Siegel RM, Marini JC, Bhattacharyya T 2018 Somatic activating mutations in MAP2K1 cause melorheostosis. ENDO, March 17 – 20, Chicago, USA, Endocrine Reviews 39, Suppl, abstract OR03-7 and oral presentation

1453. Jha S, Fratzl-Zelman N, Roschger P, Klaushofer K, Papadakis GZ, Cowen EW, Kang H, Deng Z, Ivovic A, Dasgupta A, Lange E, Katz J, Marini JC, Siegel RM, Bhattacharyya T 2018 A prospective study of clinical, genetic and pathological findings in melorheostosis. ENDO, March 17 – 20, Chicago, USA, Endocrine Reviews 39, Suppl, abstract 7736 and poster presentation

1454. Paschalis E, Gamsjaeger S, Eriksen E, Glorieux F, Rauch F, Dempster D, Zhou H, Shane E, Cohen A, Recker R, Bilezikian J, Rubin M, Moreira C, Lane J, Pavo I, Stepan J, Papapoulos S, Brozek W, Fratzl P, Klaushofer K 2018 Organic matrix quality at actively forming trabecular surfaces is strongly associated with fragility fracture incidence independent of BMD and the clinical diagnosis. ECTS, May 26 – 29, Valencia, Spain, Calcif Tissue Int 102, Suppl 1:S22, abstract P065 and oral poster presentation

1455. Blouin S, Misof B, Berzlanovich A, Gruber GM, Klaushofer K, Fratzl P, Roschger P 2018 Microarchitecture variation in the vicinity of the standard transiliac biopsy site assessed by microCT. ECTS, May 26 – 29, Valencia, Spain, Calcif Tissue Int 102, Suppl 1:S68, abstract P130 and poster presentation

1456. Hassler N, Blank M, Spitzer S, Klaushofer K, Varga F 2018 Kruppel-like factor 10 (KLF10) as a mediator of shear stress in osteoblast like MC3T3-E1 cells. ECTS, May 26 – 29, Valencia, Spain, Calcif Tissue Int 102, Suppl 1:S84, abstract P176 and poster presentation

1457. Blank M, Hassler N, Blouin S, Pichler P, Mitulovic G, Spitzer S, Klaushofer K, Varga F 2018 Characterization of extracellular vesicles obtained from murine mesenchymal D1 cell cultures. ECTS, May 26 – 29, Valencia, Spain, Calcif Tissue Int 102, Suppl 1:S84, abstract P177 and poster presentation

1458. Blank M, Hassler N, Spitzer S, Klaushofer K, Varga F 2018 Differentiation and mineral deposition of murine mesenchymal D1 cell cultures. ECTS, May 26 – 29, Valencia, Spain, Calcif Tissue Int 102, Suppl 1:S87, abstract P184 and poster presentation

1459. Kang H, Jha S, Deng Z, Fratzl-Zelman N, Cabral W, Ivovic A, Meylan F, Hanson E, Lange E, Katz J, Roschger P, Klaushofer K, Cowen E, Siegel R, Bhattacharyya T, Marini J 2018 Somatic activating mutations in MAP2K1 cause melorheostosis. ECTS, May 26 – 29, Valencia, Spain, Calcif Tissue Int 102, Suppl 1:S151, abstract P357 and poster presentation

1460. Fratzl-Zelman N, Roschger P, Kang H, Jha S, Roschger A, Blouin S, Deng Z, Cabral WA, Ivovic A, Meylan F, Hanson EP, Lange E, Katz J, Cowen EW, Klaushofer K, Siegel R, Fratzl P, Bhattacharyya T, Marini JC 2018 Material properties in bone tissue from patients with Melorheostosis caused by somatic activation mutations in MAP2K1. ECTS, May 26 – 29, Valencia, Spain, Calcif Tissue Int 102, Suppl 1:S153, abstract P364 and poster presentation

1461. Tsourdi E, Jähn K, Lademann F, Wölfel EM, Busse B, Blouin S, Roschger P, Hofbauer LC, Rauner M 2018 Exogenous hyperthyroidism induces osteocytic osteolysis in male mice. ECTS, May 26 – 29, Valencia, Spain, Calcif Tissue Int 102, Suppl 1:S8, abstract PLO15 and oral presentation

1462. van Tol A, Roschger A, Chen J, Repp F, Kollmannsberger P, Roschger P, Fratzl P, Weinkamer R 2018 Assessment of fluid flow through the osteocyte lacuna-canalicular network in whole human osteons of different type. ECTS, May 26 – 29, Valencia, Spain, Calcif Tissue Int 102, Suppl 1:S92, abstract P197 and poster presentation

1463. Kämpe AJ, Costantini A, Levy-Shraga Y, Zeitlin L, Roschger P, Taylan F, Lindstrand A, Paschalis EP, Gamsjaeger S, Raas-Rothschild A, Hövel M, Jiao H, Klaushofer K, Grasemann C, Mäkitie O 2018 PLS3 deletions lead to severe spinal osteoporosis and disturbed bone matrix mineralization. ESHG, June 16 – 19, Milan, Italy abstract P04.73A / A and poster presentation

1464. Kang H, Jha S, Deng Z, Fratzl-Zelman N, Cabral WA, Ivovic A, Meylan F, Hanson EP, Lange E, Katz J, Roschger P, Klaushofer K, Cowen EW, Siegel RM, Bhattacharyya T, Marini JC 2018 Somatic activating mutations in MAP2K1 cause melorheostosis. ESHG, June 16 – 19, Milan, Italy, abstract C12.6 and oral presentation

1465. Paschalis EP, Gamsjaeger S, Rokidi S, Klaushofer K, Burr D 2018 Estrogen depletion alters regulation of mineralization at actively forming osteonal surfaces in a monkey animal model. ASBMR, September 28 – October 01, Montreal, QC, Canada, abstract FRI-0862 and poster presentation

1466. Fratzl-Zelman N, Rokidi S, Blouin S, Plasenzotti P, Nawrot-Wawrzyniak K, Rumpler M, Roetzer K, Uyanik G, Häusler G, Klaushofer K, Fratzl P, Paschalis E, Roschger P, Zwettler E 2018 Lack of mature collagen-links is associated with osteomalacia in patients with X-

linked hypophosphatemia. ASBMR, September 28 – October 01, Montreal, QC, Canada, abstract SAT-1086 and poster presentation

1467. Kang H, Jha S, Deng Z, Fratzl-Zelman N, Cabral W, Ivovic A, Meylan F, Hanson E, Lange E, Katz J, Roschger P, Klaushofer K, Cowen E, Siegel R, Bhattacharyya T, Marini J 2018 Somatic activating mutations in MAP2K1 cause melorheostosis. 2018 ASBMR, September 28 – October 01, Montreal, QC, Canada, abstract 1048 and oral presentation

1468. Paschalis EP, Rokidi S, Klaushofer K, Vennin S, Desyatova A, Turner JA, Watson P, Lappe J, Akhter MP, Recker RR 2018 Organic matrix quality discriminates between age- and BMD-matched fracturing versus non-fracturing post-menopausal women. ASBMR, September 28 – October 01, Montreal, QC, Canada, abstract LB SUN-1154 and poster presentation

1469. Misof BM, Blouin S, Roschger P, Werzowa J, Klaushofer K, Lehmann G 2018 Differences in osteocyte lacunar properties and bone matrix mineralization in high versus low bone turnover in adult patients with CKD-MBD. Austrian Bone Conference, November 23 – 24, Vienna Austria, abstract and 506.1 and oral presentation

1470. Fratzl-Zelman N, Roschger P, Kang H, Jha S, Roschger A, Blouin S, Deng Z, Cabral WA, Ivovic A, Meylan F, Hanson EP, Lange E, Katz J, Cowen EW, Klaushofer K, Siegel RM, Fratzl P, Bhattacharyya T, Marini JC 2018 Metabolic overactive bone in melorheostosis lesions caused by activating mutations in MAP2K1. Austrian Bone Conference, November 23 – 24, Vienna Austria, abstract S04.2 and oral presentation

1471. Al Kaissi A, Roschger P, Paschalis E, Rokidi S, Zandieh S, Muschitz C, Behunova J, Fahrleitner-Pammer A, Klaushofer K, Ganger R, Al-Shboul M 2018 Elevated bone matrix mineralization in a case of Nasu-Hakola disease. Austrian Bone Conference, November 23 – 24, Vienna Austria, abstract S06.2 and oral presentation

1472. Hassler N, Blank M, Spitzer S, Dechat T, Klaushofer K, Varga F 2018 Influence of shear forces on expression of stress related genes in osteoblast like MC3T3-E1 cells. Austrian Bone Conference, November 23 – 24, Vienna Austria, abstract S02.5 and oral presentation

1473. Blouin S, Misof B, Berzlanovich A, Gruber GM, Klaushofer K, Fratzl P, Roschger P 2018 Microarchitecture diversity in surrounding area of the standard transiliac biopsy site. Austrian Bone Conference, November 23 – 24, Vienna Austria, abstract S04.4 and oral presentation

1474. Blank M, Hassler N, Dechat T, Spitzer S, Klaushofer K, Varga F 2018 Murine mesenchymal D1 cells as model system to study mineral deposition and differentiation into the osteoblastic lineage. Austrian Bone Conference, November 23 – 24, Vienna Austria, abstract P01.7 and poster presentation

1475. Behanova M, Reichardt B, Zwerina J, Klaushofer K, Kocijan R 2018 Antiresorptive treatment either with bisphosphonates or denosumab reduces mortality in hip fracture patients. Austrian Bone Conference, November 23 – 24, Vienna Austria, abstract S03.3 and oral presentation

1476. Oppl B, Datz C, Huber-Schönauer U, Husar-Memmer E, Brozek W, Zenz P, Wurnig C, Engel A, Klaushofer K, Zwerina J, Bartko J 2018 Vascular Cell Adhesion Molecule 1 in patients with severe osteoarthritis of the hip - a prospective, cross-sectional study. Austrian Bone Conference, November 23 – 24, Vienna Austria, abstract P05.3 and poster presentation

1477. Paschalis EP, Gamsjaeger S, Condon K, Klaushofer K, Burr D 2018 Estrogen depletion alters mineralization regulation mechanisms in an ovariecomized monkey animal model.

LBG Meeting for Health Sciences, November 29 – 30, Vienna, Austria, abstract 18894 and poster presentation

1478. Rokidi S, Klaushofer K, Paschalis EP 2018 Bone organic matrix quality significantly correlates with fracture incidence. LBG Meeting for Health Sciences, November 29 – 30, Vienna, Austria, abstract 18942 and rapid fire and poster presentation

1479. Fratzl-Zelman N, Rokidi S, Blouin S, Plasenzotti P, Nawrot-Wawrzyniak K, Roetzer K, Uyanik G, Häusler G, Klaushofer K, Fratzl P, Paschalis E, Roschger P, Zwettler E 2018 Mature collagen-linked formation is inversely associated with osteomalacia in X-linked hypophosphatemia. LBG Meeting for Health Sciences, November 29 – 30, Vienna, Austria, abstract 19055 and poster presentation

1480. Hedjazi G, Roschger A, Cabral WA, Blouin S, Wagermaier W, Fratzl P, Roschger P, Fratzl-Zelman N, Klaushofer K, Marini JC 2018 Bone matrix characterization in diverse mouse models of osteogenesis imperfecta. LBG Meeting for Health Sciences, November 29 – 30, Vienna, Austria, abstract 19152 and poster presentation

1481. Blouin S, Misof B, Berzlanovich A, Gruber G, Klaushofer K, Fratzl P, Roschger P 2018 Microarchitecture variation in the vicinity of the standard transiliac biopsy site assessed by microCT. LBG Meeting for Health Sciences, November 29 – 30, Vienna, Austria, abstract 19159 and oral presentation

1482. Behanova M, Reichardt B, Kocijan R, Klaushofer K, Zwerina J 2018 Antiresorptive treatment either with bisphosphonates or denosumab improve survival in hip fracture patients. LBG Meeting for Health Sciences, November 29 – 30, Vienna, Austria, abstract 19088 and poster presentation

6.1.3 Invited talks

V581 Klaushofer K 2018 „Selber schuld ...! Sollen Personen mit Risikoverhalten die Therapiekosten selbst berappen?“ Radiodoktor, 1. Februar, Wien, Österreich

V582 Klaushofer K 2018 “Innovative Krebsmedikamente, ist das leistbar?” CURE Interview, 12. März, Wien, Österreich

foto: katsey

V583 Klaushofer K 2018 Podiumsdiskussion „Affordable access to medicines of everyone“ WHOCC – Vienna, 25. Juli, Wien, Österreich

6.1.4 Publications in print

Blouin S, Fratzl-Zelman N, Roschger A, Cabral WA, Klaushofer K, Marini JC, Fratzl P, Roschger P 2019 Cortical bone properties in the Brtl/+ mouse model of Osteogenesis imperfecta as evidenced by acoustic transmission microscopy. J Mech Behav Biomed Mater 90:125-32
IF 3.239

Paschalis EP, Gamsjaeger S, Condon K, Klaushofer K, Burr D 2019 Estrogen depletion alters mineralization regulation mechanisms in an ovariectomized monkey animal model. Bone 120:279-84
IF 4.455

Jha S, Fratzl-Zelman N, Roschger P, Papadakis GZ, Cowen EW, Kang H, Lehky TJ, Alter K, Deng Z, Ivovic A, Flynn L, Reynolds JC, Dasgupta A, Miettinen M, Lange E, Katz J, Klaushofer K, Marini JC, Siegel RM, Bhattacharyya T 2019 Distinct clinical and pathological features of melorheostosis associated with somatic MAP2K1 mutations. J Bone Miner Res 34:145-56
IF 6.314

Groot N, Shaikhani D, Teng YKO, de Leeuw K, Bijl M, Dolhain RJEM, Zirkzee E, Fritsch-Stork R, Bultink IEM, Kamphuis S 2019 Long-term clinical outcomes in a cohort of adults with childhood-onset Systemic Lupus Erythematosus. Arthritis Rheumatol 71:290-301
IF 7.871

Schwaiger E, Burghart L, Signorini L, Ristl R, Kopecky C, Tura A, Pacini G, Wrba T, Antlanger M, Schmaldienst S, Werzowa J, Säemann MD, Hecking M 2019 Empagliflozin in posttransplantation diabetes mellitus: A prospective, interventional pilot study on glucose metabolism, fluid volume and patient safety. Am J Transplant 19:907-19
IF 6.493

Al Kaissi A, Ryabykh S, Pavlova OM, Ochirova P, Kenis V, Chehida FB, Ganger R, Grill F, Kircher SG 2019 The Management of cervical spine abnormalities in children with spondyloepiphyseal dysplasia congenita: Observational study. Medicine (Baltimore) 98(1):e13780
IF 2.028

Shabbir H, Dellago C, Hartmann MA 2019 A high coordination of cross-links is beneficial for the strength of cross-linked fibers. Biomimetics 4, 12

Roschger P, Misof BM, Klaushofer K 2019 Chapter 5: Basic aspects of bone mineralization. In: Osteoporosis: Pathophysiology and Clinical Management, 3rd edition, Leder BZ, Wein MN (eds.), Springer Nature Switzerland AG

Shboul M, Roschger P, Ganger R, Paschalis EP, Rokidi S, Zandieh S, Behunova J, Muschitz C, Fahrleitner-Pammer A, Ng AYJ, Tohari S, Venkatesh B, Bonnard C, Reversade B, Klaushofer K, Al Kaissi A 2018 Bone matrix hypermineralization associated with low bone turnover in a case of Nasu-Hakola disease. Bone pii: S8756-3282(18)30372-7. doi: 10.1016/j.bone.2018.10.008. [Epub ahead of print]
IF 4.455

Ovejero D, Misof BM, Gafni RI, Dempster D, Zhou H, Klaushofer K, Collins MT, Roschger P 2018 Bone matrix mineralization in patients with gain-of-function calcium-sensing receptor mutations is distinctly different from that in postsurgical hypoparathyroidism. J Bone Miner Res 2018 Nov 29. doi: 10.1002/jbmr.3638. [Epub ahead of print]
IF 6.314

van der Linden M, van den Hoogen LL, Westerlaken GHA, Fritsch-Stork RDE, van Roon JAG, Radstake TRDJ, Meyaard L 2018 Neutrophil extracellular trap release is associated with antinuclear antibodies in systemic lupus erythematosus and anti-phospholipid syndrome. Rheumatology (Oxford) Mar 28. doi: 10.1093/rheumatology/key067. [Epub ahead of print]
IF 5.245

van den Hoogen LL, van der Heijden EHM, Hillen MR, Mertens JS, Fritsch-Stork RDE, Radstake TRDJ, van Roon JAG 2018 Galectin-9 reflects the interferon signature and correlates with disease activity in systemic autoimmune diseases. Reply. Ann Rheum Dis. Dec 8. pii: annrheumdis-2018-214651. doi: 10.1136/annrheumdis-2018-214651. [Epub ahead of print]
IF 12.350

J Fratzl-Zelman N, Roschger P, Kang H, Jha S, Roschger A, Blouin S, Deng Z, Cabral WA, Ivovic A, Katz J, Siegel RM, Klaushofer K, Fratzl P, Bhattacharyya T, Marini JC 2019 Melorheostotic bone lesions caused by somatic mutations in MAP2K1 have deteriorated microarchitecture and periosteal reaction. Bone Miner Res Jan 22. doi: 10.1002/jbmr.3656. [Epub ahead of print]
IF 6.314

Pekkinen M, Terhal PA, Botto LD, Henning P, Mäkitie RE, Roschger P, Jain A, Kol M, Kjellberg MA, Paschalis EP, van Gassen K, Murray M, Bayrak-Toydemir P, Magnusson MK, Jans J, Kausar M, Carey JC, Somerharju P, Lerner UH, Vesa OM, Klaushofer K, Holthuis JC, Mäkitie O 2019 Osteoporosis and skeletal dysplasia caused by pathogenic variants in SGMS2. JCI Insight Feb 19. pii: 126180. doi: 10.1172/jci.insight.126180. [Epub ahead of print]

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